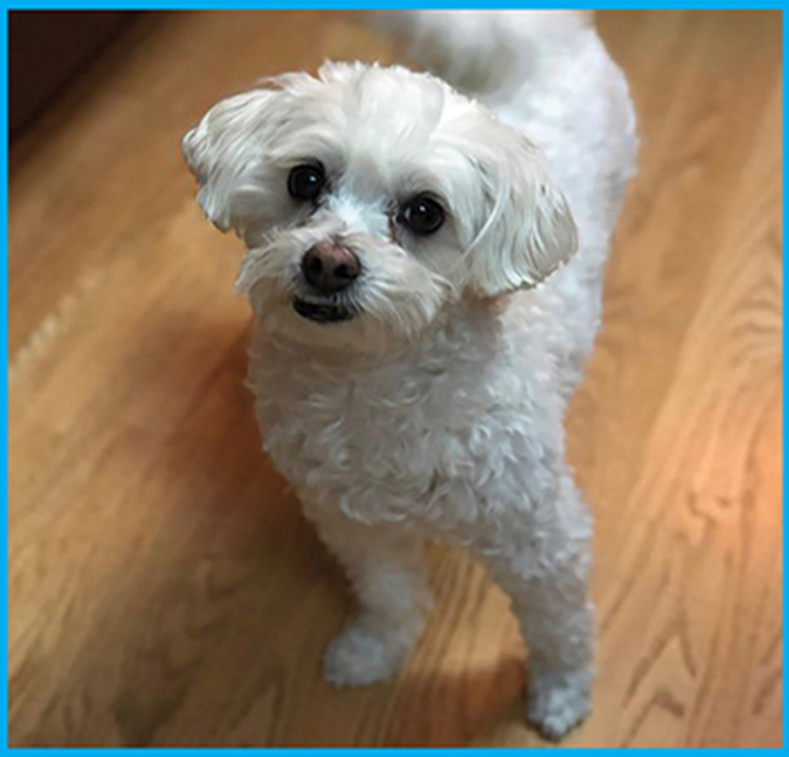
Second Edition

# Veterinary Psychopharmacology

Sharon L. Crowell-Davis
Thomas F. Murray
Leticia Mattos de Souza Dantas



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**Second Edition**

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*For my children, James Michael and Kristina Ruth, who have been a source of invaluable support through a rough few years. For my husband, Bill, who loved being married to a scientist, and who supported my work in so many ways I couldn't list them all. For my new co-author, Leticia Dantas, friend and colleague beyond compare. For my parents, Ruth and Wallace Davis, who have passed on to another world, but who are also with me every day. Thank you for everything you taught me. For all the furred and feathered beings who have taught me so much over the years. For Rhiannon, who understands.*

– Sharon L. Crowell-Davis

*This is dedicated to my wife Cristina P. Murray, daughter Lia L. Murray and family Maltipoo, Sport.*

– Thomas F. Murray

*To all my patients and beloved pets who have driven me to relentlessly seek more knowledge, more experience, and never accept defeat even when inevitable as sometimes it is in medicine.*

*To my Tiger (a.k.a. Tatá), a very special cat whose sweetness and intelligence have brought such joy to my life and taught me, my family, and many staff members and students at UGA so much. You might never know, but you will always guide and inspire me.*

*To my son, best friend and light of my life, John-Eduardo Dantas Divers (a.k.a. Dado), whose birth has awakened a larger than life quest to always be the best version of myself.*

*To my beloved husband, Steve Divers, my loving cheerleader and supporter.*

*To my friend, Sharon Crowell-Davis, who is an example of strength, kindness and resilience. It has been such a privilege to share this extraordinary project with you.*

– Leticia Mattos de Souza Dantas

# Contents

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# Preface

The first edition of this book grew out of a series of phone calls that Dr. Crowell-Davis received over the years from various veterinarians wanting information about their patients' behavior problems and the psychoactive medications that might help them. What were appropriate drugs for given problems? What were appropriate doses? What side effects should be watched for? The first answer to this steadily accumulating set of questions was a continuing education course in psychopharmacology specifically organized for veterinarians. The course was first presented at the University of Georgia in November of 2001 and is now part of UGA's Outpatient Medicine annual Continuing Education, as Behavioral Medicine has become integrated with all other specialties of our teaching hospital. From the original courses, taught by Dr. Murray and Dr. Crowell-Davis and the assistance from the clinical residents at the time (Dr. Lynne Seibert and Dr. Terry Curtis), the next logical step was a textbook so that practicing veterinarians would have a resource to turn to for the answers to their various questions. Years later, Dr. Crowell-Davis and Dr. Dantas felt an urgent need to update the book and add several new drugs that more recently are used by diplomates of the American College of Veterinary Behaviorists, so this knowledge could be available to general practitioners. Where studies were available, we tried to make this edition purely evidence-based and avoided including personal communications and short publications as much as possible. As this edition goes to print, we are already planning for the third as new information and protocols in veterinary mental health care keep being tested and developed.

Information on the effects of various psychoactive drugs in dogs, cats, and other veterinary patients comes from two major sources. First, animals were often used to test and study the actions of various drugs during their initial development. Thus, the reader who peruses the references will find papers published as early as the 1950s, when major breakthroughs in psychopharmacology were being made to much newer publications in human and veterinary neuroscience. With the establishment of the American College of Veterinary Behaviorists in 1993 and the overall rapid development of the field of Clinical Behavioral Medicine, there has been increasing research on the efficacy of various medications on the treatment of various mental health and behavioral/psychiatry disorders of companion animals, zoo animals, and other nonhuman animals.

There are often huge gaps in our knowledge, and the reader may note them throughout the book. While we can glean bits and pieces of pharmacokinetic and other data from studies done on dogs and cats during early drug development, the quality and quantity of the information are highly variable. Studies of teratology and carcinogenicity are typically done on rats, mice, and rabbits, while comprehensive studies of all aspects of pharmacological activity in the body are

done only in humans, the species that has historically been of interest. It is hoped that, as interest in this field continues to evolve, more comprehensive data will become available; new data will be supplied in future editions.

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## Acknowledgments

There is so much to be thankful for on this second edition of *Veterinary Psychopharmacology*. From all the veterinarians who request consults and always ask questions about psychoactive medications; reminding us of how important this resource is, to all of the students who push us to be updated, creative and enthusiastic about practicing and teaching. We dream of a time where mental health and psychiatry care will be fully integrated into the standard of care in veterinary medicine across the globe and part of the curriculum of every veterinary medicine school. To all of you that are eager to learn and provide the best care for your patients, we thank you. You are leading the way in our profession and this book is for you.

We wanted to keep the acknowledgments from the first edition to the many people who, besides the authors, contributed to the work involved in bringing together the information presented at that time. Of particular assistance were Linda Tumlin, Wendy Simmons, and Lucy Rowland. In their capacity as librarians and reference librarians they were invaluable in locating and obtaining much of the information provided in our first edition.

We also could not have developed and run the Behavioral Medicine Service and the didactic program at the University of Georgia to this date without the continuing support of various administrators over the years. In the first edition, Dr. Royce Roberts, Dr. Crowell-Davis' department head of many years was acknowledged. On this edition, we would like to thank Dr. Stephen Holladay for all his encouragement and support to both of us. Dr. David Anderson, Dr. Keith Prasse, Dr. Bob Lewis, and Dr. Jack Munnell have also facilitated Dr. Crowell-Davis' continuing work in this field previously. In the past 10 years, our service has had major support from our hospital director, Dr. Gary Baxter, to whom Dr. Dantas is incredibly grateful as he has supported and allowed for the service's revitalization, allowing for a more competitive and business-oriented approach to her practice.

Finally, this book is for all animals who coexist with humankind, providing us with so much affection, companionship and even health benefits, but who have to adapt to our lifestyle and often undergo significant mental suffering that can remain ignored, undiagnosed, and untreated. Our mission is to heal and to improve the quality of life of all patients we have the privilege to treat; and increase the awareness in our society that the mental and emotional suffering of animals matters.

# Part I

# Principles of Veterinary Psychopharmacology

# 1

# General Principles of Psychopharmacology

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## Drug Action

Pharmacology is the science of drug action, and a drug is defined as any agent (chemical, hormone, peptide, antibody, etc.) that, because of its chemical properties, alters the structure and/or function of a biological system. Psychopharmacology is a sub-discipline of pharmacology focused on the study of the use of drugs (medications) in treating mental disorders. Most drugs used in animals are relatively selective. However, selectivity of drugs is not absolute inasmuch as they may be highly selective but never completely specific. Thus, most drugs exert a multiplicity of effects.

Drug action is typically defined as the initial change in a biological system that results from interaction with a drug molecule. This change occurs at the molecular level through drug interaction with molecular target in the biologic system (e.g. tissue, organ). The molecular target for a drug typically is a macromolecular component of a cell (e.g. protein, DNA). These cellular macromolecules that serve as drug targets are often described as drug receptors, and drug binding to these receptors mediates the initial cellular response. Drug binding to receptors either enhances or inhibits a biological process or signaling system. Of relevance to the field of psychopharmacology, the largest group of receptors are proteins. These include receptors for endogenous hormones, growth factors, and neurotransmitters; metabolic enzymes or signaling pathways; transporters and pumps; and structural proteins. Usually the drug effect is measured at a much more complex level than a cellular response, such as the organism level (e.g. sedation or change in behavior).

Drugs often act at receptors for endogenous (physiologic) hormones and neurotransmitters, and these receptors have evolved to recognize their cognate signaling molecules. Drugs that mimic physiologic signaling molecules at receptors are agonists, that is, they activate these receptors. Partial agonist drugs produce less than maximal activation of activation of receptors, while a drug that binds to the receptor without the capacity to activate the receptor may function as a receptor antagonist. Antagonists that bind to the receptor at the same site as agonists are able to reduce the ability of agonists to activate the receptor. This mutually exclusive binding of agonists and antagonists at a receptor is the basis for competitive antagonism as a mechanism of drug action. One additional class of drugs acting at physiologic receptors are inverse agonists. At physiologic receptors that

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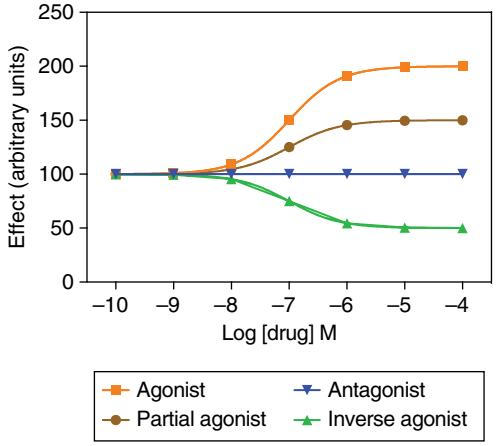


**Figure 1.1** Theoretical logarithmic concentration-response relationships for agonist, partial agonist, antagonist, and inverse agonist drugs acting at a common receptor. In this theoretical set of concentration-response curves, the agonist produces a maximum response while the partial agonist is only capable of evoking a partial response. The antagonist binds to the receptor but is not capable of activating the receptor and therefore does not produce a response. Inverse agonists bind to an inactive form of the receptor and produce an effect which is in the inverse direction of that produced by the agonist.

exhibit constitutive activity in the absence of activation by an endogenous agonist, inverse agonists stabilize an inactive conformation and therefore reduce the activation of the receptor. Thus, inverse agonists produce responses that are the inverse of the response to an agonist at a given receptor. Theoretical log concentration-response curves for these four classes of drugs are depicted in Figure 1.1.

## Dose Dependence of Drug Interaction with Receptors

Receptor occupancy theory assumes that drug action is dependent on concentration (dose) and the attendant quantitative relationships are plotted as dose- or concentration-response curves. Dose–response analysis is typically reserved to describe whole animal drug effects, whereas concentration-response curves describe *in vitro* drug action where the actual concentration of the drug interacting with a receptor is known. Inspection of dose–response relationships reveals that for any drug, there is a threshold dose below which no effect is observed, and at the opposite end of the curve there is typically a ceiling response beyond which higher doses do not further increase the response. As shown in Figure 1.2, these dose- or concentration-response curves are typically plotted as a function of the log of the drug dose or concentration. This produces an S-shaped curve that pulls the curve away from the ordinate and allows comparison of drugs over a wide range of doses or concentrations.

A drug-receptor interaction is typically reversible and governed by the affinity of the drug for the receptor. The affinity essentially describes the tightness of the binding of the drug to the receptor. The position of the theoretical S-shaped concentration-response curves depicted in Figure 1.2 reveals the potency of these drugs. The potency of a drug is a function of its affinity for a receptor, the number of receptors, and the fraction of receptors that must be occupied to produce a maximum response in a given tissue. In Figure 1.2, Drug A is the most potent and Drug C is least potent. The efficacy of all three drugs in Figure 1.2, however, is identical in that they all act as full agonists and produce

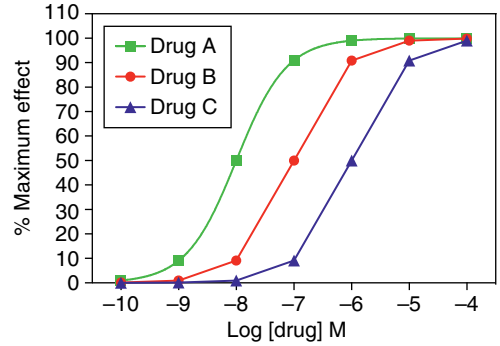


**Figure 1.2** Theoretical logarithmic concentration-response relationships for three agonists which differ in relative potency. Drug A is more potent than Drug B, which in turn is more potent than Drug C.

100% of the maximal effect. As a general principle in medicine, for drugs with similar margins of safety, we care more about efficacy than potency. The comparison of potencies of agonists is accomplished by determining the concentration (or dose) that produces 50% of the maximum response (Effective Concentration, 50% = $EC_{50}$). In Figure 1.2, the $EC_{50}$ values are $10^{-8}$, $10^{-7}$, and $10^{-6}$ M, respectively, for Drugs A, B and C; hence, the rank order of potency is Drug A > Drug B > Drug C, with Drug A being the most potent since its $EC_{50}$ value is the lowest. Figure 1.3 depicts three additional theoretical concentration-response curves for drugs with identical potencies but different efficacies. In this example, Drug A is a full agonist, producing a maximum response, whereas Drugs B and C are partial agonists, producing responses, respectively, of 50% and 25% of the maximum. Similar to receptor antagonist drugs, partial agonists can compete with a full agonist for binding to the receptor. Increasing concentrations of a partial agonist will inhibit the full agonist response to a level equivalent to its efficacy, whereas a competitive antagonist will completely eliminate the response of the full agonist.

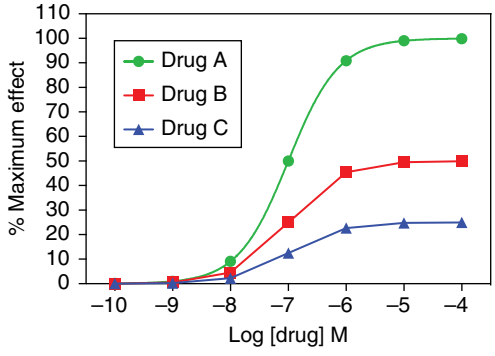


**Figure 1.3** Theoretical logarithmic concentration-response relationships for three agonists with similar potency but different efficacies. Drug A is an agonist that produces a maximum response while Drugs B and C are partial agonists only capable of evoking a partial response. Drug A is therefore more efficacious than Drug B, which in turn is more efficacious than Drug C.

## Structural Features of the Central Nervous System (CNS) and Neurotransmission

The cellular organization of the mammalian brain is more complex than any other biologic tissue or organ. To illustrate this complexity, consider that the human brain contains $10^{12}$ neurons, $10^{13}$ glia, and $10^{15}$ synapses. Understanding how this complex information processor represents mental content and directs behavior remains a daunting biomedical mystery. Recent reconstruction of a volume of the rat neocortex found at least 55 distinct morphological types of neurons (Makram et al. 2015). The excitatory to inhibitory neuron ratio was estimated to be 87:13, with each cortical neuron innervating 255 other neurons, forming on average more than 1100 synapses per neuron. This remarkable connectivity reveals the complexity of microcircuits within even a small volume of cerebral cortex.

Most neuron-to-neuron communication in the CNS involves chemical neurotransmission at up to a quadrillion of synapses. The amino acid and biogenic amine neurotransmitters must be synthesized in the presynaptic terminal, taken up, and stored in synaptic vesicles, and then released by exocytosis, when an action potential invades the terminal to trigger calcium influx. Once released into the synaptic cleft, transmitters can diffuse to postsynaptic sites where they are able to bind their receptors and trigger signal transduction to alter the physiology of the postsynaptic neuron. Just as exocytotic release of neurotransmitters is the on-switch for cell-to-cell communication in the CNS, the off-switch is typically a transport pump that mediates the reuptake of the transmitter into the presynaptic terminal or uptake into glia surrounding the synapse. A schematic of a presynaptic terminal depicted in Figure 1.4 illustrates the molecular sites that regulate neurotransmission. Once synthesized or provided by reuptake, the neurotransmitter

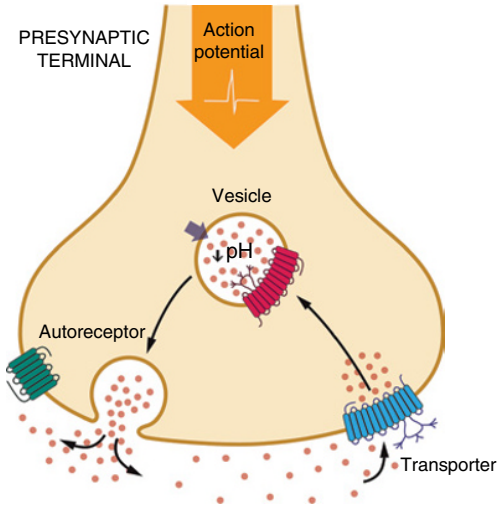


**Figure 1.4** Presynaptic terminal of monoaminergic neuron, depicting sites of vesicular release, reuptake transport, and vesicular transport and storage. Monoamine transmitters are synthesized in the cytoplasm or vesicle. Transport from the cytoplasm to the vesicular compartment is mediated by the reserpine sensitive vesicular membrane transporter (VMAT2). Release into the synapse occurs by exocytosis triggered by an action of potential invasion of the terminal. Neurotransmitters are rapidly transported from the synaptic cleft back into the cytoplasm of neuron by a process termed reuptake, which involves a selective, high-affinity, $Na^+$-dependent plasma membrane transporter.

is transported into the synaptic vesicle for subsequent exocytosis. The pH gradient across the vesicular membrane is established by the vacuolar $H^+$-ATPase, which uses ATP hydrolysis to generate the energy required to move $H^+$ ions into the vesicle (Lohr et al. 2017). This movement of $H^+$ ions creates the vesicular proton gradient and establishes an acidic environment inside the vesicle (pH of ~5.5). Specific reuptake transporters are localized on the plasma membrane where they recognize transmitters and transport them from the synaptic cleft into the cytoplasm of the terminal (Torres et al. 2003). These transporters have evolved to recognize specific transmitters such as dopamine, serotonin, norepinephrine, glutamate, and gamma-aminobutyric acid (GABA). In all cases, these presynaptic transporters regulate the extracellular concentration of transmitters and therefore a mechanism for termination of their respective synaptic actions. The monoamine transporters (dopamine, norepinephrine, and 5-hydroxytryptamine) are the pharmacological targets for antidepressants and psychostimulants.

Presynaptic terminals also express neurotransmitter autoreceptors that function as local circuit negative feedback inhibitor mechanisms to inhibit further exocytotic release of the transmitter when its synaptic concentration is elevated.

Figure 1.5 illustrates the comparison of presynaptic terminals for the biogenic amine neurons: dopamine, norepinephrine, and 5-hydroxytryptamine (serotonin). The biosynthesis of each biogenic amine transmitter is indicated with uptake and storage in synaptic vesicles. The vesicular uptake of all three biogenic amines depicted is mediated by a common transporter, vesicular monoamine transporter 2 (VMAT2). VMAT2 is the vesicular monoamine transporter that transports dopamine, norepinephrine, and 5-hydroxytryptamine into neuronal synaptic vesicles. VMAT2 is an $H^+$-ATPase antiporter, which uses the vesicular electrochemical gradient to drive the transport of biogenic amines into the vesicle (Lohr et al. 2017). In contrast to VMAT2 being expressed in all three biogenic amine neurons, each neurotransmitter neuron expresses a distinct plasma membrane transporter. These transporters are members of the SLC6 symporter family that actively translocate amino acids or amine neurotransmitters into cells against their concentration gradient using, as a driving force, the energetically favorable coupled movement of ions down their transmembrane electrochemical gradients. The dopamine transporter (DAT), the norepinephrine transporter (NET), and the serotonin transporter (SERT) are all uniquely expressed in their respective neurotransmitter neurons and couple the active transport of biogenic amines with the movement of one $Cl^-$ and two $Na^+$ ions along their concentration gradient. The ionic concentration gradient is

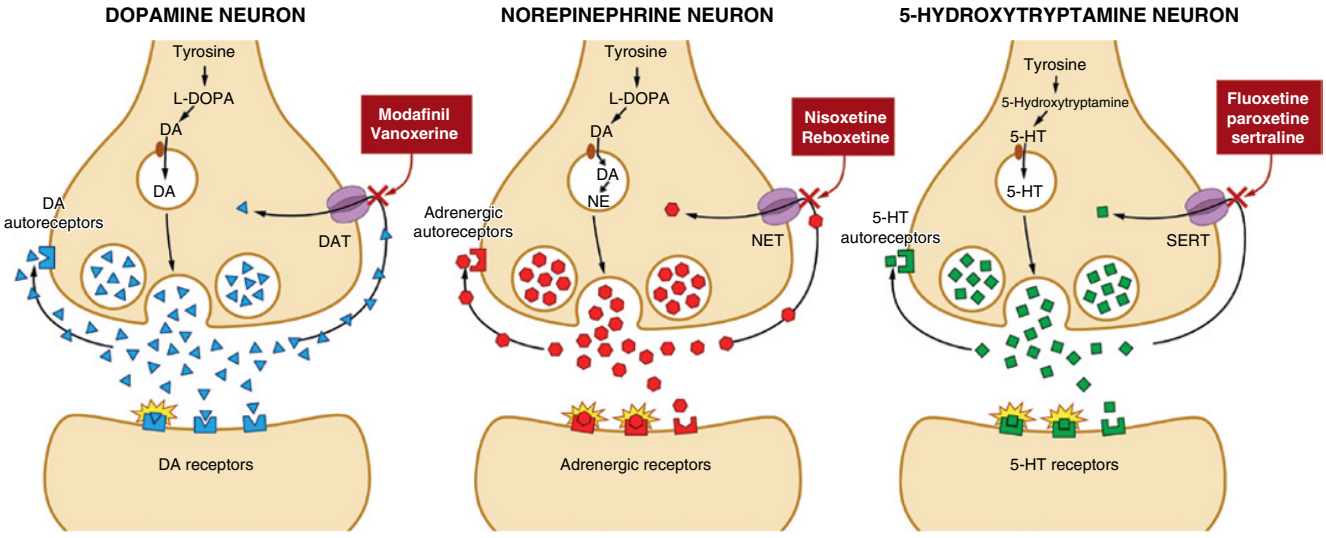


**Figure 1.5** Schematic comparison of dopamine, norepinephrine, and 5-hydroxytryptamine (serotonin) synapses. Each neuron expresses a monoamine transporter selective for its neurotransmitter. These transporters function as reuptake pumps that terminate the synaptic actions of the transmitters and promote uptake and eventual storage of the transmitter in vesicles. Selective drug inhibitors of each monoamine transporter are shown. Abbreviations: DA, dopamine; DAT, dopamine transporter; NE, norepinephrine; NET, norepinephrine transporter; 5-HT, 5-hydroxytryptamine; SERT, serotonin transporter.

created by the plasma membrane $Na^+/K^+$ ATPase and serves as the driving force for transmitter uptake. Examples of drugs that act as selective inhibitors for all three biogenic transporters are listed. The three monoamine transporters, DAT, NET, and SERT, represent important pharmacological targets for many behavioral disorders including depressive, compulsive and appetite-related behavioral problems. The three neurotransmitter terminals also express unique presynaptic autoreceptors that regulate exocytotic release.

## Biogenic Amine Neurotransmitters and Affective Disorders

The role of biogenic amines in affective disorders has a long history, beginning in the 1950s. The biogenic amine theory for affective disorders emerged as pharmacologists and psychiatrists began to explore the biologic basis for mental disorders. Initially, insights were gained from better understanding of the cellular actions of drugs and correlation of this knowledge of drug action with the therapeutic and behavioral responses to the same drugs in the clinic. In its original formulation, the biogenic amine theory for affective disorders stated that depression was due to a deficiency of biogenic amines in the brain, while mania was due to an excess of these transmitters. In the 1950s, iproniazid was used in the treatment of tuberculosis, and it was observed that in some patients with depressive symptoms, their mood improved over the course of a chronic regimen with iproniazid. Concurrently, preclinical research showed that iproniazid was an inhibitor of the enzyme monoamine oxidase (MAO). MAO catalyzes the degradation of dopamine (DA), norepinephrine (NE), and serotonin (5-HT), and inhibition of MAO was found to elevate the levels of these transmitters in animal brains. Also, in the 1950s, reserpine was being used as an antihypertensive. Some patients treated with reserpine developed depressive symptoms severe enough in some cases to produce suicide ideation. Animals given reserpine also developed depression-like symptoms consisting of marked sedation. Reserpine was shown to deplete the CNS of DA, NE, and 5-HT by virtue of its ability to block the vesicular uptake of these monoamines. Blocking the vesicular uptake of monoamines leads to a depletion of the transmitters due to degradation by the mitochondrial enzyme MAO. Therefore, vesicular storage of monoamines is not only a prerequisite for exocytosis but also a means of preventing degradation of the transmitters in the cytosolic compartment. One other observation in the 1950s was that imipramine, developed initially as an antipsychotic drug candidate, elevated mood in a subpopulation of schizophrenic patients with comorbid depressive illness. Preclinical research revealed that imipramine, and other tricyclic antidepressants, were able to block monoamine transport into presynaptic terminals. This action would therefore produce an elevation of synaptic levels of biogenic amines. All these observations with iproniazid, reserpine, and imipramine were therefore consistent with the original formulation of the biogenic amine hypothesis for affective disorders.

Although today we continue to recognize the role of biogenic amines in depression, several discrepancies in the original hypothesis are appreciated. As an example, some clinically effective antidepressants do not block the presynaptic transport of monoamines and are not MAO inhibitors. However, importantly for a hypothesis that attempts to correlate synaptic levels of monoamines with mood, while synaptic levels of monoamines are elevated within a time domain of a few hours after antidepressant administration, the symptoms of depression do not resolve until several weeks of chronic therapy with antidepressant drugs. Contemporary hypotheses to explain the mechanism of action of antidepressant drugs

therefore seek an appropriate temporal correlation between neurochemical drug action and the mitigation of the symptoms of depression. Rather than a focus on the synaptic levels of biogenic amines, contemporary views of the mechanism of action of antidepressants are focused on the regulation of receptor signaling.

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# 2

# Amino Acid Neurotransmitters

## Glutamate, GABA, and the Pharmacology of Benzodiazepines

*Thomas F. Murray*

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## Introduction

In addition to their role in intermediary metabolism, certain amino acids function as small molecule neurotransmitters in the central and peripheral nervous systems. These specific amino acids are classified as excitatory or inhibitory, based on the characteristic responses evoked in neural preparations. Application of excitatory amino acids such as glutamic acid and aspartic acid typically depolarize mammalian neurons, while inhibitory amino acids such as gamma aminobutyric acid (GABA) and glycine characteristically hyperpolarize neurons. Glutamate, aspartate, and GABA all represent amino acids that occur in high concentrations in the brain. The brain levels of these amino acid transmitters are high ($\mu mol\,g^{-1}$) relative to biogenic amine transmitters ($nanomol\,g^{-1}$) such as dopamine, serotonin, norepinephrine, and acetylcholine. In mammals, GABA is found in high concentrations in the brain and spinal cord, but is present in only trace amounts in peripheral nerve tissue, liver, spleen, or heart (Cooper et al. 2003). These observations reveal the enrichment of this amino acid in the brain and suggest an important functional role in the central nervous system (CNS).

## Glutamatergic Synapses

Glutamate and aspartate produce powerful excitation in neural preparations and glutamate is generally accepted as the most prominent neurotransmitter and major excitatory transmitter in the brain. The establishment of glutamate as a neurotransmitter in the brain was historically difficult due to its role in general intermediary metabolism. Glutamate is also involved in the synthesis of proteins and peptides, and also serves as the immediate precursor for GABA in GABAergic neurons. The enzyme glutamic acid decarboxylase (GAD) converts glutamate to GABA in these GABAergic neurons. In contrast to GABA, the glutamate content of brain outside of glutamatergic neurons is high as a consequence of its role in intermediary metabolism and protein synthesis. An array of neurochemical methods accordingly has demonstrated that all cells contain some glutamate, and in the brain all neurons contain measurable amounts of glutamate.

In neurons, glutamate is primarily synthesized from glucose through the pyruvate→ acetyl-CoA → 2-oxoglutarate pathway, and from glutamine that is synthesized in glial cells, transported into nerve terminals, and converted by neuronal glutaminase into

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glutamate. In terminals of glutamatergic neurons, glutamate is stored in synaptic vesicles from which $Ca^{2+}$-dependent release in response to depolarization occurs. This synaptically released glutamate is taken up, in part, by glial cells and converted to glutamine by the enzyme glutamine synthetase. This glutamine is then transported back to neurons where glutamate is regenerated through the action of glutaminase (Figure 2.1).

Extracellular glutamate concentrations are maintained within physiological levels by a family of transmembrane proteins known as excitatory amino acid transporters (EAATs). At least five EAATs have been identified with individual subtypes, differing with respect to their pharmacology and distribution within the CNS. Two of these EAATs are localized primarily on glial cells in the CNS with the other three EAAT subtypes being localized to neurons. The two glial glutamate transporters have been shown to be the primary regulators of extracellular glutamate in the CNS (Amara and Fontana 2002). EAATs accomplish glutamate influx driven by the cotransport of 3 $Na^+$ and 1 $H^+$ ions with the countertransport of 1 $K^+$ ion. EAAT-mediated glutamate uptake is therefore electrogenic and dependent on the $Na^+$ gradient. The 3:1 ratio of $Na^+$ to glutamate molecules transported causes a significant $Na^+$ influx into the glial cells when the glutamate uptake is stimulated (Kirischuk et al. 2016). This elevation of intracellular $Na^+$ can trigger a reverse mode of action of the $Na^+/Ca^{2+}$ exchanger (NCX), leading to a stimulation of $Ca^{2+}$ signaling pathways in glia or neurons.

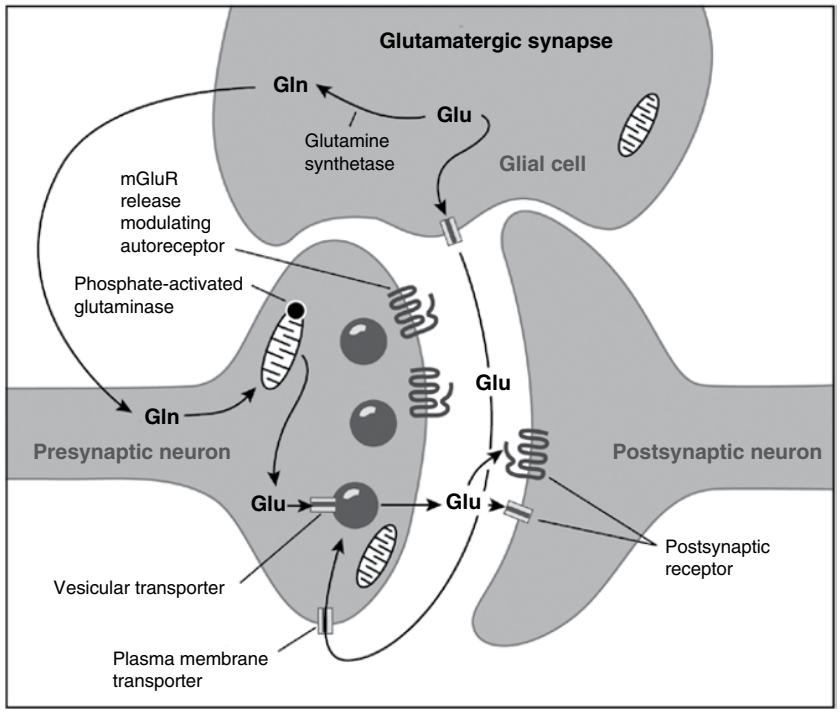



**Figure 2.1** Schematic representation of a glutamatergic synapse. Glutamine (Gln) is converted to glutamate (Glu) by mitochondrial glutaminase in glutamatergic neurons. Glutamate is released into the synaptic cleft where it may activate both pre- and postsynaptic receptors. Glutamate in the synaptic cleft is recaptured by neuronal and glial plasma membrane transporters that terminate the synaptic actions of the excitatory transmitter. Glial glutamate is converted to glutamine by the enzyme glutamine synthetase. This glutamine is then shuttled back to glutamatergic neurons to replenish the glutamate. Glutamate receptors include both G-protein coupled (mGluRs) and ligand-gated ion channel (AMPA, NMDA and kainite) receptors.

There is some evidence that neuronal EAATs are localized predominantly outside the synapse where they control extrasynaptic, rather than synaptic, glutamate concentration. This extrasynaptic glutamate may function to activate pre- and postsynaptic metabotropic glutamate receptors (mGluRs). Presynaptic mGluRs are involved in the feedback regulation of synaptic glutamate release.

In the normal brain, the prominent glutamatergic pathways are: (i) the cortico-cortical pathways; (ii) the pathways between the thalamus and the cortex; and (iii) the extrapyramidal pathway (the projections between the cortex and striatum). Other glutamate projections exist between the cortex, the substantia nigra, the subthalmic nucleus, and the pallidum. Glutamate-containing neuronal terminals are ubiquitous in the CNS and their importance in brain function and neurotransmission is therefore considerable. Estimates of the fraction of neurons in the brain that use glutamate as a neurotransmitter range from 70% to 85%.

Glutamate receptors are categorized into two main classes, namely, ionotropic glutamate receptors (iGluRs) and metabotropic receptors (mGluRs). The iGluRs were originally classified using a pharmacologic approach that led to identification of three subtypes bearing the names of selective agonists: (i) the AMPA; (ii) kainate; and (iii) NMDA receptors. These glutamate receptor subtypes are often described as being either NMDA (N-methyl-D-asparate) or non-NMDA (AMPA and kainate) receptors based on their sensitivity to the synthetic aspartate analog NMDA. All of these iGluRs represent ligand-gated cation channels permeable to $Na^+$ and $K^+$ with differing permeabilities to $Ca^{2+}$. Activation of these receptors by glutamate or selective agonists at normal membrane potentials allows $Na^+$ to enter the cell with attendant membrane depolarization; this is the underlying mechanism for the rapid excitatory response of most neurons to glutamate. In addition to $Na^+$ permeability NMDA receptors also have a high permeability to $Ca^{2+}$ and display a voltage-dependence of inward currents carried by $Na^+$ and $Ca^{2+}$ ions. The voltage dependence of the inward ionic current through the NMDA receptor arises from $Mg^{2+}$ blockade of this channel at normal resting membrane potentials. This channel-blocking action of extracellular $Mg^{2+}$ is relieved when the cell is depolarized. Thus, the NMDA receptor signaling requires depolarization of the cell through the excitatory actions of non-NMDA receptors before this ligand-gated ion channel can produce an inward current. This property of NMDA receptors has led to the channel being termed a coincident detector due to the requirement for simultaneous activation of NMDA receptors and excitatory input to a cell as a precondition for the passage of ionic current through NMDA receptor ion channels.

A molecular classification of glutamate receptors has confirmed the subdivision based on pharmacological profiles of receptor subtypes. Molecular cloning techniques have identified gene families corresponding to each functional subtype of glutamate receptor. NMDA receptors are formed by assemblies of three gene families including NR1, NR2A-D, and NR3A/3B (Mayer and Armstrong 2004). Functional NMDA receptors exist as heteromers containing two NR1 and two NR2 subunits (Erreger et al. 2004). NMDA receptors can also contain NR3A subunits that modulate the channel function. AMPA receptors are comprised of assemblies from the GluR1–GluR4 gene family, whereas kainate receptors are assemblies of GluR5–GluR7 and KA1 and KA2 subunits.

In addition to the iGluRs, there are metabotropic glutamate receptors (mGluRs) that are members of the large family of G-protein coupled receptors. These mGluRs are therefore not ligand-gated ion channels, but, rather, change cell physiology through an interaction with G-proteins that in turn regulate the activity of enzymes and/or ion channels involved in cell signaling cascades. These mGluRs are widely distributed in the brain where they mediate a variety of effects including the modulation of glutamate release from glutamatergic neurons. These

presynaptic mGluRs therefore function as autoreceptors.

Inasmuch as glutamate receptors mediate most of the excitatory transmission in the brain, they represent important potential targets for therapeutic intervention in a number of behavioral disorders.

## Pharmacology of Ketamine and Tiletamine

Ketamine is an anesthetic agent that was first introduced in clinical trials in the 1960s. It is a dissociative anesthetic, which is a term originally introduced by Domino and collaborators to describe the unique state of anesthesia produced by ketamine in which the subject is profoundly analgesic while appearing disconnected from the surrounding environment (Miyasaka and Domino 1968). Domino's laboratory attributed this unique anesthetic state to a drug-induced dissociation of the EEG activity between the thalamocortical and limbic systems. It was demonstrated that the cataleptic anesthetic state induced by intravenous ketamine ($4\,mg\,kg^{-1}$) in cats was associated with an alternating pattern of hypersynchronous δ wave bursts and low voltage, fast wave activity in the neocortex and thalamus. Subcortically, the δ wave bursts were observed prominently in the thalamus and caudate nucleus, and the EEG patterns of thalamic nuclei were closely related phasically to the δ waves of the neocortex. In contrast to the marked δ wave bursts in the neocortex, thalamus, and caudate nucleus, prominent δ waves were not observed in the cat hippocampus, hypothalamus, or midbrain reticular formation. The hippocampus showed θ "arousal" waves in spite of the appearance of high voltage, hypersynchronous δ wave bursts in the thalamus and neocortex. Thus, ketamine was demonstrated to produce a functional dissociation of the EEG activity between the hippocampus and thalamocortical systems.

Ketamine and the newer dissociative anesthetic tiletamine act as noncompetitive antagonists of NMDA receptors in the CNS (Figure 2.2). The discovery by Lodge et al. (1983) of the ability of ketamine and related arylcyclohexylamines to antagonize specifically the neuronal excitation mediated by the synthetic aspartate analog, NMDA, provided a pivotal advance in our understanding of the mechanism of action of dissociative anesthetics. Based on the earlier observation that ketamine selectively reduced polysynaptic reflexes in which excitatory amino acids were the transmitter, Lodge and coworkers investigated the action of ketamine on the excitation of cat dorsal horn interneurons by amino acids used in the classification of excitatory amino acid receptors, namely, NMDA, quisqualate, and KA (Lodge and Mercier 2015). The microionotophoretic or intravenous administration of ketamine selectively reduced the increased firing rate of dorsal horn neurons evoked by focal application of NMDA. The excitatory responses elicited by quisqualate and KA remained little affected. The selective NMDA-blocking effect was not restricted to ketamine inasmuch as the dissociative anesthetics, phencyclidine (PCP) and tiletamine, had similar actions that paralleled their relative anesthetic potencies. The primary molecular target for ketamine-induced analgesia and anesthesia therefore appears to be brain NMDA receptors. The inhibitory concentration for ketamine antagonism of NMDA responses in rat cortical preparations range from 6 μM to 12 μM. These values are comparable to the plasma concentration (20–40 μM) obtained in rats following intravenous anesthetic doses. It therefore appears likely that a large fractional occupancy of NMDA receptors may be required for ketamine induction of anesthesia (Murray 1994).

Subanesthetic doses of ketamine produce a spectrum of psychoactive actions in humans including mood elevation, distortions in body image, hallucinations, delusions, and paranoid ideation. These effects resemble those of PCP (phencyclidine) and are

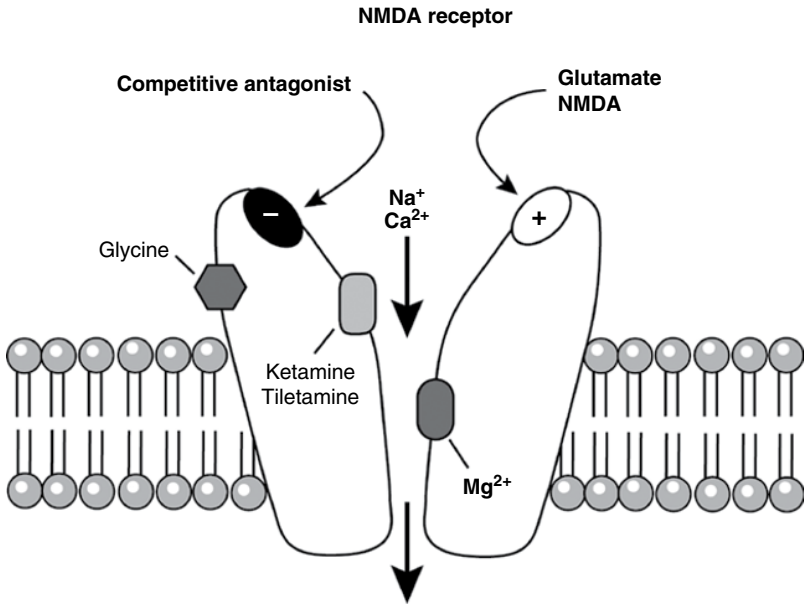



**Figure 2.2** Schematic of the NMDA subtype of glutamate receptors. NMDA receptors possess binding sites for the transmitter glutamate and the co-agonist, glycine. Competitive antagonists bind to the glutamate site, whereas noncompetitive antagonists such as ketamine and tiletamine bind to a site in the ion channel domain. $Mg^{++}$ exerts a voltage-dependent block of the ion channel.

responsible for the illicit use of ketamine. The availability of ketamine in veterinary medicine has resulted in numerous case reports of ketamine abuse by veterinarians. Similar to the anesthetic and analgesic actions of ketamine, the psychoactive properties appear to be related to the noncompetitive antagonism of NMDA receptors.

Great interest in ketamine as an antidepressant has emerged due to human clinical data that has demonstrated the rapid and sustained antidepressant effects of ketamine (Murrough et al. 2017). Ketamine has therefore been repurposed as a rapidly acting antidepressant, triggering great interest in glutamate signaling mechanisms underlying depressive disorders. Ketamine, its metabolites, and other NMDA receptor antagonists produce rapid antidepressant-like effects in mouse behavioral models that are dependent on rapid protein synthesis of brain-derived neurotrophic factor (BDNF). Experiments in animal models show that ketamine-mediated blockade of NMDA receptors at rest deactivates eEF2 kinase, resulting in a desuppression of BDNF translation (Kavalali and Monteggia 2015). A key role for BDNF in mediating antidepressant efficacy has previously been established (Bjorkholm and Monteggia 2016).

## GABAergic Synapses

Of all the putative neurotransmitters in the brain, γ-aminobutyric acid (GABA) is perhaps the one whose candidacy rests on the longest history of investigation. Glutamic acid decarboxylase (GAD), the enzyme that catalyzes the formation of GABA, appears to be largely restricted to GABAergic neurons and therefore affords a suitable marker for this population of neurons. In brain regions such as the hippocampus, histochemical studies have demonstrated that GAD is distributed in the neuropil with highest concentrations between cell bodies reflecting the presence of GABAergic neuron terminals. The abundance of GABAergic interneurons

and projection neurons in the brain has been estimated to represent 17–20% of the neurons in the brain (Somogyi et al. 1998). Upon activation, these GABAergic neurons release GABA from presynaptic terminals into the synaptic cleft. The concentration of GABA in the synaptic cleft is controlled by the high affinity uptake into presynaptic terminals and glial cells. In contrast to glutamate which is predominantly taken up by astrocytes, GABA represents the primary inhibitory neurotransmitter in the mammalian brain and is removed from the synaptic cleft mainly by the neuronal GABA transporter (GAT) subtype GAT1. Because of the high capacity and abundance of synaptic GAT1, GABA rarely escapes the synapse (Kirischuk et al. 2016).

GABA represents the major inhibitory transmitter in the brain and this inhibition is mediated by GABA binding to postsynaptic receptors. GABAergic systems serve important regulatory functions in the brain such as vigilance, anxiety, muscle tension, epileptogenic activity, and memory. In brain areas, such as the cerebral cortex and the hippocampus, GABAergic neurons are predominantly interneurons that function as primary regulators of the activity of the projecting glutamatergic pyramidal neurons. The activity of these GABAergic interneurons is largely driven by glutamatergic afferents arising from either projecting afferents or recurrent glutamatergic collaterals (Figure 2.3).

It is now generally recognized that GABAergic-mediated inhibition results from GABA activation of $GABA_A$ receptors ($GABA_A$Rs). $GABA_A$Rs are heteropentameric $Cl^-$-selective ligand-gated ion channels that mediate fast inhibition within the CNS. When activated by GABA, these $GABA_A$Rs promote the diffusion of this ion according to its concentration gradient. Thus, $GABA_A$-receptor activation may depolarize or hyperpolarize membranes depending on the difference in $Cl^-$ concentration of the postsynaptic neuron and extracellular milieu (Figure 2.4). Although excitatory responses to GABA have been described in embryonic cells that maintain high intracellular $Cl^-$ concentrations, the typical response of an activated $GABA_A$ receptor in the mature CNS is hyperpolarization mediated by $Cl^-$ influx. Functional $GABA_A$ receptors are pentameric ligand-gated ion channels assembled from members of seven different subunit classes, some of which have multiple isoforms: α (1–6), β (1–3), γ (1–3), δ, E, θ, and π. A pentameric assembly could theoretically be composed of over 50 distinct combinations of these subunits; however, $GABA_A$ receptor subunits appear to form preferred assemblies resulting in possibly dozens of distinct receptor complexes in the brain. Most $GABA_A$ receptor subtypes are presumed to be composed of α-, β-, γ-subunits. Molecular studies have demonstrated that distinct $GABA_A$ receptor assemblies often have different physiologic and pharmacologic profiles, suggesting that subunit composition is an important determinant of pharmacological diversity in $GABA_A$ receptor populations. Deficits in $GABA_A$R function have been demonstrated in a range of behavioral and CNS disorders, including anxiety, psychosis, and epilepsy.

$GABA_A$ receptors represent the molecular target for all of the characteristic pharmacological actions of benzodiazepines, including sedation, muscle relaxation, seizure suppression, and anxiety reduction (anxiolysis). Benzodiazepines allosterically enhance the $GABA_A$ receptor opening frequency, producing a potentiation of the GABA-induced inhibitory response (Rudolph et al. 1999). The benzodiazepine binding site is believed to be located at the interface between the α- and $\gamma_2$-subunits of a pentameric $GABA_A$ receptor complex. There are six types of α subunit, $\alpha_1$–$\alpha_6$, and $GABA_A$ receptors containing the $\alpha_1$-, $\alpha_2$-, $\alpha_3$-, or $\alpha_5$-subunits in combination with any β-subunit and the $\gamma_2$-subunit are sensitive to benzodiazepines, such as diazepam, alprazolam, and clonazepam (Möhler et al. 2002). $GABA_A$ receptors containing these four α-subunits are most abundant in the brain and the most prevalent receptor complex is comprised of $\alpha_1\beta_2\gamma_2$ subunits. $GABA_A$ receptors that do not respond to benzodiazepines such as

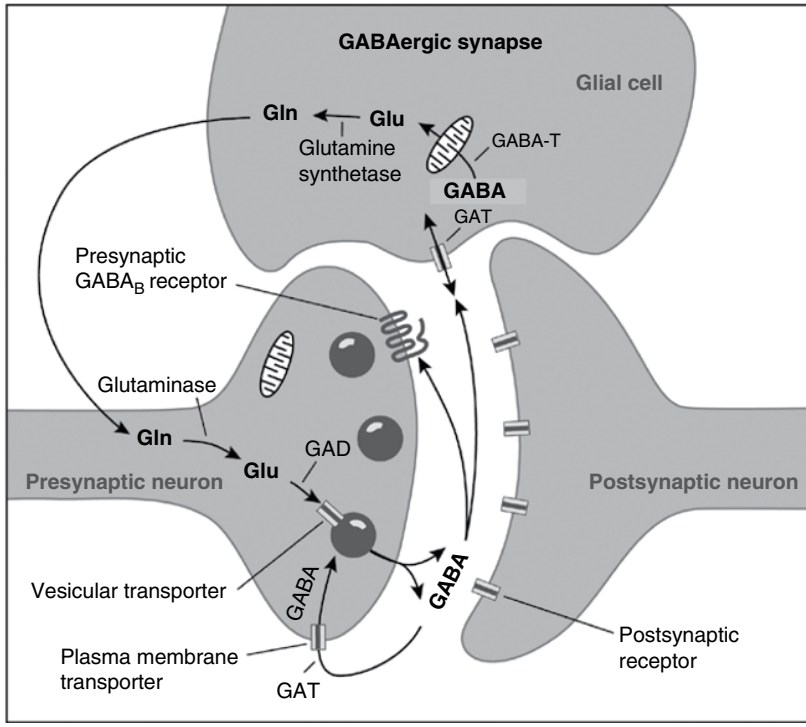
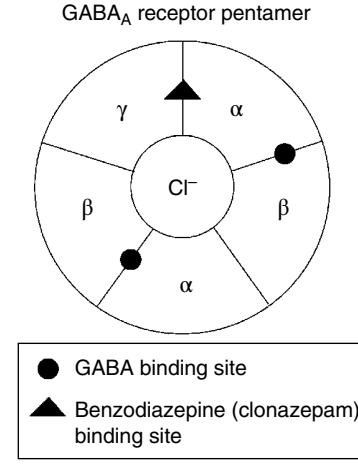



**Figure 2.3** Schematic representation of a GABAergic synapse. Glutamate is the immediate precursor of GABA in these neurons where it is metabolized by the enzyme glutamic acid decarboxylase (GAD). The GABA is stored in and released from vesicles into the synaptic cleft. Synaptic GABA activates both pre- and postsynaptic receptors. The latter are primarily ligand-gated ion channels ($GABA_A$ receptors), whereas presynaptic $GABA_B$ receptors are G-protein coupled receptors involved in the regulation of neurotransmitter release. GABA in the synaptic cleft is recaptured by an active transporter (GAT) in the plasma membrane of both neurons and glia. GABA is metabolized by the mitochondrial enzyme GABA-transaminase (GABA-T) to succinic semialdehyde which in turn is converted to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid exerts a negative feedback inhibition on GAD. Succinic semialdehyde dehydrogenase is inhibited by the anticonvulsant sodium valproate.

**Figure 2.4** Schematic structure of the $GABA_A$ receptor pentamer composed of two α-subunits, two β-subunits and one γ- subunit. The neurotransmitter GABA binds to a site at the interface between the α- and β-subunits (●) causing the $Cl^-$ channel to open. Benzodiazepines such as clonazepam and diazepam bind to a site at the interface of the α- and γ-subunits and act as positive allosteric modulators to augment the actions of GABA.



diazepam and clonazepam are less abundant in the brain and are characterized by the presence of the $\alpha_4$- and $\alpha_6$-subunits (Möhler et al. 2002). The use of transgenic mice with mutated $GABA_A$ receptors has recently demonstrated that it may be possible to develop benzodiazepine-like drugs that are anxioselective, meaning that they may reduce anxiety in the absence of sedation and muscle relaxation (leading to incoordination). The anxiolytic action of diazepam is selectively mediated by potentiation of GABAergic inhibition in a population of neurons expressing $\alpha_2$-subunit containing $GABA_A$ receptors, which constitute only 15% of all diazepam-sensitive $GABA_A$ receptors (Möhler et al. 2001). The $\alpha_2$-$GABA_A$ receptor expressing neurons in the cerebral cortex and the hippocampus are therefore specific targets for the future development of selective anxiolytic drugs. The sedative actions of benzodiazepines, in contrast, appear to be mediated by $\alpha_1$-subunit containing $GABA_A$ receptors. Changes in sleep pattern and EEG frequency associated with classical benzodiazepines are attributable to most $GABA_A$Rs (other than $\alpha_1$-containing receptors), with $\alpha_2$ receptors having the most profound influence. These studies indicate that future drug development of more subunit-specific benzodiazepine ligands may have more selective pharmacologic profiles.

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# 3

# Biogenic Amine Neurotransmitters

## Serotonin

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## Introduction

Psychopharmacology had its beginnings in the early 1950s and has steadily grown into one of the major areas of pharmacology and psychiatry. Before the advent of these psychoactive drugs, various central nervous system (CNS) agents, such as the narcotics, barbiturates, and stimulants were known, but none of these represented important psychotherapeutic agents, and psychiatrists had an extremely limited chemotherapeutic armamentarium. The initial breakthrough came when the drugs, chlorpromazine and reserpine, proved to be effective antipsychotic and anti-schizophrenic agents.

Soon after the development of the antipsychotic (or neuroleptic) drugs, the antidepressant action of iproniazid was discovered, and this therapeutic effect became correlated with the inhibition of monoamine oxidase (MAO) and a consequent rise in brain biogenic amines (serotonin, dopamine, and norepinephrine). A great deal of research has been carried out on a diverse array of psychoactive drugs in attempts to more fully understand their mechanism of action. From all of this research one striking common denominator emerges, namely, that many of these agents appear to modify in some way biogenic amines found in the CNS. Almost all of the psychoactive drugs, ranging from LSD and other hallucinogens to the antipsychotics and antidepressants, as well as other centrally acting agents, such as medetomidine, clomipramine, and l-deprenyl, are now associated with biogenic amine mechanisms.

## The Biogenic Amines

The term "biogenic amines," as used in psychopharmacology, includes the two catecholamines dopamine (DA) and norepinephrine (NE), and the indoleamine, 5-hydroxytryptamine (5-HT, serotonin), the structures of which are indicated in Figure 3.1. Norepinephrine has been known for many years as the transmitter in peripheral sympathetic neurons, and much is now known regarding its biosynthesis, storage, uptake, release, and degradation mechanisms. Serotonin has also been extensively investigated; and while its distribution is less ubiquitous, it also regulates critical functions in the CNS. Dopamine, which until the early 1960s, was considered primarily as a precursor of NE, is now established as a CNS transmitter in its own right. Its presence in the neostriatum and limbic system in high concentrations initially led to speculation of its possible role in CNS function. These observations and other related studies have demonstrated that degeneration of DA neurons of the

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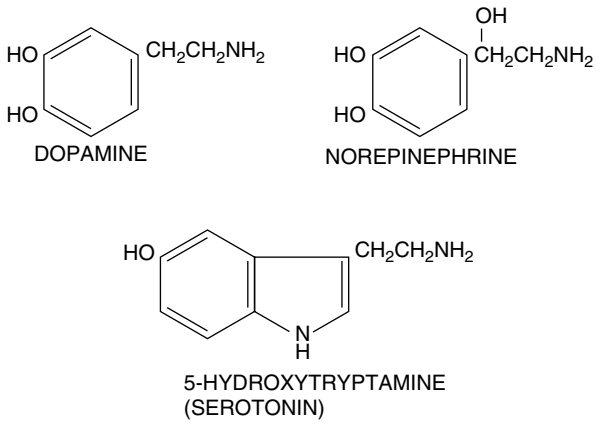


**Figure 3.1** Structures of biogenic amine (catecholamine and indolamine) neurotransmitters dopamine, norepinephrine, and serotonin.

nigro-striatal track is involved in Parkinson's disease. In fact, the use of its precursor, 1-dopa, in the treatment of this disease was historically based on this concept. The development of histochemical fluorescence techniques for the visualization of the biogenic amines within the nerve cell bodies and terminals has permitted the mapping of the biogenic amine pathways throughout the various parts of the CNS. From such investigations it is now known that NE and 5-HT neurons, whose cell bodies are found largely in the locus coeruleus and midbrain raphe nuclei, respectively, terminate more or less in the same regions of the CNS. DA cell bodies originate largely in the substantia nigra, the ventral tegmental area, and in the arcuate nucleus of the hypothalamus, and their neurons terminate in the neostriatum; limbic structures; and the median eminence and pituitary, respectively.

## Serotonin

Serotonin was first chemically identified in the 1940s, although its existence in the gastrointestinal tract was previously known. Its presence in blood serum and platelets, and the fact that it exerted vasoconstrictor activity led to the derivation of the name "serotonin." It was, however, only its discovery in mammalian brain that initiated the extensive neurochemical and pharmacologic investigations which have led to our current understanding of serotonin as a central neurotransmitter.

Early interest in serotonin functions in the brain intensified with the recognition that many hallucinogenic drugs (e.g. LSD) were structurally related to the serotonin molecule. Because these hallucinogens act like serotonin, it was postulated that the hallucinogenic activity of LSD is related to its serotonergic agonist activity. Thus, the compound bufotenin, or N,N-dimethylserotonin, a very close analog of serotonin, is a potent hallucinogen when administered centrally. Several other compounds, such as the substances psilocybin and psilocin, the indoleamines found in the "magic" mushrooms of Mexico, and other drugs of abuse, such as the dimethyl- and diethyl-analogs of tryptamine, have the basic indole ethylamine structure. Hallucinogens are now known to mediate many of their psychoactive effects by activating serotonin 2A receptors (5-$HT_{2A}$R). The 5-$HT_{2A}$R is highly expressed on pyramidal neurons in the frontal cortex and has been implicated in several mental and behavioral disorders, including schizophrenia, anxiety, and depression (Schmid and Bohn 2010).

Inasmuch as serotonin is found in many cells outside of the central nervous system that are not neurons, only about 1–2% of the whole body serotonin content is found in the brain. Serotonergic neurons synthesize this transmitter, beginning with the conversion of

dietary tryptophan to 5-hydroxytryptophan. Plasma tryptophan varies as a function of diet and elimination of dietary tryptophan can dramatically lower levels of serotonin in the brain. Following the production of 5-hydroxytryptophan by hydroxylation of tryptophan in serotonergic neurons, the 5-hydroxytryptophan is rapidly decarboxylated to produce serotonin (5-hydroxytryptamine). The serotonin precursor, 5-hydroxytryptophan is sold as an over-the-counter dietary supplement (sometimes termed Griffonia seed extract) for its claimed ability to treat conditions such as depression, headaches, obesity, and insomnia in humans (and animals). The oral administration of 5-hydroxytryptophan results in rapid absorption from the gastrointestinal tract and in turn readily crosses the blood–brain barrier (Gwaltney-Brant et al. 2000). This 5-hydroxytryptophan can be rapidly converted to serotonin in the brain and the spinal cord. Excessive stimulation of serotonin receptors due to dramatic elevations of 5-HT causes a "serotonin syndrome" that may be associated with muscle rigidity, myoclonus, salivation, agitation, and hyperthermia in animals and humans. The most common cause of this syndrome is an interaction between a monoamine oxidase inhibitor and a selective serotonin reuptake inhibitor. The accidental ingestion of 5-hydroxytryptophan by dogs, however, has been documented to result in a life-threatening syndrome resembling a serotonin syndrome (Gwaltney-Brant et al. 2000). A review of 21 cases of accidental 5-hydroxytryptophan by dogs indicated that ingestion of a single 500 mg capsule of these dietary supplements would be sufficient to produce adverse sequelae in dogs.

In the mammalian brain, serotonergic neurons are localized to clusters of cell bodies of the pons and brain stem termed the raphe nuclei (Figure 3.2). These groups of 5-HT neurons project in both ascending and descending pathways to the forebrain and spinal cord, respectively. Forebrain structures receiving 5-HT innervation include the cerebral cortex, the striatum, and the hippocampus. These ascending projections to the cerebral cortex and limbic regions emanate from rostral raphe nuclei axons, while the caudal raphe nuclei in the brainstem give rise to the descending projections terminating in the medulla and spinal cord.

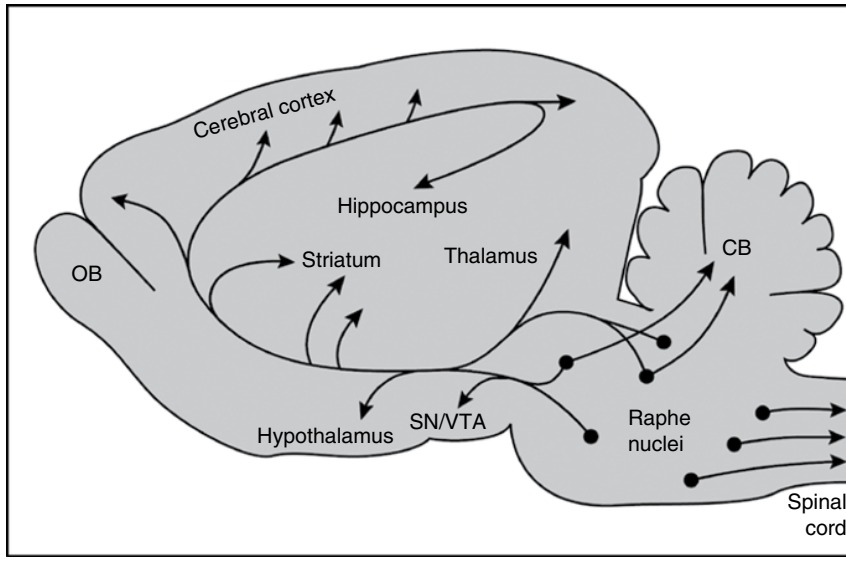


**Figure 3.2** Schematic diagram of the serotonergic pathways in animal brain. Serotonergic cell bodies are localized to clusters of cells in the pons and rostral brain stem referred to as the raphe nuclei.

Serotonergic terminals are the sites of vesicular release of the transmitter at synapses in the projection field (e.g. the cerebral cortex, limbic structures). Following the release of 5-HT in the synapse, the action of the transmitter is terminated through a high-affinity reuptake into the presynaptic terminal. This reuptake is mediated by specific transporter proteins that have evolved to recognize and transport serotonin. These serotonin transporters (SERTs) are members of a gene family of $Na^+$ and $Cl^-$-dependent transport proteins. The serotonin transporters are expressed in the brain in presynaptic and somatodendritic membranes of serotonin neurons. These 5-HT transporters also exist in other tissues, such as platelets, placenta, and the lung. Given the critical role of serotonin transporters in the regulation of the synaptic actions of 5-HT, they have been an important target for drug development. As a consequence, a number of selective serotonin reuptake inhibitors (SSRIs) have been developed, such as fluoxetine, sertraline, and paroxetine for use in the treatment of depression, anxiety, panic attack, and obsessive–compulsive disorder in humans. Both fluoxetine and clomipramine (a tryciclic antidepressant with some selectivity for the serotonin transporter) have been approved for the treatment of separation anxiety in dogs. These reuptake inhibitors act as indirect serotoninmimetics by increasing the half-life of serotonin in the synapse, resulting in prolonged activation of multiple serotonin receptor subtypes. The localization of the serotonin transporter on the presynaptic terminal of serotonergic neurons is depicted in Figure 3.3.

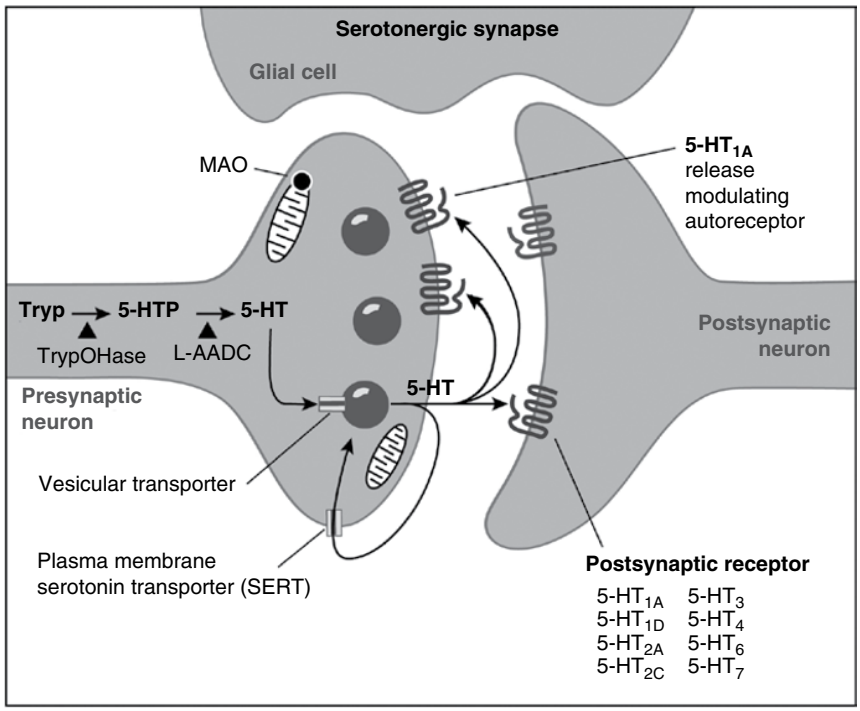


**Figure 3.3** Schematic representation of a serotonergic synapse. Tryptophan is the dietary precursor for serotonin (5-HT) synthesis and is converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase (TrypOHase). 5-HTP is converted to 5-HT by the enzyme l-aromatic amino acid decarboxylase (L-AADC). 5-HT is stored in and released from vesicles, and synaptic 5-HT activates both pre- and postsynaptic receptors. Synaptic 5-HT action is terminated by the reuptake of the transmitter into the presynaptic terminal. This reuptake is mediated by the plasma membrane serotonin transporter (SERT). Cytoplasmic 5-HT can be degraded by the mitochondrial enzyme monoamine oxidase (MAO).

The function of serotonin is exerted upon its interaction with specific receptors. There are 15 distinct 5-HT receptor genes in the human genome, and they may be expressed either pre- or postsynaptically in various brain areas. All 5-HT receptor subtypes (except the 5-$HT_3$ receptor) are G-protein coupled receptors. These serotonin receptor genes characterized to date include the 5-$HT_1$, 5-$HT_2$, 5-$HT_3$, 5-$HT_4$, 5-$HT_5$, 5-$HT_6$, and 5-$HT_7$ subtypes. Within the 5-$HT_1$ group, there are subtypes, 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1D}$, 5-$HT_{1E}$, and 5-$HT_{1F}$. There are three 5-$HT_2$ subtypes, 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ as well as two 5-$HT_5$ subtypes, 5-$HT_{5A}$ and 5-$HT_{5B}$. These receptors are coupled to G-proteins that affect the activities of enzymes such as adenylate cyclase and phospholipase C, or ion channels such as potassium channels. The 5-$HT_3$ class of receptors are unique in that they represent ligand-gated ion channels that mediate rapid excitatory signaling events. The 5-$HT_{2A}$ receptors mediate platelet aggregation and smooth muscle contractions. Serotonin, 5-hydroxy-l-tryptophan, and hallucinogenic drugs induce a head-twitch response in mice that is a behavioral proxy for brain 5-$HT_{2A}$R activation (Schmid and Bohn 2010). The 5-$HT_{2C}$ receptors are suspected in the control of food intake as mice lacking this gene become obese from increased food intake and are also subject to lethal seizures. The 5-$HT_3$ receptors are present in the gastrointestinal tract and chemoreceptor trigger zone in the area postrema and their activation can trigger vomiting. Also present in the gastrointestinal tract are 5-$HT_4$ receptors that function in secretion and peristalsis. The 5-$HT_6$ and 5-$HT_7$ receptors are distributed throughout the limbic system in the brain and 5-$HT_6$ receptors are unique in that they display high affinity for both typical (chlorpromazine) and atypical (clozapine) antipsychotic drugs.

Serotonergic drugs such as fenfluramine have a different mechanism of action than the reuptake inhibitors; fenfluramine interacts with the 5-HT transporter to promote the release of serotonin via reverse transport through SERT. Fenfluramine is also a direct acting agonist at 5-$HT_{2B}$ receptors. Until the late 1990s, it was used in human medicine as an anorectic agent in combination with phenteramine (Fen-Phen). An association between fenfluramine use and valvular heart disease and pulmonary hypertension, however, led to the removal of this preparation from the market. The 5-$HT_{2B}$ receptor is enriched in human cardiac valves and appears to be the target for a fenfluramine metabolite-induced cardiac valve abnormalities.

Serotonergic neurons possess two functional types of autoreceptors. One autoreceptor is the 5-$HT_{1B}$ receptor that is expressed primarily on serotonergic neuron terminals, and functions as a regulator of 5-HT release. Activation of the 5-$HT_{1B}$ receptor inhibits serotonin release from the axon terminals and therefore functions as a local negative feedback regulator of serotonin levels in the synapse. These 5-$HT_{1B}$ autoreceptors have been suggested to play a role in depression, anxiety states, aggression, migraine, and locomotor activity. Serotonergic involvement in aggression was indicated in studies with transgenic mice lacking the 5-$HT_{1B}$ receptor; these 5-$HT_{1B}$ knockout mice are more aggressive than the normal 5-$HT_{1B}$ receptor-expressing mice (Sari 2004). A second functional autoreceptor is the 5-$HT_{1A}$ receptor that is found on serotonergic cell bodies and dendrites (somatodendritic) in raphe nuclei serotonin neurons as well as on postsynaptic neurons receiving input from 5-HT pathways (Figure 3.4). Activation of 5-$HT_{1A}$ somatodendritic autoreceptors inhibits 5-HT neuron firing, 5-HT synthesis and 5-HT release from axon terminals. Direct application of 5-HT onto 5-HT neurons in the dorsal raphe produces an inhibitory effect on the serotonergic neuron firing activity through the activation of a hyperpolarizing potassium conductance. The 5-$HT_{1A}$ autoreceptors on the cell bodies of serotonergic neurons in the raphe nuclei presumably respond to the extracellular 5-HT released from the soma and dendrites of these neurons. These 5-HT

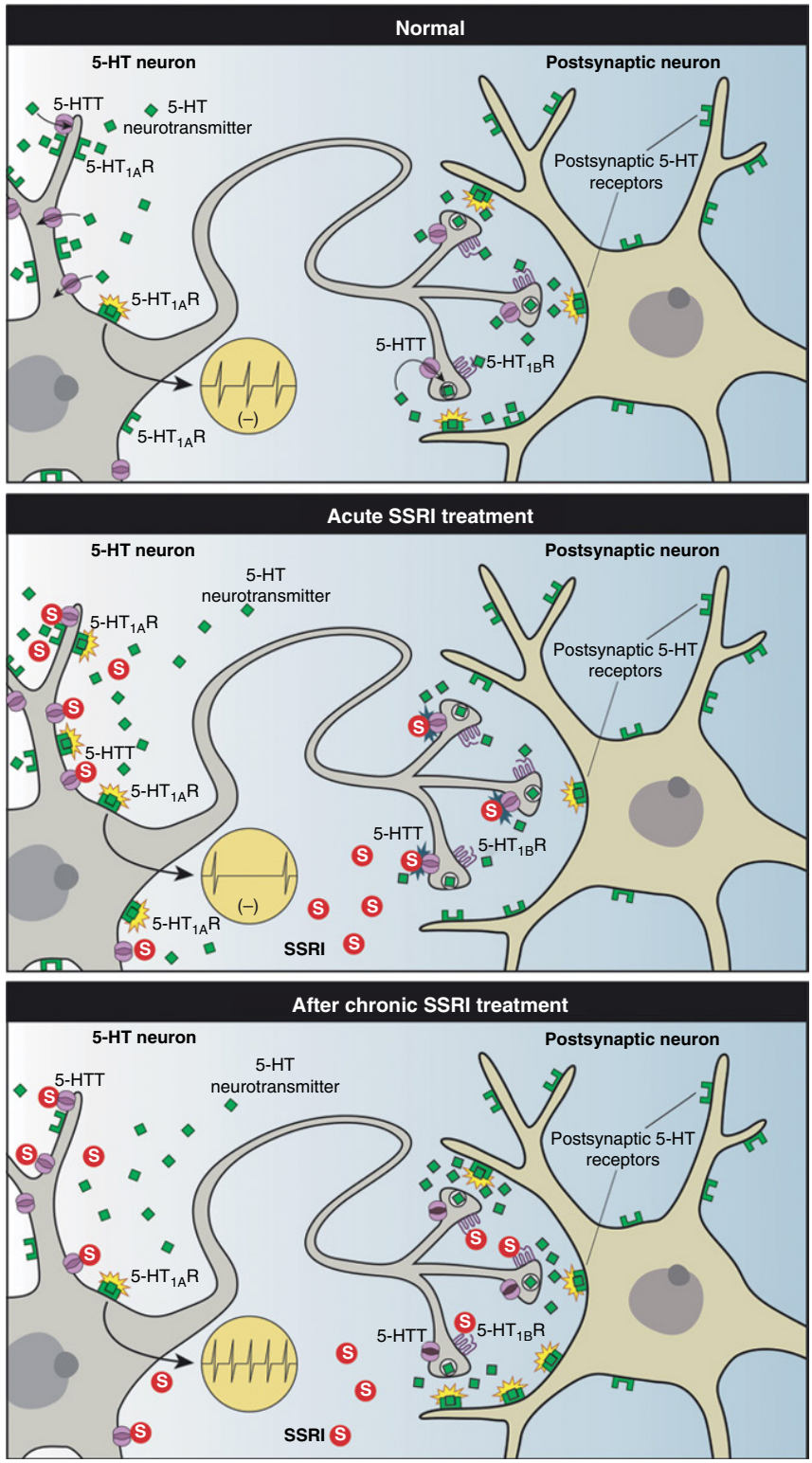


**Figure 3.4** Diagram depicting the regulation of the firing activity of 5-HT neurons by 5-$HT_{1A}$ autoreceptors localized on soma and dendrites (somatodendritic). **Normal:** Endogenous 5-HT released from dendrites of serotonergic neurons activates 5-$HT_{1A}$ autoreceptors and decreases neuronal firing activity. **Acute:** Acute administration of selective 5-HT reuptake inhibitor (SSRI) potentiates 5-HT induced decrease in neuronal firing leading to reduced release of 5-HT in forebrain structures. **Chronic:** After chronic treatment with a SSRI, the 5-$HT_{1A}$ autoreceptors desensitize and firing activity is restored or enhanced in the presence of the SSRI, leading to increased release of 5-HT in forebrain structures. This adaptive change in 5-HT neuronal control may be obligatory for an antidepressant response to manifest.

autoreceptors function in the feedback inhibition of raphe neurons to maintain a regular firing pattern of serotonin neurons.

It is well established that acute SSRI administration leads to a rapid (within one to two hours) inhibition of SERT in the CNS; however, the antidepressant effects in humans and animals take weeks to fully manifest. One of the primary postulated mechanisms of action of SSRIs is the desensitization of somatodendritic 5-$HT_{1A}$ autoreceptors after chronic administration. As depicted in Figure 3.4, the potential increase in 5-HT transmission in forebrain areas, which should result from preventing the reuptake of 5-HT in presynaptic terminals, is prevented by a decrease in the firing rate of 5-HT neurons because 5-HT reuptake is also inhibited in raphe nuclei serotonin neuron cell bodies. This was first demonstrated by examining the effects of an SSRI in the rat brain (Blier and de Montigny 1983). The receptor mediating this initial decrease of the firing of 5-HT neurons was subsequently identified as a 5-$HT_{1A}$ receptor on the 5-HT neurons themselves (autoreceptor) (Blier 2010). This 5-$HT_{1A}$ autoreceptor desensitizes over the course of chronic (two to three weeks) SSRI administration, allowing a recovery to normal of the firing of 5-HT neurons in the presence of reuptake inhibition. This increased firing rate results in a marked increase in 5-HT transmission in projecting areas because 5-HT release is highly dependent on firing. The desensitization of the 5-$HT_{1A}$ autoreceptor is therefore temporally correlated with the onset of the therapeutic action of SSRIs in depression. Studies in animals have shown that the somatodendritic 5-$HT_{1A}$ receptor desensitization may be related to the ability of SSRIs to trigger the internalization of these receptors into cytoplasmic compartments (Riad et al. 2004).

A role for limbic serotonergic neurotransmission involvement in anxiety-related behavioral traits has recently emerged from human studies of genetic differences in serotonin transporter function. These studies demonstrated that 5-HT transporter gene polymorphism was associated with SERT functional differences and increased amygdala response to fearful stimuli (Hariri et al. 2002). The link between serotonergic neurotransmission and affective disorders was further established through studies of gene–environment interaction. Individuals with a particular allele of the 5-HT transporter gene appeared to be more vulnerable to stressful events in that they were more likely to become clinically depressed (Caspi et al. 2003). These important studies indicate that rather than cause disease, genes may interact with the environment to control susceptibility to affective disorders such as depression.

Serotonin pathways have also been shown to be involved in obsessive–compulsive disorder (OCD). Clomipramine was first shown to have efficacy in the treatment of OCD in 1980. In the 1990s, this clinical effectiveness was extended to SSRIs such as fluoxetine, sertraline, and paroxetine. The therapeutic response of clomipramine and SSRIs in treating OCD in humans and acral lick dermatitis in dogs may be mediated by increased activation of 5-$HT_{2C}$ receptors through elevated synaptic levels of serotonin in forebrain structures, such as the orbitofrontal cerebral cortex. The efficacy of SSRIs in treating OCD to some extent generalizes to 5-$HT_{1A}$ receptor agonists; these direct activators of a serotonin receptor represent a group of structurally related compounds, the azapirones, best exemplified by buspirone. The azapirones possess significant affinity and selectivity for 5-$HT_{1A}$ receptors where they exert partial agonist activity. Acute treatment with buspirone produces a transient reduction in the firing rate of 5-HT neurons, similar to that seen initially with SSRIs. This response is presumed to reflect the consequences of direct activation of 5-$HT_{1A}$ somatodendritic autoreceptors by buspirone. Chronic administration with azapirones does, however, lead to a gradual increase in 5-HT neuron firing due to the progressive desensitization of 5-$HT_{1A}$ autoreceptors. In addition to the activation of 5-$HT_{1A}$ autoreceptors, buspirone acts as a partial agonist at

the postsynaptic 5-$HT_{1A}$ receptors in forebrain structures. This pharmacologic profile for azapirones differs from that of SSRIs, tricyclic antidepressants, and monoamine oxidase inhibitors (MAOI) in that these latter drug classes produce an indiscriminate activation of all serotonin receptor subtypes. This generalized activation of multiple 5-HT receptor subtypes is consequently associated with a number of adverse effects of SSRIs, MAOIs, and tricyclics, such as nausea, vomiting, sleep disturbance, and sexual dysfunction. The most common side effects of azapirones are limited to headache, dizziness, and nausea. Buspirone and other azapirone agonists are also used in the treatment of generalized anxiety disorder where they produce less sedation, less psychomotor disruption, and less cognitive impairment than benzodiazepines. Although in clinical trials buspirone is typically shown to be efficacious in treating anxiety, patients' response is more delayed than with benzodiazepines; this most likely reflects the requirement for 5-$HT_{1A}$ autoreceptor desensitization to achieve the therapeutic response. The azapirones are therefore an alternative to either SSRIs or benzodiazepines for the treatment of specific behavioral disorders in companion animals.

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# 4

# Biogenic Amine Transmitters

## Acetylcholine, Norepinephrine, and Dopamine

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## Acetylcholine

Acetylcholine was the first compound to be identified as a neurotransmitter in the peripheral nervous system; however, knowledge concerning the anatomical organization of cholinergic neurons lagged behind other transmitter substances due to the lack of suitable techniques for mapping cholinergic pathways. Many of these technical obstacles have been surmounted in recent years.

Acetylcholine is synthesized in cholinergic neurons by a reaction catalyzed by the cytosolic enzyme choline acetyltransferase (CAT). This linkage of choline and an acetate group provided by acetyl-CoA is not, however, the rate-limiting step in the biosynthesis of acetylcholine (ACh); rather, the high-affinity transport of choline from the extracellular medium by a specific transporter protein represents the rate-limiting step. ACh is stored in vesicles in cholinergic terminals and released into the synaptic cleft by exocytosis (Figure 4.1). The proteins involved in this exocytotic release of ACh are the targets for botulinum toxin; the therapeutic actions of Botox in the treatment of neuromuscular disorders derive from the ability of this toxin to block the release of ACh from cholinergic neuron terminals (Coffield 2003). Acetylcholine released from neurons into the synaptic cleft is hydrolyzed by the membrane bound enzyme, acetylcholinesterase (ACHE), which represents the mechanism for termination of the signal in cholinergic neurotransmission. ACHE has one of the highest catalytic powers ever reported for an enzyme and is therefore capable of a rapid clearance of ACh from the synaptic cleft. This distinguishes cholinergic neurons from those of other biogenic amines where the synaptic signal is terminated by the high-affinity reuptake of the transmitter. Acetylcholine is the neurotransmitter of all autonomic ganglia, postganglionic parasympathetic synapses, the neuromuscular junction, and cholinergic neurons in the central nervous system.

Cholinergic pathways in the brain have now been identified by histochemical and neurochemical methods (Figure 4.2). The majority of cholinergic neurons in the mammalian brain are found in four regions. These include: (i) the brainstem pedunculo-pontine and lateral dorsal tegmental nuclei; (ii) a subset of the thalamic nuclei; (iii) the striatum, where cholinergic neurons serve as local interneurons; and (iv) the basal forebrain nuclei, which collectively serve as the major sources of cholinergic projection neurons to the cerebral cortex, hippocampus, and amygdala (Ballinger et al. 2016). The cholinergic neurons originating in the nucleus basalis of Meynert, substantia innominata, and the diagonal band (basal forebrain) project to

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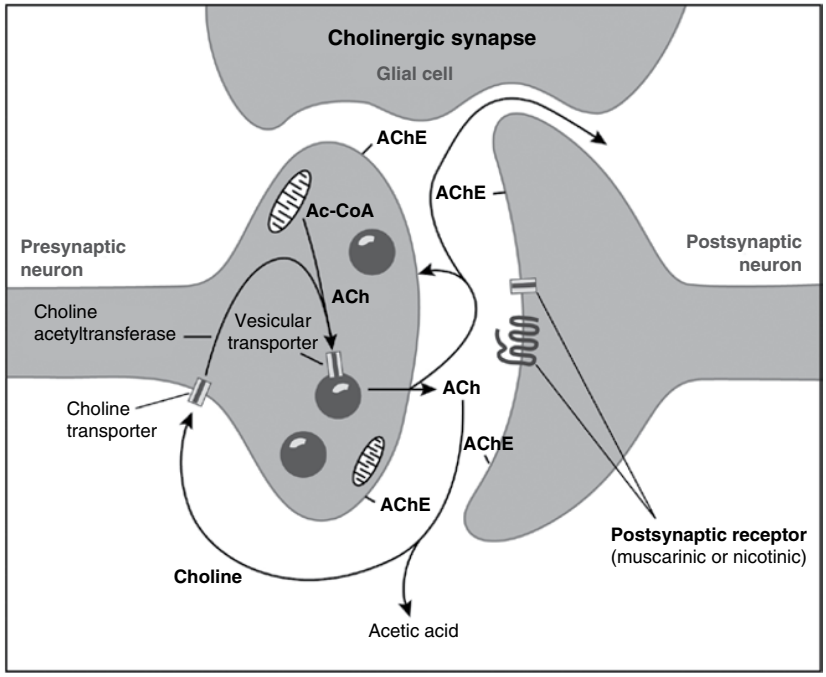


**Figure 4.1** Schematic representation of a cholinergic synapse in the central nervous system. The precursor for acetylcholine (ACh) synthesis is choline. ACh is synthesized from choline and acetyl CoA by the enzyme choline acetyltransferase. The ACh is stored in and released from vesicles. Synaptic ACh activates postsynaptic receptors comprised of both muscarinic and nicotinic subtypes. The synaptic action of ACh is terminated by the enzyme acetyl cholinesterase (AChE) through hydrolysis to acetate and choline. The choline is salvaged by a high affinity transporter for reutilization in the syntheses of ACh.

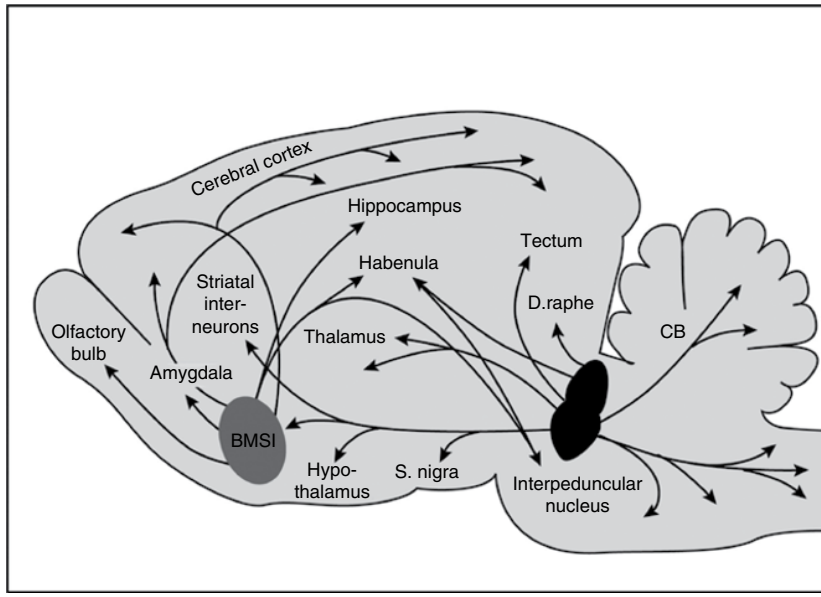


**Figure 4.2** Schematic diagram of the cholinergic pathways in animal brain. Central cholinergic neurons exist as both local circuit interneurons and projection neurons. Abbreviation: BMSI = Basal Nucleus of Meynert/ Substantia Inominata.

virtually all cerebral cortical areas and layers (Sarter et al. 2016). These projections terminating throughout the cerebral cortex degenerate in senile dementia and Alzheimer's disease and this cholinergic neuron loss has been correlated with the degree of cognitive decline. The ACh content of the brain in Alzheimer's patients at postmortem is profoundly reduced. These observations have led to the cholinergic hypothesis of cognitive decline in senile dementia that has served as the basis for pharmacological attempts to ameliorate learning and memory deficits by restoration of cholinergic neurotransmission. One pharmacologic strategy for augmenting cholinergic transmission has been the use of inhibitors of ACHE. Inhibition of this enzyme prolongs the half-life of ACh in the synapse and therefore enhances cholinergic transmission. Drugs such as tacrine, donepezil (Aricept®) and rivastigmine (Exelon®) are ACHE inhibitors (ACHEI) that have been used in the treatment of cognitive dysfunction associated with Alzheimer's disease. These drugs produce modest beneficial effects for periods of approximately one year, but do not prevent the progressive deterioration of mental function in Alzheimer's patients. Inhibition of ACHE has moreover a high propensity for adverse effects and a significant fraction of patients withdraw from treatment due to side effects.

Cholinergic receptors that mediate the synaptic actions of ACh are either muscarinic or nicotinic cholinergic receptors. The muscarinic receptors are members of the G-protein coupled receptor family and five subtypes of muscarinic cholinergic receptors (M1–M5) have been characterized. Muscarinic receptor activation therefore trigger their signaling through activation of heterotrimeric G proteins that in turn affect the opening, closing, and kinetics of $K^+$, $Ca^{2+}$, and non-selective cation channels. The alkaloids, atropine and scopolamine, act as nonselective, competitive antagonists of these muscarinic receptors. Both atropine and scopolamine are capable of disrupting working memory in humans and animals through their antimuscarinic actions in the cerebral cortex and hippocampus. High doses of either drug can also produce delirium, hyperactivity, visual hallucinations, and disorientation.

The $M_2$ muscarinic receptor predominates in hindbrain regions while the $M_1$ receptor is expressed at high levels in the cerebral cortex and hippocampus which are brain regions involved with memory and cognition. The $M_1$ muscarinic receptor has accordingly generated considerable recent interest as a target for drug discovery of agents that might facilitate learning and memory. In animal models, $M_1$ muscarinic receptor agonists restore cognitive impairment associated with damage to cholinergic pathways and may exert additional disease-modifying effects beneficial to Alzheimer's disease (Fisher et al. 2003).

The other class of cholinergic receptors that exist in the central nervous system are nicotinic receptors. These ACh receptors are members of the ligand-gated ion channel superfamily and are composed of multiple homologous subunits oriented around a central cation channel. Twelve different types of nicotinic receptor subunits have been identified in the brain (α2–10 and β2–β4) and each nicotinic cholinergic receptor is composed of five of these subunits. The combination of these subunits into a pentameric structure determines its electrophysiological and pharmacological properties. It takes the binding of two molecules of ACh to open the cation channel and allow the $Na^+$ influx and depolarization of neuronal membranes. The most common nAChR subtypes in the brain are α4β2 and α7 receptors.

In addition to responding to ACh, these receptors, as their name implies, are also activated by the alkaloid nicotine found in tobacco leaves. Nicotine shares with other drugs of abuse the ability to activate the mesocortical limbic dopaminergic pathways that represent the reward circuitry of mammalian brain. The interaction with nicotinic cholinergic receptors in this pathway underlies the rewarding and dependence-related actions of nicotine. In addition to the adverse addictive

properties of nicotine, this naturally occurring product increases mental alertness and improves memory in humans and animals. Chronic transdermal nicotine has indeed been found to improve attentional performance in Alzheimer's disease patients and in individuals with the precursor age-associated memory impairment syndrome (White and Levin 2004). There is therefore a great deal of interest in the pharmaceutical industry directed toward the development of synthetic nicotinic receptor agonists for the treatment of memory deficits and cognitive dysfunction. There are currently several nicotine analogs in various stages of preclinical and clinical development for use in neurodegenerative and Alzheimer's disease to mitigate the cognitive effects of the disease and delay clinical cognitive manifestations.

## Norepinephrine

The neurotransmitter norepinephrine is distributed throughout the brain. The relatively low concentration of norepinephrine in the brain, however, initially led physiologists to question its functional importance. Application of a fluorescent histochemical technique subsequently permitted the visualization of norepinephrine containing neurons and pathways in both the central and peripheral nervous system. Norepinephrine, dopamine, and epinephrine are catecholamines. The microanatomy of catecholamine-containing neurons in the central nervous system is distinct from amino acid and cholinergic fibers in that they possess varicosities along the axons in terminal fields. These varicosities contain all the machinery for neurotransmitter synthesis, storage, and release and are therefore the points of synaptic contact with target neurons. This unique microanatomy therefore allows a single catecholamine neuron with long terminal branches to possess thousands of varicosities. One catecholamine neuron consequently can influence the activity of thousands of target neurons.

The biosynthesis of norepinephrine in central neurons begins with the precursor tyrosine. Tyrosine is converted to l-dopa by the soluble enzyme tyrosine hydroxylase (Figure 4.3). Tyrosine hydroxylase is the rate-limiting step in the biosynthesis of norepinephrine and the activity of this enzyme is closely coupled to the neuronal firing rate. The l-dopa is in turn converted to dopamine by the enzyme l-dopa decarboxylase. In noradrenergic, but not dopaminergic, neurons the dopamine is converted into norepinephrine by dopamine-β-hydroxylase and stored in vesicles for release. Once the norepinephrine is released into the synaptic cleft, the signaling action of this transmitter is terminated by the selective, high affinity of reuptake of norepinephrine by a distinct transporter expressed on noradrenergic neurons (NET). Amphetamine and related psychostimulants exert their sympathomimetic and central stimulant properties through the inhibition of norepinephrine reuptake and the facilitation of the transmitter release.

Norepinephrine interacts with both alpha and beta adrenergic receptors expressed in the brain. There are eight subtypes of adrenergic receptors expressed in the brain including alpha-1A, 1B, 1D, alpha-2A, 2B, 2C, beta-1 and beta-2 adrenergic. All adrenergic receptors are G-protein coupled receptors. While the release of all neurotransmitters is regulated by presynaptic autoreceptors that respond to the released transmitter, this was first demonstrated in noradrenergic neurons. The noradrenergic neuron autoreceptors are members of the alpha-2 adrenergic receptor class. Agonists for alpha-2 adrenergic receptors, such as clonidine, produce an inhibition of norepinephrine release, while alpha-2 antagonists, such as yohimbine, increase the amount of norepinephrine released from presynaptic terminals. Given the existence of three subtypes of alpha-2 adrenergic receptors, the identity of the subtypes representing presynaptic autoreceptors was addressed using gene knockout strategies in mice. This approach has shown that both alpha-2A and alpha-2C-adrenergic receptors are involved

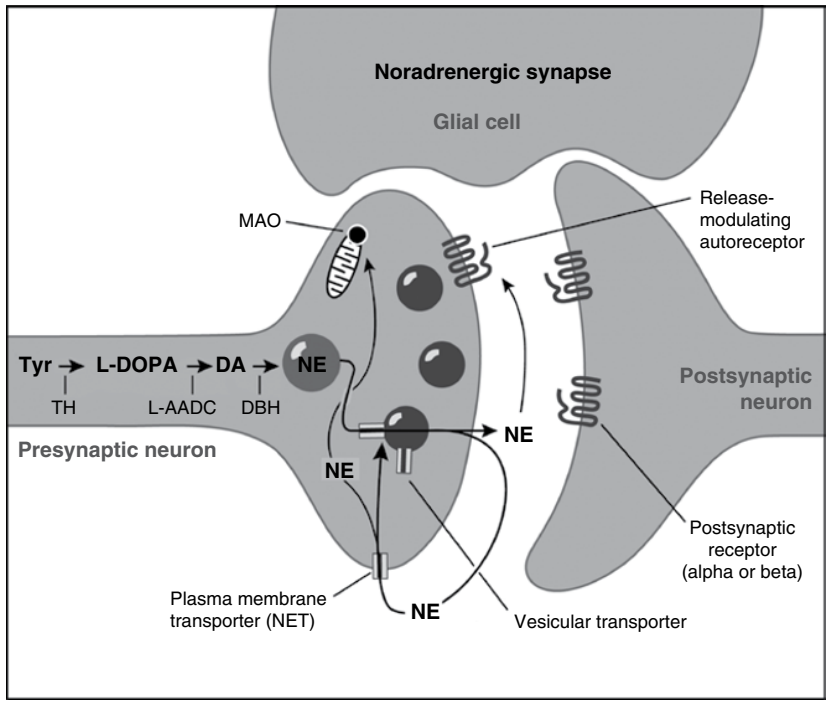


**Figure 4.3** Schematic representation of a noradrenergic synapse. The amino acid precursor tyrosine is converted to l-dopa by the enzyme tyrosine hydroxylose (TH) in noradrenergic neurons. The l-dopa is the converted to dopamine by l-aromatic amino acid decarboxylase (L-AADC), and the dopamine is in turn converted to norepinephrine (NE) by dopamine-β-hydroxylase (DBH). The NE is stored in and released from vesicles, and synaptic NE activates a complement of pre- and postsynaptic receptors. Synaptic NE action is terminated by the reuptake of the transmitter into the presynaptic terminal. This reuptake is mediated by the plasma membrane NE transporter (NET). Cytoplasmic NE can be degraded by the mitochondrial enzyme monoamine oxidase (MAO). Presynaptic release modulating autoreceptors are the $\alpha_2$-adrenergic subtype.

in the presynaptic control of transmitter release in noradrenergic neurons (Hein et al. 1999).

Noradrenergic neurons in the brain emanate from cell bodies in the pons (Figure 4.4). The primary nuclear complex from which noradrenergic neurons arise in the mammalian brain is the locus ceruleus. Norepinephrine neurons belonging to this nuclear complex branch widely in their terminal fields, allowing, for example, a single norepinephrine axon to innervate a large fraction of the cerebral cortex. Locus ceruleus noradrenergic efferents innervate target cells in cerebral cortical, subcortical, and spinomedullary fields. The sole source of norepinephrine input to the cerebral cortex and hippocampus, brain regions critical for cognitive and affective processes, is derived from the locus ceruleus. Collectively, this noradrenergic system plays a critical role in the regulation of arousal, attention, mood, and cardiovascular function. An additional group of noradrenergic neurons lies outside the locus ceruleus where they are sparsely distributed throughout the lateral ventral tegmental area of the pons (Cooper et al. 2003).

Selective alpha-2 ($\alpha_2$) receptor agonists, such as clonidine, xylazine, and medetomidine produce sedation, analgesia, and muscle relaxation in animals. As a class, $\alpha_2$-agonists are widely used as analgesic and sedative drugs in veterinary medicine. Clonidine, which is a partial agonist with high selectivity for $\alpha_{2A}$ versus α1 adrenergic receptors, has served as the prototype drug for this class and represents one of the most widely investigated

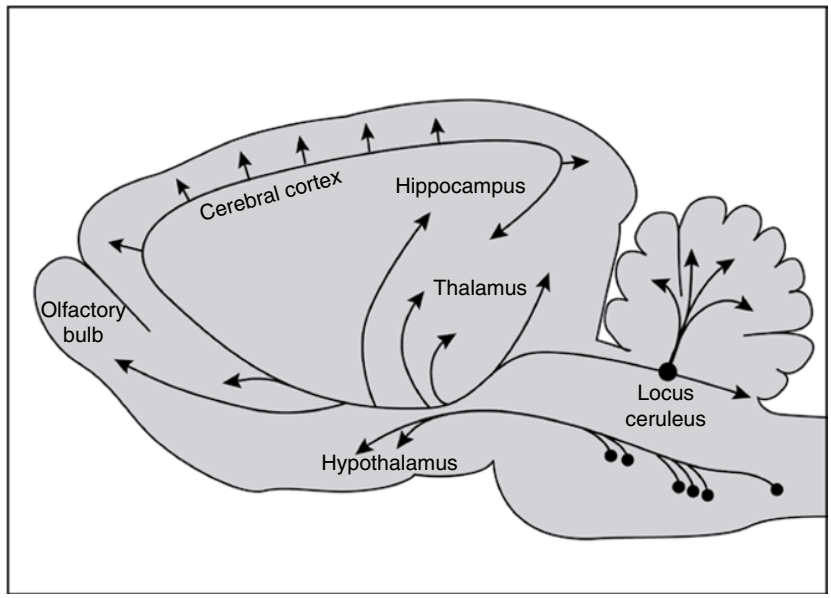


**Figure 4.4** Schematic diagram of the noradrenergic pathways in animal brain. Noradrenergic cell bodies are localized to the caudal pons in the locus ceruleus and also distributed more diffusely in the ventral tegmentum.

drugs in anesthesia and pain therapy (Giovannoni et al. 2009). The sedative effects of these drugs are mediated by the activation of $\alpha_2$ receptors on the locus ceruleus noradrenergic neurons. By selectively targeting $\alpha_{2A}$ adrenergic receptors, dexmedetomidine alters the level of arousal by reducing the firing rate of locus ceruleus neurons, and norepinephrine release (Song et al. 2017). Similarly, the sedative actions of medetomidine (Domitor®) in dogs is most likely mediated by the $\alpha_{2A}$ adrenergic receptor subtype, inasmuch as this receptor was the only $\alpha_2$ subtype recently shown to be expressed in canine brainstem (Schwartz et al. 1999). The actions of medetomidine may be reversed through the administration of atipamezole (Antisedan®) due to the $\alpha_2$ adrenergic receptor competitive antagonist properties of the latter compound. Medetomidine also affects the cardiovascular system of dogs and cats, producing marked bradycardia. The medetomidine-induced bradycardia is produced by a central action where activation of $\alpha_{2A}$ adrenergic receptors in the nucleus tractus solitarius reduces sympathetic outflow (Cullen 1996). These nucleus tractus solitarius $\alpha_{2A}$ adrenergic receptors are most likely postsynaptic receptors on dendrites of target neurons receiving input from noradrenergic neurons (Glass et al. 2001). The more variable effects of medetomidine on the blood pressure of dogs and cats is produced by a combination of stimulation of central $\alpha_{2A}$ sites and peripheral postsynaptic $\alpha_{2A}$ receptors in vascular smooth muscle.

Although throughout the 1990s the emergence of SSRIs as the primary treatment of depressive illness focused attention on serotonergic mechanisms, traditional antidepressants such as the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) increase synaptic concentrations of both norepinephrine and serotonin. Similarly, newer drugs such as venlafaxine that block the reuptake of both serotonin and norepinephrine (SNRIs) are effective antidepressants (Hardy et al. 2002). When coupled with the recent introduction of the selective norepinephrine reuptake inhibitor (NRI) reboxetine as an antidepressant, there has been a resurgence of interest in the role of noradrenergic mechanisms in depression and affective disorders in general.

The renewed attention on noradrenergic pathways is consistent with the original formulation of the biogenic amine theory of affective disorders which posited that depressive symptoms arose from a deficiency of biogenic amines such as norepinephrine (Schildkraut 1965). This hypothesis arose from the observations in the 1950s that iproniazid, an MAOI, elevated mood in depressed patients being treated for tuberculosis, and that imipramine, developed as an antipsychotic, elevated mood in patients with depressive illness. Imipramine was subsequently shown to inhibit the reuptake of the biogenic amines norepinephrine and serotonin. The demonstration of the effectiveness of imipramine as an antidepressant led to the development of an array of TCAs that remain in use in human and veterinary medicine. The TCAs that remain in clinical use are the tertiary amines amitriptyline, clomipramine, doxepin, and imipramine; and the secondary amines desipramine and nortriptyline. While the tertiary amines were originally proposed to have some selectivity for inhibiting the serotonin transporter *in vitro*, their secondary amine metabolites generated *in vivo* preferentially inhibit the norepinephrine transporter. The differential affinities of TCAs for the norepinephrine (NET) and serotonin transporters (SERT) *in vitro* have been well characterized, and indicate that several of these antidepressants are relatively selective inhibitors of norepinephrine reuptake. As indicated in Table 4.1, the TCAs desipramine and nortriptyline have selectivity for the norepinephrine transporter, while amitriptyline and imipramine display little selectivity. In contrast. the SSRIs fluoxetine, sertraline, and paroxetine preferentially inhibit the serotonin transporter.

Although technically a tricyclic compound, the structurally unique drug reboxetine is very selective as an inhibitor of norepinephrine reuptake. The human literature indicates that there is no significant difference between the antidepressant efficacies of norepinephrine- and serotonin-selective antidepressant drugs (Brunello et al. 2002). These data suggest that both noradrenergic and serotonergic mechanisms are involved in depressive symptomatology and, as a consequence, chronic inhibition of either NET- or SERT-mediated reuptake leads to improvement in the symptoms of clinical depression. An interesting observation from a preclinical investigation recently indicated that the behavioral effects of the SSRIs fluoxetine,

**Table 4.1** Interaction of antidepressants with the norepinephrine (NET) and serotonin (SERT) transporters *in vitro*.

| Drug | $K_I$ (nM) NET | $K_I$ (nM) SERT | NET Selectivity (ratio SERT/NET) |
|---|---|---|---|
| Desipramine | 0.77 | 288 | 374 |
| Reboxetine | 8 | 1070 | 130 |
| Nortriptyline | 4.34 | 190 | 44 |
| Doxepin | 40 | 355 | 9 |
| Amitriptyline | 27 | 107 | 4 |
| Imipramine | 28 | 37.2 | 1.3 |
| Fluoxetine | 1235 | 17.7 | 0.014 |
| Sertraline | 220 | 3.4 | 0.015 |
| Paroxetine | 161 | 0.033 | 0.0002 |

*Note:* The antidepressants are listed in decreasing order of NET selectivity.
*Source:* Brunello et al. (2002); Rothman and Baumann (2003).

sertraline, and paroxetine were either absent or severely attenuated in transgenic mice incapable of producing norepinephrine (Cryan et al. 2004). These results indicate that norepinephrine may play an important role in mediating the acute behavioral and neurochemical effects of many antidepressants including some widely used SSRIs.

An important concept that is germane to our current understanding of the mechanism of action of antidepressants is that the original biogenic amine theory of affective disorders is an over-simplification. A critical discrepancy in the view that mental depression is simply due to a deficiency in synaptic levels of biogenic amines is that TCAs, MAOIs, SSRIs, and NSRIs all act to increase the levels of biogenic amines in the synapse within hours whereas the therapeutic response does not manifest until two to three weeks of chronic drug administration. Newer theories of the mechanism of therapeutic action of antidepressant drugs have accordingly focused on adaptive changes in receptor sensitivities with temporal patterns that agree with those of the clinical therapeutic response. Thus chronic, but not acute, administration of antidepressants produces changes in both noradrenergic and serotonergic receptor systems. These adaptive changes provoked by chronic antidepressant drug administration include the down-regulation of β-adrenergic, alpha-1-adrenergic, alpha-2-adrenergic, 5-$HT_2$ serotonergic, and 5-$HT_{1A}$ serotonergic receptors in various brain regions (Brunello et al. 2002). These adaptive changes in receptor sensitivity typically require 14–21 days of chronic antidepressant drug treatment which mimics the time course for the therapeutic response.

Although the TCAs, MAOIs, SSRIs, and NSRIs do not appear to differ significantly with respect to the temporal pattern for onset of therapeutic response or for clinical efficacy, they do differ with respect to side effect profiles. The adverse effects of TCAs are manifold and are a function of the affinities of these compounds for alpha-1-adrenergic, alpha-2-adrenergic, $H_1$ histamine, and muscarinic-cholinergic receptors. Newer antidepressants such as the SSRIs and NSRIs have negligible affinities for these neurotransmitter receptors and therefore possess a much more favorable side effect profile (Kent 2000). First-generation TCAs commonly produce constipation, urinary retention, dry mouth, sedation, and postural hypotension, and are highly toxic on overdose. The latter side effects of sedation and postural hypotension are well correlated with affinity for alpha-1-adrenergic receptors, whereas the other autonomic responses are correlated with their respective affinities for muscarinic cholinergic receptors. TCAs also exhibit cardiac toxicities such as enhancing or slowing of cardiac conduction, and arrhythmias that are potentially lethal on overdose or in vulnerable populations.

As depicted in Table 4.2, the SSRIs and NSRI have much lower affinities for muscarinic and alpha-1-adrenergic receptors and are accordingly nonsedating and do not produce hypotension, dry mouth, constipation, or other side effects typical of TCAs. MAOIs share with TCAs the property that they can be lethal on overdose, and in addition have the added risk of potentially severe hypertensive crisis due to pressor effects of dietary tyramine or the interaction with several over-the-counter

**Table 4.2** Antidepressant affinities for $H_1$-histamine, muscarinic cholinergic, and alpha$_1$ and alpha$_2$ adrenergic receptors.

| | Receptor affinity (nM) | | | |
|---|---|---|---|---|
| **Antidepressant** | **$H_1$** | **M** | **Alpha$_1$** | **Alpha$_2$** |
| Doxepin | 0.17 | 23 | 23 | 1270 |
| Amitriptyline | 0.95 | 9.6 | 24 | 690 |
| Nortriptyline | 6.3 | 37 | 55 | 2030 |
| Desipramine | 60 | 66 | 100 | 5500 |
| Fluoxetine | 1000 | 1300 | 5900 | >10 000 |
| Sertraline | >10 000 | 500 | 300 | 5000 |
| Paroxetine | 1000 | 89 | >10 000 | >10 000 |
| Reboxetine | 1400 | 3900 | >10 000 | >10 000 |

*Source:* Kent (2000); Brunello et al. (2002).

and prescription drugs. The newer SSRI and NSRI antidepressants therefore have a much-improved therapeutic index and tolerability as compared to TCAs and MAOIs.

## Dopamine

Dopamine is a catecholamine neurotransmitter originally believed to function only as a precursor for norepinephrine and epinephrine biosynthesis. It is, however, now established that dopamine functions as an important neurotransmitter in the brain that accounts for approximately 50% of the catecholaminergic neurons in the CNS. These dopaminergic neurons exist in discrete pathways that are distinct from the distribution of noradrenergic neurons.

Similar to synthesis of norepinephrine in the CNS, dopamine is formed from the precursor tyrosine. Tyrosine is converted into l-dopa by tyrosine hydroxylase and the l-dopa is metabolized to dopamine by the enzyme l-aromatic amino acid decarboxylase (Figure 4.5). Dopaminergic neurons are,

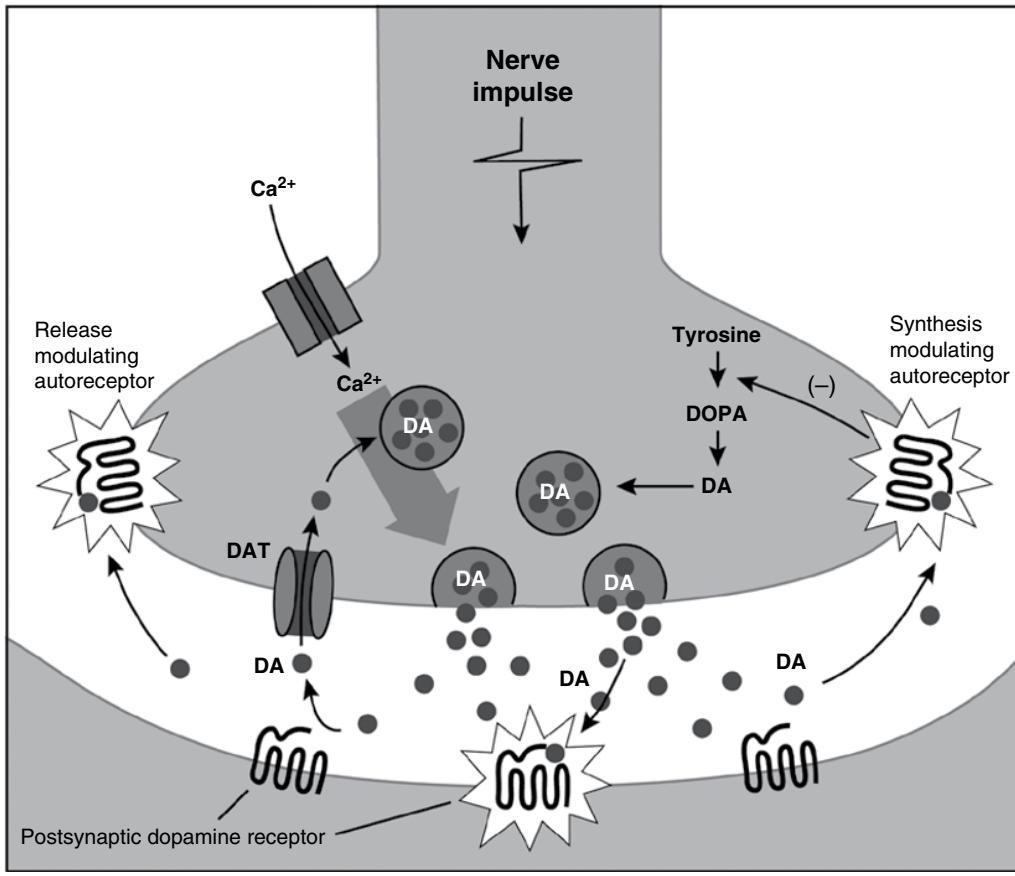


**Figure 4.5** Schematic representation of a dopaminergic synapse. As in NE neurons, tyrosine is converted to l-dopa and then to dopamine (DA) in dopaminergic neurons. These neurons lack the enzyme dopamine-β-hydroxylase and DA therefore functions as the neurotransmitter in these cells. The DA is stored in and released from vesicles, and synaptic DA activates both pre- and postsynaptic receptors. Synaptic DA action is terminated by the reuptake of the transmitter into the presynaptic terminal. This reuptake is mediated by the plasma membrane DA transporter (DAT). Cytoplasmic DA can be degraded by the mitochondrial enzyme monoamine oxidase (MAO). The presynaptic DA autoreceptors are primarily $D_2$ dopamine receptors.

however, distinct from noradrenergic neurons in that they do not express dopamine β hydroxylase, and hence do not convert dopamine into norepinephrine.

Two important nuclei containing dopaminergic cell bodies are located in the mesencephalon. One of these nuclei is the substantia nigra with long axon projections to the striatum. This nigrostriatal dopamine pathway contains the majority of total brain dopamine and is the pathway that degenerates in Parkinson's disease. Parkinsonian patients with only mild symptoms are thought to have as much as a 70–80% reduction in striatal dopamine content, whereas patients with severe symptoms have more than 90% loss of nigrostriatal dopaminergic neurons. The other major mesencephalic nucleus containing dopaminergic cell bodies is the ventral tegmental area (VTA); this nucleus lies medial to the substantia nigra in the mesencephalon. The VTA projects to limbic structures, such as the nucleus accumbens, and to the cerebral cortex (prefrontal cortex). These dopaminergic pathways are therefore termed respectively the mesolimbic and mesocortical dopamine systems. Due to the fundamental involvement of the VTA dopaminergic projection to the nucleus accumbens in the regulation of reward-related behavior, this system has been characterized as the neuroanatomical reward center in the brain (Spanagel and Weiss 1999). Synaptic dopaminergic transmission in the nucleus accumbens is increased in response to natural rewards such as food, water, and sex; and also by drugs of abuse such as amphetamine, cocaine, opioids, and nicotine. The dopamine theory of reward and addiction that began to emerge in the 1970s states that dopamine release mediates reward and thus leads to addiction. More recent refinement of this theory suggests that dopamine clearly has a central role in addiction to stimulant drugs, which act directly on dopamine synapses, but that it has a less important role, if any, in mediating reward and addiction to other drugs such as opiates, nicotine, and cannabis (Nutt et al. 2015).

Other dopaminergic projections in the brain include those of the arcuate nucleus in the hypothalamus with axons terminating in the intermediate lobe of the pituitary, where dopamine acts as an inhibitory regulator of prolactin release. Collectively these dopamine pathways therefore have many roles in normal brain function (Figure 4.6). In the cerebral cortex, dopamine is important for executive functions such as attention and working memory; in the basal ganglia, it is necessary for motivational salience, reward, and fluent motor function; and in the hypothalamus it regulates prolactin release (Nutt et al. 2015).

Within dopaminergic presynaptic terminals the mitochondrial enzyme MAO can degrade free dopamine. At these axon terminals dopamine is released by action potential-driven exocytosis from vesicles into the synaptic cleft. The synaptic action of dopamine is terminated by the high-affinity reuptake of dopamine mediated by the dopamine transporter (DAT) expressed on the presynaptic terminal. The use of dopamine transporter knockout mice has indicated that the absence of this transporter produces a 300-fold increase in the amount of time required to clear dopamine from the synapse (Gainetdinov et al. 2001). Inasmuch as the dopamine transporter protein is the molecular target for psychostimulant drugs such as cocaine, methylphenidate, modafinil, and amphetamine; the actions of these drugs are blunted in mice lacking the transporter. Dopamine in the synapse interacts with a family of dopamine receptors ($D_1$, $D_2$, $D_3$, $D_4$, and $D_5$) that are localized to either presynaptic or postsynaptic membranes. These five dopamine receptor subtypes are all G-protein coupled receptors whose cell-signaling actions are mediated by stimulation or inhibition of adenylyl cyclase, activation of phospholipase C or regulation of $K^+$ channel conductance. Dopamine $D_2$ receptors are expressed as both pre- or postsynaptic receptors. As autoreceptors at the cell body, they decrease the firing rate of dopaminergic neurons, and as autoreceptors on axon terminals,

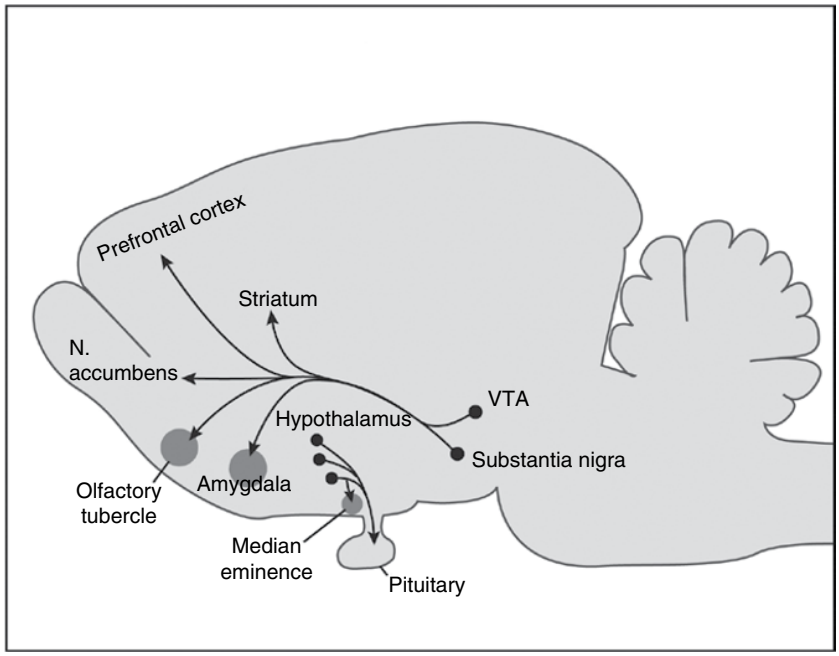


**Figure 4.6** Schematic diagram of the dopaminergic pathways in animal brain. Dopaminergic cell bodies are localized to midbrain structures including the ventral tegmental area (VTA) and substantia nigra. Additional DA cell bodies are in the arcuate and periventricular nuclei projecting to the median eminence and intermediate lobe of the pituitary. The mesolimbic DA pathway from the VTA to the nucleus accumbens represents a component of the reward circuitry of the brain.

the $D_2$ receptors regulate the release of dopamine (Schmitz et al. 2002).

The dopamine hypothesis of schizophrenia was originally formulated in the late 1960s by Van Rossum (1966). He suggested that the pathophysiology of schizophrenia might involve an over-stimulation of dopamine receptors. Key elements of this hypothesis were that drugs used to treat schizophrenia acted as dopamine receptor antagonists, and indirect acting dopaminergic agonists such as amphetamine could produce features of a psychosis in normal humans or exacerbate certain symptoms in schizophrenics. The dopamine hypothesis of schizophrenia has also derived support from the observation that the clinical potency of antipsychotic drugs is well correlated with their affinities for $D_2$ dopamine receptors. These antipsychotic drugs include first-generation compounds such as chlorpromazine (Thorazine®), trifluoperazine (Stelazine®) and haloperidol (Haldol®), as well as second-generation drugs, such as clozapine (Clozaril®) and risperidone (Risperdol®). Therapeutic doses of most antipsychotic drugs produce levels of $D_2$ receptor occupancy in the striatum of 60–80%, while atypical antipsychotics such as clozapine produce lower levels of striatal $D_2$ receptor occupancy ranging from 10 to 66% (Lidow et al. 1998; Seeman and Kapur 2000). Recent PET studies in human patients with schizophrenia have demonstrated an increased occupancy of striatal $D_2$ receptors by endogenous dopamine (Abi-Dargham et al. 2000). This observation supports the dopaminergic hyperactivity hypothesis of schizophrenia.

While much attention has been focused on striatal $D_2$ dopamine receptors in schizophrenia, these receptors are unlikely to be the primary target for the therapeutic action of antipsychotic drugs to mitigate the thought disorder of schizophrenic patients. Striatal $D_2$ dopamine receptors certainly are the

target for the Parkinson-like extrapyramidal side effects of typical antipsychotic drugs. Antipsychotic drugs such as fluphenazine have been reported to cause extrapyramidal symptoms in horses when this drug is used to produce sedation (Kauffman et al. 1989; Brewer et al. 1990). In horses, the extrapyramidal symptoms manifest as akathisia and repetitive pawing.

The $D_2$ receptor representing the target for the therapeutic effects of antipsychotic drugs are likely to be those expressed in the cerebral cortex (Lidow et al. 1998). The cerebral cortex possesses higher densities of $D_1$ than $D_2$ dopamine receptors and these $D_1$ receptors are downregulated after chronic antipsychotic drug treatment (Lidow et al. 1998). These $D_1$ dopamine receptors may be linked to some of the negative symptoms of schizophrenia such as chronic apathy and cognitive deficits such as memory impairment. The activation of prefrontal cortical $D_1$ receptors in a narrow occupancy range has been shown to enhance signaling in prefrontal cortex neurons engaged in working memory in nonhuman primates (Lidow et al. 1998). This observation points to an essential role of the $D_1$ dopamine receptor function in the prefrontal cortex during working memory.

Germane to the function of dopaminergic pathways in the brain is the introduction of l-deprenyl (or selegiline) (Anipryl®) to control canine cognitive dysfunction syndrome. Deprenyl is a selective irreversible inhibitor of the enzyme MAO-B. Monoamine oxidase exists in two forms termed MAO-A and MAO-B. MAO is a mitochondrial enzyme that is widely expressed in tissues, including the gastrointestinal tract, the liver, platelets, smooth muscle, and the brain. In the brain, the preferred substrates for MAO-A are norepinephrine and serotonin whereas the preferred substrate for MAO-B is phenylethylamine. Dopamine and tyramine are metabolized at equivalent rates by the two forms of MAO. MAO enzymes are localized to the outer membranes of mitochondria in both neuronal and non-neuronal cells. In neuronal cells these enzymes are responsible for the oxidative deamination of monoamines.

In the late 1980s, deprenyl was shown to delay the onset of disability, and hence the need for l-dopa therapy, associated with early, untreated cases of Parkinson's disease (Parkinson Study Group 1989). This observation suggested that deprenyl may exert a neuroprotective action to ameliorate an underlying disease process in Parkinson's disease. Neuroprotection in this context refers to an intervention that protects or rescues vulnerable neurons and slows the progression of the neurodegenerative disease. MAO activity could contribute to neural degeneration by producing hydrogen peroxide which, although normally detoxified by glutathione, can react with ferrous iron to generate the highly reactive and cytotoxic hydroxyl ($OH^{\cdot}$) radical. Thus, by inhibiting MAO-B, deprenyl may exert a neuroprotectant action through the reduction in the generation of free radicals. Environmental chemicals may also contribute to the development of neurodegenerative disorders such as Parkinson's disease, and chemicals structurally related to the designer drug precursor MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) may require metabolism by MAO to produce active neurotoxins. In this case, MAO inhibitors such as deprenyl would be neuroprotective due to the inhibition of the formation of neurotoxic metabolites. Postmortem studies have consistently implicated oxidative damage in Parkinson's disease and the source of reactive oxygen species may also derive from the dysfunction of the mitochondria caused by either environmental or genetic mechanisms (Greenamyre and Hastings 2004).

The ability of deprenyl to act as a neuroprotectant may therefore be involved in its therapeutic actions in canine cognitive dysfunction. Chronic deprenyl treatment dramatically elevates brain levels of the trace amine β-phenylethylamine and also produces modest increases in striatal dopamine content (Youdim and Weinstock 2004). The elevation of β-phenylethylamine may also

contribute to the pharmacological actions of deprenyl inasmuch as this compound promotes the release of dopamine and inhibits dopamine reuptake. The administration of l-deprenyl leads to the appearance of l-methamphetamine as a major metabolite in animals and this compound may contribute to the clinical benefits of this drug (Engberg et al. 1991). Chronic administration of deprenyl to elderly dogs improves decrements in hearing, activity, attention, and ability to navigate stairs (Ruehl et al. 1995). The combined neuroprotectant and indirect actions to facilitate dopaminergic neurotransmission may account for its effects on behavior and cognitive function in elderly dogs (Milgram et al. 1993).

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# 5

# Neuropeptides

## Opioids and Oxytocin

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## Introduction

Endogenous neuropeptide signaling systems have been shown to have a role in a wide array of behavioral functions ranging from promoting social attachment behavior between mating partners in certain species, to regulation of vigilance and modulation of pain perception, to name a few. Neuropeptides have major roles in regulating the activity of neuronal signaling between brain regions, and expression of neuropeptides and their receptors has served as an important genetic substrate on which evolutionary forces have optimized behaviors (McGrath 2017).

## Endogenous Opioid Peptides

Opiates are drugs derived from opium and include morphine, codeine (both alkaloids), and a variety of semisynthetic analogs derived from them or from thebaine, which is another component of opium (Pasternak and Pan 2013). Opium preparations extracted from poppy seeds have been used for thousands of years to treat pain, cough, diarrhea, and to produce euphoria. The term opioid is more general and is used to describe all drugs, irrespective of structure, with a morphine-like activity, including endogenous peptides.

The existence of specific receptors for opiates in mammalian tissues had been suspected since the 1950s based on strict structure–activity requirements, including sterospecificity, for opiate drugs. In the early 1970s, methods developed for the direct biochemical detection of receptors were applied to the search for specific opiate receptors in brain tissue. Using a radioligand binding method, Snyder and colleagues identified an opiate receptor in brain and intestinal tissue in 1973 (Snyder 2004). The identified receptor was pharmacologically relevant in that an extensive series of opiate drugs bound with affinities closely matching their analgesic potencies. These opiate receptors were found to be enriched in areas of animal brain known to be involved in the processing of sensory and pain signals such as the periaqueductal gray, medial thalamus and the substantia gelatinosa of the spinal cord and brainstem. A very high density of opiate receptors was also found in the locus coeruleus where opioids exert a regulatory influence on noradrenergic pathways (Snyder 2004). The discovery of these specific receptors for opiates immediately suggested the presence of endogenous opiate-like substances that normally target these receptors. The first description of such endogenous substances was in 1975 with the

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characterization of substances from porcine brain that had opiate agonist properties (Hughes et al. 1975). These substances consisted of two enkephalin pentapeptides: [Met]enkephalin (Tyr-Gly-Gly-Phe-Met) and [Leu]enkephalin (Tyr-Gly-Gly-Phe-Leu). Subsequent to the identification of these two enkephalin pentapeptides, other investigators characterized several additional endorphins (endogenous opioids) from porcine hypothalamus-neurohypophysis. The endorphins all contain the N-terminal Tyr-Gly-Gly-Phe (Met or Leu) sequence followed by varied C-terminal extensions yielding peptides from 5 to 31 amino acids in length (Akil et al. 1998). Two important members of the endorphin family are β-endorphin, an extremely potent endogenous opioid and dynorphin A, a 17-amino acid peptide with a distinctive neuroanatomical distribution and physiology. In mammals, the endogenous opioid peptides are derived from four precursors: pro-opiomelanocortin (POMC), pro-enkephalin, pro-dynorphin, and pro-nociceptin/orphanin FQ. The characterization of the POMC gene revealed that it codes for the stress hormone ACTH and the opioid peptide β-endorphin. The endogenous opioid peptides and their respective precursors are listed in Table 5.1.

The Pro-enkephalin precursor encodes for multiple copies of [Met]enkephalin as well as one copy of [Leu]enkephalin. Similarly, Pro-dynorphin encodes for three opioid peptides of distinct lengths including dynorphin A, dynorphin B, and the neoendorphins.

The POMC-derived peptides have a limited distribution in the central nervous system (CNS) with high levels found in the arcuate nucleus and pituitary. The pro-dynorphin and pro-enkephalin peptides have a wider distribution in the CNS and are frequently found in the same pathways. The pro-enkephalin peptides are present in areas of the CNS that are involved with the perception of pain such as laminae I and II of the spinal cord, the spinal trigeminal nucleus, and the periaqueductal gray. These peptides are also found in limbic structures regulating affective behavior and reward, such as the amygdala, the nucleus accumbens, the hippocampus, the locus ceruleus, and the cerebral cortex. Although there are a few long axon enkephalinergic tracts in the brain, these peptides are typically expressed in interneurons. One group of long axon

**Table 5.1** Mammalian endogenous opioids.

| Precursor | Endogenous opioid | Amino acid sequence |
|---|---|---|
| Pro-opiomelanocortin | β-endorphin | Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu |
| Pro-enkephalin | [Met]enkephalin<br>[Leu]enkephalin | Tyr-Gly-Gly-Phe-Met<br>Tyr-Gly-Gly-Phe-Leu |
| Pro-dynorphin | Dynorphin A | Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln |
| | Dynorphin A (1–8)<br>Dynorphin B | Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile<br>Tyn-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr |
| | α-neoendorphin | Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Pro-Lys |
| | β-neoendorphin | Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Pro |
| Pro-nociceptin/OFQ | Nociceptin | Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln |

pro-dynorphin and pro-enkephalin gene product-containing pathways comprise part of the output neurons of the striatum and accumbens (Akil et al. 1998). In the dorsal striatum, the striatonigial neurons contain pro-dynorphin products, substance P and GABA; whereas the striatopallidal neurons contain enkephalin and GABA. As a result of the limited distribution of β-endorphin in the brain, the enkephalins and dynorphins are considered to be the predominant central opioid peptide neurotransmitters.

It is now well established that these endogenous opioids interact with an opioid receptor family composed of three subtypes. Pharmacological studies using opioid peptides, alkaloids, and synthetic derivatives of opiates indicated multiple subtypes of opioid receptors. This classification of multiple opioid receptors was originally based on the production of distinct syndromes in dogs by derivatives of morphine (Martin et al. 1976). The three drugs used in these early studies were morphine as the prototype for the mu (μ) opioid receptor, ketocyclazocine for the kappa (κ) opioid receptor and SKF-10,047 (N-allylnormetazocine) for a sigma receptor. The morphine syndrome (mu μ) in the dog was characterized by miosis, bradycardia, hypothermia, a general depression of the nociceptive responses, and indifference to environmental stimuli. Ketocyclazocine (kappa κ) constricted pupils, depressed the flexor reflex, and produced sedation but did not markedly alter pulse rate or the skin twitch reflex. SKF-10047 (sigma σ), in contrast to morphine and ketocyclazocine, caused mydriasis, tachypnea, tachycardia, and mania (Martin et al. 1976). The sigma site was subsequently demonstrated not to represent an opioid receptor inasmuch as the actions of SKF-10047 were not blocked by prototypic opioid antagonists such as naloxone and naltrexone. Investigations with both nonpeptide and peptide derivatives led to the demonstration of the delta (δ) opioid receptor as the third subtype. In fact, the first opioid receptor to be cloned was the delta receptor (Kieffer et al. 1992) and this was soon followed by successful isolation of cDNA clones for the mu and kappa receptors. The cloning and sequencing of all three opioid receptors from a variety of species verified that these receptors belonged to the G-protein coupled family of receptors.

Opioids modulate neuronal activity and the three opioid receptor subtypes mediate this neuromodulation by activating multiple signaling pathways. Signaling through the cognate mu opioid receptor and the $G_i$ protein, for example, reduces neuronal excitability through physical interactions with the potassium and calcium channels. Opioid-induced decreases in $Ca^{2+}$ influx into presynaptic neurons inhibit neurotransmitter release. Opioid receptors also activate or reduce the activity of multiple kinases, including those of the G-protein receptor kinase family (GRK), the mitogen activated protein kinase family (MAPK), and the protein kinases A and C (PKA and PKC). These kinases not only play an important role in turning off opioid receptor signaling (desensitization), but also function to shape cellular function on short- and long-term timescales through protein phosphorylation and gene transcription.

The affinity of endogenous opioid peptides for μ-, δ- and κ-receptors varies, but none of the peptides bind exclusively to only one receptor. β-endorphin has similar affinities for μ- and δ-opioid receptors but has very low affinity for κ-receptors. [Met] and [Leu] enkephalins have high affinity for δ-opioid receptors and have approximately 10-fold lower affinity for μ-opioid receptors; these endogenous enkephalins possess negligible affinity for κ-receptors. Of the three subtypes of opioid receptors, the subtype with the greatest selectivity for endogenous peptides is unquestionably the κ-opioid receptor. The κ-receptor displays sub-nanomolar (nM) affinities for the dynorphins, while its affinity for [Leu] enkephalin is 100 nM; a potency difference of 1000-fold (Akil et al. 1998). The endogenous ligands for κ-opioid receptors are the dynorphins. With the exception of the dynorphins, most endogenous opioid

peptides have a higher affinity for δ- rather than μ-receptors. Notwithstanding this pharmacological signature of endogenous opioids, the μ-receptor clearly mediates the analgesic and euphorigenic actions of opioid drugs. The δ-opioid receptor is much less involved in the analgesic and rewarding effects of opioid drugs, while κ-opioid receptors mediate spinal analgesia and dysphoria. The use of transgenic mice that lack μ-opioid receptors has revealed that morphine-induced analgesia, reward, respiratory depression, and constipation are virtually absent in these mice (Keiffer 1999).

A summary of the receptor selectivities and efficacies of opioid drugs is given in Table 5.2. Similar to other drugs, these opioids exert either an agonist, partial-agonist, or antagonist action at a given receptor. The term mixed agonist/antagonist, although confusing, is sometimes used to describe the pharmacology of specific opioids such as buprenorphine. This term implies that a given drug may exert agonist or partial agonist activity at one opioid receptor subtype while exerting an antagonist action at a different opioid receptor subtype.

**Table 5.2** Actions and selectivity of opioids at opioid receptor subtypes (μ, δ, and κ).

| | Receptor | | |
|---|---|---|---|
| **Drug** | **μ** | **δ** | **κ** |
| Morphine | +++ | + | + |
| Methadone | +++ | + | |
| Etorphine | +++ | +++ | +++ |
| Fentanyl | +++ | + | |
| Sufentanil | +++ | + | + |
| Butorphanol | p.a. | | ++ |
| Buprenorphine | p.a. | | ant. |
| Pentazocine | p.a. | | ++ |
| Nalbuphine | ant. | | + |
| Diprenorphine | ant. | ant. | ant. |
| Naloxone | ant. | ant. | ant. |
| Naltrexone | ant. | ant. | ant. |

*Note:* + = agonist; p.a. = partial agonist; ant. = antagonist.

As indicated in Table 5.2, compounds such as morphine and etorphine exhibit a preference for μ-opioid receptors but also activate δ- and κ-receptors with lower affinity. Similarly, the opioid receptor antagonists, naloxone, naltrexone, and diprenorphine are promiscuous in the sense that they do not discriminate well between opioid receptor subtypes.

Veterinary pharmacology of opioids is characterized, and complicated, by the dramatic species differences that exist with regard to drug-induced responses. As with humans, morphine activation of μ-opioid receptors produces CNS depression in the dog and monkey, whereas excitation is observed in the cat, horse, goat, sheep, pig, mouse, and cow. The excitatory effects of opioids such as fentanyl have indeed been used illegally in racehorses. The physiological basis for these species differences in response to opioids is poorly understood, but is likely a function of the distinct distribution and/or density of opioid receptors in the neurocircuitry of the limbic system. The "morphine mania" that is characteristic in cats is avoided by either repeated administration of small doses or concurrent administration of an antipsychotic (neuroleptic) or sedative. In all species, however, morphine and related opioids are capable of relieving intense pain associated with injury or surgery.

The chronic administration of opioids such as morphine to laboratory rodents produces a sensitization to the locomotor-enhancing effects of these drugs. This sensitization, or reverse tolerance, also develops to the oral gnawing stereotypy observed in rats (Kornetsky 2004). This sensitization in response to chronic exposure to an opioid indicates that a long-lasting change in opioid receptor signaling mechanisms develops that is distinct from those mechanisms subserving tolerance development to particular pharmacologic actions of opioids. A hyperactive endogenous opioid neurotransmission caused

by opioid receptor sensitization may be involved in the expression of animal behavioral stereotypies. This may have relevance to the effectiveness of opioid antagonists in stereotypic self-licking and self-mutilation behavior in dogs and horses (Dodman et al. 1987, 1988). The effectiveness of opioid antagonists such as naltrexone, naloxone, and diprenorphine may therefore be related to their ability to reverse or attenuate a sensitization that develops to endogenous opioid peptide activation of opioid receptors. Antagonists such as naltrexone, naloxone, and diprenorphine are nonselective and also interact with kappa-opioid receptors (KOR). KORs are expressed in the brain, spinal cord, and peripheral tissues in structures related to pain circuits such as dorsal root ganglia (Hall et al. 2016). KOR agonists have antinociceptive effects without the characteristic adverse effect profile associated with μ-opioid receptor activation (Hall et al. 2016). KOR agonists do, however, have the potential to induce dysphoria in animals.

In the context of the treatment of self-mutilation stereotypies, one other aspect of the pharmacology of compounds structurally related to opioids that deserves discussion is the effectiveness of dextromethorphan. This compound is the stereoisomer of levomethorphan, a potent morphine-like analgesic. As described earlier in this chapter, opioid drugs display pronounced stereospecificity with respect to their ability to bind to opioid receptors. Thus, the levorotatory isomer of morphine, l- or (–) morphine, is pharmacologically active while the dextrorotatory isomer, d- or (+) morphine, is essentially inactive. Similarly, the levorotatory isomer levomethorphan substitutes for morphine whereas its dextrorotatory isomer dextromethorphan is over 1000-fold less active at opioid receptors. The inactivity of dextromethorphan at opioid receptors does not, however, generalize to the NMDA subtype of glutamate receptor where this compound acts as a potent noncompetitive antagonist (Franklin and Murray 1992). Dextromethorphan is widely used in human medicine as an over-the-counter antitussive drug. Dextromethorphan has been demonstrated to reduce stereotypic cribbing in horses and self-directed mutilation stereotypies in dogs (Dodman et al. 2004; Rendon et al. 2000). This pharmacologic effect of dextromethorphan may be presumed to derive from its ability to antagonize glutamate activation of NMDA receptors in the CNS.

## Oxytocin

The neurohypophyseal hormone oxytocin (OT) regulates biological functions in both peripheral tissues and the CNS. OT is a critical mediator for two of the fundamental defining reproductive characteristics in mammals, namely, placental birth and lactation. OT has also been shown to be critical in the formation and maintenance of mother–infant bonds in mammals and in the regulation of social behavior beyond the maternal context, including social attachments among adults, social cognition, and aggression (French et al. 2016). OT signaling impacts forebrain structures that are important in the regulation of attachment, parental care, reward, emotional and social memory.

In mammals, the nonapeptide OT structure is highly conserved with leucine in the 8th position ($Leu^8$-OT). However, in marmosets (*Callithrix*), a nonsynonymous nucleotide substitution in the gene codes for proline in the 8th residue position ($Pro^8$-OT) (French et al. 2016). OT binds to its cognate G protein-coupled receptor (OTR) and exerts diverse effects, including stimulation of cAMP production ($G_s$), inhibition of adenylyl cyclase ($G_{i/o}$), inhibition or stimulation of potassium channel currents ($G_i$), and activation of phospholipase C ($G_q$) (Stoop 2012). In the brain, OT neuron cell bodies are located exclusively in the hypothalamus with projections to both cortical and subcortical structures, including the limbic system (Charlet and Grinevich 2017). In this regard, OT and dopamine neurons project to similar forebrain regions including the prefrontal

cortex, the nucleus accumbens, and striatum, where they control social and affiliative behaviors, such as sexual behavior and pair bonding (Charlet and Grinevich 2017). The distribution of OT and the closely related nonapeptide arginine vasopressin (AVP) neurons and receptors (for OT, the OTR and, for AVP, the V1aR, V1bR, and V2R) have been well characterized in rodents. OTRs in the rodent brain have most prominently been found in the accessory olfactory bulb, the anterior olfactory nucleus islands of Calleja, the central and extended amygdala, the CA1 of hippocampus, the ventral medial hypothalamus, the nucleus accumbens, the brain stem, and the spinal cord (Stoop 2012). This distribution includes substantial overlap with the social behavior network. The social behavior network includes forebrain and midbrain nuclei and has extensive connectivity with the mesolimbic reward system (French et al. 2016).

The OTR can be linked to different G proteins leading to different functional effects. OTR coupling to the pertussis-insensitive heterotrimeric $G_{q/11}$ protein activates the phospholipase Cβ pathway, which accumulates phosphoinositide and mobilizes intracellular $Ca^{2+}$. This pathway underlies uterus smooth muscle cell contraction, and, in neurons, can inhibit inward rectifying conductances (Stoop 2012). In neurons, however, OT can also activate inward rectifying currents through a pertussis-sensitive $G_{i/o}$ protein. In addition, OT can activate adenylate cyclase via coupling to $G_s$ protein and increase cAMP production, which directly leads, without PKA activation, to a sodium-dependent TTX-resistant sustained inward current (Stoop 2012). Considered together both OT and AVP can exert either inhibitory or excitatory effects in the CNS depending on the brain region being studied. These neuropeptides act as neuromodulators, unlike conventional neurotransmitters, in that they do not simply excite or inhibit an electrically excitable cell, but rather alter the effects of other ongoing events occurring at the cell.

In domesticated animals, such as the dog, visual contact with humans has been found to be sufficient to increase OT compared to isolation in dogs, suggesting that there is a positive feedback loop between OT and gazing (i.e. visual contact) in dogs interacting with humans (Rault et al. 2017). Additional physical contact increases OT for a longer duration, and more frequent interactions initiated toward humans correlate with higher OT increase in CSF. Although the OT literature is full of such positive responses, there is contrasting evidence that negative situations also mobilize OT. It has accordingly been proposed that OT may be evolutionarily linked to social coping strategies (Rault et al. 2017).

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# Part II

# Practice of Veterinary Psychopharmacology

# 6

# Introduction to Clinical Psychopharmacology for Veterinary Medicine

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## Introduction

The term *psychopharmacology* derives from three Greek words. *Psyche* means soul or mind; *pharmacon* means drug. Finally, the term *logos* means to study. Thus, psychopharmacology, in a basic sense, is the study of drugs that affect the soul or mind. We are interested in such drugs because psychoactive medications affect the brain's physiology and endocrinology, consequently causing changes in behavior and motivation. Therefore, these drugs can be beneficial for animals with mental health and behavior problems. They have been used with varying results in human psychiatry for several decades, and their efficacy has improved over time as we have come to better understand the complex interrelationships between brain chemistry, emotional states, and overt behavior. We are also developing an improved understanding of the genetics and neuroanatomy of various major behavior problems such as aggression, major depressive disorder, and bipolar disorder (e.g. Krishnan 1999; Vadodaria et al. 2018). Nevertheless, much remains to be discovered.

While a great deal is understood about what happens on cell surfaces, the exact mechanism by which receptors and the molecules that interact with them affect mood and behavior is poorly understood. Progress is being made via *in vitro* growth of neurons derived from psychiatric patients with specific diagnoses (Burke 2004; Vadodaria et al. 2018). The serotonin production, serotonergic receptor activity, serotonin transporter activity, and other specific chemical activity can then be studied from these *in vitro* cells derived from known phenotypes (Vadodaria et al. 2018).

While we can never truly understand the animal mind, we can measure changes in animal behavior that occur as a consequence of the administration of various drugs that enter the brain. We can also place those changes within the context of species-typical social organization and communication to interpret what is likely happening in terms of changes in the emotional and motivational state of the animal. The use of psychoactive medications has rapidly been integrated into the practice of veterinary clinical behavioral medicine because they can often be of tremendous assistance in the treatment of the serious behavioral and mental health problems that are routinely encountered in this field.

Psychoactive medications can be extremely useful in the treatment of mental health conditions and behavior problems in animals, but it is rare for medication alone to provide a cure. In most cases, treatment is most effective if medication is used in combination with

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environmental management and behavior therapy, such as desensitization and counterconditioning interventions. The most common protocols for behavior therapy are defined and discussed briefly in this chapter but are not the focus of this book.

While data on the effect of psychoactive medications on brain pathologies observed in the pet population are increasing yearly, much of the available data on actual efficacy for specific problems is derived from human psychiatric use and extrapolated to use in veterinary clinical behavioral medicine. When using a medication with little historical use in pets, it must be remembered that sometimes medications have different efficacy and different side effect profiles in different species. A medication that works well in humans may work better or worse in a cat or dog, and those species may exhibit side effects never observed in humans. Some drugs, such as tricyclic antidepressants, are safer in cats and dogs than in humans. Wherever possible, data from studies on the use of a given medication in domestic species are provided. Beyond this, drugs that are commonly used by specialists in veterinary clinical behavioral medicine, but about which there is little published data, are discussed with reference to use in humans. Some medications have been used little or not at all in the pet population, but based on their use in humans, might reasonably be tried in pets that have been refractory to better-tested treatments when the owner is willing to take the chance that their species of pet will have a side effect that has not been observed in humans. In all cases, the species from which particular information on clinical use of a medication has been derived will be identified.

## Prescribing in the United States: The Animal Medicinal Drug Use Clarification Act (AMDUCA 1994)

As this book goes to press, the use of most psychoactive medications in veterinary medicine is extra-label. The only label uses of psychoactive medication for the treatment of behavior problems in animals are Clomicalm (clomipramine) for separation anxiety disorder in dogs, Anipryl (L-deprenyl) for cognitive dysfunction in elderly dogs, Sileo (dexmedetomidine) for noise aversions in dogs and Reconcile (fluoxetine) for dogs with separation anxiety disorder. Extra-label use means that the medication has not been approved by the Food and Drug Administration (FDA) for the specific problem and the specific species for which it is being prescribed. Thus, use of Clomicalm for separation anxiety disorder in cats or storm phobia in dogs would be extra-label use. Use of all other psychoactive medications for any behavior problem on any species constitutes extra-label use.

This does not mean that use of medications other than clomipramine, L-deprenyl, fluoxetine or dexmeditomidine is contraindicated for behavioral problems in animals or that the extra-label use of clomipramine, L-deprenyl, fluoxetine or dexmeditomidine is contraindicated. In veterinary clinical behavioral medicine, the off-label status of most drugs means that the substantial safety and efficacy trials required by the FDA for on-label use have not been conducted. In many cases, for economic reasons, such trials will never be conducted, despite substantial scientific evidence that a given drug has a real usefulness, with minimal side effects, for a particular problem in a particular species.

There are specific requirements for extra-label use of any medication, psychoactive, or otherwise. First and foremost, there must be a valid veterinarian-client-patient relationship. The veterinarian must have personally examined the patient and, based on their own knowledge of the patient's physical and behavioral status, determined that extra-label use of medication is appropriate and may be beneficial. To come to this determination, the veterinarian must conduct a physical exam and take both a medical and behavioral history. While some behaviors cannot be

observed in the examination room, objective information about the patient's behavioral history can be gathered by interviewing the owner and other persons who have personally witnessed the problem.

Because of widespread use and some degree of knowledge of psychoactive medications in society at large, it is not uncommon for persons who are not qualified or licensed to make decisions regarding medications to attempt to do so. Dog trainers, behaviorists who are not veterinarians, and others, may attempt to convince a pet's owner and/or the pet's veterinarian to use a particular drug that the veterinarian does not feel is appropriate. Likewise, news shows that mention use of a particular drug in a pet may result in many calls to veterinarians in the area requesting that the drug be prescribed. In all cases, it must be remembered that the decision regarding which drug to use for a given problem in a given pet is the veterinarian's responsibility and therefore the veterinarian's decision. It is likewise the veterinarian's responsibility to remain current in her or his understanding of the use of psychoactive drugs. When a prescription is written for a given medication, the veterinarian must have a specific rationale for the use of that medication in that patient, and its use must be accepted under current standards of evidence-based clinical behavioral medicine.

Because some psychoactive medications are used very commonly and to good effect for behavior problems, it can be easy to slip into habits of treating such medications as if their use was on-label. In all cases of extra-label use of medication, however, clients should be informed of the extra-label status of the drug and of what the term extra-label means. Clients should be informed of known side effects and the risk of novel side effects occurring in their pet. An informed consent statement that describes the extra-label status of the drug, explains why the medication is being prescribed, lists known side effects, and states the risk of novel side effects can be provided to the client. One copy can be provided to the client to take home for reference and a signed copy kept in the patient's medical records.

When prescribing psychoactive medications, one should keep in mind that some have the potential for human abuse. For example, diazepam, which can be very helpful for a variety of phobias, is a Schedule IV drug that has a rapid onset of effect and is addictive. Methylphenidate, used in dogs with true hyperkinesis, is a Schedule II drug that is sold illegally. It is essential that detailed records be kept of the exact prescription and that the patient be monitored closely for response.

Also, the practitioner must follow specific state laws regarding prescribing such medications. For example, in Georgia, as of 2003, U.S. Drug Enforcement Administration (DEA) Class II medications must be prescribed in writing only. Telephone prescriptions can be done on an emergency basis, but there must be a written follow-up within one week. DEA Class III–IV drugs can have five refills or up to six months' prescription written. Laws covering these details will vary from state to state and country to country. Some of the drugs discussed in this book cannot be used legally in certain countries. In all cases, it is the veterinarian's responsibility to be aware of both national and local laws that apply to the individual's practice.

Because of the nature of behavioral and mental health problems in pets, it is often not advisable to provide prescriptions for long periods without rechecking the patient in person. Since progress, behavior therapy techniques, environmental management, and physical health must be monitored, all patients on psychoactive medication should come in for outpatient rechecks regularly for a prescription to be continued. At this time, progress and prognosis are assessed and the medication may be changed, the dose increased or decreased, or the medication be continued as during the previous months.

## Cost

Unlike human medicine, where cost issues are often of low priority when making a decision as to which medication to use, cost

is often a significant issue in all areas of veterinary medicine, including clinical behavioral medicine. Large chain pharmacies can often offer significantly lower prices than small, individually operated and owned pharmacies. However, the latter are sometimes the only viable source of special compounding that may be needed for particular patients. The cost of a daily dose can also vary with how much medication is purchased at one time, especially if compounding is required. Often, medication is less expensive if bought in bulk, for example a 90-day supply as opposed to a 30-day supply. For cats and parrots, many medications must routinely be compounded. For cats and small dogs, if tablets are available, they can be reasonably split into smaller doses than allowed by the scoring with the use of a pill cutter.

For some patients that can be pilled but that refuse to consume flavored liquids, and will even spit them out, compounding into small capsules will be necessary. While initial purchases should be small in order to allow time to determine if the pet does not exhibit serious side effects and does respond positively to the medication, clients may obtain considerable savings over the long term if a bulk purchase is made once long-term use is expected. Because some psychoactive medications can be expensive, it is recommended that the practitioner is aware of the relative costliness of these medications at pharmacies in their area and via legitimate mail order pharmacies and that clients contact multiple pharmacies to get price quotes for their specific prescription.

## Drug Selection

Specific information on drug selection will be given in the chapters on various classes of drugs; however, there are certain general considerations that will be discussed here. First, it is important to remember that our understanding of drug selection for specific behavior problems is changing rapidly as new clinical trials are completed and studies are published. Thus, some statements made in this book will become outdated as a result of new research findings. It is important for the practitioner to keep up to date with research publications.

Each patient is a unique individual. At this time, we can only choose what to use based first on the species, the diagnosis, and the health status of the individual patient in a combination of evidence regarding the efficacy of various medications for the particular problem being treated. However, if the first medication used is not effective or generates unacceptable side effects, it is not necessarily the case that no medication will work. Sometimes a different medication in the same class of drugs will work well, even if the first medication was ineffective. Sometimes a medication from a totally different class is required. Sometimes combinations or augmentation are required. Using combinations in particular requires that the clinician understand exactly how each medication works in the brain so that overdosing and adverse drug interactions do not occur. Details of using combinations of drugs are discussed in Chapter 19, as well as throughout the discussion of specific medications.

When choosing a drug, selectivity of mechanism is an issue that has at times been considered advantageous in human psychiatry. However, the topic is controversial and will not be discussed in depth in this book. In general, a potential advantage to multiple mechanisms of action in a single drug, for example, norepinephrine reuptake inhibition and serotonin reuptake inhibition, is possible increased robustness of efficacy. This presupposes that both or all of the multiple mechanisms of action in some way benefit the particular patient's problem. A potential problem is a greater possibility of multiple side effects. Better decision-making protocols on this issue will be more feasible when very exact relationships are discovered between specific behaviors or behavior problems in a given species and a particular molecular

action in the brain. The following should always be considered when choosing a medication:

What are the species and signalment?
What is the diagnosis?
Is the drug being considered indicated for that species, signalment, and diagnosis?
How experienced is the veterinarian with the drug or drug combination?
Are there any studies published on the actual efficacy for this diagnosis? If so, what is the actual efficacy?
What is the side effect profile?
What is the health status of the patient? Does the patient have any conditions that are contraindicated with this drug?
How much is cost an issue of concern for the client? How expensive is the drug?
What other drugs have been tried, and how did the patient respond?
How can the patient be medicated? If special forms of dosing are required, can the drug be provided in those forms, for example, a palatable liquid to be hidden in food?

## Medicating the Patient

Often there are issues of the patient being resistant to taking medication. This is particularly problematic if the medication has an unpleasant taste, which is the case with undisguised tricyclic antidepressants. Also, many medications must be given daily for a long period of time. For the patient that is fearful and/or aggressive, which are common problems, the difficulties are compounded. Owners may not be able to handle the pet without frightening it, and they may also run the risk of being bitten if they attempt to force-pill the patient. Different approaches are helpful for dogs and cats, but in general developing some routine of food intake prior to beginning medication can be useful.

Many dogs gulp highly palatable foods without pausing to taste. This is especially the case if a routine has been established with a highly palatable food. If the owner and dog do not already have such a routine, it can be initiated by first offering a highly palatable, small, semifirm amount of food. This can be a piece of hot dog, cheese, canned dog food that is not too moist or one of the various pill pockets that are on the market. It should be offered in whatever fashion works best for the patient. Tossing works well for some dogs, who will catch the treat and gulp it. Other dogs will respond best if they are hand-fed or if the treat is offered on a small plate. Once the dog consumes the treat rapidly and without pausing to chew, a pill or capsule can be hidden in it. Pilling should always be followed by the reward of a highly palatable treat.

For the cat that cannot be pilled at all, it may be necessary to hide the medication in palatable food. First, identify a food that the cat finds very desirable, such as tuna fish, a particular brand of canned food, or shredded chicken. Begin offering the cat a small amount of the food on a regular routine. Have the medication compounded as a liquid that is compatible in flavor with the treat, for example, tuna juice. Then begin mixing the medication in with the treat. If the cat rejects a full dose, it may be necessary to initially mix in a partial dose. The dose can then be gradually increased over several days until the cat is eating the complete dose.

Transdermal medication of cats that are difficult to medicate would be desirable if it was effective. However, research to date on azapirones, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants has invariably identified this method of medication to be ineffective. Blood levels of drugs administered transdermally are substantially lower than blood levels of drugs administered orally (Ciribassi et al. 2003; Mealey et al. 2004). Raising the level of drug in the transdermal medication to levels that produce comparable blood levels might result in dermatitis.

Because of the difficulty in medicating veterinary patients, slow-release forms of various medications are desirable so that a

single action of medicating the patient can result in the long action of the drug. Slow-release forms of several medications have been developed for humans. However, in all cases remember that the medications have been designed for the human digestive tract, which is substantially different physiologically from that of the carnivorous cat and dog and the herbivorous rabbit and horse. Thus, rates of absorption are likely to vary substantially in these species from the rates that occur in humans.

## Competition Animals

Treating nonhuman animals that are shown in conformation or performance classes or that are raced presents special ethical and legal issues. Many organizations that oversee the racing, conformation competition, and performance competition of purebred animals specifically prohibit the use of psychoactive medications, at least during competition. It is because of the problem of illegally doping racehorses with psychoactive medications during racing that we have data on the pharmacokinetics of several drugs in the horse. Other organizations, especially small, breed-specific organizations that foster interest in a breed or activity in which there are not large amounts of money at stake, allow medication, at least under certain situations. Such situations might include the treatment of a behavior problem diagnosed by a veterinarian and with notification of the judge that the animal is on medication for the diagnosed problem. When treating purebred animals that are placed in any form of competition, it is important to communicate openly with the owner and, as appropriate, the organization sponsoring the competition, as to whether or not certain medications are allowed. The owner may have to make a choice between continuing to enter their animal in competitions or using medication. Sometimes it is legal and desirable to remove the patient from competition for a period of a few months while the problem is treated, after which it might be legally returned to competition once all traces of medication have been metabolized and cleared from its system.

The existence of serious behavioral problems in animals owned for competition of any sort also begs the question of breeding that animal. Animals with significant behavioral problems should probably not be bred. This issue should be discussed with the owner if they are likely to breed an animal with a behavior problem.

## Taking the Behavioral History

As discussed above, a diagnosis must be arrived at before a decision is made on which drug or drugs to use. Coming to a diagnosis requires that a detailed behavioral history be taken. This applies to cases that are entirely behavioral or psychological in nature as well as cases that involve an interaction between behavior problems and medical problems or behavior problems and physical injury. An example of the latter might be a traumatic injury that the patient licks at and mutilates even when the original injury has healed entirely.

Behavioral histories can be collected in two main ways. First, a standardized form can be provided for the client to fill out. This technique can be particularly useful in the case of a client who brings up a behavior problem during a routine exam for which 10 or 15 minutes of the veterinarian's time have been scheduled. This will not be adequate time to address a serious problem. However, the moment can be used to verify that the client's pet has a problem that requires a longer appointment with the veterinarian in order to address. The client can be given the history form and instructed to make an appointment to return for a behavioral evaluation or a referral to a specialist can be discussed. Ideally, the client should mail the form back in advance so that the veterinarian has the time to review it before the client and patient return. The other way that information can

be collected is by a direct interview. The direct interview has the disadvantage that some clients will digress at length, requiring skillful interviewing techniques to tactfully bring them back to the problem at hand. The advantage is that information can often be obtained that is not likely to come out on the written form.

A blended technique involves using both means of collecting history. Have the client fill out the written form in advance and either mail it to you or turn it in upon arrival for the appointment. Read the written answers before entering the room with the client. From those responses, develop a list of questions that build on the information you have obtained from the initial document. The history needs to include the following seven areas: signalment, problem behaviors, current environment, early history, any types of interventions or training methods attempted, miscellaneous behaviors, and medical history.

The signalment gives information about probabilities of certain diagnoses with given chief complaints. If the complaint is elimination of urine in the house, cognitive dysfunction is more likely in a 12-year-old than in a 7-year-old dog, while it does not occur in a 2-year-old. If the complaint is owner-directed aggression in a cat, play aggression is more likely in a 2-year-old than in a 12-year-old.

A great deal needs to be learned about the main problem behavior or chief complaint. First, it is necessary to get a good description of what behavior it is that the owner perceives as a problem. Owners often initially give their subjective interpretation of the behavior, rather than describing what the pet is actually doing and what its body language looks like. It is necessary to get a specific description of exactly what is happening, with objective indicators of intensity, frequency, duration, and recovery time. For example, the owner may say that their dog "gets angry" whenever they go near the food bowl while it is eating. In the author's experience, the following diversity of scenarios may lead to the use of this phrase.

1) My dog lowers his head and tucks his tail between his legs whenever I get near while he's eating. Then he'll just cringe and stare at the floor so long as I'm near. If I stay for long, he may start growling.
2) My dog stops eating whenever anyone gets near him. If I stand by his food bowl, he'll walk away.
3) Once I put the food bowl down, I leave the kitchen. If I don't leave fast enough, my dog will chase after me, barking, and growling. I've been bitten twice when I didn't leave fast enough. Everyone knows to stay out of the kitchen while he's eating.

These three dogs clearly have three very different problems. However, owners may use the same subjective language in interpreting those problems. Since the veterinarian needs to make a diagnosis based on facts and clinical indicators, not opinions and interpretations, it is essential to get descriptions of what the patient is doing that is a problem. A phrase that can be helpful in leading the client into this is: "Can you describe what (your pet) does that makes you say he/she is angry (or sad, jealous, spiteful, depressed, etc.)? What is his/her body language like?" Most people will understand what is needed once this question has been posed two or three times and will begin giving objective descriptions. A few will say things like "Oh, you know. He just acts jealous." At this point, it may be helpful to ask the client to pretend that they were a neutral observer, totally uninvolved in the situation, or to pretend that they witnessed the pet's behavior on TV. Again, from this point of view, ask them to describe what the problem pet and other involved people and animals actually did. It may require the description of multiple specific incidents for any underlying patterns to become clear. In the case of aggression, get complete, detailed descriptions of every incident of aggression that the client can recall. It may be necessary to get information from multiple people, because the client may not have personally witnessed some of the

important incidents. For this reason, it is often desirable to have the entire family, or at least multiple family members, present for the interview.

Beyond a good description of what is actually occurring, several specific pieces of information are needed. When did the problem begin? As a general rule, problems of long duration are more difficult to resolve than problems of recent onset but that depends on the etiology or neurophysiology that is behind the behavior. However, duration of the problem can affect the prognosis. Problems of long duration are likely to have undergone progressive changes in behavior and brain remodeling. For example, a feline elimination behavior problem that began as avoidance of the dirty litter and/or separation anxiety disorder when the owners were absent on vacation may have evolved into a location preference for the carpet under the dining room table and, most recently, into a generalized carpet preference. Changes over time in manifestation of the problem and in probable causes of the problem need to be examined carefully throughout the history-taking procedure.

The examining veterinarian also needs to know the frequency of the problem behavior and the circumstances in which the problem occurs. The frequency is needed in order to have baseline information from which to evaluate response to treatment. Spraying three times a week can be good or bad, depending on whether the patient was spraying two times a month or 10 times a week at the beginning of treatment. Information about the circumstances in which the problem behavior occurs can lead to improved understanding of the motivation for the behavior and, possibly, to identification of circumstances that the owner needs to avoid with environmental management. For example, if an aggressive cat is particularly prone to attacking a woman when she is wearing a broomstick skirt, it may be necessary for her to discontinue wearing broomstick skirts when at home, at least temporarily.

Changes in the frequency or form of the problem that have happened over time also need to be identified. Changes generally happen for a reason; understanding why the change has occurred will lead to a better understanding of the problem and, hence, identification of a specific treatment.

It is important to know what has been done so far to attempt to correct the problem. Clients may have read books, found information on the Internet or taken advice from unqualified professionals. Again, find out exactly what they actually did, and do not rely on client familiarity with behavioral jargon. The author has frequently had clients tell her that they had already tried "desensitization," only to learn that, in fact, they had not done so. Either the technique had been incorrectly described to them, or they had not understood the technique, or they had not adapted the technique to their pet's specific needs. In contrast, if they have been trying something that seems to be working and that is appropriate, instruct them to continue. Sometimes a technique has been working, but has stopped working because the pet has reached a stage at which it needs a modification of the technique in order for progress to resume. Find out the specific dosages and dosing schedules that have been prescribed by other veterinarians. Find out exactly what the client did, as well, because they may have modified the original instructions for various reasons. It is not uncommon to find that a suitable medication has been previously prescribed, but at only the lowest dose, and the client discontinued the medication when it didn't work at that dose. Alternatively, the client may have given the medication more or less frequently or at a lower or higher dose than prescribed without telling the veterinarian who originally prescribed the drug. The author has found it to be important, as a matter of routine, to ask referring veterinarians exactly what dosage schedule they prescribed and to also ask the client the exact schedule by which they medicated their pet.

Client education about what to expect from psychoactive medications and how to dose is

critical. For example, SSRIs may not take effect for four to six weeks with daily dosing. However, many of my clients have been giving them only on an as-needed basis and decided from that schedule that the medicine doesn't work. Also verify exactly what side effects the patient has experienced with a particular medication. This information may tell you that the medication is contraindicated with this particular patient or that the client needs further education about the medication. For example, some pets experience transient, mild sedation of a few days' duration when first put on a SSRI. Usually, they recover from this in one to two weeks and return to normal levels of activity. Clients who have not been warned of this potential side effect may have taken their pet off medication or decreased the dose too early in the treatment and done so without telling their veterinarian.

A different area for discussion is the question of whether there are other behavior problems besides the chief complaint that caused them to bring their pet to you in the first place. While some clients will state that the pet is "perfect" except for that one problem, others will have a short or long list of other dysfunctional behaviors they do not like or perceive as a problem. In some cases, the other problems will be even more serious than the presenting complaint. The client may have brought the pet in for the original complaint because they heard through some means that this problem was treatable. The client may have assumed that the other problems were untreatable and would not have brought them up except for your specifically asking. Sometimes the client will not have mentioned other problems because he or she considers them minor. If it turns out that the pet has multiple problems, it is good to make a problem list and have the client prioritize them as to which he or she most wants to have treated first. Sometimes it is not possible to treat two particular problems at once because there is some degree of conflict in the treatment techniques for the two problems. More often, the problems cannot all be addressed at once simply because even the most dedicated client has a finite amount of time they can spend helping their pet. On the other hand, in some cases, different problems can be caused by the same etiology or brain pathology. This is commonly the case with generalized anxiety disorder, which can cause several secondary phobias. Often, the frequency, duration, and severity of the episodes will decrease once the patient is treated for the main condition.

The patient's current environment has many facets, any, or all, of which can affect behavior. Main categories are: (i) the humans in the environment; (ii) other animals in the environment; and (iii) the physical environment, which includes all aspects of housing and management.

Regarding the human environment, it is important to know who lives with the pet or is a frequent visitor. This will include all family members who live in the home, but may also include housekeepers, babysitters, gardeners, and other domestic personnel. Identify when individuals are typically at the house and how they interact with the patient or are involved with the patient's care. Also ask if there have been any significant departures, especially around the time the problem began. Examples would include older children leaving for college and spouses who have departed due to separation or divorce.

Also find out what other animals, typically but not necessarily household pets, interact with the pet. The species, gender, age, and behavioral relationship with the patient should be identified for all household pets. An example of non-pet animals that may be of importance would include neighborhood cats or dogs that frequently visit the yard or even house. This is of potential significance with urine marking and any stress-induced behavior problem. A different example would be a large number of squirrels living outside that cause frequent arousal in a patient that has arousal-induced aggression.

The degree and type of detailed information about the environment that will be needed

will necessarily vary somewhat with species and chief complaint. The following basic information should always be obtained: (i) a description of the housing the patient lives in, for example, the size of the house and what areas of the house the patient has access to and, in the case of dogs, whether or not the backyard is fenced; (ii) information about diet and feeding schedules; and (iii) the entire daily routine for handling and caring for the patient. In the case of cats, identify how many litter boxes there are in the house, whether or not they are hooded, what type of litter is in them, where they are located in the house, and how often they are cleaned. Much of this will be important background information that you will need in designing your total treatment program.

Learning the early history is not always useful in coming to a diagnosis or designing a treatment program (although it is important for prognosis evaluation). However, sometimes quality information is identified that may help the owners better understand their pet. If there is a background of abandonment, owners are likely to be more sympathetic to their pet's current difficulty with being left alone. Information to obtain includes the source of the pet, the age when obtained, and any information that is available about previous owners, including the pet's possible experiences with them, such as abuse, and their reports about the pet's early behavior.

Learning about training and other structured learning experiences the patient has had is important with all species, but especially with species that typically undergo extensive formal training, such as the dog and the horse. The veterinarian needs to be familiar not only with ethical and appropriate training techniques, but also with commonly used abusive training techniques and devices. While there are many ethical and competent animal trainers, there are also, unfortunately, plenty of unethical and abusive animal trainers. Owners sometimes take their pet, in good faith, to a trainer whom they do not realize is using abusive and inappropriate techniques. Impressed by advertising and the charisma of the trainer or simply due to ignorance or despair to resolve their pet's problem, they may leave the pet with the trainer or do things to the pet under the trainer's directions that make them uncomfortable, make their pet afraid or even hurt them. In taking the history, first get a good description of exactly what has been done to the patient. If there are problems, explain objectively why they are problems. In cases of clear abuse, the trainer should be reported to the state veterinarian's office. Often, owners feel guilty about what has happened to the pet. This is especially likely to be the case if they stood by while the pet was mistreated and the mistreatment has now resulted in a major behavior problem, typically fear of people or fear-induced aggression. Some owners will become defensive, both of their own actions and of their trainer. In this case, calmly conducted client education about appropriate animal training techniques is essential.

Often, operant conditioning-based techniques are involved in a treatment program's behavior therapy interventions. Understanding a pet's response to various learning situations will be important. For example, the author once worked with an aggressive dog that was often tense during interactions with the family. However, the command "Gimme five," which meant to raise the paw to be touched by the palm of a human family member, consistently resulted in relaxation and an amicable interaction. The command "Gimme five," accompanied by a treat, was an important part of the initial phase of treatment.

Miscellaneous other behaviors that need to be touched on briefly or in depth, depending on the chief complaint, include sexual behaviors, maternal behaviors, and grooming. In particular, grooming, in all of its aspects of bathing, brushing the coat and teeth, clipping the nails, and cleaning the ears can be a source of historical problems that the family has simply accepted. However, identifying what parts of grooming result in

behaviors of escape, fear, or aggression can be essential to understanding the patient. It is important to ask about the patient's behaviors of self-grooming, as well. Early cases of obsessive-compulsive disorders, discussed below, may manifest as simple increased amounts of grooming with lesions just beginning to develop, which the clients will not have thought to mention.

If you have been the patient's veterinarian its entire life, you will know its medical history. Often, though, you will treat patients who have been previously cared for by one or more other veterinarians. If at all possible, obtain copies of the medical records from all previous veterinarians. Medical issues of particular relevance include: (i) illness, injuries, or elective surgery that occurred around the time the problem began; (ii) chronic medical problems; and (iii) previous or current medication for the behavior or other problems.

## The Behavioral Exam

While you are taking the history, even if it is a brief history to supplement a written history given to you by the owner, you will be able to conduct your initial direct behavioral exam of the animal. For horses and other large animals, it is ideal that this initial interview be conducted in a location where you can comfortably observe the patient as you talk with the client. You may be able to observe the actual problem, for example, cribbing or head shaking, but also discern such important information as whether or not the horse is constantly alert and never relaxes, avoids people, rushes people with its ears pinned back, approaches people and solicits attention, etc. Likewise, with dogs, which will usually be observed in the exam room, note what signaling the patient sends to the human family members, yourself, and your staff. If there are any concerns about aggression to you or your staff, the patient should be kept on a leash at all times. Otherwise, allow the patient to wander freely around the exam room so that you can note its general demeanor, for example, hiding under a chair, curiously investigating the exam room and visiting people, or climbing into the owner's lap and soliciting attention. If there are serious concerns about possible biting incidents, the patient should be wearing an appropriately fitted basket muzzle. It is essential that a basket muzzle be used so that the patient can pant and drink water. Most patients can be taught to calmly accept the basket muzzle, or even voluntarily place their muzzles into it, by pairing wearing of the basket muzzle with receipt of delicious food treats.

In the case of other pets such as cats, parrots, and rabbits, again, much can be learned by direct observation of the patient. Unless it is not safe to do so, allow the patient to move freely around the exam room while you interview the client.

Sometimes it is desirable to do a specific, direct exam of the behavioral responses of the patient to specific stimuli. Before doing this, carefully consider what you have learned from the owner and from direct observation of the pet's spontaneous behavior and what is safe to do.

Finally, it is important to discuss with the owners what their specific goals are for their pet. Discuss whether or not the goals are realistic and potentially attainable and give an initial estimate of how long it is likely to take to achieve their goals. While we may think, based on prior discussion, that we understand the owner's goals, we may not.

## Duration of Treatment

Once a patient's problem has been diagnosed and a treatment plan devised, a common question is how long the treatment will take. Many owners are concerned that their pet will have to be on medication for the rest of its life. The exact duration will vary not only with the treatment, the species, and the problem, but with the individual patient. Also, the family's ability to follow through with management changes and behavior therapy interventions will affect the duration of treatment.

Nevertheless, behavior problems and anxiety disorders are not cured in a week or 10 days. The goal is remission of clinical signs whenever possible. Commonly, several months are required and so are maintenance therapy and management. Severe or refractory cases may take years or never completely resolve or go into remission. When treatment is initiated, the authors instruct the owner that our goal is, first, to identify and conduct treatments that entirely resolve the problem. After that, treatment should be continued for several months after the problem appears to be resolved. A gradual weaning process can be discussed but, depending on the original diagnosis, the client needs to be informed that the patient might relapse clinically. Some anxiety disorders do require lifelong medical management.

## Limitations

Information on FDA-approved and unique uses of medications in humans is given because, sometimes, this can be a valuable reference tool when considering what to attempt with a nonhuman patient. However, some cautions are in order. First, it is important to understand that the fact that Drug A and not Drug B is listed as approved for disorder X does not necessarily mean that Drug B is not useful for disorder X, or even that Drug A is better. It means that the company that owns the patent on Drug A has invested the money in the trials mandated by the FDA to prove that Drug A is better than placebo. It might be the case that Drug B is better for disorder X, but the company owning the patent for Drug B does not consider it economical to seek to obtain approval for disorder X. Or Drug B might be available generically, and there is no company willing to invest the large amounts of money necessary for FDA approval.

Additionally, while human psychiatric disorders and the research on their treatment can sometimes be considered to be models for animal behavioral and mental health disorders, there is not always a good analogy as neurophysiology, neuroendocrinology, and neuroanatomy can significantly differ among species. Looking at the literature on human obsessive-compulsive disorder, patients who are persistent hand washers may seem useful in investigating possible best treatments for dogs that persistently lick their paws. In the long run, it may or may not turn out that treatment of human obsessive-compulsive disorder is a good model for treatment of canine compulsive disorders as these conditions are not even considered to be a single entity in the same species. It is probably a further stretch to look to treatments approved for social phobia in humans and assume that this is necessarily a good model for excessively shy cats. As stated above, the underlying neurochemistry and learning processes may well be different so keeping up with evidence-based neuroscience is paramount. Nevertheless, until more trials are conducted comparing the efficacy of various drug treatments on specific populations, we must rely on the vast literature of human psychiatry as a starting point.

Not all drugs commercially available in a given class are covered in this book, and not all classes of psychiatric drugs are covered. Selection of specific drugs to be discussed is based on a combination of the authors' experience with the medication, published reports on the medication, and current availability of the medication. Some of the newest drugs that have been developed for human psychiatric disorders may have great potential for veterinary patients but are not covered in this edition because of a lack of experience or safety/clinical studies in veterinary populations. Future editions will doubtless include a further expanded drug list, just as this second edition includes drugs that were not in the first edition.

Likewise, while there is some discussion of effects on mice and rats, the extensive and detailed information available in the literature on the various metabolic effects and behavioral changes that occur in laboratory testing are not covered comprehensively,

because such coverage would double the size of this book without greatly increasing its usefulness to the veterinarian whose practice is directed to the care of privately owned domesticated or exotic animals rather than laboratory populations.

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# 7

# Benzodiazepines

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## Action

The benzodiazepines work by facilitating GABA in the central nervous system (CNS). They do this specifically by binding to $GABA_A$ receptors. The behavioral effects are due to action on the hypothalamus and the limbic system.

## Overview of Indications

Benzodiazepines are anxiolytic medications with a rapid onset of action that lasts for a few to several hours, depending on the specific drug and the species. There are specific binding sites in the brain for benzodiazepines, with the highest density being in the central cortex, the cerebellum, and the limbic system (Braestrup and Squires 1977; Möhler and Okada 1977; Danneberg and Weber 1983). There are benzodiazepine receptors elsewhere in the body, for example, on bovine adrenal chromaffin cells (Brennan and Littleton 1991). Thousands of benzodiazepine molecules have been synthesized, although only a small segment of these are available commercially (Sternbach 1973). While thousands of papers have been published on laboratory studies of the effects of benzodiazepines on nonhuman animals and the clinical studies of their effect on humans, few clinical studies or even case reports of their effect on nonhuman animals have been published. Fortunately, there are a few, and some of the laboratory studies conducted on animals provide useful information on such topics as toxicity, half-life and dose–response relationships.

Of the commercially available benzodiazepines, only alprazolam, chlordiazepoxide, clonazepam, clorazepate dipotassium, diazepam, flurazepam, lorazepam, oxazepam, and triazolam will be discussed in this chapter. Benzodiazepines are potentially useful for any problems involving anxiety, fear, or phobia in which a rapid onset of action is desired. Their immediate and discrete efficacy makes them particularly useful for fears that are induced by specific stimuli that can be predicted in advance. Examples of appropriate use include fear-based urination, urine marking, or specific phobias such as storm phobia or separation anxiety with panic, and fear of people (without aggression) in dogs; feather-picking and fear of people in birds; foal rejection due to fear in mares; urine marking, storm phobia, separation anxiety, and fear/anxiety in cats. In humans, benzodiazepines reduce somatic symptoms of generalized anxiety disorder, but do not reduce cognitive symptoms, that is, chronic

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worry (Gorman 2003). Thus, they are probably not an ideal drug of choice for veterinary patients that exhibit chronic anxiety independent of external stimuli. Benzodiazepines with active metabolites, especially diazepam, should be used with caution in cats because of the rare possibility of medication-induced hepatic necrosis.

The use of benzodiazepines in cases involving aggression is controversial. When chlordiazepoxide and diazepam were first released in the early 1960s for use in psychiatry, they were considered to have great potential in the treatment of aggression in humans because in various studies of laboratory animals it was noted that they had an effect of calming and taming "wild" or "vicious" animals (DiMascio 1973). However, the potential initially believed to be present did not turn out to be either consistent or reliable. Effect on aggression varies between species and between individuals and depends on the type of aggression being measured and how it is provoked, the specific benzodiazepine, the specific dose, and whether or not the benzodiazepine is given as a single, acute dose or whether it is given repeatedly over a period of days (see Randall 1960, 1961; Boyle and Tobin 1961; Heise and Boff 1961; Heuschele 1961; Horowitz et al. 1963; Scheckel and Boff 1966; Valzelli et al. 1967; Boissier et al. 1968; Fox and Snyder 1969; Hoffmeister and Wuttke 1969; Sofia 1969; Bauen and Possanza 1970; Christmas and Maxwell 1970; Cole and Wolf 1970; Fox et al. 1970; Guaitani et al. 1971; Langfeldt and Ursin 1971; Miczek 1974; Salzman et al. 1974; Kochansky et al. 1975; Miczek and O'Donnell 1980; Rodgers and Waters 1985; Mos et al. 1987; Mos and Olivier 1989; Olivier et al. 1991; Gao and Cutler 1993; Miczek et al. 1995; Tornatzky and Miczek 1995 for some examples of research on humans and animals that repeatedly identify these discrepancies). While benzodiazepines sometimes decrease aggressiveness, their use sometimes results in increased aggression.

Relief from anxiety can result in the loss of inhibition of behavior (e.g. Margules and Stein 1968). This results in modern textbooks of veterinary behavior being ambivalent on the subject of the use of benzodiazepines in the treatment of nonhuman aggression. For example, Landsberg et al. (2003) state: "Benzodiazepines can be considered for the treatment of any condition that may have a fear or anxiety component, including fear aggression …," but later in the same paragraph they point out that benzodiazepine's "disinhibition could lead to an increase in aggression." In more recent publications, caution is still advised (Horwitz and Neilson 2007; Landsberg et al. 2013). Clinically, just as alcohol or benzodiazepines can result in loss of inhibitions and consequent atypical behavior, including aggression, in humans, so can the use of benzodiazepines result in loss of normal inhibitions and consequent atypical behavior in animals. The challenge is distinguishing between inhibited and uninhibited behaviors, since an animal that is already showing aggression, in theory, is not inhibited. However, that does not mean that the aggressive behavior could not further escalate. In addition, benzodiazepines, particularly diazepam, appear to increase impulsivity (Thiébot et al. 1985), which is a component that, when present in aggressive behavior, is a poor prognostic indicator for nonhuman patients. Generally, lacking good clinical guidelines as to the specific aggression situations in which benzodiazepines might be helpful or risky, they should be avoided or used with extreme caution in cases involving aggressive animals. It is essential that companion animal owners are educated about the potential risks.

The benzodiazepines may result in increases in affiliative behavior. For example, rhesus monkeys (*Macaca mulatta*) treated with chloridazepoxide, diazepam, or lorazepam exhibit increased social grooming, social approach, and social contact (Kumar et al. 1999).

All benzodiazepines are metabolized in the liver and excreted through the kidneys. Therefore, premedication blood work to assess the function of these organs is recommended.

## Contraindications, Side Effects, and Adverse Events

Side effects include sedation, ataxia, muscle relaxation, increased appetite, paradoxical excitation, increased friendliness, anxiety, hallucinations, muscle spasticity, insomnia, and idiopathic hepatic necrosis in cats. The latter has specifically been reported as a response to diazepam.

## Overdose

Treatment of overdose is primarily supportive. Activated charcoal can be used to adsorb benzodiazepines within the gastrointestinal tract. In cats, vomiting can be induced with 0.05 mg $kg^{-1}$ of apomorphine subcutaneously (SC) or 1 mg $kg^{-1}$ xylazine SC. Flumazenil (Mazicon), a benzodiazepine receptor antagonist, can be given to partially or fully reverse the effects. Typically administered intravenously in veterinary medicine, a study with dogs as an animal model for children showed that the intralingual and submucosal routes can be viable alternatives for reversing benzodiazepine sedation (Unkel et al. 2006). That warrants further investigation in companion animals as these options could be practical for hypotensive and hypovolemic patients. Three hours after ingestion, gastric lavage or induction of vomiting is not recommended, because benzodiazepines are rapidly absorbed from the gastrointestinal tract. By this time, gastric lavage or induction of vomiting is not useful and sedation or convulsions will make these procedures counterproductive. Hypothermic patients should be kept in a warm environment. Intravenous fluids can help increase the rate of excretion of the benzodiazepine.

In a study of benzodiazepine poisoning in companion animals, specifically dogs and cats, the 10 most common signs observed in dogs were, in order of prevalence, ataxia, prostration, agitation, vomiting, hyperesthesia, muscle tremors, coma, hypersalivation, aggressiveness, and paresis. In cats, the 10 most common signs were prostration, ataxia, muscle tremors, agitation, coma, mydriasis, polypnea, decubitus, bradypnea, and vomiting (Bertini et al. 1995). Several publications that are more recent have pointed out that the accidental ingestion of an owner's benzodiazepines is common, and highlights the need of veterinarians to discuss safety measures with clients (Campbell and Chapman 2000; Gusson et al. 2002; Wismer 2002; Cope et al. 2006; Cortinovis et al. 2015).

## Clinical Guidelines

Benzodiazepines are DEA Schedule IV drugs. While they are available by prescription, there is potential for human abuse due to both psychological and physical dependency.

Benzodiazepines are excreted through the milk and pass through the placenta. They therefore should be used with caution and generally avoided in pregnant or lactating females.

While benzodiazepines are good anxiolytics, they can have an amnesic effect and sometimes interfere with learning. Thus, they may be more useful in situations in which the control of intense fear is more important than ongoing learning. Nevertheless, the fact that they can have an amnesic effect does not mean that they always do, and research on the ability to learn while under the influence of benzodiazepines exhibits as much variation as research on the effect of benzodiazepines on aggression (e.g. Iwasaki et al. 1976; Vachon et al. 1984; Hodges and Green 1987). The authors have had numerous cases in which learning that was subsequently retained long term clearly occurred while the patient was given a benzodiazepine.

The potential deleterious effects of benzodiazepines for human patients with cognitive impairment and dementia disorders (such as Alzheimer's disease) have been under investigation. Accelerated cognitive deterioration has been reported (Billioti de Gage et al. 2012; Billioti de Gage et al. 2015; Defranchesco

et al. 2015; Pariente et al. 2016). Such studies raise a concern regarding the prescription and long-term treatment of senior and elderly veterinary patients, even though similar investigations have not been carried out in veterinary medicine yet. Benzodiazepines have also been associated with falls in elderly people (Pariente et al. 2008; Ballokova et al. 2014) and increased mortality with long-term use (Charlson et al. 2009). The use of benzodiazepines for sedation of patients with post-traumatic stress disorder has been associated with greater post-intensive care symptoms (Parker et al. 2015).

There is wide variation in the optimum dose for a given patient. It is best to have the client give the pet a test dose in the low range of the dosage schedule at a time when they will be home to watch the pet for several hours. It is also necessary to give clients safety instructions due to the potential of benzodiazepines causing ataxia and incoordination (e.g. blocking access to stairs and balconies), among other concerns such as hyperphagia. In this way they can observe whether their pet has such side effects as paradoxical excitement or sedation at that dose. Paradoxical excitement generally occurs at a specific window of dosage. Therefore, if paradoxical excitement occurs, the dose should be increased, while if sedation occurs, the dose should be decreased. If the patient exhibits no side effects, the medication can then be tried at that dose in the situation that induces fear. If the low dose used at the beginning is insufficient to alleviate the fear, steadily increase the dose until fear is alleviated or side effects are encountered.

Withdrawal of patients that have been frequently dosed with benzodiazepines over a period of several weeks should be gradual. This allows the identification of a specific dose that may still be required to control the problem behavior. Also, sudden termination in a patient that has been continuously on a benzodiazepine for several weeks can result in rebound, that is, a resumption of symptoms that may be more intense than they were before treatment. While specific schedules for decreasing medication will vary with the patient, a general rule is to decrease no faster than 25–33% per week. Many patients will require that the decrease occur more slowly.

In addition to the above considerations, all benzodiazepines have the potential to produce physical addiction. Generally, benzodiazepine dependency in human medicine is associated with high dosage drug regimens, use of benzodiazepines of higher potency and short duration of action, and with long duration of treatment (Riss et al. 2008; Brett and Murnion 2015). However, investigation of these factors is lacking in veterinary medicine and ignores the role of genetics and other physiological factors in physiological tolerance. Different benzodiazepines produce different kinds of physical dependence. In studies of flumazenil-induced abstinence in dogs that had been treated chronically with diazepam, nordiazepam, flunitrazepam, alprazolam, oxazepam, halazepam, and lorazepam, it was found that oxazepam and lorazepam resulted in a less-intense physical dependence than did the other benzodiazepines (Martin et al. 1990). Therefore, if it is anticipated that a dog will need to be regularly medicated with a benzodiazepine for an extended period of time, oxazepam or lorazepam may be a better choice than the other benzodiazepines. Dogs made dependent on diazepam by prolonged administration of $60\,mg\,kg^{-1}\,day^{-1}$ and acutely withdrawn by administration of flumazenil exhibit tremor, rigidity, decreased food intake, and tonic, clonic convulsions (McNicholas et al. 1983).

Tolerance is a phenomenon that also occurs with these medications; that is, when a patient is on a benzodiazepine for an extended period, steadily greater doses may be required to achieve the same behavioral effect (Danneberg and Weber 1983).

Benzodiazepines can safely be used with a variety of other psychoactive medications. Details of these combinations are discussed further in Chapter 19.

The doses of the various benzodiazepines are shown in Tables 7.1 and 7.2.

Table 7.1 Doses of various benzodiazepines for dogs and cats.

| Medication | Dogs | Cats |
|---|---|---|
| Alprazolam (Xanax) | 0.02–0.1 mg kg$^{-1}$ q4h | 0.0125–0.25 mg kg$^{-1}$ q8h |
| Chlordiazepoxide (Librium) | 2.0–6.5 mg kg$^{-1}$ q8h | 0.2–1.0 mg kg$^{-1}$ q12h |
| Clonazepam (Klonopin) | 0.1–0.5 mg kg$^{-1}$ q8–12h | 0.015–0.2 mg kg$^{-1}$ q8h |
| Clorazepate dipotassium (Tranxene) | 0.5–2.0 mg kg$^{-1}$ q4h | 0.5–2.0 mg kg$^{-1}$ q12h |
| Diazepam (Valium) | 0.5–2.0 mg kg$^{-1}$ q4h | 0.1–1.0 mg kg$^{-1}$ q4h |
| Flurazepam (Dalmane) | 0.1–0.5 mg kg$^{-1}$ q12h | 0.1–0.4 mg kg$^{-1}$ q12h |
| Lorazepam (Ativan) | 0.02–0.5 mg kg$^{-1}$ q8–12h | 0.03–0.08 mg kg$^{-1}$ q12h |
| Oxazepam (Serax) | 0.04–0.5 mg kg$^{-1}$ q6h | 0.2–1.0 mg kg$^{-1}$ q12–24h |

*Note:* All doses given are orally and are given as needed until the desired effect is reached. The hourly schedules are the maximum frequency at which the medication should be given. As a general rule, start at the lowest dose and titrate upward if needed. See text for further explanation.
*Source:* Scherkl et al. (1985), Dodman and Shuster (1994), Simpson and Simpson (1996), Overall (1994b, 1997, 2004), Simpson (2002), Crowell-Davis et al. (2003), Landsberg et al. (2003).

Table 7.2 Dose of diazepam for parrots, horses, and rabbits.

| Parrot | Horse | Rabbit |
|---|---|---|
| Two drops of 5 mg ml$^{-1}$ solution per ounce of drinking water | 10–30 mg q8h | 0.1–0.6 mg kg$^{-1}$ |

*Source:* Ryan (1985), Crowell-Davis (1986).

## Specific Medications

### I. Alprazolam

**Chemical Compound:** 8-Chloro-1-methyl-6-phenyl-4H-*s*-triazolo [4,3-$\alpha$] [1,4] benzodiazepine

**DEA Classification:** DEA Schedule IV drug

**Preparations:** Generally available as 0.25-, 0.5-, 1.0-, and 2.0-mg tablets. Also available as a 1 mg ml$^{-1}$ oral solution. The extended release form comes in 0.5-, 1-, 2-, and 3-mg tablets.

#### Clinical Pharmacology

Alprazolam is readily absorbed following oral administration. In humans, peak concentrations occur in the plasma at one to two hours, and the plasma levels are proportionate to the dose given. Mean plasma elimination half-life in healthy humans is about 11.2 hours. However, in humans, changes in absorption, distribution, metabolism, and excretion occur in various disease states; for example, impaired hepatic or renal function. This is no doubt also the case in nonhuman animals. Doses should be decreased in old or obese veterinary patients and in those with impaired liver or renal function (Pharmacia and Upjohn 2001).

The two most common metabolites are $\alpha$-hydroxy-alprazolam and a benzophenone. The benzophenone is inactive, but $\alpha$-hydroxy-alprazolam has about half the activity of alprazolam. Metabolism is initiated by hydroxylation that is catalyzed by cytochrome P450 3A. Therefore, any drugs that inhibit the activity of this metabolic pathway are likely to result in decreased clearance of alprazolam (Pharmacia and Upjohn 2001).

In humans, extended-release tablets are absorbed more slowly than non-extended-release tablets, resulting in steady-state concentration that is maintained for 5–11 hours after dosing. Time of day, consumption of a meal, and type of meal affect the absorption rate (Pharmacia and Upjohn 2001). Since the digestive physiology and typical diet of veterinary patients differ significantly from the

digestive physiology and diet of humans, it is likely that there is substantial variation from the human data.

In African green monkeys, the mean elimination half-life is 5.7 hours (Friedman et al. 1991).

### Uses in Humans

In humans, alprazolam is approved for use in generalized anxiety disorder, anxiety with depression, and panic disorder with or without agoraphobia. Effective treatment of panic disorder requires several months, and withdrawal must be very gradual, taking at least eight weeks, in order to avoid rebound (Pecknold et al. 1988).

### Contraindications

Alprazolam is contraindicated in patients with known hypersensitivity to benzodiazepines, glaucoma, or severe liver or kidney disease. It is also contraindicated in pregnant or lactating females. It should not be given with medications that significantly impair the oxidative metabolism of cytochrome P450 3A, such as the antifungal agents ketoconazole or itraconazole (Pharmacia and Upjohn 2001).

### Side Effects

Side effects typical of the benzodiazepines, including sedation, ataxia, muscle relaxation, increased appetite, paradoxical excitation, and increased friendliness, may occur.

Rats treated with 3–30 $mg\,kg^{-1}\ day^{-1}$ of alprazolam over a two-year period showed a dose-related tendency to develop cataracts in females and corneal vascularization in males. Lesions appeared after at least 11 months of treatment. Rats given doses of alprazolam up to 30 $mg\,kg^{-1}\ day^{-1}$ and mice given doses up to 10 $mg\,kg^{-1}\ day^{-1}$ for a period of two years showed no evidence of increased cancer. Alprazolam has not been shown to be mutagenic in rats. In rats given alprazolam at doses up to 5 $mg\,kg^{-1}\ day^{-1}$, fertility was unimpaired. The $LD_{50}$ (the dose that kills half of the animals tested) in the rat is 331–2171 $mg\,kg^{-1}$ (Pharmacia and Upjohn 2001).

## Overdose

Clinical signs reported in dogs that had consumed overdoses of up to 5.55 $mg\,kg^{-1}$ alprazolam included ataxia, disorientation, depression, hyperactivity, vomiting, weakness, tremors, vocalization, tachycardia, tachypnea, hypothermia, diarrhea, and increased salivation. In 38% of the cases, clinical signs developed within 30 minutes of ingestion. Ataxia typically resolved within 9 hours, but some dogs were ataxic for up to 24 hours. Depression lasted 10–31 hours. There was no correlation between the dose consumed and paradoxical excitement (Wismer 2002).

Treat an overdose with gastric lavage and supportive treatment, including fluids. Flumazenil may be given for complete or partial reversal; however, administration of flumazenil to a patient that has received alprazolam daily for several weeks may result in convulsions.

### Doses in Nonhuman Animals

Initiate treatment at the lowest dose. If no undesirable side effects occur, titrate dose up to the desired effect.

### Discontinuation

If a patient has been receiving alprazolam daily for several weeks, discontinuation should be gradual, and conducted over a period of at least one month.

### Other Information

While liver failure has not been reported in cats or other veterinary patients given alprazolam for behavior problems, it has occurred in humans. While it is a rare event even in humans, liver failure should always be considered as a possible sequela to medication with alprazolam.

Dogs given alprazolam at an escalating dose over 18–26 days until a dose of 12 $mg\,kg^{-1}$ four times a day (q.i.d.) is attained, then maintained on that dose for about three weeks, become physically addicted, as demonstrated by flumazenil-precipitated abstinence (Sloan et al. 1990). These doses are much higher than would be given for the

clinical treatment of anxiety disorders. Acute withdrawal of an addicted dog may result in seizures. Other sequelae to withdrawal reported in humans include insomnia, abnormal involuntary movement, headaches, muscle twitching, and anxiety. Dogs addicted to alprazolam that underwent acute withdrawal due to administration of flumazenil exhibited wild running, barking, and lunging at nonexistent objects, and uncontrolled splaying, rigidity, and jerking of the limbs (Martin et al. 1990). As with humans, veterinary patients that have been on alprazolam daily for several weeks should have their dose gradually decreased.

As with other benzodiazepines, alprazolam is particularly noted for its rapid action. For example, in the treatment of humans with panic disorder, patients treated with alprazolam respond within the first week of treatment, while patients treated with imipramine, a tricyclic antidepressant, respond, but not until the fourth week of treatment (Charney et al. 1986). This rapid response has been observed clinically in veterinary patients, making alprazolam a good choice for dogs that exhibit panic behaviors to the degree that rapid improvement is essential.

#### Effects Documented in Nonhuman Animals

##### *Cats*

While the use of alprazolam to treat behavior problems in cats is mentioned in several textbooks, the authors are unaware of any papers presenting results of clinical use in this species with the exception of a report on humane handling of cats in the veterinary hospital. Anseeuw et al. (2006) suggested using alprazolam to decrease arousal in cats returning home from medical visits, especially if their housemates become reactive upon the reunion.

##### *Dogs*

Crowell-Davis et al. (2003) used alprazolam as part of a treatment protocol for dogs with storm phobia. Alprazolam is most likely to be effective if it is given 30–60 minutes before the occurrence of the earliest stimuli that elicit fear responses, for example, the sound of rain or strong winds. To do this, owners of storm-phobic pets must monitor weather conditions closely. As a general rule for patients with severe signs of this phobia, medication should be given if there is any likelihood that weather conditions that induce fear responses will occur. If, however, the fear-inducing stimuli have already begun and the patient is showing fear when the owner realizes there will be a problem, alprazolam should still be administered. For alprazolam-responsive patients, fear is likely to be somewhat abated, although a higher dose may be required for full relief from signs of fear.

In a case report published by Duxbury (2006), alprazolam was used as an adjunctive medication to a treatment protocol with clomipramine to control anxiety signs during the owner's absence in a dog diagnosed with separation anxiety disorder. Alprazolam was administered orally one hour before departures.

Dogs chronically dosed with increasing quantities of alprazolam until they began losing weight did so at doses of 48 mg $kg^{-1}$ by day 18–28 of the increasing regimen (Martin et al. 1990).

### II. Chlordiazepoxide HC1

**Chemical Compound:** 7-Chloro-2-(methylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride
**DEA Classification:** DEA Schedule IV drug
**Preparations:** Generally available in 5-, 10-, and 25-mg capsules.

## Clinical Pharmacology

Chlordiazepoxide HCl acts on the limbic system of the brain, modifying emotional responses. It has antianxiety, appetite-stimulating, and sedative effects. It is also a weak analgesic. It does not have an autonomic blocking effect, so moderate doses do not affect blood pressure or heart rate (Randall et al. 1960). It crosses the blood–brain barrier, is highly bound to plasma proteins, and is metabolized by the liver. Metabolites generated in

the liver include desmethyldiazepam (nordiazepam), demoxepam, desmethylchlordiazepoxide, and oxazepam (Schwartz and Postma 1966; Kaplan et al. 1970; ICN Pharmaceuticals 1996). These metabolites are active and typically have long half-lives. In humans, peak blood levels are not reached until several hours after taking the medication. Chlordiazepoxide has a half-life in humans of 24–48 hours, and plasma levels decline slowly over several days. Chlordiazepoxide is excreted in the urine, with only 1–2% in unchanged form (ICN Pharmaceuticals 1996).

In dogs, plasma levels peak around 7–8 hours after a single dose of 4 mg kg$^{-1}$ or 20 mg kg$^{-1}$ of chlordiazepoxide. Plasma levels are about half the peak value after 24 hours and chlordiazepoxide is still being excreted in the urine 96 hours after administration. This dose causes mild sedation with high plasma levels for 24 hours in this species. When dogs are redosed daily, there is no cumulative effect on blood levels or sedation. Dogs given doses of 50 mg kg$^{-1}$ by mouth (PO) for six months have shown no adverse effects (Randall 1961). Doses of 10–40 mg kg$^{-1}$ may produce ataxia, while doses of 80 mg kg$^{-1}$ produce sleep when dogs are not stimulated (Randall et al. 1960). Doses of 2.5–20 mg kg$^{-1}$ have an appetite-stimulating effect (Randall et al. 1960).

When dogs are given a single dose of 0.5–0.8 mg kg$^{-1}$ PO, peak plasma levels occur earlier, just two to five hours after dosing, and the half-life is likewise shorter, 12–20 hours (Koechlin and D'Arconte 1963). Seven days after administration of a single dose of 4 mg kg$^{-1}$, 44% of the dose is recovered through the urine, while five days after the same dose an additional 44% is recovered in the feces. Urinary excretion rate peaks at 10 hours after oral administration (Koechlin et al. 1965).

In the dog, demoxepam, one of the metabolites of chlordiazepoxide, has a half-life of 10–20 hours, with substantial individual variation. Some of the demoxepam is subsequently converted to oxazepam (Schwartz et al. 1971). Slightly over 1% (1.1%) of chlordiazepoxide given as a single 26 mg kg$^{-1}$ dose PO or as a daily dose of 5 mg kg$^{-1}$ PO for nine weeks is ultimately excreted in the urine as oxazepam, while an additional 1.3% is excreted in the feces on either regimen (Kimmel and Walkenstein 1967).

Electroencephalographic studies in the cat have shown that the peak drug effect for chlordiazepoxide, when given at 1.25 mg kg$^{-1}$ intraperitoneally (IP), occurs within 90 minutes (Fairchild et al. 1980).

The $LD_{50}$ in mice is 123 ± 12 mg kg$^{-1}$ IV and 366 ± 7 mg kg$^{-1}$ intramuscularly (IM). In rats, the $LD_{50}$ is 120 ± 7 mg kg$^{-1}$ IV and more than 160 mg kg$^{-1}$ IM (ICN Pharmaceuticals 1996). The oral dose $LD_{50}$ is 590 mg kg$^{-1}$ in rabbits, 1315 mg kg$^{-1}$ in rats, and 620 mg kg$^{-1}$ in mice (Randall et al. 1965). In cats, a dose of 200 mg kg$^{-1}$ PO was fatal in five days (Randall and Kappell 1973).

#### Uses in Humans

Chlordiazepoxide is used in the treatment of various anxiety disorders, for short-term relief of symptoms of anxiety, for example, preoperatively, and for relief from symptoms of alcoholism.

#### Contraindications

Chlordiazepoxide is contraindicated in patients with known sensitivity to this or other benzodiazepines. Avoid or use with extreme caution in patients with a history of aggression, because chlordiazepoxide, like all benzodiazepines, may cause loss of learned inhibitions.

Reduced doses should be used in geriatric patients and patients with mild to moderate liver or kidney disease.

Chlordiazepoxide crosses the placental barrier and enters the milk. There is an increased risk of congenital malformations when chlordiazepoxide is given during the first trimester of pregnancy. Therefore, its use should be avoided in pregnant as well as lactating females.

#### Side Effects

Various side effects, including sedation, ataxia, paradoxical excitation, and rage may

occur. In humans, there have been isolated reports of effects on blood coagulation in patients receiving chlordiazepoxide at the same time that they are given anticoagulants. Blood dyscrasias, jaundice, and hepatic dysfunction occasionally occur in humans (ICN Pharmaceuticals 1996). Any veterinary patient that is maintained on chlordiazepoxide for an extended period of time should have complete blood counts and blood chemistries conducted regularly. Tolerance may develop, particularly to the sedative effects (Goldberg et al. 1967).

Two out of six dogs given chlordiazepoxide at 127 mg kg$^{-1}$ died with evidence of circulatory collapse, as did six out of six given 200 mg kg$^{-1}$ day$^{-1}$. Dogs given 80 mg kg$^{-1}$ exhibited nonspecific toxic changes (Wyeth Laboratories Inc. 1999b).

Rat pups of mothers given 10, 20, and 80 mg kg$^{-1}$ during conception and pregnancy had normal growth and showed no congenital anomalies. Lactation of the mothers was unaffected. When rats were given 100 mg kg$^{-1}$, there was a significant decrease in fertilization rate. There was also a decrease in the viability and body weight of the pups. These problems were attributed to the sedation induced at this dose, which resulted in less mating activity and decreased maternal care. Some of the offspring also exhibited skeletal defects at this dose (ICN Pharmaceuticals 1996).

### Overdose

In case of overdose, conduct gastric lavage immediately, then provide general supportive therapy. Administer intravenous fluids and maintain an adequate airway. If excitation occurs, do not use barbiturates. Flumazenil is indicated for the complete or partial reversal of the sedative effects of chlordiazepoxide.

### Doses in Nonhuman Animals

Initiate treatment at the lowest dose. If no undesirable side effects occur, titrate dose up to the desired effect.

### Discontinuation

As with other benzodiazepines, if the patient has been receiving chlordiazepoxide daily for several weeks, discontinuation should be gradual and conducted over at least a one-month period of time.

### Other Information

Chlordiazepoxide has been shown to cause delayed reversal learning and failure to accomplish successive discrimination learning in the rat, although it does not disrupt simultaneous discrimination (Iwahara and Sugimura 1970; Iwasaki et al. 1976).

### Effects Documented in Nonhuman Animals

Taming effects have been noted in multiple species, including monkeys, rats, tigers, lions, dingos, and squirrels at doses that did not induce sedation (e.g. Harris 1960; Heise and Boff 1961; Scheckel and Boff 1966).

#### *Cats*

Laboratory cats given chlordiazepoxide intraperitoneally at doses ranging from 1.25 to 5 mg kg$^{-1}$ exhibited dose-related stimulation and decreased sleep. They were also observed to be playful or mildly aggressive on this medication, although what form of aggression was exhibited is not specifically described (Fairchild et al. 1980). At 10 mg kg$^{-1}$ PO, cats exhibit muscle relaxation when suspended by the scruff of the neck (Randall 1961).

#### *Dogs*

Angel et al. (1982) treated a strain of nervous pointer dogs with chlordiazepoxide or placebo at 3.5 mg kg$^{-1}$ in the morning for seven consecutive days. The dogs' avoidance of humans was significantly attenuated with the chlordiazepoxide treatment, but not the placebo. The dogs' behavior returned to baseline four days after discontinuation of medication (Angel et al. 1982).

Five of eight laboratory beagle dogs with abnormal withdrawn and depressed behavior exhibited improvement when given 5 mg kg$^{-1}$ daily of chlordiazepoxide, while the behavior of all three of three beagles with the same symptoms, given 2.5 mg kg$^{-1}$ daily of chlordiazepoxide, was resolved (Iorio et al. 1983).

Chlordiazepoxide has an appetite stimulation effect in dogs, with a single low dose increasing food intake of fasted dogs. Chronic treatment with chlordiazepoxide for 90 days results in weight gain (Randall et al. 1960).

#### *Monkeys*

Chlordiazepoxide has been used to tame monkeys at a dose of 1 mg kg$^{-1}$ (Zbinden and Randall 1967).

In social colonies of rhesus monkeys, chlordiazepoxide (2.5–5.0 mg kg$^{-1}$ PO daily) produces dose-dependent increases in social grooming, approach, contact, self-grooming, feeding, and resting with the eyes open. There is also decreased vigilance and aggression (Kumar et al. 1999).

#### *Zoo Animals*

A number of zoo animals changed from being aggressive or intensely frightened to being calm, nonaggressive, and even friendly when given chlordiazepoxide. These include a male European lynx (*Lynx lynx*; 6 mg kg$^{-1}$ PO), a female dingo (*Canis familiaris dingo*; 3–7 mg kg$^{-1}$ PO), a female Guinea baboon (*Papio papio*; 13 mg kg$^{-1}$ PO), a male California sea lion (*Zalophus californianus*; 7 mg kg$^{-1}$ PO), a male Burmese macaque (*Macaca nemestrina andamensis*; 5 mg kg$^{-1}$ IM), a female red kangaroo (*Macropus rufus*; 11 mg kg$^{-1}$ PO), a female mule deer (*Odocoileus hemionus*; 2.2 mg kg$^{-1}$ IV), a male white-bearded gnu (*Connochaetes taurinus*; 4 mg kg$^{-1}$ IM), a female gerenuk (*Litocranius walleri*; 5 mg kg$^{-1}$ IM), and three golden marmosets (*Leontocebus rosalia*; 15 mg kg$^{-1}$ PO) (Heuschele 1961).

Animals that did not respond as desired to chlordiazepoxide included a male klipspringer (*Oreotragus oreotragus saltatrixoides*), a female South American tapir (*Tapirus terrestris*), and a Hensel's cat (*Felis pardinoides*) (Heuschele 1961).

## III. Clonazepam

**Chemical Compound:** 5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

**DEA Classification:** DEA Schedule IV controlled substance

**Preparations:** Generally available as 0.5-, 1.0-, and 2.0-mg tablets.

#### Clinical Pharmacology

Clonazepam is completely and rapidly absorbed following oral dosing. In humans, maximum plasma concentrations are reached in one to four hours, with an elimination half-life of 30–40 hours. Dogs given 0.2 mg kg$^{-1}$ IV exhibit an elimination half-life of 1.4 ± 0.3 hours. Most clonazepam is metabolized to various inactive metabolites. In humans, less than 2% is excreted in the urine in an unchanged form. Because extensive metabolism occurs in the liver, hepatic disease may result in impaired elimination. Thus, clonazepam is not the best choice for patients with liver disease. Pharmacokinetics are dose-dependent throughout the dose range (Al-Tahan et al. 1984, Roche Laboratories 2001).

Cats given 1000 mg kg$^{-1}$ clonazepam PO survived. In contrast, cats given bromazepam died at a dose of 1000 mg kg$^{-1}$, while several benzodiazepines proved fatal in cats at much lower doses (Randall and Kappell 1973).

In dogs given 0.5 mg kg$^{-1}$ of clonazepam every 12 hours (q12h) for a period of three weeks, the elimination half-life of clonazepam increases with each passing week. In week one, the average half-life is about two hours, while by week three it is almost eight hours. Acute withdrawal from clonazepam after three or more weeks of treatment has been shown to result in anorexia, hyperthermia, and weight loss (Scherkl et al. 1985). Plasma concentrations in the range considered to be therapeutic in humans can be maintained in dogs by dosing 0.5 mg kg$^{-1}$ two times a day (b.i.d.) or three times a day (t.i.d.) (Al-Tahan et al. 1984).

#### Uses in Humans

Clonazepam is used to treat a variety of seizure disorders and panic disorder.

#### Contraindications

Clonazepam is contraindicated in patients with a history of sensitivity to benzodiazepines, severe liver or kidney disease, or

glaucoma. Clonazepam should not be given to pregnant or lactating females.

Low doses should be used in patients with mild to moderate kidney or liver disease, because their ability to metabolize and excrete clonazepam will be compromised.

#### Side Effects

As with all benzodiazepines, clonazepam may result in sedation, ataxia, muscle relaxation, increased appetite, paradoxical excitation, increased friendliness, anxiety, and hallucinations.

Carcinogenicity of clonazepam has not been studied. Genotoxic studies are insufficient to conclude if clonazepam has any genotoxic potential. In rats given 10–100 $mg\,kg^{-1}\,day^{-1}$ over two generations, there was a decrease in the number of pregnancies and the number of offspring that survived until weaning. With administration of clonazepam to pregnant rabbits during the period of organogenesis at doses ranging from 0.2 to 10.0 $mg\,kg^{-1}\,day^{-1}$, various malformations, including cleft palate, open eyelids, fused sternebrae, and defects of the limbs occurred at a low, non-dose-related rate. Pregnant rabbits given 5 $mg\,kg^{-1}\,day^{-1}$ or higher doses exhibited reductions in maternal weight gain, while reductions in embryo-fetal growth occurred at doses of 10 $mg\,kg^{-1}\,day^{-1}$. However, no adverse effects were observed on the mothers, embryos, or fetuses when mice and rats were given doses up to 15 and 40 $mg\,kg^{-1}\,day^{-1}$, respectively (Roche Laboratories 2001).

Elimination of clonazepam from both plasma and the cerebral cortex becomes slower with age (Barnhill et al. 1990).

#### Drug Interactions

Ranitidine and propantheline, which decrease stomach acidity, and fluoxetine, an SSRI, have little to no effect on the metabolism of clonazepam. Cytochrome P-450 inducers, including phenytoin, carbamazepine, and phenobarbital, facilitate clonazepam metabolism, resulting in a 30% decrease in clonazepam levels in humans. Strong P-450 3A inhibitors, such as oral antifungal agents, should be combined cautiously with clonazepam, because concurrent use may result in clonazepam overdose due to insufficient metabolism (Roche Laboratories 2001).

#### Overdose

Symptoms of overdose that are characteristic of CNS depressants may occur, including sedation, confusion, diminished reflexes, and coma. Gastric lavage should be initiated as soon as possible, followed by appropriate supportive treatment and monitoring of respiration, pulse, and blood pressure. Flumazenil, a benzodiazepine-receptor antagonist, can be used to partially or completely reverse the effects, but should be avoided in patients that have been treated with clonazepam daily for an extended period of time because seizures may be induced.

#### Doses in Nonhuman Animals

Initiate treatment at the lowest dose. If no undesirable side effects occur, titrate dose up to the desired effect.

#### Discontinuation

As with all benzodiazepines, clonazepam should be reduced gradually in patients that have been receiving it on a daily basis for several weeks.

#### Other Information

Clonazepam is not useful in the treatment of myoclonus caused by serotonin syndrome.

#### Effects Documented in Nonhuman Animals

##### *Cats*

In laboratory studies, clonazepam is substantially less toxic to cats than chlordiazepoxide, diazepam, or flurazepam (Table 7.3).

##### *Dogs*

In a case report, Carter (2011) used clonazepam to treat noise phobias in a dog diagnosed with hyperactivity. This dog was treated initially with fluoxetine (which helped control the hyperactivity signs) but the patient still presented with noise phobias. The dog was less reactive to noises within a week of initiation of treatment.

**Table 7.3** Dose at which muscle relaxation is achieved and lethal dose of some benzodiazepines when given orally to cats.

| Benzodiazepine | Muscle relaxation mg kg$^{-1}$ PO | Lethal dose mg kg$^{-1}$ PO |
|---|---|---|
| Chlordiazepoxide hydrochloride | 2 | 200 |
| Clonazepam | 0.05 | >1000 |
| Diazepam | 0.2 | 500 |
| Flurazepam | 2 | 400 |

*Note:* The lethal dose for clonazepam is listed as >1000 mg kg$^{-1}$ because this dose was not fatal, and higher doses were not given. The data are based on only two cats per benzodiazepine, and individual variation in metabolism would be expected to produce a wider range of doses than given in this table. However, the data show the relative differences between drugs in these effects.
*Source:* Randall and Kappell (1973).

#### *Other*

Clonazepam has been shown to have a taming effect on aggressive primates, with concurrent muscle weakness and hypnosis.

## IV. Clorazepate Dipotassium

**Chemical Compound:** Potassium 7-chloro-2,3,-dihydro-2-oxo-5-phenyl-1H-1,4 benzodiazepine-3-carboxylate

**DEA Classification:** DEA Class IV non-narcotic agent

**Preparations:** Generally available as 3.75-, 7.5-, 11.25-, 15-, 22.5-mg tablets and 3.75-, 7.5-, 15-mg capsules.

### Clinical Pharmacology

Clorazepate is metabolized in the liver and excreted in the urine. In the acidity of the digestive tract, it is rapidly decarboxylated to form nordiazepam, also called desmethyldiazepam, which is the active metabolite (Troupin et al. 1979; Greenblatt et al. 1988). Plasma levels of nordiazepam will be proportionate to clorazepate dose. Nordiazepam is further metabolized by hydroxylation to conjugated oxazepam (3-hydroxynordiazepam) and *p*-hydroxynordiazepam (Abbott Laboratories 2004).

Nordiazepam is also an active metabolite of diazepam. Clorazepate provides higher concentrations of nordiazepam over a longer period of time than does diazepam and has less sedative effect (Lane and Bunch 1990).

After administration of a 50-mg dose of clorazepate to humans, 62–67% of the radioactivity was excreted in the urine and 15–19% was excreted in the feces within 10 days (Abbott Laboratories 2004).

As with other benzodiazepines, dogs metabolize clorazepate more rapidly than do humans. After administrations of oral clorazepate, humans have been reported to have a half-life elimination of nordiazepam of 40.8 ± 10.0 hours (Wilensky et al. 1978) or over 80 hours (Boxenbaum 1980). In contrast, the half-life of nordiazepam in dogs is about nine hours (Brown and Forrester 1991).

In humans, Tranxene SD (sustained delivery) has longer efficacy than does the regular-release product, Tranxene. In dogs, there is no difference in either time of peak plasma concentration or serum concentrations two hours after administration. However, 12 hours after administration of a single 2.5–3.8 mg kg$^{-1}$-dose serum concentration of regular release was 24 ± 77.9 ng ml$^{-1}$ of nordiazepam, while serum concentration of nordiazepam with sustained delivery was 215 ± 66.1 ng ml$^{-1}$ (Brown and Forrester 1991). There was no gender effect on disposition of the drug, although this study only involved four males and three females and so cannot be considered conclusive on this issue. Peak nordiazepam concentrations were 372–1140 ng ml$^{-1}$ with the regular release. Peak nordiazepam concentrations were 450–1150 ng ml$^{-1}$ with sustained

delivery. Overall, the bioavailabilities of the two products were not different.

In healthy adult dogs given a single dose of clorazepate orally at a dose of 2 mg kg$^{-1}$ maximum nordiazepam concentrations at 59–180 minutes after administration range from 446 to 1542 ng ml$^{-1}$. After multiple such doses given q12h, maximum nordiazepam concentration is reached at 153 ± 58 minutes and ranges from 927 to 1460 ng ml$^{-1}$. The mean elimination half-life after a single dose is 284 minutes, while the mean elimination half-life after multiple doses is 355 minutes. After multiple doses of clorazepate, there are significant decreases in serum chemical values of albumin, total protein, and calcium, while there are significantly increased concentrations of urea nitrogen and glucose. There are also significant increases in total white blood cell count, segmented neutrophils, lymphocytes, and eosinophils. Urine pH decreases significantly. Also, serum alkaline phosphatase activity increases while alanine transaminase (ALT) values decrease. Despite these changes, all values remain within normal reference ranges after 21 days on 2 mg kg$^{-1}$ b.i.d. (Forrester et al. 1990).

Concurrent administration of clorazepate and phenobarbital in dogs results in significantly lower concentrations of nordiazepam, necessitating higher doses in dogs that are on phenobarbital because of epilepsy (Forrester et al. 1993).

#### Uses in Humans

Clorazepate is used for management of anxiety disorders and short-term relief of anxiety.

#### Contraindications

Clorazepate is contraindicated in patients with a history of adverse reactions to clorazepate and in patients with acute narrow-angle glaucoma. Since clorazepate has depressant effects on the CNS, avoid concurrent use with other CNS depressants.

#### Side Effects

As with all benzodiazepines, sedation, ataxia, muscle relaxation, increased appetite, paradoxical excitation, increased friendliness, anxiety, and a variety of other side effects may occur. Transient sedation and ataxia were observed in one of eight healthy adult dogs given a single dose of 2 mg kg$^{-1}$ of clorazepate (Forrester et al. 1990).

Potential mutagenic effects of clorazepate have not been studied sufficiently to come to any conclusions. However, other minor tranquilizers, for example, diazepam, have been associated with an increased risk of fetal abnormalities if given during the first trimester of pregnancy. Nordiazepam is excreted in milk. Therefore, use of clorazepate in pregnant and nursing females should be avoided.

#### Dependence

As with all benzodiazepines, continuous administrations of clorazepate can result in dependence. In humans, the severity of withdrawal symptoms has been shown to be related to the dose that has been taken. Dogs and rabbits have exhibited seizures when clorazepate was abruptly withdrawn after dependence was established (Abbott Laboratories 2004). In all cases, it is recommended that if a patient has received clorazepate regularly over a period of several weeks, the dose be decreased gradually.

#### Overdose

In case of overdose, immediate gastric lavage and supportive measures should be conducted. Administer intravenous fluids and maintain an open airway. Flumazenil, a benzodiazepine receptor antagonist, can be used to completely or partially reverse the effects of an overdose. Treatment with flumazenil may result in seizures, especially in patients that have frequently been given clorazepate for a long period of time.

#### Doses in Nonhuman Animals

For nonhuman animals, initiate treatment at the lowest dose. If no undesirable side effects occur, titrate the dose up to the desired effect.

#### Effects Documented in Nonhuman Animals

Clorazepate is used in dogs when a long duration of action is desired, for example, in

cases of separation anxiety in which a serotonin reuptake inhibitor has not had time to take effect and the shorter-acting anxiolytics are not sufficient to keep the dog calm while the owner is gone for a full day. Irimajiri and Crowell-Davis (2014) used clorazepate in a dog diagnosed with separation anxiety disorder for 30 days, 30–60 minutes before the owner's departures, while waiting for clomipramine to take full effect. The drug was discontinued as the dog showed consistent improvement, with no problems.

Pineda et al. (2014) investigated the effectiveness of clorazepate used in combination with fluoxetine and behavior modification for the treatment of anxiety disorders in dogs. Thirty-six dogs diagnosed with anxiety disorders (with and without aggressive behavior) completed the trial. Clorazepate dipotassium was administered orally at 1.0 mg kg$^{-1}$ every 24 hours for 4 weeks and fluoxetine at 1.0 mg kg$^{-1}$ every 24 hours for 10 weeks. Improvement was reported in 25 dogs. This study did not observe increase in aggression during treatment with clorazepate. The majority of dogs in both groups (anxious patients with and without aggression) showed improvement over time. Greater improvement in clinical signs was observed for anxious non-aggressive dogs. The authors suggested that benzodiazepines might not be an ideal choice for the treatment of fear aggression, in agreement with Crowell-Davis (2008).

## V. Diazepam

**Chemical Compound:** 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

**DEA Classification:** DEA Class IV non-narcotic agent

**Preparations:** Generally available as 2-, 5-, and 10-mg tablets. Also available as a 1 and 5 mg ml$^{-1}$ suspension for oral administration and a 5 mg ml$^{-1}$ injectable solution. Rectal gels are available in 2.5-, 5-, 10-, 15-, and 20-mg sizes.

### Clinical Pharmacology

Diazepam has a CNS depressant effect, specifically on the limbic system, thalamus, and hypothalamus, which results in anxiolytic, calming, sedative, skeletal muscle relaxation, and anticonvulsant effects. It does not have any peripheral autonomic blocking action or produce extra-pyramidal side effects. It acts by activation of the γ-aminobutyric acid system at the $GABA_A$ receptor complex. This results in decreased neural transmission throughout the CNS (Roche Laboratories 2000).

Following oral administration, the usual route in treating behavior cases, diazepam is rapidly absorbed, with peak plasma levels occurring 0.5–2 hours after administration in humans and one hour after administration to rats (Schwartz et al. 1965). Diazepam readily crosses the blood–brain barrier, is highly bound to plasma proteins, is highly lipid-soluble, and is widely distributed through the body. Blood concentrations are proportional to the dose given. In horses, 87% of diazepam is bound to plasma protein when the serum concentration is 75 ng ml$^{-1}$. This is a lower percentage than for humans (Plumb 2002). The half-lives of diazepam and its two primary metabolites are shown in Table 7.4.

Diazepam undergoes extensive first-pass hepatic metabolism when given orally. In the liver, diazepam is changed into multiple metabolites, including desmethyldiazepam (nordiazepam), temazepam, and oxazepam. In dogs given an intravenous injection of 1 mg kg$^{-1}$ of diazepam, about 61% of it is excreted in the urine while about 34% is

Table 7.4 Half-life of diazepam, in hours, and some of its metabolites in the dog, cat, and horse.

| Benzodiazepine | Dog | Cat | Horse |
|---|---|---|---|
| Diazepam | 2.5–3.2 | 5.5 | 7–22 |
| Nordiazepam | 3.6–10 | 21.3 | 12 |
| Oxazepam | 3.5–5.7 | | 18–28 |

*Source:* Löscher and Frey (1981), Norman et al. (1997), Shini et al. (1997), Plumb (2002).

excreted in the feces, either as diazepam or, predominantly, as a metabolite. In humans, only about 10% of diazepam is excreted in the feces, again predominantly as a metabolite. In contrast to dogs and humans, diazepam given to rats is excreted predominantly through the feces, whether it is given intraperitoneally or orally (Schwartz et al. 1965). Thus, the exact metabolism of diazepam varies between species. This variation happens at many levels and may account for much of the variation in clinical response.

In the cat, the half-life of diazepam is approximately 5.5 hours, and the half-life of nordiazepam is 21.3 hours (Plumb 2002). There is an initial rapid increase in levels of nordiazepam for two hours after intravenous injection of diazepam, with about 54% of diazepam being biotransformed to nordiazepam (Cotler and Gustafson 1978; Cotler et al. 1984). After this, nordiazepam levels are maintained within 50% of peak nordiazepam levels for 24–48 hours. Approximately 70% of diazepam given by intravenous injection is excreted in the urine, 50% as known metabolites. Approximately 20% is excreted in the feces, 50% of that as nordiazepam (Cotler and Gustafson 1978). Diazepam is fatal to cats within one day when given at a dose of 500 mg $kg^{-1}$ PO (Randall and Kappell 1973) but hepatic failure is also documented in therapeutic doses (Park 2011; Beusekom et al. 2015). A study by Beusekom et al. (2015) shed light on how hepatic CYP450-mediated biotransformation of diazepam differs between cats and dogs. Cats have a limited capacity to glucuronidate diazepam hydroxyl metabolites.

Diazepam is rapidly metabolized in dogs, with a half-life of 2.5–3.2 hours while the half-life of nordiazepam is 3.6–10 hours (Vree et al. 1979; Löscher and Frey 1981). The metabolite oxazepam reaches maximal plasma concentration in about two hours, then declines with a half-life of about 3–5.7 hours (Vree et al. 1979; Löscher and Frey 1981). Greyhounds seem to metabolize diazepam and its metabolites in a slower fashion, but further studies are required (Kukanich and Nauss 2011). When dogs were given 25 mg $kg^{-1}$ of diazepam per day for 10 days, no diazepam was subsequently found in urine extracts. In these dogs, the main pathway of metabolism of diazepam was *N*-demethylation and hydroxylation, followed by excretion as oxazepam glucuronide. While oxazepam can be conjugated with glucuronic acid, diazepam has first to be hydroxylated in order to produce a compound that can subsequently be excreted as a glucuronide (Ruelius et al. 1965). Dogs chronically administered doses of 0.56, 4.5, 9, or 36 mg $kg^{-1}$ daily of diazepam exhibit a linear relationship between total plasma levels and brain levels of diazepam, nordiazepam, and oxazepam, and the chronic dose of diazepam. At higher doses, there is more free nordiazepam and oxazepam, and less free diazepam in the plasma, cerebrospinal fluid, and brain (Wala et al. 1995).

The half-life of diazepam is 7–22 hours in the horse. The half-life of nordiazepam is 18–28 hours while the half-life of oxazepam, another active metabolite, is 12 hours (Norman et al. 1997; Shini et al. 1997; Plumb 2002). Peak levels of diazepam occur in the serum 40 minutes after an intramuscular injection of a dose of 10 mg per horse. Diazepam is not detected in horse serum more than six hours after administration. Nordiazepam levels in the serum peak three hours after administration of diazepam. The metabolites oxazepam and temazepam can be found in the urine up to 121 and 79 hours, respectively, after injection of diazepam, but are not found in the serum after administration by assays that do not detect levels below 1.1 ng $ml^{-1}$. Overall, diazepam is excreted in the urine mainly as oxazepam (37%), temazepam (33%), and nordiazepam (29%), with <0.2% being excreted as diazepam (Marland et al. 1999). More recent studies by Hayami et al. (2013) and Nakayama et al. (2016) show temazepam as the major metabolite produced from microsomial reactions in the liver. CYP3A seems to be the main enzyme responsible for the metabolism of diazepam (Nakayama et al. 2016). Measurements of various cardiopulmonary parameters in

horses given clinically usual doses of diazepam intravenously have identified few significant changes. Doses greater than 0.2 mg kg$^{-1}$ IV are likely to induce recumbency in this species due to muscle relaxant properties (Muir et al. 1982; Matthews et al. 1991; Kerr et al. 1996).

In rabbits, there are multiple metabolites with the primary metabolite being oxazepam (Jommi et al. 1964; Sawada et al. 1976).

Comparison of research on guinea pigs, rats, rabbits, and mice demonstrates the existence of substantial interspecies variation in metabolism. Rat liver predominantly hydroxylates diazepam in the $C_3$ position and only slightly causes *N*-demethylation; mouse liver predominantly *N*-demethylates, but does hydroxylate, whereas in the guinea pig only *N*-demethylation occurs. Rabbits, like mice, predominantly demethylate but hydroxylate to some degree. The major metabolite of diazepam in blood, brain, and adipose tissue of guinea pigs is *N*-demethyldiazepam. Oxazepam is not a significant metabolite in this species, but it is in the mouse (Jommi et al. 1964; Marcucci et al. 1969; Marcucci et al. 1970a, 1970b; Marcucci et al. 1971; Mussini et al. 1971).

Bergamottin, a furanocoumarin that occurs in grapefruit juice, reduces the activity of the P450 enzymes CYP3A12 and CYP1A1/2, concurrently causing an increase in plasma levels of diazepam in dogs, but not in Wistar rats (Sahi et al. 2002).

#### Uses in Humans

Diazepam is used in humans for the relief of symptoms of anxiety and management of anxiety disorders. It is also used in the treatment of convulsive disorders, for relief of skeletal muscle spasms, and for symptomatic relief of acute alcohol withdrawal.

#### Contraindications

Diazepam is contraindicated when there is a known hypersensitivity of the patient to the drug, in patients with glaucoma, and in cats that have been exposed to the insecticide chlorpyrifos, because diazepam may potentiate organophosphate toxicity (Plumb 2002).

Lower doses should be used in patients with compromised liver or renal function and in geriatric or debilitated patients. Diazepam may cause loss of inhibitions and result in increased aggression in aggressive patients. Its use should be avoided in working animals, for example, drug detection dogs, because their ability to perform their working tasks may be compromised. Extreme caution should be used in giving riding and driving horses diazepam since the muscle fasciculations, ataxia, and sedative properties may be dangerous.

The use of diazepam in cats should be avoided as hepatic failure has been documented even in therapeutic doses (Park 2011; Beusekom et al. 2015). Longer-acting benzodiazepines without active metabolites (clonazepam, lorazepam, and oxazepam) are a safer option for this species (author's note).

Diazepam crosses the placental barrier and enters the milk. There is an increased risk of congenital malformations when diazepam is given during the first trimester of pregnancy. Therefore, its use should be avoided in pregnant and lactating females (Roche Laboratories 2000).

#### Side Effects

Side effects include ataxia, sedation, increased appetite, paradoxical excitation, transient cardiovascular depression, muscle relaxation, increased friendliness, anxiety, apparent hallucinations, muscle spasticity, insomnia, and idiopathic hepatic necrosis in cats. Idiopathic hepatic necrosis in cats is discussed further below. There have been occasional reports of neutropenia and jaundice in humans. Muscle fasciculations may occur in horses given diazepam.

The rate of metabolism may be decreased if diazepam is given concurrently with other medications that compete with it for the P450 isoenzyme system by which it is metabolized, including the selective serotonin reuptake inhibitors.

Reproduction studies on rats given 1, 10, 80, and 100 mg kg$^{-1}$ daily of diazepam during pregnancy resulted in lowered pregnancy

rates and surviving offspring in rats given 100 mg kg$^{-1}$. There were no teratological effects, lowered pregnancy rates, or reduced survival of offspring given up to 80 mg kg$^{-1}$ (Beall 1972). In humans, however, research has suggested a risk of congenital malformations when diazepam is used during the first trimester. Because diazepam crosses the placenta and enters the milk, its use should be avoided in pregnant and lactating females of all species.

The oral $LD_{50}$ in rats is 1240 mg kg$^{-1}$ and in mice is 720 mg kg$^{-1}$ (Roche Laboratories 2000). The oral $LD_{50}$ in rabbits is 328 mg kg$^{-1}$ (Randall et al. 1965).

#### Overdose

Immediate gastric lavage and supportive measures should be conducted. Administer intravenous fluids and maintain an open airway. Flumazenil, a benzodiazepine receptor antagonist, can be used to completely or partially reverse the effects of an overdose. Treatment with flumazenil may result in seizures, especially in patients that have frequently been given diazepam for a long period of time.

#### Doses in Nonhuman Animals

Initiate treatment for nonhuman animals at the lowest dose. If no undesirable side effects occur, titrate dose up to the desired effect. There is a wide range of clinically effective doses for diazepam in veterinary populations. As discussed above under clinical guidelines for benzodiazepines, an initial test dose of the lowest usual dose for the species should be given when the owners will be home to observe the pet for sensitivity to the medication. This guideline is mentioned because diazepam is often used to treat anxiety problems for which symptoms may be exhibited primarily or entirely when the owners are absent. If the pet does not exhibit untoward side effects, this dose can then be used in the context of the situation for which the medication is being used, for example, storms or being alone. If humans will not be present, as is the case with separation anxiety, a video camera should be positioned to evaluate whether or not this dose of medication is effective in treating the behavioral signs. As stated before, making sure that the house is proofed against potential accidents (such as blocking the animal's access to stairs, countertops, balconies, etc.) should be highlighted. If the dose is insufficient, the dose can gradually be increased over a period of days until a clinically effective dose is identified or undesirable side effects occur. If the anxiety is effectively controlled before significant side effects occur, the dose that accomplishes this result can then be used. If significant side effects occur before effective treatment is accomplished, then the use of this particular medication in the patient must be reevaluated.

#### Discontinuation

Patients that have been treated with diazepam on a daily basis for several weeks should be gradually withdrawn. Diazepam is more addicting than some of the other benzodiazepines, such as lorazepam and oxazepam.

#### Other

Diazepam appears to interfere with the acquisition of new learning, but not with the recall of material already learned (e.g. Ghoneim et al. 1984).

Diazepam is commonly used in the treatment of seizure disorders in various species. A detailed discussion of this use is beyond the subject of this book.

Protein malnutrition has been shown to induce alterations in the GABAergic neurotransmitter system and produce hyperreactivity to the effects of diazepam in male Wistar rats used as model of anxiety (Françolin-Silva et al. 2007). It is well established that malnutrition imposed early in life produces morphological, neurochemical, neurophysiological, and functional alterations in the brain of rats (Morgane et al. 1993; Tonkiss et al. 1993; Almeida et al. 1996a, 1996b, 1996c). Considering the significant population of dogs and cats adopted at shelters and animal control facilities that have been in a situation of neglect

in the first weeks or months of life, studies that investigate what a less than ideal upbringing causes in the brain of companion animals (prone to need psychoactive medication to treat behavior and brain pathologies) are shockingly lacking.

### Effects Documented in Nonhuman Animals

#### *Cats*

A single oral dose of diazepam has no prominent behavioral effects at a dose of 0.2 mg $kg^{-1}$. A mixture of ataxia, muscle relaxation, increased playfulness, and exploratory behavior occurs at a single oral dose of 1 mg $kg^{-1}$. Interestingly, the higher of these two doses produces increased wakefulness and decreased REM sleep during the one- to four-hour period after administration, while the lower dose produces no change in wakefulness when compared with placebo (Hashimoto et al. 1992).

Captive feral cats injected with 1 mg $kg^{-1}$ of diazepam exhibit decreased defensive aggression but have no change in flight behavior (Langfeldt and Ursin 1971).

Spraying urine is a common behavior problem in cats, affecting about 10% of prepubertally castrated males and about 5% of prepubertally neutered females (Hart and Cooper 1984). While the causes and function of spraying are poorly understood, the behavior often decreases or ceases if an anxiolytic is administered. Marder (1991) gave 19 castrated male cats and 4 spayed female cats with problems of spraying behavior 1 mg q12h. If spraying did not cease after three days, the dose was increased to 2 mg q12h. Treatment was continued for one month, at which point the dose was halved. Subsequently medication was gradually reduced at weekly intervals until the cats were off medication one month after beginning to decrease the dose. Success was defined as at least a 75% reduction and owner satisfaction at a 1- to 10-month follow-up. Sixteen out of the 19 castrated males exhibited reduced spraying, while one out of the four females exhibited reduced spraying. Eleven of the cats had previously been treated with synthetic progestins. All of those cats responded to diazepam. However, 75% of the cats that had responded well relapsed at a later date. Side effects observed by Marder were increased affection, lethargy, increased appetite, and ataxia.

Cooper and Hart (1992) also evaluated the effect of diazepam on spraying. Their subjects were 14 castrated males and 6 spayed females. Diazepam was given at 1–2 mg/cat q12h for two weeks. If spraying was eliminated or reduced to the client's satisfaction, this dose was continued for an additional six to eight weeks. If the cat still sprayed, however, the dose was increased 50% for an additional two weeks. If the cat responded favorably at the higher dose, treatment was continued for another six to eight weeks. If the cat still sprayed at the higher dose, it was weaned off medication over a two-week period. For the cats that responded to the 1- or 2-mg q12h doses, treatment continued for 8 to 12 weeks, after which the cat was weaned off medication. If, during weaning, a cat resumed spraying, dosage was increased back to the previously effective dose. Some cats were treated for four years. Eleven out of 20 cats responded by complete cessation or decrease to a level that was acceptable to the owner. However, 10 of those 11 resumed spraying when treatment was discontinued. Eleven of the initial 20 cats had previously been treated ineffectively with progestins. Five of these responded to diazepam. Side effects observed in this study included sedation, ataxia, increased appetite, weight gain, reduced aggression, and a calmer and more affectionate temperament. Treatment with buspirone has subsequently been found to result in a lower recidivism rate than treatment with diazepam. See the discussion of buspirone in Chapter 9.

Overall (1994a) treated a spraying cat with diazepam 1 mg q12h PO with initial success. However, the cat could not be weaned off of medication without recurrence of the problem, and the spraying gradually recurred over

a one-year period. An increase to 2 mg q12h was likewise initially successful, for three months, but was again followed by relapse. This cat was later treated with buspirone with greater success, although the cat could not be weaned off of medication (Overall 1994a).

In the cat, about 50% of diazepam is transformed into nordiazepam. Several clinicians have documented acute onset of hepatic necrosis in cats given diazepam (Levy 1994; Levy et al. 1994; Center et al. 1996; Hughes et al. 1996). Onset was usually eight to nine days after daily medication with diazepam was initiated. Initial signs include anorexia, vomiting, dehydration, lethargy, hypothermia, jaundice, and coma (Center et al. 1996). Most affected cats have died, usually within 24 hours, even with vigorous supportive therapy, but some have survived (Levy et al. 1994). The exact cause is unknown. Speculations have included: (i) a toxic intermediate metabolite produced by some cats; and (ii) a toxic substance incorporated into the pill during manufacture. The latter hypothesis is questionable due to the hepatic necrosis having occurred with multiple different brands of diazepam (Center et al. 1996). Hughes et al. (1996) reviewed the premedication health status of six cats that developed hepatic necrosis subsequent to medication with diazepam. In all cases, the cat had prior cardiac, pancreatic, or renal disease. Current recommendations for the use of diazepam in cats are to do a baseline physical exam, complete blood count (CBC), and blood chemistries to confirm that the cat is in good health. Repeat the blood chemistries at three to five days. If there is elevated ALT or aspartate transferase (AST), discontinue the medication (Center et al. 1996). While hepatic necrosis in response to treatment with diazepam is usually fatal, the problem itself is rare. Some clients who have cats for which diazepam is otherwise a good choice, and for whom cost is a significant issue, may wish to try diazepam without monitoring of liver function. In all cases, however, the client should be informed of the rare, but present, potential for a fatal consequence with this drug.

***Dogs***

Dogs medicated with increasing doses of diazepam until they started losing weight did so at doses of 20–36 $mg\,kg^{-1}\,day^{-1}$ after 11–29 days on the increasing dose regimen (Martin et al. 1990; Sloan et al. 1991). Acute withdrawal of these dogs, precipitated by administering flumazenil, results in tremors, twitches, jerks, and seizures (Martin et al. 1990; Sloan et al. 1991). Dogs given 0.05625, 0.225, 0.5625, 4.5, 9, or 36 $mg\,kg^{-1}\,day^{-1}$ of diazepam exhibited dose-dependent variation in both the quantity and quality of symptoms that occurred when acute withdrawal was precipitated by administration of flumazenil. At the two lowest doses, only minimal signs were precipitated. Seizure activity occurs only with dogs at the two highest doses of 9 and 36 $mg\,kg^{-1}\,day$, both of which are well above routinely used clinical doses (Sloan et al. 1993).

All four of four laboratory beagles treated for abnormal withdrawn and depressed behavior resolved on 2.5 $mg\,kg^{-1}$ of diazepam (Iorio et al. 1983).

Diazepam has been reported to be more effective than chlorpromazine in reducing signs of fear in dogs (Hart 1985).

In a study that investigated developing and validating a laboratory model of noise-induced fear and anxiety in dogs using open-field and thunderstorm tests, diazepam decreased inactivity (freezing-like behavior) duration in both test naïve and experienced subjects (Araujo et al. 2013).

Ibáñez and Anzola (2009) evaluated the use of fluoxetine, diazepam and behavior modification for the treatment of various anxiety disorders in dogs (with and without aggressive behavior). Diazepam was administered orally at a dosage of 0.3 $mg\,kg^{-1}$ once a day for 4 weeks and fluoxetine was administered orally at a dosage of 1.0 $mg\,kg^{-1}$ once a day for 10 weeks. Thirty-four dogs completed the study and clinical improvement was reported in 76% of them. Increased aggression was not reported in any of the subjects, including those with aggression as part of the initial clinical presentation.

In a cross-sectional study of 37 dogs with behavior pathologies and their owners, Herron et al. (2008) investigated the effects and adverse effects of diazepam and the owner's perception of treatment. Diazepam was considered as very (24%) or somewhat (43%) effective by most owners. Reasons reported for discontinuation of treatment included adverse effects (58%) and lack of efficacy (53%). Adverse effects reported were sedation, increased appetite, ataxia, agitation, increased activity, vomiting, diarrhea, and aggression.

#### *Horses*

Sexual behavior in stallions can be inhibited both by a novel environment and by classical conditioning. Sexual behavior has been shown to be normalized by slow intravenous injection of 0.05 mg kg$^{-1}$ of diazepam (McDonnell et al. 1986, 1987; McDonnell 1999).

Performance horses are sometimes given diazepam as an anxiolytic and muscle relaxant, a practice which is generally illegal (Jaussaud and Courtot 1990). Medication of a horse with diazepam can be detected at least 38 days later using gas chromatography-high resolution mass spectrometry (Jouvel et al. 2000).

#### *Parrots*

Diazepam has been suggested as a treatment for feather-picking at a starting dose of two drops of the 5 mg ml$^{-1}$ solution per ounce of drinking water, with subsequent increases in dose until feather-picking discontinues or the bird becomes excessively sedated. However, no data on results are presented (Galvin 1983) and it has been discussed that diazepam's sedative effects may be detrimental to such patients, suggesting that it is probably more appropriate to suppress acute self-mutilation episodes and not indicated for chronic treatment (Johnson 1987).

#### *Rabbits*

Diazepam given to rabbits at a dose of 0.05–0.1 mg kg$^{-1}$ decreases behavioral arousal as measured by electroencephalogram (Goldberg et al. 1974). When given at doses of 0.6 mg kg$^{-1}$ day$^{-1}$ PO for 30 days, it has no effect on blood sugar levels (Dixit et al. 2001).

#### *Other Species*

Diazepam decreases fear in the marmoset (*Callithrix penicillata*) when exposed to a potential predator. Doses of 1 mg kg$^{-1}$ IM produce only a small reduction in behaviors considered indicative of fear. Doses of 2 mg kg$^{-1}$ IM produce a much stronger anxiolytic effect without a significant sedative effect. Doses of 3 mg kg$^{-1}$ IM produce a sufficient sedative effect that overall activity levels are compromised (Barros et al. 2000).

Diazepam has been used to tame monkeys at a dose of 1 mg kg$^{-1}$ (Zbinden and Randall 1967). Within social colonies of rhesus monkeys, diazepam (2.5–5 mg kg$^{-1}$ by mouth daily) produces dose-dependent increases in social grooming, approach, contact, self-grooming, feeding, and resting with the eyes open. There is also decreased vigilance and aggression (Kumar et al. 1999).

In an experiment that investigated the behavioral consequences of exposing male Wistar rats to a live cat (using the elevated T-maze test of anxiety), administration of diazepam at 2 mg kg$^{-1}$ decreased the immediate avoidance response to the cat and the neophobic reaction to a dummy cat used as a control stimulus (Bulos et al. 2015).

Diazepam (1 mg kg$^{-1}$) increased feeding behaviors and movement in a group of wild-caught *Hemignatus virens* during a short period in captivity (Gaskins et al. 2008).

## VI. Flurazepam Hydrochloride

**Chemical Compound:** 7-Chloro-1-[2-(diethylamino)ethyl]-5-(*o*-fluorophenyl)-1,3-dihydro-2 *H*-1,4-benzodiazepin-2-one-dihydrochloride

**DEA Classification:** DEA Schedule IV drug

**Preparations:** Generally available as 15- and 30-mg capsules.

### Clinical Pharmacology

Flurazepam is rapidly absorbed from the gastrointestinal (GI) tract, rapidly metabolized, and excreted primarily through the urine. In humans, peak flurazepam plasma concentrations occur 30–60 minutes after a single oral dose. The half-life in

humans is 2.3 hours. In humans, its major metabolite is $N_1$–desalkyl-flurazepam with a half-life of 47–100 hours. The long half-life of this metabolite may be responsible for the clinical observation that flurazepam is increasingly effective on the second and third nights of consecutive use and that efficacy continues for one to two nights after discontinuation (Roche Laboratories 1994).

In humans, older men have a longer elimination half-life of desalkyl-flurazepam than younger men, after both single dose and multiple dose treatment. There is no difference between older women and younger women (Roche Laboratories 1994). Whether this age/gender interaction exists in nonhuman patients has not been tested.

When dogs are given $^{14}C$-labeled flurazepam at a dose of 2 mg kg$^{-1}$ PO or IV, fecal excretion predominates, and over 80% is eliminated by either route within nine days (Schwartz and Postma 1970).

Flurazepam is fatal to cats within one hour when given at a dose of 400 mg kg$^{-1}$ PO (Randall and Kappell 1973).

#### Uses in Humans

Flurazepam is used to treat insomnia.

#### Contraindications

Flurazepam is contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Flurazepam crosses the placenta and also enters milk. Its use should therefore be avoided in pregnant and lactating females.

#### Side Effects

Side effects are similar to those reported for other benzodiazepines and include sedation and ataxia. Flurazepam has not been as extensively used in nonhuman patients as some of the other benzodiazepines. Therefore, it is likely that some probable side effects have not yet been reported.

Rare cases of leucopenia, granulocytopenia, elevated AST/ALT, elevated total/direct bilirubin, elevated alkaline phosphatase, and skin rashes have been reported in humans. Two cases of cholestatic jaundice secondary to treatment with flurazepam have been reported in humans (Fang et al. 1978; Reynolds et al. 1981). Blurred vision has been reported in humans (Roche Laboratories 1994). While subtle changes in vision are difficult to detect in nonhuman patients, this should be kept in mind if significant difficulty navigating the environment occurs after administration of flurazepam.

Rebound insomnia can occur with discontinuation. However, it is less likely to occur than with shorter-acting benzodiazepines such as triazolam (Rickels 1983).

#### Overdose

In case of overdose, conduct gastric lavage and provide supportive measures, including intravenous fluids. Flumazenil, a benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of flurazepam toxicity.

#### Doses in Nonhuman Animals

Initiate treatment at the lowest dose. If no undesirable side effects occur, titrate the dose up to the desired effect.

#### Effects Documented in Nonhuman Animals

Flurazepam may be a preferred benzodiazepine for pets that wake during the night due to its long half-life (Landsberg et al. 2003). There are no reports of clinical studies on the use of flurazepam in the treatment of pets.

### VII. Lorazepam

**Chemical Compound:** 7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepine-2-one

**DEA Classification:** DEA Schedule IV drug

**Preparations:** Generally available in 0.5-, 1-, and 2-mg tablets and 2 mg ml$^{-1}$ oral solution.

#### Clinical Pharmacology

Lorazepam is identical to oxazepam except that it has a chlorine atom on the phenyl ring (Elliott 1976). Absorption of lorazepam is fairly rapid, except in the cat (Ruelius 1978). In humans, peak concentrations in the plasma occur in approximately two hours.

The time to peak plasma levels of lorazepam in the cat, dog, pig, and rat is given in Table 7.5. In humans, the mean half-life for lorazepam is about 12 hours, while the half-life for its major metabolite, lorazepam glucuronide, is about 18 hours. In African green monkeys, the mean half-life of lorazepam is 1.7 hours (Friedman et al. 1991; Wyeth Laboratories Inc. 1999b).

Lorazepam glucuronidate is the primary metabolite in the dog, cat, human, and pig, but not in the rat (Schillings et al. 1971). Lorazepam glucuronidate has no significant CNS activity (Gluckman and Stein 1978). Peak plasma levels of unchanged lorazepam are almost identical in humans and dogs when dogs are given a dose about 30 times higher than a human on a per kilogram basis. This is because formation of lorazepam glucuronide is much faster in dogs than in humans (Ruelius 1978). Cats do glucuronidate lorazepam, but not as rapidly or extensively as dogs. However, the finding that cats form the glucuronide is unexpected, because they often conjugate exogenous molecules with glucuronic acid poorly or not at all (Ruelius 1978).

When cats are given a single dose of 1 mg kg$^{-1}$ PO, plasma levels of unconjugated lorazepam peak at 12 hours and then begin declining, with a half-life of 17 hours. Plasma levels of conjugated lorazepam run at about one-third to one-half the levels of unconjugated lorazepam in this species (Schillings et al. 1975).

Dogs and pigs excrete lorazepam primarily in the urine, rats predominantly in the feces, and cats excrete it roughly equally in urine and feces (Ruelius 1978). Six days after a single dose of 1 mg kg$^{-1}$ lorazepam PO, cats will have excreted about 47% in the urine and about 54% in the feces (Schillings et al. 1975). In a species, no gender effect has been identified in the qualitative urinary excretion pattern (Schillings et al. 1971; Schillings et al. 1975). No changes in urinary excretion patterns have been identified in dogs, pigs, rats, and humans treated with lorazepam for periods of five to eight weeks (Schillings et al. 1971).

In rats, about three times as much lorazepam occurs in the brain as in plasma for about 0.5–12 hours after dosing (Ruelius 1978).

Both lorazepam and lorazepam glucuronide are transferred by the placenta (Wyeth Laboratories Inc. 1999b).

There is good separation between anxiety-reducing doses and sedative-hypnotic doses (Gluckman and Stein 1978).

### Uses in Humans

Lorazepam is used for the short-term relief of symptoms of anxiety and for management of anxiety disorders in humans.

### Contraindications

Lorazepam is contraindicated in patients with a history of sensitivity to lorazepam or other benzodiazepines and in patients with acute narrow angle glaucoma. It should be used with extreme caution in aggressive animals because it may cause disinhibition

**Table 7.5** Peak plasma levels and percentage of lorazepam eliminated in the urine and feces of cats, dogs, rats, and pigs.

| Species | Dose | Time to peak plasma concentration | Peak plasma concentration (ng ml$^{-1}$) | Eliminated in the urine (%) | Eliminated in the feces (%) |
|---|---|---|---|---|---|
| Cat | 20 mg kg$^{-1}$ PO | 12 | 9310 | 47.3 | 54 |
| Dog | 1 mg kg$^{-1}$ PO | 0.5 | 28 | 66.4 | 22 |
| Pig | 0.04 mg kg$^{-1}$ PO | 3 | 1.2 | 87.8 | 7.9 |
| Rat | 1 mg kg$^{-1}$ IG | 0.5 | 108 | 21.7 | 68.9 |

*Source:* Ruelius (1978).

and in pregnant or nursing females because it may cause fetal malformations and loss, and is probably transmitted through the milk.

#### Side Effects

As with all benzodiazepines, sedation, ataxia, muscle relaxation, increased appetite, paradoxical excitation, increased friendliness, anxiety, and a variety of other side effects may occur. When they occur, side effects are usually observed early in therapy and disappear with continued treatment or a decreased dose.

No evidence of carcinogenesis has been identified. In rabbits used to study effects on reproduction, random anomalies of various sorts occurred at all doses. At doses of $40\,mg\,kg^{-1}$ fetal resorption and increased fetal loss occur in rabbits (Wyeth Laboratories Inc. 1999b).

#### Overdose

If an overdose occurs, induce vomiting and/or conduct gastric lavage. Provide supportive therapy as needed. Flumazenil may be used to partially or fully reverse the effect of lorazepam.

#### Doses in Nonhuman Animals

Initiate treatment at the lowest dose. If no undesirable side effects occur, titrate dose up to effect. While variation between individuals and species makes exact comparison impossible, $1\,mg\,kg^{-1}$ of lorazepam is about equivalent to $5\,mg\,kg^{-1}$ of diazepam (Gluckman and Stein 1978).

#### Discontinuation

As with all the benzodiazepines, withdrawal of a patient that has been on lorazepam should be accomplished gradually. Dogs that have been addicted to lorazepam by chronic administration of $100\,mg\,kg^{-1}\,day^{-1}$ and acutely withdrawn by administration of flumazenil exhibit tremor, rigidity, and decreased food intake (McNicholas et al. 1983).

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Dogs given an increasing dose of lorazepam until they reached a dose of $140\,mg\,kg^{-1}\,day^{-1}$ at 16 days of treatment, and subsequently for another 52 days, did not lose weight but did become physically addicted to lorazepam. However, in dogs, physical dependence on lorazepam was found to be less intense than was physical dependence on some other benzodiazepines such as diazepam (Martin et al. 1990).

##### *Primates*

Lorazepam reduces anxiety and conflict behavior in squirrel monkeys (Stein and Berger 1971; Gluckman and Stein 1978).

In social colonies of rhesus monkeys, lorazepam ($0.5–1.0\,mg\,kg^{-1}$ PO daily) produces dose-dependent increases in social grooming, approach, contact, self-grooming, feeding, and resting with the eyes open. There is also decreased vigilance and aggression (Kumar et al. 1999).

##### *Rats and Mice*

Lorazepam reduces conflict behavior in rats. In mice, it suppresses foot shock-induced fighting behavior (Gluckman and Stein 1978). Rats treated with lorazepam at $1.25\,mg\,kg^{-1}\,day^{-1}$ for over a year have shown no adverse effects. However, rats treated at $6\,mg\,kg^{-1}\,day^{-1}$ for the same period of time developed esophageal dilation. The esophageal dilation reversed if medication was withdrawn within two months of detection.

## VIII. Oxazepam

**ChemicalCompound:**7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one

**DEA Classification:** DEA Schedule IV controlled substance

**Preparations:** Generally available as 10-, 15-, and 30-mg capsules and as 15- and 30-mg tablets.

#### Clinical Pharmacology

Oxazepam has no active intermediate metabolites and therefore may be safer for patients with liver disease, obese patients,

and geriatric patients than some of the other benzodiazepines. An inactive glucuronide conjugation of oxazepam is the primary metabolite, accounting for over 95% of urinary metabolites in pigs and humans and likewise being the primary metabolite in rabbits (Sisenwine et al. 1972; Sawada et al. 1976). There are at least six other minor metabolites that account for <5% of the urinary metabolites in these species. In the rat, conjugated oxazepam is a minor metabolite, and conversion to inactive metabolites that are minor in humans and pigs is conversely greater (Sisenwine et al. 1972).

In human studies, absorption has been identified as equivalent when oxazepam is given as a tablet, capsule, or suspension. Mean elimination half-life is approximately 8.2 hours, while peak plasma levels occur at about 3 hours after oral dosing in humans (Wyeth Laboratories Inc. 1999a).

In dogs given 5–10 mg kg$^{-1}$ PO of $C^{14}$-labeled oxazepam, peak plasma levels occur in 4–6 hours, with some drug, or a metabolite, remaining in the system for at least 120 hours. Twenty-four hours after administration, about three-quarters of the total dose are excreted. At 96 hours (four days) after administration, urinary excretion has accounted for about 68% of the $C^{14}$, while fecal excretion has accounted for about 35% of the $C^{14}$ (Walkenstein et al. 1964).

Oxazepam exerts an anticonvulsant effect in 50% of mice given a dose of 0.6 mg kg$^{-1}$ orally, while ataxia is observed in 50% of mice given a dose of 5 mg kg$^{-1}$ orally. Thus, there is a wide separation of effective doses and doses that induce side effects. There is also a significant dose separation between effective antianxiety levels in rats subjected to shock and the doses required to produce motor incoordination.

Oxazepam has a larger spread than either chlordiazepoxide or diazepam between the minimal effective dose and the dose that causes side effects. It causes better anxiolytic effects with less depressant effects as well (Gluckman 1965).

The acute oral $LD_{50}$ in mice is more than 5000 mg kg$^{-1}$.

### Uses in Humans

Oxazepam is used for the management of anxiety disorders and for the short-term amelioration of anxiety symptoms that occur with or without depression. It is considered to be especially useful in the treatment of anxiety, tension, agitation, and irritability in geriatric patients.

### Contraindications

Oxazepam is contraindicated in patients with a history of hypersensitivity to this or other benzodiazepines. Because it crosses the placental barrier and enters the milk, it should not be used in pregnant or lactating females.

### Side Effects

As with all benzodiazepines, sedation, ataxia, and temperament changes due to loss of inhibition may occur.

Rarely, leucopenia and hepatic dysfunction have been reported in humans treated with oxazepam. Fetal abnormalities have not been observed in rats subjected to breeding studies of oxazepam.

Rats given oxazepam as 0.5% of their diet for six weeks exhibit fatty metamorphosis of the liver without necrosis or fibrosis.

Mice given 35 or 100 times the human dose of oxazepam for nine months exhibit dose-related increases in liver adenomas (Fox and Lahcen 1974). Rats given 30 times the human maximum dose over two years showed an increase in benign thyroid follicular cell tumors, testicular interstitial cell adenomas, and prostatic adenomas. There is no evidence that clinical use of oxazepam is carcinogenic.

### Overdose

In case of an overdose, induce vomiting and/or conduct gastric lavage. Provide supportive treatment. Flumazenil can be used to partially or fully reverse the effect of oxazepam.

### Doses in Nonhuman Animals

Initiate treatment at the lowest dose for nonhuman animals. If no undesirable side

effects occur, titrate the dose up to the desired effect.

#### Discontinuation

As with all benzodiazepines, dose reduction should be done gradually for patients that have been medicated daily for several weeks. However, oxazepam is less addicting than some other benzodiazepines, such as diazepam.

#### Other Information

Some research in humans has suggested that oxazepam may be more effective than chlordiazepoxide in treating aggression (Gardos et al. 1968; Kochansky et al. 1975).

#### Effects Documented in Nonhuman Animals

##### *Cats*

Oxazepam is used as an appetite stimulant in cats, with a longer duration of action than diazepam (Landsberg et al. 2003).

##### *Dogs*

Dogs given increasing doses of oxazepam to 270 mg $kg^{-1}$ by day 72 of treatment, and subsequently given this dose for an additional 30 days, did not lose weight. While chronic administration of oxazepam at such a high dose did produce physical dependence, the dependence was not as intense as with some other benzodiazepines such as diazepam (Martin et al. 1990).

Dogs given 480 mg $kg^{-1}$ daily for four weeks showed no specific changes. Two of eight dogs given 960 mg $kg^{-1}$ died with evidence of circulatory collapse. In chronic toxicity studies, dogs given 120 mg $kg^{-1}$ $day^{-1}$ for 52 weeks exhibited no toxic effects. Thus, there is a wide margin of safety.

## IX. Triazolam

**Chemical Compound:** 8-Chloro-6-(*o*-chlorophenyl)-1-methyl-4H-s-tria-zolo-[4,3-$\alpha$][1,4] benzodiazepine

**DEA Classification:** DEA Schedule IV controlled drug

**Preparations:** Generally available as 0.125-, 0.25-, and 0.5-mg tablet.

#### Clinical Pharmacology

Triazolam has a short plasma half-life, 1.5–5.5 hours in humans. The initial step in metabolism is hydroxylation, which is catalyzed by cytochrome P450 3A (CYP 34A). The primary metabolites are conjugated glucuronides, which are presumably inactive. Both triazolam and its metabolites are excreted primarily in the urine (Pharmacia and Upjohn 1999).

When triazolam is administered orally to pregnant mice, it is uniformly distributed in the fetus. The fetal brain develops approximately the same concentration in the brain as does the mother (Pharmacia and Upjohn 1999).

Initially, triazolam decreases latency to sleep and number of nocturnal awakenings and increases the duration of sleep. However, after two weeks of consecutive nightly doses, its efficacy decreases. On the first and/or second night after discontinuation from two weeks of continuous use, a rebound effect occurs, with the total time asleep becoming less than at baseline (Pharmacia and Upjohn 1999).

#### Uses in Humans

Triazolam is used for the short-term (7–10 days) treatment of insomnia in humans.

#### Contraindications

Triazolam is contraindicated in any patient with a history of sensitivity to this or other benzodiazepines. Triazolam should not be given concurrently with any medications that substantially impair metabolism mediated by cytochrome P450 3A, including ketoconazole, itraconazole, and nefazodone (Pharmacia and Upjohn 1999).

#### Side Effects

Interdose withdrawal sometimes produces daytime anxiety in human patients after as little as 10 days' treatment with triazolam (Pharmacia and Upjohn 1999). Increased anxiety should be considered as a potential side effect in nonhuman patients for which this short-acting benzodiazepine is being

used to treat night-time restlessness or anxiety.

Otherwise, side effects common to the benzodiazepines, including sedation, ataxia, and temperament changes due to loss of inhibition, may occur.

In a 24-month study of carcinogenesis that was conducted on mice given up to 4000 times the recommended human dose, no evidence of carcinogenesis was identified (Pharmacia and Upjohn 1999).

#### Overdose

Triazolam is a very potent benzodiazepine. Therefore, signs of overdosage may occur at moderate overdoses, for example, four times the maximum recommended therapeutic dose in humans.

In case of overdose, conduct immediate gastric lavage and provide supportive treatment. Flumazenil can be used for the complete or partial reversal of triazolam.

#### Doses in Nonhuman Animals

Initiate treatment at the lowest dose. If no undesirable side effects occur, titrate the dose up to the desired effect.

#### Effects Documented in Nonhuman Animals

##### *Rabbits*

Triazolam, at doses of 0.01 or 0.1 mg kg$^{-1}$ IV or PO given to rabbits, reduces wakefulness during the subsequent six hours and, in most cases, significantly increases non-REM sleep (except that at 0.01 mg kg$^{-1}$ PO it significantly increases REM, rather than non-REM, sleep) (Scherschlicht and Marias 1983).

## Important Information for Owners of Pets Being Placed on Any Benzodiazepine

The following should be considered when placing an animal on a benzodiazepine.

1) Benzodiazepines are fast-acting, but only last a few hours.
2) Some pets become unsteady, sleepy, or excited when on a benzodiazepine. The first dose should be given when the owner is home and can observe the pet.
3) There is wide variation between individuals regarding the optimal dose to use to treat a particular problem. Also, some pets respond well to one benzodiazepine but not to another. Pet owners should work closely with their veterinarian until the best drug and dose for their pet is identified.
4) If the owner's pet is medicated with a benzodiazepine for several weeks, withdrawal needs to be gradual.
5) Benzodiazepines are DEA Schedule IV drugs. Therefore, special restrictions apply to their prescription and use.

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# 8

# Selective Serotonin Reuptake Inhibitors

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## Action

The selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants that inhibit the reuptake of serotonin. This results in an increase in serotonergic neuro-transmission by allowing serotonin molecules to act for extended periods of time. With prolonged use, there is also down-regulation of serotonin receptors. Currently the Food and Drug Administration (FDA) has approved six of them in human medicine to treat depression: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil, Pexeva), and sertraline (Zoloft). Fluoxetine is also available as an FDA-approved veterinary product named Reconcile®.

## Overview of Indications

The SSRIs are classified as antidepressants; however, they have anxiolytic, anticompulsive, and some antiaggressive effects (e.g. Charney et al. 1990; Coccaro et al. 1990; Kavoussi et al. 1994; Sanchez and Hyttel 1994; Stein and Stahl 2000; Walsh and Dinan 2001). It is primarily for these reasons that they are used in veterinary medicine. The onset of all effects is usually slow, and clients who have pets on treatment with SSRIs must be informed of this so that they do not have unrealistic expectations. While some response may be observed within a few days of initiation of treatment, improvement commonly does not occur for three to four weeks, or even longer. Thus, if an SSRI is recommended, caution the client that the pet's response to the medication will not be evaluated until it has been on medication daily for at least one month. SSRIs should never be given on an "as-needed" basis, because they will generally be ineffective if used this way. They can be used in cases of specific phobias (such as agoraphobia or storm phobia) and are particularly useful in cases of anxiety that occurs pervasively and frequently, as in the case of generalized anxiety disorder (e.g. Gorman 2002). Animals with generalized anxiety disorder exhibit an almost constant state of low-level anxiety, regardless of their current environment, and are hyperreactive to a variety of fear-inducing environmental stimuli.

Fluoxetine has been used in the treatment of behavior problems in domestic animals more commonly than any other SSRI. As a consequence, there is more information about safety, side effects, and efficacy in various species for this medication than any other. Following fluoxetine, paroxetine and sertraline have been used the most and are mentioned in various

*Veterinary Psychopharmacology*, Second Edition. Sharon L. Crowell-Davis, Thomas F. Murray, and Leticia Mattos de Souza Dantas.

textbooks, even though there is a lack of clinical trials on their use for mental health treatment in veterinary medicine.

Common uses for behaviour problems in domestic animals include anxiety disorders, affective aggression, obsessive compulsive disorders, and urine marking. They can potentially be used for offensive and predatory aggression (Carrillo et al. 2009). However, medication should never be considered a substitute for adequate restraint and safety measures for patients with this or any other type of aggressive behavior. As discussed in Chapter 1, serotonin is involved in the control of aggression. Reisner et al. (1996) measured cerebrospinal fluid (CSF) levels of 5-hydroxyindole acetic acid (5-HIAA) in 21 dogs with a diagnosis of "dominance" aggression and 19 control dogs. The dogs with "dominance" aggression had significantly lower concentrations of CSF 5-HIAA than did the 19 controls (Reisner et al. 1996). When used in the treatment of compulsive disorders, response to serotonin reuptake inhibitors (SSRIs) varies with the specific signs of the disorder and the duration of the problem (Irimajiri et al. 2009).

All SSRIs are metabolized in the liver and excreted through the kidneys. Therefore, premedication blood work to assess the function of these organs is recommended. It is also worth noting that SSRIs can cause urinary incontinence or retention through predominant serotonin receptor subtypes at the site of action. The excitatory effects on the bladder sphincter seem to be medicated by 5-HT2 receptors, whereas the inhibitory effects on the bladder seem to be mediated by 5-HT1 receptors (Espey et al. 1998; Lowenstein et al. 2007). There is an indication that the effect might be various among species (Thor et al. 2002).

## Contraindications, Side Effects, and Adverse Events

Side effects observed in various species include sedation, tremor, constipation, diarrhea, nausea, anxiety, irritability, agitation, insomnia, decreased appetite, anorexia, aggression, mania, decreased libido, hyponatremia, and seizures. Mild sedation and decreased appetite are the most common side effects observed by the authors in dogs. Both are typically transient. If the appetite decrease is sufficient to cause concern about adequate food intake, temporarily increasing the palatability of the diet and/or hand feeding is usually sufficient to induce adequate food consumption until this phase passes.

Serotonin syndrome is a phenomenon reported in humans. It is a consequence of taking excessive quantities of medications that increase serotonin levels and/or taking certain medications that are incompatible with SSRIs concomitantly. Signs and symptoms can be grossly grouped into mental changes, neuromuscular changes and autonomic changes. Treatment should include decontamination, anticonvulsants, thermoregulation, and fluid therapy (Mills 1995; Brown et al. 1996; Martin 1996). This phenomenon is discussed in further detail in Chapter 19 (Combinations).

When mothers are given various SSRIs (fluoxetine, sertraline, paroxetine, or one of the previous with clonazepam), the neonatal acute pain response is decreased and parasympathetic cardiac modulation during the recovery period is increased (Oberlander et al. 2002).

## Adverse Drug Interactions

SSRIs are competitive inhibitors of a number of cytochrome P450 liver enzymes. Therefore, if a patient is placed on an SSRI and another medication that is metabolized by the P450 liver enzymes, elevated plasma levels may develop in the medications, potentially resulting in toxic side effects (Albers et al. 2002). To date, there is minimal data on variation between breeds and species in the P450 enzymes as it relates to the metabolism of various psychoactive drugs. Therefore, findings in humans must be substantially relied upon for the time being. Since there is substantial variation, even within the human population, it is expected that further studies will also

reveal substantial variation in veterinary populations (DeVane 1994).

All of the SSRIs can increase levels of warfarin due to P450 interactions and due to competition for plasma protein binding sites. Fluoxetine and fluvoxamine are the strongest inhibitors of CYP1A2 and CYP2C9, P450 (both enzymes that metabolize warfarin) (Albers et al. 2002).

Fluoxetine, fluvoxamine, sertraline, and paroxetine cause significant inhibition of CYP2D6, which metabolizes amitriptyline, amphetamine, clomipramine, desipramine, haloperidol, imipramine, and nortriptyline (Crewe et al. 1992; Albers et al. 2002).

Fluvoxamine causes the greatest degree of inhibition of CYP3A4, which metabolizes alprazolam, buspirone, clomipramine, clonazepam, and imipramine (Albers et al. 2002).

Fluoxetine and fluvoxamine cause the greatest degree of inhibition of CYP2C19, which metabolizes amitriptyline, clomipramine, diazepam, imipramine, and propranolol (Albers et al. 2002).

Fluvoxamine causes the greatest degree of inhibition of CYP1A2, which metabolizes amitriptyline, caffeine, clomipramine, clozapine, haloperidol, imipramine, and olanzapine, in addition to warfarin (Brøsen et al. 1993; Albers et al. 2002).

In addition, SSRIs should not be given with monoamine oxidase inhibitors (MAOIs), because fatal drug interactions can occur.

## Overdose

In case of overdose, conduct gastric lavage, give activated charcoal, give anticonvulsants as needed, and provide supportive therapy.

## Clinical Guidelines

SSRIs should generally be given once a day. If large doses are required for efficacy, the total daily dose can be divided to minimize side effects. SSRIs should not be given on a sporadic, as-needed basis. Efficacy of a given SSRI on a given patient should not be evaluated until the patient has been on medication daily for at least a month. If, at one month, some degree of improvement is observed, the medication should be continued at the same dose, or at a higher dose if improvement has been only slight.

SSRIs may alter blood glucose levels. Therefore, while they can be used with diabetic patients, they should be used with caution, and blood glucose levels should be monitored closely. Decreased doses should be used in patients with mild dysfunction of the liver or kidneys. SSRIs should not be used at all in patients with severe dysfunction of the liver or kidneys. There is no relationship between plasma levels of SSRIs and clinical response. Therefore, measuring plasma levels is not useful (Albers et al. 2002). Animal doses are given in Table 8.1.

**Table 8.1** Doses of various SSRIs for dogs, cats, horses, and parrots.

| SSRI | Dog | Cat | Parrot | Horse |
|---|---|---|---|---|
| Citalopram | 0.5–1.0 mg kg$^{-1}$ | | | |
| Fluoxetine | 1.0–2.0 mg kg$^{-1}$ | 0.5–1.5 mg kg$^{-1}$ | 2.0–5.0 mg kg$^{-1}$ | 0.25–0.5 mg kg$^{-1}$ |
| Fluvoxamine | 1–2 mg kg$^{-1}$ | 0.25–0.5 mg kg$^{-1}$ | | |
| Paroxetine | 1.0–1.5 mg kg$^{-1}$ | 0.5–1.5 mg kg$^{-1}$ | 2.0 mg kg$^{-1}$ q12h | 0.5 mg kg$^{-1}$ |
| Sertraline | 0.5–4.0 mg kg$^{-1}$ | 0.5–1.5 mg kg$^{-1}$ | | |

*Note:* All doses given are orally, once daily, unless otherwise specified. Do not evaluate efficacy until the patient has received the medication daily for at least one full month.

## Specific Medications

### I. Citalopram Hydrobromide

**Chemical Compound:** (±)-1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3 dihydroisobenzofuran-5-carbonitrile

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10-, 20-, and 40-mg tablets and as a 2-mg $ml^{-1}$ peppermint-flavored oral solution.

#### Clinical Pharmacology

Citalopram is a strong inhibitor of serotonin reuptake and has little effect on reuptake of dopamine or norepinephrine. Of the currently available SSRIs, it appears to be the most selective inhibitor of 5-hydroxytryptamine (5-HT) uptake (Pollock 2001). It has very little to no effect on the 5-$HT_{1A}$, 5-$HT_{2A}$, dopamine $D_1$ and $D_2$, $\alpha_1$, $\alpha_2$ and β-adrenergic, histamine $H_1$, γ-aminobutyric acid (GABA), muscarinic cholinergic, and benzodiazepine receptors.

Citalopram is metabolized to desmethylcitalopram (DCT), di-desmethylcitalopram (DDCT), citalopram-*N*-oxide, and a deaminated propionic acid. At steady state, while the parent compound, citalopram, is the predominant component, DCT and DDCT occur in significant amounts. Citalopram is more effective than its metabolites in preventing serotonin reuptake. Dogs appear to convert more citalopram to metabolites than do humans. Specifically, in dogs, peak DDCT concentrations are approximately equal to peak citalopram concentrations, whereas in humans, steady-state peak DDCT plasma concentrations are less than 10% of citalopram concentrations (Forest Laboratories, Inc. 2002).

In humans, when a single oral dose is given, peak blood levels are reached in two to four hours (Pollock 2001). When it is given daily, steady-state plasma concentrations are reached in about seven days (Forest Laboratories, Inc. 2002). The half-life in humans is about 1.5 days, while the half-life of demethylcitalopram is 2 days and of DDCT, 4 days (Pollock 2001).

Citalopram is metabolized by CYP2C19, CYP3A4, and CYP2D6 (Pollock 2001; Forest Laboratories, Inc. 2002). Since citalopram is metabolized by multiple enzyme systems, it is not expected that concurrent medication with drugs that affect only one of these systems would cause clinically significant effects.

In geriatric populations and individuals with reduced hepatic or renal function citalopram clearance time is slower than for younger populations without reduced hepatic or renal function. Citalopram doses should be reduced in these populations (Forest Laboratories, Inc. 2002).

#### Uses in Humans

Citalopram is used to treat depression. It has also been shown to be significantly more effective than placebo in treating impulsive aggressive behavior in humans (Reist et al. 2003).

#### Contraindications

Citalopram is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). MAOIs should be discontinued for at least two weeks before beginning treatment with citalopram. Likewise, citalopram should be discontinued for at least two weeks before beginning an MAOI.

#### Side Effects

In a small number of patients, treatment with citalopram can result in anxiety, changes in appetite, vomiting, diarrhea, changes in urinary frequency, insomnia, sedation, excitement, seizures, hyponatremia, abnormal bleeding, mydriasis, and various other side effects unique to individuals, including anaphylaxis.

In studies of carcinogenesis, mice were given up to 240 mg $kg^{-1}$ $day^{-1}$ of citalopram for 18 months, and rats were given up to 24 mg $kg^{-1}$ $day^{-1}$ for 24 months. No increased carcinogenesis occurred in the mice. Rats exhibited an increased incidence

of small intestine carcinoma. Albino rats given 80 mg kg$^{-1}$ day$^{-1}$ for two years exhibited degeneration and atrophy of the retinas. Retinal degeneration did not occur in rats given 24 mg kg$^{-1}$ day$^{-1}$, mice treated at doses of up to 240 mg kg$^{-1}$ day$^{-1}$ for 18 months, or dogs treated for a year with doses of up to 20 mg kg$^{-1}$ day$^{-1}$. These doses are greater than what would be used therapeutically in mice and rats. The implication of these findings for other domestic species is not known.

Citalopram has been mutagenic in some bacterial assays. It has not been found to be mutagenic in mammalian assays, however (Forest Laboratories, Inc. 2002).

Citalopram at doses of 16–72 mg kg$^{-1}$ day$^{-1}$ decreased mating behavior in both male and female rats and decreased fertility at doses ≤32 mg kg$^{-1}$ day$^{-1}$. In rat embryo/fetal development studies, pregnant rats were given citalopram at doses of 32, 56, or 112 mg kg$^{-1}$ day$^{-1}$. This resulted in decreased embryo/fetal growth and survival and an increased rate of abnormalities at the high dose of 112 mg kg$^{-1}$ day$^{-1}$. Toxicity, with clinical signs, occurred in the pregnant females at this dose. There were no harmful effects on the fetuses at 56 mg kg$^{-1}$ day$^{-1}$ or lower. In rabbit embryo/fetal development studies, pregnant females were given 15 mg kg$^{-1}$ day$^{-1}$ with no adverse consequences (Forest Laboratories, Inc. 2002).

Citalopram is excreted in milk. In humans, sedation, decreased feeding, and weight loss have been recorded in the infants of mothers being treated with citalopram. When considering giving citalopram to a pregnant or nursing female, the potential benefits must be weighed against the potential risks to the embryo, fetus, or young animal (Forest Laboratories, Inc. 2002).

Citalopram has a longer half-life in geriatric patients than in younger patients. It is recommended that the lower range of the dose be given in geriatric patients (Forest Laboratories, Inc. 2002).

Five of 10 beagles given citalopram at a dose of 8 mg kg$^{-1}$ day$^{-1}$ died between days 17 and 31 after initiation of treatment. Some data suggest that dogs convert citalopram to its metabolites more than do humans. The phenomenon of sudden death was not observed in rats given up to 120 mg kg$^{-1}$ day$^{-1}$, which produced plasma levels of citalopram and its metabolites similar to those observed in dogs on 8 mg kg$^{-1}$ day$^{-1}$. Subsequent intravenous studies showed that DDCT produced prolonged QT intervals. Combined with the fact that dogs metabolize more citalopram to DDCT than do other species studied, this medication should not be considered a first-choice SSRI to use in this species (Forest Laboratories, Inc. 2002).

#### Overdose

Gastric lavage may be useful if conducted soon after ingestion. Induction of emesis is not recommended. Give activated charcoal and provide supportive therapy. There is no specific antidote.

#### Other Information

While the peppermint-flavored solution may seem an obvious choice for use in very small animals, taste aversion could be a problem with various species and individuals. Other SSRIs may be better choices for animals under 10 kg.

In humans, citalopram has not been shown to significantly affect the metabolism of digoxin, warfarin, theophylline, or triazolam (Forest Laboratories, Inc. 2002).

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Citalopram has been effectively used to treat canine acral lick dermatitis (ALD) in dogs when given at a dose of 0.5–1.0 mg kg$^{-1}$ daily. Specifically, six of nine dogs responded, with the average time to achieving a status of "much improved" or better being 2.6 weeks. Side effects that were observed in this population included sedation, anorexia, and constipation. Long-term follow-up of more than one year was available on three dogs. One was continued on a dose of 0.5 mg kg$^{-1}$ and remained lesion-free. One relapsed on

two occasions when medication was discontinued, but recovered when medication was resumed at a maintenance dose of 0.33 mg kg$^{-1}$; a third relapsed when medication was discontinued. This dog was changed to fluoxetine for economic reasons and responded to that agent, on which it was likewise maintained for more than one year (Stein et al. 1998).

## II. Fluoxetine Hydrochloride

**Chemical Compound:** (+)-N-methyl-3-phenyl-3-(ααα-trifluoro-ρ-tolyl) oxypropylamine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10- and 20-mg tablets, 10-, 20-, and 40-mg capsules, a slow release 90-mg tablet, and a mint-flavored solution of 20 mg/5 ml. Reconcile is available in 8-, 16-, 32- and 64 mg chewable tablets.

### Clinical Pharmacology

Fluoxetine is a strong inhibitor of serotonin reuptake and a very weak inhibitor of norepinephrine reuptake. Fluoxetine also has very little binding to muscarinic, histaminergic, and α 1-adrenergic receptors compared with other antidepressants such as the tricyclic antidepressants.

Fluoxetine is well absorbed after oral administration, although food may delay its absorption by one to two hours. Metabolism is not proportional to dose; that is, when fluoxetine is given repeatedly, it is metabolized more slowly than if it is given as a single dose. In humans, peak plasma concentrations of a single oral dose occur in six to eight hours, while the elimination half-life is one to six days (Altamura et al. 1994; Eli Lilly 2004). It is extensively metabolized in the liver to norfluoxetine, its principal metabolite, which is a less-potent SSRI, but has an elimination half-life of 4–16 days. In animal models, S-norfluoxetine has been found to be comparable to the parent compound in inhibition of serotonin reuptake (Altamura et al. 1994; Eli Lilly 2004). In the dog fluoxetine is well absorbed (up to 72%) after oral administration and it is largely metabolized in the liver. After a single dose with approximately 2 mg/kg body weight, peak plasma concentrations occur around 1.8 hours (fluoxetine) and around 12.8 hours (norfluoxetine) while elimination half-life ranged from 3 to 12.9 hours (fluoxetine) and from 33 to 64 hours (norfluoxetine) (Elanco Animal Health 2007).

The elimination half-life of fluoxetine is substantially delayed in patients with liver disease as compared to patients without liver disease. In contrast, human patients on dialysis had steady-state fluoxetine and norfluoxetine concentrations similar to those of patients with normal kidneys. Thus, while the presence of liver disease should always be considered cause for reducing the dose, patients with renal disease may be able to tolerate a normal dose. Elderly patients have not been observed to have a higher incidence of adverse events than young adult patients (Eli Lilly 2004).

The median lethal dose in rats is 452 mg kg$^{-1}$ PO. The median lethal dose in mice is 248 mg kg$^{-1}$. Phospholipids have been shown to increase in the tissues of dogs, mice, and rats chronically medicated with fluoxetine (Eli Lilly 2004).

### Uses in Humans

Fluoxetine hydrochloride is used to treat depression, premenstrual dysphoric disorder, obsessive-compulsive disorder (OCD), and bulimia in humans.

### Contraindications

The combination of fluoxetine and MAOIs can result in serious and sometimes fatal drug interactions. The two medications should never be given together. Because of the long half-life of fluoxetine, treatment with a MAOI should not be initiated until five weeks have passed since the discontinuation of fluoxetine. Conversely, fluoxetine treatment should not be initiated until two weeks have passed since the discontinuation of an MAOI. Thioridazine

should also not be given with fluoxetine or until at least five weeks have passed since discontinuation of fluoxetine, because fluoxetine may result in elevated levels of thioridazine. Rarely, various allergic events may occur in response to fluoxetine, including anaphylactoid reactions.

Fluoxetine inhibits the liver enzymes cytochrome CYP2C9, CYP2D6, CYP2C19, and CYP3A4. Therefore, elevated levels of medications that are metabolized by any of these enzymes may occur when given concurrently, for example, tricyclic antidepressants, benzodiazepines, carbamazepine, and haloperidol. Low doses should be used when these are combined with fluoxetine.

Co-administration of fluoxetine and tryptophan may lead to adverse events. Because tryptophan is available over the counter, clients should be cautioned to not supplement their pet with tryptophan when it is being medicated with fluoxetine or any other serotonin reuptake inhibitor.

Co-administration with warfarin can result in increased bleeding.

#### Side Effects

In a small number of patients, treatment with fluoxetine can result in anxiety, changes in appetite, vomiting, diarrhea, changes in urinary frequency, insomnia, sedation, excitement, seizures, hyponatremia, abnormal bleeding, and decreased sexual motivation. Decreased sexual motivation has been documented to occur in nonhuman animals, as well as humans (Matuszcyk et al. 1998). While this side effect makes fluoxetine undesirable for use in breeding animals, it makes it potentially useful for treatment of problems of undesirable sexual behavior in neutered animals and is irrelevant for animals with behavior problems that are not intended for breeding. Veterinary patients that exhibit increased anxiety with administration of fluoxetine may improve and be subsequently maintained on this medication if the dose is decreased.

Fluoxetine may alter the metabolism of blood glucose. In particular, hyperglycemia may develop during treatment with fluoxetine, while hypoglycemia may develop upon withdrawal from fluoxetine. However, in humans, fluoxetine is effectively used to treat depression in diabetic patients (Lustman et al. 2000). In diabetic patients, insulin doses may need to be modified when initiating and discontinuing treatment with fluoxetine.

Fluoxetine is tightly bound to plasma protein. Therefore, concomitant administration with drugs that are also tightly bound to plasma protein (e.g. digitoxin) can produce plasma levels of either (or both) drugs that are high compared with what they are if given alone, resulting in adverse side effects.

Fluoxetine can alter anticoagulant effects and cause increased bleeding in patients concurrently given warfarin.

Fluoxetine has not been found to be carcinogenic, mutagenic, or impair fertility. However, in rats given 7.5 mg $kg^{-1}$ daily or 12 mg $kg^{-1}$ daily of fluoxetine during pregnancy, there was increased postpartum pup death. Rats given 5 mg $kg^{-1}$ daily did not have increased pup mortality. Also, when ewes in late gestation are given a 70 mg IV bolus of fluoxetine over a two-minute period, transient decreases in uterine artery blood flow, fetal $PO_2$, and oxygen saturation occur within the first 15 minutes. These values do not return to normal after the passage of 24 hours. In addition, fetal pH decreases and fetal $PCO_2$ increases during the first 4 hours and then they return to normal within 24 hours. There are no differences in uterine artery blood flow, blood gas status, or cardiovascular measures between fluoxetine-treated ewes and control ewes (Morrison et al. 2002).

Because of potential risks to the fetus, fluoxetine should not be given to pregnant females unless the potential benefits clearly outweigh the potential risks to the fetus. Likewise, because fluoxetine is excreted in milk, it is recommended that it not be given to nursing females unless either a clear need outweighs the fact that the offspring are also being medicated or the offspring are fed a milk substitute. While caution is indicated, children of women who took fluoxetine throughout pregnancy did not show any decrement in birth weight, preschool IQ,

language development, or behavior (Nulman et al. 2001).

During toxicity testing, rats were given up to 12 mg $kg^{-1}$ daily of fluoxetine for two years without any evidence of carcinogenicity.

#### Overdose

There are no specific antidotes for overdose with fluoxetine. In 87 cases in which humans ingested an acute overdose of fluoxetine without concurrent ingestion of other drugs, the most common symptoms were tachycardia, drowsiness, tremor, vomiting, or nausea. Thirty of the patients (47%) did not develop any symptoms. Asymptomatic patients ingested a mean dose of 341 mg and a maximum dose of 1200 mg (Borys et al. 1992). Gastric lavage may be helpful if done soon after the overdose. Induction of emesis is not recommended. Give activated charcoal and supportive therapy. Give diazepam for seizures.

#### Doses in Nonhuman Animals

Doses reported for dogs generally range from 1.0–2.0 mg $kg^{-1}day^{-1}$, while doses reported for cats run a bit lower, generally ranging from 0.5–1.5 mg $kg^{-1}$ $day^{-1}$. Smaller animals and/or species with faster metabolism, such as birds, will need higher doses to obtain clinical efficacy. Doses reported for birds range from 2.0 to 5 mg $kg^{-1}$ $day^{-1}$. Conversely, larger animals are likely to need smaller doses on a per kilogram basis. While there are no clinical reports of the treatment of rats, mice, or rabbits with fluoxetine, these species have tolerated very high doses in laboratory studies of toxicity. Horses may be effectively treated with 100–200 mg daily, or approximately 0.25–0.50 mg $kg^{-1}$.

#### Discontinuation of Fluoxetine

For patients that have been on fluoxetine for several weeks or months, it is recommended that discontinuation be done gradually rather than abruptly. In practice, if fluoxetine is effective in the treatment of the target behavior or anxiety-related problem, continue medication for another one to three months, depending on the severity of the primary problem. Once it is confirmed that the problem has achieved long-term remediation with medication, fluoxetine is decreased at a rate not to exceed 25% of the maintenance dose per week. Some patients experience relapses at given decreases. If this happens, go back up to the lowest effective dose and continue for another one to three months, and then attempt to decrease the dose again.

#### Other Information

Fluoxetine has been more extensively used in the treatment of behavior problems in domestic animals than any other SSRI. Cats exhibit a strong distaste for the mint-flavored solution designed for humans. Rather than attempt to give this orally, it is recommended that a compounding pharmacist prepare a solution in a tuna- or chicken-flavored liquid or that tablets are dispensed.

While fluoxetine is not approved for use in the treatment of aggression in humans, several small studies have supported the hypothesis that it is effective in treating aggression (e.g. impulsive aggression, self-injurious behavior) in some patients (see, e.g. Charney et al. 1990; Coccaro et al. 1990; Cornelius et al. 1991; Markowitz 1992; Kavoussi et al. 1994). In addition, a meta-analysis of 3992 patients treated with fluoxetine or placebo during clinical trials revealed that aggressive events were four times less likely to occur in fluoxetine-treated patients than in placebo-treated patients (Heiligenstein et al. 1993). Fluoxetine has been shown to suppress aggression in various laboratory animal species, for example, golden hamsters (*Mesocricetus auratus*) and lizards (*Anolis carolinensis*) (Deckel 1996; Deckel and Jevitts 1997; Ferris et al. 1997).

#### Effects Documented in Nonhuman Animals

Administration of fluoxetine to dogs and cats is quite common in small animal practice in North America. One survey study using 127 veterinary professional participants in North America showed 83% of clinician prescribed it to their feline and canine patients for an array of behavior problems. These were

anxiety disorders, aggressive behavior, compulsive disorders, phobias/fear and other problem behaviors, with anxieties being more common in dogs. While in cats, elimination behaviors, anxiety disorders, aggression, dermatologic/grooming, compulsive disorders and others, elimination behaviors being most common (Kaur et al. 2016).

***Cats***

Fluoxetine in a 15% pluronic lecithin organogel (PLO gel) formulation can be absorbed through the skin of cats into the systemic circulation. However, bioavailability of transdermally administered fluoxetine is only 10% that of the oral route although it was administered in a single dose. When concentrations are increased to achieve clinically effective levels, dermatitis results. Thus, transdermal administration of fluoxetine is not recommended (Ciribassi et al. 2003). Eichstadt et al. (2017) made a comparison of serum concentration between daily administration of transdermal ($5\,mg\,kg^{-1}$) with the proprietary transdermal base (PCCA Lipoderm) and oral ($1\,mg\,kg^{-1}$) fluoxetine in cats. The drug administration for both routes was daily for 60 days. The blood concentrations or fluoxetine and norfluoxetine were seemingly accumulated by time and the concentrations between the two routes were significantly different at the 30-day point. Oral administration was much higher for both concentrations. Since this study did not evaluate the clinical effects, the author did not conclude if the given transdermal dose was clinically sufficient.

Hartmann (1995), in a letter to the *American Journal of Psychiatry*, reported on a cat with ALD that had not responded to more conventional treatments, including hypoallergenic diets, diphenhydramine, and diazepam, but the condition resolved when given fluoxetine at $0.25–0.38\,mg\,kg^{-1}$ daily. The only side effect observed was mild sedation.

Romatowski (1998) described two clinical cases of cats that responded to fluoxetine. One was a 16-month-old, 3-kg, spayed female Siamese cat that was presented with symmetrical, self-induced alopecia on the forelimbs. The cat was also a nervous and hyperactive pet. There were no cutaneous lesions other than the hair loss, and the cat had no fleas or flea manure. Treatment with methylprednisolone, phenobarbital, a commercial lamb and rice diet, and finally, megestrol acetate, all failed to resolve the problem. In fact, during these treatments, the hair loss became more extensive and eventually involved the abdomen, flanks, and thighs in a symmetrical pattern. Finally, treatment with fluoxetine, $0.66\,mg\,kg^{-1}$ (2 mg daily) was attempted. The cat discontinued the excessive licking and after five months had grown a full hair coat. The owner also reported that the cat was more relaxed and a more pleasant pet.

The second case described by Romatowski involved two five-year-old, spayed female, domestic shorthair littermates. The two cats had gotten along well until they were moved to a new home approximately one year prior to presentation. Before the move, the cats had been entirely indoors. After the move, they were allowed access to the backyard. One cat began rejecting the other, hissing whenever she approached. The rejected cat began intermittently urinating in various places in the house on a variety of substrates, for example, countertops, plastic or paper bags, the sleeping place of the cat that was rejecting her, and the owner's clothes. Urinalysis of the cat with the elimination behavior problem was unremarkable. Treatment with buspirone, 5 mg two times a day (b.i.d) for 30 days, was ineffective, as was treatment with diazepam, 1 mg b.i.d. Both cats were then placed on 2 mg fluoxetine daily. This treatment resulted in a discontinuation of the hissing behavior. The cats resumed sleeping together and grooming each other, behavior that had not occurred since the move. Inappropriate elimination was decreased by 50%.

Pryor et al. (2001) treated 17 neutered urine-spraying cats, all over one year of age, with fluoxetine or a fish-flavored liquid placebo in a randomized, double-blind, placebo-controlled trial. The initial dose was

1 mg kg$^{-1}$ PO given once daily. If the patient did not achieve a 70% reduction in urine spraying by the fifth week, the dose was increased to 1.5 mg kg$^{-1}$. To maintain blinding, any cat that did not show improvements, including those on placebo, were given a 50% increased dose of their compounded medication. Treatment was carried out for eight weeks, followed by an additional four weeks of monitoring the cats after they had discontinued medication.

Standardized environmental management was as follows: (i) the owners were provided with an enzymatic cleaner that they were to use on all soiled areas; (ii) the owners were instructed to provide as many litter boxes as cats in the household, plus one more; (iii) the owners were instructed to clean all feces and urine from the litter boxes once a day and to completely change the litter material and wash the litter boxes once per week; and (iv) the owners were instructed to refrain from physically or verbally punishing the cats.

Cats on the treatment showed a significant decrease in spraying behavior, compared with baseline premedication measures after two weeks of treatment. Their spraying rate continued to decrease throughout treatment. In contrast, the mean weekly spraying rate of cats on placebo decreased slightly during the first week and did not decrease further thereafter. This slight decrease was probably a response to the environmental management and increased regular supervision that was necessarily occurring because of the research. By the end of the trial, all cats on treatment had demonstrated a 90% reduction in the number of urine marks each week. Total cessation of spraying occurred in 66% of the cats on treatment by the eighth week. For weeks two through eight, there was a significant difference in response for the cats on placebo versus the cats on treatment. The most common side effect reported was decreased food intake; however, this was reported in four of the nine cats on treatment and three of the seven cats on placebo. The decreased food intake was never to such a degree that it was cause for concern or considered clinically significant. Vomiting occurred in one cat on treatment and two cats on placebo. Lethargy occurred in three cats on treatment and two cats on placebo.

After medication was discontinued, two of the nine cats that had been treated did not resume spraying. However, the other seven cats resumed some degree of marking. There was a linear correlation between the rate of marking during baseline and the rate of marking four weeks after treatment. Because of this finding, it is recommended that most cats, particularly those with higher rates of urine marking prior to treatment, that is, four or more marks per week, should be treated for a period longer than eight weeks.

***Dogs***

Six laboratory dogs overdosed with fluoxetine given orally developed grand mal seizures that were controlled with intravenous boluses of diazepam. In another study, the electrocardiogram (ECGs) of dogs given high doses of fluoxetine were evaluated. Tachycardia and increased blood pressure occurred. However, no changes occurred in the PR, QRS, or QT intervals (Eli Lilly 2004).

Overall (1995) described a case of a dog with "dominance-related" interdog aggression, "dominance aggression" to the dog's owner, fear of strangers, and stereotypic circling. Initial treatment with behavior modification alone resulted in resolution of the aggression toward the owner, but did not resolve the interdog aggression or fear of strangers. Therefore, medication treatment was initiated. After an initial period of treatment with fluoxetine alone, then buspirone, then buspirone with fluoxetine, and finally fluoxetine alone, the dog was maintained on fluoxetine at a dose of 0.54 mg kg$^{-1}$ daily for a period of 28 months. During this time, there was only one incident of interdog aggression, and there was no owner-directed aggression. Side effects included constant mydriasis after the initiation of treatment with fluoxetine. Renal and hepatic function were not compromised while on the long-term fluoxetine treatment.

In a later study, Dodman et al. (1996) conducted a single-blind crossover trial of the treatment of owner-directed "dominance" aggression in nine dogs. Diagnosis was based entirely on context and frequency of aggression and did not include signaling behavior. Therefore, patients with what the author considers to be other forms of affective aggression may have been included in this study's population. Patients were treated with fluoxetine at a dose of 1 mg kg$^{-1}$ PO q24h, and one week of a placebo. The fluoxetine and placebo were placed into gelatin capsules so that they were visually indistinguishable. While owners were not told which week their dog would be getting the placebo, all dogs received the placebo during the first week of the trial to avoid a carryover effect from the fluoxetine, since it has a long half-life. No behavior modification or training was carried out during the five-week study.

A significant reduction in owner-directed incidents of aggression was observed by the end of treatment. While on medication, some dogs exhibited changes in level of activity, changes in food or water intake, increased alertness, shaking, barking, and reclusion. While it is not recommended that medication be used alone in the treatment of canine affective aggression, it is clear from this report that SSRI medications such as fluoxetine can be useful adjuncts to treatment with behavior modification. Fluoxetine has also been used to treat additional cases of inter-dog aggression (at 1.1 mg kg$^{-1}$ PO daily, in combination with behavior modification) (Dodman 2000).

Rapoport et al. (1992) compared fluoxetine to fenfluramine in 14 dogs with ALD in an 11-weeks crossover treatment trial. Dogs were treated for five weeks with up to $0.96 \pm 0.29$ mg kg$^{-1}$ daily of fluoxetine and for another five weeks with up to $0.92 \pm 0.24$ mg kg$^{-1}$ daily of fenfluramine. Owners used a 10-point scale to rate their dogs' licking with 0 being no licking at all and 10 being the worst licking ever observed. There was no order effect, so ratings were combined across both orders. Dogs on fluoxetine exhibited, on average, a 39% decrease from baseline scores. By five weeks, improvement on fluoxetine was significantly greater than improvement on fenfluramine, which was slight. Concurrent studies were carried out on an additional 13 dogs that were treated with clomipramine or desipramine and another 10 dogs that were treated with sertraline or placebo in a similar crossover trial. Comparisons in response across trials showed that fluoxetine was more effective than desipramine, fenfluramine, and sertraline in reducing licking. Four of the 14 dogs treated with fluoxetine showed lethargy, 1 showed loss of appetite, and 1 showed hyperactivity. Two of the dogs treated with fluoxetine showed complete remission of excessive licking, while four showed a 50% reduction in licking.

Stein et al. (1992) likewise used fluoxetine, 1–2 mg kg$^{-1}$ daily for an eight-week open trial on five dogs with ALD. One dog almost entirely discontinued self-injurious behavior, but developed polyuria and polydipsia. Two others showed substantial improvement with no side effects. One dog was removed from the study at two weeks when there was no response, while another was removed from the study because it exhibited sedation. Subsequent use of fluoxetine in cases of OCD manifested as canine acral lick have been reported as having about a 50% success rate (Karel 1994). In the author's experience, improvement may not be exhibited for four weeks or more. Sedation, when it occurs, is often transient, and dogs usually return to normal levels of activity after a couple of weeks.

Wynchank and Berk (1998) subsequently conducted a double-blind, randomized, placebo-controlled trial of the use of fluoxetine in the treatment of ALD in dogs. All dogs on treatment were dosed at 20 mg day$^{-1}$, regardless of size, for six weeks. The smallest dog was 5 kg. Thus, this dog was dosed at 4 mg kg$^{-1}$. For a dog to qualify for the study, a veterinarian must have diagnosed the dog with ALD at least six months before

the beginning of the trial. Other causes of licking behavior must have been ruled out, as well.

Fifty-eight dogs, ranging in age from 1 to 13 years, completed the trial. For dogs that were on the treatment, owner rating of the licking behavior and appearance of the lesion decreased significantly over the course of treatment. The placebo group did not exhibit a significant decline. There was a significant difference between treatment and placebo groups in both change in appearance of the lesion and general condition of the dog by the end of the study. Veterinarians who were blinded as to whether or not the photographs were before or after treatment evaluated photographs of the lesions. Changes in the scores for lesion severity were significantly better for the treatment group than for the placebo group. No adverse events were reported.

Irimajiri et al. (2009) reported the efficacy of fluoxetine for compulsive disorders in dogs by randomized, controlled clinical trial. Sixty-three dogs with compulsive disorders were randomly assigned to treatment with fluoxetine (1–2 mg $kg^{-1}$ daily) or a placebo without any behavior or environmental modification during 42 day study. The owners kept daily diary of the severity of episodes and the researchers collected the information through telephone interviews every 2 weeks. It was found that the severity of the condition was more likely to decrease (odds ratio, 8.7) in the fluoxetine group compared to the placebo group. However, mean number and duration of compulsive episodes, as determined from daily diary entries, did not differ significantly between groups. They also reported that the most common adverse effects were decreased appetite and mild lethargy. When fluoxetine was used to treat anxiety, Reisner (2003) reported forty dogs treated for generalized anxiety disorder with fluoxetine at 0.37–1.2 mg $kg^{-1}$, 27 (67%) improved, 9 showed no significant behavior change, and 4 got worse while on this treatment (Reisner 2003).

Reconcile, a chewable tablet form of fluoxetine, is the another FDA approved veterinary medication for the treatment of separation anxiety in dogs, but only in conjunction with behavior modification. Sherman-Simpson et al. (2007) conducted a multiple-center, placebo-controlled, double-blind, parallel-arm study to investigate the clinical efficacy and safety of Reconcile (1–2 mg $kg^{-1}$ daily), in conjunction with behavior management for the treatment of separation anxiety in dogs. A total of 242 client-owned dogs were randomized into the study for 8-week treatment. They found about 42% of dogs treated with Reconcile improved within 1 week of treatment, which was significantly greater than the 17% of dogs with placebo. Although dogs in both groups continued to improve over the course of the 8-week treatment period, dogs in reconcile group demonstrated a significant improvement compared to the placebo group (72% improvement vs. 50% respectively). Later, another multi-center, placebo-controlled, double-blind randomized parallel-arm study on 208 client-owned dogs diagnosed with separation anxiety conducted without behavior modification training (Landsberg et al., 2008). In this study Reconcile (1–2 mg $kg^{-1}$ daily ) or placebo was given for 6 weeks. Without behavior modification the dogs showed 58% improvement in overall separation anxiety severity scores comparing to its pre-treatment score, however, the there was no significant difference when it was compared to the placebo group. Based on the outcome between two studies, the authors of the study recommended that pharmacotherapy should have the conjunction with behavior modification to get the optimal outcome.

#### *Parrots*

Mertens (1997) reported that 12 of 14 birds treated with fluoxetine for feather-picking (2.3 mg $kg^{-1}$ daily for at least four weeks) exhibited initial improvement but subsequently relapsed. An increased dose up to as high as 3 mg $kg^{-1}$ b.i.d. again resulted in improvement with a subsequent relapse. Side effects observed included frequent sneezing (two birds) one week after initiation of

treatment, temporary ataxia, and lethargy about one hour after medication (two birds). Additionally, one bird that had an extensive vocabulary, including songs and poems, forgot word sequences and exhibited a reduced vocabulary. All problems disappeared after treatment was discontinued. All birds were kept in good housing conditions, with provision of intra- and interspecific social contact, good dietary management, and exercise.

Seibert (2004) treated a 3.5-year-old white female cockatiel (*Nymphicus hollandicus*) (1 mg kg$^{-1}$ of fluoxetine PO, q24h) with a compulsive disorder that was specifically manifested as chewing the third digit of the right foot. The bird responded two weeks after initiation of treatment. After three months of treatment, the dosage was decreased. By five months treatment was successfully discontinued.

#### *Primates*

Vervet monkeys with various stereotypic behaviors, for example, saluting, somersaulting, weaving, and head tossing, were treated with fluoxetine (1 mg kg$^{-1}$ daily for six weeks) or placebo. Results of assessment by a rater blind to treatment status identified a significant difference between fluoxetine-treated and placebo-treated monkeys by the end of the trial (Hugo et al. 2003).

## III. Fluvoxamine

**Chemical Compound:** 5-Methoxy-4′-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 25-, 50-, and 100-mg tablets.

### Clinical Pharmacology

Fluvoxamine specifically inhibits reuptake of serotonin in both blood platelets and brain synaptosomes (Claassen et al. 1977). It has a weak affinity for histaminergic, α- or β-adrenergic, muscarinic, or dopaminergic receptors. Absorption is not affected by food intake. In humans, steady-state plasma concentrations are achieved in about 10 days. Once people have achieved steady state, peak plasma concentrations occur in three to eight hours. The pharmacokinetics of fluvoxamine are nonlinear. Specifically, higher doses of fluvoxamine produce proportionally higher concentrations in the plasma than do lower doses.

Fluvoxamine is metabolized by the liver, primarily via oxidative demethylation and deamination. Nine metabolites have been identified. The major human metabolites are fluvoxamine acid, the *N*-acetyl analog of fluvoxamine acid, and fluvoxethanol, all of which have little to no serotonin reuptake prevention activity. Humans excrete only about 2% of fluvoxamine as the parent compound. The remaining 98% is excreted as various metabolites (Solvay Pharmaceuticals 2002).

Excretion occurs primarily via the kidneys. In healthy humans, an average of 94% of the medication is excreted in the urine within 71 hours of dosing. Geriatric patients clear fluvoxamine more slowly than young adults. Patients with liver disease clear fluvoxamine more slowly than do healthy patients. However, patients with renal disease have not been found to clear fluvoxamine any more slowly than do persons without renal disease (Solvay Pharmaceuticals 2002).

### Uses in Humans

Fluvoxamine is used to treat OCD in humans.

### Contraindications

Fluvoxamine should not be administered with terfenadine or cisapride. These are metabolized by the P450 isozyme 3A4. While there is no definitive proof that fluvoxamine is a 3A4 inhibitor, there is strong evidence that it is. Thus, co-administration could result in elevated terfenadine or cisapride levels, which could result in QT prolongation, ventricular tachycardia, and other cardiac symptoms (Solvay Pharmaceuticals 2002).

Fluvoxamine should not be administered at the same time as MAOIs. It should not be

used in patients that have previously received an MAOI until the patient has been off the MAOI for at least two weeks. Conversely, MAOIs should not be given until a patient has stopped fluvoxamine for at least two weeks.

The metabolism of benzodiazepines by hepatic oxidation, including alprazolam, midazolam, and triazolam (see Chapter 3) can be reduced by combined use with fluvoxamine. Benzodiazepines metabolized by glucuronidation, including lorazepam, oxazepam, and temazepam, are not likely to be affected by co-administration with fluvoxamine (Solvay Pharmaceuticals 2002).

Fluvoxamine can alter the efficacy and activity of warfarin, propanaolol, tricyclic antidepressants, and theophylline, as well as other drugs metabolized by the P450 enzyme system. Tryptophan may increase the serotonergic activity of fluvoxamine and should be used in combination with caution (Solvay Pharmaceuticals 2002).

#### Side Effects

In a small number of patients, treatment with fluvoxamine can result in anxiety, changes in appetite, vomiting, diarrhea, changes in urinary frequency, insomnia, sedation, excitement, seizures, hyponatremia, abnormal bleeding, mydriasis, decreased libido, and various other side effects unique to individuals, including anaphylaxis.

Studies of the potential for carcinogenicity, mutagenicity, and impairment of fertility by fluvoxamine have not revealed any such effects. Rats were treated with doses of up to 240 mg kg$^{-1}$ day$^{-1}$ for 30 months, and hamsters were treated with doses of up to 240 mg kg$^{-1}$ day$^{-1}$ for up to 20 months, with no carcinogenic effect. In fertility studies, male and female rats were given up to 80 mg kg$^{-1}$ day$^{-1}$ PO of fluvoxamine, with no deleterious effects on mating, duration of gestation, or pregnancy (Solvay Pharmaceuticals 2002).

In teratology studies in which pregnant rats were given up to 80 mg kg$^{-1}$ day$^{-1}$ PO and pregnant rabbits were given up to 40 mg kg$^{-1}$ day$^{-1}$ PO, there were no fetal malformations. In other studies, in which pregnant rats were dosed through weaning with 5, 20, 80, and 160 mg kg$^{-1}$ day$^{-1}$ PO there was an increase in pup mortality at birth in rats that were dosed at 80 mg kg$^{-1}$ and higher, decreased neonatal pup weights at 160 mg kg$^{-1}$, and decreased long-term survival of the pups at all doses. Results of a cross-fostering study suggested that some of the postnatal deficits in survival were due to maternal toxicity; that is, the mothers being chronically medicated at such high doses were not as competent mothers as were unmedicated rats. However, there may have been some direct drug effect on the offspring.

Fluvoxamine is excreted in the milk. In deciding whether to medicate pregnant or lactating females, potential risks to the offspring must be weighed against the potential benefits to the mother (Solvay Pharmaceuticals 2002).

In human studies, the side-effect profile for pediatric patients has been found to be similar to the side-effect profile for adult patients (Solvay Pharmaceuticals 2002).

#### Overdose

Gastric lavage may be useful if it is conducted soon after ingestion of an overdose. Give activated charcoal and provide supportive therapy. There is no specific antidote.

#### Other Information

Comparisons of humans treated with either placebo or fluvoxamine showed no significant effect of fluvoxamine on various vital sign indicators, serum chemistries, hematology, urinalysis, or ECG changes. Fluvoxamine has not been found to significantly affect the pharmacokinetics of digoxin (Solvay Pharmaceuticals 2002).

#### Effects Documented in Nonhuman Animals

Fluvoxamine has a specific antiaggressive effect on maternal aggression, because it results in decreased aggression at doses that do not cause concurrent nonspecific decreases in activity (Olivier and Mos 1992).

## IV. Paroxetine Hydrochloride

**Chemical Compound:** (–)-Trans-4R-(4′-fluorophenyl)-3S-[(3′, 4′-methylenedioxyphenoxyl)methyl]piperidine hydrochloride hemihydrate

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10-, 20-, 30-, and 40-mg tablets and a 2-mg $ml^{-1}$ orange-flavored suspension. Controlled-release tablets are available in 12.5-, 25-, and 37.5-mg sizes.

### Clinical Pharmacology

Paroxetine has weak effects on neuronal reuptake of norepinephrine and dopamine, but is primarily a highly selective inhibitor of serotonin reuptake. It has little affinity for muscarinic, $\alpha_1$-, $\alpha_2$-, β-adrenergic, dopamine ($D_2$)-, 5-$HT_1$-, 5-$HT_2$-, or histamine ($H_1$) receptors. Thus, there are fewer anticholinergic, sedative, and cardiovascular side effects than some other serotonin reuptake inhibitors, such as amitriptyline, that also have substantial effects on muscarinic, histaminergic and $\alpha_1$-adrenergic receptors. Paroxetine has multiple metabolites, each about 1/50th as potent as the parent compound. Thus, clinical efficacy of paroxetine is essentially from the parent compound, and there are no significant contributions from metabolites (SmithKline Beecham Pharmaceuticals 2004).

Paroxetine is completely absorbed when given orally and can be given with or without food. In humans, the half-life is about 10 days, with 64% being excreted in the urine, 2% as paroxetine, and the remainder as metabolites of paroxetine. The remaining 36% is excreted in the feces, <1% as paroxetine, and the remainder as metabolites. With chronic daily dosing, steady-state plasma concentrations are achieved in about 10 days. Paroxetine is distributed throughout the body, including the central nervous system, with about 95% being bound to plasma protein (SmithKline Beecham Pharmaceuticals 2004).

The presence of renal or hepatic disease produces increased concentrations of paroxetine in the plasma. Therefore, patients with mild renal or hepatic impairment should be started on a very low dose and the dose titrated upward over time. Plasma levels in older patients are also elevated. Therefore, the starting dose should be low in all geriatric patients and subsequently titrated upward as necessary (SmithKline Beecham Pharmaceuticals 2004).

Paxil CR tablets are formulated so that dissolution occurs gradually over a period of several hours. There is also an enteric coat that prevents release of the active ingredient until after the tablet has left the stomach. The consumption of food does not significantly affect release or absorption. For the slower release to occur, the tablet cannot be cut, broken, or chewed (SmithKline Beecham Pharmaceuticals 2004). This limits its potential usefulness in animals weighing less than approximately 10 kg. Even in animals large enough to theoretically be given the controlled release tablets, it is important to remember that these tablets are designed for the human digestive system and dissolve and are absorbed at substantially slower or faster rates in various other species.

### Uses in Humans

Paroxetine is used to treat depression, OCD, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder (PTSD).

### Contraindications

Do not use paroxetine in combination with any MAOI or with thioridazine, because serious and sometimes fatal drug interactions can result. Patients should not be given paroxetine for at least two weeks before initiating medication with either of these drugs. Patients should not have been given MAOIs for at least two weeks before initiation of paroxetine (SmithKline Beecham Pharmaceuticals 2004).

Paroxetine inhibits the liver enzyme CYP2D6 but otherwise causes less inhibition

of liver enzymes than do other SSRIs such as fluoxetine and fluvoxamine. Nevertheless, there are a large number of medications that are metabolized by this enzyme, including amitriptyline, clomipramine, dextromethorphan, imipramine, propranolol, and thioridazine. Thus, lower doses should be used in patients concurrently receiving any drug that is metabolized by this enzyme (SmithKline Beecham Pharmaceuticals 2004).

Do not use in patients with narrow angle glaucoma.

Concurrent use of paroxetine and tryptophan can result in adverse events. Because tryptophan is available over the counter, clients should be advised of this (SmithKline Beecham Pharmaceuticals 2004).

Paroxetine may interact with warfarin, altering its effect on bleeding. Paroxetine is strongly bound to plasma protein, resulting in a greater plasma concentration of any drug administered concurrently that is likewise strongly bound to plasma protein (SmithKline Beecham Pharmaceuticals 2004).

#### Side Effects

In a small number of patients, treatment with paroxetine can result in anxiety, changes in appetite, vomiting, diarrhea, changes in urinary frequency, insomnia, sedation, excitement, seizures, hyponatremia, abnormal bleeding, mydriasis, decreased libido, and various other side effects unique to individuals, including anaphylaxis (SmithKline Beecham Pharmaceuticals 2004). Studies conducted in humans have shown that the incidence of many side effects is dose-dependent, that is, the higher the dose, the more likely it is that side effects will occur. Withdrawal reactions occur at a higher rate for paroxetine than for fluoxetine, fluvoxamine, or sertraline in the human population (Price et al. 1996). In case of decreased libido, while this side effect makes paroxetine undesirable for use in breeding animals, it makes it potentially useful for treatment of animals with undesirable sexual behavior. In cats, constipation is a potential side effect of paroxetine (Frank and Dehasse 2003).

Carcinogenicity studies were conducted in mice and rats on paroxetine for two years. Mice were given 1, 5, or 25 mg $kg^{-1}$ daily, and rats were given 1, 5, or 20 mg $kg^{-1}$ daily. The male rats in the high-dose group had significantly more sarcomas than did the male rats in the low- or medium-dose group or on placebo. There was no carcinogenic effect identified in mice or female rats. The implications of these findings for other domestic animals are unknown (SmithKline Beecham Pharmaceuticals 2004). Since the dose that induced cancer in male rats was greater than what would be used as a therapeutic dose for the treatment of behavior problems in pet rats, the findings are probably not of concern in treating this group. Nevertheless, owners should be cautioned.

Studies of potential mutagenicity of paroxetine have not identified any mutagenic effects of this medication.

Female rats experienced a reduced pregnancy rate when given 15 mg $kg^{-1}$ daily of paroxetine. Male rats given 25 mg $kg^{-1}$ daily had atrophic changes in the seminiferous tubules and aspermatogenesis. Male rats given 50 mg $kg^{-1}$ $day^{-1}$ had vacuolation of the epididymal tubular epithelium (SmithKline Beecham Pharmaceuticals 2004).

In studies of teratogenic effects, pregnant rabbits were given 6 mg $kg^{-1}$ daily, and pregnant rats were given 50 mg $kg^{-1}$ daily during organogenesis. There were no teratogenic effects in either species and no increased postnatal pup deaths in rabbits. However, in rats there was increased pup mortality when paroxetine was continued during the last trimester and lactation. The cause of this mortality has not been identified. The implications of these findings for other domestic animals are not known. However, because of these findings and the fact that paroxetine is secreted in milk, it should be used in pregnant and lactating females only when the potential benefits clearly outweigh the risks (SmithKline Beecham Pharmaceuticals 2004).

Geriatric patients have decreased clearance time as compared with younger patients.

Therefore, lower dosing is recommended in geriatric patients (SmithKline Beecham Pharmaceuticals 2004).

#### Overdose

Gastric lavage may be useful if conducted soon after ingestion. Induction of emesis is not recommended. Give activated charcoal, and provide supportive therapy. There is no specific antidote.

#### Discontinuation of Paroxetine

For patients that have been on paroxetine for several weeks, it is recommended that discontinuation be done gradually rather than abruptly. While abrupt discontinuation of a variety of SSRI treatments can cause withdrawal symptoms, this phenomenon has been most frequently reported with paroxetine in the human literature (Price et al. 1996; Michelson et al. 1998). In practice, if paroxetine is effective in the treatment of the target behavior problem, continue medication for another one to three months, depending on the severity of the primary problem. Once it is confirmed that the problem has achieved long-term remediation with medication, paroxetine is decreased at a rate not exceeding 25% of the maintenance dose per week. Some patients experience relapses at given decreases. If this happens, go back up to the lowest effective dose and continue for another one to three months, then attempt to decrease the dose again.

#### Other Information

In double-blind placebo-controlled trials conducted on humans, paroxetine was not found to produce any significant changes in ECGs, heart rate, blood pressure, or liver enzymes.

Paroxetine has an insignificant effect on the liver enzyme CYP2C19. Therefore, there is no need for lower doses of benzodiazepines, which are metabolized by this enzyme, as is the case with fluoxetine and fluvoxamine (SmithKline Beecham Pharmaceuticals 2004).

#### Effects Documented in Nonhuman Animals

##### *Cats*

Paroxetine has been used to treat cats for urine marking and aggression toward humans and cats (Frank and Dehasse 2003; Pryor 2003; Pachel 2014).

##### *Dogs*

Of 12 dogs treated with paroxetine (0.96–1.75 mg $kg^{-1}$ PO q24h), for generalized anxiety disorder, 6 (50%) showed improvement, 4 showed no change, and 1 dog got worse (Reisner 2003). The response of the twelfth dog is not reported.

##### *Horses*

A mare with a five-year history of weaving exhibited a 95% decrease in this behavior when given 0.5 mg $kg^{-1}$ daily PO. Even when stressed, the mare exhibited a 57% improvement over baseline. Specifically, the frequency of weaving changed from 43.5 per minute with kicking to less than 1 per minute. When the mare was stressed, weaving increased to 18.75 per minute (Nurnberg et al. 1997).

## V. Sertraline Hydrochloride

**Chemical Compound:** (1S-*cis*)-4-(3, 4-dichlorophenyl)-(1, 2, 3, 4-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 25-, 50-, and 100-mg tablets and a 20-mg $ml^{-1}$ liquid.

#### Clinical Pharmacology

Sertraline is a selective inhibitor of neuronal serotonin reuptake. It has very weak effects on reuptake of norepinephrine and dopamine. Sertraline has no substantial affinity for adrenergic ($\alpha_1$, $\alpha_2$, and $\beta$), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_2$), or benzodiazepine receptors. Therefore, the anticholinergic, sedative and cardiovascular effects seen with some other

psychoactive drugs, such as the tricyclic antidepressants, are minimal. Chronic administration of sertraline also down-regulates brain norepinephrine receptors. The half-life in humans is about 26 hours. Blood levels reach a steady state after approximately one week of daily dosing in a healthy adult. More time is required to achieve steady state in older patients. Sertraline can be given with or without food (Pfizer Inc. 2004).

Sertraline is metabolized extensively during its first pass through the liver, primarily to *N*-desmethylsertraline, which has a plasma elimination half-life of 62–104 hours. *N*-desmethylsertraline is a less potent serotonin reuptake inhibitor than is the parent compound. In human subjects given a single radiolabeled dose of sertraline, 40–45% of the radioactivity was recovered via the urine within nine days. Another 40–45% was recovered in the feces. The urine contained only metabolites of sertraline, while the feces contained 12–14% of the original sertraline in an unchanged form, the remainder being metabolites produced by oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation (Pfizer Inc. 2004).

In human pediatric studies, it was found that children and teenagers (6–17 years of age) metabolized sertraline more efficiently than did adults. There was no difference between males and females. In contrast, geriatric patients clear sertraline more slowly than adults (Pfizer Inc. 2004).

Patients with chronic mild liver impairment clear sertraline more slowly than do age-matched patients with normal liver function. This is not a surprising finding given the significant metabolism of the drug in the liver in normal patients. As discussed above, clearance of unchanged sertraline in the urine is a minor mode of elimination of the parent compound, and almost half of the metabolites are eliminated in the feces. In patients with mild to severe renal impairment the pharmacokinetics of sertraline metabolism and excretion are not significantly different from healthy controls (Pfizer Inc. 2004).

The minimum lethal doses are 350 mg $kg^{-1}$ PO in male mice, 300 mg $kg^{-1}$ PO in female mice, 1000 mg $kg^{-1}$ in male rats, and 750 mg $kg^{-1}$ in female rats. Death occurs after one to two days (Pfizer Inc. 2004).

#### Uses in Humans

Sertraline is used to treat depression, OCD, PTSD, panic disorder, and premenstrual dysphoric disorder in humans.

#### Contraindications

Do not use sertraline in combination with any MAOI, because serious and sometimes fatal drug interactions can result. Patients should not be given sertraline for at least two weeks before initiating medication with an MAOI. Patients should not have been given monoamine oxidase inhibitors for at least two weeks prior to initiation of paroxetine (Pfizer Inc. 2004).

#### Side Effects

In a small number of patients, treatment with sertraline can result in anxiety, changes in appetite, vomiting, diarrhea, changes in urinary frequency, insomnia, sedation, excitement, seizures, hyponatremia, abnormal bleeding, mydriasis, decreased libido, and various other side effects unique to individuals, including anaphylaxis. Rarely, patients on sertraline may have altered platelet function and abnormal bleeding (Pfizer Inc. 2004).

Sertraline has some effect of inhibiting the biochemical activity of the liver enzyme CYP2D6. While its effect is not as substantial as paroxetine or fluoxetine (Albers et al. 2002), it should be used with caution with drugs that are metabolized by this enzyme, such as the tricyclic antidepressants dextromethorphan and propranolol.

Lifetime carcinogenicity studies have been conducted on mice and rats given up to 40 mg $kg^{-1}$ $day^{-1}$ of sertraline. Male mice experienced a dose-related increase in liver adenomas. Female mice did not experience this increase. Female rats experienced an increase in the rate of follicular adenomas of

the thyroid gland at 40 mg kg$^{-1}$ day$^{-1}$. This change was not accompanied by thyroid hyperplasia. There was an increase in uterine adenocarcinomas in female rats given 10–40 mg kg$^{-1}$ day$^{-1}$ compared with placebo (Davies and Kluwe 1998; Pfizer Inc. 2004).

In tests of mutagenicity, no mutagenic activity has been identified. Doses of 80 mg kg$^{-1}$ day$^{-1}$ result in decreased fertility in rats (Davies and Kluwe 1998; Pfizer Inc. 2004).

Pregnant rats have been given sertraline up to 80 mg kg$^{-1}$ day$^{-1}$, while pregnant rabbits have been given sertraline up to 40 mg kg$^{-1}$ day$^{-1}$. Sertraline was not teratogenic at these doses. When the pregnant rats and rabbits were medicated during the period of organogenesis, delayed ossification occurred in the fetuses when their mothers were on doses of 10 mg kg$^{-1}$ day$^{-1}$ in rats and 40 mg kg$^{-1}$ day$^{-1}$ in rabbits. At a dose of 20 mg kg$^{-1}$ day$^{-1}$ given to rats during the last third of gestation and lactation, there was decreased body weight gain in the pups and increased early postnatal mortality. There was no effect at 10 mg kg$^{-1}$ day$^{-1}$. The increased pup mortality was due to the *in utero* exposure to sertraline at the higher doses (Davies and Kluwe 1998; Pfizer Inc. 2004).

Dogs given ≥40 mg kg$^{-1}$ PO of sertraline daily orally for two weeks exhibit mydriasis, hindlimb weakness, hyperactivity, and anorexia. Alkaline phosphatase (Alk Ph) activity is increased in dogs given 80 mg kg$^{-1}$ day$^{-1}$ for two weeks, while serum transaminase activity (ALT) is increased in dogs receiving 160 mg kg$^{-1}$ for this period of time. Dogs given ≥10 mg kg$^{-1}$ daily PO for three months or longer exhibit mydriasis. In addition, dogs given ≥ 30 mg kg$^{-1}$ daily PO for up to 12 months exhibit transient hyperactivity and restlessness with anorexia and body weight loss or decreased body weight loss. Convulsions may occur at 90 mg kg$^{-1}$. Dogs treated with sertraline for one year exhibit increased Alk Ph activity when dosed at ≥10 mg kg$^{-1}$ daily PO, increased relative liver weight when dosed at ≥ 30 mg kg$^{-1}$ daily PO, and increased ALT when dosed at 90 mg kg$^{-1}$ daily PO. Lymphoid depletion may occur in dogs given 15–160 mg kg$^{-1}$ for a short period of time, but has not been observed in dogs treated chronically (Davies and Kluwe 1998).

It is unknown whether sertraline is excreted in milk. As with the other SSRIs, medicating pregnant or lactating females with sertraline should be done cautiously, with the potential benefits to the female being weighed against the risks to the fetus and neonate (Pfizer Inc. 2004).

### Other Information

While sertraline is not labeled for use in the treatment of aggression in humans, beneficial effects for patients with borderline personality disorder with impulsive aggression have been observed (e.g. Kavoussi et al. 1994).

### Effects Documented in Nonhuman Animals

#### *Dogs*

Rapoport et al. (1992) studied the effects of sertraline versus placebo on dogs with ALD in an 11-week crossover treatment trial, with five weeks each on placebo and on sertraline. Sertraline was dosed at up to 3.42 ± 0.52 mg kg$^{-1}$ daily. Sertraline was significantly better than placebo, producing a 21% decrease in licking behavior at five weeks as compared with baseline. However, sertraline was less effective than fluoxetine, which was being studied in a similar crossover trial with fenfluramine. Fluoxetine produced a 39% decrease by five weeks when compared to baseline. No side effects were reported for dogs on sertraline. However, only one dog showed clinically significant (50%) improvement in licking behavior.

#### *Reptiles*

Male *A. carolinensis* given sertraline at a dose of 10 mg kg$^{-1}$ exhibit decreased aggressiveness. In addition, if sertraline is given only to the "dominant" male of a pair that has established their hierarchical relationship prior to treatment, the rank order often reverses. In addition, nonaggressive associative behavior increases (Larson and Summers 2001).

## VI. Escitalopram Oxalate

**Chemical Compound:** 5-[5-(3,4-dimethoxyphenyl)-3-(2-fluorophenyl)-3,4-dihydropyrazol-2-yl]-5-oxopentanoic acid

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 5-, 10-, and 20-mg tablets. The 10- and 20-mg tablets are scored. Although escitalopram oxalate equivalent to 1 mg $ml^{-1}$ escitalopram base oral solution is also available, it contains the following inactive ingredients: sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methylparaben, propylparaben, and natural peppermint flavor.

### Clinical Pharmacology

Escitalopram is S-enantiomer of the racemic citalopram with antidepressant activity and is the newest marketed SSRI. Escitalopram has no significant affinity for adrenergic (alpha-1, alpha-2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors. Although it shares the same mechanistic target, the serotonin transporter (SERT) with other SSRIs, it is further classified as an allosteric SSRI. The additional interaction of escitalopram with an allosteric binding site on the SERT modulates the affinity of escitalopram at the primary (orthosteric) site. This unique pharmacological characteristic of excitalopram leads it to be more efficacious than other SSRIs (Sanchez et al. 2013). Additionally, in the human medicine literature, when efficacy and tolerability are compared, the overall evidence supports that escitalopram could be the first choice before paroxetine, sertraline and citalopram (Sanchez et al. 2013).

In humans when taken orally, escitalopram reaches Tmax in five hours, is 56% protein bound, and reaches steady-state concentration in the blood within one to two weeks (Spina et al. 2012). The half-life in humans is about 27–33 hours (Sanchez et al. 2013). Absorption of escitalopram is not affected by food. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2–2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Escitalopram pharmacokinetics in subjects 65 years of age were compared to younger subjects in a single dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and Cmax was unchanged. Therefore, 10 mg $day^{-1}$ is the recommended dose for elderly patients (Forest Pharmaceuticals, Inc. 2004).

Clinically significant interaction has been observed between low dosages of escitalopram (5 mg $day^{-1}$) and clonidine, with an increase of central effects of clonidine such as hypothermia and sedation in humans. The molecular mechanisms underlying this interaction are presently unknown (Nikolic et al. 2009).

### Uses in Humans

Escitalopram is used to treat major depression and generalized anxiety disorder.

### Contraindications

Although the same caution, as being suggested in other SSRIs, to avoid serotonin syndrome is advised, escitalopram is metabolized by at least CYP3A4 and CYP2C19 and to a lesser extent by CYP2D6. *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., co-administration of escitalopram (20 mg $day^{-1}$ for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in Cmax and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the co-administration of escitalopram and drugs metabolized by CYP2D6 (Forest Pharmaceuticals, Inc. 2004).

Overall, comparing to other SSRIs such as paroxetine and sertraline, escitalopram has little inhibitory action against other CYP enzymes or P-glycoprotein and it has a low potential for drug–drug interactions (Sanchez et al. 2013).

### Side Effects

According to a meta-analysis reviewing 117 randomized controlled trials involving 25 928 participants with all 6 SSRIs as well as 6 new-generation antidepressants, escitalopram and sertraline were the SSRIs that showed a highest tolerability (Cipriani et al. 2009). When side effects are observed in the treatment of major depression with either 10 mg day$^{-1}$, or 20 mg per day of escitalopram, they usually include insomnia, diarrhea, dry mouth, somnolence, dizziness, sweating increased, constipation, fatigue, and indigestion. The incidence rate was dose-dependent (Forest Pharmaceuticals Inc. 2004).

In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg kg$^{-1}$ day$^{-1}$) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately 56 times the maximum recommended human dose [MRHD] of 20 mg$^{-1}$ day$^{-1}$ on a body surface area [mg/m2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg$^{-1}$ kg$^{-1}$ day$^{-1}$, was present at all dose levels. The developmental no-effect dose of 56 mg kg$^{-1}$ day$^{-1}$ is approximately 28 times the MRHD on a mg/m2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg kg$^{-1}$ day$^{-1}$) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg kg$^{-1}$ day$^{-1}$ which is approximately 24 times the MRHD on a mg/m$^2$ basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg kg$^{-1}$ day$^{-1}$. The no-effect dose was 12 mg kg$^{-1}$ day$^{-1}$ which is approximately 6 times the MRHD on a mg/m$^2$ basis.

There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (Forest Pharmaceuticals Inc. 2004).

### Overdose

Gastric lavage may be useful if it is conducted soon after ingestion of an overdose. Give activated charcoal, and provide supportive therapy. There is no specific antidote.

### Other Information

Paroxetine, sertraline and escitalopram have high affinity at the SERT while paroxetine has the highest affinity at the SERT, whereas escitalopram has the highest degree of selectivity (i.e. >1000-fold relative to a large number of receptors and neurotransmitter transporters) as compared with paroxetine (>200-fold) and sertraline (>60-fold) (Sanchez et al. 2013).

### Effects Documented in Nonhuman Animals

#### *Dogs*

One study using five clinically healthy beagles (4 male, 1 female, age 5 ± 2 years, weight 12 ± 4 kg) to determine the optimal dosing regimen and the relationship between the dose and the SERT-occupancy has been published (Taylor et al. 2017). It reported that the elimination half-life of escitalopram in these beagle dogs was 6.7 hours, therefore, three times a day (t.i.d.) is recommended.

According to the PET scan study, to occupy 80% of the SERT-sites in the basal ganglia and to elicit a therapeutic effect, the minimal dose requirement in the dogs was of 1.85 mg kg$^{-1}$ day$^{-1}$ divided over three administrations. It was also observed that this dose regimen resulted in an occupancy at 81% in the hippocampus, 78% in both the colliculi and thalamus, and 77% in the brainstem region containing the raphe nuclei (Taylor et al. 2017).

The main plasma metabolite of escitalopram in dogs is didesmethylmetabolite of escitalopram (S-DDCT). As mentioned under citalopram, the QT interval on an EEG can be affected by DDCT when the concentrations were more than 300 ng $ml^{-1}$ in beagle dogs that is a known risk factor of sudden deaths (Le Bloc'h et al. 2003). Taylor et al. (2017) mentioned that the S-DDCT concentrations from their suggested dose of 1.85 mg $kg^{-1}$ $day^{-1}$ divided over three administrations was equal to 290 ng $ml^{-1}$, however, for long-term therapy with escitalopram with this dose in dogs, regular cardiac screening is recommended. Due to its highest selectivity on the receptors and transporters as well as little CYP 450 inhibition, these data provided potential options of using escitalopram in dogs.

## Important Information for Owners of Pets Being Placed on Any SSRI

The following should be considered when placing an animal on an SSRI.

1) It is essential that owners inform their veterinarian of all other medication, herbal supplements, and nutritional supplements they are giving their pet, because some of these may interact with the medication.
2) While their pet may respond within a few days, it may be a month before their pet begins responding. They must be patient.
3) If their pet exhibits mild sedation in the beginning, it will probably return to normal levels of activity in two or three weeks as its body adjusts to the medication.
4) If their pet should experience any adverse events such as vomiting, diarrhea, or seizures, they should contact their veterinarian immediately.
5) All use of the medication being given is extra-label use. This does not mean that the drug is not indicated for the problem. In fact, there may be an extensive body of scientific and clinical evidence supporting the use of this drug for their pet's problem. It means that the extensive testing required by the FDA for on-label usage of the drug for their particular species of pet and their particular pet's problem has not been conducted or, if in progress, has not been completed. Exceptions to this may occur after the publication of this book if the FDA subsequently approves any of the SSRIs for treatment of various behavior problems in domestic animals.

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# 9

# Miscellaneous Serotonergic Agents

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## Introduction

The psychotropic medications discussed in this chapter have different classifications and different modes of action. They are grouped together due to having in common serotoninergic properties and being the only drugs in their class to be currently used in veterinary behavioral medicine.

## Azapirones

### Action

Azapirones are serotonin 1A agonists.

### Overview of Indications

Azapirones can be used for a variety of anxiety disorders and behaviors that may be affected by chronic anxiety and fear, including generalized anxiety disorder, urine marking, separation anxiety disorder, and anxious cats that are the regular recipients of aggression. Azapirones may be helpful in certain cases of aggression that are triggered by stress and fear signs by one animal, but should be used cautiously for this problem.

### Contraindications, Side Effects, and Adverse Events

Buspirone is the only azapirone that is commercially available in the United States. See the detailed discussion under buspirone below.

### Adverse Drug Interactions

Azapirones should not be given in combination with monoamine oxidase inhibitors (MAOIs).

### Overdose

See information under buspirone below.

### Clinical Guidelines

Buspirone is anxioselective with no substantial sedative effect. While there may be a rapid response, it may require one to four weeks to take effect. The patient should be medicated daily, rather than on an as-needed basis. Doses for dogs, cats, and rabbits are given in Table 9.1.

Azapirones are commonly combined with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) in

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**Table 9.1** Dose of buspirone given orally for various species.

| Species | Dose | Example |
|---|---|---|
| Dog | 0.5–2.0 mg kg$^{-1}$ q8–24h | 20-kg dog<br>30-mg, #30<br>Give 1/2 q12h |
| Cat | 2.5–7.5 mg/cat q12h<br>or<br>0.5–1.0 mg kg$^{-1}$ q12h | 5-kg cat<br>5 mg, #30<br>Give 1/2 q12h |
| Rabbit | 0.25–1.0 mg kg$^{-1}$ q12h | |

patients that do not respond to either of those two drugs alone. This topic is discussed in further detail in Chapter 19 (Combinations).

## Specific Medications

### I. Buspirone

**Chemical Compound:** 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7, 9-dione monohydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 5-, 10-, 15-, and 30-mg tablets. The 15- and 30-mg tablets are scored so that they can readily be split into two or three pieces.

#### Clinical Pharmacology

Buspirone is a serotonin 1A partial agonist that has been available in the United States since 1987. It is believed to exert its action by blocking presynaptic and postsynaptic serotonin-1A (5-HT$_{1A}$) receptors. It fully antagonizes presynaptic receptors, but only partially antagonizes postsynaptic 5-HT$_{1A}$ receptors. It also down-regulates 5-HT$_2$ receptors (Eison 1989; Cole and Yonkers 2004). It has moderate affinity for D2-dopamine receptors in the brain (Peroutka 1985). It does not have anticonvulsant, muscle relaxant, or sedative effects and is therefore often referred to as anxioselective. The anxiolytic effect appears to be due, at least in part, to action on neurons in the dorsal raphe (Trulson and Trulson 1986).

In humans, buspirone has extensive first-pass metabolism. Food slightly decreases the extent of presystemic clearance of buspirone, but this effect is not known to have any clinical significance. Buspirone is given with or without food (Bristol-Myers Squibb Co. 2000). It reaches maximum concentrations in about one hour in humans, with a subsequent elimination half-life of about 2.5 hours.

Buspirone is primarily metabolized by oxidation by the P450 liver enzyme CYP3A4. It has one pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), and several inactive metabolites. In animal tests, there has been found to be about 20 times as much 1-PP as the parent compound in the plasma, but 1-PP is about one-fourth as active (Bristol-Myers Squibb Co. 2000). Urinary excretion of unchanged buspirone accounts for about 0.1% of the initial dose. Thus, it is eliminated almost entirely in a biotransformed state (Caccia et al. 1986).

Buspirone has nonlinear pharmacokinetics so that repeated dosing results in higher blood levels than would be predicted from studies of blood levels after a single dose is given (Bristol-Myers Squibb Co. 2000).

Buspirone does not displace highly protein-bound medications such as phenytoin, warfarin, and propranolol. Thus, concurrent medication with buspirone does not generate the risk of inducing higher plasma levels of such drugs (Bristol-Myers Squibb Co. 2000).

No significant difference has been found between geriatric and younger adult subjects in the pharmacokinetics of buspirone. Both liver and kidney disease result in decreased clearance and higher levels of buspirone (Bristol-Myers Squibb Co. 2000). Buspirone appears to have no significant effect on blood sugar levels (Dixit et al. 2001). In contrast to benzodiazepines, it stimulates rather than depresses respiration (Garner et al. 1989). Buspirone does not appear to have cardiovascular effects at clinical anxiolytic doses (Hanson et al. 1986).

In horses, buspirone and three major metabolite classes can be detected in the

urine 1 to 12 hours after administration (Stanley 2000).

### Uses in Humans

Buspirone is used to treat generalized anxiety disorder in humans. In humans with generalized anxiety disorder, buspirone is more effective than placebo and similar in efficacy to diazepam and clorazepate, although with a slightly slower onset of action (Goldberg and Finnerty 1979; Rickels et al. 1982, 1988). The benefit of buspirone over the benzodiazepines includes avoidance of excessive sedation and physical dependence. Use of buspirone likewise avoids the sedation and anticholinergic side effects of TCAs, which are also used in generalized anxiety disorder. It is also more effective than placebo in the treatment of major depression with moderate anxiety (Fabre 1990; Rickels et al. 1990).

### Contraindications

Buspirone should be used cautiously with MAOIs (Cole and Yonkers 2004). In humans, co-administration of buspirone and erythromycin results in substantial increases in plasma levels of buspirone with concurrent increases in side effects. The implications of this finding in nonhuman animals are unknown. Nevertheless, if a patient being chronically medicated with buspirone must be given erythromycin, the dose of buspirone should be decreased. Ideally, other antibiotics that do not exhibit this interaction should be selected. Co-administration with itraconazole also results in substantial increases in plasma levels of buspirone (Bristol-Myers Squibb Co. 2000).

### Side Effects

Side effects are uncommon, which is one advantage to the use of buspirone. Sedation does not occur in humans, but has been reported in nonhuman animals (e.g., see Hart et al. 1993). In humans, the more common side effects are dizziness, insomnia, nervousness, nausea, headache, and fatigue. One cat placed on buspirone by one of the authors (Crowell-Davis) began hiding in the closet. This may have been a behavioral response to increased anxiety, analogous to the nervousness reported in some human patients. Mania has also occasionally been reported in humans (Liegghio and Yeragani 1988; Price and Bielefeld 1989; McDaniel et al. 1990). As with all medications, some individuals may have unique, adverse reactions to buspirone.

Unlike the benzodiazepine anxiolytics, buspirone does not produce dependence, even after several months of treatment (Robinson 1985).

In rats and mice given high doses of buspirone for 24 and 18 months, respectively, there was no evidence of carcinogenicity. Studies of mutagenicity have also revealed no such effect (Bristol-Myers Squibb Co. 2000).

In studies of rats and rabbits given high doses of buspirone during pregnancy, there was no impairment of fertility or damage to the fetuses (Bristol-Myers Squibb Company 2000).

Buspirone is excreted in milk (Bristol-Myers Squibb Co. 2000).

The $LD_{50}$ given orally in dogs is approximately 300 mg kg$^{-1}$. Death results from compromised respiratory function (Kadota et al. 1990).

### Overdose

Conduct gastric lavage and provide supportive treatment if an overdose is given. There is no specific antidote (Bristol-Myers Squibb Co. 2000).

Dogs given 3 or 10 mg kg$^{-1}$ may exhibit emesis. The 10 mg kg$^{-1}$ dose produces significantly increased urinary volume and electrolyte excretion (Hanson et al. 1986).

### Other Information

Buspirone causes decreased territorial and maternal aggression in rats concurrently with a substantial decrease in social activity and interest, suggesting that the decreased aggression is nonspecific (Olivier and Mos 1992). On the other hand, it causes no significant changes in social or solitary behavior patterns

of rhesus monkeys (*Macaca mulatta*) when given at a dose of 5–10 mg kg$^{-1}$ daily PO. This is an interesting example of species differences in response because it contrasts with the increased social interaction noted clinically in the domestic cat.

Buspirone has also been observed to decrease territorial aggression in rats but not in mice (Mos et al. 1992; Gao and Cutler 1993).

Many cats on buspirone begin behaving in ways that their owners often summarize as "more affectionate." Specifically, they will stay near the owner more, rub the owner's limbs more, climb in the owner's lap more, and remain in the owner's lap for longer periods of time than before. The end point of this effect appears to be related to the baseline. Thus, cats that were already affectionate become intensely affectionate, whereas cats that were previously not very sociable begin exhibiting some degree of social behavior. While the cat is on medication, it is capable of learning, and the social dynamic between cat and owner changes so that many cats retain increased levels of social behavior even after the medication is discontinued, although it may decrease from peak levels that occur while on buspirone.

### Effects Documented in Nonhuman Animals

#### *Cats*

Absorption of buspirone is poor when administered transdermally as opposed to orally. Therefore, until such time as a transdermal administration technique is developed that is proven to be effective, it is recommended that buspirone always be given orally (Mealey et al. 2004). Cháveza et al. (2015) did not see a significant difference in the reduction of urine marking between cats that received either oral (1 mg kg$^{-1}$ SID for five weeks) or transdermal (4 mg kg$^{-1}$ SID applied inside of the ear for five weeks) buspirone. Two patients on the transdermal treatment group (2/19) left the study due to presenting allergic reactions to the medication (itching, skin dryness, and erythema of the ear). A significant reduction in marking frequency was observed following treatment ($p < 0.05$) for both forms of buspirone administration. This study, however, did not evaluate the blood levels of buspirone during treatment so it remains unclear if the transdermal treatment actually achieved therapeutic doses.

At a dose of 5 mg kg$^{-1}$ PO buspirone causes increased wakefulness and decreased REM sleep in cats (Hashimoto et al. 1992).

Buspirone, at an average dose of 0.46 mg kg$^{-1}$, blocks motion sickness in cats (Lucot and Crampton 1987). Pet cats susceptible to car sickness and other forms of motion sickness may benefit from a dose of approximately 1.0 mg kg$^{-1}$ prior to trips since this will alleviate vomiting and may help with anxiety, although the latter effect may only occur with multiple doses.

Hart et al. (1993) conducted an open trial of the effectiveness of buspirone on spraying and urine marking in cats. The subjects were 47 castrated males and 15 spayed females. Forty-two of the males were from multiple cat households while only five were from single cat households. Thirteen of the females were from multiple cat households while only two were from single cat households. Cats were initially medicated with 2.5 mg/cat q12h PO. If this dose resulted in cessation or substantial reduction by the second week, it was maintained for eight weeks. If the initial dose was not sufficiently effective, the dose was increased to 5 mg/cat q12h PO for an additional two weeks. If the spraying or marking was substantially decreased or ceased at this higher dose, the cats were maintained on buspirone at this dose for eight weeks. Cats that initially stopped spraying on the 5-mg dose, but subsequently resumed spraying during the eight weeks, were increased to 7.5 mg/cat q12h.

After the completion of eight weeks of treatment, the dose of buspirone was gradually decreased over a two-week period. If the cat continued to not spray, medication was discontinued entirely. If the cat resumed spraying at a given lower dose, the cat was then treated for 6–12 months at the lowest effective dose.

Thirty-two of the 62 cats treated with buspirone responded favorably. Thus, about

one-half of the cats had a positive response. The majority of cats (81%) were given the 5-mg dose and 12 cats were given the 7.5-mg dose. Twenty-one of the responders exhibited complete cessation of spraying, whereas the remaining 11 responders exhibited a decrease of 75% or more. There was a clear effect of household type. Thirty-two of the 55 cats from multiple cat households responded, whereas none of the 7 cats from single cat households responded. There was no significant effect of sex, although proportionately more females than males responded favorably. Further studies with larger numbers of cats would be required to determine if this trend would become significant with an adequate sample size.

Of the responders, contact was maintained with the owners of 30 cats after treatment. When treatment was discontinued, half of these resumed spraying and half did not resume spraying. When the relapsing cats were placed back on buspirone, 2 failed to respond to the second treatment, while 13 responded.

Owners of 4 of the 62 cats reported sedation. Nine of the cats exhibited increased aggression toward other cats. In at least in some of these cases, the cats that became more aggressive had previously been withdrawn and timid, particularly in their relationship with other cats. While on buspirone, they became more assertive in their social interactions. Five of the cats became agitated. Twelve owners reported increased friendliness toward humans.

Forty of the cats had been previously treated with progesterone. Of these, 30 were nonresponders to progesterone. Fourteen of the 30 that had not responded to progesterone responded to buspirone. Seventeen cats had been previously treated with diazepam, eight of these being nonresponders. Of the diazepam nonresponders, only two responded to buspirone.

While buspirone has approximately the same initial efficacy as diazepam in the treatment of spraying, there is a lower recidivism rate. Specifically, only about 50% of the cats responding to buspirone resume spraying when treatment is discontinued, while over 90% of cats that respond to diazepam relapse when treatment is discontinued (Cooper and Hart 1992). Given the lower incidence of serious side effects and lower rate of recidivism, buspirone is clearly a better choice than diazepam for the treatment of urine spraying and urine marking in cats, especially considering the risks of using diazepam in cats (see Chapter 7 for a detailed discussion).

Overall (1994) used buspirone at 2.5 mg q12h PO to successfully treat spraying in a cat that had previously responded to diazepam, but had stopped responding. The patient had also been socially isolated by its own volition from other cats in the household. While on buspirone, the cat not only stopped spraying, but began venturing into other parts of the house. The cat could not be weaned off buspirone without resumption of the spraying. At the time of publication, the cat had been on buspirone for 16 months with no adverse effects.

Sawyer et al. (1999) reported on four cats with psychogenic alopecia that were treated with buspirone at 5 mg/cat q12h PO. While the frequency of grooming decreased in one cat, the problem resumed when treatment was discontinued. The problem stopped again when treatment with buspirone was resumed at a dose of 2.5 mg $kg^{-1}$ q12h PO. While the cat was on treatment for a second time, the owner moved to a new home. When medication was discontinued for a second time, the problem remained resolved. This result begs the question of whether the second treatment cured the problem or whether the problem was caused by environmental stresses at the original home. The other three cats treated with buspirone did not respond at all. While these poor results suggest that buspirone may not be a good treatment for psychogenic alopecia, the sample size is too small to come to any conclusions other than that buspirone may be effective in some cases.

Ogata (2013) treated a 2.5-year-old castrated male domestic shorthair presenting chronic fear-induced behavior responses to

sudden and loud noises, sudden movements, and people. Buspirone was administered at a dose of 1 mg kg$^{-1}$, PO, q12h. During the second week of administration, the behavior of the cat improved and no adverse effects were observed. After three months of treatment, the medication was discontinued for one week and the cat noise phobia relapsed. One week after buspirone administration was resumed, the cat was playful and the clinical signs had again improved.

#### *Dogs*

Overall (1995) reported on one case of a dog with multiple behavior problems, including fear of approaches by strangers. As part of the overall treatment program, buspirone was used (10 mg q24h PO, 23-kg dog; 0.4 mg kg$^{-1}$ daily) for the fear of strangers. The dog became less fearful and made a clear transition to friendly behavior, jumping up and licking faces, and playing with toys with strangers. This response is similar to the increased friendliness to humans seen in cats.

Marder (1991) has used buspirone in combination with acepromazine or diazepam in intense fear-inducing situations, such as thunderstorms, with no serious side effects, although she does not state the effectiveness of the combination. Acepromazine was also used at a lowered dose. Marder (1991) has also used buspirone in dogs with mild separation anxiety.

#### *Horses*

Because buspirone does not have sedative or muscle-relaxant side effects, it is a better drug for treating anxiety in horses than the benzodiazepines. Dodman (personal communication, 1996) has treated horses with buspirone at up to 250 mg day$^{-1}$ per horse with no adverse side effects. Although it may be useful in the treatment of anxiety disorders, it must not be used in performance horses preparing for competition. A 50-mg dose can be detected in the urine (Stanley 2000).

#### *Rabbits*

The rabbit cerebral cortex has 5-HT$_{1A}$ receptors, and the binding rate of buspirone is similar to the binding rate of buspirone in rats and humans (Weber et al. 1997). Rabbits treated with buspirone at 0.05 mg kg$^{-1}$ day$^{-1}$ PO for one month do not exhibit any changes in blood sugar (Dixit et al. 2001).

In a study aiming to investigate the role of 5-HT and its receptors in mediating novelty-elicited head-bob behavior in rabbits, pretreatment with buspirone significantly attenuated novelty-elicited head bobs (Aloyo and Dave 2007). Buspirone may be a useful treatment for timid, anxious rabbits.

#### *Parrots*

Juarbe-Díaz (2000) used buspirone (0.2 mg, PO, q12h) as an adjunct agent in a treatment with clomipramine (3.6 mg, PO, q12h) and environmental modification for a Congo African Gray parrot with feather-picking and self-injurious behavior. Buspirone was added to treat paradoxical anxiety caused by an increase in the dose of clomipramine. Six weeks after addition of buspirone to the treatment regimen, the owner reported that intensity of the feather-picking and self-injurious behavior was greatly decreased and new feather growth was seen.

#### *Other Species*

Buspirone was used in an experiment that aimed to validate the marmoset (*Callithrix penicillata*) as a model of fear and anxiety. Seven subjects were first subjected to seven 30-min maze habituation trials in the absence of a taxidermized wild oncilla cat (*Felis tigrina*). Subsequently, the subjects were randomly assigned to five treatment trials in the presence of the "predator" (three buspirone sessions at 0.1, 0.5 and 1.0 mg kg$^{-1}$, saline and sham injection controls). Buspirone significantly decreased the frequency of scent marking, while increasing the time spent in proximity to the predator stimulus (Barros et al. 2001).

## Serotonin Antagonist/ Reuptake Inhibitors (SARIs)

### Action

Serotonin antagonist/reuptake inhibitors block serotonin 2A and 2C receptors and serotonin reuptake.

### Overview of Indications

SARIs, more specifically trazodone, can be used for a plethora of situations where fear and anxiety need to be controlled in companion animals (such as in surgery recovery and veterinary visits) and to treat anxiety disorders. It can be used as a single agent or as an adjunct drug to enhance another pharmacological treatment. It has also been used in the treatment of neuralgia and other painful conditions. The prescription of nefazodone, another SARI, is uncommon due to its potential liver toxicity documented in human medicine.

### Contraindications, Side Effects, and Adverse Events

Trazodone is the only widely used SARI. See the detailed discussion below.

### Adverse Drug Interactions

SARIs should not be given in combination with MAOIs.

### Overdose

See information under trazodone below.

### Clinical Guidelines

Trazodone has antidepressant effects when used in moderate to high doses. In lower doses, it is useful to treat insomnia and in situations where sedation or activity restriction is desirable and appropriate (i.e. to decrease panic during veterinary visits or to control behavior after surgery). It can be used as needed (PRN) for situational fear and anxiety (i.e. specific phobias), or daily for long-term treatment of anxiety disorders. Trazodone can also be used with caution as an adjunct drug to treatments with SSRIs and TCAs and in other polypharmaceutical treatments.

Doses for dogs and cats are given in Table 9.2.

**Table 9.2** Dose of trazodone given orally for dogs and cats.

| Species | Dose range |
|---|---|
| Dog | 1.7–19.5 mg $kg^{-1}$ $day^{-1}$ PO (daily or PRN)[a]<br>or<br>1.7–9.5 mg $kg^{-1}$ PO q8–24h[b] |
| Cat | 50–100 mg/cat PO PRN[c]<br>or<br>10.6–33.3 mg $kg^{-1}$ PO PRN[c] |

[a] Gruen and Sherman (2008).
[b] Overall (2013).
[c] Orlando et al. (2015).

## Specific Medications

### I. Trazodone Hydrochloride

**Chemical Compound:** 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Available as 50-, 100-, 150-, and 300-mg (scored) tablets and extended release 150- and 300-mg tablets.

#### Clinical Pharmacology

Trazodone is a triazolopyridine antidepressant agent. The action of $5HT_{2A/AC}$ antagonism with inhibition of the serotonin transporter (SERT or 5-HTT) occurs on moderate to high doses. In low doses, besides effective $5HT_{2A}$ antagonism, trazodone also acts as a $H_1$ histaminic and $\alpha_1$ adrenergic receptor antagonist. This mode of action

causes a hypnotic effect. When trazodone reaches the antidepressant action via SERT inhibition and raising serotonin levels, the concomitant $5HT_{2A/AC}$ antagonism avoids some of the side effects seen in treatments with SSRIs and TCAs, such as sexual dysfunction, insomnia, and anxiety (Stahl 2009). This combination of $5HT_{2A/AC}$ antagonism additionally enhances the neurotransmission of neropinephine and dopamine in the prefrontal cortex (Balsara et al. 2005; Stahl 2009). Trazodone may also increase serotonin concentrations by attenuating the inhibitory tone of γ-aminobutyric acid neurotransmitters in the cerebral cortex (Luparini et al. 2004). Its dose-dependent antinociceptive effects seem to be mainly influenced by the μ1- and μ2-opioid receptor subtypes combined with the serotoninergic receptor (Schreiber et al. 2000).

The immediate release formulations of trazodone have rapid onset and short duration of action, so when used to treat evening symptoms (insomnia, phobias with onset at night) one dose before bedtime is usually sufficient. However, for daily treatment of anxiety disorders, trazodone commonly needs to be administered twice to three times a day, which can lead to undesired sedation (Stahl 2009). It has fewer anticholinergic effects than TCAs (Haria et al. 1994). In a study in anesthetized dogs, trazodone had little effect on cardiac function when compared to imipramine. There was no evidence of heart block or sign of rhythm disturbances other than slowing in normal sinus rhythm (Gomoll et al. 1979). When studied in rats, trazodone was found to have the lower cardiac toxicity compared to etoperidone and imipramine (Lisciani et al. 1978). Trazodone is among the antidepressants with lower seizure risk (Pisani et al. 2002).

In humans, trazodone is extensively metabolized in the liver, with < 1% being excreted unchanged in the urine (Al-Yassiri et al. 1981). The most important metabolite, m-chlorophenylpiperazine (m-CPP) is generated by CYP3A4 metabolism and is broken down by CYP2D6. M-CPP has agonistic effects at serotonin 1 receptors, is active at serotonin 2C receptors and may account for some of the adverse effects reported in the literature (i.e. nausea, headache) (Odagaki et al. 2005). Excretion is mostly via renal mechanisms and only a very small amount (0.13%) is excreted unchanged in the urine. About 21% is excreted in the feces. Elimination half-life of the parent compound is approximately 7 hours for the immediate-release tablets and 10 hours for the extended release tablets.

Peak blood concentrations occur approximately one hour after oral administration in fasted human subjects, versus two hours when taken with food (Al-Yassiri et al. 1981). The plasma concentration-time curve is increased when trazodone is taken with a meal. Oral availability is approximately 65% (immediate-release tablets) (Bryant and Ereshefsky 1992). Approximately 90–95% is bound to plasma proteins. Trazodone has a biphasic elimination pattern with a fast phase of three to five hours followed by a slower phase lasting six to nine hours (Stahl 2011).

In dogs given 8 mg $kg^{-1}$ IV, volume of distribution was 2.53 ml $kg^{-1}$ (mean), elimination half-life 169 minutes, and plasma total body clearance was 11.15 ml $min^{-1}$ $kg^{-1}$. After the same dose PO, bioavailability was 85% and elimination half-life was 166 minutes. Peak plasma levels occurred at 445 minutes (mean) but there was a great inter-subject variation. IV administration was associated with tachycardia in all dogs in this study, and aggression in half of the subjects (Jay et al. 2013).

Trazodone is a substrate of the cytochrome P450 3A4 (CYP3A4) enzyme and its metabolism can be inhibited by the CYP3A4 inhibitors such as ketoconazole (Plumb 2015).

Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg $day^{-1}$ with trazodone 100–300 mg daily in humans, carbamazepine reduced plasma concentrations of trazodone (as well as m-CPP) by 76% and 60%, respectively, compared to pre-carbamazepine values (Otani et al. 1996).

### Uses in Humans

Trazodone is mainly used to treat depression, insomnia, anxiety, and neuralgia (Papakostas and Fava 2007; Stahl 2011).

### Contraindications

Trazodone should not be used in conjunction with MAOIs (Stahl 2011) or in patients that are hypertensive (Plumb 2015). A minimum two to three weeks washout period is advisable before or after MAOI administration (Virga 2010). It should be used with caution in patients with severe cardiac disease, hepatic and/or renal disease, and glaucoma. In humans, co-administration of trazodone and SSRIs such as fluoxetine may raise trazodone plasma levels. The implications of this finding in nonhuman animals is unknown but caution when combining more than one serotoninergic pharmaceutical is always warranted due to the increased risk for serotonin syndrome (Pilgrim et al. 2010). Co-administration with azole antifungals, macrolide antibiotics, and phenothiazides may increase plasma levels of trazodone. Trazodone may block the hypotensive effects of some hypotensive drugs and might interfere with the antihypertensive effects of clonidine (Al-Yassiri et al. 1981).

There are reports of increased and decreased prothrombin time in humans taking warfarin and trazodone. Priapism is reported in human medicine. Trazodone is considered to be an antidepressant with a low seizure risk compared to other classes of antidepressant drugs, but it should still be used with caution in patients with a history of seizures. Tramadol increases the risk of seizures in patients taking antidepressants and metoclopramide may increase the risk of serotonin syndrome. Concurrent use of trazodone with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of gastrointestinal (GI) bleeding. The use of central nervous system (CNS) depressants with trazodone may cause addictive effects and trazodone may increase digoxin or phenytonin concentrations (Plumb 2015).

### Side Effects

Nausea, vomiting, diarrhea, edema, drowsiness, dizziness, incoordination, sedation, lethargy, blurred vision, changes in weight, headache, muscle pain, dry mouth, bad taste in the mouth, stuffy nose, constipation, or change in sexual interest/ability are reported in human medicine. Additionally, tremors, seizures, mania, priapism, allergic reactions (rare), suicidal behavior, QT prolongation, arrhythmias, hypotension, syncope, and sinus bradycardia have also been reported in humans. Low levels of potassium or magnesium in the blood can increase the risk of QT prolongation, so conditions that cause severe sweating, diarrhea, or vomiting and diuretics used together with trazodone may increase the risk (Al-Yassiri et al. 1981; Tarantino et al. 2005).

In a study in 56 dogs (Gruen and Sherman 2008) vomiting (1 subject), gagging (1), colitis (1), increased excitement (2), sedation (2), increased appetite (2) and perceived behavioral disinhibition (2) were the side effects reported. Further details on this study are outlined in the species-specific section below.

Tolerance is not associated with trazodone use in the immediate release form. The extended release form causes less daytime sedation than the immediate release form in humans, allowing for higher dosages that reach antidepressant effects (Stahl 2009). A comparison between the two forms of trazodone has not been done in companion animals so far.

Trazodone passes into breast milk. Its safety during pregnancy and lactation has not been studied in companion animals and the Food and Drug A (FDA)classifies it as a category C drug for use during pregnancy.

The oral $LD_{50}$ of the drug is 610 mg kg$^{-1}$ in mice, 486 mg kg$^{-1}$ in rats, and 560 mg kg$^{-1}$ in rabbits.

Trazodone is non-habit-forming but should be tapered off gradually to avoid withdrawal effects (Stahl 2011).

### Overdose

There is no specific antidote for trazodone. The most severe reactions reported to have

occurred with overdose of trazodone in humans have been priapism, respiratory arrest, seizures, and electrocardiogram changes. Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation and gastric lavage is recommended. Forced diuresis may be useful in facilitating elimination of the drug.

### Other Information

Veasey et al. (1999) evaluated the use of trazodone with L-tryptophan on sleep-disordered breathing in the English bulldog. Based on the hypothesis that in obstructive sleep apnea hypopnea syndrome (OSAHS) reduced serotoninergic drive plays a role in upper airway collapse, the authors performed multitrials/dose, multidose, randomized sleep studies testing the effectiveness of a combination of trazodone, and L-tryptophan, in an animal model of OSAHS (English bulldog). Trazodone/L-tryptophan caused dose-dependent reductions in respiratory events in non-rapid-eye-movement sleep (NREMS) and rapid-eye-movement sleep (REMS). Trazodone/L-tryptophan dose-dependently reduced sleep fragmentation, increased sleep efficiency, enhanced slow-wave sleep, and minimized sleep-related suppression of upper airway dilator activity. The study concluded that trazodone with L-tryptophan can effectively treat sleep-disordered breathing (SDB) in this canine model of OSAHS and that the effectiveness of this therapy may be related to increased upper airway dilator activity in sleep and/or enhanced slow-wave sleep. Potential serotoninergic mechanisms for reducing SDB include direct 5-HT excitatory effects at upper airway motoneurons through increased production of 5-HT after administering L-tryptophan, or through direct excitation by trazodone's metabolite, m-CPP and excitation of respiratory-related premotor neurons through similar mechanisms. The dose range of trazodone used was 3.3–13.3 mg $kg^{-1}$ and of L-tryptophan was 44.3–174.3 mg $kg^{-1}$. No adverse effects were reported.

### Effects Documented in Nonhuman Animals

#### *Cats*

Orlando et al. (2015) conducted a study, the aim of which was to evaluate the safety and efficacy of oral trazodone as a single dose agent for sedation in cats. The objective of the study was to test if trazodone can be a useful drug to decrease fear and anxiety prior to veterinary visits.

Six male neutered laboratory cats were given single 50, 75 and 100 mg doses of trazodone and placebo PO. The cats' weight ranged from 3.0 to 4.7 kg. Each cat served as its own control and received the four treatments over a four-week period (doses were respectively 10.6–16.7 mg $kg^{-1}$, 16.0–25 mg $kg^{-1}$ and 21.3–33.3 mg $kg^{-1}$). There was a washout period of four to seven days between treatment days. Pre- and post-study laboratory values of complete blood count, chemistry panel, and urinalysis and physical examinations were compared; during each four hours period post-treatment, sedation was measured via accelerometers and video observations scored by an observer blinded to treatment. Behavioral responses and stress measurements were scored and examinations were performed on the cats 90 minutes after treatment. Six behaviors were scored to measure behavioral responses to examinations (vocalization, struggling, aggression, hypersalivation, immobility, and open mouth breathing). Stress was measured using McCune's cat stress assessment scale pre-examination, during the exam and post-examination.

Accelerometer data showed trazodone 50 mg, 75 mg, and 100 mg caused sedation as measured by activity reduction (83%, 46%, and 66%, respectively), which contrasted with a 14% activity increase after placebo. There was a significant reduction in video observation scores when cats were given trazodone 100 mg compared with placebo. Mean latency to peak sedation for trazodone 100 mg occurred at two hours. Scores for behavioral response to examination, performed at 90 minutes post-treatment, were

not significantly different between cats receiving trazodone 100 mg and placebo. This study did not report any adverse effects, changes in physical examinations or laboratory values after trazodone administration. The authors concluded that trazodone was well tolerated and caused sedation at all doses.

This study used a small sample of cats and not all doses were randomized, but it pioneers the documentation of the use of trazodone in feline patients. More studies are warranted to evaluate trazodone's safety and efficacy in different behavioral pathologies in cats.

Stevens et al. (2016) designed a study that aimed at evaluating the efficacy of a single dose of trazodone for reducing anxiety in cats during transport to a veterinary hospital and facilitating medical handling. Ten client-owned cats with a history of anxiety during transport or examination were included. Each cat was randomly assigned to receive 50 mg of trazodone or a placebo 1–1.5 hours prior to being put in their carriers and driven to the hospital (dose ranged from 7.7 to 15.2 mg $kg^{-1}$). Owners were blinded to treatment and scored signs of anxiety in their cats (using three different scoring systems) before and during transport, at the clinic's waiting room, during and immediately after examination. The attending veterinarian also scored the cats during their physical exam. After a one to three-week wash-out period, each cat received the opposite treatment and the protocol was repeated. Trazodone resulted in a significant improvement in the cats' signs of anxiety during transport compared to placebo. Veterinarian and owner scores for ease of handling also improved with trazodone. No significant differences were identified between treatments in heart rate or other physiological variables measured by the participant clinicians. The only side effect reported was sleepiness in one cat.

#### *Dogs*

Gruen and Sherman (2008) explored the use of trazodone as an adjunctive treatment for anxiety disorders in dogs. This was the first study to exam trazodone's efficacy for behavior pathologies in companion dogs, as well as treatment protocol, dose range, concurrent drug use, adverse events, and therapeutic response in patients unresponsive to other pharmacologic agents.

The study was a retrospective case series with 56 privately owned dogs with anxiety disorders treated at a referral veterinary behavior clinic between 1995 and 2007. Medical records of dogs with anxiety disorders adjunctively treated with trazodone were retrospectively evaluated with respect to signalment, primary and secondary behavioral diagnoses, physical examination results, hematologic data (complete blood count and serum biochemical panel), pharmacologic management, and outcome. The dogs included were given a primary or secondary diagnosis of an anxiety or phobic disorder, had been treated with trazodone, and had subsequent follow-up for at least one month. Anxiety or phobic disorders diagnosed included generalized anxiety, separation anxiety, travel anxiety, storm phobia, noise phobia, and combinations thereof.

All dogs were treated with individually tailored behavior therapy in conjunction with medication. The general pharmacologic treatment protocol consisted of a baseline dose of a TCA (clomipramine, amitriptyline, or imipramine) or an SSRI (fluoxetine, sertraline, or citalopram), that at the time were providing insufficient relief of clinical signs of anxiety prior to the addition of trazodone.

Trazodone administration was given at an initiation dose (half of the initial target dose administered for three days) to identify potential adverse effects. This strategy was implemented because according to the authors, in a preliminary trial, a small percentage of dogs that initially received the full target dose developed sedation or adverse effects (transient soft feces or diarrhea) presumptively attributed to trazodone. After the initiation dose, the target dose was established as the lowest effective dose needed for behavioral calming. Additional dose

increments were made empirically as needed. The number of dose adjustments made varied by individual, severity of clinical signs, and duration of trazodone administration.

The dogs in the study were 26 spayed females, 29 neutered males, and 1 sexually intact male that was neutered during the course of treatment. All dogs were medically screened via physical examination, complete blood count, serum biochemical profile, and thyroid panel prior to pharmacotherapy. All dogs had follow-up for at least one month following initiation of trazodone administration.

Thirty-seven (66%) dogs were followed up for at least one year following initiation of trazodone treatment. Of the remaining 19 dogs, 3 were in their first year of trazodone treatment at the time of the study, 12 were lost to follow-up prior to 1 year of treatment, and 4 received trazodone for < 1 year. Those four dogs included three in which trazodone administration was discontinued because of adverse effects and one that was euthanatized for unrelated health reasons.

Concomitant psychoactive medications included TCAs (clomipramine, amitriptyline, and imipramine) in 31 dogs, SSRIs (fluoxetine, sertraline, and citalopram) in 21 dogs, benzodiazepines (alprazolam, lorazepam, and clorazepate) in 18 dogs, the azaspirone buspirone in 12 dogs, the antipsychotic reserpine in 2 dogs, and a nutraceutical (melatonin) in 1 dog. Twenty-one dogs received more than two psychoactive medications concomitantly, including 12 dogs treated with an SSRI or TCA in combination with a benzodiazepine. Concurrent nonpsychoactive medications prescribed by the referring veterinarian included antimicrobials, heartworm-preventative products (oral and topical administration), flea-preventative products, antihistamines, nonsteroidal anti-inflammatory medication, and thyroid hormone supplementation. No amitraz products were coadministered. One dog was also receiving potassium bromide for seizures that existed prior to trazodone administration. Several dogs were anesthetized without complications for elective surgeries during their course of trazodone treatment.

Three administration schedules were used in combination with an SSRI or TCA: 14 dogs received trazodone as a daily medication, 20 received trazodone as needed for anxiety, and 22 received trazodone both daily and as needed. In general, dogs with generalized forms of anxiety disorders were treated daily with trazodone, whereas dogs with anxiety that appeared more episodic or had recognized triggers were treated as needed. Seven dogs with storm phobia received daily and as-needed administration during the storm season (April through September). The highest dosage (19.5 mg $kg^{-1}$ [8.86 mg $lb^{-1}$]) represented dogs in which trazodone was given both daily and as needed (at the maximum dose allowed as needed). No dog received an individual dose of trazodone > 300 mg. The maximum daily dose was 600 mg, which represented a combined twice-daily and as-needed dose in a dog that weighed 36 kg (79.2 lb). For as-needed doses, most clients observed that behavioral effects occurred within one to two hours of trazodone administration. See a comprehensive list of the adverse effects observed in the dogs in this study in the section on Side Effects. In general, adverse effects were mild, with only three dogs requiring discontinuation of the drug.

Most clients for whom a direct comment was recorded in the clinical record (n = 40) stated that their dog was either very (29 [73%]) or somewhat (5 [13%]) improved as a result of use of trazodone as an adjunctive agent. Three (8%) clients reported no effect of trazodone on their dog's anxiety, and 3 (8%) reported adverse effects that led to discontinuation of treatment. For 16 (29%) dogs, no direct comment was made in the record regarding the specific effect of the medication. Using continuation of treatment for > 3 months as a measure of treatment satisfaction, trazodone administration was useful in the treatment of anxiety for 46

(82%) dogs. Duration of treatment with trazodone for those dogs ranged from 3 to 95 months (almost eight years), with a mean of 24.8 months.

Another important observation of this study is that even though trazodone was not used as a treatment for aggression, several dogs had some aggression as part of their spectrum of signs and no increase of aggression was reported. Aggression was also not reported as an adverse event in any of the dogs that were part of this study.

Gruen et al. (2014) investigated the safety and efficacy of oral administration of trazodone to facilitate confinement and calming after orthopedic surgery in dogs. This study was a prospective open-label clinical trial and 36 client-owned dogs were included. On the day after surgery, the dogs were administered trazodone (approximately 3.5 mg kg$^{-1}$ [1.6 mg lb$^{-1}$], PO, q12h) with tramadol (4–6 mg kg$^{-1}$ [1.8–2.7 mg lb$^{-1}$], PO, q8 to 12h) for pain management purposes. After three days, administration of tramadol was discontinued, and the trazodone dosage was increased (approximately 7 mg kg$^{-1}$ [3.2 mg lb$^{-1}$], PO, q12h) and maintained for at least four weeks. When needed, trazodone dosage was increased (7–10 mg kg$^{-1}$ [3.2–4.5 mg lb$^{-1}$], PO q8h). The clients completed an electronic survey rating their dogs' confinement tolerance, calmness or hyperactivity level, and responses to specific provocative situations prior to surgery and 1, 2, 3, and 4 weeks after surgery and at the post-surgery evaluation (at 8–12 weeks). Most (32/36 [89%]) of owners reported that their dogs, when given trazodone during the 8–12 weeks following orthopedic surgery, improved moderately or extremely with regard to confinement tolerance and calmness, as compared to their tolerance prior to the initiation of trazodone treatment. Trazodone was well tolerated even when combination with NSAIDs, antimicrobials, and other medications. No dogs were withdrawn from the study due to adverse reactions. Owner-reported median onset of action of trazodone was 31–45 minutes, and median duration of action was ≥ 4 hours.

In a proceeding's abstract, Virga (2004) shared the outcome of 18 dogs diagnosed with a variety of anxiety-based behaviors and anxiety disorders that were previously refractory to treatment with SSRIs (either fluoxetine, paroxetine, sertraline or citalopram). Trazodone was added as an augmenting pharmaceutical in doses ranging from 1.41 to 5.14 mg kg$^{-1}$ PO b.i.d. Client-based global assessment of patient responses was scored on a five-point scale (0 = no improvement; 5 = complete resolution of clinical signs); global assessment scores were reported as no or minimal improvement with SSRI mono-therapy. After trazodone was titrated to a clinically effective dose for a period of four weeks, global assessment scores recorded marked improvement to complete resolution of clinical signs in seven patients. Follow-up at three and six months demonstrated sustained clinical response for all seven patients.

Three case reports on the clinical use of trazodone for behavioral pathologies have been published after Gruen and Sherman's (2008) study. Gruen and Sherman (2012) treated a four-year-old castrated male golden retriever diagnosed with stormphobia with behavior therapy, trazodone (5 mg kg$^{-1}$ PO one hour prior to storms or at the first sign of storm-related anxiety behaviors) and a collar impregnated with a chemical marketed as being calming to dogs.[1] Five weeks later, the clients reported that the dog was tolerating the medication well with no side effects, and that the clinical signs decreased in intensity. The most concerning clinical sign to the clients (destruction) was no longer seen after 10 weeks of treatment.

Bennett (2013) treated an 11-month-old neutered male Great Dane diagnosed with separation anxiety disorder with behavior therapy, environmental enrichment, fluoxetine (1.8 mg kg$^{-1}$ PO q24h), and clonazepam (0.085–0.128 mg kg$^{-1}$ PO) one to two hours prior to owner departure. Due to side effects, the clonazepam dose was decreased to 0.085 mg kg$^{-1}$ and trazodone (1.6 mg kg$^{-1}$ PO q12h initially and increased to 3.2 mg kg$^{-1}$

within a week) was added to the treatment regimen. After the patient received the first trazodone dose, it became lethargic, anorexic, and developed diarrhea. A physical examination did not find another cause of the reported clinical signs, so trazodone was discontinued and the dog was prescribed a bland diet, which resolved the clinical signs. The clients did not allow for any laboratory testing and diagnosis that could have ruled out other causes for gastroenteritis or colitis.

Moesta (2014) treated a nine-year-old spayed female mixed breed dog presented for stereotypical motor behavior (spinning) as a clinical sign of separation anxiety disorder, besides other more common signs of this mental illness (anxiety signs related to owner departure and destruction when left alone). Treatment consisted of behavior therapy, the adoption of a consistent and predictable schedule, exercise, environmental enrichment, fluoxetine (1.1 mg kg$^{-1}$ PO q24h), and clonazepam (0.11–0.44 mg kg$^{-1}$ PO one hour before owner departures). Clonazepam was decreased to 0.33 mg kg$^{-1}$ (0.44 mg kg$^{-1}$ caused ataxia) and fluoxetine was switched to paroxetine (0.3 mg kg$^{-1}$ PO q24h initially, titrated up to 1.5 mg kg$^{-1}$ PO q24h) due to anorexia. Six months after the initial appointment, the spinning behavior had completely ceased. However, it started reoccurring when the dog was left alone. Paroxetine was switched to clomipramine (titrated up to 3 mg kg$^{-1}$ PO q12h), which decreased the spinning. At the nine-month recheck appointment, the spinning seemed to be recurring, possibly due to the development of tolerance to clonazepam. Trazodone (5.5 mg kg$^{-1}$ PO as needed, before leaving the dog alone) was added to the treatment program. The dog seemed to be moderately sedate one to two hours after trazodone administration but spinning no longer occurred.

Gilbert-Gregory et al. (2016) evaluated the effects of treatment with trazodone on stress signs of hospitalized dogs. Sixty dogs were observed for signs or behaviors indicative of stress ≤ 45 (time 1) and 90 minutes (time 2) after the administration of trazodone. A second group of 60 dogs was enrolled to control for environmental factors and did not receive the drug. Trazodone administration was initiated at 4 mg kg$^{-1}$ every 12 hours with the dose increased to 10–12 mg kg$^{-1}$ or the frequency to every eight hours when needed for desired calming and anxiolytic effects. The amount given did not exceed 300 mg dose$^{-1}$ or 600 mg 24 hours$^{-1}$. For dogs that were receiving tramadol, trazodone was started at 3.5 mg kg$^{-1}$ every 12 hours. Signs or behaviors (scored as present or absent by an observer) were assessed individually and grouped into behavioral summation categories (frenetic: lip licking, pacing, panting, spinning, trembling, etc.; freeze: averting gaze, pinning back ears and showing whale eyes; fractious: growling, lunging, showing teeth, snapping). Results were compared within the treatment group and between treatment and environmentally matched animals. Lip licking, panting, and whining were reduced (present at time 1 and absent at time 2) in the treatment group and not in the control group. The median number of stress-related behaviors of frenetic and freeze behaviors was significantly lower at time 2 compared to time 1 in the treatment group. No significant changes were identified between time points for these summary variables for environmentally matched dogs. One dog presented aggression following administration of trazodone twice and treatment was discontinued. No other adverse events were reported. The results support the use of trazodone to alleviate stress in hospitalized dogs.

## Note

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# 10

# Anticonvulsants and Mood Stabilizers

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## Action

Anticonvulsants or antiepileptic medications are used primarily for the treatment of epilepsy. However, it has been recognized in human medicine that antiepileptic drugs may be effective for psychiatric conditions such as bipolar depression and anxiety disorders (Stahl 2008). Some of these drugs have also been proven to be effective in the treatment of painful conditions, such as neuropathic pain (Backonja et al. 1998).

Anticonvulsants have a variety of mechanisms and actions on neurotransmitter receptors, so it is not surprising that these medications can be useful in mental health care (Piedad et al. 2012). Some anticonvulsants can change and modulate neuronal membrane polarity, neurotransmitter activity, and neuronal firing, affecting signal transduction (Stahl 2008; Piedad et al. 2012). Anticonvulsants act principally by reducing glutaminergic excitation, gamma-aminobutyric acid (GABA)-A stimulation for GABA-ergic activation, and blocking voltage-gated $Na^+$ or $Ca^+$ channel (Table 10.1).

Psychiatric or mental health disorders are often treated effectively with antidepressants and/or anxiolytics. However, these medications can interact with anticonvulsant drugs. Phenobarbital is commonly used for dogs with seizures. It increases neuronal responsiveness to GABA and decreases Ca inflow in neurons.

Phenobarbital may affect behavior in some animals because it can reduce anxiety. This effect is reported in mice, rats, monkeys, and baboons (Patel and Migler 1982; Kilfroil et al. 1989; Griffiths et al. 1991; Bertoglio and Carobrez 2002). However, phenobarbital and other GABA-A-stimulating drugs such as benzodiazepines can increase agitation and anxiety in dogs (Siracusa 2016).

Gabapentin and pregabalin selectively bind to and have high affinity to the α2 delta site of voltage-sensitive calcium channels (VSCCs) (Stahl 2008). They seem to have little or no effect as mood stabilizers in humans but are used for various pain conditions from neuropathic pain to fibromyalgia, and for various anxiety disorders (Stahl 2008).

Carbamazepine binds to the alpha subunit of VSCCs and could act on the calcium and potassium ion channels. This mechanism of action may enhance the inhibitory actions for GABA. Carbamazepine is used to treat manic phases of bipolar disorder in humans, and it is also found to be effective in controlling aggressive behavior in bipolar depression or dementia in humans (Tariot et al. 1998; Stahl 2008). Carbamazepine has been used to treat aggression and agitation in

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**Table 10.1** Activity profiles on selected anticonvulsants.

| Anticonvulsant | Voltage-gated ion channel blockade |
|---|---|
| Carbamazepine | Inhibit Na↑ |
| Gabapentin | Inhibit Ca2↑ (L-type)[a]<br>Inhibit α2δ subunit[b] |
| Pregabalin | Inhibit Ca2↑<br>Inhibit α2δ subunit |

*Source:* Piedad et al. (2012).
[a] L type = voltage gated calcium channel subtypes with varying levels of threshold activation.
[b] α2δ subunit = a constituent subunit within different channel subtypes.

psychotic and bipolar affective disorders in humans. Carbamazepine has also been used to control aggression in dogs and cats (Schwartz 1994; Galliccio and Notali 2010).

## Overview of Indications

Anticonvulsant drugs were primarily developed for the treatment of epilepsy, a neurological condition that affects approximately 50 million people worldwide (Mackey 2010). They reduce seizure frequency by suppressing neuronal excitability via various molecular targets in the synapse, including voltage-gated ion channels, voltage-gated sodium channels, $GABA_A$ (γ-aminobutyric acid type A) receptors, and glutamate receptors (Piedad et al. 2012).

In the veterinary literature, indications for anticonvulsants (besides treating disorders that cause seizures) include stereotypic behavior and obsessive-compulsive disorders, including tail-chasing, fly-snapping, or excessive self-licking in dogs and cats (Bain 2012). Some of these conditions have been proven to be caused by seizure activity as opposed to anxiety, so the actual reason for efficacy of treatment can vary.

## Clinical Guidelines

The ultimate choice of anticonvulsants for an individual patient with recently diagnosed or untreated epilepsy in humans usually includes consideration of the strength of the evidence for each medicine, along with other variables such as the medication's safety and tolerability profile, its pharmacokinetic properties, formulations, and expense (Glauser et al. 2006).

The treatment of epilepsy in pregnancy is particularly challenging in that the fetal and maternal risks associated with maternal seizures need to be balanced against the potential teratogenic effects of antiepileptic drugs (AEDs). No systematic information is available on the pharmacokinetics of the newer AEDs (e.g. gabapentin, pregabalin, tiagabine, topiramate, or zonisamide) during pregnancy (Tomson and Buttino 2007). In an open prospective clinical study, plasma clearance of phenytoin, phenobarbitone, and carbamazepine was assessed in 14 epileptic patients during and after pregnancy. Plasma clearance showed a marked increase during pregnancy, reached a maximum just before or after delivery, and then decreased to early pregnancy values (Dam et al. 1979).

In veterinary clinical behavioral medicine, when stereotypic/compulsive behaviors such as tail-chasing, self-licking or self-injurious behaviors are observed, these clinical signs have traditionally been diagnosed as compulsive or obsessive-compulsive disorders. However, some of these cases are multifactorial and other medical problems such as psychomotor seizure activity and pain can coexist, and polypharmacy might be the most effective approach.

## Specific Medications

### I. Carbamazepine

**Chemical Compound**: $C_{15}H_{12}N_2O$ 5H-dibenz[b,f]azepine-5-carboxamide

**DEA Classification**: Not a controlled substance

**Preparation**: Available as chewable 100- or 200-mg tablets, as 100-, 200- and 400-mg XR tablets, and as a suspension of 100 mg/5 ml (teaspoon).

### Clinical Pharmacology

Carbamazepine is one of the oldest anticonvulsant drugs available. In spite of this, its mechanism of action has still not definitively been established. It apparently decreases postsynaptic response and blocks post-tetanic activation. It is metabolized in the liver by CYP3A4. It has one active metabolite, carbamazepine-10,11-epoxide. Its half-life in humans is highly variable, ranging from 25 to 65 hours. Excretion is 72% in the urine and 28% in the feces (PDR Staff (2017).

Carbamazepine is still extensively used for treatment of epilepsy in children. Oral bioavailability of carbamazepine in children is about 75–85%, and it is approximately 75–85% bound to plasma proteins. Pharmacokinetics of carbamazepine in children is dependent on age and body weight and is highly variable due to the influence of the dosing regimen and any co-medication. The importance of human leukocyte antigen (HLA) typing for prediction of adverse drug reactions to carbamazepine in children was confirmed (Djordjevic et al. 2017). For safe and effective use of carbamazepine in this population, physicians are asked to adjust the dosing regimen according to existing patterns of genetic and environmental influences (Djordjevic et al. 2017).

This medication can be effective in the manic phase of bipolar disorder treatment (Stahl 2008). It is also effective for the treatment of neuropathic pain (Stahl 2008).

### Side Effects

Carbamazepine has suppressant effects on the bone marrow, requiring blood cell counts to be monitored. It can cause fetal toxicity, such as neural tube deficit (Stahl 2008).

### Effects in Non-human Animals

#### *Dogs*

In one report, a dog with unpredictable aggression to people was examined and an MRI found an arachnoid cyst in the retrocerebellar location. The dog was treated with dexamethasone but showed avoidance behaviors to the owner, so carbamazepine ($10\,mg\,kg^{-1}$ Q12h) was prescribed. Until the dog was euthanized, aggression toward the owner was under control while increasing the carbamazepine dosage as needed (Galliccio and Notali 2010).

In 126 epileptic dogs with spontaneously recurring generalized tonic–clonic (grand mal) seizures, epidemiological aspects and the efficacy of chronic oral treatment with common antiepileptic drugs were studied. Furthermore, the pharmacokinetics of antiepileptic drugs in dogs was compared with the values known for humans. Comparison of the pharmacokinetics of antiepileptic drugs showed that some drugs were suited for maintenance therapy in dogs (primidone, phenobarbital, ethosuximide, trimethadione) whereas others appeared not to be ideally suited because of their short half-lives (phenytoin, carbamazepine, valproic acid, diazepam, clonazepam, nitrazepam) (Loscher et al. 1985). Currently, this is not a common medication for use in veterinary medicine.

#### *Cats*

Schwartz (1994) reported successful treatment of two cats with owner-directed aggression using carbamazepine at 25 mg q12h.

## II. Gabapentin

**Chemical Compound**: $C_9H_{17}NO_2$

**DEA Classification**: The status of gabapentin as a controlled substance is changing, as some individual states are now changing its classification within that state, while the DEA does not yet list it as a controlled substance

**Preparations**: Veterinary approved product: none. Available as: 100-, 300-, 400-mg oral capsules and as 600- and 800-mg tablets, and as a $50\text{-mg}\,ml^{-1}$ pint bottle.

### Clinical Pharmacology

Gabapentin is a GABA analogue. It binds with high affinity to α2-delta subunits of voltage-activated $Ca^{2+}$ channels. Its half-life in humans is five to seven hours. It is eliminated, unchanged, in the urine (PDR Staff (2017).

### Uses in Humans

Gabapentin can be an effective adjunctive treatment for patients with refractory partial epilepsy. It is usually well tolerated and it appears to have a favorable efficacy-to-toxicity ratio in human study (UK Gabapentin Study Group 1990). Gabapentin also provides analgesic activity for patients with neuropathic pain and has the advantage of a low side effect profile and drug toxicity (Rosner et al. 1996). One study showed that gabapentin is effective for pain in post-herpetic neuralgia syndrome without side effects (Rowbotham et al. 1998). It can also be effective for pain from peripheral neuropathy in diabetes mellitus (Backonja et al. 1998).

### Contraindications

Allergy to gabapentin or any of the inactive ingredients in the medication. Severe liver or kidney disease.

### Side Effects

Of 462 dogs reported to the ASPCA's APCC (Animal Poison Control Center), for gabapentin overdose between 2009 and 2013, the primary symptoms were ataxia, lethargy, and vomiting. Of 103 cats reported during the same time period, the main side effects were lethargy, sedation, and ataxia (Plumb 2015).

Seven epileptic children who received gabapentin (GBP) 10–50 mg $kg^{-1}$ $day^{-1}$ (mean dose, 26.7 mg $kg^{-1}$ daily) as adjunctive medication subsequently developed behavioral side effects, including tantrums, aggression directed toward others, hyperactivity, and defiance. All behavioral changes were reversible and were managed by dose reduction or discontinuation of gabapentin. All children in this report had baseline attention deficit hyperactivity disorder and developmental delays (Khurana et al. 1996; Lee et al. 1996).

### Overdose

Treatment of overdose in animals should be supportive (Plumb 2015). In humans, gabapentin overdose can cause drowsiness, ataxia, dizziness, nausea/vomiting, tachycardia, and hypotension (Klein-Schwartz et al. 2003). Large overdoses can cause fatality (Middleton 2011).

### Doses in Nonhuman Animals

For patients that have been on higher doses and/or medicated for a long period of time, a gradual decrease in dose, rather than an abrupt discontinuation, is recommended. Abrupt discontinuation can lead to seizures.

### Other Information

Preliminary clinical studies suggested that gabapentin might produce analgesia and reduce the need for opioids in postoperative patients. Gabapentin in a total dose of 3000 mg, administered before and during the first 24 hours after abdominal hysterectomy, reduced morphine consumption by 32%, without significant effects on pain scores. No significant differences in side effects were observed between study-groups (Dierking et al. 2004). Gabapentin was tested to see if it reduces pain scores, analgesia consumption, and/or analgesia-related side effects in the first 24 hours following surgery. Eight placebo-controlled, randomized controlled trials and meta-analyses were performed using the primary outcomes of pain scores, total analgesia consumption, and side effects over a 24-hours period. Patients who received gabapentin preoperatively reported significantly lower pain scores and opioid consumption with no difference in the incidence of side effects (Seib and Paul 2006).

A 2.1-T magnetic resonance imager-spectrometer and an 8-cm surface coil technology were used to measure a 13.5-$cm^3$ volume in the occipital cortex in humans. GABA was elevated in patients taking gabapentin compared with 14 complex partial epilepsy patients, matched for antiepileptic drug treatment. Brain GABA levels appeared to be higher in patients taking

high-dose gabapentin (3300–3600 mg day$^{-1}$) than in those taking standard doses (1200–2400 mg day$^{-1}$). Gabapentin appears to increase GABA levels in the brain (Petroff et al. 1996).

### Effects Documented in Non-human Animals

#### *Cats*

When gabapentin is given to cats orally, its distribution is best described by a one-compartment model, whereas the distribution is best described by a three-compartment model when gabapentin is given intra-venously (IV). Cats exhibit high variation in absorption with peak levels being around 100 minutes, and the half-life being about 2.8 hours (Siao et al. 2010). There is no information regarding safety and efficacy of chronic use of gabapentin in cats but oral doses of 5–10 mg kg$^{-1}$ every 8–12 hours are used (Deway 2006) (Table 10.2). One report by Inkpen (2015) discussed the multimodal approach of analgesic medicine in cats to control pain. For chronic progressive polyarthritis in cats, on top of predonisolone and cyclosporine, buprenorphine (0.01 mg kg$^{-1}$ BW, PO, q8h) and also gabapentin (compounded) 5 mg kg$^{-1}$ BW, PO, q24h were used for additional pain management with success (Inkpen 2015).

### Cattle

Oral gabapentin, with or without meloxicam, may be useful for the treatment of neuropathic pain in cattle. Beef calves given gabapentin only at 10 mg kg$^{-1}$ achieved peak blood levels of 2.97 µg ml$^{-1}$ at 9.33 ± 2.73 hours and had a half-life of 11.02 ± 3.68 hours. When they were given 15 mg kg$^{-1}$ of gabapentin with 0.5 mg kg$^{-1}$ of meloxicam, peak blood levels of gabapentin were 2.11 ± 0.19 µg ml$^{-1}$, which were achieved at 11.67 ± 3.44 hours. The half-life gabapentin given in this combination was 20.47 ± 9.22 hours. Plasma concentrations of >2 µg ml$^{-1}$ lasted for up to 15 hours (Coetzee et al. 2011).

Six Holstein-Friesian cows given a single oral dose of 10 or 20 mg kg$^{-1}$ of gabapentin in combination with 1 mg kg$^{-1}$ of meloxican were followed for seven days, including measures of milk concentration as well as plasma concentration. When the gabapentin dose was 20 mg kg$^{-1}$, the maximum levels for both blood and plasma were almost double what they were at 10 mg kg$^{-1}$. The milk to plasma ratio of gabapentin levels was 0.23 + 0.06, suggesting that treated cows will have low levels of gabapentin in their milk once plasma levels have dropped below the clinically effective level of 2 µg ml$^{-1}$ (Malreddy et al. 2012).

**Table 10.2** Dose range for gabapentin in cats and dogs.

| | Cats | Dogs |
|---|---|---|
| Daily medication | 3–10 mg kg$^{-1}$ q8h | 2–20 mg kg$^{-1}$ q8h |
| Situational medication[a] | 5–20 mg kg$^{-1}$ | 10–20 mg kg$^{-1}$ |

*Source:* Overall (2013), Plumb (2015).
[a] Situational medication refers to using the medication for particular stressful events, such as visits to the veterinary office.
The low dose is a recommended starting point.
The dose can be titrated up, as needed.

#### *Dogs*

According to the pharmacokinetic study done with several species (mice, rat, dog, monkey), the dog was the only animal studied that metabolized gabapentin to N-methylgabapentin (~34% of dose) while in the mouse, rat, and monkey this was minimal. The principal route of excretion was via urine (Radulovic et al. 1995). KuKanich and Cohen (2011) administered clinically relevant dosage (10–20 mg kg$^{-1}$) to six greyhounds to assess the pharmacokinetics of gabapentin in dogs. The half-life of 10 and 20 mg in dogs were 1.3 and 1.5 hours. Terminal half-lives are 5.54 and 13.22 µg kg$^{-1}$. Gabapentin was rapidly absorbed and eliminated in dogs. Thus, frequent dosing might be needed (KuKanich and Cohen 2011). A sustained-release

tablet formulation of gabapentin did not produce substantially different pharmacokinetic results from an immediate release formulation when given to six beagle dogs (Rhee et al. 2008).

Long-term toxicity trials for gabapentin have not been reported in dogs but it seems to be well tolerated with few to no side effects (Deway 2006).

Platt et al. (2006) reported that 11 dogs diagnosed with refractory idiopathic epilepsy were treated orally with gabapentin for a minimum of three months at an initial dose of 10 mg $kg^{-1}$ every eight hours. A minimum 50% reduction in the number of seizures per week was interpreted as a positive response to gabapentin, and six of the dogs showed a positive response. After the addition of gabapentin, both the number of seizures per week ($p = 0.005$) and the number of days with any seizures in a one-week period ($p = 0.03$) were significantly reduced. Mild side effects of ataxia and sedation were observed in five of the dogs (Platt et al. 2006).

One clinical report from Bain (2012) used gabapentin an as adjunct drug to fluoxetine to treat tail-chasing in a male bull terrier (12 kg), who had presented the behavior since four months old. Initially, the dog was treated with fluoxetine alone. However, for a sedative effect, acepromazine was prescribed and gabapentin (100 mg Q24h) was prescribed for treatment for potential neuropathic pain and underlying seizure activity. Gabapentin was discontinued after one week and acepromazine was discontinued after one month. The tail-chasing behavior was better after one month (Bain 2012).

#### *Horses*

The pharmacokinetic profile, pharmacodynamics, cardiovascular and behavioral effects have been reported in the horse (Dirikolu et al. 2008; Terry et al. 2010). When given as a single oral dose of 5 mg $kg^{-1}$, gabapentin exhibits a peak level at about 1.4 hours. It has a half-life of 3.4 hours (Dirikolu et al. 2008). Gabapentin caused a significant increase in sedation after IV (20 mg $kg^{-1}$) compared to orally (PO) (20 mg $kg^{-1}$). Horses tolerated both IV and PO. There were no significant differences in terminal half-life from PO or IV. Oral administration yielded much lower plasma concentrations because of low bioavailability (Terry et al. 2010).

Gabapentin has been used to treat painful conditions such as laminitis or post-colic surgery (Sanchez and Robertson 2014). A pregnant Belgian draft horse with femoral neuropathy and severe pain after colic surgery was treated with gabapentin (2.5 mg $kg^{-1}$ PO Q 12 hours) for six days with success. No side effects on mare and foal were reported (Davis et al. 2007).

#### *Zoo Animals*

Six healthy great horned owls (*Bubo virginianus*) were given an oral dose of a gabapentin suspension at 11 mg $kg^{-1}$. Peak concentration occurred at 51.43 + 5.66 minutes (about one hour). The half-life was 264.6 + 69.35 minutes (about 2½ hours). Plasma gabapentin was maintained at >2 µg $ml^{-1}$ for almost nine hours. This is the level considered effective in treating epilepsy and neuropathic pain in humans. Thus, treating great horned owls q8h is probably the appropriate dose interval for this bird (Yaw et al. 2015).

## III. Pregabalin

**Chemical Compound:** $C_8H_{17}NO_2$ (s)-3-aminomethyl-5-methylhexanoic acid

**DEA Classification:** C-V controlled substance

**Preparations:** Available as 25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg capsules. Also as a 20-mg $ml^{-1}$ oral solution.

### Clinical Pharmacology

Pregabalin is similar in mode of action to gabapentin. It is structurally related to GABA but inactive at GABA receptors and does not appear to mimic GABA physiologically. It works by binding to the α2 delta subunits of the voltage-dependent calcium channels present in presynaptic neurons (Arain 2009). This decreases the calcium influx via reduced release in glutamate and substance P at the synapse (Salzar et al. 2009). The mode of action is the same as gabapentin (Plumb 2015).

### Uses in Humans

Pregabalin is a neuroactive compound currently used for several conditions including partial onset focal seizure disorders (Dewey et al. 2009; Salzar et al. 2009), neuropathic pain (Baron et al. 2008), postoperative pain in arthroplasty (Dong et al. 2016), and anxiety disorders (Frampton 2014; Buoli et al. 2017).

This medication is approved for use in human for the treatment of peripheral neuropathic pain and in epilepsy in the European Union (EU). In the US, it is approved for treating neuropathic pain from post-herpetic neuralgia, diabetic neuropathy, and adjunctive treatment for partial-onset (focal) seizures (Salzar et al. 2009).

### Side Effects

For six weeks 600 mg $day^{-1}$ pregabalin were given to patients with diabetic neuropathy. Dizziness was the most common side effect. These study results showed it to be safe and effective in reducing the pain and other associated symptoms of painful diabetic neuropathy (Richter et al. 2005).

Most frequent adverse reactions are of a neuropsychiatric nature and include fatigue, dizziness, sedation, somnolence, and ataxia; peripheral edema and weight gain are also frequently described. Pharmacokinetic interactions are scarce; however, pharmacodynamic interactions have been described in association with drugs with depressant effects on the central nervous system (Calandre et al. 2016).

### Effects Documented in Nonhuman Animals

#### *Cats*

The half-life of pregabalin in cats is 10.4 hours. The recommended dose is 1–2 mg $kg^{-1}$ q12h (Plumb 2015).

#### *Dogs*

The half-life of pregabalin in dogs is 6.9 hours. Oral dosing should start at 2 mg $kg^{-1}$ q12h. Then titrate up in 1 mg $kg^{-1}$ increments per week up to a maximum of 8 mg $kg^{-1}$ q8h (Plumb 2015).

Pregabalin is reported to be promising as a safe and effective adjunct anticonvulsant medicine for dogs who are poorly controlled with standard drugs. Dewey et al. (2009) reported on dogs treated with 3–4 mg $kg^{-1}$ PO q8h for three months. Adverse effects were mild sedation and ataxia. One owner in the study reported several episodes of dizziness and weakness in their dogs when the drug was administered at 4 mg $kg^{-1}$ (Dewey et al. 2009).

#### *Horses*

Pharmacokinetics of pregabalin in five healthy mares were tested. A regimen of 4 mg $kg^{-1}$ was administered via nasogastric tube and IV. Signs of mild transient colic or behavior abnormality were seen in all horses after IV. After intragastric administration, half-life was about eight hours. It was concluded that with an intragastric dosage of 4 mg $kg^{-1}$ every eight hours, the median pregabalin steady-state plasma concentration occurred. Therapeutic concentrations and safety of this dosage have not been established in horses (Mullen et al. 2013).

#### *Others*

At this time, the price of pregabalin makes it cost-prohibitive (which probably explains the small number of publications in its use on domestic species so far) with a one-month supply costing 20–30 times as much as medication with gabapentin.

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# 11

# Sympatholytic Agents

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## Action

Sympatholytic medications work by blocking noradrenaline (NA) in the central nervous system (CNS). Excess noradrenalin results from acute and repeated traumatic stress. They are antagonists or adrenergic agonists binding primarily on the presynaptic receptors. The behavioral effects are due to the response of the limbic system and locus coeruleus.

## Overview of Indications

Sympatholytics (antiadrenergics) target alterations in noradrenergic neurotransmission. The central noradrenaline (NA) system is a modulator of the mammalian response to stress. The noradrenergic system originates in a relatively small number of cells located in the locus coeruleus (LC) and in other cell groups in the medulla and pons. The axons of these neurons project from the olfactory bulb to the spinal cord, including the prefrontal cortex, the amygdala, the hippocampus, the hypothalamus, the periaqueductal gray matter, and the thalamus. As a result, NA activity influences a wide range of psychobiologic functions including decision-making, attention, and stress response with anxiogenic or anxiolytic effects that vary depending on acute or chronic stress (Goddard et al. 2010; Carlson 2013). LC firing is caused by the meaning of stimuli as well as their intensity, especially acute stress and fear-related stimuli activate LC to release NA.

The adrenergic receptors where noradrenaline binds are divided into two major types: alpha and beta adrenoreceptors. Alpha-1, beta-1, beta-2 and beta-3 receptors are postsynaptic while alpha-2 is pre- and postsynaptic. Additionally, there is an NA transporter that reuptakes extracellular NA. Rapid increase in NA is likely to contribute to the organism's ability to respond effectively in dangerous situations and then return to normal through negative feedback loops by the restoration of the autoreceptor function. However, prolonged repeated and uncontrollable stress increases the responsivity of LC neurons, which exaggerate NA reactivity. Therefore, pharmacologic agents specifically target NA hyper-reactivity through these adrenergic receptors.

In humans, alpha-1 antagonists (e.g. prazosin), alpha-2 agonists (e.g. clonidine, guanfacine), and beta blockers (e.g. propranolol) are the most studied (Strawn and Geracioti 2008). Historically, in small animals, it was not until the late 1900s that medetomidine was licensed for intramuscular (IM) and intravenous (IV) use only in dogs for sedation and analgesia in

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Canada and the United States, while other countries approved its use in cats as well. Later, dextomedetomidine (the active isomer of the medetomidine formulation) was approved by the Food and Drug Administration (FDA) for use in dogs and cats for sedation, for analgesia as well as preanesthetic in dogs. Dexmedetomidine induces similar effects to medetomidine by using half-dose (Savola and Virtanen 1991). Atipamezole is an antagonist so alpha-2 agonists can be reliably and safely reversed. Atipamezole is 200–300 times more specific for the alpha2 adrenoreceptor than traditional antagonists, such as yohimbine (Lamont et al. 2001).

Alpha-2 adrenergic receptors are known to have four subtypes, alpha-2A, 2B, 2C, and 2D. Their diversity, density, and locations among species appear to be different. For example, alpha-2A receptors predominate in the central nervous system in dogs (Schwartz et al. 1999). The effects of the alpha-2 agonist in the individual is affected by these receptors' distribution as well as the choice of the drug, as each medication has a different selectivity and affinity between alpha-1 and alpha-2 receptors.

The respective alpha-2/alpha-1 selectivity in different sympatholytics is: dexmedetomidine and medetomidine (1620 : 1), detomidine (260 : 1), clonidine (220 : 1), and xylazine (160 : 1), based on the study in rats (Scheinin et al. 1989). The more selective a drug is, the more potent its effect. It is suggested that the removal of the L-isomer from racemic medetomidine may provide dexmedetomidine with a therapeutic advantage (Granholm et al. 2006). Dexmedetomidine seems to be slightly more potent as its analgesic effect lasts longer than the same dose of medetomidine (Kuusela et al. 2000). Several papers have reported that the potential effects of sedation, analgesia, muscle relaxation, and physiological responses, such as bradycardia, and hypothermia induced by alpha-2 agonist are dose-dependent. Due to its effect on the antidiuretic hormone (ADH) and the renin-angiotensin system, alpha-2 agonists lead to low specific gravity urine when animals are recovering from sedation (Sinclair 2003). There is a ceiling effect for sedation, however (Kuusela et al. 2000, Messenger et al. 2016) and the level of sedation actually decreased when the blood concentration reached beyond a certain level in a few studies (Vainio et al. 1986; Ansah et al. 2000).

While oral transmucosal (OTM) detomidine has been available for horses as an FDA-approved medication, there was no such FDA-licensed product for small animals until Sileo (OTM dexmedetomidine) was released in 2016. Some authors reported using either injectable dexmedetomidine or medetomidine orally as a less invasive and less painful procedure compared to IM injection, to assess its effects of sedation in cats and dogs (Ansah et al. 1998; Cohen and Bennett 2015). Both spraying onto the buccal mucous membrane beneath the tongue or into the mouth have been attempted with mixed outcomes. Oral dosing caused excessive salivation (particularly in cats) and a substantial amount of medication was lost in that case (Ansah et al. 1998).

Other studies reported the use of non-injectable forms of alpha-2 agonists or beta blockers to reduce fear and anxiety in dogs. These studies used clonidine (oral tablet) (Ogata and Dodman 2011), detomidine (OTM gel) (Hopfensperger et al. 2013), and propranolol (Walker et al. 1997).

## Contraindications, Side Effects, and Adverse Events

Regardless of the administration route, a decrease has been commonly observed in the heart rate, in the respiratory rate, and in the rectal temperature, induced by alpha-2 agonists. The degree of effect is varied among alpha-2 agonists as well as depending on the dose used (Sinclair 2003). For example, mean heart rate (n = 6) with OTM form of detomidine dropped less than 60 bpm with second degree atrioventricular (AV) block observed in one dog (Hopfensperger et al. 2013), while the mean heart rate decrease (n = 27) with OTM form of dexmedetomidine was mild (e.g. 98 bpm) (Zoetis 2016).

The biphasic response of arterial blood pressure after alpha-2 agonist administration is reported although one study did not observe an increase but a decrease of blood pressure after administration (Lamont et al. 2001). In humans, sudden withdrawal of clonidine after long-term administration for treatment of hypertension has been associated with rebound hypertension, which may occur up to 20 hours after cessation of the drug. Additionally, emesis is typically induced by alpha-2 agonists due to stimulation of the chemoreceptor trigger zone (Hikasa et al. 1989; Thawley and Drobatz 2015; Willey et al. 2016). Occurrence of emesis is more common in cats than dogs with xylaxine (50% of dogs, 90% of cats) and medetomidine (8–20% of dogs, up to 90% of cats) (Vainio et al. 1986; Sinclair 2003). Individual sensitivity to each alpha-2 mediation also seems to exist (Lucot and Crampton 1986, Willey et al. 2016). Although overall adverse effects with an oral or OTM dose of alpha-2 agonists are mostly mild, caution should be taken, particularly in animals with cardiovascular disease, in shock, or under extreme weather conditions.

## Overdose

In veterinary medicine, treatment of overdose is reversed by the alpha-2 antagonists yohimbine, tolazoline, atipamezole, and idazoxan. Each antagonist has a different selectivity and affinity for the alpha-2 and alpha-1 receptors. The stronger alpha-2 reversal specificity is atipamezole's following idazoxan, yohimbine, and tolazoline (Sinclair 2003). In the treatment of behavioral and mental conditions in animals, alpha-2 agonists are mostly administered by non-injectable route (i.e. OTM or oral), which limits the potential for overdosing. However, individuals that are hypersensitive to alpha-2 agonists or with severe cardiovascular, respiratory, liver or kidney disease can be potentially overdosed. Common signs of overdosing are sedation, decrease in heart rate, blood pressure, and body temperature. Supportive treatment should be provided along with the administration of an antagonist.

## Clinical Guidelines (Table 11.1)

It is possible that preexisting stress, fear, and excitement leading to increased endogenous catecholamine levels can interfere with the effect of alpha-2 agonists (Sinclair 2003). Some studies showed that the arousal at the onset of sedation delayed the effect of medetomidine IM when dogs were in a noisy environment (Clarke and England 1989). Therefore, providing an appropriate environment (e.g. a quiet room) when administering the medication is important so the alpha-2 can be efficacious. That can be

**Table 11.1** Doses of various sympatholytics for dogs, cats, and horses for the treatment of fear and anxiety disorders.

| | Sympatholytic | Dog | Cat | Horse |
|---|---|---|---|---|
| Alpha2 agonist | Clonidine (oral) | 0.01–0.05 mg kg$^{-1}$, PRN | | |
| | Detomidine (OTM) | 0.35 mg m$^{-2}$ (=0.012–0.016 mg kg$^{-1}$) PRN | | 0.04 mg kg$^{-1}$, PRN |
| | Dexmedetomidine (OTM) | 0.125 mg m$^{-2}$ PRN | | |
| Beta blocker | Propranolol | 0.25–3 mg kg$^{-1}$ BID | 0.2–1 mg kg$^{-1}$ TID | |

*Source:* Ogata and Dodman (2011), Zoetis (2013, 2016), Hopfensperger et al. (2013), Lansberg et al. (2013).

interpreted clinically as the importance of provision of the adequate level of triggers even though the medication is used in the behavior treatment context. It is reported that after reaching a ceiling effect, higher doses did not increase the depth of sedation but only the duration of sedation in dogs and cats (Vainio et al. 1986). Although alpha-2 agonists have been used in small animal medicine for a long time, the approval label by the FDA was only given for injectable forms recently. Only in 2016 did the FDA approve OTM dextomedetomidine gel for the treatment of noise aversion in dogs (Zoetis 2016). All other uses described in this chapter are "off-label."

The advantage of OTM administration over oral administration is that it can avoid hepatic first-pass metabolism, therefore, it takes full effect faster than oral administration (Ansah et al. 1998; Hopfensperger et al. 2013). Due to the lower bioavailability of OTM administration (compared to IM administration), it causes less sedation and physiological effects. When the OTM form is administered, impermeable gloves should be worn to protect skin contact.

## Specific Medications

### I. Clonidine

**Chemical Compound:** N-(2,6-Dichlorophenyl)-4,5-dihydro-1H-Imidazol-2-amine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 0.1-, 0.2-, and 0.3-mg tablets. Also available as 0.1-, 0.2-, and 0.3-mg transdermal patches. The extended release (12-hour) form comes in 0.1-, and 0.2-mg tablets. Clonidine HCl injection for epidural use is available as 0.1 mg $ml^{-1}$ and 0.5 mg/preservative-free in 10 ml vials.

#### Clinical Pharmacology

Clonidine is sometimes called a selective alpha-2 adrenergic agonist with some alpha-1 agonist activity, though guanfacine is known to be more selective for alpha-2 receptors. Clonidine binds to alph-2A, alpha-2B, and alpha-2C receptors as well as imidazoline receptors, which are partially related to sedation and hypotension. The analgesic effects of epidural clonidine in domestic species have been studied (Plumb 2015). Clonidine is also useful as a diagnostic agent to determine growth hormone deficiency in dogs (Frank 2005) and as an adjunctive treatment for refractory inflammatory bowel disease in dogs and cats (Plumb 2015).

Clonidine has an inhibitory action and reduces the firing of presynaptic neurons that release noradrenaline into the prefrontal cortex, thereby reducing fear or anxiety in rodents and primates (Soderpalm and Engel 1988) and improves the impulsive and hyperactive behavior seen in attention deficit hyperactivity disorder (ADHD) in humans (Nguyen et al. 2014). Studies in children comparing the effects between clonidine and midazolam to decrease preoperative anxiety to ensure smooth induction found that the anti-anxiety effects of clonidine are similar or better than midazolam. Clonidine has a slower onset of action (e.g. 60 minutes) than midazolam (e.g. 30 minutes), however (Fazi et al. 2001; McCann and Kain 2001; Cao et al. 2009). A similar slow onset effect (90–120 minutes) was observed in dogs when clonidine was used to treat fear-based behavior problems (Ogata and Dodman 2011).

#### Uses in Humans

In human medicine, clonidine has historically been used in the treatment of hypertension. As an extra label use, clonidine is also used for a variety of conditions including treatment of substance abuse, ADHD, and as sedative and analgesic agent. In perioperative patients or patients in intensive care, clonidine is also used to reduce their anxiety (Cao et al. 2009).

#### Contraindications

Do not give clonidine to patients with a history of sensitivity to clonidine or any alpha-2

agonists. Patients with severe cardiovascular, respiratory, liver or kidney disease can be potentially overdosed, so caution is recommended. In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within five days. The significance of this finding for dogs, cats, and horses is unknown.

#### Side Effects

In Ogata and Dodman's (2011) study, one owner reported increased sound sensitivity in a noise-phobic dog with the use of oral clonidine administration (1 in 22 dogs). In humans, the most frequent side effects (which appear to be dose-related) are dry mouth (40%); drowsiness (33%); dizziness (16%); constipation, and sedation (10% each) (Boehringer Ingelheim International GmbH 2011).

#### Other Information

In humans, tolerance to the antihypertensive effect is reported in some cases. Sudden cessation of clonidine treatment has resulted in symptoms such as nervousness, agitation, headache, and tremor, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma in humans (Boehringer Ingelheim International GmbH 2011; Nguyen et al. 2014). Therefore, clonidine dose should be tapered off gradually to avoid withdrawal symptomatology (Boehringer Ingelheim International GmbH 2011).

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Ogata and Dodman (2011) studied the use of clonidine for situational use with other anti-anxiety medications as a treatment for fear-based behavior problems and anxiety disorders, such as noise phobia, separation anxiety, or fear/territorial aggression. According to owners' reports, with the dose of 0.01–0.05 mg kg$^{-1}$ oral administration, the reduction of fear-based behavior was observed 1.5–2 hours after administration of clonidine and the effect waned after 4–6 hours (in 7 out of 10 fear-related problems but aggressive dogs, and in 11 out of 12 fear-related aggressive dogs).

Clonidine is used as an antidiarrheal agent for inflammatory bowel disease in dogs and cats at 0.005–0.01 mg kg$^{-1}$ BID-TID SC or PO (Plumb 2015).

##### *Cattle (extra-label)*

Epidural analgesia, 0.002–0.003 mg kg$^{-1}$ of clonidine in cattle provided bilateral perineal analgesia/anesthesia with a dose-dependent onset and duration of action (DeRossi et al. 2003).

## II. Detomidine

**Chemical Compound:** 4-(2,3-Dimethylbenzyl)-1H-imidazole hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Available as injection form 10 mg ml$^{-1}$ in 5 ml, and 20 ml vials and as 7.8 mg ml$^{-1}$ in 3 ml graduated dosing syringes.

#### Clinical Pharmacology

Detomidine is approved for sedation and restraint primarily in equine medicine. From a clinical standpoint for sedation and analgesic effects, detomidine is the most potent of these alpha-2 adrenergic agonists, if compared to xylazine and romifidine (Hamm et al. 1995; Moens et al. 2003). Target-animal safety studies showed that dosages of 0.2 mg kg$^{-1}$ (ten times the approved low dosage and five times the high dosage) given IV on three consecutive days were well tolerated in healthy, mature horses (Welker 2009).

Detomidine can be also used for anesthesia and analgesia in sheep, goats, camelids, and birds (Plumb 2015).

In horses, detomidine gel following OTM (sublingual) administration has an elimination half-life of approximately 1.5 hours, and bioavailability of approximately 22% (Kaukinen et al. 2010; Knych and Stanley 2011). Pharmacokinetic studies in dogs with the detomidine OTM form reported that time to maximum concentration and bioavailability for detomidine gel was one hour and 34.52%,

respectively. Harmonic mean elimination half-life was 0.63 hours (Messenger et al. 2016).

### Use in Humans

Detomidine has not been used in humans.

### Contraindications

Do not give detomidine to patients with a history of severe cardiovascular conditions such as atrioventricular (AV) block or sinoauricular (SA) block sensitivity to detomidine or any alpha-2 agonists. Other contraindications are similar to other alpha-2 agonists.

Concomitant use with phenothiazines (e.g. acepromazine) can result in severe hypotension.

Possible drug interactions have been reported concurrently with sulfonamides, and potentiated sulfonamides as fatal dysrhythmias may occur (Plumb 2015).

### Side Effects

According to a field study with 202 horses, the most frequent side effects (which appear to be dose-related) are sweating (10%), penile relaxation (6%), bradycardia, (5%), second-degree AV block, and frequent urination (4% each) (Zoetis 2013).

Detomidine gel is reported to cause transient bradycardia in five out of six dogs and intermittent second-degree AV block in one out of six dogs in a study (Hopfensperger et al. 2013).

### Other Information

Atipamezole may be a useful antagonist but only partially reverses detomidine sedation in horses (Hubbell and Muir 2006). In comparison, intravenous administration of yohimbine effectively and rapidly reversed detomidine-induced sedation, bradycardia, atrioventricular heart block, and hyperglycemia (Knych and Stanley 2011).

### Effects Documented in Nonhuman Animals

#### *Horses*

When using a FDA-approved sublingual gel, for the best results, allow adequate time (a minimum of 40 minutes) between the administration of the sublingual gel and the beginning of a procedure. In general, horses show sedative effects lasting approximately 90–180 minutes.

When using an injection, for the best results, allow adequate time (2–5 minutes) between administration of 0.02–0.04 mg $kg^{-1}$ IV (only for analgesia) or IM and beginning the procedure. A lower dose will generally provide 30–90 minutes of sedation and 30–45 minutes of analgesia. The higher dose will generally provide 90–120 minutes of sedation and 45–75 minutes of analgesia. For sedation, chemical restraint, analgesia in horses (extra-label): Table 11.2.

**Table 11.2** Detomidine doses for sedation, chemical restraint, and analgesia in horses (extra-label).

| Use | Dose | Effect |
|---|---|---|
| Premedicant | 0.005–0.03 mg $kg^{-1}$ IV | |
| Caudal epidural analgesia | 0.06 mg $kg^{-1}$, given between S4-S5 | Duration of analgesia is 2–3 hours |
| | 0.03 mg $kg^{-1}$ with morphine 0.2 mg $kg^{-1}$, given between S1-L6 | Duration of analgesia is >6 hours |
| Constant rate infusion (CRI) for total intravenous anesthesia (TIVA) | Guaifenesin-Ketamine-Detomidine (GKD) triple-drip protocol: 10 mg of detomidine, 500–1000 mg of ketamine to 500 ml of 5% guaifenesin | CRI rate is 1.2–1.6 ml $kg^{-1}$ $hour^{-1}$ |
| CRI for sedation | 0.022 mg $kg^{-1}$ $hour^{-1}$ | |
| Partial intravenous anesthesia (PIVA) | 0.013–0.038 mg $kg^{-1}$ $hour^{-1}$ | |

*Source:* Plumb (2015).

**Table 11.3** Detomidine doses to produce standing sedation with a low incidence of recumbency in cattle (extra-label).

| | IV | IM |
|---|---|---|
| Tractable cattle | 0.002–0.005 mg kg$^{-1}$ | 0.006–0.01 mg kg$^{-1}$ |
| Anxious cattle | 0.005–0.0075 mg kg$^{-1}$ | 0.01–0.015 mg kg$^{-1}$ |
| Extremely anxious or unruly cattle | 0.01–0.015 mg kg$^{-1}$ | 0.0015–0.02 mg kg$^{-1}$ |
| Analgesia | 0.01 mg kg$^{-1}$ | |

*Source:* Plumb (2015).

#### *Dogs*

Hopfensperger et al. (2013) studied the use of equine oromucosal gel administered via the OTM route on six laboratory dogs. The dose was 0.35 mg m$^{-2}$ (= 0.012–0.016 mg kg$^{-1}$) and sedation was observed (four out of six dogs) for 45 minutes after administration of detomidine OTM and the duration of maximum sedation effect was 30 minutes.

#### *Cattle*

For standing sedation, see Table 11.3.

#### *Sheep, Goats*

For anesthesia: detomidine at 0.01 mg kg$^{-1}$ IM, followed by propofol at 3–5 mg kg$^{-1}$ IV. For analgesia: 0.005–0.05 mg kg$^{-1}$ IV or IM q3–6 hours.

#### *Llamas, Alpacas*

For analgesia: 0.005–0.05 mg kg$^{-1}$ IV or IM q3–6 hours.

#### *Birds*

For sedation/analgesia: 0.3 mg kg$^{-1}$ IM.

## III. Dexmedetomidine

**Chemical Compound:** 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H imidazole hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as injection form 0.1, and 0.5 mg ml$^{-1}$ in 10 ml vials (dogs and cats). Also available as 0.1 mg ml$^{-1}$ in 3 ml prefilled multidose oral syringe (dogs).

### Clinical Pharmacology

Dexmedetomidine is FDA-approved for sedation and analgesia in dogs and cats. Dexmedetomidine is also indicated for use as a preanesthetic to general anesthesia in dogs and cats. Oromucosal (OTM) gel form is FDA-approved for the treatment of noise aversion in dogs. Time to maximum concentration and bioavailability for dexmedetomidine OTM gel (Sileo®) were 0.6 hour, and 28%, respectively and elimination half-life was 0.5–3 hours.

Target-animal safety studies showed a satisfactory margin of safety when administered IV or IM at doses as high as five times the recommended dose in healthy, mature dogs and cats (Orion Corporation 2006).

### Use in Humans

In humans, dexmedetomidine is approved as an adjunct to anesthesia and as an agent for sedation in the intensive care unit patients. Administration routes are IV, IM transdermal, and via the oral mucosa. Dexmedetomidine administered transmucosally via the buccal mucosa has the bioavailability of approximately 82% (Anttila et al. 2003).

### Contraindications

Do not give dexmedetomidine to patients with a history of sensitivity to dexmedetomidine or other alpha-2 agonists. Patients with severe cardiovascular, respiratory, liver, or kidney disease can be potentially overdosed so caution is warranted.

Sileo (dexmedetomidine OTM form) is contraindicated in dogs with shock, severe debilitation and stress due to extreme heat, cold, or fatigue. The response of Sileo has not been investigated in dogs younger than 16 weeks of age, in ones that have dental or gingival diseases, are used for breeding, are pregnant or lactating.

#### Side Effects

In dexmedetomidine OTM form in dogs, the most common adverse reaction was sedation, which occurred in 2 out of 12 dogs in the 125 mcg $m^{-2}$ dose group and in 4 out of 12 dogs in the 250 mcg $m^{-2}$ dose group (2 times above the standard clinical dose) in a pilot study where dogs between 2 and 11 years of age and weighing between 4 and 52 kg were included. All dogs were healthy and had a history of noise aversion (Orion Corporation 2015).

In another study on dogs with the history of fear of fireworks, dexmedetomidine OTM form of 125 mcg $m^{-2}$ dose was used in 89 dogs that ranged between 2 and 17 years and whose body weight ranged between 4 and 67 kg. The most common adverse reaction in this study was emesis, which occurred in 4 out of 89 dogs in the dexmedetomidine OTM group, while in 1 out of 93 dogs in the control group. When repeated administration was given to the dogs, it was up to five times during one noise event with a minimum interval of two hours between doses.

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Dexmedetomidine OTM gel should be administered on the oral mucosa between the dog's cheek and gum at the dose of 125 mcg $m^{-2}$. The first dose should be administered approximately 30–60 minutes before the aversive stimulus (e.g. loud noise) or immediately after the dog shows early or mild signs of anxiety or fear related to the auditory stimulus. If the stimulus lasts longer than two to three hours and the dog's signs of fear and/or anxiety reappear, another dose may be given. During one noise event, up to five doses with minimum of two hours interval can be administered.

According to the randomized, double-blind, placebo-controlled study to assess the effect of dexmedetomidine OTM gel for noise-associated acute anxiety and fear, a total of 182 privately owned dogs with a history of acute anxiety and fear associated with noises were assessed, with 89 dogs receiving 0.1 mg $ml^{-1}$ dexmedetomidine OTM gel at a dose of 125 mcg $m^{-2}$ and 93 dogs receiving placebo (Korpivaara et al. 2017). For the New Year's Eve fireworks, the owners were instructed to apply the gel (either dexmedetomidine OTM or placebo) on the buccal mucosa without allowing the dog to swallow the gel. The dose application was decided by each owner. Thus, the dosing was done one hour before the anticipated start of fireworks, or immediately after the first fireworks, or when the dog's anxiety or fearful signs were first noticed, as needed. Re-dosing was also allowed up to five times when the dog started to show anxiety or fearful signs again with a minimum of a two-hour interval between the administration. No dogs received any other anti-anxiety treatments including behavioral or environmental management. The effect of the treatment was assessed by the owners, and an excellent or good effect was reported in 72% of dexmedetomidine dogs while in only 37% in the placebo dogs. The dogs with the treatment showed significantly fewer anxiety or fearful signs than the dogs with placebo when compared with each baseline. The most common adverse effect was emesis that was observed in 4 out of 89 dogs with the treatment and 1 out of 93 dogs with placebo. None of them were serious and no local irritation of oral mucosa was reported. Transient local paleness of the oral mucosa was observed in 13.3–16.9% in the treatment dogs and 2.1–6.6% until two hours after the third dose.

Injection (FDA-approved): for sedation and analgesia, 375 mcg $m^{-2}$ IV, and 500 mcg $m^{-2}$ IM; preanesthesia, 125 or 375 mcg $m^{-2}$ IM.

***Cats***

Injection (FDA-approved) for sedation, analgesia, and preanesthesia, 40 mcg $kg^{-1}$ IM.

## IV. Propranolol

**Chemical Compound:** 1-naphthalen-1-yloxy-3-(propan-2-ylamino) propan-2-ol

**DEA Classification:** Not a controlled substance

**Preparations:** Available as 1 mg $ml^{-1}$ injection form; as 4 and 8 mg $ml^{-1}$ in 500 ml oral solution; as 10-, 20-, 40-, 60-, 80-mg oral tablets; and as 60-, 80-, 120-, 160-mg capsules extended release.

### Clinical Pharmacology

Propranolol is a beta blocker that competes primarily at beta1 and beta2 receptors. It is used for hypertension, coronary artery disease and tachyarrhythmias in human medicine. In veterinary medicine, it is used primarily for acute treatment of cardiovascular conditions, such as atrial premature complexes, ventricular premature complexes, supraventricular premature complexes, and tachyarrhythmias. Propranolol can be also used for hypertrophic cardiomyopathy in ferrets and ventricular tachycardia in horses.

Although in humans, propranolol is well absorbed from the gastrointestinal tract, in dogs, oral bioavailability is not good in comparison. One study reported approximately 8% of bioavailability (Lo et al. 1982), so other beta blockers have been alternatively used.

### Use in Humans

In addition to the traditional use to target peripheral sites of the noradrenergic system, in psychiatry, propranolol has attracted attention since 1960s. Its effect is to compete the beta adrenoreceptor with catecholamine, thus, blocking orthosympathetic effects, and it was used to treat several psychiatric conditions, such as anxiety, autism, or aggression. It has also been commonly used to attenuate stressful conditions such as performance anxiety in musicians, exam nerves, or stage fright. Recently, propranolol has been used for the amnesic effect on retrieved fear memory. According to the research, it has been shown that noradrenergic transmission is not required for the consolidation of auditory fear conditioning, but once a memory is reactivated, noradrenergic signaling plays a critical role in the reconsolidation of retrieved memory in knockout mice. It was shown that the disruptive effects of the beta adrenergic antagonist on reconsolidation produce long-lasting changes in the retrieval of the memory in rats (Dębiec and Ledoux 2004). Several studies and trials in humans followed these psychopharmacological effects of propranolol, yet they have never been systematically reviewed until recently. Steenen et al. (2016) conducted a systematic review and meta-analysis by using four studies concerning panic disorder with or without agoraphobia (total n = 130), two studies with specific phobia (total n = 37), a study with social phobia (n = 16), and a study with post-traumatic stress disorder (PTSD) (n = 19). These meta-analyses found no statistically significant differences between the efficacy of propranolol and benzodiazepines regarding the short-term treatment of panic disorder with or without agoraphobia. Also, no evidence was found for the effects of propranolol on PTSD symptom severity through inhibition of memory reconsolidation. The conclusion of this review was that the quality of evidence for the efficacy of propranolol was insufficient to support the routine use of propranolol in the treatment of any of the anxiety disorders.

### Contraindications

Do not give propranolol to patients with a history of sensitivity to it or other beta blockers. Patients with severe cardiovascular, respiratory, liver, or kidney disease can be potentially overdosed, therefore use with caution.

### Side Effects

Like other sympatholytics, bradycardia, AV block, hypotension, and peripheral vasocon-

striction can occur. Propranolol may exacerbate preexisting renal impairment. After long-term usage, the dose should be tapered off gradually to avoid withdrawal symptoms.

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Few studies have reported on the use of propranolol in dogs. Walker et al. (1997) published case reports in the treatment of phobias in dogs. According to this publication, in all cases, phenobarbital and propranolol were used together and in conjunction with behavior modification. The dose used for phenobarbital was 2–3 mg $kg^{-1}$ BID while propranolol was 5 mg or more TID in small dogs, 10–20 mg TID or 2–4 mg $kg^{-1}$ $day^{-1}$ (divided into TID) in large dogs. For example, a propranolol dose of a dog weighing 30 kg will be 40 mg TID. They also reported that propranolol given 2–3 mg $kg^{-1}$ BID with phenobarbital 2–3 mg $kg^{-1}$ BID was effective if that was easier for some owners to comply. Duration of treatment would be from a minimum of three months up to six months and infrequent triggers such as thunderstorms tended to take longer for the treatment. When the dog responded the treatment positively, both medications were tapered off. Notari (2005) reported on treating dogs for thunderstorm and fireworks phobia with selegiline (0.5 mg $kg^{-1}$ $day^{-1}$) in addition to propranolol (2.5 mg $kg^{-1}$) and alprazolam (0.05 mg $kg^{-1}$) as given situationally in conjunction with behavior modification. All cases improved within three to six months of treatment.

##### *Cats*

Walker et al. (1997) stated that 5 mg of propranolol BID combined with 7.5 mg of phenobarbital BID were an effective dose for cats. No other details were mentioned about cat cases.

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# 12

# N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

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## Action

Glutamate (or glutamic acid) is an excitatory amino acid that works as the major neurotransmitter in the central nervous system. It triggers the long-term potentiation (LTP) of neuronal firing and synaptic plasticity. The N-Methyl-D-aspartate (NMDA) receptor, which is located not only within the synapse but also at extrasynaptic sites, is one of the three classes of glutamate-gated ionotropic channels and is well known with the other two receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and the kainate receptors. NMDA receptors are ionotropic, ligand-gated, glutamate-sensitive neurotransmitter receptors. Each NMDA receptor is a tetraheteromeric complex formed through the assembly of two GluN1 and two GluN2 protein subunits. The NMDA receptor is the most permeable to $Ca^{2+}$, therefore, excessive activation of the NMDA receptor leads to increased intracellular $Ca^{2+}$. Although glutamate binds with one of these sites on the receptor, a molecular of glycine (an inhibitory neurotransmitter) must be attached to the glycine binding site that is located on the outside of the NMDA receptor to open the calcium channel (Carlson 2013). Several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis, neuropathic pain, and glaucoma are caused by neuronal cell injury or death that is due to the overstimulation of NMDA receptors (Lipton 2006). Acute disorders of stroke, central nervous system trauma, seizures as well as hyperalgesia in pain syndromes are also led by the excitotoxicity of glutamate. Therefore, it is considered that NMDA receptor antagonists can be beneficial in a number of neurological disorders.

Additionally, NMDA receptor-mediated glutamate neurotransmission has been considered to be involved in human depression for over 20 years (Vale et al. 1971). Reports in rodents as animal models of depression and humans from postmortem tissue have shown alterations in central NMDA receptor after periods of chronic stress (Newport et al. 2015). Even though the effects of combating the excitotoxicity of glutamate and neuroprotective efforts were of interest, severe side effects from inhibiting the excitotoxicity of glutamate were challenging when in the clinical applications of NMDA receptor antagonists. This was more pronounced with competitive NMDA receptor antagonists where the antagonists simply compete with glutamate or glycine at the agonist-binding sites to block normal functions, causing severe side effects such as

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drowsiness, hallucinations, and even coma (Kemp and McKernan 2002). After several investigations, researchers have shifted to using NMDA receptor antagonists that block partially to avoid unwanted side effects. These medications are called noncompetitive/uncompetitive antagonists. Examples are amantadine, memantine (uncompetitive), and ketamine.

It is hypothesized that chronic treatment with conventional antidepressants results in the same functional endpoint as the administration of NMDA receptor antagonists (Skolnick 1999). However, a systematic review and meta-analysis of ketamine and other NMDA receptor antagonists in the treatment of major depression concluded the antidepressant efficacy was only observed in ketamine. Because ketamine also has a potential for abuse and neurotoxicity as well as its potential therapeutic benefit, clinical use has started in humans but warrants caution (Newport et al. 2015). A recent paper discussed the possibility of developing a better and safer antidepressant medication than ketamine (Zanos et al. 2016).

## Overview of Indications

Of the three excitatory amino acid receptor subtypes, the NMDA receptor seems more specifically linked to long-term changes in neurons that play an important role in both inflammation and nerve injury-induced central sensitization (De Kock and Lavand'homme 2007). Therefore, NMDA receptor antagonists have been implicated in postoperative and neuropathic pain management in humans (Collins et al. 2010). A systematic review in the human literature was not conclusive on its efficacy on neuropathic pain. The authors recommended that additional randomized control trials in homogeneous groups of pain patients are necessary for further conclusions (Collins et al. 2010).

In the veterinary literature, the indication of NMDA receptor antagonists (such as ketamine and amantadine) is primarily for adjunctive analgesia to minimize the sensitization of the dorsal horn neurons (Lamont 2008). For example, it was reported that dogs that received ketamine infusions before, during, and after surgery had significantly lower pain scores after surgery and were significantly more active or had improved feeding behavior during postoperative observation compared to control dogs (Wagner et al. 2002; Sarrau et al. 2007). In both studies, opioid requirements used concomitantly were not significantly different between groups (Lamont 2008).

Amantadine was originally used as an antiviral drug and to treat Parkinson's disease in human medicine. Recently in both human and veterinary medicine, it has also been used to treat chronic pain. Lascelles et al. (2008) conducted a randomized, blind, placebo-controlled study to evaluate its analgesic effects as an adjunct to an analgesic regimen in dogs with naturally occurring osteoarthritis. They reported that the addition of amantadine improved the dog's physical activity and that it might be a useful adjunct therapy for dogs with osteoarthritic pain.

In veterinary behavioral medicine, published information regarding NMDA receptor antagonists include the treatment of stereotypic behaviors, obsessive-compulsive disorders, and putative complex partial seizures. The drugs used in these studies were dextromethorphan (Rendon et al. 2001; Dodman et al. 2004), memantine (Schneider et al. 2009b) and Huperzine-A (Schneider et al. 2009a), which is a herbal medication.

## Contraindications/Side Effects, and Adverse Events

According to the literature, except for ketamine, noncompetitive or uncompetitive NMDA receptor antagonists in general are

well-tolerated drugs with no serious adverse effects reported, when used in instructed doses in humans, for example, an open trial of amantadine in depressed patients (bipolar or major depression) with Borna disease virus (BDV) infection, where 100–300 mg day$^{-1}$ of amantadine were administered for a mean of 11 weeks. Major unwanted effects were observed in only one out of 25 patients that led to a drop-out from the study. The signs reported were restlessness and blurring of vision but the rest of patients tolerated the amantadine therapy till the end of the study (Dietrich et al. 2000). Another study with memantine reported that in a randomized, pilot clinical trial for neuropathic pain following surgery, evaluating 5–20 mg day$^{-1}$ of memantine for four weeks, no adverse effects were observed (Morel et al. 2016). When NMDA receptor antagonists are used for outpatient oral treatment in dogs, cats, and horses, relatively few side effects have been reported so far. Dodman et al. (2004) conducted a randomized, double-blind, crossover-designed study for 14 dogs with chronic allergic dermatitis for two weeks with dextromethorphan (2 mg kg$^{-1}$ b.i.d.). Vomiting, retching, diarrhea, and lethargy were reported. A dog with lethargy and a dog with diarrhea withdrew from the study. All recovered once the treatment was discontinued. Schneider et al. (2009b) treated 11 dogs for compulsive disorder with memantine 0.3–1 mg kg$^{-1}$ twice a day. One client reported a possible side effect from the drug on their dogs (increased frequency of urination). Since use of NMDA receptor antagonists is not yet widespread and research has been scarce, the presence or absence and the clinical significance of side effects should be interpreted prudently.

## Clinical Guidelines

For decades, most of the research on human mood disorders, especially major depression, has been based on monoaminergic systems. However, in the early 2000s, ketamine, a non-competitive NMDA receptor antagonist, specifically received attention for its rapid and robust antidepressant effects in major depression (Zarate et al. 2006). Its action is not fully understood but recent results from studies in rodents suggested that ketamine activated the mammalian target of rapamycin pathway and subsequent synaptogenesis in the prefrontal cortex as well as glycogen synthase kinase-r beta (GK-3β) inactivation (Scheuing et al. 2015). Although ketamine is generally used for anesthesia, at low doses, it also works as an antidepressant. When the dose is increased, it evokes psychotomimetic actions (Miller et al. 2016) that challenge its clinical applications. In veterinary behavioral medicine, using ketamine in the treatment of behavior problems or mental health disorders has not yet been reported.

Another psychiatric disorder where imbalances in glutamatergic neurotransmission might be involved is obsessive-compulsive disorder (OCD) or compulsive disorder. The nature of glutamate perturbation in OCD remains poorly understood. Research in this area has been largely experimental with off-label use of available medications (Pittenger 2015).

## Specific Medications

### I. Dextromethorphan

**ChemicalCompound:** Morphinan,3-methoxy-17-methyl-, (9α, 13α, 14α)-, hydrobromide monohydrate

**DEA Classification:** Not a controlled substance

**Preparations:** Available in pills, gel caps, lozenges, liquids and syrups, either alone or in combination with analgesics (acetaminophen), antihistamines (brompheniramine, chlorpheniramine, and diphenhydramine), decongestants (pseudoephedrine) and/or expectorants (guaifenesin). Dextromethorphan is also available in bulk powder from internet sites. Dose for antitussive use: 1–2 mg kg$^{-1}$ q6–8h PO in cat and dog (Kuehn 2015).

### Clinical Pharmacology

Dextromethorphan (DXM) is a noncompetitive NMDA receptor antagonist, available for use in many prescription products, as well as in its most common form as over-the-counter (OTC) products for the treatment of cough.

The typical antitussive adult human dose is 15 or 30 mg TID to QID. The antitussive effects of DXM persist for five to six hours after oral administration. When taken as directed, side effects are rarely observed (Drug Enforcement Administration 2014).

Dextromethorphan is the dextro isomer of levomethorphan, a semisynthetic morphine derivative. Although structurally similar to other narcotics, DXM does not act as a *mu*-receptor opioid (e.g. morphine, heroin). The antitussive activity of DXM is based on its action on σ-opioid receptors and DXM also has analgesic and CNS depressant effects. DXM and its metabolite, dextrorphan, act as potent blockers of the NMDA receptor. At high doses used by those who abuse it, DXM causes dissociative effects, similar to the controlled substances phencyclidine (PCP) and ketamine, and inhibition of catecholamine reuptake. Approximately 5–10% of Caucasians are poor DXM metabolizers, which increases their risk for overdose and death (Chyka et al. 2007).

In the veterinary field, it is used as an antitussive and few side effects have been reported when given clinically relevant doses. In the veterinary behavior field, IV administration of DXM is used for cribbing horses (Rendon et al. 2001) and oral DXM is used for dogs with repetitive behavior problems (Dodman et al. 2004).

### Contraindications and Side Effects

DXM has been available as an OTC antitussive medication for over 50 years and has been considered to have a high margin of safety with a clinical relevant dose.

Since DXM binds to serotonergic receptors, the human literature states that it might not be safe to administer DXM with antidepressants due to the risk of inducing a life-threatening serotonergic syndrome (Chyka et al. 2007).

Vomiting, retching, diarrhea, and lethargy were reported in dogs with oral DXM ($2\,mg\,kg^{-1}$ b.i.d.) (Dodman et al. 2004). A dog with lethargy and a dog with diarrhea withdrew from the study reported above. All patients recovered once the treatment was discontinued.

### Other Information

According to the pharmacokinetics study of dextromethorphan after intravenous and oral administration in six healthy beagles (KuKanich and Papich 2004), the drug had a short half-life, and had poor bioavailability, such as 11% in oral administration. The authors concluded that its potential use with chronic oral administration is limited. Therefore, its effectiveness and long-term safety need to be further studied (Moriello 2005; Saridomichelakis and Olivry 2016).

Recently pharmacology studies in mice showed antidepressant-like effects of DXM through forced swim and tail suspension tests (Nguyen and Matsumoto 2015). According to the study, it is speculated that DXM may modulate the glutamatergic function through an NMDA blockade that indirectly activates AMPA receptors. It is considered that AMPA receptors may contribute to the efficacy of antidepressant medications, including that of ketamine (Sanacora et al. 2008).

### Effects Documented in Nonhuman Animals

#### *Dogs*

Dodman et al. (2004) conducted a randomized, double-blind, crossover designed study to test the efficacy of oral DXM ($2\,mg\,kg^{-1}$ b.i.d. for two weeks) on 14 dogs with repetitive behavior problems (e.g. self-licking, self-chewing, and self-biting associated with chronic allergic dermatitis). Based on a dermatology score and the owners' daily observations, it was concluded that DXM induced a mild to moderate improvement in clinical signs (i.e. reduced the percentage of time that allergic dogs spent in repetitive behaviors). Saridomichelakis and Olivry

(2016) recommended further studies to fully appreciate the effectiveness and long-term safety of DXM in atopic dermatitis.

Maurer and Dodman (2007) published one case report of the treatment for compulsive disorder in a dog using dextromethorphan as an alternative medication to memantine due to its cost. Details are given in the memantine section of this chapter.

#### Horses

Rendon et al. (2001) reported DXM effects on cribbing horses. Jugular injection of DXM (1 mg $kg^{-1}$) was administered to nine cribbing horses and eight horses responded with mean of 48% decrease in frequency compared to baseline, and its effect lasted 35–60 minutes following injection in almost half of the horses. Although no major side effects were reported, one horse in the study showed higher rate of cribbing rate after the injection.

## II. Amantadine

**Chemical Compound:** Adamantan-1-amine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Available in 100-mg capsules, tablets or 50 mg/5 ml oral solution.

#### Clinical Pharmacology

Amantadine is a weak, noncompetitive NMDA receptor antagonist. It has been used treat Parkinson's disease, drug-induced extrapyramidal reactions, and virus infections. Although its mechanism of action for each condition is not clearly understood, it appears to exert its antiviral effect by preventing penetration of the virus into the host cell, and it is also known to prevent virus assembly during virus replication (Endo Pharmaceuticals Inc. 2009). Amantadine is considered to have direct or indirect effects on dopamine neurons and oftentimes is prescribed with L-Dopa for the management of L-Dopa-induced dyskinesia in Parkinson's disease (Oertel and Schulz 2016). Analgesic effects in orally administered amantadine in humans had inconsistent results (Taira 1998; Kleinböhl et al. 2006). Lascelles et al. (2008) published a randomized, blind, and placebo-controlled study on the use of oral amantadine in addition to meloxicam (a nonsteroidal anti-inflammatory drug) on refractory osteoarthritis pain in 31 client-owned dogs. In the study, physical activity in dogs was improved per client-specific outcome measures with the addition of amantadine (3–5 mg $kg^{-1}$ orally every 24 hours) to meloxicam treatment (0.1 mg $kg^{-1}$ administered orally every 24 hours after a 0.2 mg $kg^{-1}$ oral loading dose) within three weeks of the treatment. No abnormalities were reported on the patients' laboratory work or adverse effects during the study.

#### Use in Humans

Based on the oral administration of a single amantadine 100 mg dose in 24 healthy adult humans, the time to peak concentration was 3.3 ± 1.5 hours (range: 1.5–8.0 hours). The half-life was 17 ± 4 hours (range: 10–25 hours). Amantadine is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion. Therefore, compared with otherwise healthy adult individuals, the clearance of amantadine is significantly reduced in adult patients with renal insufficiency. The apparent oral plasma clearance of amantadine is reduced and the plasma half-life and plasma concentrations are increased in healthy elderly individuals age 60 and older (Endo Pharmaceuticals Inc. 2009). Vale et al. (1971) reported on the antidepression effects of amantadine.

#### Contraindications

Careful observation is required when amantadine is administered concurrently with central nervous system stimulants.

Agents with anticholinergic properties may potentiate the anticholinergic-like side effects of amantadine.

#### Side Effects

Although amantadine has not been shown to possess direct anticholinergic activity in animal studies, clinically, it exhibits

anticholinergic-like side effects such as dry mouth, urinary retention, and constipation as well as nausea, dizziness, and insomnia in humans (Endo Pharmaceuticals Inc. 2009; Collins et al. 2010).

#### Overdose

Deaths have been reported from overdose with amantadine. The lowest reported acute lethal dose in humans was 1 g. Acute toxicity may be attributable to the anticholinergic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, renal, or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia, and hypertension.

The toxic dose reported for cats is 30 mg kg$^{-1}$ and behavioral effects may be noted at 15 mg kg$^{-1}$ in dogs and cats.

#### Effects Documented in Nonhuman Animals

##### *Dogs*

The pharmacokinetics of amantadine have been incompletely described in dogs. Based on urinary excretion studies in two beagle dogs, amantadine seems to be well absorbed in dogs, about 10% is metabolized to N-methylamantadine, and the half-life of amantadine was short: 5 hours after a single oral dose of 30 mg kg$^{-1}$. No reports are available assessing the activity or lack thereof for the metabolite. Dogs administered amantadine 50 mg kg$^{-1}$ every 24 hours by mouth for 30 days had negligible amounts of drug in tissue samples collected 24 hours after the last dose with the investigators concluding that a dose of amantadine is eliminated within 24 hours (Bleidner et al. 1965).

Norkus et al. (2015) reported a single oral dose of 100 mg amantadine (mean dose 2.8 mg kg$^{-1}$ as amantadine hydrochloride) was given to five healthy greyhound dogs for pharmacokinetics study. The terminal half-life in greyhound was similar (5.9 hours) to the aforementioned study in the two beagle dogs.

Dogs appear to tolerate higher doses of amantadine than humans. Safety data in dogs administered 80 mg kg$^{-1}$ a day for a period up to two years did not report any specific toxicity (Novartis New Zealand Limited 2011). Norkus et al. (2015) discussed the re-evaluation of the dosing interval in the veterinary literature (3–5 mg kg$^{-1}$ P.O. q24h [Lamont 2008]) as the majority of the drug was metabolized or eliminated within 24 hours (Bleidner et al. 1965). KuKanich (2013) recommended every 12 hours dosing due to the short half-life for both dogs and cats.

##### *Cats*

Amantadine is clinically used as an analgesic adjunct in cats, usually in combination with low doses of opioids. In six cats in the pharmacokinetics study, it showed high oral bioavailability and the terminal half-life 5.8 hours after IV administration and 5.4 hours after oral administration, while half-life in humans is 9–15 hours (Siao et al. 2011).

## III. Memantine

**Chemical Compound:** 3,5-dimethyladamantan-1-amine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Available in 10-, 20-mg tablets and oral solution: 2 mg ml$^{-1}$. An extended release capsule is also available in 7-, 14-, 21-mg, and 28- mg doses.

#### Clinical Pharmacology

Memantine is a low to moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics (Forest Laboratories Inc. 2003). It has been used to safely treat patients with moderate to severe Alzheimer's disease for more than two decades. Memantine is a derivative of amantadine. Originally due to its effect in Parkinson's disease, it was believed that memantine was a dopaminergic or anticholinergic drug. However, in the early 1990s it was found to be neither dopaminergic nor anticholinergic at its clinically useful dosage, but rather an NMDA receptor antagonist (Lipton 2006). It was also reported that memantine does not

affect the release of serotonin, nor does it alter monoamine oxidase (MAO-A or B) or adenylate cyclase activity. In humans, memantine is 100% bioavailable after an oral dose, undergoes minimal metabolism, and exhibits a terminal elimination half-life of 60–80 hours (75% or greater of the dose is eliminated intact in the urine). It rapidly crosses the blood–brain barrier with a CSF/serum ratio of 0.52. Memantine also showed antagonistic effects at the $5HT_3$ receptor with a potency similar to that of the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency (Forest Laboratories Inc. 2003). In humans, co-administration of memantine with acetylcholinesterase inhibitors (AChEI) such as donepezil HCl did not affect the pharmacokinetics of either compound and they are commonly used together (Gauthier and Molinuevo 2013).

It is demonstrated that memantine improves hippocampal long-term potentiation (LTP), working memory-based learning in rats (Zajaczkowski et al. 1997; Ma et al. 2015) and functional, global, and cognitive efficacy in moderate to severe Alzheimer's disease patients (Reisberg et al. 2006). It is generally considered that the effect of memantine to slow cognitive decline in Alzheimer's disease patients is based on its neuroprotective action.

However, there is yet no general agreement on how NMDA receptor channels are blocked by memantine (Povysheva and Johnson 2016).

#### Use in Humans

After the antidepressant effect of ketamine was found, other NMDA receptor antagonists that are considered safer, such as memantine, were studied for their possible antidepressant effects (Ladarola et al. 2015). So far, based on the meta-analysis of the three studies which used memantine at or about a daily dose of 20 mg during an eight-week trial, its efficacy to treat depression did not exceed the results of the placebo groups (Newport et al. 2015).

Memantine has been also studied to treat obsessive-compulsive disorder (OCD) as an augmentative regimen and several case series or open label studies have been published (Stewart et al. 2010; Wu et al. 2012). According to a double-blind, placebo-controlled trial, 38 patients were administered either memantine (10 mg $day^{-1}$ for the first week, and 20 mg $day^{-1}$ for the rest of the trial) or placebo plus fluvoxamine for eight weeks. All patients received fluvoxamine 100 mg $day^{-1}$ for the first four weeks of the trial followed by 200 mg $day^{-1}$ for the rest of the study. At the end of the trial 89% of patients in the memantine group compared with 32% in the placebo group had achieved remission. The authors considered that the positive outcome might be partially due to the effect of fluvoxamine, however, the overall outcome rate of this study was still higher than fluvoxamine monotherapy (Ghaleiha et al. 2013). Another study conducted with 11 patients, had treatment groups of either memantine (5–10 mg $day^{-1}$) or placebo combined with either selective serotonin reuptake inhibitors or clomipramine for 12 weeks. One week before starting the study and throughout the study, patients were treated with a standard SSRI or clomipramine at therapeutic dosages for at least 12 consecutive weeks. There was a positive effect in the memantine group seen after 8–12 weeks. The authors concluded that a minimum of 12 weeks of treatment may be necessary for marked improvement.

#### Side Effects

Most common adverse reactions reported in the human literature (≥5% and greater than placebo) are dizziness, headache, confusion, and constipation although usually at high doses of 40–60 mg $day^{-1}$ (Lipton 2006). It should be used with caution in patients with severe renal impairment.

#### Other Information

When circulatory function parameters and respiratory function parameters were compared to baseline in five female beagle

dogs at 3, 10 and 30 mg kg$^{-1}$ of oral memantine, a dose-related decrease in cardiac minute output at 10 mg kg$^{-1}$ (7.5% of the dogs) and 30 mg kg$^{-1}$ (20% of the dogs) and a decrease in stroke volume at 10 mg kg$^{-1}$ (14% of the dogs) and 30 mg kg$^{-1}$ (32% of the dogs) were observed compared to controls, 10 minutes after dosing.

Systolic left ventricular blood pressure decreased at 30 mg kg$^{-1}$ compared to control at 15 minutes (9% of the dogs) and 30 minutes (18% of the dogs) after administration (Center for Drug Evaluation and Research 2003).

### Effects Documented in Nonhuman Animals

#### *Dogs*

Maurer and Dodman (2007) published a case report on a miniature Dachshund with daily repetitive circling behavior (spinning) that also had a history of grand mal seizures. After no improvement had occurred when the dog was treated with a monotherapy of fluoxetine for three weeks or clomipramine for four weeks previously, in addition to behavior modification and environmental management, using a liquid preparation of memantine (2 mg ml$^{-1}$) at 0.4 mg kg$^{-1}$, every 12 hours by mouth was started as a monotherapy. On the second day of treatment the client reported about 25% improvement in the circling behavior (decreased frequency and intensity) as well as becoming more playful. After three days, the dosage of memantine was increased to 0.5 mg kg$^{-1}$ every 12 hours. After that, the client reported about 50% of clinical improvement. After five days at a dosage of 0.5 mg kg$^{-1}$ (PO, every 12 hours) with stable improvement, the dosage was increased to 0.8 mg kg$^{-1}$ (PO every 12 hours) for one day and then to 1 mg kg$^{-1}$ (PO every 12 hours) in an attempt to gain further improvement. However, the dog relapsed at this higher dosage rate to the point that the repetitive behavior returned to its pretreatment level. The dosage was reduced to 0.6 mg kg$^{-1}$ in the morning and 0.8 mg kg$^{-1}$ at night. With this reduced dose, the improvement level was not much as 50% that was the peak improvement for the dog so far. At this point, fluoxetine 1 mg kg$^{-1}$ q24h was added and the memantine dose was reduced to 0.4 mg kg$^{-1}$, every 12 hours. After two weeks of this combination therapy, the improvement level was 50–75% (higher than when fluoxetine was used as monotherapy for five weeks previously). Due to the cost of memantine, dextromethorphan 2 mg kg$^{-1}$ every 12 hours was added (fluoxetine's dose was still at 1 mg kg$^{-1}$) but no positive change was observed in the first two weeks of this combination. The dose of dextromethorphan was increased to 2 mg kg$^{-1}$ every eight hours and the owner reported 50–75% improvement, i.e. similar than what was observed with memantine and fluoxetine combination. After one week, the dose of dextromethorphan was increased to 3 mg kg$^{-1}$ every eight hours but the owner reported little change. Fluoxetine was increased to 2 mg kg$^{-1}$ q24h at that time. As the result the highest improvement level (85%) was reported and it continued or got better for four months of the treatment period. No adverse effects were reported during the treatment period of this dog.

According to the case-series by Schneider et al. (2009b), 11 dogs that had compulsive disorders in different clinical manifestations such as light or shadow chasing, spinning/circling or tail-chasing for longer than six weeks were enrolled for a 4-week study of either memantine monotherapy (7 out of 11 dogs) or augmentation therapy of the ongoing fluoxetine treatment (4 out of 11 dogs). All dogs were prescribed behavior modification, adapted appropriately to each case. Memantine was administered orally twice a day at a starting dose of 0.3–0.5 mg kg$^{-1}$. The dose was increased over time if necessary, and side effects permitting, to a dose not higher than 1 mg kg$^{-1}$. Seven out of 11 dogs showed a reduction in the severity of their compulsive disorder symptoms, assessed by the clients. Within two weeks of the memantine treatment, reduction of the clinical signs was reported but considerable improvement was seen by the third week in

most dogs. Possible adverse effects were observed in one dog (increased frequency of urination), which subsided when the owner withdrew the dog from the study. Based on the results of this investigation, the authors concluded that memantine may be an effective, well-tolerated option for the treatment of compulsive disorders in dogs either as a sole treatment or as an augmentation to fluoxetine.

## IV. Huperzine A

**Chemical Compound:** Chinese folk medicine *Huperzia serrata* (Qian Ceng Ta)

**DEA Classification:** Not a controlled substance

**Preparations:** Nutraceutical product is available in the USA by tablet, capsule and transdermal patch.

### Clinical Pharmacology

Huperzine A (Hup A) is derived from *Huperzia serrata* (Qian Ceng Ta). It is a licensed drug to treat Alzheimer's disease (AD) in China and was classified as a dietary supplement by the FDA in 1997 for memory impairment. Huperzine A is a reversible, potent, and selective acetylcholinesterase (AChE) inhibitor and a noncompetitive NMDA receptor antagonist (Tang and Han 1999; Zhang et al. 2002). Several pharmacological properties have been reported such as anti-inflammatory, antinociceptive (see overdose section below), and anticonvulsant properties (Ferreira et al. 2016) as well as the ability to reverse or attenuate cognitive deficits in rodents (Tang and Han 1999; Wang and Tang 2005). Additionally, some clinical trials have also demonstrated that Huperzine A significantly relieves memory deficits in aged subjects, patients with benign senescent forgetfulness, AD, and vascular dementia (Wang and Tang 2005).

A pharmacokinetic study in six Chinese volunteers after a single oral dose of 0.99 mg, which is the double the therapeutic dose in humans, showed its peak serum concentration (Cmax of 8.4 $\mu g l^{-1}$) was reached at 79.6 minutes (Tmax) post-dosing. The estimated value for the elimination half-life was 288.5 minutes, allowing a b.i.d. or t.i.d. dosing in humans (Qian et al. 1995; Ferreira et al. 2016). Li et al. (2007) used a single oral therapeutic dose (0.4 mg) to study the pharmacokinetic in humans and reported the peak plasma concentration (Cmax of $2.59 \pm 0.37$ ng $ml^{-1}$) was reached at $58.33 \pm 3.89$ minutes (Tmax) while the mean elimination half-life was longer than the previous result ($716.25 \pm 130.18$ minutes) despite its lower dose administration.

In the pharmacokinetic study using beagle dogs, the peak serum concentration (Cmax $9.8 \pm 1.0$ ng $ml^{-1}$) by giving a 500 µg tablet was reached in three hours (Tmax) and the half-life was $5.9 \pm 1.3$ hours (Ye et al. 2005). In toxicological studies, histopathological changes were found in the liver, the kidney, the heart, the lung, and the brain in rats (1.5 mg $kg^{-1}$ oral administration) and dogs (0.6 mg $kg^{-1}$ IM injection) (Tang and Han 1999). According to a study, in rats, no tolerance phenomena occur after multiple dosing treatments (Little et al. 2008).

### Use in Humans

In the US, Huperzine A is available in a twice-daily tablet or in capsule forms (200–400 µg $day^{-1}$) for memory impairment (Perry and Howes 2011).

### Overdose and Side Effects

Huperzine A is well tolerated in humans, rodents, and dogs. Its adverse effects are less pronounced than other AChE inhibitors (Tang and Han 1999). Side effects observed in published studies are mild and only observed at high doses, with no adverse signs seen at doses lower than 0.3–0.5 mg $kg^{-1}$ in rats, 0.1 mg $kg^{-1}$ in monkeys, and 0.5 mg $kg^{-1}$ in humans (Filliat et al. 2002).

In rodent studies, an antinociceptive effect was also reported, though it is noted that its effective dose is much higher than the median toxic dose ($TD_{50}$) (Ferreira et al. 2016).

### Effects Documented in Nonhuman Animals

#### *Dogs*

Schneider et al. (2009a) published a case report on the use of Huperzine A to treat

putative complex partial seizures in a 34-month-old Bernese Mountain dog. The dog presented with clinical signs of "star gazing," "fly snapping," licking, vacuous chewing, and ongoing anxiety. The authors used a starting dose of Huperzine A 50 μg (approximately 1 $\mu g\,kg^{-1}$) twice a day. The client noticed a reduction of the clinical signs within one week from the initiation of treatment. Within four weeks of the treatment, the owner noticed mild regression of the episodes and the dose was increased from twice a day to three times a day, which kept the clinical signs decreased or absent for another five months (six months from the initiation of the treatment). The patient relapsed when presenting a joint condition. At this point, Huperzine A was discontinued and switched to phenobarbital. No side effects were reported during the treatment of Huperzine A in this case.

The authors of this case report discussed the potential use of Huperzine A for patients presenting benign focal seizures due to its antiseizure and NMDA receptor antagonist effects, and the fact that Huperzine A has so far caused less side effects compared to conventional medications in dogs.

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# 13

# Monoamine Oxidase Inhibitors

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## Action

Monoamine oxidase (MAO) is an enzyme of the outer mitochondrial membrane that occurs in a variety of tissues, including the heart, the liver, kidneys, the spleen, platelets, the peripheral nervous system, and the central nervous system (CNS) (Obata et al. 1987). In the CNS, MAO, primarily MAO-B, catabolizes the oxidative deamination of catecholamines, including dopamine, norepinephrine, epinephrine, β-phenylethylamine (2-phenylethylamine), and serotonin. In the intestinal tract and liver, MAO, primarily MAO-A, is also important in catabolizing exogenous amines, for example, tyramine, derived from various foods and drugs. The name is not entirely accurate since MAO enzymes can also deaminate long-chain diamines (Gerlach et al. 1993).

MAO inhibitors prevent the action of MAO-A, MAO-B, or both. Drugs in this category, while classified according to their action of inhibiting MAO, also have a variety of other actions, many of which enhance the activity of catecholamines. For example, l-deprenyl, in addition to inhibiting MAO activity, inhibits presynaptic catecholamine receptors, inhibits the uptake of catecholamines, induces the release of catecholamines from their intraneuronal stores, and stimulates action potential-transmitter release coupling (Knoll et al. 1996). Thus, they should not be considered solely as drugs that just have a simple and specific activity.

They are also likely to exhibit substantially different actions on different species because there are species differences in the ratios of MAO-A to MAO-B, both overall and in given organ systems. For example, in humans and monkeys, dopamine in the brain is a substrate of both MAO-A and MAO-B (Glover et al. 1977; O'Carroll et al. 1983). As a consequence, basal levels of brain dopamine increase with chronic administration of l-deprenyl in these species (Riederer and Youdim 1986; Boulton et al. 1992). MAO-B has little effect on dopamine metabolism in the rat brain, however. Thus, dopamine levels in the brain of the rat are less affected by l-deprenyl treatment than those of humans (Kato et al. 1986; Paterson et al. 1991). The guinea pig appears to be a better model of dopamine metabolism by MAO in humans than either mice or rats (Ross 1987). Human platelet MAO is primarily or entirely of the B form, while dog platelet MAO is of both the A and B forms (Collins and Sandler 1971; Donnelly and Murphy 1977; Obata et al. 1987). As a consequence of these species variations in the metabolism, initiation of use of a MAO inhibitor in a new species should be done cautiously.

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## Overview of Indications

MAO-B inhibitors, specifically selegiline, have been shown to increase the life span when given to healthy mice, rats, hamsters, and dogs (Knoll 1988; Knoll et al. 1989; Milgram et al. 1990; Kitani et al. 1992; Ivy et al. 1994; Ruehl et al. 1997b). (–)Deprenyl was found to enhance anti-oxidant enzyme activities not only in the brain's dopaminergic regions but also in extra-brain tissues such as the heart, the kidneys, the adrenal glands, and the spleen (Kiray et al. 2007, 2008, 2009). Several studies have also observed mobilization of many humoral factors and enhancement of natural killer (NK) cell functions with (–)deprenyl administration (Kitani et al. 2002). Selegiline also increases the survival of human patients with Parkinson's disease (Birkmayer et al. 1985). Selegiline likewise causes a decreased accumulation of lipofuscin in various parts of the brain of aging rats (Amenta et al. 1994a, 1994b, 1994c; Zeng et al. 1994; Tseilikman et al. 2009). It also appears to facilitate activation of astrocytes that are associated with increased secretion of trophic factors, resulting in increased neuronal survival and growth (Biagini et al. 1994). It blocks the pathological changes induced by the neurotoxin 1-methyl,4,phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Battistin et al. 1987). Selegiline's protective central nervous system and anti-aging effects also seem to be due to its action potentiating the activity of the free radical scavenging enzymes, and possibly to a counteraction of free radicals and a membrane-stabilizing action (Takahata et al. 2006; Subramanian and James 2010a, 2010b).

Medications that significantly inhibit MAO-A exist but are not used in the treatment of behavioral and mental problems in animals. Only the MAO-B inhibitor selegiline will be discussed in detail. Therefore, all discussion of contraindications, side effects, adverse drug interactions, and treatment of overdose is presented in coverage of that drug.

## Specific Medications

### I. Selegiline Hydrochloride

**Chemical Compound:** (R)-(–)-*N*,2-dimethyl-*N*-2-propynylphenethylamine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 2-, 5-, 10-, 15-, and 30-mg tablets and as 5-mg capsules. FDA approved for use in dogs with canine cognitive dysfunction.

#### Clinical Pharmacology

Selegiline is an irreversible inhibitor of MAO. It has a substantially greater affinity for MAO-B than for MAO-A and therefore functions as a selective MAO-B inhibitor when given at clinically appropriate doses (Knoll and Magyar 1972; Yang and Neff 1974; Glover et al. 1977; Pfizer Animal Health and Product Information 2000). It was the first drug to be developed that was specific in its inhibition of MAO-B (Knoll 1983). Inhibition of MAO happens in two stages: an initial reversible reaction followed by a second irreversible reaction (Heinonen et al. 1994). However, selectivity is not absolute, and rare patients may exhibit signs of MAO-A inhibition. In average adult humans, the selectivity of selegiline's MAO inhibition seems to disappear at a dose of about 30–40 mg total dose per day (Somerset Pharmaceuticals Inc. 2003).

Following administration of 1 mg $kg^{-1}$ of selegiline PO, absorption in dogs is rapid, with peak plasma concentration occurring after 20–30 minutes. Measurable concentrations are detectable in the plasma up to three hours later. The absorption half-life is about 41 minutes whereas the elimination half-life is about 78 minutes (Mahmood et al. 1994).

Selegiline also inhibits the reuptake of dopamine, norepinephrine, and serotonin into presynaptic nerves, inhibits dopamine autoreceptors, increases the turnover of dopamine, reduces oxidative stress caused by the degradation of dopamine, increases free

radical elimination by enhancing superoxide dismutase and catalase activity, potentiates neural responses to dopamine by the indirect mechanism of elevating phenylethylamine, a neuromodulator of dopaminergic responses, and enhances scavenger function in the CNS. At clinically appropriate doses, it does not have the "cheese effect," that is, it does not potentiate the hypertensive effects of tyramine, which is characteristic of MAO-A and mixed MAO inhibitors (Lai et al. 1980; Knoll 1983; Fagervall and Ross 1986; Knoll 1987; Heinonen and Lammintausta 1991; Berry et al. 1994; Fang and Yu 1994; Hsu et al. 1996; Pfizer Animal Health and Product Information 2000). Nevertheless, it is probably best to avoid regular use of cheese as a treat for dogs on selegiline, since a rare dog may, as happens in humans, exhibit a cheese response despite selegiline generally being very MAO-B specific.

Selegiline has three principal metabolites: l-(–)amphetamine, l-(–)methamphetamine, and *N*-desmethylselegiline (Reynolds et al. 1978a, 1978b; Philips 1981; Yoshida et al. 1986; Dirikolu et al. 2003), and some of its pharmacological actions appear to be the result of the sympathomimetic properties caused by its metabolites (Fozard et al. 1985). See Chapter 15, CNS Stimulants, for further discussion of amphetamine. Phenylethylamine, a modulator of catecholamine neurotransmission in the CNS, is a substrate of MAO-B, and levels of this molecule also increase following treatment with selegiline (Philips and Boulton 1979; Philips 1981; Paterson et al. 1990; Durden and Davis 1993). A study by Schrickz and Fink-Gremmels (2014) found that selegiline did not inhibit the function of the drug transporter P-gp in the dog.

#### Uses in Humans

Selegiline is used to treat Parkinson's disease, in which it potentiates the effects of L-dopa, and Alzheimer's disease (see, e.g. Tariot et al. 1987; Parkinson Study Group 1989, 1993; Tariot et al. 1993; Olanow et al. 1995; Sano et al. 1997; Heikkila et al. 1981). Selegiline is also used to treat major depressive disorder and anxiety disorders such as social phobia and panic disorder (Stahl 2011, 2013).

#### Contraindications

Selegiline is contraindicated in patients with a known history of sensitivity to this drug. Severe CNS toxicity, potentially resulting in death, can ensue from combining selegiline with various other drugs, particularly tricyclic antidepressants (TCAs), for example, amitriptyline, clomipramine, and selective serotonin reuptake inhibitors (SSRIs), for example, fluoxetine and paroxetine. The phenomenon is called serotonin syndrome (see Chapter 19 for further discussion). The detailed mechanism of this serious drug interaction is poorly understood. Therefore, these drugs should never be combined. Because of medication half-life, no TCA or SSRI should be given for at least two weeks following discontinuation of selegiline. Due to fluoxetine's long half-life, selegiline should not be given for at least five weeks following discontinuation of that drug. Even after a five-week washout period, MAO inhibitors should be initiated with caution and the patient closely monitored, because metabolites of fluoxetine may remain in the system for longer periods of time and still induce serotonin syndrome (Coplan and Gorman 1993; Pfizer Animal Health and Product Information 2000; Somerset Pharmaceuticals 2003).

Selegiline should not be given with potential MAO inhibitors including amitraz, a topical ectoparasiticide (Pfizer Animal Health and Product Information 2000).

Possible drug interactions have been observed in dogs concurrently on metronidazole, prednisone, and trimethoprim sulfa.

Combining selegiline with meperidine, a synthetic narcotic analgesic, is also contraindicated in humans due to the occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature in some patients receiving this combination. While it is not known if this will occur in veterinary patients, it is recommended that this combination also be avoided in

nonhuman animals as well (Somerset Pharmaceuticals 2003).

Also, in humans, concurrent use of MAO inhibitors in conjunction with α-2 agonists sometimes results in extreme fluctuations of blood pressure (Somerset Pharmaceuticals 2003). Blood pressure monitoring is therefore recommended in veterinary patients concurrently given selegiline and any α-2 agonist. A study that investigated the influence of selegiline (10 mg daily$^{-1}$, orally for one week) on vascular alpha-1- and alpha-2 adrenoceptor responsiveness in conscious unrestrained dogs showed that treatment induced vascular alpha-1 and alpha-2 adrenoceptor-hyposensitivity (probably associated with the increase in sympathetic tone) (Pelat et al. 2001).

#### Side Effects

In one clinical trial of dogs treated with selegiline, 4% of the study population experienced events sufficiently adverse to result in a reduction of dose or withdrawal from medication. Side effects experienced by these dogs included restlessness, agitation, vomiting, disorientation, diarrhea, and diminished hearing. Also, during clinical trials conducted on dogs as a part of safety and efficacy testing, three dogs showed an increase in aggression (Pfizer Animal Health and Product Information 2000).

Studies to date have not identified any mutagenic or chromosomal damage potential.

No evidence of teratogenic effects was identified in rats given 4, 12, or 36 mg kg$^{-1}$ selegiline daily during pregnancy or in rabbits given 5, 25, or 50 mg kg$^{-1}$ during pregnancy. However, in the two higher doses given to rats, fetuses exhibited a decreased body weight. At the highest dose given to rabbits, there was an increase in resorption and percentage of postimplantation losses, with a concurrent decrease in the number of live fetuses. In another study in which pregnant rats were given 4, 16, or 64 mg kg$^{-1}$ daily, there was an increase in the number of stillbirths and a concurrent decrease in pup body weight, the number of pups per dam, and pup survival. At the highest dose (64 mg kg$^{-1}$) no pups survived to postpartum day 4 (Somerset Pharmaceuticals Inc. 2003).

#### Overdose

In early overdose, induction of emesis or gastric lavage may be helpful, otherwise provide supportive treatment. Convulsions and other signs of CNS overstimulation should be treated with diazepam. Avoid use of phenothiazine derivatives and all CNS stimulants. Treat hypotension and vascular collapse with IV fluids.

#### Discontinuation

Because selegiline is used to treat an irreversible degeneration of the CNS, it should not be discontinued in patients that respond to it. It is worth noting that in veterinary medicine, it is recommended that treatment is initiated as early as possible for better results in controlling clinical signs of cognitive decline (Overall 2013) even though long-term studies are lacking (Studzinski et al. 2005).

#### Other Information

The term cognitive dysfunction syndrome (CDS), as used in veterinary clinical behavioral medicine, refers to geriatric onset changes in behavior that cannot be attributed to medical conditions such as neoplasia or organ failure in dogs and cats. In dogs, a number of categories of behavior may be altered. First, dogs with CDS often exhibit various behaviors that suggest disorientation, for example, they may wander around the house in an aimless fashion, appear not to be able to find something, such as their bed, or get stuck behind open doors. Second, there is often altered social interaction. Usually, this is noted as a decrease in social interaction with human family members, other pets in the household, or both. Third, there is a loss of prior learned behaviors, including housetraining and basic obedience cues, such as "sit." Fourth, sleep habits change. Total sleep increases, but nighttime wakefulness may

develop. Finally, overall activity, particularly purposeful activity, decreases. Clinical signs are progressive (Bain et al. 2001; Neilson et al. 2001) and early treatment is warranted. A detailed discussion on CDS is beyond the scope of this book but age-related behavioral changes have a high prevalence among geriatric dogs and cats and should not be overlooked (Azkona et al. 2009). Consult Araujo et al. (2005), Landsberg (2005), Head et al. (2008), Landsberg et al. (2012), and Cory (2013) for comprehensive reviews.

Histologic lesions identified postmortem in the brains of dogs with CDS closely resemble lesions in the brains of humans with Alzheimer's disease (Cummings et al. 1996b). Specifically, dogs that exhibited geriatric behavior problems before death have been identified as having meningeal fibrosis, lipofuscinosis, generalized gliosis, and ubiquitin-containing granules in the white matter upon postmortem histological examination (Ferrer et al. 1993). There are also age-related cerebral vascular changes and gliosis, dilation of the ventricles, and thickening of the meninges (Uchida et al. 1992; Shimada et al. 1992). β-Amyloid plaques develop in the brains of old dogs that are similar to those found in the brains of humans with Alzheimer's disease (Cummings et al. 1993). Deficits in discrimination learning, reversal learning, and spatial learning are strongly associated with degree of deposition of β-amyloid in the dog brain (Cummings et al. 1996a).

Dogs with CDS have hypothalamic–pituitary–adrenal axis dysregulation that occurs without typical signs of Cushing's syndrome or other medical conditions expected to activate the hypothalamic–pituitary–adrenal axis (Ruehl et al. 1997a).

Geriatric cognitive decline also occurs in the cat, although it is not as well studied as in the dog. A study by Zhang et al. (2006) found that the thickness of the molecular layer and total cerebellar cortex of older cats was significantly decreased when compared to young adults. The granular layer was increased and the density of neurons in each layer was significantly lower as well. Astrocytes were significantly denser with hypertrophy of cell bodies, and Purkinje cells showed fewer neurofilament immunoreactive dendrites. The authors concluded that these findings might underlie the functional decline of afferent efficacy and information integration in the aging cerebellum. Other reported pathological changes in the aging cat brain are neuronal loss with cerebral atrophy, widening of sulci, and increases in ventricular size. Similar to dogs, perivascular changes such as microhemorrhage or infarcts in periventricular vessels, increase in oxidative damage, and diminished cholinergic function have also been reported. Dogs and cats show Aβ brain deposition and pre-tangle pathology with increasing age, but cats demonstrate more diffuse Aβ plaques than humans with Alzheimer's disease and dogs with CDS (Head et al. 2005; Gunn-Moore et al. 2006; reviewed by Landsberg et al. 2012). Among the most frequent behavioral changes in feline CDS are spatial or temporal disorientation, altered social interactions, changes in sleep–wake cycles, house-soiling with inappropriate urination or defecation, changes in activity, and increased vocalizations (Gunn-Moore et al. 2007).

The mechanisms by which selegiline reverses CDS are not fully understood. It increases dopamine activity by several mechanisms, inhibition of MAO-B (a dopamine metabolizer), increasing the impulse-mediated release of catecholamines, decreasing presynaptic dopamine reuptake, increasing concentrations of phenylethylamine, which potentiates dopamine action, and increasing synthesis of aromatic L-amino acid decarboxylase, which results in increasing dopamine synthesis (e.g. Heinonen and Lammintausta 1991; Knoll et al. 1996; Jurio et al. 1994). Selegiline also decreases free radical production and increases the activity of superoxide dismutase, which scavenges free radicals (Carillo et al. 1994). These actions are beneficial to the aging brain since free radicals contribute to the pathogenesis of neurodegenerative disorders (Gerlach et al. 1993).

**Table 13.1** Doses of selegiline for dogs and cats.

| | Dose |
|---|---|
| Cat | 0.5–1.0 mg kg$^{-1}$ |
| Dog | 0.5–1.0 mg kg$^{-1}$ |

Better results with selegiline treatment are generally reported when the medication is started early in the progression of the disease and clinical signs are still mild (Overall 2013). Nonetheless, only a subset of dogs seems to benefit from selegiline use, with minimal clinical improvement and no research has established long-term benefits in dogs or cats (Studzinski et al. 2005).

Doses for treating cats and dogs with selegiline are given in Table 13.1.

### Effects Documented in Nonhuman Animals

#### *Cats*

Although selegiline is not approved for use in cats, signs of Alzheimer's disease-like pathology have been reported in them (Cummings et al. 1996b) and signs of CDS are common in aging cats (Gunn-Moore et al. 2007; Landsberg et al. 2012). Cats have been treated with up to 10 times the therapeutic dose with no toxicity (Ruehl et al. 1996), and geriatric cats treated with selegiline for signs of cognitive decline have shown improvement (Landsberg 1999).

#### *Dogs*

In dogs, selegiline hydrochloride is used to treat CDS at a dose of 0.5–1.0 mg kg$^{-1}$ given once daily in the morning, and pituitary-dependent hyperadrenocorticism is treated at a dose of 1.0–2.0 mg kg$^{-1}$ daily. It has also been shown to have anticataleptic activity in research dogs, though this effect is due to activity of the stimulant metabolites rather than by MAO-B inhibition (Milgram et al. 1993; Nishino et al. 1996; Nishino and Mignot 1997). Activity is specific to certain brain regions. In dogs, three weeks of medication with 0.1, 0.5, or 1.0 mg kg$^{-1}$ day$^{-1}$ PO caused significant, dose-dependent increases in superoxide dismutase activity in the striatum but not in the hippocampus (Carillo et al. 1994).

Dogs given 1 mg kg$^{-1}$ of selegiline daily PO for one year do not show any sign of hepatic damage or dysfunction. There was no significant difference in bile acid concentrations between treated and placebo groups (Ruehl et al. 1993).

A detailed discussion of its use in the treatment of pituitary-dependent hyperadrenocorticism is beyond the scope of this book. Further discussion can be found in Bruyette et al. (1995), Bruyette et al. (1997a, 1997b), Peterson (1999), and Reusch et al. (1999).

Ruehl and Hart (1998) suggested that selegiline prolongs life in otherwise healthy elderly dogs (>10 years) when given at a dose of 1 mg kg$^{-1}$ daily. Further studies are necessary to confirm if these results apply to the general dog population.

In clinical trials of the treatment of CDS with selegiline at recommended doses, dogs show improvement in sleeping patterns, house-training, and activity level after four weeks of treatment (Ruehl et al. 1994), with treated dogs showing significant improvement over dogs receiving placebo (Head et al. 1996). Individual response varies substantially and some dogs continue to show additional improvement for up to three months. Geriatric, but not young, dogs given L-deprenyl exhibit improved spatial short-term memory over dogs given placebo. The best effect occurred at 0.5–1.0 mg kg$^{-1}$, with smaller or larger doses being less effective (Head et al. 1996).

Selegiline causes a dose-dependent inhibition of MAO-B activity in the striatum, the hippocampus, the liver, and the kidney of dogs. When selegiline is given at doses of 0.5–1.0 mg kg$^{-1}$ over a two-week period, it has no detectable effect on MAO-A activity in the same tissues (Milgram et al. 1995). This contrasts with the rat, in which a single dose of selegiline does not cause MAO-A inhibition, but repeated doses do cause MAO-A inhibition (Waldmeier et al. 1981; Zsilla et al. 1986; Terleckyi et al. 1990; Murphy et al. 1993).

Likewise, there are no significant changes in levels of dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, 3-methoxy-turamine, 5-hydroxytryptamine, or 5-hydroxyindoleactic acid in the striatum or cortex (Milgram et al. 1995). At least in the rat, sex, as well as dose and route of administration, affect the activity of selegiline on MAO-A and MAO-B. Females respond to selegiline at a lower dose than do males, and subcutaneous injection is more efficient than oral dosing (Murphy et al. 1993).

Healthy adult dogs given 0, 0.1, 0.5, or 1 mg kg$^{-1}$ of selegiline for two weeks exhibit no changes in locomotor activity, inactivity, sniffing, or urination as assessed in an open field test. At this dose range, the development of repetitive behavior has not been observed (Milgram et al. 1995). However, a single dose of 3 mg kg$^{-1}$ produces repetitive locomotion in females, decreased frequency of urination in males, and decreased exploratory sniffing in both genders (Head and Milgram 1992).

In safety studies, beagle dogs have been given selegiline at doses of 0, 1, 2, 3, and 6 mg kg$^{-1}$ daily, that is, up to three times the maximum recommended daily doses. Dogs on the 3 and 6 mg kg$^{-1}$ dose exhibited increased salivation, decreased pupillary response, and decreased body weight. The latter occurred despite normal to increased feed consumption. Additionally, at the 6 mg kg$^{-1}$ dose, the dogs exhibited increased panting, dehydration, and increased stereotypic behaviors, that is, weaving. Interestingly, this latter problem was observed several hours after dosing but was no longer present 24 hours later. There were no changes in blood pressure, ophthalmic assessment, heart rate, or electrocardiogram parameters. The drug was assessed as being safe in the dogs given 2 mg kg$^{-1}$ daily or less.

In a study with 641 dogs with CDS clinical signs treated with selegiline (0.5–1.0 mg kg$^{-1}$ orally once daily) for 60 days, 77.2% of dogs showed clinical improvement but side effects such as diarrhea (4.2%), anorexia (3.6%), vomiting and salivation (3.4%) were reported. Anxiety, restlessness, or hyperactivity (2.2%), dermatological disorders (2.2%), disorientation (2.0%), hindlimb paresis and ataxia (2.0%), lethargy (1.9%), orthopedic disorders (1.7%), polydipsia (1.7%), and seizures (1.6%) were also mentioned but the majority of these reports were not considered to be drug-related. Treatment was discontinued due to side effects in 5% of dogs and due to lack of response to treatment in 2% of dogs. Dogs with disorientation, decreased social interactions, and loss of house-training had a better response to therapy than dogs with changes in activity and/or sleep-wake cycle on day 30. Most dogs continued to show improvement by day 60, with the greatest improvement seen in dogs with disorientation and decreased social interactions (77.8%) and less (68.6%) in dogs with loss of house-training and changes in activity and/or sleep-wake cycle (Campbell et al. 2001).

Plasma levels of the L form of amphetamine in dogs given selegiline are detectable within two hours of medication and exhibit a significant dose-dependent effect (Salonen 1990; Milgram et al. 1995). Levels continue to increase for the seven days of daily dosing until the end of the first week of medication, after which there is no further increase. Plasma levels of amphetamine after two weeks of administration of selegiline at 1.0 mg kg$^{-1}$ daily are about 30 ng ml$^{-1}$. This level of amphetamine is unlikely to have significant behavioral effects (Milgram et al. 1995). Within 24 hours of discontinuation of selegiline, plasma amphetamine levels are substantially decreased and are undetectable five days after discontinuation of selegiline.

When dogs are given 3 mg kg$^{-1}$ of selegiline, amphetamine and methamphetamine are detectable in the serum for 48 hours, while desmethylselegiline is detectable for only about 80 minutes. When dogs are given 10 mg kg$^{-1}$, desmethylselegiline is detectable in the serum for up to four hours (Salonen 1990).

Plasma levels of phenylethylamine likewise increase in dogs given selegiline, though it is only by the second week of treatment that

plasma levels are significantly greater than dogs given placebo. Plasma phenylethylamine levels decrease within 24 hours of administration. Levels of phenylethylamine in the hypothalamus and striatum, but not the cortex, are significantly elevated in dogs given 0.1 mg kg$^{-1}$ for two weeks, with levels in the striatum increasing almost 400% and levels in the hypothalamus increasing about 1000% (Milgram et al. 1995).

Selegiline may have beneficial effects on learning in young, healthy dogs. Specifically, in a study conducted on various breeds aged one to seven years, dogs given 0.5 mg kg$^{-1}$ daily for three weeks prior to training and testing exhibited greater success when trained with motivationally significant cues and were more likely to walk near novel objects and were less distracted than a placebo group (Mills and Ledger 2001). Selegiline has been shown to improve spatial short-term memory in aged dogs in a dose-dependent fashion (Ivy et al. 1994).

Selegiline has also been used to treat anxiety and emotional disorders in dogs (Notari 2006; Beata et al. 2007; Pageat et al. 2007; Landsberg et al. 2013). In a study of 141 dogs of various breeds, ages, and sexes, with a variety of behavior problems considered to be based on dysfunctional emotional status, 80% of the cases were considered improved or cured after treatment with 0.5 mg kg$^{-1}$ of selegiline daily for periods of time ranging from 36 days to over a year. Behavior modification specific to the case was also used. Improvement at 30 days after initiation of treatment was a good predictor of the final outcome of treatment. Vomiting or diarrhea was occasionally observed in dogs in this study (Pobel and Caudrillier 1997).

In a 56-day trial of 38 dogs diagnosed with anxiety disorders, treatment with either selegiline (at 0.5 mg kg$^{-1}$ orally every 24 hours) or alphacasozepine (a tryptic bovine as1-casein hydrolysate) at 15 mg kg$^{-1}$ orally every 24 hours was sufficient to decrease the EDED score (emotional disorder evaluation in dogs) in all subjects. This study did not include a placebo group. The only adverse effect noted in the selegiline group was one case of cystitis, which was not considered to be associated with treatment (Beata et al. 2007).

In a study on a rat model for impulsive behavior, treatment with selegiline had no effect in impulse control and decreased motor activity (Bert et al. 2006).

In a study on experimental model of anxiety in mice, De Angelis and Furlan (2000) investigated the anxiolytic-like properties of selegiline and moclobemide (another selective MAOI). The investigators used a standard and an enhanced light/dark aversion test. Selegiline failed to significantly alter the anxiogenic-like behaviors in the subjects. Additionally, research investigating the potential protective effects of selegiline on the central nervous system neurons of individuals exposed to social isolation has at times found beneficial effect in rats, but results are still inconsistent and cannot be applied to dogs without further studies (Pascual and Zamora-Leon 2007; Pascual et al. 2013).

Pageat (1996) reported an 85% success rate when treating cocker spaniels with "rage syndrome" with selegiline.

Selegiline, at a dose of 2 mg kg$^{-1}$ PO, suppresses cataplexy in dogs (Nishino et al. 1996).

#### *Horses*

Selegiline is considered to have high abuse potential in racehorses and is classified as a class 2 agent by the Association of Racing Commissioners International (ARCI). Traces of selegiline, amphetamine, and methamphetamine can be recovered in thoroughbred horse urine when a single oral dose of 40 mg is given. Relatively higher urinary concentrations of *N*-desmethylselegiline (2-methyl-*N*-2-propynylphenethylamine) are found in the horse. *N*-desmethylselegiline concentration peaks in horse urine at 480 ng ml$^{-1}$ at two hours. Amphetamine peaks in the urine at 38 ng ml$^{-1}$ 24 hours after oral dosing, while methamphetamine peaks in the urine at 6.1 ng ml$^{-1}$ after four hours. Horses given

30 mg kg$^{-1}$ of selegiline orally or intravenously while confined to box stalls (3.4 × 3.4 m) do not exhibit any significant changes in heart rate or motor activity (Dirikolu et al. 2003).

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# 14

# Antipsychotics

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## Introduction

Antipsychotics are used to treat most forms of psychosis, including schizophrenia, in humans. They do not have the same significance in animal behavior therapy and are usually most appropriately used on a short-term, intermittent basis. The first antipsychotic, chlorpromazine, was developed in 1950. Individual antipsychotic drugs show a wide range of physiological effects, resulting in tremendous variation in side effects. The most consistent pharmacological effect is an affinity for dopamine receptors. In humans, antipsychotics produce a state of relative indifference to stressful situations. In animals, antipsychotics reduce responsiveness to a variety of stimuli, exploratory behavior, and feeding behavior. Conditioned avoidance responses are lost in animals that are given antipsychotics.

Antipsychotic agents are divided into two groups based on side effect profiles (low-potency and high-potency drugs) or by structural classes (Table 14.1). Low-potency antipsychotics have a lower affinity at D2 receptor sites, higher incidence of anticholinergic effects (sedation), stronger α-adrenergic blockade (cardiovascular side effects), and require larger doses (1–3 mg $kg^{-1}$), but have a lower incidence of extrapyramidal side effects. High-potency antipsychotics show a greater affinity for D2 receptor sites, have fewer autonomic effects, less cardiac toxicity, a higher incidence of extrapyramidal signs, and are effective in smaller doses (0.5–1 mg $kg^{-1}$) (Simpson and Simpson 1996). The phenothiazine neuroleptics are antipsychotics that are commonly used in veterinary medicine for sedation and restraint.

## Action

Antipsychotic agents block the action of dopamine, a catecholamine neurotransmitter that is synthesized from dietary tyrosine. Dopamine regulates motor activities and appetitive behaviors. Dopamine depletion is associated with behavioral quieting, depression, and extrapyramidal signs. Excess dopamine is associated with psychotic symptoms and the development of stereotypies. A large proportion of the brain's dopamine is located in the corpus striatum and mediates the part of the extrapyramidal system concerned with coordinated motor activities. Dopaminergic neurons project to the basal ganglia and extrapyramidal neuronal system. Side effects associated with blockade of this system are called extrapyramidal responses. Dopamine is also high in

*Veterinary Psychopharmacology*, Second Edition. Sharon L. Crowell-Davis, Thomas F. Murray, and Leticia Mattos de Souza Dantas.

**Table 14.1** Classes of antipsychotic drugs.

| |
|---|
| *Phenothiazine tranquilizers* |
| *High potency* |
| Fluphenazine (Prolixin) |
| *Low potency* |
| Acepromazine (Promace) |
| Chlorpromazine (Thorazine) |
| Promazine (Sparine) |
| Thioridizine (Melleril) |
| *Butyrophenones* |
| Haloperidol (Haldol) |
| Droperidol (Innovar) |
| Azaperone (Stresnil, Suicalm) |
| *Diphenylbutylpiperidines* |
| Pimozide (Orap) |
| *Dibenzoxazepines* |
| Clozapine (Clozaril) |
| *Atypical antipsychotics* |
| Sulpiride (Sulpital) |

some regions of the limbic system (Marder and Van Putten 1995).

The nigrostriatal pathway consists of cell bodies originating in the substantia nigra and mediates motor activities. The mesolimbic pathway consists of neuronal cell bodies that originate in the ventral tegmental area, project to ventral striatum and limbic structures, and mediate appetitive behaviors. Dopamine is broken down by monoamine oxidase inside the presynaptic neuron or by catechol-*O*-methyltransferase outside the presynaptic neuron. There are five dopamine receptor subtypes. Traditional antipsychotics are D2 receptor antagonists and block 70–90% of D2 receptors at therapeutic doses.

Antipsychotics have a wide spectrum of physiological actions. Traditional antipsychotics have antihistaminic activity, dopamine receptor antagonism, α-adrenergic blockade, and muscarinic cholinergic blockade. Blocking the dopamine receptors in the basal ganglia and limbic system produces behavioral quieting, as well as depression of the reticular-activating system and brain regions that control thermoregulation, basal metabolic rate, emesis, vasomotor tone, and hormonal balance. Antipsychotics produce ataraxia: a state of decreased emotional arousal and relative indifference to stressful situations. They suppress spontaneous movements without affecting spinal and pain reflexes.

## Overview of Indications

Antipsychotic agents are most often used in veterinary practice when chemical restraint is necessary. Antipsychotic agents are used for restraint or the temporary decrease of motor activity in cases of intense fear or stereotypic behavior. A complete behavioral and medical history is necessary to determine which pharmacological agents will be the most beneficial for any given case. A comprehensive treatment plan that includes behavior modification exercises and environmental modifications, along with drug therapy, has the best chance for success (Overall 1997).

Antipsychotic agents have poor anxiolytic properties and should not be the sole treatment for any anxiety-related disorder. Therefore, while they can be useful in preventing self-injury or damage to the environment by an animal exhibiting a high-intensity fear response, they are not appropriate for long-term therapy and treatment of phobias.

Antipsychotic agents are indicated for the treatment of intense fear responses requiring heavy sedation to prevent self-injury or property damage. Sedation to the point of ataxia may be necessary to control frantic responses in storm-phobic dogs, but owners often report that their dogs still appear to be frightened.

Antipsychotic agents have also been used in game capture operations and to allow physical examination in intractable animals. Antipsychotics can also be used as antiemetics and for the treatment and prevention of motion sickness. When used as

preanesthetic agents, antipsychotics may induce a state of indifference to a stressful situation.

Antipsychotic agents produce inconsistent results for the treatment of aggressive behavior, and in some cases have induced aggressive behavior in animals with no history of aggressiveness (Overall 1997).

## General Pharmacokinetics

Antipsychotic agents have a high hepatic extraction ratio. Metabolites are generally inactive compounds and excreted in the urine. Maximal effect occurs about one hour after administration. Duration of action ranges from 4 to 24 hours. Half-lives range from 10 to 30 hours in humans. These agents are highly lipid soluble and highly protein bound.

## Contraindications, Side Effects, and Adverse Events

Significant side effects can occur with acute antipsychotic use because of decreased dopaminergic activity in the substantia nigra. Side effects may include motor deficits or Parkinsonian-like symptoms, such as difficulty initiating movements (akinesis), muscle spasms (dystonia), motor restlessness (akathisia), and increased muscle tone resulting in tremors or stiffness.

Behavior effects include indifference (ataraxia), decreased emotional reactivity, and decreased conditioned avoidance responses. Antipsychotic agents may also cause a suppression of spontaneous movements, a decrease in apomorphine-induced stereotypies, a decrease in social and exploratory behaviors, a decrease in operant responding, and a decrease in responses to non-nociceptive stimuli.

Tardive dyskinesia occurs as a result of the upregulation of dopamine receptors with chronic antipsychotic use. An increase in postsynaptic receptor density due to dopamine blockade can result in the inability to control movements or torticollis, and hyperkinesis. The dopaminergic system is unique in that intermittent use of antipsychotic medications can result in the upregulation of postsynaptic receptors. Chronic side effects may occur after three months of treatment. At least 10–20% of human patients treated with antipsychotics for more than one year develop tardive dyskinesia, and the symptoms are potentially irreversible even after the medication is discontinued.

Bradycardia and transient hypotension due to α-adrenergic blocking effects can occur. Syncope has been reported, particularly in brachycephalic breeds. Hypertension is possible with chronic use.

Endocrine effects include an increase in serum prolactin, the luteinizing hormone, follicle-stimulating hormone suppression, gynecomastia, gallactorhea, infertility, and weight gain. Parasympatholytic autonomic reactions are possible. Other side effects include lowered seizure threshold, hematological disorders (thrombocytopenia), hyperglycemia, and electrocardiographic changes. Priapism has been reported in stallions.

Antipsychotic agents should be used with caution, if at all, in patients with seizure disorders, hepatic dysfunction, renal impairment, or cardiac disease, and in young or debilitated animals, geriatric patients, pregnant females, giant breeds, greyhounds, and boxers.

## Overdose

Neuroleptic malignant syndrome is a rare, but potentially fatal, complex of symptoms associated with antipsychotic use. It results in muscular rigidity, autonomic instability, hyperthermia, tachycardia, cardiac dysrhythmias, altered consciousness, coma, increased liver enzymes, creatine phosphokinase, and leukocytosis. Mortality reaches 20–30% in

affected humans. Treatment includes discontinuation of the antipsychotic medication, symptomatic treatment, and medical monitoring.

## Clinical Guidelines

Antipsychotic agents will typically have an immediate effect on behavior and so do not require chronic dosing, but can be used as needed for their behavioral quieting effects. When used intermittently, antipsychotic agents do not need to be gradually withdrawn. An owner consent form is helpful to outline potential adverse events and ensure that the owner is aware of these.

## Specific Medications

### I. Acepromazine Maleate

**Chemical Compound:** 2-Acetyl-10-(3-dimethylaminopropyl) phenothiazine hydrogen maleate

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available in 5-, 10-, 25-mg tablets and 10 mg $ml^{-1}$ injectable forms.

#### Clinical Pharmacology

Acepromazine is a low-potency phenothiazine neuroleptic agent that blocks postsynaptic dopamine receptors and increases the turnover rate of dopamine. Acepromazine has a depressant effect on the central nervous system (CNS) resulting in sedation, muscle relaxation, and a reduction in spontaneous activity. In addition, there are anticholinergic, antihistaminic, and α-adrenergic blocking effects.

Acepromazine, like other phenothiazine derivatives, is metabolized in the liver.

Both conjugated and unconjugated metabolites are excreted in the urine. Metabolites can be found in the urine of horses up to 96 hours after dosing. Horses should not be ridden within 36 hours of treatment.

#### Indications

Acepromazine is indicated as a preanesthetic agent, for control of intractable animals, as an antiemetic agent to control vomiting due to motion sickness in dogs and cats, and as a tranquilizer in horses.

#### Contraindications

Acepromazine can produce prolonged depression when given in excessive amounts or when given to animals that are sensitive to the drug. The effects of acepromazine may be additive when used in combination with other tranquilizers and will potentiate general anesthesia. Tranquilizers should be administered in smaller doses during general anesthesia and to animals that are debilitated, animals with cardiac disease, or animals with sympathetic blockage, hypovolemia, or shock. Phenothiazines should be used with caution during epidural anesthetic procedures because they may potentiate the hypotensive effects of local anesthetics. Phenothiazines should not be used prior to myelography.

Acepromazine should not be used in patients with a history of seizures and should be used with caution in young or debilitated animals, geriatric patients, pregnant females, giant breeds, greyhounds, and boxers. Studies in rodents have demonstrated the potential for embryotoxicity. Phenothiazines should not be used in patients with bone marrow depression.

#### Side Effects

Phenothiazines depress the reticular activating system and brain regions that control vasomotor tone, basal metabolic rate, and hormonal balance. They also affect extrapyramidal motor pathways and can produce muscle tremors and akathisia (restlessness, pacing, and agitation).

Cardiovascular side effects include hypotension, bradycardia, cardiovascular collapse, and reflex tachycardia. Hypertension is possible with chronic use. Syncope, collapse,

apnea, and unconsciousness have been reported. Other side effects include hypothermia, ataxia, hyperglycemia, excessive sedation, and aggression. Paradoxical excitability has been reported in horses, cats, and dogs.

Hematological disorders have been reported in human patients taking phenothiazines, including agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, thrombocytopenia, and pancytopenia.

There is anecdotal evidence that chronic use may result in the exacerbation of noise-related phobias. Startle reactions to noise can increase with acepromazine use. Acepromazine is contraindicated in aggressive dogs, because it has been reported to facilitate acute aggressiveness in rare cases.

Priapism, or penile prolapse, may occur in male large animals. Acepromazine should be used with caution in stallions, as permanent paralysis of the retractor muscle is possible.

In a safety study, no adverse reactions to acepromazine occurred when it was administered to dogs at three times the upper limit of the recommended daily dosage ($1.5\,mg\,lb^{-1}$). This dose caused mild depression that resolved within 24 hours after termination of dosing. The $LD_{50}$ (the dose that kills half of the animals [mice] tested) is $61\,mg\,kg^{-1}$ for intravenous administration and $257\,mg\,kg^{-1}$ for oral administration.

#### Adverse Drug Interactions

Additive depressant effects can occur if acepromazine is used in combination with anesthetics, barbiturates, and narcotic agents. Concurrent use of propranolol can increase blood levels of both drugs. Concurrent use of thiazide diuretics may potentiate hypotension.

#### Overdose

Gradually increasing doses of up to $220\,mg\,kg^{-1}$ PO were not fatal in dogs, but resulted in pulmonary edema. Hypotension can occur after rapid intravenous injection causing cardiovascular collapse. Epinephrine is contraindicated for the treatment of acute hypotension produced by phenothiazine tranquilizers because further depression of blood pressure can occur.

Overdosage of phenothiazine antipsychotics in human patients is characterized by severe CNS depression, coma, hypotension, extrapyramidal symptoms, agitation, convulsions, fever, dry mouth, ileus, and cardiac arrhythmias. Treatment is supportive and symptomatic, and it may include gastric lavage, airway support, and cardiovascular support.

#### Doses in Nonhuman Animals

Dosages should be individualized depending upon the degree of tranquilization required. Generally, as the weight of the animals increases, the dosage requirement in terms of milligram of medication per kilogram weight of the animal decreases. Doses that are 10 times lower than the manufacturer's recommended dose may be effective.

Arousal is most likely in the first 30 minutes after dosing. Maximal effects are generally reached in 15–60 minutes, and the duration of effect is approximately 3–7 hours. There may be large individual variation in response (Table 14.2 and Table 14.3).

#### Effects Documented in Nonhuman Animals

Several incidences of idiosyncratic aggression in dogs and cats treated with acepromazine have been reported (Meyer 1997; Waechter 1982). In an incident report received by the United States Pharmacopeia Veterinary Practitioners' Reporting Program, a German shepherd dog being treated with acepromazine following orthopedic surgery attacked and killed the other dog in the household, with no prior history of aggression. There were two incidences of aggression following acepromazine administration identified by the FDA Adverse Drug Experience Summary between 1987 and 1994. There are reports of aggressive behavior following oral and parenteral administration of acepromazine. While this is a rare side effect, the potential for serious injury should prompt practitioners

Table 14.2 Doses for antipsychotics for dogs and cats.

| Drug | Dogs | Cats |
|---|---|---|
| Acepromazine | 0.5–2.0 mg kg$^{-1}$ PO q8h or prn | 1.0–2.0 mg kg$^{-1}$ PO prn |
| Chlorpromazine | 0.8–3.3 mg kg$^{-1}$ PO q6h | 3.0–6.0 mg kg$^{-1}$ PO |
| Promazine | 2.0–6.0 mg kg$^{-1}$ IM or IV q4–6h prn | 2.0–4.5 mg kg$^{-1}$ IM |
| Thioridizine | 1.0–3.0 mg kg$^{-1}$ PO q12–24h | |
| Haloperidol | 0.05–2.0 mg kg$^{-1}$ PO q12h | 0.1–1.0 mg kg$^{-1}$ PO |
| Pimozide | 0.03–0.3 mg kg$^{-1}$ PO | |
| Clozapine | 1.0–70 mg kg$^{-1}$ PO | |
| Sulpiride | 5.0–10.0 mg kg$^{-1}$ PO | |

prn, according to need.

Table 14.3 Doses of antipsychotics for horses.

| Drug | Dose |
|---|---|
| Acepromazine | 0.02–0.1 mg kg$^{-1}$ IM |
| Promazine | 0.4–1.0 mg kg$^{-1}$ IV or 1.0–2.0 mg kg$^{-1}$ PO q4–6h |
| Haloperidol decanoate | 0.004 mg kg$^{-1}$ IM |

to educate owners about this possibility and suggest appropriate precautions

In horses, acepromazine can be detected in the urine for at least 25 hours after injection of 0.1 mg kg$^{-1}$ (Smith and Chapman 1987).

## II. Azaperone

**Chemical Compound:** 4′-Fluoro-4-[4-(2-pyridyl)-1-piperazinyl] butyrophenone

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as a 40 mg ml$^{-1}$ injectable form.

### Clinical Pharmacology

Azaperone is a butyrophenone antipsychotic agent that blocks dopamine receptors. The peak sedative effect occurs approximately 30 minutes after intramuscular injection, and the effects last two to four hours. Azaperone is metabolized by the liver, with 13% excreted in feces.

### Indications

Azaperone is labeled for control of aggression when mixing or regrouping weaning or feeder pigs and as a general tranquilizer for swine. It is not approved for use in other species and should not be used in horses.

### Doses in Nonhuman Animals

Azaperone is administered at a dose of 1.0 mg kg$^{-1}$ IM for sedation, 2.2 mg kg$^{-1}$ IM for mixing feeder pigs, 2.0–4.0 mg kg$^{-1}$ IM as a preanesthetic, and 5.0–10.0 mg kg$^{-1}$ for immobilization.

## III. Chlorpromazine

**Chemical Compound:** 10-(3-Dimethylaminopropyl)-2-chlorphenothiazine

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10-, 25-, 50-, 100-, 200-, and 300-mg tablets; 30-, 75-, 150-, 200-, and 300-mg capsules; 2, 30, and 100 mg ml$^{-1}$ oral orange-flavored syrup; 25- and 100-mg suppositories; and a 25 mg ml$^{-1}$ injectable dose.

### Clinical Pharmacology

Chlorpromazine is a phenothiazine antipsychotic agent with properties similar to acepromazine. It has anticholinergic, antiadrenergic, antihistaminic, and antiserotonin activity. It is less potent than acepromazine and has a longer duration of action. It is

highly protein bound and metabolized extensively in the liver, with more than 100 potential metabolites, some that are active.

#### Uses in Humans

Chlorpromazine is indicated in humans for the treatment of psychotic disorders, nausea and vomiting, mania, intractable hiccups, and as an adjunct in the treatment of tetanus.

#### Indications in Veterinary Medicine

Chlorpromazine is used primarily as an antiemetic, but also as a preanesthetic agent in dogs and cats. It is not recommended for use in horses.

#### Contraindications

Contraindications and precautions are similar to acepromazine. Horses given chlorpromazine may develop ataxia and excitability with potentially violent consequences. In human patients being administered lithium in combination with chlorpromazine, an encephalopathic syndrome has been reported, which resulted in irreversible brain damage in a few cases.

#### Side Effects

Side effects are similar to acepromazine. Chlorpromazine may cause significant extrapyramidal side effects in cats if given in high doses, including tremors, rigidity, lethargy, and loss of sphincter tone. Electrocardiographic changes include prolongation of Q-T and P-R intervals, S-T depression, and T wave blunting. There is evidence that chlorpromazine is excreted in breast milk of nursing mothers.

#### Effects Documented in Nonhuman Animals

The effects of chlorpromazine, compared with diazepam, were evaluated in dogs in a placebo-controlled trial (Hart 1985). Friendliness, excitability, and fearfulness were measured in response to human handling. Chlorpromazine significantly reduced excitability, but did not affect fear responses or friendliness.

## IV. Clozapine

**Chemical Compound:** 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4] diazepine

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 25- and 100-mg tablets.

#### Clinical Pharmacology

Clozapine is an atypical antipsychotic agent, a tricyclic dibenzodiazepine derivative. Clozapine blocks dopaminergic activity at D1, D2, D3, and D5 receptors and has high affinity for D4 receptor subtypes. It is more active at limbic system sites than at nigrostriatal receptors, resulting in fewer extrapyramidal symptoms. In addition to dopaminergic receptors, clozapine has blocking activity at serotonergic receptors. It is an adrenergic, cholinergic, and histaminergic antagonist. Traditional neuroleptic agents block 70–90% of D2 receptors at therapeutic doses. Clozapine blocks 30–60% of D2 receptors and 85–90% of 5-HT2 receptors (Tarsy et al. 2002).

Clozapine is highly protein bound and almost completely metabolized by the liver prior to excretion. The major metabolites have been measured in dogs following a single dose administration of clozapine (Mosier et al. 2003).

#### Uses in Humans

Clozapine is indicated for the treatment of severe psychotic disorders in human patients who have failed to respond to traditional therapy.

#### Contraindications

Clozapine is contraindicated in patients with myeloproliferative disease or seizure disorder.

#### Side Effects

Clozapine can cause life-threatening bone marrow suppression or agranulocytosis. In human patients, 32% of agranulocytosis

cases were fatal. White blood cell counts must be monitored during treatment. Cardiac side effects are also possible. Anticholinergic effects may include increased intraocular pressure, urinary retention, constipation, and ileus.

#### Doses in Nonhuman Animals

Reliable dose–response data have not been established for veterinary patients (Table 14.2).

#### Effects Documented in Nonhuman Animals

According to Dodman (1998), preliminary results of treatment of aggressive dogs with clozapine were disappointing. Antiaggressive properties of clozapine have been reported in other species (Chen et al. 2001; Garmendia et al. 1992).

In a review of animal models of acute neuroleptic-induced akathisia, Sachdev and Brune (2000) compared the effects of haloperidol and clozapine in dogs. Haloperidol ($0.3\,mg\,kg^{-1}$) induced more hyperkinesia and stereotypic movements than clozapine ($7\,mg\,kg^{-1}$), measured four hours after administration. Persistent scratching, licking, rotating, self-grooming, and continuous walking were considered evidence of extrapyramidal symptoms.

The effects of orally administered neuroleptic agents on conditioned avoidance tasks in dogs were evaluated for chlorpromazine, thioridazine, haloperidol, and clozapine (Cohen 1981). All drugs blocked conditioned avoidance responses, inhibited escape behavior, and caused ataxia. Clozepine produced excessive salivation. Sedation was most common with chlorpromazine and thioridazine, and haloperidol and thioridazaine produced tremors.

## V. Fluphenazine

**Chemical Compound:** 10-[3-[4-(2-Hydroxyethyl)-piperazin-1-yl] propyl]-2-(trifluoromethyl)-phenothiazine; 4-[3–2-(trifluoromethyl) phenothiazin-2-yl] propyl-1-piperazine ethanol

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 1-, 2.5-, 5-, and 10-mg tablets; 2.5, 5, and $25\,mg\,ml^{-1}$ solution; a 2.5 mg/5 ml elixir; a $2.5\,mg\,ml^{-1}$ short-acting injectable; and 25 and $100\,mg\,ml^{-1}$ long-acting injectables (fluphenazine decanoate or enanthate).

#### Clinical Pharmacology

Fluphenazine is a high-potency phenothiazine agent, showing a greater affinity for D2 receptor sites, fewer autonomic effects, less cardiac toxicity, but a higher incidence of extrapyramidal signs.

#### Contraindications and Side Effects

Contraindications and side effects are similar to those noted for other phenothiazines.

#### Effects Documented in Nonhuman Animals

Fluphenazine was used as a sedative in an equine patient (thoroughbred filly) at a dose of $0.1\,mg\,kg^{-1}$ IM (Brewer et al. 1990). The onset of extrapyramidal symptoms occurred at 15 hours after injection when the horse began sweating, pawing at the air, circling, head swinging, and licking her forelimbs. Rhythmic neck flexion, facial grimacing, and muscle fasciculations were observed. Periods of hyperexcitability were interspersed with periods of immobility. Serum fluphenazine levels were $20.3\,ng\,ml^{-1}$ at admission and $<1\,ng\,ml^{-1}$ 24 hours after admission. Symptoms persisted 45 hours after the initial intramuscular dose. The horse was treated with 250 mg intravenous diphenhydramine (centrally acting anticholinergic agent), was behaving normally within three minutes, and remained normal for 18 hours. She was re-treated with 300 mg diphenhydramine and then required no further treatment.

Fluphenazine has been used successfully in individual cases to treat flank biting in horses (Dodman 1994).

## VI. Haloperidol

**ChemicalCompound:**4-[4-(p-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 0.5-, 1-, 2-, 5-, 10-, and 20-mg tablets; a 2 mg ml$^{-1}$ solution (haloperidol lactate); 50 and 100 mg ml$^{-1}$ long-acting injectables (haloperidol decanoate); and a 5 mg ml$^{-1}$ short-acting injectable.

### Clinical Pharmacology

Haloperidol is a butyrophenone antipsychotic that has dopamine-blocking activity. There is one major metabolite with low activity. Haloperidol decanoate may require three months in human patients to reach steady state. Substantial plasma concentrations can be detected months after treatment has been discontinued. Because it is administered once per month, patients require significantly less medication per month and potentially lower their risk of developing extrapyramidal side effects.

### Uses in Humans

Haloperidol is indicated for use in the management of psychotic disorders and to control tics associated with Tourette's disorder.

### Contraindications

Neurotoxicity is possible in patients with thyrotoxicosis that are also receiving haloperidol.

### Side Effects

The most common side effects experienced by human patients in clinical trials were extrapyramidal reactions, including involuntary facial, arm, leg, and body movements. Tardive dyskinesia is also possible, as well as cardiovascular side effects, hematological disorders, and endocrine abnormalities. Additional side effects reported in human patients include jaundice, anorexia, constipation, diarrhea, hypersalivation, nausea, vomiting, dry mouth, urinary retention, priapism, laryngospasm, bronchospasm, visual disturbances, and sudden death (Physicians' Desk Reference 2002).

Reported side effects in psittacine birds include sedation, incoordination, vomiting, agitation, severe depression, and anorexia. Haloperidol may lower the seizure threshold.

The $LD_{50}$ (dog) is 90 mg kg$^{-1}$ when given orally, and 18 mg kg$^{-1}$ for intravenous injection. A dose of 12 mg kg$^{-1}$ day$^{-1}$ for 12 months resulted in liver toxicity, tremors, and convulsions in dogs. The therapeutic index for dogs is 900 (50% of the lethal dose/the median effective dose or $LD_{50}/ED_{50}$).

Fatal cases of bronchopneumonia have been reported in human patients, resulting from lethargy, decreased sensation of thirst leading to dehydration, hemoconcentration, and reduced pulmonary ventilation.

### Overdose

Overdose in human patients is characterized by severe extrapyramidal signs, hypotension, sedation, respiratory depression, electrocardiographic changes, and shock. There is no specific antidote, so treatment primarily involves supportive care.

### Doses in Nonhuman Animals

Reliable dose–response data have not been established for veterinary patients (Tables 14.2–14.4).

### Effects Documented in Nonhuman Animals

Dodman (1998) has reported minimal success using haloperidol to treat aggression in dogs. Luescher (1998) also reported lack of

Table 14.4 Doses of antipsychotics for parrots.

| Drug | Dose |
|---|---|
| Haloperidol | 0.2 mg/kg–0.4 mg kg$^{-1}$ q12h; begin at lowest dose and increase in 0.02 increments q2d to effect |
| Haloperidol decanoate | 1–2 mg kg$^{-1}$ IM q14–21d; lower dose for cockatoos, African gray parrots, and Quaker parakeets |

success and undesirable side effects when using haloperidol in dogs to treat stereotypic behaviors.

Yen et al. (1970) evaluated the effects of antipsychotic agents, chlorpromazine and haloperidol, on conflict-induced behaviors in laboratory cats. In this experimental situation, cats were taught to press a pedal for a food reward and then were later punished for opening the reward box with a compressed air blast. Cats displayed a variety of conflict-induced behaviors after four to five weeks, including restlessness, depression, immobility, pupil dilation, altered feeding behavior, and avoidance of the pedal. Chlorpromazine administration resulted in mild improvement of conflict-induced behaviors. Haloperidol administration caused a complete normalization of operant responding, and even increased reward-seeking activity despite the air blasts. Treatment with amphetamine facilitated the development of conflict-induced behaviors, and pretreatment with neuroleptics blocked the effects of amphetamine-induced behaviors.

There are case reports of haloperidol use for the treatment of self-mutilation in psittacine birds (Iglauer and Rasim 1993; Lennox and VanDerHeyden 1993). Lennox and VanDerHeyden reported that haloperidol was more effective for birds that mutilate soft tissue, when compared with birds that limit self-trauma to feathers. They report agitation, depression, decreased appetite, and excitability in patients treated with haloperidol. Response to treatment occurred within two to three days. Iglauer and Rasim (1993) report great variability in response to haloperidol and length of treatment required. They medicated patients by placing haloperidol in the drinking water, so dosing may have been less reliable. Cockatoo species and Quaker parakeets may require lower doses than other species (Cooper and Harrison 1994). One study compared feather-picking behavior in White Eyed parakeets (*Aratinga leucophthalma*) treated with environmental enrichment vs. haloperidol given at a dose of 0.9 mg $kg^{-1}$ and identified that, while both treatments resulted in improvement, the specific environmental enrichments used resulted in greater improvement than the haloperidol. (Telles et al. 2015).

Haloperidol given at a dose of 0.50 mg $kg^{-1}$ to domestic chickens did not cause sedation and resulted in a significant decrease in feather-pecking but not of aggression (Kjaer et al. 2004).

Haloperidol has been used successfully in game capture operations to increase the tractability of wild hoof stock (Hofmeyer 1981). It may be most effective for antelope species. Doses ranging from 0.1 to 0.4 mg $kg^{-1}$ IV facilitated handling for 7 to 12 hours, resulting in a decrease in injuries and mortality during transportation. The presence of extrapyramidal signs was species-specific and was believed to be exacerbated by hyperthermia, noise, and excitability.

## VII. Pimozide

**Chemical Compound:** 1-[1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 1- and 2-mg tablets.

### Clinical Pharmacology

Pimozide is a diphenylbutylpiperidine antipsychotic agent with dopamine-blocking activity. It undergoes extensive first-pass metabolism. Two major metabolites are produced by dealkylation in the liver. Pimozide has a long half-life in humans (55 hours).

### Uses in Humans

Pimozide is indicated for the treatment of Tourette's syndrome in human patients when other standard treatments have failed.

### Contraindications

Pimozide is contraindicated with cardiac disease and in patients taking macrolide antibiotics, antifungal agents, or other drugs

metabolized by cytochrome P450 3A enzyme system.

#### Side Effects

Side effects are similar to those of other antipsychotic agents. Pimozide can cause prolongation of the QT interval, predisposing patients to ventricular arrhythmias. Sudden death has been reported. Electrocardiographic monitoring is recommended. Pimozide produces anticholinergic side effects and may lower the seizure threshold.

According to Luescher (1998), the presence of side effects in dogs given relatively low doses of pimozide limits its usefulness. The $LD_{50}$ in dogs is 40 mg kg$^{-1}$. Oral doses as low as 0.16 mg kg$^{-1}$ can cause catalepsy and sedation. Chronic dosing at 3 mg kg$^{-1}$ resulted in weight loss, muscle tremors, and mammary and gingival dysplasia.

#### Doses in Nonhuman Animals

Reliable dose response data have not been established for veterinary patients (see Table 14.2).

#### Effects Documented in Nonhuman Animals

The effects of pimozide on human avoidance in the Arkansas line of nervous pointer dogs were evaluated in a placebo-controlled crossover design (Angel et al. 1982). The human interaction test was used to assess behaviors. Positive responses included approaching, wagging tail, sniffing hands, jumping up, and nuzzling the human subject. Negative responses included retreating, circling, trembling, urinating, or defecating. Dogs were given 0.3 mg kg$^{-1}$ daily for seven days. Pimozide treatment attenuated avoidance responses. Maximum effect occurred at four days, and the effects persisted nine days past treatment. Pimozide was more effective than a benzodiazepine in attenuating avoidance responses.

Pimozide was not effective in the treatment of a Doberman pinscher with acral lick dermatitis (Dodman 1994). The dog developed head bobbing at a dose of 4 mg day$^{-1}$.

## VIII. Promazine

**Chemical Compound:** 10-[3-(Dimethylamino)propyl]-phenothiazine

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 25-, 50-, and 100-mg tablets, a 2 mg ml$^{-1}$ oral syrup, 2 mg/ml and 5 mg ml$^{-1}$ injectables, and granules approved for use in horses.

#### Clinical Pharmacology

Promazine is a phenothiazine agent with properties similar to acepromazine. It is metabolized by the liver to glucuronide conjugates, which are excreted by the kidneys.

#### Indications

Promazine has been used as a preanesthetic agent, tranquilizer, and antiemetic in dogs and as a tranquilizer in cats, horses, cattle, and swine.

#### Contraindications

There are reports of violent reactions in horses and increased sensitivity to noise.

#### Side Effects

Side effects are similar to acepromazine.

## IX. Sulpiride

**Chemical Compound:** N-[(1-Ethyl-2-pyrrolidinyl)-methyl]-5-sulfamayl-o-anisamide

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 50-mg capsule, 200- and 400-mg tablets, 25 mg/5 ml and 200 mg/5 ml oral solution.

#### Clinical Pharmacology

Sulpiride is a substituted benzamide derivative with selective dopamine D2 antagonist properties. Other benzamide derivatives include metoclopramide, tiapride, and sultopride. In contrast to other neuroleptics, sulpiride appears to lack effects on norepinephrine, acetylcholine, serotonin, and

histamine. Specificity may explain the relatively low incidence of extrapyramidal and other adverse effects observed with sulpiride use. Sulpiride also stimulates secretion of prolactin. Sulpiride has also been shown to improve blood flow and mucus secretion in the gastroduodenal mucosa and has been investigated for the treatment of ulcers.

Sulpiride does not appear to be extensively metabolized by the liver and thus is primarily excreted renally. No metabolites have been identified. The half-life in humans is six to eight hours and is prolonged with renal insufficiency.

#### Uses in Humans

Sulpiride is indicated for the treatment of depression, duodenal ulcer, Huntington's disease, inadequate lactation, neuroses, schizophrenia, and Tourette's syndrome, and to suppress the symptoms associated with tardive dyskinesia in human patients.

#### Contraindications

Sulpiride is contraindicated with pheochromocytoma and Parkinson's disease. Caution is advised in patients with cardiovascular disease, mania, renal insufficiency (dose reductions appropriate for the individual patient and extent of renal insufficiency), patients with epilepsy, hyperthyroidism, pulmonary disease, or urinary retention, and elderly patients.

#### Side Effects

Side effects are similar to those of other neuroleptic agents.

#### Doses in Nonhuman Animals

Reliable dose–response data have not been established for veterinary patients (see Table 14.2).

#### Effects Documented in Nonhuman Animals

The effects of neuroleptic drugs in cats were evaluated following intracerebroventricular injection (Beleslin et al. 1985). Chlorpromazine, haloperidol, and droperidol injection induced profound motor impairment (ataxia). Emotional reactions, including restlessness and aggression, and autonomic changes were inconsistent with chlorpromazine, haloperidol, and droperidol administration. Sulpiride injection did not produce any behavioral, autonomic, or motor activity changes.

Bruhwyler and Chleide (1990) evaluated the behavioral, motor, and physiological effects of neuroleptic agents in dogs. Subjects were trained in an operant task and then given chlorpromazine, haloperidol, thioridazine, pimozide, clozapine, sulpiride, and several other anxiolytic agents in a random order prior to each trial. There was a decrease in operant responding and an increase in incomplete responses with neuroleptic administration. The drugs causing the most neurovegetative effects (palpebral ptosis and urination) were clozapine, thioridazine, pimozide, and sulpiride. Low doses of thioridazine and clozapine caused excitation. Loss of motivation was significant for haloperidol, pimozide, clozapine, and sulpiride. Pimozide cause significant hyperkinesia. Ataxia occurred with all drugs except pimozide and sulpiride. Catalepsy was not produced by haloperidol or clozapine. Sulpiride did not produce akinesia.

### X. Thioridazine

**Chemical Compound:** 10-[2-(1-Methyl-2-piperidinyl)ethyl]-2-(methylthio)-phenothiazine

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10-, 15-, 25-, 50-, 100-, 150-, and 200-mg tablets; 30 and 100 mg $ml^{-1}$ solution; and 5 and 20 mg $ml^{-1}$ suspension.

#### Clinical Pharmacology

Thioridazine has pharmacological activity similar to other phenothiazine agents, but may produce less extrapyramidal symptoms. Thioridazine has minimal antiemetic

properties. Some metabolites may be more active than the parent compound.

#### Uses in Humans

Thioridazine is used to treat psychotic disorders in human patients, and for the short-term treatment of depression, agitation, anxiety, tension, and sleep disturbances.

#### Contraindications

Contraindications are similar to those noted for acepromazine.

#### Side Effects

Side effects are similar to acepromazine. Extrapyramidal responses are generally minimal. Electrocardiography abnormalities (marked T-wave effects), arrhythmias, and sudden death are reported.

#### Doses in Nonhuman Animals

Reliable dose response data have not been established for veterinary patients (see Table 14.2).

#### Effects Documented in Nonhuman Animals

Thioridazine was used in the treatment of a dog with motor disturbances (Jones 1987). A male Pekinese dog that presented with fly biting, barking, restlessness, nocturnal activity, muscular tremor, self-trauma, and unprovoked aggression was treated with 1.1–2.2 mg $kg^{-1}$ of thioridazine. The dog's physical examination was unremarkable, skin scrapings were negative, and fluorescent antibody for distemper was negative. The patient had failed to respond to phenobarbital. The patient responded within two days of starting the higher dose of thioridazine. Symptoms recurred with two missed doses. Side effects observed were mild tachycardia and dry feces, but no extrapyramidal signs.

## Important Information for Owners of Pets Being Placed on an Antipsychotic

The following should be considered when placing an animal on an antispychotic:

1) Antipsychotic agents have minimal anxiolytic properties and are not appropriate as the sole treatment for anxiety or phobias.
2) A wide range of side effects is possible, and some may occur acutely with a single dose.
3) Idiosyncratic aggressive responses may occur with some of the drugs in this class and precautions should be taken to prevent injury to humans and other animals.
4) Chronic treatment with antipsychotic agents has been associated with tardive dyskinesia in human patients, which in some cases is irreversible.
5) The effects of antipsychotics in animals vary greatly in the degree of sedation and the duration of effect.

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# 15

# CNS Stimulants

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## Action

Central nervous system (CNS) stimulants increase synaptic dopamine and norepinephrine.

## Overview of Indications

CNS stimulants are used to treat attention deficit disorder (ADD), also called attention deficit hyperactivity disorder (ADHD), or hyperkinesis in dogs (Corson et al. 1976).

## Contraindications, Side Effects, and Adverse Events

While CNS stimulants may decrease overall activity in animals with true hyperkinesis, the effects that give the medications their names will occur in animals that do not have true hyperkinesis. Therefore, during a testing situation, preparations should be made for this possibility. A variety of other side effects can occur in animals with and without hyperkinesis. These include pain and difficulty with urination due to contraction of the urethral sphincter, gastrointestinal disturbance, decreased appetite, anorexia, dry mouth, convulsions, hyperthermia, increased blood pressure, tachycardia, and cardiac arrhythmias. CNS stimulants are contraindicated in animals with cardiovascular disease or glaucoma.

CNS stimulants should not be given to patients with significant anxiety, because these symptoms may be exacerbated.

## Adverse Drug Interactions

Do not give CNS stimulants with monoamine oxidase inhibitors (MAOIs) or within 14 days of discontinuing MAOIs.

## Overdose

In case of overdose, the main goals are decontamination, control of body temperature, correction of any acid-base and electrolytic disturbances, and symptomatic control of any CNS or cardiovascular symptoms.

Removal of the stomach contents can be initiated with 3% hydrogen peroxide or apomorphine. However, if the patient is showing CNS signs, such as hyperactivity, do not induce emesis. In some cases, it can be beneficial to anesthetize the patient and conduct gastric lavage or nasogastric intubation and aspiration after an endotracheal tube

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has been placed and cuffed. Acepromazine or chlorpromazine may be beneficial in reducing the symptoms of hyperactivity, tremors, and other behavioral changes related to stimulation (Genovese et al. 2010). Diazepam is not recommended in dogs since it has caused cases of increased arousal in dogs with amphetamine toxicosis (Albretsen 2002). Propofol and phenobarbital can be used to control seizures, while propranolol can be used to control tachycardia. Muscle tremors can be controlled with methocarbamol (Genovese et al. 2010). Minimize external stimuli that will exacerbate the existing drug-induced hyperexcitement. Provide supportive therapy, including procedures to cool the body if hyperthermia is occurring.

## Clinical Guidelines

True hyperkinesis, or ADD, appears to be rare in animals, but it has been identified in dogs. In a group of telomian dogs that had hyperkinetic syndrome and were therefore used as research models for the study of ADD in humans, dogs that responded to treatment with amphetamines were identified as being biochemically different from dogs that did not respond. Specifically, they had low levels of norepinephrine, dopamine, and homovanillic acid (HVA) in the brain and low levels of HVA in the cerebrospinal fluid (Bareggi et al. 1979a).

However, if the chief complaint is hyperactivity, care should be taken to ensure that other, more common, possibilities are ruled out before a trial with a CNS stimulant is conducted. Young, healthy animals are normally very active. One possible cause of a complaint of hyperactivity is that the owner is simply not exercising their pet enough. Owners may have unrealistic expectations of how quiet and calm their pet will be or be keeping the pet in an unsuitable environment. For example, an elderly, sedentary couple living in a small apartment may get a Great Dane, supposedly for protection, and then find that they have a "hyperactive," out-of-control pet on their hands because they are unable to meet the dog's need for basic exercise.

Sometimes owners unintentionally reinforce intensely active behaviors, especially in dogs and parrots. These and other pets may learn that they do not get attention when they are quiet, but they do get attention when they are noisy and rambunctious, specifically engaging in such behaviors as barking, screaming, spinning, running, or jumping. If the pet is primarily motivated by the need for social contact, even reprimands and screaming at the pet may simply make the problem worse.

Owners of pet dogs may focus more on issues of training and consider the dog to be inattentive because it is not learning well in obedience school. In this case, again, environmental factors rather than a true pathology in the pet are likely to be the cause of the problem. Inappropriate training techniques include issues of failure to use appropriate reinforcers, use of inappropriate or excessive punishment, and inappropriate timing on the part of the trainer and/or owner can all result in failure of obedience training. In particular, the use of inappropriate and excessive punishment is quite common in dog training in the United States. This can lead to problems of chronic anxiety that interfere with the dog's ability to learn because of emotional arousal.

If a dog persists in hyperactive and/or inattentive behavior despite adequate exercise, reinforcement of quiet, calm behavior, ignoring of rambunctious behaviors, and appropriate obedience training techniques, it may have true hyperkinesis and respond to medication with CNS stimulants. Specifically look for: (i) a short attention span, (ii) constant movement, and (iii) failure to learn obedience, even with strong rewards. The truly hyperkinetic dog is likely to be unable to learn to sit on command, not because it does not want a delicious treat held over its head, but because it is unable to maintain the sitting position even for the brief moment required to reinforce a sit. Behavioral signs must have

been present for an extended period of time and the patient must have been unresponsive to appropriate attempts to facilitate calmer behavior. Not all humans with ADD respond to medication, and this is likely to be the case with dogs.

If a dog with an appropriate history becomes calmer and more attentive when given a CNS stimulant, the diagnosis of hyperkinesis is confirmed. It is important when working with families that have a hyperkinetic dog to discuss the fact that identifying a useful medication is just the beginning. Historically, the dog is likely to have not learned any basic obedience due to its inability to be attentive. Additionally, its previous hyperactivity may have led to the development of various bad habits that the owners have given up on. Once responsiveness to medication has been identified, it is important that appropriate training techniques, using positive reinforcement, be initiated immediately to teach the dog what is acceptable and desirable behavior. Table 15.1 gives the doses of CNS stimulants used for ADD in dogs.

## Specific Medications

### I. Amphetamine

**Chemical Compound:** (+)-α-methylphenethylamine; (–)-β-methylphenethylamine and d,l-amphetamine aspartate monohydrate; dextro-isomer of the d,l-amphetamine sulfate

Table 15.1 Doses of CNS stimulants for dogs with true hyperkinesis or canine ADD.

| CNS stimulant | Dose |
|---|---|
| Dextroamphetamine | 0.1–1.3 mg kg$^{-1}$ |
| Levoamphetamine | 1–4 mg kg$^{-1}$ |
| Methylphenidate | 2–4 mg kg$^{-1}$ |

*Source:* Dodman and Shuster (1994), Overall (1994).
*Note:* Medication should only be given as needed, but can be repeated several times a day

**DEA Classification:** d-Amphetamine is a DEA class II, non-narcotic medication. While there are recognized medical uses, it has a high potential for abuse. d-Amphetamine is more potent than l-amphetamine (e.g. Taylor and Snyder 1970; Angrist and Gershon 1971; Wallach et al. 1971; Balster and Schuster 1973)

**Preparations:** Generally available in 5-, 7.5-, 10-, 12.5-, 15-, 20-, and 30-mg tablets; Adderall XR available in 5-, 10-, 15-, 20-, and 30-mg extended-release capsules; Dexedrine is available in 5-mg tablets and in 5-, 10-, and 15-mg sustained-release capsules; Spansule available as sustained-release capsules. Extended- and sustained-release capsules are designed for the human digestive system and may not function in an equivalent fashion in dogs and other veterinary patients.

#### Clinical Pharmacology

Amphetamines are believed to block reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of norepinephrine and dopamine into the extraneuronal space. They are noncatecholamine, sympathomimetic amines that stimulate the CNS. Peripherally, they stimulate both systolic and diastolic blood pressure, stimulate respiration, and dilate the bronchi (Shire US, Inc. 2003).

Gastrointestinal acidifying agents will lower the absorption of any amphetamine, while urinary acidifying agents increase excretion. Thus, either type of medication will decrease the efficacy of amphetamine. In contrast, gastrointestinal alkalinizing agents increase the absorption of amphetamine, while urinary alkalinizing agents decrease the excretion of amphetamines. Either of these types of medications will therefore increase blood levels of amphetamines (GlaxoSmithKline 2003).

In the dog, plasma levels of amphetamine peak at about 1.5 hours after oral administration, while cerebral spinal fluid (CSF) levels peak at about 2.5 hours (Bareggi et al. 1978). However, differences between

breeds have been identified. Telomian-beagle hybrids form less of the active metabolite of amphetamine, *p*-hydroxyamphetamine, than do purebred beagles and exhibit less stereotypic behavior and hyperthermia when given the same dose of amphetamine (Bareggi et al. 1979b).

#### Uses in Humans

Amphetamines are used to treat ADD and narcolepsy.

#### Contraindications

Do not use amphetamines in patients that have known hypersensitivity to sympathomimetic amines, cardiovascular disease, hyperthyroidism, or glaucoma. Do not give amphetamines with an MAOI or within 14 days of discontinuing medication with an MAOI. Amphetamines can increase the activity of tricyclic antidepressants and any sympathomimetic agents. Avoid using these medications together.

MAOIs and a metabolite of furazolidone decrease the rate of metabolism of amphetamines, thus increasing their effects and side effects. The CNS stimulant effects of amphetamines are blocked by a variety of drugs, including chlorpromazine, haloperidol, and lithium (GlaxoSmithKline 2003).

#### Side Effects

Patients that do not have hyperkinesis will exhibit increased arousal and activity. Stereotypic behavior may also occur, as well as cardiac effects, including tachycardia, gastrointestinal disturbances, dry mouth, urticaria, and decreased libido. In dogs, D-amphetamine is 1.4 times more potent than levoamphetamine in inducing stereotypic behavior. Doses of 1–2 mg kg$^{-1}$ given as a single intravenous injection induce various stereotyped behavior, including bobbing, head turning, circling, pacing, and sniffing (Wallach et al. 1971).

Amphetamines have been shown to have embryotoxic and teratogenic effects in mice, but not in rabbits. Human infants born to women addicted to amphetamines have increased risk of low birth weight and premature birth. They may also exhibit signs of withdrawal, including both agitation and lassitude. Amphetamines are excreted in milk (GlaxoSmithKline 2003).

#### Overdose

In case of overdose, conduct gastric lavage and give activated charcoal, cathartics, and sedatives. Acidifying the urine increases renal excretion, but increases the probability of acute renal myoglobinuria occurring. Chlorpromazine blocks the stimulant effects of amphetamines and can be used in the treatment of overdose. In rats, the $LD_{50}$ (the dose that kills half of the animals tested) is 96.8 mg kg$^{-1}$ (GlaxoSmithKline 2003).

#### Discontinuation

Chronic use can result in both tolerance and dependence. If a patient has been on amphetamines for an extended period, gradual withdrawal is recommended.

#### Other Information

Do not give amphetamines in the evening, because they may cause nighttime restlessness.

Amphetamines may cause increases in plasma corticosteroid levels and interfere with measurements of urinary steroids (GlaxoSmithKline 2003).

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Healthy, fasted laboratory beagles given 2.5 mg kg$^{-1}$ or 0.6 mg kg$^{-1}$ amphetamine orally exhibited increased amounts of stereotypic behavior that peaked 2.5 hours after administration, as did CSF levels of amphetamine. Stereotypic behaviors were elevated between 2.5 and 6.5 hours after administration and then began to decrease. The relationship between stereotypic behavior and levels of amphetamine was exponential, suggesting that the amphetamine metabolite *p*-hydroxyamphetamine contributes to stereotypic behavior when this drug is given. Increasing body temperature, on the other hand, has a

linear relationship with the amount of amphetamine in the plasma, peaking at about 1.5 hours after administration, suggesting that this phenomenon is related to the presence of amphetamine in the plasma (Bareggi et al. 1978).

In a telomian-beagle hybrid used as a model for research on ADD in children, dogs exhibited hyperactivity, impulsiveness, and impaired learning ability. When these dogs are given D-amphetamine, 1.2–2.0 mg kg$^{-1}$ by mouth (PO), some dogs show significant improvement. Dogs that improved had higher peak blood levels of amphetamine than those that did not improve, and improvements paralleled blood levels of amphetamine (Bareggi et al. 1979b).

Five of six pet dogs of various breeds diagnosed with canine hyperkinesis responded positively to treatment with D-amphetamine at doses ranging from 0.21 mg kg$^{-1}$ twice a day (b.i.d.) to 0.83 mg kg$^{-1}$ b.i.d., although the duration of response varied. For some patients, the improvement was only transient, while for others the positive response was both substantial and permanent (Luescher 1993).

Brown et al. (1987), during evaluation of a bull terrier with severe compulsive tail-chasing, gave it a test dose of 1.0 mg kg$^{-1}$ of D-amphetamine orally. By subjective assessment, clinical signs worsened between two and four hours after administration of the D-amphetamine.

D-amphetamine has been successfully used to treat narcolepsy in a long-haired dachshund. However, treatment was discontinued because the dog also exhibited undesirable side effects, including hyperactivity, anorexia, excessive sniffing of the ground, and substantially increased activity of climbing into inaccessible spaces (Van Heerden and Eckersley 1989).

#### *Cats*

Cats given 13 mg kg$^{-1}$ amphetamine IP exhibited stereotyped head movements starting 20 minutes to two hours after injection. Stereotypic behavior subsequently lasted more than four hours. Two of eight cats (25%) vomited and died about two hours after amphetamine administration. One cat, that was otherwise friendly, hissed and spat during the head movements (Randrup and Munkvad 1967).

To date, a behavior problem analogous to human ADD has not been reported in cats, nor has the author had any feline cases in this category.

#### Other Species

Stereotypic behaviors have been observed in rats given 5 mg kg$^{-1}$ subcutaneously (SC), mice given 7.5–10 mg kg$^{-1}$ SC, guinea pigs given 5–20 mg kg$^{-1}$ SC, and squirrel monkeys given 1.7 mg kg$^{-1}$ intramuscularly (Randrup and Munkvad 1967).

## II. Atomoxetine HCl

**Chemical Compound:** R(–) isomer of (–)-N-methyl-3-phenyl-3-(o-tolyloxy)-propylamine hydrochloride

**DEA Classification:** Not a controlled substance. Atomoxetine does not cause dependence or have stimulant or euphoriant properties. While it is not a CNS stimulant, it is included in this section because it is used to treat the same behavioral problem for which stimulants are used

**Preparations:** Generally available in capsules containing 10-, 18-, 25-, 40-, or 60-mg of atomoxetine.

#### Clinical Pharmacology

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter. In humans, atomoxetine is rapidly absorbed after oral administration and can be given with or without food. It is metabolized by the P450 enzyme CYP2D6 with subsequent glucuronidation, but does not inhibit the CYP2D6 pathway. In humans, it has a mean half-life of 21.6 hours. When doses were standardized to a milligram per kilogram basis, atomoxetine had similar pharmacokinetics in children, adolescents, and adults. There are also no gender effects.

Maximum plasma concentrations occur in one to two hours.

The major oxidative metabolite of atomoxetine is 4-hydroxyatomoxetine, which is primarily formed by CYP2D6, but also by other cytochrome P450 enzymes. 4-hydroxyatomoxetine inhibits transport of norepinephrine as much as the parent compound. CYP2C19 and some other cytochrome P450 enzymes form *N*-Desmethylatomoxetine, which has less pharmacological activity than atomoxetine.

Atomoxetine is excreted primarily in the urine as 4-hydroxyatomoxetine-*O*-glucuronide. Less than 17% is excreted in the feces. There is extensive biotransformation, so that <3% of atomoxetine is excreted in an unchanged form (Eli Lilly 2003).

#### Uses in Humans

Atomoxetine is used to treat ADHD.

#### Contraindications

Atomoxetine should not be given to patients with a history of hypersensitivity to the drug. It should not be given concurrently with an MAOI or within 14 days of discontinuing an MAOI. There is an increased risk of mydriasis; therefore, atomoxetine should not be given to patients that have narrow-angle glaucoma. It should be used with caution in patients with cardiovascular disease, because it can cause increased blood pressure and heart rate, and with patients with a history of urinary retention, because it can cause urinary retention.

Paroxetine and fluoxetine can significantly inhibit the CYP2D6 liver enzyme pathway, thus decreasing the rate of metabolism of atomoxetine. Giving these drugs in combination should be avoided or carried out at lower doses.

Atomoxetine doses need to be decreased in patients with hepatic insufficiency, but not in patients with renal disease (Eli Lilly 2003).

#### Side Effects

Atomoxetine can cause increased blood pressure and heart rate. Occasionally, its use results in orthostatic hypotension or urinary retention. Some patients may have impaired sexual function.

Rats given up to 47 $mg\,kg^{-1}\,day^{-1}$ and mice given up to 458 $mg\,kg^{-1}\,day^{-1}$ for a period of two years exhibit an increased rate of cancer. A variety of tests have not identified atomoxetine as being mutagenic. Rats given doses of 57 $mg\,kg^{-1}\,day^{-1}$ did not exhibit impaired fertility.

Pregnant rabbits given up to 100 $mg\,kg^{-1}\,day^{-1}$ through the period of organogenesis exhibited a decrease in live fetuses and an increase in early resorptions. There was also a small increase in incidents of atypical arterial origin. There were no harmful effects at doses of 30 $mg\,kg^{-1}\,day^{-1}$.

In studies of rats, females were treated with doses of up to 50 $mg\,kg^{-1}\,day^{-1}$ from two weeks prior to mating through all of pregnancy and lactation, while males were treated with comparable doses from 10 weeks prior to mating. This resulted in decreases in pup weight and survival at the highest dose. There was decreased pup survival only at 25 $mg\,kg^{-1}$ and no decrease in survival or weight at 13 $mg\,kg^{-1}$. In a similar study in which the rats were given 20 or 40 $mg\,kg^{-1}\,day^{-1}$ only through the period of organogenesis, there was a decrease in the weight of female fetuses and an increase in the occurrence of incomplete ossification of the vertebral arch at the higher dose. However, no adverse effects occurred if pregnant female rats were given up to 150 $mg\,kg^{-1}\,day^{-1}$ only during the period of organogenesis. Atomoxetine is excreted in milk (Eli Lilly 2003).

#### Overdose

Gastric lavage and repeated administration of activated charcoal, with or without cathartics, may prevent or minimize systemic absorption. Provide supportive therapy (Eli Lilly 2003).

#### Discontinuation

Atomoxetine does not require dose tapering for discontinuation (Eli Lilly 2003).

#### Other Information

In humans, atomoxetine does not affect the binding of warfarin, acetylsalicylic acid, phyenytoin, or diazepam to albumin. Drugs that change gastric pH have no effect on atomoxetine bioavailability (Eli Lilly 2003).

#### Effects Documented in Nonhuman Animals

There are no publications on the use of atomoxetine for the use of clinical behavior disorders in nonhuman animals. In the future, however, it may prove to be useful for the treatment of hyperkinesis in dogs, as it is in the treatment of ADD in humans, without the concomitant problem of using a Class II medication.

## III. Methylphenidate Hydrochloride

**Chemical Compound:** Methyl α-phenyl-2-piperidineacetate hydrochloride

**DEA Classification:** DEA class II, nonnarcotic medication; while there are recognized medical uses, it has a high potential for abuse

**Preparation:** Generally available in 5-, 10-, and 20-mg tablets; Ritalin-SR in 20-mg slow-release tablets; Ritalin-LA in 20-, 30-, or 40-mg capsule with an extended-release formulation; Concerta in 18-, 27-, 36-, and 54-mg tablets designed to have 12 hours of effect due to delayed absorption in the human digestive tract. The delay of the SR and LA forms of Ritalin and of Concerta may or may not occur in an equivalent fashion in canine and other veterinary patients.

#### Clinical Pharmacology

Methylphenidate is a mild CNS stimulant. It is believed to activate the brain stem and cortical arousal system, but the mechanism by which it has its behavioral and mental effects is not truly understood (Novartis Pharmaceuticals Corporation 2003).

Therapeutic activity is mainly due to the parent compound. Methylphenidate is rapidly biotransformed, resulting in rapid de-esterification to $\alpha$-phenyl-2-piperidine acetic acid (ritalinic acid). Methylphenidate has a low rate of binding to plasma protein, with a range of 10–52%. In children the average half-life of methylphenidate is 2.5 hours, whereas in adults it is 3.5 hours. The half-life of ritalinic acid is three to four hours. After a single, oral dose of immediate-release methylphenidate, almost all is excreted in the urine within 48–96 hours, most as ritalinic acid, although some is excreted as other, minor metabolites. Very little, <1%, is excreted as the parent compound (Novartis Pharmaceuticals Corporation 2003). The dog has multiple metabolites of methylphenidate, including α-phenyl-2-piperidineacetic acid (24%) and the lactam acid of 6-oxo-α-phenyl-2-piperidineacetate (27%) (Egger et al. 1981). Dogs absorb oral methylphenidate more rapidly than humans, with maximum blood levels occurring only 0.21 hours after administration for immediate release methylphenidate and 0.46 hours after administration of sustained release methylphenidate (Giorgi et al. 2010; Lavy et al. 2011).

Methylphenidate can be given with or without food. The effects of renal impairment and hepatic insufficiency on metabolism of methylphenidate have not been adequately studied. However, renal and hepatic impairment should have little effect on the metabolism and the excretion of methylphenidate. Metabolism occurs primarily due to the activity of nonmicrosomal hydrolytic esterases, which are distributed widely throughout the body.

No gender differences have been identified in the metabolism of methylphenidate (Novartis Pharmaceutals Corporation 2003).

Concerta tablets are designed to use osmotic pressure for the delivery of methylphenidate at a controlled rate over an extended period of time. There is an immediate-release outer layer within which lies an osmotically active core with a precision laser-drilled orifice. When the tablet enters the gastrointestinal tract, the outer layer dissolves, providing immediate release. Subsequently, as water enters the interior of

the tablet, the osmotically active portion expands, pushing methylphenidate out of the orifice. The inert shell is eliminated in the stool. Obviously, this tablet cannot be split, because doing so would destroy the mechanism for gradual release. In adult humans this medication minimizes the peaks and troughs that result from repeated dosing of the regular, short-acting form of methylphenidate (ALZA Corporation 2003). Nevertheless, this tablet was designed for the length and chemical mix of the human digestive tract, not the digestive tract of any domestic animal, so it is probably not very useful to veterinarians.

#### Uses in Humans

Methylphenidate is used to treat ADD and narcolepsy. ADD is characterized by impulsivity, emotional lability, moderate to severe distractibility, a short attention span, and, in some cases, hyperactivity (Novartis Pharmaceuticals Corporation 2003).

#### Contraindications

Do not give to patients that exhibit significant symptoms of anxiety, because these symptoms may be exacerbated. Do not give to patients with any history of intolerance to CNS stimulants, cardiac disease, or glaucoma. Do not give with MAOIs or within 14 days of administering MAOIs.

Methylphenidate may decrease the metabolism of coumarin anticoagulants, anticonvulsants, tricyclic antidepressants, and phenylbutazone. If these drugs are given concurrently with methylphenidate, the dose should be decreased.

#### Side Effects

Side effects have not been reported in veterinary patients given clinically relevant doses of methylphenidate, except that patients given test doses may exhibit increased arousal and activity. This finding is interpreted as indicating that the drug will not likely be useful in that particular patient, and no further medication is conducted with this drug. Decreased appetite, tachycardia, and sleeplessness are all side effects that may be expected in the pet population.

In humans, there is some evidence of growth suppression in some cases of long-term use of stimulants. A causal relationship has not been established, and the mechanism of this effect is unknown (Novartis Pharmaceuticals Corporation 2003). The effect identified in humans is not substantial and not likely to be of concern in veterinary patients. While it might theoretically be of concern in animals destined to be show and breeding stock, it is probably not appropriate to show an animal with true hyperkinesis, given the unverified possibility of some degree of genetic effect.

Methylphenidate may lower the seizure threshold in patients with a history of seizures, with abnormal electroencephalograms (EEGs) but no seizures, and, very rarely, patients with no history of seizures and no abnormalities of the EEG. The safety of concurrent use of methylphenidate and anticonvulsants has not been determined; therefore, treatment with methylphenidate should not be initiated in patients with seizures and should be discontinued in patients that develop seizures while on it.

Some humans have reported difficulties of accommodation and blurring of vision when taking methylphenidate. The possibility of worsening of vision should be considered in assessing a nonhuman animal's response to medication.

Methylphenidate is teratogenic in rabbits when given at doses of 200 $mg\,kg^{-1}\,day^{-1}$, but not when given at 60 $mg\,kg^{-1}\,day^{-1}$ during the period of organogenesis. In rats, the teratogenic effect is not evident at doses of 75 $mg\,kg^{-1}\,day^{-1}$. Pups of rats given up to 45 $mg\,kg^{-1}\,day^{-1}$ during both pregnancy and lactation exhibited decreased weight gain. Weight gain was normal if the mothers were given 15 $mg\,kg^{-1}\,day^{-1}$ throughout pregnancy and lactation. Methylphenidate has not been found to be mutagenic (ALZA Corporation 2003; Novartis Pharmaceuticals Corporation 2003).

In a study of the effect of methylphenidate on development, rat pups were given doses of up to 100 mg kg$^{-1}$ day$^{-1}$, starting at day 7 of life and continuing through week 10. Tests administered at weeks 13 to 14 demonstrated decreased spontaneous locomotor activity at doses of 50 mg kg$^{-1}$ day$^{-1}$ and higher. There was a deficit in the acquisition of specific learning tasks in females that had been given the highest dose of 100 mg kg$^{-1}$ day$^{-1}$. There were no long-term effects in rats that had been given 5 mg kg$^{-1}$ day$^{-1}$ (Novartis Pharmaceuticals Corporation 2003).

The fertility of male and female rats given up to 160 mg day$^{-1}$ was not impaired (ALZA Corporation 2003).

Carcinogenicity studies carried out on mice resulted in increased frequencies of hepatocellular adenomas in both genders and, in males, an increase in hepatoblastomas when the mice were dosed at 60 mg kg$^{-1}$ day$^{-1}$. The total number of malignant hepatic tumors did not increase, however. Carcinogenicity studies conducted on rats at doses up to 45 mg kg$^{-1}$ day$^{-1}$ did not result in any increase in tumor development. A study conducted on a transgenic mouse strain that was sensitive to genotoxic carcinogens and using doses of up to 74 mg kg$^{-1}$ day$^{-1}$ did not reveal any increase in cancers (ALZA Corporation 2003; Novartis Pharmaceuticals Corporation 2003).

#### Overdose

Various sequelae may be produced by overstimulation of the CNS and excessive sympathomimetic arousal. Evacuate the stomach contents with gastric lavage. If necessary, give a short-acting barbiturate to allow for this procedure. Also give activated charcoal and cathartics. Place the animal in a dim, quiet location to avoid further stimulation induced by the environment. Monitor vital signs, and provide supportive therapy.

A report of 128 cases of methylphenidate toxicosis in dogs from 2001 to 2008 found that the most common clinical signs were hyperactivity, tachycardia, vomiting, agitation, and hyperthermia. Doses ranged from 0.36 to 117.0 mg kg$^{-1}$. While the severity of clinical signs was not strongly associated with dose, more severe and prolonged clinical signs occurred in dogs that had ingested extended release forms of methylphenidate. Three dogs that had consumed the extended release form died. The minimum dose that was considered toxic, i.e. the dogs showed adverse clinical signs were 0.59 mg kg$^{-1}$ and, for the extended release form, 0.39 mg kg$^{-1}$. Note that the toxic dose for regular methylphenidate is lower than the clinical dose. This is not surprising since, in dogs that do not have ADHD, the usual effects of a stimulant drug would be expected (Genovese et al. 2010). In a 13-week oral toxicity study in dogs that were treated with 7.5 mg kg$^{-1}$ daily or 15 mg kg$^{-1}$ daily, dogs exhibited effects of CNS stimulation, including increased locomotor activity, excitement, and body weight loss secondary to the increased activity (Bakhtiar et al. 2004).

#### Doses in Nonhuman Animals

When it is effective for a given dog, methylphenidate can be given on an as-needed basis, which is useful given the need to compromise between making the dog a functional family pet and minimizing the amount of medication it receives. For example, if the dog is only with the family during the evenings and some weekends, and is kept in a large pen of suitable size and with toys present for it to exercise and play with during the day and weekends when the family is away from home, medication can be given that fits the times that the dog needs to be calm and attentive. When the first adult arrives home in the late afternoon or gets up on a weekend morning, they can medicate the dog, then leave it alone for a minimum of 30 minutes while the methylphenidate has time to take effect. After this time, the dog can be released from its pen to interact with the family.

The slow-release and long-acting forms of methylphenidate (Ritalin-SR, Ritalin-LA, and Concerta) have tremendously benefited humans with ADD because of the drugs' extended activity, so that only one or perhaps

two doses need be taken during the day. These forms, however, tend to be substantially more expensive than the regular release form and are not desirable for working families that interact significantly with their dog only in the evenings. Additionally, the various slow-release forms have been designed for the human digestive tract and may act differently in the digestive tracts of veterinary patients. In the author's experience, when regular release methylphenidate is used in dogs, they appear to metabolize it very rapidly, with clinical efficacy existing for only two or three hours. Thus, owners need to be aware of the necessity of remedicating regularly so long as the dog is remaining with the family.

For canine cataplexy, methylphenidate is given once daily, in the morning (Shell 1995).

#### Discontinuation

Chronic administration of methylphenidate can result in dependence. Therefore, discontinuation after administration for several weeks or longer should be done gradually.

#### Other Information

Periodic complete blood counts, differential and platelet counts are recommended if methylphenidate is prescribed in the long term.

#### Effects Documented in Nonhuman Animals

##### *Cats*

One case of methylphenidate toxicosis in a cat has been reported. A 10-year-old, 5.1 kg spayed female domestic longhair cat had accidentally been given 5 mg of methylphenidate (1 mg $kg^{-1}$), When she was presented to the veterinarian 13 hours after being given the medication, she presented with restlessness, vocalization, episodes of hurtling into walls, hyperresponsiveness to external stimuli, significant generalized tremors, ataxia, mydriasis and a sluggish light response, sinus tachycardia and elevated blood pressure. Repeated treatments with diazepam (1 mg $kg^{-1}$ IM) and lactated Ringer's solution (180 ml SC) to facilitate removal of the methylphenidate via the kidneys, combined with being placed in a dark, padded, quiet location, resulted in gradual lessening of the clinical signs (Gustafson 1996).

##### *Dogs*

A Yorkshire terrier diagnosed with canine hyperkinesis that did not respond to D-amphetamine subsequently responded to treatment with methylphenidate at a dose of 1.25 mg $kg^{-1}$ $t^{-1}$.i.d. A 10-month-old Weimaraner diagnosed with attention deficit hyperactivity disorder was treated with methylphenidate, 120 mg t.i.d. for 12 months, at which time medication was discontinued without a relapse (Piturru 2014).

Methylphenidate, given at a dose of 0.25 mg $kg^{-1}$ PO daily has some anticataleptic effects in dogs (Baker et al. 1983; Chrisman 1991; Braund 1994; Shell 1995).

##### *Horses*

Although illegal, methylphenidate may be given to racing and performance horses. In one study of both pharmacokinetic and behavioral effects of methylphenidate on thoroughbred horses, the horses increased their rate of responding to an operant task when given methylphenidate. Subcutaneous injection of 0.35 mg $kg^{-1}$ of methylphenidate is followed by a rise in plasma concentration for about one hour, after which plasma concentrations decreased with a half-life of about 1.5 hours. Urine concentrations peaked at about three times the plasma concentrations, at two hours after injection. Subsequently urine concentration decreased with a half-life of about one hour. IM injection of the same dose gave similar results (Shults et al. 1981). Plasma levels can be detected at levels lower than 1 ng $ml^{-1}$, and can be quantitated at levels down to 2 ng $ml^{-1}$ (Huffman et al. 1974).

## Important Information for Owners of Pets Being Placed on CNS Stimulants

Do not medicate your pet in the evening, because this may result in nighttime restlessness.

## Clinical Examples

### Case 1

#### Signalment

Brownie was a tan-and-white, one-year-old, spayed female cocker spaniel weighing 11.7 kg.

#### Presenting Complaint

Brownie presented with hyperactivity.

#### History

The owners had gotten Brownie from a pet store as a 10-week-old puppy. They reported that since they first had her, she had been extremely active, climbed onto countertops, chewed clothes and shoes whether the owners were home or absent, did poorly in obedience class, rested very little, and did not seem to be able to focus her attention. The owners reported that, at home, Brownie would only lie down for any significant period of time when she was locked in her crate at night. During the interview, she was almost constantly active, though friendly, investigating and walking around the room. She lay down for about 10 seconds three times, but was panting and looking around alertly while she did so.

Obedience training and paroxetine had been attempted to treat her behavior. The physical exam was unremarkable.

#### Diagnosis

Brownie was diagnosed with ADHD.

#### Treatment Plan

The owners were instructed to give Brownie a test dose of 5 mg of methylphenidate and observe her for any changes from her typical behavior. Behavior management of dogs with hyperactivity was discussed. The owners had already raised a child with ADHD and understood that finding a medication that helped was only the beginning and that they would have to put a lot of effort into training Brownie in new ways of behaving.

#### Follow-Up

The owners reported that about 30–45 minutes after being medicated Brownie became calmer and lay down. She subsequently lay still for about 30 minutes. The owners were instructed to increase the methylphenidate to a test dose of 10 mg the next day. Brownie's response to 10 mg was better than to 5 mg, that is, she was even calmer and appeared to be able to focus her attention when one owner attempted a training session using positive reinforcement.

Brownie's behavior continued to improve with the combination of methylphenidate and training using positive reinforcement.

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# 16

# Tricyclic Antidepressants

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## Action

The tricyclic antidepressants (TCAs) act as inhibitors of both serotonin and norepinephrine. They also have antihistaminic and anticholergic effects and are $\alpha$-1 adrenergic antagonists. The extent of these effects varies widely between the different TCAs (see Table 16.1). Some have strong serotonin reuptake inhibition and weak norepinephrine reuptake inhibition. Others have strong norepinephrine reuptake inhibition and weak serotonin reuptake inhibition. Other molecular activities vary widely as well. For example, amitriptyline has much stronger antihistaminic effects than clomipramine.

Chronic administration of TCAs results in decreased numbers of β-adrenoceptors and serotonin receptors and altered function of various serotonin receptors in the forebrain (Vetulani and Sulser 1975; Sulser et al. 1978; Heninger and Charney 1987; Potter et al. 1995). These long-term changes in receptor number and function are believed to contribute to the significant changes in behavior that evolve over time when a pet is maintained on these medications.

All of the TCAs are readily absorbed from the gastrointestinal tract. Peak plasma levels occur over a wide range of time, two to six hours being the mean peak time for various drugs. Half-lives vary widely as well, but are long, somewhere in the range of 24 hours. In the liver, they undergo demethylation, aromatic hydroxylation, and glucuronide conjugation of the hydroxy metabolite (Potter et al. 1995).

Tricyclic antidepressants are so named because of their central three-ring structure. The tertiary amines have two methyl groups at the end of their side chain, while the secondary amines have only one. The type of side chain is substantially related to the molecular action. Tertiary amines have a proportionately greater effect on blocking serotonin transport, while the secondary amines have a proportionately greater effect on blocking norepinephrine transport (Bolden-Watson and Richelson 1993; Tatsumi et al. 1997; Nelson 2004). Only the six TCAs that have been most commonly used in veterinary behavior will be discussed in this chapter: the tertiary amines amitriptyline, clomipramine, doxepin, and imipramine, and the secondary amines desipramine and nortriptyline.

## Overview of Indications

Like the selective serotonin reuptake inhibitors (SSRIs), the TCAs have anxiolytic, anticompulsive, and antiaggressive effects, in addition to antidepressant effects. In veterinary clinical behavioral medicine, they are used primarily

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**Table 16.1** Acute *in vitro* biochemical activity of selected tricyclic antidepressants.

| TCA | NE | 5-HT | α-1 | α-2 | $H_1$ | Musc |
|---|---|---|---|---|---|---|
| Amitriptyline | ± | ++ | +++ | ± | ++++ | ++++ |
| Clomipramine | + | +++ | ++ | 0 | + | ++ |
| Desipramine | +++ | 0 | + | 0 | 0 | + |
| Doxepin | ++ | + | ++ | 0 | +++ | ++ |
| Imipramine | + | + | + + | 0 | + | ++ |
| Nortriptyline | ++ | ± | + | 0 | + | ++ |

*Source:* (Potter 1984; Potter et al. 1991; Richelson and Nelson 1984; Richelson and Pfenning 1984; Potter et al. 1995).

for the first three effects. As with the SSRIs, the onset of effect takes several days to several weeks, and clients whose pets are placed on a TCA need to be cautioned of that so that they do not have unrealistic expectations. While occasional pets have a rapid response to a single dose, as a general rule, they should not be prescribed on an as-needed basis.

One of the TCAs, clomipramine, is the only psychoactive medication with anxiolytic properties to be FDA-approved for an anxiety disorder. Specifically, Clomicalm is approved for the treatment of separation anxiety in dogs, when used in combination with behavior modification. Clomipramine is the most serotonin-selective of the commercially available TCAs.

Common uses in domestic animals include anxiety, affective aggression, compulsive disorder, and urine marking.

## Contraindications, Side Effects, and Adverse Events

Side effects vary widely, as there is a substantial range of effect on serotonin and norepinephrine between the various TCAs, as well as substantial variation between the TCAs in molecular effects other than those on serotonin and norepinephrine. In general, side effects may include sedation, constipation, diarrhea, urinary retention, appetite changes, ataxia, decreased tear production, mydriasis, cardiac arrhythmias, tachycardia, and changes in blood pressure.

There is some evidence from the human literature that antidepressant drugs that have a sedative action and an antimuscarinic effect can interfere with memory. Amitriptyline is an example of one such medication that has both a high occurrence of antimuscarinic and sedative effects. Clomipramine, on the other hand, has some antimuscarinic and sedative effects, but not as much as amitriptyline, and has no measurable effect on learning and memory (Liljequist et al. 1974; Thompson 1991). However, mice injected with 10 mg $kg^{-1}$ of either amitriptyline or clomipramine did not show any deficits in learning or memory when tested in a maze test (Nurten et al. 1996).

## Adverse Drug Interactions

TCAs should never be given in combination with MAOIs. This includes such various compounds as selegiline, which is used for the treatment of canine cognitive dysfunction, and amitraz, which is used for the treatment of demodicosis and is also a common compound in collars designed to prevent infestation with ticks.

## Overdose

There is no antidote for overdose of any of the TCAs, although physostigmine given intravenously has been shown to be useful in alleviating cardiac and central nervous

Table 16.2 Doses of selected tricyclic antidepressants in dogs and cats.

| TCA | Cat | Dog |
|---|---|---|
| Amitriptyline | 0.5–2.0 mg kg$^{-1}$ q12–24 h | 1–6 mg kg$^{-1}$ q12h |
| Clomipramine | 0.25–1.3 mg kg$^{-1}$ q24h | 1.0–3.0 mg kg$^{-1}$ q12h |
| Desipramine | | 1.5–3.5 mg kg$^{-1}$ q24h |
| Doxepin | 0.5–1.0 mg kg$^{-1}$ q12h | 3.0–5.0 mg kg$^{-1}$ q8–12 h |
| Imipramine | 0.5–1.0 mg kg$^{-1}$ q12–24 h | 0.5–2.0 mg kg$^{-1}$ q8–12 h |
| Nortriptyline | 0.5–2.0 mg kg$^{-1}$ q12–24 h | 1.0–2.0 mg kg$^{-1}$ q12h |

*Note:* Always start with a low dose and titrate up as necessary if the patient does not exhibit side effects. All doses are given orally.

system (CNS) toxic effects in humans (Falletta et al. 1970; Slovis et al. 1971). Treatment must consist of decontamination and supportive therapy; however, emesis is contraindicated.

## Discontinuation

While discontinuation of a TCA does not generally produce significant withdrawal symptoms per se, it is generally recommended that a patient that has been medicated with a TCA for several months be weaned off gradually. It may be that, while a behavior problem has resolved at a given dose, it recurs when the patient is off medication or even on a lower dose. Therefore, tapering of the dose while monitoring can allow for identification of dose levels at which the problem returns, and initiation of appropriate management and behavior modification protocols.

## Clinical Guidelines

As with the SSRIs, the TCAs should not be given on an as-needed basis, because they act by producing a gradual shift in levels of serotonin and/or norepinephrine and by down-regulation of the postsynaptic neurons. While some patients may begin to exhibit a response after just a few days of daily administration, others that ultimately have a good response may not respond for several weeks.

## Specific Medications

Doses of selected TCAs in cats, dogs, horses, and parrots are given in Tables 16.2 and 16.3.

### I. Amitriptyline

**Chemical Compound:** 3-(10,11-Dihydro-5*H*-dibenzo [a,*d*]cycloheptene-5-ylidene)-*N*, *N*-dimethyl-1-propanamine hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available in 10-, 25-, 50-, 75-, 100-, and 150-mg tablets and as a sterile solution for intramuscular injection.

Table 16.3 Doses of selected tricyclic antidepressants in horses and parrots.

| Animal | Dose |
|---|---|
| Parrots | |
| Clomipramine | 2.0–4.0 mg kg$^{-1}$ q12h |
| Doxepin | 0.5–5.0 mg kg$^{-1}$ q12h |
| Horses | |
| Imipramine | 0.75–2.0 mg kg$^{-1}$ |

*Note:* Always start with a low dose and titrate up as necessary if the patient does not exhibit side effects. All doses are given orally.

### Clinical Pharmacology

Amitriptyline inhibits the reuptake of norepinephrine and serotonin. It is rapidly absorbed and metabolized. Plasma concentrations correlate with total intake of amitriptyline (Rudorfer and Robins 1982). In dogs, the primary metabolic pathways are hydroxylation, glucuronide hydroxylation, methyl hydroxylation and N-demethylation, respectively (Lee et al. 2015), It is metabolized into nortriptyline and a variety of other metabolites (Diamond 1965).

In dogs, the peak concentration occurs at two hours (Kukes et al. 2009). The half-life in humans is 5–45 hours (Nelson 2004), and the half-life in dogs given amitriptyline orally is 4.5–8 hours (Shanley and Overall 1992; Kukes et al. 2009; Norkus et al. 2015a). Being fed vs. fasted prior to administration of oral amitriptyline does not significantly affect the half-life (Norkus et al. 2015a). However, giving amitriptyline IV extends the half-life to 10–11 hours (Norkus et al. 2015b).

Amitriptyline is excreted in the milk. In rabbits given carbon-14-labeled amitriptyline, the concentration of radioactivity in the milk is equivalent to concentrations in the serum. Concentrations of radioactivity in neonates consuming the milk are substantially lower than concentrations in the equivalent organs in the mother (Aaes-Jørgensen and Jørgensen 1977).

### Uses in Humans

Amitriptyline is approved for the treatment of depression.

### Contraindications

Amitriptyline is contraindicated in patients with a history of sensitivity to this or other TCAs. It should not be given concurrently with MAOIs, because serious side effects, including convulsions and death, may result. If a patient is to be changed from an MAOI to amitriptyline, discontinue the MAOI for at least two weeks before beginning amitriptyline. Avoid or use it cautiously in patients with a history of seizures, urinary retention, or glaucoma. In humans, amitriptyline has been shown to cause cardiac arrhythmias, tachycardia, and prolonged conduction time. While dogs do not appear to be as susceptible to cardiotoxic side effects as humans (e.g. Reich et al. 2000), it should be avoided or used cautiously in veterinary patients with existing cardiac disease. Sufficiently large doses can induce cardiotoxicity. In a study in which anesthetized dogs were given a continuous intravenous infusion of amitriptyline until cardiotoxicity occurred, toxic effects were observed at an average of 25 $mg\,kg^{-1}$ (range 15–80 $mg\,kg^{-1}$) in one study and an average 36 $mg\,kg^{-1}$ in another study (Lheureux et al. 1992a, 1992b). Rabbits given amitriptyline by intravenous injection exhibit decreased blood pressure and increased heart rate (Elonen et al. 1974). Amitriptyline may enhance the effects of barbiturates and other CNS depressants (Merck 1998).

Amitriptyline is metabolized in the liver and excreted through the kidneys. It should therefore be used cautiously and at lowered doses in patients with mild to moderate liver disease and avoided entirely in patients with severe liver disease.

Levels of amitriptyline may be elevated in patients concomitantly given drugs that are metabolized by cytochrome P450 2D6 (Merck 1998).

Systemic absorption of amitriptyline is poor when administered transdermally as opposed to orally. Therefore, transdermal administration of amitriptyline is not recommended at this time (Mealey et al. 2004).

### Side Effects

The most common side effects in cats and dogs are sedation, miosis, and urinary retention. Weight gain, decreased grooming, and transient cystic calculi may also occur (Chew et al. 1998). A variety of cardiovascular, CNS, anticholinergic, hematologic, gastrointestinal, and endocrine side effects are reported in humans.

Amitriptyline has teratogenic effects in mice and hamsters when pregnant females are given doses of 28–100 $mg\,kg^{-1}\,day^{-1}$. In the rat, medicating pregnant females with

25 mg kg$^{-1}$ day$^{-1}$ results in delayed ossification in the fetal vertebrae. In rabbits, if pregnant females are medicated with 60 mg kg$^{-1}$ day$^{-1}$, ossification of the cranial bones is delayed. Amitriptyline crosses the placenta, and there have been some reports of adverse events in human babies when the mother was medicated with amitriptyline during pregnancy. However, there is insufficient documentation to determine if the amitriptyline was the cause of the adverse events.

Amitriptyline is also excreted into breast milk. Because of the potential for adverse effects on fetuses or young, pregnant or lactating females should not be medicated with amitriptyline.

The intravenous $LD_{50}$ (the dose that kills 50% of the animals tested) is 18–22 mg kg$^{-1}$ in mice and 6–11 mg kg$^{-1}$ in rabbits. The oral $LD_{50}$ is 286–359 mg kg$^{-1}$ in rats and 100–216 mg kg$^{-1}$ in mice (Ribbentrop and Schauman 1965). Toxic signs include respiratory depression, ataxia, tremors, convulsions, and prostration.

### Overdose

There is no specific antidote for overdose of amitriptyline. Decontaminate and provide supportive therapy. Emesis is contraindicated. Lipid therapy may be beneficial in amitriptyline overdose (Kiberd and Minor 2012).

### Discontinuation

Patients that have been on amitriptyline daily for several weeks should be withdrawn gradually.

### Other Information

Amitriptyline has historically been commonly used in general practice for the treatment of anxiety disorders in dogs and cats, apparently initially for economic reasons and, later, because of familiarity with the medication. However, compared with other drugs such as fluoxetine and clomipramine, which have become much more economically feasible for the pet owner in recent years, amitriptyline has a relatively low clinical efficacy and high incidence of side effects.

### Effects Documented in Nonhuman Animals

#### *Cats*

In a retrospective study, two of three cats with psychogenic alopecia that were treated with amitriptyline at doses of 2.5 mg q12h or 5.0 mg q24h (total dose) responded (Sawyer et al. 1999).

Amitriptyline has been used successfully to treat hypervocalization in a cat (Houpt 1994).

Amitriptyline (2 mg kg$^{-1}$ orally [PO], daily) may decrease clinical signs of severe recurrent idiopathic cystitis in cats, possibly in part because of analgesic effects such as those that occur in human patients (Hanno et al. 1989; Chew et al. 1998).

High doses of amitriptyline, 7–10 mg kg$^{-1}$ intravenously (IV) result in loss of electroencephalogram changes in cats that are subjected to loud tones or pinching. Lower doses result in attenuation of the response (Vernier 1961).

#### *Dogs*

Dogs given amitriptyline at a dose range of 0.74–2.5 mg kg$^{-1}$ q12h for ≥45 days do not exhibit any electrocardiogram (EKG) changes. P-wave duration has a significant negative correlation with serum concentration of amitriptyline at clinically usual doses, but remains within normal parameters (Reich et al. 2000).

In a retrospective study of 103 dogs with various presentations of compulsive disorder, amitriptyline was found to be significantly less effective than clomipramine (Overall and Dunham 2002).

In a prospective, randomized, double-blind, placebo-controlled trial of treatment of canine aggression with amitriptyline plus behavior modification versus clomipramine plus behavior modification, amitriptyline was no more effective than placebo (Virga et al. 2001). One dog diagnosed with a combination of "dominance aggression" and food-defense aggression responded positively to a combination of amitriptyline and behavior modification (Reich 1999).

In an open trial, 15 of 27 dogs (56%) with separation anxiety that were treated with

amitriptyline in addition to behavior modification improved (Takeuchi et al. 2000).

Suspected neuropathic pain may be successfully treated with amitriptyline (Cashmore et al. 2009).

#### *Horses*

Amitriptyline is rapidly metabolized in the horse. A single dose of 750 mg followed by collection of urine through a catheter during the zero- to three-week period after administration revealed that almost all of the medication being excreted during this period was nortriptyline (Fenwick 1982).

## II. Clomipramine Hydrochloride

**ChemicalCompound:**3-Chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 25-, 50-, and 75-mg capsules (Anafranil and generic), and as 20-, 40-, and 80-mg chewable tablets (Clomicalm).

### Clinical Pharmacology

Clomipramine affects both the serotonergic and noradrenergic neural transmission in the CNS. The primary mechanism of action is probably prevention of reuptake of serotonin in the CNS, and it is the most serotonin-specific of the commercially available TCAs (see Table 16.1). It is highly lipophilic and therefore passes easily through lipophilic membranes. The major route of biotransformation is demethylation, resulting in desmethylclomipramine. Subsequently, further metabolic processes produce various water-soluble substances that are eliminated through the bile or the urine (Faigle and Dieterle 1973). In humans, the half-life is 15–60 hours (Nelson 2004).

In the dog, it is almost totally absorbed when given orally. In the dog and the rat, the main mode of excretion is through the bile, with the dog eliminating about 80% of an oral or intravenous dose of 5 mg kg$^{-1}$ of clomipramine via the bile within four days, most of the remainder being excreted via the kidneys in the same amount of time. In humans, more clomipramine is excreted via the kidneys than the bile (Faigle and Dieterle 1973).

Following intravenous injection, clomipramine is rapidly distributed throughout the body, penetrating various tissues and organs, as demonstrated by whole-body autoradiography performed on mice given 10 mg kg$^{-1}$. High concentrations initially occur in the lung, adrenal gland, thyroid, the kidney, the pancreas, the heart, and the brain, which would be predicted based on clomipramine's lipophilic nature. The affinity of clomipramine for tissues containing fat results in rapid decreases in blood levels (Faigle and Dieterle 1973).

In humans, there is no relation between dose and plasma level of clomipramine, but plasma concentrations of desmethylclomipramine, the primary active metabolite, are correlated with dose (Jones and Luscombe 1977).

After both single-dose and multiple-dose oral treatment of dogs with clomipramine, peak concentrations of clomipramine occur in the plasma within three hours, while peak concentrations of the primary active metabolite, desmethylclomipramine, usually occur within four to six hours. Subsequently, plasma levels decline rapidly, with a plasma half-life for clomipramine of about four hours. However, there is a substantial range in elimination half-life, and it can be as great as 16 hours. The measured plasma half-life for desmethylclomipramine is likewise about four hours, but since this is a combination of the interaction between generation of new desmethylclomipramine as clomipramine is metabolized, and elimination of desmethylclomipramine, the actual half-life of desmethylclomipramine is shorter. With intravenous administration in dogs, the mean elimination half-life is five hours (Hewson et al. 1998a; King et al. 2000a, 2000b). The half-life in humans is longer, with a mean of about 20 hours when given orally (Nagy and Johansson 1977; Evans et al. 1980).

In dogs, plasma concentrations of clomipramine are higher than concentrations of desmethylclomipramine (about 3:1), which is the opposite of humans, in which plasma concentrations of clomipramine are lower than those of desmethylclomipramine (about 1:2.5) (Broadhurst et al. 1977; Jones and Luscombe 1977; Kuss and Jungkunz 1986; Hewson et al. 1998a; King et al. 2000a; King et al. 2000b). This may be one of the reasons that adverse events appear to be less frequent in dogs than in humans, since clomipramine is the molecule that acts predominantly on serotonin whereas desmethylclomipramine has stronger anticholinergic activity (Benfield et al. 1980). When dogs are dosed daily with clomipramine, steady-state plasma levels are achieved within four days (King et al. 2000a). *In vitro*, cat microsomes transform clomipramine more slowly than do rat or dog microsones. The cat also exhibits a gender difference, with male cat microsomes being less efficient demethylators and hydroxylators than female cat microsomes (Lainesse et al. 2007b)

In a study of the pharmacokinetics of clomipramine in six adult spayed cats, the mean half-life of clomipramine after administration of a single IV dose of 0.25 mg $kg^{-1}$ was 12.3 hours, with a range of 7.7 hours to 18.7 hours (Lainesse et al. 2006) Seventy-six spayed and neutered cats given a single dose of clomipramine in the dose range of 0.32 to 0.61 mg $kg^{-1}$ orally had peak levels of clomipramine occur at one to six hours, with a mean of three hours, while peak doses of the active metabolite desmethylclomipramine occurred at 1 to 24 hours, with a mean of seven hours. Females had a significantly faster $ClF^{-1}$ (0.36 l $h^{-1}$ $kg^{-1}$) than males 0.21 l $h^{-1}$ $kg^{-1}$) and a significantly higher mean MR (0.53 compared to 0.36) (Lainesse et al. 2007a).

Normal dogs treated with 3 mg $kg^{-1}$ clomipramine daily, PO, have a lower ratio of 5-hydroxyindoleacetic acid (HIAA) to 3-methyl 4-hydroxyphenylglucol (MHPG) in the cerebrospinal fluid than do dogs treated with placebo (Hewson et al. 1995).

Desmethylclomipramine has anticholinergic effects on gastrointestinal smooth muscle, inhibiting motility and antagonizing muscarinic receptors, but does not do so as much as clomipramine. It is a more potent inhibitor of norepinephrine and dopamine reuptake than clomipramine. It has antidepressant activities that are probably due to its monoamine uptake inhibition (Benfield et al. 1980).

There is a faster rate and higher levels of absorption in dogs that are fed than in dogs that are fasted. Overall bioavailability is about 25% greater in dogs that are fed as opposed to fasted. Plasma half-life is 2 to 9 hours in fed dogs, but 3 to 21 hours in fasted dogs, presumably due to delayed absorption (Novartis 2000; King et al. 2000b).

When dogs are repeatedly dosed, the half-lives of clomipramine and desmethylclomipramine increase with increased dosage. At doses of 1, 2, and 4 mg $kg^{-1}$ twice a day (b.i.d.), the accumulation ratios for clomipramine are 1.4, 1.6, and 3.8, respectively, while for desmethylclomipramine they are 2.1, 3.7, and 7.6. There are two main possibilities for this observation. First, the main route of elimination of both clomipramine and desmethylclomipramine may be saturable. Second, the increasing numbers of molecules may themselves directly inhibit the elimination process (King et al. 2000a).

In dog cells, clomipramine inhibits P-glycoprotein, a multidrug transporter that removes toxins and certain other molecules from cells (Schrickx and Fink-Gremmels 2014).

#### Uses in Humans

Clomipramine is used to treat obsessive-compulsive disorder in humans.

#### Contraindications

Clomipramine should not be given to patients with a history of sensitivity to clomipramine or other TCAs. It should not be given in conjunction with an MAOI or within two weeks of discontinuation of administration of an MAOI. Avoid or use cautiously in patients with a history of

epilepsy, cardiac arrhythmias, glaucoma, or urine or stool retention.

While clomipramine is not as cardiotoxic in dogs as it is in humans, sufficiently large doses can induce cardiotoxicity. In a study in which anesthetized dogs were given a continuous intravenous infusion of clomipramine until cardiotoxicity occurred, toxic effects were observed at an average of 65 mg kg$^{-1}$ (range 53–72). This is much higher than the dose at which cardiotoxicity occurred in dogs infused with amitriptyline (Lheureux et al. 1992a).

Clomipramine should not be given to male breeding dogs, as testicular hypoplasia may occur (Novartis 2000).

In humans, concurrent administration of phenobarbital with clomipramine results in increased plasma levels of clomipramine.

### Side Effects

Side effects include sedation, mydriasis, regurgitation, appetite changes, and urinary retention (Pfeiffer et al. 1999; Litster 2000). Clomipramine may also potentiate the side effects of various CNS depressants, including benzodiazepines, barbiturates, and general anesthetics. In humans, on which there is much more data than in the veterinary population, a broad spectrum of side effects has been reported, including cardiovascular effects, mania, hepatic changes, hematologic changes, CNS disorders, sexual dysfunction, and weight changes (Novartis 1998).

Rats given approximately five times the maximum daily human dose exhibited no impairment of fertility, while rats given up to 20 times the maximum daily human dose exhibited no clear evidence of carcinogenicity of clomipramine. A rare tumor, hemangioendothelioma, did occur in a small number of the rats. When pregnant rats and mice were given up to 20 times the maximum daily human dose, there were no teratogenic effects, although there was some evidence of fetotoxic effects. Clomipramine does enter the milk (Novartis 1998). Use in pregnant and nursing females should be avoided if possible.

### Overdose

There is no specific antidote for overdose with clomipramine. Decontaminate and provide supportive therapy. Emesis is contraindicated.

### Discontinuation

Animals that have been given clomipramine daily for several weeks should be withdrawn gradually.

### Effects Documented in Nonhuman Animals

#### *Cats*

Cats given up to five times the clinical dose for 28 days exhibited mild sedation, occasional pupillary dilatation, and a slight decrease in food consumption (Landsberg 2001).

Cats given 10 mg day$^{-1}$ of clomipramine did not exhibit any significant changes in their electrocardiogram. Cats given 10 mg day$^{-1}$ of clomipramine for 28 days did exhibit some decreases in total thyroxine ($T_4$), triiodothyronine ($T_3$), and free throxine ($fT_4$), specifically 25%, 24%, and 16% serum values, respectively. This effect could lead to a misdiagnosis of euthyroidism in cats with subclinical hyperthyroidism (Martin 2010).

In an open trial of cats with various anxiety-related and compulsive disorders, six cases of urine spraying, three cases of overgrooming, and one case of excessive vocalization resolved or were substantially improved when treated with clomipramine at a dose of 0.2–0.55 mg kg$^{-1}$ daily, combined with behavior modification. Some cats became sedated at the higher dose range, but were successfully treated when the dose was lowered (Seksel and Lindeman 1998, 1999).

In a double-masked clinical trial of spraying cats, clomipramine at 0.5 mg kg$^{-1}$ q24h was found to be equally effective as fluoxetine given at 1 mg kg$^{-1}$ q24h (Hart et al. 2005). In a single-blind trial Dehasse (1997) reported a 75% decrease in the number of urine-spraying incidents in 80% of cats given 5 mg day$^{-1}$ of clomipramine as opposed to when they were on placebo. A few of the cats were mildly sedated while on medication. Landsberg (2001) and Landsberg and Wilson

(2005) likewise have had improvement in over 80% of spraying cats given 0.5 mg kg$^{-1}$ for one month. Six of 25 cats, or about a quarter of the patients, became calmer, friendlier and more affectionate while on clomipramine. The most common side-effects were increased sleep and lethargy, decreased appetite and anticholinergic effects, including decreased frequency of urination or defecation, and dry mouth (Landsberg and Wilson 2005). In a meta-analysis of the use of clomipramine as a treatment for urine spraying in cats, Mills et al. (2011) found a significant association between clomipramine use and the number of cats that ceased urine spraying or decreased the behavior by 90%.

Clomipramine has also been used to successfully treat cats with psychogenic alopecia. In a retrospective study, five of five cats treated with clomipramine at doses of 1.25–2.5 mg (total dose) q24h responded (Sawyer et al. 1999). In a prospective, double-blind, placebo-controlled, randomized trial, clomipramine, at a dose of 0.5 mg kg$^{-1}$ q12h PO was more effective than placebo in the treatment of feline psychogenic alopecia (Mertens and Torres 2003; Mertens et al. 2006). A cat with psychogenic alopecia manifesting as mutilation of the tail responded with a treatment of clomipramine at 0.5 mg kg$^{-1}$ daily, combined with behavior modification and environmental changes for two months. The cat had previously had a partial caudectomy because of the self-mutilation of the tail. The caudectomy failed to resolve the problem (Talamonti et al. 2017).

Of 14 cats treated with clomipramine for a variety of anxiety-related behavior problems, including spraying (12 cats), tail-chasing (one cat), nocturnal vocalization (one cat), and aggression to the owner (one of the cats that sprayed), the problem resolved in six cats and was improved in the remaining eight cats. The total daily dose ranged from 0.4 to 1.32 mg kg$^{-1}$ (Litster 2000).

The most definitive results on the efficacy of clomipramine in the treatment of urine spraying in cats were obtained in a randomized, double-blind, placebo-controlled, multicenter clinical trial. Sixty-seven neutered cats were treated with placebo, 0.125–0.25 mg kg$^{-1}$ daily (low dose), 0.25–0.5 mg kg$^{-1}$ daily (moderate dose), or 0.5–1.0 mg kg$^{-1}$ daily (high dose) for three months. Various other treatments had been tried previously and been unsuccessful, including pheromones (17 cats), amitriptyline (7), buspirone (2), diazepam (4), megestrol acetate (12), progestogens (4), and corticosteroids (1).

At all doses, clomipramine was more effective than placebo. The moderate and high doses were more effective than the low dose. There was no effect of age, sex, whether or not previous attempts had been made to treat the urine spraying and whether or not the cat lived in a single-cat household versus a multicat household. Aggression toward familiar cats, unfamiliar cats, and animals other than cats was significantly decreased in the high-dosage group. During the third month of treatment, the amount of time spent in stereotypic behaviors other than licking or grooming was also significantly decreased in both the moderate and high-dosage groups as compared with the low-dosage group. Sedation was the most common side effect and always occurred during the first month of treatment. The frequency and severity of sedation were dose related. However, the overall behavior patterns were not changed, and it is possible that some of what the owners were reporting as sedation was simply the consequence of the cat being less confrontational and more relaxed with its housemates. This possibility requires further study (King et al. 2004a).

The substantial variation in rate of metabolism of clomipramine in cats, discussed in the Clinical Pharmacology section, may explain some of the variation in clinical response to this medication (Lainesse et al. 2007a; Lainesse et al. 2007b).

#### *Dogs*

In humans, only moderate overdoses of clomipramine are cardiotoxic, with such sequelae as increased heart rate, decreased

blood pressure, and slow intracardiac conduction. Research conducted on dogs has demonstrated that this drug is more benign in this species. Dogs given 20 mg kg$^{-1}$ daily for seven days, which is five times the maximum recommended label dose, exhibited a significant reduction in heart rate, with the peak effect occurring about 12 hours after medication. Doses of 4 or 12 mg kg$^{-1}$ of clomipramine did not induce any changes in heart rate. There were no significant changes in the electrocardiogram (EKG) (Pouchelon et al. 2000). In another study, canine patients given clomipramine at doses of 1.5–2.49 mg kg$^{-1}$ q12h for ≥45 days did not exhibit EKG changes. Duration of the P-wave significantly positively correlates with serum concentration of clomipramine, but in studies to date has remained within the clinically normal range for dogs given clinically appropriate doses (Reich et al. 2000).

In healthy dogs given 3 mg kg$^{-1}$ of clomipramine q12h for 112 days, there are significant decreases in total thyroxin ($T_4$), free thyroxin ($fT_4$), and 3, 3′, 5′–triiodothyronine (reverse $T_3$, $rT_3$). $T_4$ decreased 35% while $fT_4$ decreased 38%. However, clinical hypothyroidism was not reported at this dose. There was no change in basal or post-thyrotropin-releasing hormone stimulation at serum thyroid-stimulating hormone concentrations (Gulikers and Panciera 2003).

Testicular hypoplasia has occurred in male dogs given 12.5 times the maximum daily dose for one year (Novartis 2000). It is not known whether usual clinical doses induce some degree of compromise of testicular function.

Clomicalm, a chewable tablet form of clomipramine, is FDA-approved for the treatment of separation anxiety in dogs, but only in conjunction with behavior modification. In a prospective, randomized, double-blind, placebo-controlled, parallel-group, international, multicenter clinical trial, clomipramine, given at a dose of 1–<2 mg kg$^{-1}$ PO q12h plus behavior modification was shown to be more effective than behavior modification alone. Only dogs that exhibited both anxiety when their owner was absent and hyperattachment when their owner was present were included in this study. A low-dose group, given 0.5 to <1 mg kg$^{-1}$ PO q12h did not have a better response than dogs given placebo. Mild and transient vomiting due to gastritis and mild and transient sleepiness, attributable to clomipramine, occurred in some dogs. One greyhound collapsed with hyperthermia, which may or may not have been an idiosyncratic response to the clomipramine. Beagle dogs given doses of up to 50 mg kg$^{-1}$ PO q24h have never exhibited this response (Simpson 1997; King et al. 2000c).

Long-term follow-up of the dogs in the trial described above did not identify any undesirable effects in the dogs given the highest dose (1–2 mg kg$^{-1}$ q12h). Acute worsening of separation anxiety occurred in three dogs that had been given the low-dose clomipramine (King et al. 2004b).

Another study compared four different dose ranges for the treatment of separation anxiety with clomipramine. A total daily dose of 2.1–4.0 mg kg$^{-1}$ was found to be more effective than 1.1–2 mg kg$^{-1}$, 0.51–1 mg kg$^{-1}$, or 0.25–0.5 mg kg$^{-1}$ (Petit et al. 1999).

Dogs diagnosed with separation anxiety that were filmed at days 0, 7 and 14 of treatment with clomipramine at a dose of 1 mg kg$^{-1}$ q12h for seven days, followed by an increase in dose to 2 mg kg$^{-1}$, showed improvement at seven days and greater improvement at 14 days (Cannas et al. 2014).

One trial that was based on owner surveys rather than recording of the dogs' actual behaviors compared placebo with clomipramine at 0.5–1.0 mg kg$^{-1}$ q12h or clomipramine at 1.0–2.0 mg kg$^{-1}$ q12h failed to find a significant effect of clomipramine for signs the authors considered "typical" of separation anxiety (Podberscek et al. 1999). However, general activity and attachment-related behaviors did decrease with clomipramine. The authors also did not evaluate whether or not the dogs had improved in some fashion that was relevant to the

particular case based on baseline symptoms; that is, there was no global assessment.

Clomipramine is also used in the treatment of various forms of compulsive disorder, including acral lick dermatitis (ALD), a condition in which the dog persistently licks itself, producing a dermatitis. In an 11-week-long crossover trial, clomipramine has been shown to be more effective than desipramine in the treatment of ALD, when both drugs were titrated up to 3 mg kg$^{-1}$ daily (Rapoport et al. 1992). Similarly, in a 15-week A-B-A design study, clomipramine was more effective than desipramine in the treatment of canine acral lick dermatitis (Goldberger and Rapoport 1991). Subsequently, in a retrospective open trial, clomipramine given at 2 mg kg$^{-1}$ q24h resulted in decreased self-licking and the healing of ALD lesions in eight of ten cases (Mertens and Dodman 1996).

Clomipramine given at 3 mg kg$^{-1}$ PO q12h for four weeks has been shown to be more effective than placebo in the treatment of compulsive disorder. However, treatment for such a short period of time was not curative (Hewson et al. 1998b).

In a prospective study of tail-chasing terriers (bull terrier, miniature bull terrier, American Staffordshire terrier, and Jack Russell terrier), 18 dogs were started on treatment with clomipramine at 1 mg kg$^{-1}$ q24h, which was subsequently titrated upward depending on side effects and clinical response. Four dogs were withdrawn from the study between four and eight weeks. Of the remaining 14 dogs, 9 had a 75% or greater improvement in tail chasing when given doses of clomipramine ranging between 1 and 5 mg kg$^{-1}$ total daily dose (Moon-Fanelli and Dodman 1998). In a separate case report, a Cairn terrier exhibiting stereotypic tail-chasing was successfully treated with clomipramine titrated up to 3 mg kg$^{-1}$ q24h (Thornton 1995).

Three dogs with compulsive disorder manifested as stereotypic motor behavior were successfully treated with clomipramine titrated up to a maximum dose of approximately 3 mg kg$^{-1}$ PO q12h. One dog had previously been unsuccessfully treated with phenobarbital, while the other two had previously been unsuccessfully treated with amitriptyline. Treatment was conducted over a period of months (Overall 1994).

A dog that exhibited stereotypic motor behavior whenever the owner departed or was out of the dog's sight, that had not responded to previous treatment with amitriptyline or buspirone, did respond well to treatment with clomipramine combined with behavior modification. In this case, an increasing dosage schedule of 1 mg kg$^{-1}$ PO q12h for two weeks, then 2 mg kg$^{-1}$ PO q12h for two weeks, then 3 mg kg$^{-1}$ PO q12h, was used (Overall 1998).

Brain imaging using single-photon emission computed tomography and the dopamine transporter specific radiopharmaceutical $^{123}$I-FP-CIT on a Cavalier King Charles Spaniel with shadow-chasing identified that the dog had an elevated dopamine transporter activity in the left and right striatum. The dog was treated with clomipramine, 2.5 mg kg$^{-1}$ PO q12h. The shadow-chasing steadily decreased over several weeks. At two months after the initiation of treatment, the brain imaging was repeated and the dopamine activity in the striatum had decreased on both the left and right sides to normal or near normal levels. The dog was continued on clomipramine. Discontinuation of the medication resulted in a resumption of shadow-chasing within two days (Vermeire et al. 2010).

In a clinical trial comparing clomipramine, fluoxetine, and placebo for the treatment of tail-chasing in dogs, both clomipramine and fluoxetine were found to be more effective than placebo. There was no significant difference in the efficacy of clomipramine vs. fluoxetine (Yalcin 2010).

A randomized, double-blind, placebo-controlled, clinical trial of the use of clomipramine (1.5 mg kg$^{-1}$ q12h) to treat human-directed "dominance-motivated aggression" in dogs failed to demonstrate a significant difference between medicated and placebo-treated dogs. In this trial, medication was the only

treatment; there was no behavior modification at all (White et al. 1999). Therefore, this trial only addressed the question of whether or not clomipramine is better than nothing, not whether it facilitates improvement if given in conjunction with behavior modification. Clomipramine's licensure for the treatment of separation anxiety is specifically *with* behavior modification, precisely because of the expectation that clomipramine will allow and facilitate learning taking place that ultimately results in changed behavior. Again, as discussed in Chapter 1, all medications for the treatment of behavior problems in nonhuman animals should be used only in conjunction with appropriate environmental management and behavior modification.

In a case report of interdog aggression, clomipramine was prescribed for one dog that was highly reactive. Treatment began at 1.38 mg kg$^{-1}$ b.i.d. for one week, and was subsequently increased to 2.76 mg kg$^{-1}$ b.i.d. The other dog, which was not highly reactive, was treated with fluoxetine. Both dogs were also treated with environmental management and behavior modification. The dog treated with clomipramine gradually became less reactive. After several months of treatment, the problem was resolved (Siracusa 2016).

In a retrospective study of 103 dogs with various presentations of compulsive disorder, clomipramine was found to be significantly more effective than amitriptyline (Overall and Dunham 2002).

Clomipramine has also been used, at a dose of 2 mg kg$^{-1}$ b.i.d. in combination with the benzodiazepine alprazolam to successfully treat storm phobia in dogs. Over 90% of dogs treated with this combination improved. Improvement over baseline continued for at least eight months after discontinuation of treatment, which was as long as the dogs were followed. Storm phobia, while problematic when dogs exhibit intense fear of even light rain, is not a behavior that can always be expected to be totally resolved, because some degree of fear of intense storms is normal behavior (Crowell-Davis et al. 2003; see also Case 1).

Clomipramine has also been used effectively to treat cataplexy in a dog (Soo-Yeon 2013).

In a study of 24 dogs with various disorders, including OCD, separation anxiety, noise phobia and global fear, the dogs were given clomipramine at a starting dose of 1 to 2 mg kg$^{-1}$ b.i.d. along with instructions for environmental management and behavior modification. As needed, the dose was titrated up to a maximum dose of 4 mg kg$^{-1}$ b.i.d. Some dogs had only one disorder, while others had multiple disorders. Fifteen of the dogs exhibited resolution of the problem or great improvement. Four of the dogs exhibited moderate improvement, while 5 of the dogs showed no improvement. Some of the dogs were able to be successfully weaned off of their medication after the problem was resolved, while others had to be maintained on medication because the problem resumed when medication was withdrawn (Seksel and Lindeman 2001).

#### *Horses*

Clomipramine (2.2 mg kg$^{-1}$ IV) combined with xylazine (0.5 mg kg$^{-1}$ IV) has been used to successfully obtain semen from a stallion that was disabled due to a fracture of the radius (Turner et al. 1995b).

#### *Parrots*

In an open trial of the treatment of feather-picking disorder in various parrot species (five Moluccan cockatoos, one umbrella cockatoo, one sulfur-crested cockatoo, two cockatiels, one yellow-headed Amazon, and one scarlet macaw), birds were titrated over several weeks up to 1.0 mg kg$^{-1}$ daily. The sulfur-crested cockatoo, the yellow-headed Amazon, and the scarlet macaw all exhibited dramatic decreases in feather-picking and/or self-mutilation within the first month of treatment. The two cockatiels and the Moluccan cockatoo had positive personality changes, but the feather-picking did not improve. The other five birds exhibited no response. Three birds exhibited post-treatment regurgitation. Drowsiness

was observed in three birds, and one Moluccan cockatoo exhibited ataxia for one day (Ramsay and Grindlinger 1992). Some birds on clomipramine gain weight (Grindlinger and Ramsay 1991). Later research (see below) suggests that the poor response rate may have been due to the dose being too low.

Seibert et al. (2004) conducted a double-blind, placebo-controlled trial of the treatment of feather-picking disorder in cockatoos. A dose of 3 mg kg$^{-1}$ q12h, suspended in raspberry syrup with 2% carboxymethyl cellulose as a suspending agent, was more effective than placebo, based on the evaluations of both the owner and an avian veterinarian who was blinded to treatment. Species used in this study included Goffin's, umbrella, Moluccan, sulfur-crested, and citron-crested cockatoos. No adverse events were reported.

A Congo African gray parrot with feather-picking and self-injurious behavior responded well to treatment with 9.47 mg kg$^{-1}$ of clomipramine combined with 0.5 mg kg$^{-1}$ buspirone q12h. The initial dose of clomipramine was 4 mg kg$^{-1}$ PO q12h, and the dose was subsequently titrated to effect. At a dose of 18.8 mg kg$^{-1}$ q12h PO the bird became paradoxically fearful and appeared to be hallucinating. It was at this time that buspirone was added to the treatment regimen, with the dose of clomipramine being concurrently titrated downward. Seventeen months after initiation of treatment, the bird was fully feathered except for its wing tips (Juarbe-Diaz 2000).

A blue and gold Macaw treated with clomipramine for three days at a dose of 3.9 mg kg$^{-1}$ q12h presented with extrapyramidal symptoms, included disseminated dystonia, intermittent ataxia, and coarse-muscle tremors. This had been going on for 60 hours when the bird was presented. It was treated with oral and IM diphenhydrame at 2 mg kg$^{-1}$ q12h, and a steadily decreasing dose of clomipramine. Resolution of clinical signs occurred with this treatment (Starkey et al. 2008).

## III. Desipramine

**Chemical Compound:** 5*H*-Dibenz[*bf*]-azepine-5-propanamine, 10,11-dihydro-*N*-methyl-monohydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available in 10-, 25-, 50-, 75-, 100-, and 150-mg tablets.

### Clinical Pharmacology

Desipramine inhibits the reuptake of norepinephrine and serotonin. Desipramine is the opposite of clomipramine in that it has substantially more effect on norepinephrine than on serotonin, and is the most norepinephrine selective of the TCAs. The primary metabolite is 2-hydroxydesipramine. In humans, the half-life is 10–30 hours (Nelson 2004).

Desipramine is rapidly absorbed from the gastrointestinal tract, metabolized in the liver, and, primarily, excreted through the kidneys. In humans, 70% is excreted through the kidneys (Merrell Pharmaceuticals 2000), and the half-life is about 18 hours (Potter et al. 1995).

Desipramine is metabolized by the P450 2D6 cytochrome. Therefore, levels may be elevated in patients concurrently being given drugs that also use this pathway (Merrell Pharmaceuticals 2000).

### Uses in Humans

Desipramine is used in humans to treat depression.

### Contraindications

Desipramine should not be given to patients with a history of sensitivity to TCAs, to patients currently taking MAOIs or within two weeks of taking a MAOI. It should be avoided or used cautiously in patients with cardiovascular disease, a history of urinary retention or glaucoma, thyroid disease, or a seizure disorder (Merrell Pharmaceuticals 2000).

### Side Effects

A variety of side effects have been reported in humans, including adverse cardiovascular

effects, neurologic effects, anticholinergic effects, gastrointestinal effects, endocrine effects, and hematologic effects (Merrell Pharmaceuticals 2000).

The oral $LD_{50}$ in male mice is 290 mg kg$^{-1}$, while in female rats it is 320 mg kg$^{-1}$ (Merrell Pharmaceuticals 2000).

#### Overdose

There is no specific antidote. Decontaminate and provide supportive therapy. Emesis is contraindicated.

#### Effects Documented in Nonhuman Animals

##### *Dogs*

One small trial has been conducted comparing desipramine to clomipramine and placebo for the treatment of compulsive licking behavior in dogs. Desipramine was not as effective as clomipramine and was no more effective than placebo (Rapoport et al. 1992).

Desipramine has also been shown to be effective in the treatment of cataplexy in dogs. However, it is not as effective as nortriptyline for this disorder (Mignot et al. 1993).

## IV. Doxepin

**Chemical Compound:** 1-Propanamine, 3-dibenz [*b,e*]oxepin-11(6H)ylidene-*N*, *N*-dimethyl-, hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10-, 25-, 50-, 75-, 100-, and 150-mg capsules and as a cream containing 50 mg of doxepin per gram of cream.

#### Clinical Pharmacology

Doxepin prevents the reuptake up norepinephrine and serotonin. It also has H1 and H2 receptor-blocking activity, which is believed to be the basis for its antipruritic effect. It undergoes hepatic metabolism into desmethyldoxepin and nordoxepin (GenDerm 1997). In humans, it has a half-life of 8–25 hours (Ziegler et al. 1978; Potter et al. 1995; Nelson 2004). In the dog, it is rapidly absorbed after oral administration with plasma levels peaking in 30–60 minutes, declining thereafter (Hobbs 1969; Kimura et al. 1972). Repeated administration produces higher concentrations than a single dose (Hobbs 1968). Doxepin and some of its metabolites enter various tissues. Initial high levels occur in the kidney, the liver, the spleen, and the lung (Hobbs 1969; Kimura et al. 1972). When doxepin is administered to rabbits, concentrations in the heart range from 40 to 200 times more than occur in the plasma at the same time (Elonen et al. 1975). The active metabolite, desmethyldoxepin, also occurs in appreciable amounts in various tissues (Ribbentrop and Schaumann 1965). Only desmethyldoxepin and doxepin enter the brain (Hobbs 1969; Kimura et al. 1972). Dogs excrete various metabolites, including desmethyldoxepin, doxepin-*N*-oxide, a hydroxydoxepin and its glucuronide, as well as doxepin, in their urine (Hobbs 1969).

Doxepin is marketed as a mixture of geometric isomers. The more active *cis*-isomer comprises 15% of a total doxepin dose while the *trans*-isomer comprises 85% of the dose. In human plasma the ratio of the isomers remains the same (*cis*/*trans* = 15:85) or shifts so that the *cis*-isomer is even less than 15%. The ratio of the isomers of the desmethyldoxepin metabolite change so that they are approximately equal or the proportion of the *cis*-isomer is even greater than the *trans*-isomer. There is wide individual variation (Midha et al. 1992; Yan et al. 1997). In the rat, the metabolites are similar to humans, but in the dog, rabbit, and guinea pig, the percentage of cis-desmethyldoxepin remains proportionately lower than *trans*-desmethyldoxepin, averaging 26% in the dog and 32% in the rabbit and guinea pig (Yan et al. 1997). In horses, the relative composition of the *cis* and *trans* metabolites likewise remain similar to the original ratio (Hagedorn et al. 2001).

In dogs, doxepin and its metabolite, desmethyldoxepin, peak at one to three hours after administration of an oral dose. Approximately 50% of radioactive doxepin is excreted in the urine in this species (Hobbs 1969).

Dogs given 15 mg kg$^{-1}$ daily for 30 days show mild sedation and vomiting, while increased heart rate, miosis, sedation, and twitching occur at a dose of 50 mg kg$^{-1}$ for 30 days. Dogs given 5 mg kg$^{-1}$ daily for a year were almost asymptomatic. Dogs given 25 mg kg$^{-1}$ daily for a year exhibited occasional vomiting. Dogs given 50 mg kg$^{-1}$ daily for a year exhibit ptosis, sedation, tremors, and vomiting (Brogden et al. 1971).

Both the *cis-* and *trans*-isomers of the metabolite desmethyldoxepin are detectable in horses' urine and plasma up to at least 48 hours after an intravenous injection of 1 mg kg$^{-1}$ of doxepin (Hagedorn et al. 2002). When doxepin is given intravenously, the half-life of the more active *cis*-isomer is 3.1 hours, whereas the half-life of the *trans*-isomer is 3.5 hours (Hagedorn et al. 2001).

#### Uses in Humans

Doxepin is recommended for anxiety and depression in humans. Doxepin cream is used as an antipruritic (Drake et al. 1994; Breneman et al. 1997).

#### Contraindications

Doxepin is contraindicated in individuals with a history of sensitivity to doxepin or other TCAs. It should not be given in conjunction with MAOIs or within two weeks of administration of MAOIs.

#### Side Effects

Various side effects related to the CNS, cardiovascular, hematologic, gastrointestinal, and endocrine areas have been observed in humans (Pfizer 1996). Dogs given 10 mg kg$^{-1}$ exhibit some sedative effect (Yan et al. 1997). Rabbits given doxepin by intravenous injection exhibit decreased blood pressure and increased heart rate (Elonen et al. 1974).

In humans, doxepin is considered safe in elderly patients. Reproductive studies conducted in dogs, rats, rabbits, and monkeys have failed to demonstrate adverse effects.

Doxepin is metabolized by the P450 2D6 enzyme system; therefore, levels may be elevated in patients concurrently given other drugs that also use this enzyme system.

Use of the cream may result in stinging or burning sensations or drowsiness (Drake et al. 1994).

Rats given 5, 10, 20, 40, or 80 mg kg$^{-1}$ day$^{-1}$ PO for 180 days exhibited no adverse effects at 5, 10, or 20 mg kg$^{-1}$ day$^{-1}$. At doses of 40 mg kg$^{-1}$ day$^{-1}$ there was decreased weight gain. No changes were observed in hematology, urine analysis, blood chemistries, or food intake (Noguchi et al. 1972b). In rats, males appear to be more susceptible to toxic effects than females (Noguchi et al. 1972a). The oral $LD_{50}$ in the dog is 200 mg kg$^{-1}$ whereas the intravenous $LD_{50}$ is 16 mg kg$^{-1}$ in this species. In mice the oral $LD_{50}$ is 117–178 mg kg$^{-1}$ and the intravenous $LD_{50}$ is 14.6–30 mg kg$^{-1}$. In rats the oral $LD_{50}$ is 114–460 mg kg$^{-1}$ and the intravenous $LD_{50}$ is 12.7–19 mg kg$^{-1}$. In rabbits, the intravenous $LD_{50}$ is 8–14 mg kg$^{-1}$ (Ribbentrop and Schaumann 1965; Noguchi et al. 1972c).

#### Overdose

There is no antidote for doxepin. Decontaminate and provide supportive therapy. Emesis is contraindicated.

#### Effects Documented in Nonhuman Animals

##### *Dogs*

Doxepin centrally and dose-dependently inhibits 2-deoxy-D-glucose-stimulated gastric acid secretion in dogs (Leitold et al. 1984; Shimatani et al. 2001).

##### *Parrots*

Johnson (1987) reported successful use of doxepin in the treatment of destructive preening and mutilation, post-shipment stress, and as a general aid to taming and handling birds.

##### *Horses*

Doxepin is banned in competition horses where it may be used to attempt to calm excited horses. When given at a dose of 1 mg kg$^{-1}$ IV, it can be detected up to at least 48 hours later in both blood and urine. Higher concentrations are present in the

blood than in the urine. It is therefore recommended that blood be used for assaying the presence of doxepin metabolites in competition horses (Hagedorn et al. 2002).

After administration of 1 mg kg$^{-1}$ IV, respiratory rate remains stable, heart rate decreases, and body temperature decreases slightly but returns to normal within five hours. Heart rate also returns to normal within five hours. Within the first hour after injection, horses may appear to be moderately sedated (Hagedorn et al. 2001).

## V. Imipramine

**Chemical Compound:** 5-[3-(Dimethylamino) propyl]-10, 11-dihydro-5-*H*-dibenz [b,f] azepine monohydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 10-, 25-, and 50-mg tablets; 75-, 100-, 125-, and 150-mg capsules; and ampules for intramuscular injection.

### Clinical Pharmacology

Imipramine primarily blocks the reuptake of norepinephrine at adrenergic synapses and, to a lesser degree, blocks the reuptake of serotonin.

When given orally, imipramine is substantially demethylated in the liver during first-pass metabolism, resulting in higher blood levels of desipramine as opposed to the parent molecule. The other active metabolite is norimipramine. When imipramine is injected, the absence of first-pass metabolism results in higher blood levels of imipramine than desipramine (Gram and Christiansen 1975; Dencker et al. 1976; Nagy and Johansson 1977). In humans, it has a half-life of 5–30 hours (Potter et al. 1995; Nelson 2004).

In cattle, imipramine has a terminal elimination half-life of 140 ± 15 minutes. It has extensive peripheral distribution, probably due to high lipid solubility and low plasma binding (Cordel et al. 2001).

Halothane anesthetized dogs given IV imipramine at a dose of 10 mg kg$^{-1}$ over 10 minutes exhibited decreased peripheral vascular resistance, resulting in decreased mean blood pressure. This dose also caused prolonged PR and AH intervals, indicating that imipramine at this dose can inhibit cardiac $Ca^{2+}$ channels. QRS and HV intervals also increased at this dose, indicating that imipramine can inhibit $Na^{+}$ channels (Mitsumori et al. 2010).

MAO-A and MAO-B activity are both inhibited in the brains of the dog, mouse, rat, and monkey in a dose-dependent fashion. In the rat and mouse, imipramine inhibits MAO-B more potently than MAO-A. In the dog and monkey, MAO-B activity is more inhibited than MAO-A activity at low concentrations, while MAO-A activity is more inhibited than MAO-B activity at relatively higher concentrations (Egashira et al. 1999).

### Uses in Humans

Imipramine is used in humans to treat depression and childhood enuresis.

### Contraindications

Imipramine should not be given to patients with a history of sensitivity to imipramine or other TCAs. It should not be given in conjunction with an MAOI or within two weeks of giving an MAOI. In humans, imipramine can cause cardiac arrhythmias. While studies of cardiac function in normal dogs given clomipramine and amitriptyline have revealed that this species does not have the same sensitivity to cardiac effects that humans do, similar studies have not been conducted on the use of imipramine in dogs. It should be avoided in patients with cardiac arrhythmias (Ciba-Geigy 1996).

Imipramine is metabolized by the P450 2D6 cytochrome; therefore, levels may be elevated if drugs that are also metabolized by this pathway are given concurrently.

### Side Effects

Side effects in humans include various cardiovascular problems, anticholergic effects, gastrointestinal effects, and endocrine changes.

In humans, children are known to be more sensitive to overdose than adults. While it is not known if the same sensitivity occurs in other species, imipramine should be used cautiously in juveniles.

When imipramine is given to mice and rats at 2.5 times the maximum human dosage and to the rabbit at up to 25 times the maximum human daily dose, there is no teratogenic effect. There is some evidence of embryotoxic effect, as shown by a reduced litter size, an increase in the stillborn rate, and a reduction in the mean birth weight. Acute oral $LD_{50}$ is 100–215 mg kg$^{-1}$ in the dog and 355–682 mg kg$^{-1}$ in the rat (Ciba-Geigy 1996).

Cattle and horses given 2 mg kg$^{-1}$ may exhibit generalized weakness and ataxia. Hemolysis and discolored urine may also occur (McDonnell et al. 1987; McDonnell and Odian 1994; Cordel et al. 2001).

In guinea pigs, potency for QTC prolongation is 1.7 fold greater with imipramine than with fluvoxamine, an SSRI (Ohtani et al. 2001).

#### Overdose

There is no specific antidote for imipramine. Decontaminate and provide supportive therapy. Emesis is contraindicated.

### Effects Documented in Nonhuman Animals

#### *Cats*

Cats that were known mouse-killers but that had consistently deferred to another cat when competing for access to a mouse, that is, were considered to be "subordinate" by the experimenters, rose in "rank" when injected intramuscularly with 12.5 or 25 mg of imipramine (Zagrodzka et al. 1985).

#### *Dogs*

Imipramine is used for nocturnal enuresis in human children and may be particularly helpful for treatment of fear-based and excitement urination in dogs, although no controlled studies addressing this specific use have been published. Research on dogs has shown that 1 mg kg$^{-1}$ imipramine decreases the responses of the urethra and bladder to pelvic nerve stimulation. It also reduces response of the bladder, but not the urethra, to histamine, and causes some reduction in bladder and urethra responses to acetylcholine and 5-hydroxytryptamine. It is possible that imipramine acts selectively as a local anesthetic agent in the urinary tract of the dog (Creed and Tulloch 1982). Imipramine also causes increased tone of the urethral sphincter of the dog (Khanna et al. 1975; Tulloch and Creed 1979).

A golden retriever given imipramine (1.85 mg kg$^{-1}$ PO q24h) for the treatment of storm phobia initially had no problems. However, after two weeks of treatment, the owner removed the three-month-old tick collar and replaced it with a new one. The collar contained amitraz, a nonspecific MAOI that is commonly used in the treatment of demodicosis and that is present in some collars designed to prevent tick bites. The dog subsequently became lethargic, weak, anorexic, ataxic, and brady-cardic. After the collar was removed, clinical signs resolved within eight hours (Simpson 1997).

Dogs given imipramine intramuscularly at doses ranging from 1.4 to 6.25 mg kg$^{-1}$ exhibit decreased motor activity in open field tests. Improved learning and decreased fear also occurred in some dogs (Zagrodzka et al. 1981).

#### *Horses*

In horses, imipramine commonly induces mild sedation, erection, and masturbation. Intravenous injection of imipramine (2.0 mg kg$^{-1}$), with or without supplemental injection of xylazine (0.3 mg kg$^{-1}$), may be effective in the treatment of ejaculatory dysfunction in stallions (McDonnell et al. 1987; McDonnell and Odian 1994). It can also be given orally as 500–1000 mg added to the grain feed two to four hours before breeding (McDonnell 1999).

Imipramine has also been used to assist in the treatment of urospermia in a stallion with a dysfunctional bladder (Turner et al. 1995a).

Imipramine may be useful for the treatment of narcolepsy in horses. Narcoleptic

horses given a single dose of 4 mg kg$^{-1}$ of imipramine IV exhibited hyperexcitability, muscle fasciculations, hypersalivation, and overreaction to external stimuli. Horses given this dose also exhibited hemolysis. Horses given 2 mg kg$^{-1}$ as a single IV dose had milder adverse reactions (Peck et al. 2001).

#### *Rodents*

Single doses of imipramine have been shown to decrease digging behavior, aggressive behavior, and social investigation in mice, while chronic dosing results in increased social investigation indicative of anxiolytic effects (Gao and Cutler 1994).

## VI. Nortriptyline

**Chemical Compound:** 1-Propanamine, 3-(10, 11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*-methyl-, hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available in 10-, 25-, 50-, and 75-mg capsules.

### Clinical Pharmacology

Nortriptyline is antihistaminic and blocks the reuptake of serotonin and norepinephrine. In humans, it has a half-life of 20–55 hours (Nelson 2004).

Nortriptyline is excreted in the milk. In rabbits given carbon-14-labeled nortriptyline, the concentration of radioactivity in the milk is equivalent to concentrations in the serum. Concentrations of radioactivity in neonates consuming the milk are substantially lower than concentrations in the equivalent organs in the mother (Aaes-Jørgensen and Jørgensen 1977).

### Uses in Humans

Nortriptyline is used to treat depression in humans.

### Contraindications

Nortriptyline is contraindicated in patients with a history of sensitivity to nortriptyline or other TCAs. It should not be used concurrently with MAOIs or within two weeks of using an MAOI.

Nortriptyline is metabolized by the P450 2D6 cytochrome system. Therefore, concurrent administration of nortriptyline with other drugs metabolized by this system may result in increased blood levels (Sandoz Pharmaceuticals 1996).

### Side Effects

Side effects reported in humans have included various cardiovascular, neurologic, anticholinergic, gastrointestinal, and endocrine effects.

Rabbits given nortriptyline by intravenous injection exhibit decreased blood pressure and increased heart rate (Elonen et al. 1974).

### Overdose

There is no specific antidote for nortriptyline. Decontaminate and provide supportive therapy. Emesis is contraindicated.

### Effects Documented in Nonhuman Animals

#### *Dogs*

Nortriptyline is one of the most effective drugs in the treatment of cataplexy in dogs (Mignot et al. 1993). A study of the effects of nortriptyline on the QT interval, conducted on Beagles, concluded that it is unlikely that nortriptyline has an effect on the ventricular repolarization process when used at therapeutic doses (Jeon et al. 2011).

## Important Information for Owners of Pets Being Placed on any TCA

The following should be considered when placing an animal on a TCA.

1) It is essential that owners inform their veterinarian of all other medication, herbal supplements, and nutritional supplements they are giving their pet because some of these may interact with the medication.

2) While their pet may respond within a few days, it may be a month before their pet begins responding.
3) If their pet exhibits mild sedation in the beginning, they will probably return to normal levels of activity in two or three weeks as their body adjusts to the medication.
4) If their pet should experience any adverse events such as vomiting, diarrhea, or seizures, they should contact their veterinarian immediately.
5) With the exception of Clomicalm being used in combination with behavior modification for the treatment of separation anxiety in dogs, all use of the medication for nonhuman animals is extra-label use. This does not mean that the drug is not indicated for the problem. It means that the extensive testing required by the FDA for on-label usage of the drug for their particular species of pet and their particular pet's problem has not been conducted, or, if in progress, been completed. Exceptions to this may occur after the publication of this book if the FDA subsequently approves any of the TCAs for treatment of various behavior problems in domestic animals or approves Clomicalm for uses other than separation anxiety in dogs.

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# 17

# Opioids and Opioid Antagonists

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## Action

Opioids and opioid antagonists are a heterogenic group of pharmaceuticals, included in this textbook due to the clinical use of some drugs for particular mental conditions. Narcotic antagonists can be effective in the treatment of stereotypies and compulsive disorders in nonhuman animals. One possibility is that stress, such as an overstimulating or understimulating environment, causes an animal to initiate stereotypic behavior. Carrying out the stereotypic behavior then causes the release of endogenous endorphins, which reinforce the behavior. Narcotic antagonists would block this release of the endogenous endorphins, thereby blocking the reinforcement. This would result in the animal discontinuing the behavior. However, studies confirming this theory are lacking in veterinary medicine. An alternative hypothesis is that opioids are directly involved in the initiation of the stereotypic behavior. The narcotic antagonists then block the opioids, thereby preventing their inducing stereotypic behavior. This hypothesis is supported by the rapid clinical response that occurs when opioid antagonists are administered. Opioids do enhance amphetamine-induced stereotypic behavior, and naloxone blocks this enhancement.

While both morphine ($0.1–0.5\,mg\,kg^{-1}$) and oxymorphone ($0.125–0.50\,mg\,kg^{-1}$) have been reported as alleviating the crying of separation distress in puppies, they also decreased motor activity, indicating sedation (Panksepp et al. 1978). Timid beagle/telomian hybrids have also been treated with morphine at $0.25\,mg\,kg^{-1}$. While they did show some improvement with the combination of morphine and behavior modification, they also became less socially solicitous than placebo-treated dogs, possibly as a consequence of the sedative effects (Panksepp et al. 1983). Morphine has also been shown to decrease a variety of aggression types in laboratory animals (Gianutsos and Lal 1978). Nevertheless, these medications are not recommended for these or other problems, which are best treated with safer medications that can be used in the long term in association with behavior therapy.

## Overview of Indications

Indications of opiate antagonists include stereotypic behavior, obsessive-compulsive disorder, including lick granulomas and tail-chasing in dogs, and self-mutilation and cribbing in horses. Opiate antagonists have been found to be beneficial in the treatment of some

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forms of self-injurious behavior in humans as well as nonhuman animals (Richardson and Zaleski 1983; Herman et al. 1987; Smith and Pittelkow 1989; Sandman et al. 1990).

## Contraindications, Side Effects, and Adverse Events

Gastrointestinal effects, especially diarrhea, may occur with the use of opioid antagonists.

## Clinical Guidelines

While opioid antagonists have shown substantial promise in the treatment of stereotypic behaviors in multiple species, their use is not yet widespread for a number of reasons. Some can only be given parenterally and all are expensive. Also, opioid antagonists may be more effective in the early phases of obsessive-compulsive disorder, though this phenomenon has not been studied across all species and all manifestations of compulsive behaviors. Nevertheless, dramatic results in some cases make them a class of drugs that should be considered in the treatment of any stereotypic behavior, especially if the patient's safety is at stake.

Diprenorphine, which is not reviewed below, has been used in the treatment of cribbing in horses (Dodman et al. 1987). Cribbing is a behavior that occurs in horses kept in confinement. During cribbing, the horse grabs a horizontal object with its teeth, bites down hard, and flexes its neck. It may or may not swallow air as it does this. Diprenorphine was twice administered to a horse with a problem with cribbing behavior, once at 0.02 mg kg$^{-1}$ and the second time at 0.03 mg kg$^{-1}$ intramuscularly (IM). In both cases, after a latency period of 30 minutes, injection of diprenorphine resulted in almost total discontinuation of cribbing for periods of 3–5.5 hours. Animal doses are given in Table 17.1.

## Specific Medications

### I. Nalmefene

**Chemical Compound:** 17-(Cyclopropylmethyl)-4,5 $\alpha$-epoxy-6-methylenemorphinan-4,14-diol, hydrochloride salt

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 1-ml ampules containing 100 µg ml$^{-1}$ and 2-ml ampules containing 1 mg ml$^{-1}$ of a sterile solution suitable for intravenous, intramuscular, and subcutaneous administration (Baker Norton Pharmaceuticals, Inc. 1997).

#### Clinical Pharmacology

Nalmefene reverses and prevents the effects of opioids, including respiratory depression, sedation, and hypotension. It has a longer

Table 17.1 Doses of various opiate antagonists inhibitors for dogs, cats, horses, and parrots.

| Opiate antagonist | Cat | Dog | Parrot | Horse |
|---|---|---|---|---|
| Naltrexone | 25–50 mg cat$^{-1}$ q24h | 1–2.2 mg kg$^{-1}$ q12–24 h | 1.5 mg kg$^{-1}$ q12h | 0.7 mg kg$^{-1}$ q24h |
| Naloxone | | 0.01 mg kg$^{-1}$ SC as a test dose | | |
| Pentazocine | | 2.5 mg kg$^{-1}$ q12h | | |

All doses for naltrexone are oral.
*Source:* Brown et al. (1987a); Turner (1993); Overall (1997); Nurnberg et al. (1997).

duration of action than naloxone. It is equally bioavailable if given by intravenous, intramuscular, or subcutaneous routes. Peak levels are reached within minutes if it is given intravenously. However, there is a delay to maximum plasma concentration if it is given subcutaneously (about 1.5 hours in humans) or intramuscularly (about 2.3 hours in humans). If nalmefene is given parenterally, it blocks 80% of brain opioid receptors within five minutes (Baker Norton Pharmaceuticals, Inc. 1997).

Nalmefene is primarily metabolized by glucuronide conjugation, which occurs in the liver, after which the metabolites are excreted in the urine. Less than 5% of the urinary excretion is the parent compound. Fecal excretion accounts for only 17% of a nalmefene dose (Baker Norton Pharmaceuticals 1997).

The pharmacokinetics of nalmefene have been studied in three mixed-breed dogs given 0.5–0.9 $mg\,kg^{-1}$ IV. Elimination half-life was 120–218 minutes (Dodman et al. 1988b).

In the horse, nalmefene has a half-life of three to five hours following intramuscular injection of 1 $mg\,kg^{-1}$. With intravenous injection the half-life is only 50 minutes. After oral administration of 2 $mg\,kg^{-1}$, no intact nalmefene is detectable in the plasma. High levels of nalmefene glucuronide appear rapidly after oral administration and are detectable for up to 16 hours. In this species, therefore, nalmefene must be administered parenterally, as it has poor oral bioavailability with extensive first-pass metabolism (Dixon et al. 1992).

### Uses in Humans

Nalmefene is used in humans for reversal of the effects of opioid medications. It has also been used to treat pathological gambling (Grant et al. 2006).

### Contraindications

Nalmefene is contraindicated in patients with a known history of intolerance to the medication. In humans with hepatic or renal disease, there is a decrease in plasma clearance (Baker Norton Pharmaceuticals 1997).

### Side Effects

Side effects have not been reported in non-addicted animals given clinically relevant doses.

Administration of up to 1200 $mg\,m^{-2}\,day^{-1}$ to rats has not resulted in any decrease in fertility, reproductive performance or offspring survival. Giving up to 2400 $mg\,m^{-2}\,day^{-1}$ orally to rats or up to 96 $mg\,m^{-2}\,day^{-1}$ intravenously to rabbits did not result in any harm to the fetuses. Administration of up to 205 $mg\,m^{-2}\,day^{-1}$ in rat pups did not cause any adverse events (Baker Norton Pharmaceuticals 1997).

### Other Information

Nalmefene has been administered to humans after administration of benzodiazepines with no adverse interactions (Baker Norton Pharmaceuticals 1997).

### Effects Documented in Nonhuman Animals

#### *Dogs*

Dodman et al. (1988b) studied the use of various narcotic antagonists for the treatment of stereotypic self-licking, self-chewing, and scratching in nine dogs. Nalmefene was injected subcutaneously (SC) at a dose of 1–4 $mg\,kg^{-1}$ after a baseline rate of self-licking, self-chewing, and scratching was measured. During the 90-minute period following the injection, the amount of time spent in these behaviors was significantly reduced in six of the nine dogs. The problem behaviors were completely suppressed for 75 minutes in two dogs. No side effects were reported.

#### *Horses*

Dodman et al. (1987) treated five crib-biting horses with nalmefene across 20 trials by a variety of routes, specifically intramuscularly (IM), subcutaneously, intravenously via continuous infusion and via a sustained

release implant. Doses for the IM and SC injections ranged from 0.08 to 0.1 mg kg$^{-1}$. A single injection resulted in discontinuation of cribbing for 2.75–13 hours. The sustained release preparations resulted in a substantial decrease in cribbing for a minimum of two days.

Dodman et al. (1988a) reported a case study of a 500-kg Arabian stallion with a four-year history of self-mutilation, specifically biting the flank and pectoral region. The stallion was treated, on successive days, with doses of 0.2 mg kg$^{-1}$, 0.4 mg kg$^{-1}$, 0.8 mg kg$^{-1}$, and 1.6 mg kg$^{-1}$ given IM as a single dose. There was a dose-specific decrease in acts of self-mutilation or attempted self-mutilation during the four hours following the injection, with a 94% decrease at the highest dose. While this result seems promising, the authors report that, in preliminary pharmacokinetic studies, horses excrete nalmefene rapidly and the bioavailability of nalmefene given to horses is low.

## II. Naloxone HCl

**Chemical Compound:** (–)-17-Allyl-4,5a-epoxy-3, 14-dihydroxy morphinan-6-one-hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as a 0.02 mg, 0.4 mg or 1 mg ml$^{-1}$ solution for subcutaneous, intramuscular, or intravenous injection.

### Clinical Pharmacology

Naloxone is a pure opioid antagonist. As such, it prevents or reverses the effects of opioids, such as respiratory depression, hypotension, and sedation. Product literature for humans states that in the absence of opioids or opioid agonists, it exhibits essentially no pharmacological activity. However, it is precisely because of its efficacy in some animals exhibiting stereotypic behavior that it is used in clinical behavioral medicine (as opposed to veterinary behavior). It does not produce dependence or tolerance. The mechanism of action is not fully understood, but it appears to act by competing with opioids for receptor sites (Endo Pharmaceuticals 2001).

Naloxone undergoes glucuronide conjugation in the liver and is excreted in the urine. In human adults, the serum half-life is 30–81 minutes (Endo Pharmaceuticals 2001).

### Uses in Humans

In humans, naloxone is used for reversal of opioid depression, including respiratory depression. It is also used as an adjunctive agent in the management of septic shock, in which situation it facilitates the raising of blood pressure (Endo Pharmaceuticals 2001).

### Contraindications

Naloxone is contraindicated in patients with a known sensitivity to it. It should be used with caution in patients with preexisting cardiac disease (Endo Pharmaceuticals 2001).

### Side Effects

Some decrease in activity has been observed in cats (see below). Studies of reproduction in mice and rats given high doses of naloxone have not resulted in any impairment of reproduction or teratogenicity (Endo Pharmaceuticals 2001).

Chemical impurities in naloxone, specifically noroxymorphone and bisnaloxone, may produce emesis in dogs when administered intravenously at high doses (Endo Pharmaceuticals 2001).

The intravenous $LD_{50}$ (the lethal dose that kills 50% of the animals tested) is 150 mg kg$^{-1}$ in rats and 109 mg kg$^{-1}$ in mice. Subcutaneous injection of 100 mg kg$^{-1}$ day$^{-1}$ for three weeks produces transiently increased salivation and partial ptosis. No side effects were observed at 10 mg kg$^{-1}$ day$^{-1}$ for three weeks.

### Overdose

Treat an overdose symptomatically and monitor.

#### Doses in Nonhuman Animals

Because it is injected and short-acting, naloxone is not a practical medication for maintenance treatment of stereotypic behaviors or obsessive-compulsive disorders. It is best used as a tool for testing whether or not opioid antagonists are likely to be effective in the treatment of a given patient. In this capacity, they can be very useful. The patient should be checked into the hospital and monitored to determine a baseline for exhibition of the stereotypic behavior and to allow the patient time to acclimate to the hospital environment. Naloxone is then injected at a time when the patient can be closely monitored for at least the next two hours, and preferably longer.

In the first case, one of the authors (Crowell-Davis) was involved in treating the patient, a dog, which chased its tail incessantly to the point of exhaustion. It was covered with bruises and lacerations from running into walls. It would not eat or drink unless it was physically restrained and its head was held still in a food or water bowl. When naloxone was injected, it began exploring its environment, interacting with students and clinicians, and voluntarily eating and drinking for the first time since presentation to the hospital (see Brown et al. 1987a, 1987b for further information).

#### Discontinuation

Since only a few doses should be given to test the patient's response to an opioid antagonist, discontinuation is not an issue.

#### Effects Documented in Nonhuman Animals

##### *Cats*

Cats given 0.4 mg kg$^{-1}$ of naloxone IV are somewhat less active than when not given naloxone, but exhibit no cardiac changes (Waldrop et al. 1987).

##### *Dogs*

In a case of severe compulsive tail-chasing in a 20-kg Bull terrier, Brown et al. (1987a, 1987b) gave 0.2 mg (0.01 mg kg$^{-1}$) of naloxone SC. This resulted in nearly complete cessation of the tail-chasing behavior within 20 minutes. The effect lasted about three hours. This dose was repeated multiple times over the next two days with the same effect. The patient was sent home on an oral, mixed narcotic agonist–antagonist combination of pentazocine (50 mg, see below) and naloxone (0.5 mg) given b.i.d. The pentazocine/naloxone combination was readily administered by the owners and resulted in a low rate of compulsive tail-chasing in the home environment. Eventually, the dog was weaned off the pentazocine/naloxone combination and maintained fairly normal behavior. It continued to chase its tail during periods of intense excitement, but was otherwise a normal pet.

##### *Horses*

Dodman et al. (1987) gave naloxone to one cribbing horse in a series of three trials at 0.02 mg kg$^{-1}$, 0.03 mg kg$^{-1}$, and 0.04 mg kg$^{-1}$ IV. After a 12- to 23-minute latent period, crib-biting stopped for an average of 20 minutes.

##### *Pigs*

Sows injected with naloxone, 0.64–1.0 mg kg$^{-1}$, exhibit a 57% decrease in the amount of time spent in stereotypic behaviors such as sham chewing, chain chewing, and tether chain chewing. The decrease begins about 10–15 minutes after injection and lasts two to three hours (Cronin et al. 1985, 1986).

## III. Naltrexone Hydrochloride

**Chemical Compound:** 17-(Cyclopropylmethyl)-4,5$\alpha$-epoxy-3, 14-dihydroxymorphine-6-one hydrochloride

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available in 50-mg, scored tablets.

#### Clinical Pharmacology

Naltrexone hydrochloride is an opioid antagonist, with no opioid agonist properties, that acts by competitive binding. It does not

produce tolerance or dependence. It is well absorbed orally, after which it undergoes extensive first-pass metabolism. In humans, oral bioavailability ranges from 5% to 40%. Both the parent drug and one of the metabolites, 6- β-naltrexol, are active, with peak plasma levels of both occurring about one hour after oral dosing. Most of a dose is excreted as various metabolites, primarily by the kidney. Very little fecal excretion occurs. In humans, the half-life for naltrexone is four hours and for 6- β-naltrexol is 13 hours. While hepatic metabolism occurs, there are also extrahepatic sites of metabolism (Mallinckrodt Inc. 2002).

Its pharmacological efficacy in humans is 24–74 hours, depending on the dose (Mallinckrodt Inc. 2002).

#### Uses in Humans

Naltrexone is used in the treatment of alcoholism, opioid addiction, and impulse control disorders (Raymond et al. 2002; Grant et al. 2009).

#### Contraindications

A history of sensitivity to naltrexone, liver failure, kidney failure.

#### Side Effects

Pupillary constriction may occur. The mechanism for this effect is not known (Mallinckrodt Inc. 2002).

Naltrexone can cause hepatocellular injury when given in overdose. In humans, the apparently safe dose of naltrexone and the dose causing hepatic injury is only a fivefold increase. Five of 26 human patients given 300 $mg\,day^{-1}$ exhibited elevated ALT after three to eight weeks of treatment (Mallinckrodt Inc. 2002). This ratio is unknown in dogs, cats, and other veterinary patients.

One case has been reported of naltrexone-induced pruritus in a dog that was being given naltrexone at 1 $mg\,kg^{-1}$ q6h, which is at the high end of the normal clinical dose range (Schwartz 1993). Another dog being medicated with naltrexone at 2.2 $mg\,kg^{-1}$ q24h exhibited drowsiness. This side effect resolved after withdrawal of the medication for 48 hours (White 1990).

Rats given 100 $mg\,kg^{-1}\,day^{-1}$ of naltrexone over two years had a slightly increased incidence of mesotheliomas in males and of vascular tumors in both males and females. A dose of 100 $mg\,kg^{-1}\,day^{-1}$ results in an increase in pseudopregnancy and a decrease in true pregnancy in the rat. Male fertility is unaffected at this dose. Naltrexone is both embryocidal and fetotoxic in rats and rabbits when given at doses of 30 $mg\,kg^{-1}\,day^{-1}$ (rats) or 60 $mg\,kg^{-1}\,day^{-1}$ (rabbits). However, there is no evidence of teratogenicity when pregnant rabbits and rats are given doses of up to 200 $mg\,kg^{-1}\,day^{-1}$ during the period of organogenesis (Mallinckrodt Inc. 2002).

In the mouse, rat, and guinea pig, the oral $LD_{50}$ for each is 1100 $mg\,kg^{-1}$, 1450 $mg\,kg^{-1}$, and 1490 $mg\,kg^{-1}$, respectively. In the mouse, rat, and dog, death occurs due to clonic–tonic convulsions and/or respiratory failure when given large doses in acute toxicity studies. In one study, humans given 800 mg daily for up to one week did not exhibit toxicity (Mallinckrodt Inc. 2002).

#### Overdose

Treat an overdose of naltrexone symptomatically and monitor the situation.

#### Discontinuation

Patients that have been maintained on naltrexone for treatment of severe stereotypic behavior should undergo gradual discontinuation.

#### Other Information

The liver function of patients that are maintained on naltrexone for the treatment of stereotypic behavior problems should be monitored regularly.

#### Uses Documented in Nonhuman Animals

##### *Dogs*

Seven of 11 dogs with acral lick dermatitis that were treated with naltrexone, 2.2 $mg\,kg^{-1}$ q12–24 h, responded positively to treatment.

When naltrexone was discontinued, all responders relapsed after durations of time ranging from one week to three years. Five of these dogs again responded to naltrexone treatment. The other two were euthanized due to unrelated health problems (White 1990).

Dodman et al. (1988b) gave naltrexone, 1 mg kg$^{-1}$ SC, to two dogs with stereotypic self-licking, self-chewing, and scratching behavior. Both showed a significant reduction in these behaviors for at least 90 minutes after the injection. No side effects were reported.

Intense pruritus has occurred in one dog given a dose of 1 mg kg$^{-1}$ q6h (Schwartz 1993).

#### *Horses*

Dodman et al. (1988a) gave naltrexone to three horses with crib-biting behavior at a dose of 0.04–0.4 mg kg$^{-1}$ IV. After a brief latent period, crib-biting was substantially decreased or completely suppressed for 1.5–7 hours. One horse was subsequently implanted with a pellet of 0.6 g of naltrexone. Its crib-biting was substantially decreased for two days, with occasional breakthroughs.

A 10-year-old thoroughbred mare with a five-year history of weaving exhibited a 30% reduction in weaving behavior when given naltrexone at 0.7 mg kg$^{-1}$ day$^{-1}$ PO. Specifically, weaving decreased from 43.5 min$^{-1}$ to 32.3 min$^{-1}$ (Nurnberg et al. 1997).

#### *Parrots*

Turner (1993) treated 41 birds with feather-picking with naltrexone, 1.5 mg kg$^{-1}$ b.i.d. A solution was created by dissolving a 50-mg tablet of naltrexone, which is highly soluble in water, in 10 ml of sterile water. The species treated were, specifically, 2 eclectus, 6 African gray, 1 cockatiel, 7 Amazons (1 orange wing, 3 yellow nape, 1 red-lored, 1 blue front, and 1 double), 9 macaws (2 hyacinth, 1 scarlet, 4 blue/gold, 1 green wing, and 1 Catalina) and 16 cockatoos (4 umbrellas, 1 rosebreast, 6 Moluccan, 2 citron, and 3 lesser sulfur). Treatment duration ranged from one to six months. Thirty-five of the 41 birds responded positively to treatment. However, relapse often occurred within a few months. Pre- and posttreatment blood panels did not identify any changes. Undesirable behavioral effects were not induced.

#### *Pigs*

Naltrexone, at a dose of 1.0–1.3 mg kg$^{-1}$ IM, partially blocks the relaxation response in pigs (Grandin et al. 1989).

#### *Other Species*

Turner (1993) reported remission of a tail wound in a cougar that was maintained by self-mutilation when the cougar was treated with naltrexone, but did not report the dose. The cougar was monitored for a subsequent two years, with no relapse.

Kenny (1994) used naltrexone to treat a variety of psychogenically induced dermatoses in zoo animals, as follows, with variable efficacy.

A 36-kg Amur leopard (*Panthera pardus orientalis*) that was pulling hair out of the dorsal part of its tail and back was initially treated with prednisone, 20 mg PO 124 h. After an initial small improvement, the behavior worsened, and naltrexone was added to the treatment at 25 mg (1.4 mg kg$^{-1}$) PO q24h. After one week, no adverse effects had been noted, so the dose was increased to 50 mg (2.8 mg kg$^{-1}$) q24h. The prednisone dose was gradually reduced and discontinued. Relapses occurred after a loud concert was held close to the hospital and subsequent to the keeper discovering the leopard removing the naltrexone tablets from its meat. The tablets were thereafter crushed and mixed into the meat. Total remission of the hair-pulling occurred after this protocol, and the leopard was subsequently maintained on 50 mg of naltrexone daily (Kenny 1994).

A clouded leopard (*Panthera nebulosa*) that was excessively grooming the medial surface of her thighs was treated with prednisone, 25 mg PO q12h for five days, after which the prednisone was discontinued. The behavior relapsed and the leopard was

treated with prednisone seven times over the following three years. When the leopard was immobilized for examination, she was found to have a subacute to chronic ulcerative pyogranulomatous dermatitis. She was initially treated with 1.6 mg kg$^{-1}$ naltrexone, q24h. When she was immobilized three months later, the lesions were completely resolved. There were no changes in values for alanine transaminase before and after treatment. The dose of naltrexone was then decreased to 0.8 mg kg$^{-1}$, resulting in recurrence of the problem. Returning to the higher dose did not result in improvement until prednisone (40 mg, q24h) was added. Once the prednisone was discontinued, she was maintained on 1.6 mg kg$^{-1}$ without further relapse (Kenny 1994).

A tricolored squirrel (*Callosciuis prevostii*) had repeated episodes of self-mutilation that responded to treatment with glucocorticoid. Skin scrapings and fungal cultures taken after immobilization were unremarkable. The squirrel was treated with naltrexone at 1.0 mg kg$^{-1}$ q24h, which resulted in resolution of the problem. Serum transaminase levels were not notably different before and after six weeks and 10 weeks of treatment (Kenny 1994).

An Arctic wolf (*Canis lupus hudsonicus*) with repeat episodes of acute moist dermatitis did not respond to treatment with 1.0 mg kg$^{-1}$ PO of naltrexone given q24h. This problem responded only to high doses of glucocorticoids. No adverse events were reported from the treatment attempt with naltrexone (Kenny 1994).

A polar bear (*Ursus maritimus*) mutilated its perineum by rubbing it on concrete as part of ritualized pacing behavior. Treatment with 1.2 mg kg$^{-1}$ q24h had no beneficial effect and treatment was discontinued after one month (Kenny 1994). No adverse events were reported.

Naltrexone has also been used to treat macaques with self-injurious behaviors. In a study to assess the efficacy of extended-release naltrexone in the pharmacologic treatment of self-injurious behavior (SIB) in rhesus macaques (*Macaca mulatta*), Kempf et al. (2012) showed that both the frequency and the percentage of time spent displaying SIB decreased during the treatment phase, and the percentage of time remained decreased during the post-treatment phase. The authors did not report any side effects of treatment for the time of the study. Lee et al. (2015) demonstrated that innate immune activation of astrocytes (which was increased in rhesus macaques with SIB in the study) was markedly decreased in animals receiving naltrexone, as was atrophy of both gray and white matter astrocytes. These findings were concomitant with a decrease in SIB.

## IV. Pentazocine

**Chemical Compound:** 1,2,3,4,5,6-Hexahydro-6, 11–dimethyl-3-3(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride

**DEA Classification:** DEA Schedule IV controlled substance

**Preparations:** Generally available as a tablet containing 50 mg of pentazocine and 0.5 mg of naloxone (see naloxone).

### Clinical Pharmacology

Pentazocine is an analgesic with some opiate antagonistic effects. The naloxone is combined with pentazocine in this medication because at the dose of 0.5 mg it antagonizes both pentazocine and various narcotics; misuse of pentazocine by grinding the tablets up and injecting them as a solution is effectively prevented. Naloxone at this dose does not counteract pentazocine when given orally (Synofi-Synthelabo, Inc. 1999).

In humans, onset of analgesia typically occurs 15–30 minutes after oral administration (Synofi-Synthelabo, Inc. 1999).

### Uses in Humans

For humans, pentazocine is for oral use only for cases of moderate to severe pain.

### Contraindications

Do not give pentazocine to patients with a history of sensitivity to either naloxone or

pentazocine. Use with caution in patients with renal or liver disease.

#### Side Effects

Seizures may occur in patients with a history of seizures, though the mechanism for this is not known. Various side effects include cardiovascular (e.g. hypotension, tachycardia, syncope), respiratory (respiratory depression), central nervous system (e.g. hallucinations, disorientation, sedation, weakness), gastrointestinal (e.g. emesis, constipation, diarrhea), and decreased white blood cell count (Synofi-Synthelabo, Inc. 1999).

#### Overdose

In case of overdose, provide supportive therapy and monitor. If respiratory depression occurs, administer naloxone, a specific antagonist.

#### Discontinuation

Discontinue pentazocine by gradual tapering of dose.

#### Other Information

Pure opiate antagonists, such as naltrexone, should be the first drug of choice for treatment of pets with stereotypic behavior problems that exhibit a positive response to a naloxone trial. Cost may be a prohibitive factor. The use of pentazocine may be considered after consideration of the potential for human abuse, the risk of side effects, and the fact that pentazocine is not a pure opiate antagonist. While pentazocine has been shown to be effective in at least some cases of stereotypic behaviors, trials comparing the relative efficacy of pentazocine with various pure opiate agonists have not been conducted.

#### Effects Documented in Nonhuman Animals

##### *Dogs*

A dog with severe compulsive tail-chasing responded well to a test treatment with naloxone given subcutaneously (Brown et al. 1987a, 1987b). It was subsequently successfully treated at home with Talwin, at a combination of 50 mg pentazocine and 0.5 mg naloxone given orally b.i.d. The medication was eventually discontinued, and the dog remained relatively normal, exhibiting tail-chasing only during periods of intense excitement.

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# 18

# Hormones

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## Introduction

While progestins were used to treat behavior problems in the 1970s and 1980s, they fell out of favor as better, safer medications became available. Recent research into the use of oxytocin for social anxiety and autism in humans (e.g. Kanat et al. 2017; Procyshin et al. 2017) has led to the beginnings of attempts to identify their potential for treating various behavior disorders in domestic animals.

Historically, studies of oxytocin have focused on its relevance in reproduction and birth. Research conducted in the last several years has identified oxytocin as being critical to prosocial and co-operative behavior in many species (see Romero et al. 2016 for a review). Oxytocin has been found to be important in the positive psychosocial and psychophysiological changes that occur during a variety of human-animal interactions (see Beetz et al. 2012 for a review).

In the dog, an oxytocin-gaze positive loop has been identified, with oxytocin levels increasing in both human and dog when they gaze at each other (Fiset and Plourde 2015; Nagasawa et al. 2015). This loop has been hypothesized to be important in the coevolution of the human-dog social bond (Buttner 2016; Kekecs et al. 2016). Being sprayed with oxytocin has been shown to increase prosocial behaviors toward both conspecifics and human partners (Romero et al. 2014). Furthermore, oxytocin has been identified as having an effect on dog's responses to specific human behaviors and human-related stimuli (e.g. Hernádi et al. 2015; Kis et al. 2015; Oliva et al. 2015a, 2015b; Kovács et al. 2016a; Kovács et al. 2016b; Macchitella et al. 2017). With generations of selective breeding, humans have modified the distribution of oxytocin receptor gene polymorphisms in different breeds (Kis et al. 2014; Kis et al. 2017). For example, Border Collies, which have been bred for cooperative work with each other and with humans, are more responsive to the intranasal administration of oxytocin than are Siberian Huskies, which have been bred to work more independently (Kovács et al. 2016a, 2016b). One study speculates on its possible use in the treatment of separation anxiety, but emphasizes that careful study must be done to identify the stage of behavior modification at which the use of oxytocin might be beneficial (Thielke and Udell 2017). However, to the author's knowledge, no case reports or clinical studies have been published on the use of oxytocin for any kind of anxiety disorders in dogs.

Less research has been conducted on the effect of oxytocin on cats than on dogs. In one study in which the temperament of cats was assessed via owner questionnaire and

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their oxytocin receptor genes were analyzed, it was found that, among neutered females, cats with the A allele in the single nucleotide polymorphism G738A had higher scores for "roughness," than cats without the A allele. While extensive further study is needed, in purebred cat breeding it may be that selecting for specific types of oxytocin receptor genes will facilitate selection of optimal temperaments (Arahori et al. 2016).

## Oxytocin

**Chemical Compound:** Oxytocin is a neuropeptide with the chemical formula $C_{43}H_{66}N_{12}O_{12}S_2$

**DEA Classification:** Not a controlled substance

**Preparations:** Available for intravenous (IV) or intramuscular (IM) injection at a concentration of 10 IU $ml^{-1}$. It is also available over the counter (OTC) in various nasal sprays, usually advertised as having 10 IU per spray. These sprays may or may not contain other molecules. There is currently no universal standard for verifying quantity and dose in each spray.

### Clinical Pharmacology

Oxytocin stimulates contraction of the smooth muscle of the uterus.

### Indications

Intercat aggression and anxiety disorders.

### Side Effects

No studies have been conducted on the carcinogenicity or toxicity of oxytocin in humans or animals.

### Doses in Nonhuman Animals

Cats: 2–8 international units (IU) per cat daily; dogs: 10–40 IU per dog daily (Stephanie Borns-Weil, pers. comm.).

### Effects Documented in Nonhuman Animals

A compounded formulation of 40 units/mL of oxytocin that is administered transmucosally via the buccal pouch appears to have facilitated resolution of multiple cases of intercat aggression (Stephanie Borns-Weil, pers. comm.).

## Progestins

This section is included for completeness and historical reference, rather than because progestins are recommended for the treatment of behavior problems in nonhuman animals. Progesterone and its metabolites act in various parts of the body (e.g. brain, smooth muscle, uterus, sperm, oocyte) through multiple mechanisms of action (Mahesh et al. 1996). Therefore, progesterone's effects are not discrete and specific, but instead are widespread and varied. A variety of side effects, including polydypsia, polyuria, polyphagia, weight gain, sedation, overproduction of growth hormone, suppression of the hypothalamic–pituitary-adrenocortical axis, insulin resistance, and cancer, make their use for the treatment of behavior problems very risky for the patient. Behavioral effects are attributable to both an antiandrogenic effect and a calming effect on the limbic system (Henik et al. 1985).

The use of a hormone, methyloestrenolone, which is not currently available commercially, in the treatment of behavior problems of dogs and cats was first reported in 1964 (Gerber and Sulman 1964). It was found that, in bitches and queens, estrus could be postponed or prevented and pseudopregnancy could be terminated with this medication. In male cats, roaming and urine marking were also reported as being effectively treated, as were roaming, urine marking, and mounting in male dogs.

### Action

The progestins have a variety of actions. They inhibit the secretion of pituitary gonadotropin,

suppress the production of testosterone, alter the binding of transcription factor to DNA, alter membrane fluidity, act on the $GABA_A$ receptors to produce effects similar to those caused by benzodiazepines, and possibly increase the levels of β-endorphin and met-enkephalin in the hippocampus. There are various mechanisms of action, including an intracellular receptor-mediated mechanism, a steroid action involving phospholipid layers, a steroid action mediated by second messenger systems, a steroid action exerted at the cell membrane, and steroid effects initiated by interaction with the GABA receptors and ligand insertion (Mahesh et al. 1996).

## Overview of Indications

In-depth discussion of the use of progestins to modify reproductive status is beyond the scope of this book and is covered elsewhere, for example, Evans and Jemmett (1978). Progestins can be useful in cases of excessive sexual behavior, aggression in dogs and cats, urine marking, persistent mounting by neutered males, excess vocalization in neutered male cats responding to estrous queens, and human-directed sexual aggression in cats. More generally, progestins can be effective in suppressing behaviors that are more predominant in males than in females (Hart 1979c; Hart and Eckstein 1998). These effects occur even with castrated males.

In an early report on 50 cats treated with either medroxyprogesterone acetate (MPA) or megestrol acetate (MA), Hart (1979a) reported that about one-third of 31 spraying cats improved to the client's satisfaction. Two of 11 cats with inappropriate urination resolved, and five of eight aggressive cats showed improvement.

Pemberton (1980, 1983) subsequently reported that progestins were effective in the treatment of a spectrum of behavior problems including territorial aggression, "jealousy," dog fighting, hyperkinesis, persistent barking, anorexia nervosa, tail-chasing, timidity, destructiveness, phobias, predatory aggression, viciousness, unacceptable sexual activity, roaming, digging holes, self-mutilation, night howling, attention-seeking behavior, and urine marking. However, no data from either retrospective or prospective clinical surveys were given, except for urine spraying in cats. A success rate of 80% was reported for this problem, a rate that has not been replicated in other studies.

## Contraindications, Side Effects, and Adverse Events

The use of progestins is contraindicated in breeding animals and diabetics. There are many side effects. In the author's experience, polyphagia, polydipsia, and sedation are all so common that the owner should be told to expect them. In a retrospective clinical report, 25% of cats treated with progestins for behavior problems exhibited an increased appetite and about 20% of cats exhibited sedation; that is, the owner reported that they were depressed, lethargic, or inactive. Mammary gland enlargement, without tumor development, occurred in three of the 50 cats (Hart 1979a).

Various pathological changes have been identified as occurring in the uteruses of both cats and dogs given progestins, with the changes being dependent on both dose and duration of medication (e.g. Dow 1958; Anderson et al. 1965; Brodey and Fidler 1966; Withers and Whitney 1967; Cox 1970; Austin and Evans 1972; Teale 1972). Even remnants of reproductive tissue left after neutering have been reported to undergo changes and infection (Jones 1975). Other side effects include elevated blood glucose, mammary hyperplasia (e.g. Hinton 1977), diabetes, endometrial hyperplasia, pyometra, and carcinoma. These side effects, while serious, generally occur when a patient has been on progestins for weeks or months.

## Overdose

To treat progestin overdose, evacuate stomach if within first 30 minutes and then provide supportive therapy.

### Clinical Guidelines

Because of the common and potentially very serious side effects that can occur with progestins, and the availability of many drugs that are safer for use in the treatment of behavior problems, their use is not standard practice at this time. They are included only for historical reasons and to verify that they are not a drug of choice for behavior disorders.

## Specific Medications

### I. Medroxyprogesterone Acetate (MPA)

**Chemical Compound:** Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6α)

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 2.5-, 5-, and 10-mg tablets and as a 150 mg $ml^{-1}$ injectable solution.

#### Clinical Pharmacology

MPA inhibits the secretion of gonadotropins. In humans, a single intramuscular injection of MPA results in increasing plasma concentrations of MPA for three weeks, followed by an exponential decrease in plasma concentrations. MPA levels in the plasma become undetectable in 120–200 days (Pharmacia and Upjohn 1999).

#### Uses in Humans

MPA is used in humans to treat abnormal uterine bleeding, amenorrhea, renal or endometrial cancer, and endometrial hyperplasia.

#### Contraindications

Use of MPA is contraindicated when sensitivity to MPA, pregnancy, liver disease, or mammary tumors are present. Do not use MPA to treat behavior problems in intact females.

#### Side Effects

Dogs treated with eight doses of MPA at 10 mg $kg^{-1}$ SC or proligestone (PROL) at 50 mg $kg^{-1}$ SC at three-week intervals exhibited a variety of histologic changes. The adrenal cortex atrophied, foci of hyperplastic ductular epithelium developed in the mammary glands, benign mammary tumors developed, steroid-induced hepatopathy occurred, and the cells of the islets of Langerhans became vacuolated. There were no significant differences between the dogs treated with MPA and the dogs treated with PROL (Selman et al. 1995).

#### Adverse Drug Interactions

Aminoglutethimide significantly depresses serum concentrations of MPA (Pharmacia and Upjohn 1999).

#### Effects Documented in Nonhuman Animals

##### *Cats*

MPA, given as a single injection of 100 mg to males and 50 mg to females, resulted in successful treatment of urine spraying or urine marking in 29% of cases. Less than 10% of the treated cats exhibited depression and/or increased appetite. Both males and cats from single-cat homes responded better than did females or cats from multicat homes, with males from single-cat homes having the best response. Some cats that were initially treated with MA subsequently responded to MPA (Hart 1980). When used as a treatment for urine spraying or marking in cats, injections of MPA are repeated once per month or as needed.

In a later study of 35 male and 25 female cats, Cooper and Hart (1992) found that MA and MPA were equally effective, with about 42% of cats treated with a progestin showing a positive response to treatment. Progestins were less effective for females than for males and, in females, were less effective than diazepam or buspirone. In males, progestins were about as effective as diazepam or buspirone.

##### *Dogs*

Male dogs given MPA at 10–20 mg $kg^{-1}$ SC have been observed to exhibit 75–100%

improvement of various problems, including aggression toward other males, urine marking, and mounting of dogs, people, or inanimate objects. There was poor efficacy for human-directed aggression in the male (Hart 1979b). Three out of four males treated with 10 mg kg$^{-1}$ MPA SC for fighting with other males responded to therapy, whereas only one out of seven males given the same treatment for human-directed aggression exhibited improvement. Side effects observed included increased appetite and weight gain (Hart 1981).

MPA was once used as a canine contraceptive. However, this was discontinued in the early 1970s due to problems with endometritis and pyometra. While these problems are most likely to occur when MPA is given during proestrus, estrus, in overdose, or in dogs with genital disease, it should not be used in intact females (Stabenfeldt 1974). Spayed female beagles given doses of MPA as low as 3 mg kg$^{-1}$ every three months almost invariably develop mammary nodules within four years. At the higher dose of 30 mg kg$^{-1}$ there is a threefold increase in the development of nodules. In addition, levels of serum growth hormone and insulin increase in a dose-dependent fashion, while levels of triiodothyronine, cortisol, and 17 β-estradiol decrease (Frank et al. 1979).

#### *Parrots*

MPA has been used in the treatment of feather-picking in parrots at a dose of 0.07 mg g$^{-1}$ IM as a single dose. Side effects reported include increased appetite, polydipsia, polyuria, and sedation (Galvin 1983; Ryan 1985).

## II. Megestrol Acetate

**Chemical Compound:** 17 α -(acetyloxy)-6-methylpregna-4,6-diene-3,20-dione

**DEA Classification:** Not a controlled substance

**Preparations:** Generally available as 40 mg ml$^{-1}$ oral suspension and as 5-, 20-, and 40-mg tablets.

#### Clinical Pharmacology

MA is a steroid with rapid onset of action. It has antigonadotropic and antiandrogenic effects and glucocorticoid activity. There is slight mineralocorticoid activity. It does not have anabolic or estrogenic activity and does not have masculinizing effects on the developing fetus (David et al. 1963; Gupta et al. 1978; Muller et al. 1983; Henik et al. 1985).

In humans, the major route of elimination is the urine, although some fecal excretion occurs (Bristol-Myers Squibb 2000). The opposite occurs in the dog. When MA is given to bitches at a dose of 2 mg kg$^{-1}$ PO for eight days, it is rapidly eliminated, primarily through the feces (about 87%) and to some degree in the urine (about 9%). One week after the last dose, 90% of the medication has been excreted, although there is further gradual elimination up to three weeks later (Chainey et al. 1970).

#### Uses in Humans

MA is used to treat anorexia, cachexia (e.g. Aisner et al. 1990), and adenocarcinoma of the breast and endometrium in humans.

#### Contraindications

MA should not be used in dogs with evidence of any disease of the reproductive organs, prior to first estrus, in pregnant dogs, or in dogs with mammary tumors (Schering-Plough 2003).

MA should not be used for treatment of behavior problems in intact females.

#### Adverse Drug Interactions

Concurrent administration of MA with dofetilide, an antiarrhythmic drug, causes decreased dofetilide elimination and increased dofetilide plasma concentrations. This can result in ventricular arrhythmias (Yamareudeewong et al. 2003).

#### Side Effects

Side effects reported in cats include mammary hyperplasia, induction of lactation, mammary carcinoma, pyometra, diabetes mellitus, polyphagia with weight gain,

adrenocortical atrophy, and personality changes including listlessness and depression (e.g. Aspinall and Turner 1972; Long 1972; Wilkins 1972; Baker 1973; Chesney 1976; Nelson and Kelly 1976; Oen 1977; Nimmo-Wilkie 1979; Hart 1980; Chastain et al. 1981; Gosselin et al. 1981; Kwochka and Short 1984; Tomlinson et al. 1984; Middleton 1986; Middleton et al. 1987).

MA given at 0.25 mg $lb^{-1}$ for 32 days during the second half of pregnancy in the bitch results in decreased litter size and increased mortality in the puppies. No adverse events are reported when it is given during the first half of pregnancy. Dogs treated with 2 mg $kg^{-1}$ $day^{-1}$ for 64 days exhibit signs of early cystic endometritis. When MA was administered orally at 0.5 mg $kg^{-1}$ for five months, mild uterine hyperplasia has been observed, which subsequently regresses. MA at 0.1–0.25 mg $kg^{-1}$ $day^{-1}$ for 36 months also results in cystic endometrial hyperplasia, which likewise reverses if dosing is discontinued (Schering-Plough 2003).

In a two-year chronic toxicity/carcinogenicity study in rats, there was evidence of decreased lymphocyte counts, increased neutrophil counts, and increased frequency of respiratory infections (Bristol-Myers Squibb 2000).

MA induced both benign and malignant mammary tumors in female beagles given 0.01, 0.1, or 0.25 mg $kg^{-1}$ $day^{-1}$ for up to seven years (Nelson et al. 1973; Owen and Briggs 1976). Female monkeys did not develop mammary tumors. Male offspring of females treated with MA during pregnancy exhibit decreased fertility. Additionally, female rats treated with MA had a reduction in the number of live births and fetal weight and feminization of male offspring (Bristol-Myers Squibb 2000).

### Overdose

Single doses of up to 5 g $kg^{-1}$ in mice and 1600 mg $day^{-1}$ in humans have not produced toxic effects. There is no specific treatment. In case of large overdose, monitor the patient and provide supportive therapy.

### Effects Documented in Nonhuman Animals

#### *Cats*

In a clinical trial of the treatment of urine marking and spraying using megestrol acetate, 13 cats were treated as follows: 5 mg $cat^{-1}$ were given daily PO for 7–10 days. If improvement occurred within seven days, the frequency of dosing was decreased to every other day for two weeks. If this dose continued to control the problem, the frequency of dosing was further reduced to twice a week for one month. Frequency of dosing was then further reduced to once a week for two to six months. If the behavior recurred when frequency of dosing was decreased, the client was instructed to return to the previously effective frequency of dosing (Hart 1980).

This treatment resulted in 36% of the patients showing substantial improvement. Both males and cats from single-cat homes responded better than did females or cats from multicat homes, with males from single-cat homes having the best response. Some other cats that were initially treated with MPA subsequently responded to treatment with MA. Over 30% of the cats exhibited increased appetite, while almost 30% of the cats became depressed. In addition, one female developed mammary gland enlargement that regressed when treatment was discontinued (Hart 1980). In the author's experience, this regimen almost invariably produces decreased activity. Fewer side effects are achieved with a faster regimen of decreasing frequency for cats that are responding to treatment.

Romatowski (1989) recommends, for behavioral abnormalities, 2 mg $kg^{-1}$ $day^{-1}$ for five days, followed by 1 mg $kg^{-1}$ $day^{-1}$ for five days, and then 0.5 mg $kg^{-1}$ $day^{-1}$ for five days.

Of 244 cats that were given MA to delay estrus, five owners reported that their cats exhibited increased aggression while 34 owners reported that their cats were less aggressive (Oen 1977). Additionally, two nonaggressive cats have been reported to become aggressive when placed on MA (Baker 1973).

Cats treated with MA at 5 mg cat$^{-1}$ day$^{-1}$ for eight days exhibit increased fasting blood glucose concentration and decreased glucose excretion rate (Middleton and Watson 1985). Cats treated with MA at a dose of 5 mg cat$^{-1}$ day$^{-1}$ for two weeks, and then 5 mg cat$^{-1}$ three times a week for a total of one year of treatment, have been shown to produce a progressive deterioration in glucose tolerance, an increase in mean fasting plasma glucose concentration, and a decrease in mean plasma glucose clearance rate. There was also a progressive decrease in resting plasma cortisol concentrations and cortisol concentrations subsequent to administration of ACTH. The glucose intolerance resolved three months after discontinuation of treatment (Peterson 1987).

Cats given 1 mg kg$^{-1}$ of MA every other day for three weeks did not exhibit changes in plasma glucose or insulin concentrations in response to intravenous glucose administration (Mansfield et al. 1986).

#### *Dogs*

MA is used to postpone estrus and disrupt false pregnancy in the dog (Schering-Plough 2003). When given at a dose of 2.2 mg kg$^{-1}$ for eight days during proestrus, it suppresses estrus in 92% of bitches (Burke and Reynolds 1975).

Pemberton (1980) has recommended doses as high as 15 mg kg$^{-1}$ daily in dogs. This is substantially higher than doses the author has used. When treating dogs with MA, the author has typically used the following schedule: 2.0 mg kg$^{-1}$ q24h for 14 days, followed by 1.0 mg kg$^{-1}$ q24h for 14 days, followed by 0.5 mg kg$^{-1}$ q24h for 14 days, then discontinue. If the problem resumes when the dose is decreased, go back up to the last dose that worked for two to three weeks, then try reducing again. Even on this schedule, decreased activity, polyphagia, and polydypsia may be observed during the initial two weeks of treatment.

#### *Parrots*

MA has been used in the treatment of feather-picking at a dose of 1.25 mg PO daily for 7–10 days, then twice weekly (Petrak 1969; Galvin 1983; Ryan 1985).

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# 19

# Combinations

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## Introduction

In the first edition of this book, the focus of this chapter was drug augmentation (adding a second agent when a patient's response to the current medication was subpar). In the second edition of *Veterinary Psychopharmacology*, this chapter has been expanded to address common questions and concerns when it comes to using psychoactive drugs.

## Overview of Drug Augmentation

When a patient fails to respond to a given drug at a given dose, the clinician has three main options. They can: (i) increase the dose of the drug currently being given if the maximum dose has not been reached and the patient is not exhibiting any undesirable side-effects; (ii) change drugs; or (iii) augment or complement the first drug with a second (or more) drug(s). There are not set protocols or controlled clinical studies in veterinary clinical behavioral medicine, which leaves the clinician with a process of trial and error to endure. However, some combinations are supported by studies in human medicine (and others might have contraindications and should be avoided). Caution is always warranted when data are lacking in a given species.

A common example of a synergistic effect (in which two drugs will, together, be more effective than either alone) is the augmentation of a serotonin reuptake inhibitor with a serotonin agonist. These drugs work together to facilitate serotonin activity. Other drug combinations have a complementary effect. A common example is treatment of a patient with chronic anxiety that peaks under certain conditions or have specific phobias. In these cases, daily administration of a maintenance anti-anxiety medication (such as selective serotonin reuptake inhibitor or other antidepressant) can be supplemented with context specific administration of a fast-acting drug such as a benzodiazepine or an alpha-2 agonist.

A complementary effect can also be achieved by combining drugs with different speeds of onset and duration of action. For example, patients are sometimes presented with severe separation anxiety disorder or other problems that lead to destruction and excessive vocalization, to the point of clients facing eviction or the animal being under the risk of euthanasia. In this situation, waiting for a slow onset of action medication to take effect (which is the case with most antidepressants used in veterinary medicine)

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is not the best option. Short-acting drugs that target panic signs may be chosen in the early stages of treatment until antidepressants and behavior therapy have time to take effect.

## Potentially Beneficial Combinations

In cases of serotonin dysregulation leading to anxiety and behavioral changes, augmentation of a serotonin reuptake inhibitor with an azapirone (such as buspirone) or serotonin antagonist and reuptake inhibitor (SARI) (such as trazodone) may be beneficial (Bakish 1991; Gruen and Sherman 2008). For example, human patients with major depression who have been unresponsive to fluoxetine (at least 30 mg daily) or citalopram (at least 40 mg daily) have shown better improvement when they received buspirone augmentation of 20–60 mg $day^{-1}$ vs. placebo. No serious events were observed (Appelberg et al. 2001). Likewise, patients with obsessive-compulsive disorders may respond positively when fluoxetine treatment is supplemented with buspirone (e.g. Jenike et al. 1991). The combination of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and desipramine, a tricyclic antidepressant (TCA), results in more rapid improvement in patients with major depression than treatment with desipramine alone, presumably because of more rapid down-regulation of ß-adrenergic receptors (Baron et al. 1988; Nelson et al. 1991).

Even though there are numerous clinical examples published to support a working knowledge to prescribers, the level of scientific evidence is still weak. The examples are primarily combining slow onset of action medications (such as SSRIs or TCAs) with fast onset of action medications (such as benzodiazepines, a SARI, or an alpha-2 agonist). The combination of clomipramine and alprazolam has been shown to be beneficial in the treatment of storm phobia in dogs (Crowell-Davis et al. 2003). Fluoxetine and alprazolam have been combined in the treatment of urine spraying in a cat (Seibert 2004a, 2004b). This logic is also used in human anxiety disorders (e.g. Goddard et al. 2001; Stahl 2002). Ogata and Dodman (2011) reported a clinical case series of combination administration with either SSRI, TCA, or azapirone with oral administration of an alpha-2 agonist (clonidine) to manage fear-based behavior problems in dogs such as noise phobias, separation anxiety disorder, or fear/territorial aggression. The owners' feedback to adding clonidine was positive in 18 out of 22 cases in this study. Combinations of SSRIs, TCAs, benzodiazepines, azapirones, or antipsychotics and trazodone to treat canine anxiety disorders (n = 56) were also reported by Gruen and Sherman (2008) where 34 out of 56 clients reported that the combination treatment helped to improve their dog's anxiety.

Another example of drug combination introduced in veterinary clinical behavioral medicine is treatment of canine compulsive disorders where fluoxetine and the NMDA receptor antagonist, memantine, were used together (Maurer and Dodman 2007; Schneider et al. 2009). Although the case number of these reports was small (total of five cases), the author concluded that combination of the two medications caused higher improvement when it was compared with monotherapy of fluoxetine.

Gabapentin and pregabalin have been shown to be effective in neuropathic pain conditions, and are widely used off-label to treat other conditions such as anxiety and insomnia in humans (Smith et al. 2016). Accordingly, they have been increasingly used in clinical behavioral medicine as well. In a (human) randomized double-blind, placebo-controlled study, the adjunctive effect of pregabalin in refractory generalized anxiety patients was shown. In this study, patients were randomized into two groups, receiving either pregabalin adjunctive (n = 180) or placebo (n = 176) adjunctive for eight weeks in addition to their original monotherapy with an SSRI (escitalopram or paroxetine) or a serotonin norepinephrine reuptake inhibitor

(SNRI) (venlafaxine-XR). The result was that 50% of the patients who failed to respond adequately to SSRI or SNRI monotherapy responded better with the addition of pregabalin. The response rate was significantly different from those with placebo but adverse effects were the same between the groups, and none of the serious adverse events were considered to be related to the study drug (Rickels et al. 2012). Since there is so far no literature available about combination treatments in veterinary clinical behavioral medicine with either gabapentin or pregabalin, a prudent approach is recommended.

## Adverse Interactions and Contraindications

In addition to potential issues of producing overdoses by giving two drugs that either act the same, or are metabolized by the same mechanisms (and thus compete with each other), combining drugs can present the risk of producing adverse consequences specific to the way particular drugs interact with each other.

Serotonin syndrome has been reported in monkeys, rats, rabbits, dogs, and humans (e.g. Oates and Sjoerdsma 1960; Hess and Doepfner 1961; Curzon et al. 1963; Grahame-Smith 1971; Sinclair 1973; Brown et al. 1996; Martin 1996). This is a consequence of taking excessive quantities of medications that increase serotonin levels and/or taking certain medications that interact incompatibly in regards to serotonin metabolism. There is no diagnostic test for serotonin syndrome, and diagnosis is based on a history of medication with drugs that may interact incompatibly or a history of medication with excessive quantities of drugs that facilitate serotonin activity, combined with presenting symptoms and the exclusion of other medical conditions. The potential for serotonin syndrome is one reason that it is important to get a complete listing of all herbal medications being given to a patient, as some, such as St. John's Wort, act on serotonin. The mechanism for serotonin syndrome is not fully understood, but most investigators believe the primary mechanism is excess 5-$HT_{1A}$-receptor stimulation (Brown et al. 1996; Martin 1996).

Signs and symptoms can be grossly grouped into mental changes, neuromuscular changes, and autonomic changes. In humans, the problem is usually mild and resolves in 24–72 hours, but it can cause death (Beaumont 1973; Mendis et al. 1981; Tackley and Tregaskis 1987; Brennan et al. 1988; Kline et al. 1989; Neuvonen et al. 1993; Kuisma 1995). The most serious cases result when an SSRI has been taken with (i) an MAO inhibitor, which decreases serotonin metabolism, (ii) a serotonin receptor agonist, such as buspirone, (iii) a tricyclic antidepressant, which is a non-selective serotonin reuptake inhibitor, or (iv) meperidine, tryptophan, or dextromethorphan. Specific changes in mental status symptoms reported in humans include confusion, agitation, coma, hypomania, and anxiety. Motor abnormalities include myoclonus, hyperreflexia, muscle rigidity, restlessness, tremor, ataxia, shivering, nystagmus, and seizures. Cardiovascular changes include hypertension, hypotension, and sinus tachycardia. Gastrointestinal signs and symptoms include nausea, diarrhea, abdominal pain, and excessive salivation. Other signs include diaphoresis, hyperpyrexia, tachypnea, and unreactive pupils (Brown et al. 1996). Some of these signs can be similar to the most common reported side effects of antidepressants. Due to this, the authors warrant caution when side effects are reported in patients. Serotonin syndrome should be considered and increasing the dose (to "see if the patient will get over side effects") is risky and not recommended.

Treatment and management include discontinuation of all serotonergic medications and supportive treatment. Benzodiazepines such as diazepam or lorazepam may be given for myoclonus and the hyperthermia resulting from myoclonus. However, clonazepam is not effective with serotonin syndrome (Nierenberg and Semprebon 1993; Skop et al. 1994; Brown and Skop 1996). In severe cases,

5-HT antagonists such as cyproheptadine, methysergide, or propranolol can be given (Goldberg and Huk 1992; Brown et al. 1996; Martin 1996).

Gwaltney-Brant et al. (2000) reported on 21 cases of dogs that had been exposed through accidental poisoning to the nutritional supplement 5-Hydroxytryptophan, which is the immediate precursor to serotonin. The dose consumed ranged from 2.5 to 573 mg kg$^{-1}$. The dog that had been exposed to 2.5 mg kg$^{-1}$ received no treatment and exhibited no symptoms. One dog, which had consumed a dose of 222 mg kg$^{-1}$, had emesis induced within 30 minutes. This dog exhibited no symptoms. The lowest dose at which signs developed was 23.6 mg kg$^{-1}$. The lowest dose at which death occurred was 128 mg kg$^{-1}$. The time of onset of clinical signs varied from 10 minutes to 4 hours after ingestion. Nineteen of the dogs developed clinical toxicosis. Of these, three died. Mental status changes included depression, coma, and disorientation. Sensorimotor changes included tremors, hyperesthesia, ataxia, paresis, hyperreflexia, and weakness. Respiratory and cardiovascular signs included tachycardia, cyanosis, and dyspnea. Gastrointestinal signs included vomiting, diarrhea, abdominal pain, flatulence, and bloat. Other signs included mydriasis, transient blindness, hypersalivation, hyperthermia, hypothermia, and vocalization. Treatment included decontamination by inducing emesis, anticonvulsants, thermoregulation, and fluid therapy. The 16 dogs that exhibited clinical toxicosis and recovered all did so within 36 hours of beginning treatment. Clinical blindness, if present, was the last sign to resolve.

Because of their long half-lives, serotonin syndrome has occurred five to six weeks or later after discontinuation of fluoxetine, paroxetine, sertraline or irreversible MAOIs (Pato et al. 1991; Coplan and Gorman 1993; Martin 1996).

According to a meta-analysis in humans regarding safety and tolerability of antidepressant co-treatment in acute major depressive disorder with 23 studies of 2435 samples, noradrenergic and specific serotonergic antidepressants (NsSSA) or TCA or SSRIs were associated with more adverse events such as tremor, sweating, or weight gain. Although it was sparse data, the authors suggested this augmentation should be chosen with caution (Galling et al. 2015).

P-glycoprotein (P-gp) plays one of the important roles in the pharmacokinetics and clinical effects (Akamine et al. 2012). Since fluoxetine and clomipramine are known to inhibit several drug-metabolizing enzymes as well as P-gp in humans, a study was done to specifically assess the risk of drug interactions for fluoxetine, clomipramine, and selegiline in dogs by assessing canine P-gp. Its result showed that fluoxetine and clomipramine are weak inhibitors of canine P-gp and they can cause low risk of drug-drug interactions, while selegiline did not inhibit P-gp. Therefore, it is unlikely to cause drug-drug interactions (Schrickx and Fink-Gremmels 2014). Underlying mechanisms impacting potential interaction with psychotropic drugs have not been fully understood in both human and veterinary medicines and further information is needed.

The combination of a TCA and an alpha-2 agonist might also raise concerns. According to the product information of clonidine (Catapres®), if a patient who is receiving clonidine is also taking a TCA, the hypotensive effect of clonidine may be reduced, which might warrant an increase in the clonidine dose. In the toxicology study done in rats, concomitant administration of amitriptyline and clonidine enhances the manifestation of corneal lesions (Boehringer Ingelheim International GmbH 2016).

The recent interest in using alpha-2 agonists in clinical behavioral medicine has raised questions such as the possibility of associating two drugs from this group (e.g. clonidine and dexmedetomidine). The authors caution that this type of combination is not commonly suggested in the human literature and there are no studies or publications to support it in veterinary medicine.

Hypotensive effects (among others) are likely and a ceiling effect for the sedation should be considered (Kuusela et al. 2000; Messenger et al. 2016). See details in Chapter 11, Sympatholytic Agents.

## Changing and Weaning Patients off Medications

It is recommended that at least 14 days should be taken between discontinuation of selegiline (Anipryl®) and initiation of treatment with a TCA or a SSRI, while a minimum of a five-week washout interval is recommended for the discontinuation of fluoxetine due to its long half-life and the long half-life of its metabolite (norfluoxetine), and the initiation of any drug that may adversely interact with fluoxetine and norfluoxetine (Zoetis 2013).

Evidence-based data are lacking in veterinary medicine when it comes to stopping and switching guidelines of each medication. In people, it is advised to avoid abruptly stopping administration of SSRIs, TCAs, and MAOIs after more than a few weeks of treatment due to possible discontinuation reactions. Usually a minimum period of a four-week taper is advised after longer-term treatment (Cleare et al. 2015).

## Cytochrome P450 (CYP)

The cytochrome P450 enzyme system is critical in hormone biosynthesis and catabolism, the biotransformation of toxins and the metabolism of a variety of drugs (He et al. 2001). While the specific distribution and quantities of the various specific enzymes, including mutant variations, have been extensively studied in humans, less research has been conducted in the various species treated by veterinarians (e.g. von Moltke et al. 1995). While there are many similarities, there are also differences which, in many cases, have not been quantitatively identified. See Tables 19.1–19.3 for a summary of relevant information.

## Interactions That Can Affect Dosing

Some drugs interact in a way that can affect dosing schedules or specific drug selections within a class when it is desired to use two or

**Table 19.1** Inhibitors and inducers of CYP 450 enzymes for various BZD substrates.

| CYP 450 enzyme | BZD substrate | Inhibitor | Inducer |
|---|---|---|---|
| CYP 2C19 | Diazepam | Fluvoxamine<br>Omeprazole<br>Oxcarbazepine | Dexamethazone<br>Phenobarbital<br>Phenytoin<br>St. John's wort |
| CYP 3A4 | Clonazepam | Azole anti-fungals (e.g. ketoconazole) | Carbamazepine |
| | Diazepam<br>Midazolam | Cimetidine<br>Clarithromycin<br>Diltiazem<br>Erythromycin<br>Fluoxetine<br>Nefazodone<br>Sertraline | Phenobarbital<br>Phenytoin<br>St. John's wort |
| UGT | Lorazepam<br>Oxazepam | Valproate | Carbamazepine<br>Phenobarbital<br>Phenytoin |

*Source:* Adapted from Riss et al. (2008).

**Table 19.2** Behavioral medications that are inhibitors or inducers of the CYP enzyme listed; *inducers* slow the rate at which the substrate medication is available, and lower the amount available; *inhibitors* increase the rate at which the substrate medication is available and increase the amount available.

| P-450 enzyme | Substrate | Inhibitor | Inducer |
|---|---|---|---|
| CYP 1A2 | TCAs<br>Fluvoxamine<br>Mirtazapine<br>Duloxetine | Fluvoxamine<br>Fluoxetine<br>Paroxetine<br>Sertraline<br>Some TCAs | Phenobarbital<br>Carbamazepine<br>Phenytoin |
| CYP 2A6 | | | |
| CYP 2B6 | | | |
| 2 CYP C9/ CYP 2C9/10 | Sertraline<br>Fluoxetine<br>Amitriptyline | Fluvoxamine<br>Fluoxetine<br>Sertraline | Carbamazepine |
| 2C19/CYP2C19 | Citalopram<br>Sertaline<br>Clomipramine<br>Imipramine | Fluvoxamine<br>Fluoxetine<br>Sertraline | Carbamazepine |
| CYP 2D6 | Fluoxetine<br>Fluvoxamine<br>Citalopram<br>Duloxetine<br>Paroxetine<br>Venlafaxine<br>Trazadone<br>Nefazodone<br>TCAs | Duloxetine<br>Fluoxetine<br>Paroxetine<br>Norfluxietine<br>Citalopram<br>Sertaline<br>Some TCAs | |
| CYP 2E1 | | | |
| CYP 3A4 | Nefazodone<br>Sertaline<br>Venlafaxine<br>Trazodone<br>TCAs | Fluvoxamine<br>Norfluoxetine<br>TCAs<br>Nefazadone | Carbamazepine |

*Source:* Table from Overall (2013).

more classes of drugs. For example, in adult male humans, fluoxetine impairs the clearance of alprazolam by microsomal oxidation, but does not affect the rate of clearance of clonazepam by nitroreduction. Thus, in adult human males, fluoxetine can be administered with clonazepam without affecting clonazepam's efficacy, while co-administration of fluoxetine and alprazolam will result in a significantly prolonged half-life of alprazolam (Lasher et al. 1991; Greenblatt et al. 1992). Similarly, fluvoxamine results in a significantly longer half-life for alprazolam (Fleishaker and Hulst 1994). As with many other aspects of the application of psychopharmacology to veterinary science, these detailed interactions remain to be studied in the veterinary population. For this reason, we must proceed cautiously with combinations while beginning by extrapolating from human clinical trial data.

## Algorithms: Possible Future Direction

An algorithm is "a computational procedure whose application yields a solution to an associated class of problems" (Hartley 1999). Put simply, they are a set of decision-making protocols for patient management at different stages of treatment, depending upon response

**Table 19.3** Commonly used medications that could be given concomitantly with behavioral medication and that are inducers or inhibitors of the CYP enzyme listed; *inducers* slow the rate at which the substrate medication is available, and lower the amount available; *inhibitors* increase the rate at which the substrate medication is available and increase the amount available.

| P-450 enzyme | Inhibitor | Inducer |
|---|---|---|
| CYP 1A2 | Fluoroquinolones | Charcoal-broiled beef<br>Cruciferous vegetables<br>Marijuana smoke<br>Omeprazole<br>Phenobarbital<br>Phenytoin |
| CYP 2A6 | Tranylcypromine | Barbiturates |
| CYP 2B6 | | Phenobarbital |
| CYP 2C9/CYP 2C9/10 | D-Propozyphene, Disulfiram, Fluconazole, Sulfaphenazole | Rifampin<br>Phenobarbital<br>Phenytoin |
| CYP 2C19 | Omeprazole | Rifamoin<br>Phenytoin |
| CYP 2D6 | | |
| CYP 2E1 | Disulfram | Ethanol |
| CYP 3A4 | Fluconazole<br>Ketoconazole<br>Cimetidine<br>Clarithromycin, Erythromycin (Macrolides, in general)<br>Propofol | Barbiturates<br>Dexamethasone/Chronic Glucocorticoids<br>Phenytoin<br>St. John's wort (hyperforin is the compound that is the inducer)<br>Flucloxicillin |

*Source:* Table from Overall (2013).

to given treatments. Algorithms for clinical decision-making have become common in psychiatric medicine. They also have a place in veterinary behavioral medicine, although the same disadvantages, as well as advantages, that apply in human psychiatry, apply here. Algorithms that are based on extensive research literature, particularly research that focuses on success or failure of treatments that are initiated after an initial non-response, can be useful in guiding clinicians into decision-making processes that are based on evidence. Unfortunately, the amount of research on success rates of various primary treatments for veterinary patients, much less second-tier treatments, is still small (Stein and Jobson 1996).

At this time, algorithms in veterinary clinical behavioral medicine must be based on clinical experience of specialists, rather than data. However, the development of such algorithms will provide a basis for developing research that tests their veracity. In the long run, this will result in refinement, modification, and ultimately improvement of clinical algorithms. Even when algorithms have become well developed and well tested, they necessarily reduce a complicated medical situation into a simple decision-making process. In so doing, they may present an oversimplified view, failing to take into consideration all the complicating medical, management, and experiential factors that can apply in a given case. Thus, they should be taken as guidelines, rather than irrefutable laws. It is up to the clinician to consider all relevant information in a given case before making a decision as to the best course of treatment (Stein and Jobson 1996).

## Conclusion

Combining medications can be useful in particular situations and for patients that do not respond to treatment with any one drug. However, there are potential risks to this approach, including competition between drugs for metabolic pathways and direct, adverse interactions between drugs. Human medicine treatment guidelines do not recommend combination treatment as the first line of treatment because the risk of adverse effects have not been fully evaluated (Mojtabai and Olfson 2010; Rush et al. 2011). Ongoing research in the use of psychoactive medications for the treatment of mental health and behavior problems in nonhuman animals will continue to provide a stronger knowledge base for these decisions.

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