Medication for Behavior Modification in Birds

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KEYWORDS

• Psittaciformes • Psychoactive drugs • Benzodiazepines • Tricyclic antidepressants
• Serotonin reuptake inhibitors • Dopamine antagonists • Opioid antagonists
• Hormone therapy

KEY POINTS

- Behavior modification therapy and provision of an appropriate living environment are key elements of management of problem behaviors in parrots.
- The use of behavior modifying drugs can be considered adjunct therapy under specific circumstances but only once a proper diagnosis has been established.
- Various classes of behavior modifying drugs exist. To enable selection of the most appropriate drug to use in an individual bird, a thorough diagnostic work-up is needed.
- Due to lack of information on safety and efficacy, psychoactive drugs should be used with caution and gradually titrated to effect.
- When available, therapeutic drug monitoring helps guide therapy, aiming to identify the most appropriate dose and resulting in the least number of side-effects.

INTRODUCTION

Pharmacologic intervention with psychoactive or psychotropic drugs has been long-standing practice in human medicine to treat a variety of mental health issues (eg, schizophrenia, depression, bipolar disorder, and generalized anxiety disorder). Similarly, in veterinary medicine, these drugs have been used with increasing frequency to manage problem behaviors, such as anxiety, aggression, and compulsive behaviors. In addition to psychoactive drugs, hormones, antihistamines, analgesics, and anticonvulsant drugs are also used to alleviate behavior problems that are associated with increased levels of sex hormones, allergies, pain, and/or neurologic dysfunction (eg, epilepsy), respectively. When applied correctly, medication can aid in the treatment of abnormal pathologic behaviors (eg, stereotypic behaviors or those that lack impulse control), help stabilize a patient's emotional state (eg, in case of fear, anxiety, aggression, or hormonal imbalances), and improve its receptiveness to a behavior modification plan, thereby increasing the chances of a successful outcome.

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Without proper diagnosis of the problem and adequate knowledge of behavior modification drugs (including their mechanism of action, appropriate uses, side effects, and interactions with other medications), however, veterinarians are likely to select an inappropriate drug or implement it incorrectly, which not only poses a risk of therapeutic failure but also can seriously harm a patient because of unintended drug interactions or side effects. Therefore, this article, aims to provide guidelines to the veterinary practitioner in the circumstances in which behavior modification drugs can or cannot be applied as well as provide an overview of the various medications currently used in the pharmacologic management of behavior problems in birds.

BEHAVIOR PROBLEMS: WHEN TO PRESCRIBE AND WHEN NOT TO PRESCRIBE MEDICATION

Just like dogs and cats, parrots and other pet birds can exhibit problem behaviors that can be frustrating for owners and veterinarians to deal with. Some of the more common complaints concern aggression and biting, excessive vocalization (screaming), and feather-damaging and/or self-injurious behavior (**Figs. 1** and **2**).[1] In addition,

Fig. 1. Feather-damaging behavior (FDB), also referred to as feather-destructive behavior, feather plucking, feather picking, or pterotillomania, is one of the more common behavior problems seen in practice. Underlying causes can vary greatly for each individual case. Often a multifactorial origin is reported, in which various medical, genetic, psychological, neurobiologic, and socioenvironmental factors may play a role. (*Courtesy of* Nico Schoemaker, DVM, PhD, DECZM, DABVP-Avian, Utrecht University, Utrecht, The Netherlands; Yvonne van Zeeland, DVM, MVR, PhD, DECZM, CPBC, Utrecht University, Utrecht, The Netherlands.)

Fig. 2. Aside from feather-damaging behavior, self-injurious behaviors are also commonly seen in psittacine birds. Often times, the self-mutilation is localized to a specific area, whereby the favored area can differ according to the species involved. Cockatoos, for example, often present with severe self-mutilation of feathers, skin, and muscles of the breast, axilla, or patagium (as seen in this galah parrot), whereas Amazon parrots seem to primarily traumatize the feet and legs, and lovebirds predominantly injure themselves in the patagium, neck, axillary region, and back. (*Courtesy of* Nico Schoemaker, DVM, PhD, DECZM, DABVP-Avian, Utrecht University, Utrecht, The Netherlands; Yvonne van Zeeland, DVM, MVR, PhD, DECZM, CPBC, Utrecht University, Utrecht, The Netherlands.)

stereotypic behaviors, anxiety-related disorders (fears and phobias), destructive behaviors, and inappropriate sexual behaviors (eg, excessive egg laying, masturbating, and regurgitation) can be encountered. In many cases, these problem behaviors can be traced back to shortcomings in a bird's living environment or early life history, or represent normal behavior that is misinterpreted or misunderstood by a bird's caregiver (**Box 1**). Moreover, many of the problem behaviors can become exacerbated due to inadvertent reinforcement by 1 or more of the family members. For example, in an attempt to distract a bird that is feather damaging, an owner may worsen the behavior as the bird learns that it will receive attention when it is plucking its feathers. Especially in these situations, where the behavior is the resultant of an attempt of a bird to cope with an inappropriate environment (so-called maladaptive behavior)[15] or in which ignorance or unawareness of an owner plays a part, treatment should first and foremost focus on addressing these underlying issue(s) instead of initiating medical treatment.

Box 1
Common behavior problems in psittacine birds, including their origin and some appropriate interventions

- Destructive behaviors, including chewing, shredding, and stripping of furniture, books, telephone cords, plants, wallpaper, or woodwork, often arise if appropriate chewing substrates and toys are lacking, especially in birds in which the instinctive need to chew is strong (eg, cockatoos and macaws). Provision of appropriate shredding or shredding materials and chewing toys (preferably combined with food to both provide an additional reward and stimulate natural foraging/feeding behavior) as well as supervision of the bird when outside of the cage often help combat these behaviors.
- In the wild, parrots vocalize loudly to keep in touch with the other flock members when leaving to the foraging grounds at dawn and repeat this pattern in the evening when they return to their roosting sites.[2,3] Although attempts can be made to minimize these vocalizations (eg, by darkening the room where the bird is placed in, covering the cage, or providing food or toys as distraction to the bird before the screaming starts), it often is difficult to completely eliminate this behavior. Owners should thus be made aware that these vocalizations are part of the normal behavioral repertoire of a parrot. Similarly, the vocalizations may have had a primary function as a contact call to identify the whereabouts of the family members or gain attention but over time have become excessively loud due to inadvertent reinforcement by 1 or more family members. In those situations, rather than trying to medicate the bird to quiet it down, owners should be made aware of their role in the exacerbation of the problem and provided with advice on how to manage the situation (eg, responding to appropriate calls, providing effective time outs, prevent reinforcement of screaming, and providing other activities that keep the bird preoccupied such as foraging).
- Abnormal repetitive behaviors, such as feather-damaging and stereotypic behaviors, often find their origin in a suboptimal design of the living environment.[4–8] Especially when the bird is unable to perform species-typical behaviors for which it is highly motivated, onset of abnormal repetitive behaviors is likely to occur because of the frustration being redirected (eg, lack of foraging opportunities or allopreening resulting in redirection of this motivation to the bird's plumage) or displaced (eg, feather-damaging behavior occurring in response to exposure of an aversive stimulus). Rather than trying to solve these problem behaviors with medical therapy, these cases benefit the most from a thorough assessment and appropriate management of the bird's living environment.[4,5,9,10] Only in those cases where the bird appears refractory to the husbandry changes that have been made should medical intervention be considered.
- Fear is a common underlying motivation for biting and aggression in prey species, such as parrots. In addition to resorting to biting in an attempt to defend itself (fear biting), a parrot may also bite to protect its territory (territorial aggression) or to protect a person or other bird that is considered its partner (mate-related aggression).[11] Similar to other problem behaviors, positive outcomes of the behavior (eg, retrieving of a hand) can reinforce the behavior (conditioned aggression).[11] The history often reveals the biting to occur only under certain circumstances, for example, in a specific location, such as the cage, or when a specific person is in the vicinity of the bird. Based on the situations under which the biting is occurring, inferences can be made on the underlying motivation, after which recommendations can be made to reduce the biting (eg, use of a 2-enclosure system to reduce territorial aggression, ensuring appropriate bond formation to minimize mate-related aggression).
- Fear is seen in response to a perceived threat in the immediate environment and often results in a classic fight, fright, or flight response. Initially, most birds try to escape and/or avoid the aversive stimulus, but if escape is not possible, fear-biting may result. Over time, classical conditioning (ie, a neutral stimulus becomes aversive through pairing with an aversive stimulus) and operant conditioning (ie, negative reinforcement of the behavior due to removal of the threatening stimulus) can intensify the fear response shown by the bird.[12] In general, fearful behavior can be alleviated by systematic desensitization (ie, reduction or elimination of the fear response by graduated exposure to the aversive stimulus),

counterconditioning (ie, pairing the aversive stimulus with a pleasant stimulus to replace the fear with a more pleasant emotion), and response substitution (ie, replacing the fearful behavior with a different, more desirable behavior).[12,13] Generalized anxiety and phobias, however, are often related to poor socialization or traumatic experiences and can be more difficult and time-consuming to treat.[13] To maximize the changes for success, correct identification and control of the aversive stimulus are essential.[13] Moreover, owners need to be able to recognize subtle signs of fear to be able to successfully implement desensitization and counter-conditioning strategies.[13] Use of medication can be considered an adjunct to behavior modification therapy but only if medication can be administered without causing additional stress or fear.

- Inappropriate sexual behaviors (eg, courtship feeding and copulation) often arise due to triggering of the hypothalamus-pituitary-gonadal axis by cues received from the environment, for example, pair bonding stimulated by excessive cuddling and stimulation of the caudal back by the owner, offering of high-caloric diets, and/or provision of nesting materials and an appropriate nesting site.[14] Although hormonal intervention can be used to help alleviate these behaviors, long-term control of these behaviors requires modification of a bird's living environment and ensuring a more appropriate bond formation between owner and the bird.[10,14]

The major reasons the author recommends a reserved approach toward medication in the initial phases of a behavior modification plan are as follows:

- Several studies in humans have shown cognitive behavior therapies (eg, relaxation techniques, mental distractions, or finding of substitute activities to help control addictions) at least equally (if not more) effective than medical treatment, especially in the long term.[16–21] Similar effects are likely to be expected in parrots and other animals.
- Although psychoactive drugs can induce positive changes in the behavior of a patient, they generally only blunt or mask the resulting behavior without addressing the underlying processes or environmental factors that contribute to the behavior problem.
- When adding medication to the treatment regimen, owners may easily perceive this as the mainstay of the therapy and rely on the drugs to deliver a quick fix to the problem. This in turn might affect clients' compliance with the remainder of the treatment plan because they may be less inclined to make the necessary changes in the living environment and/or change their approach to the bird. This likely results in treatment failure and disappointment of an owner.
- Success of behavior therapy and training is highly dependent on adequate memory and learning, which can be negatively influenced by certain psychoactive drugs (especially benzodiazepines [BZPs][22–25]), thus requiring veterinarians to be cautious when administering medication that can potentially affect these processes.
- In various patients, administering the medication can pose challenges because owners are not able to adequately handle a bird or because the handling and medication cause additional stress and anxiety in an already anxious bird, thereby potentially worsening the problem.
- Like any drug, behavior modification drugs can lead to side effects that can be detrimental to a patient.

Thus, rather than starting with medication, a series of interventions should be initiated that aim to educate owners (including the management of their expectations), optimize a bird's living conditions (including elimination of any potential inciting causes), and modify a bird's behavior through implementation of behavior modification strategies (see **Box 1**).[10]

In many patients, environmental management and behavior modification alone allow a problem behavior to be adequately addressed. Nevertheless, some patients may show lack of or insufficient response to these interventions, thereby warranting drugs to be considered an addition to the treatment regimen. This predominantly includes birds with problem behaviors (especially abnormal repetitive behaviors) that have been ongoing for longer periods of time (thereby allowing these to become ritualized)[26] or birds in which the problem behavior can be linked to traumatic events or poor socialization in the past. In these birds, the problem behavior (even though it may have been initiated by an abnormal environment) is suspected to be associated with an abnormal psychology, brain development, or neurochemistry (so-called malfunctional behavior).[15,27] Aside from this group, the use of behavior modifying drugs can also be considered in situations when an (aversive) stimulus cannot be controlled or avoided or when a bird shows overwhelming fear, anxiety, or aggression.

In all these situations, the main goal of the addition of drugs is to increase a bird's receptiveness to the behavioral interventions and changes of the environment. In particular, medications, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), which mediate and modulate the stress-induced block of long-term potentiation (ie, a persistent increase in synaptic strength that underlies the processes of memory and learning),[28] can facilitate implementation of a behavioral and environmental modification plan.[29] As such, behavior modification drugs can also help a bird to improve faster, thereby increasing client satisfaction and motivation to continue the behavior modification plan. Thus, even in patients in which the medication is not an essential part of the treatment regimen, behavior modification drugs may prove a valuable addition as long as they are used appropriately.

DIAGNOSTIC WORK-UP ESSENTIALS — ESTABLISHING A (DIFFERENTIAL) DIAGNOSIS AND RATIONALE FOR THE USE OF BEHAVIOR MODIFICATION DRUGS

Accurate diagnosis and classification of the behavior problem are essential to establishing a behavior modification plan and determine whether a patient could benefit from adding behavior modification drugs to the treatment regimen. Unlike human psychiatry, in which much attention has been paid to diagnosis and classification of psychiatric and behavioral disorders (eg, the *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition][30]), clearly structured diagnostic systems to help classify behavioral disorders in animals are not well established in veterinary medicine. Nevertheless, although classification systems clearly have their benefits (eg, facilitating communication between practitioners and behaviorists, allowing comparison of outcomes of different trials, and establishing of ready-to-use protocols for intervention), they are not necessarily the solution to everything. Even in human psychiatry, therapeutic efficacy is seen in only 60% of patients who were provided a treatment that matched their specific diagnosis,[31] emphasizing that accurate diagnosis at most provides clues to develop effective therapeutic strategies. This is because classifications and labeling also have inherent limitations, the primary being that diagnoses are mere phenotypic labels that are unable to capture the entireness of the complex processes that underlie the observed behavioral signs.[32] For example, by labeling a bird "hormonal" or "phobic," it is impossible or at least difficult to formulate specific behavioral modifications, whereas this becomes much easier when the behavior, including the situation in which it occurs, is described in more objective terms (eg, hormonal = a bird lunges toward a person and bites when that person is sitting next to the caregiver while the bird is sitting on the caregiver's lap, or phobic = a bird is making high-

pitched vocalizations, flapping its wings, and falls down the perch once someone is approaching it with a large object).

The obvious limitations when dealing with animals instead of human patients do not exempt clinicians from performing a sound diagnostic work-up to try and establish a tentative working diagnosis or list of differential diagnoses that form the basis of a behavior modification plan. This diagnostic-work-up relies on 3 important sources of information:

1. The history of the bird, including a detailed description of the bird's behavior by the owner
2. Direct observations of the bird's behavior by the clinician
3. The physical examination, including any additional diagnostic testing

Based on the findings during these steps, some initial hypotheses can be generated about the underlying motivations and factors contributing to the behavior problem. The antecedent-behavior-consequence method as used by applied behaviorists, in particular, is considered useful in this process (for reviews, see eg, Friedman[33] and van Zeeland and colleagues[10]).

Aside from helping to generate hypotheses about underlying causes, the steps also help establish a rationale for behavioral and medical intervention (ie, whether and which interventions and drugs would be most beneficial to a patient).[34] For example, observation of escape and avoidance behaviors (eg, a bird is trying to retreat from a presented stimulus, such as a hand or object by moving backwards or flying away) provides an indication for anxiety as an underlying motivation (thereby likely requiring desensitization and counter-conditioning strategies with or without anxiolytics), whereas a history or observation of regurgitation, rubbing of the cloaca against objects or nest building behaviors hint toward a potential role for hormones in the problem behavior (which are more likely to benefit from environmental changes and hormone therapy to derail the sexually oriented behavior). Likewise, scratching, wing flapping, and/or sudden, fast, and vigorous biting of the skin or feathers may hint toward pain, irritation, or itch that requires further work-up and treatment of potential underlying medical causes, including the use of drugs such as antihistamines or analgesics.

History

Owners should be thoroughly questioned about their bird's problem behavior, during which the following aspects should be taken into consideration:

- Phenomenology of the behavior (ie, exact description of the behavior displayed by a bird that the owner considered a problem)
- Frequency with which the problem behavior occurs (including its duration)
- Environmental circumstances under which the behavior occurs
- Responses of the owner and other family members after the behavior
- Time of onset of the problem behavior, including age of the bird at that time
- Changes in pattern, frequency, intensity, or duration of the problem behavior over time
- Previous corrective measures or treatments that have been initiated to alleviate the problem behavior, including their effects

Besides questions about the behavioral problem(s), questions should also be asked about a bird's overall behavior, including its relationship and responses to family members and strangers, new situations, and other types of stimuli. Similarly, a parrot's background (eg, rearing history and origin) and current living conditions, including

its nutrition, physical, and social environment, daily routine, and preferred enrichments and activities, should be thoroughly evaluated.

Direct Behavioral Observations

A behavioral assessment can either be made by direct observation of a bird's behavior in the clinic or indirectly using recordings of the bird's behavior at home. Direct observations are preferably made at the beginning of a visit or shortly after or during the history taking to prevent significant alterations due to stress from handling.[35,36] It should be emphasized, however, that a bird's behavior in the clinic may be significantly altered by, for example, the presence of an (unfamiliar) observer, a new location, and/or transport to the clinic. To exclude potential influence of these external factors on the bird's behavior, video recordings made by the owner in the home environment often, therefore, provide a helpful addition to complement the direct observations in the clinic.

Aside from observing the bird's behavior in the examination room, it is also important to observe the owner's responses to the bird's behavior (because this may uncover unintended reinforcement of the problem behavior by the owner) as well as the bird's responses to environmental stimuli that are offered as a distraction when performing the problem behavior. If a bird appears to be fixated on a problem behavior and is hardly or not at all distracted by external stimuli, this could either indicate established, hard-to-reverse stereotyped behavior[37] or presence of a strong (internal) stimulus or motivation for the behavior, which is more likely to require medical intervention (eg, using antipsychotics, TCAs, or SSRIs that influence obsessive compulsive behaviors). Similarly, behavior change is more likely difficult to accomplish and to require medical intervention in birds that show either an overwhelming response (eg, fear or aggression) or a total lack of interest in the stimuli they are presented with or are seemingly difficult to engage in activities, such as playing with enrichments (particularly in the home situation).[34,38]

Physical Examination and Ancillary Tests

A full physical examination, consisting of an observation of the patient from a distance, followed by a hands-on examination, is performed to detect physical abnormalities indicative of an underlying disease process that may cause or contribute to the behavioral signs and warrants further diagnostic work-up (eg, blood biochemistry and hematology or imaging) to be performed. Similarly, a further work-up can be indicated in patients in which medical intervention is considered, because certain drugs are contraindicated or may require adjustment of the dosing regimen in case concurrent medical conditions are present. For example, caution is warranted when administering drugs to geriatric patients or those suffering from metabolic, liver, renal, or cardiac diseases.[32] Moreover, because most drugs are metabolized through the hepatic and renal pathways, establishing baseline values is considered essential for monitoring potential side effects.[32] In addition, some medications (eg, SSRIs) are reported to have cardiac side effects,[39] thereby recommending baseline ECGs, especially in patients that have a history of cardiac disease and those that might need sedation or anesthesia.[32]

CHOOSING THE APPROPRIATE DRUG — CONSIDERATIONS FOR DRUG SELECTION

Selection of the appropriate drugs to use for a specific patient necessitates an accurate diagnosis of the behavioral problem of the patient as well as knowledge of drug efficacy and safety (**Box 2**). Veterinarians are, therefore, encouraged to familiarize

Box 2
Checklist for administering medication for behavior modification in birds

The author recommends veterinarians ask themselves the following questions when considering using pharmacologic intervention for behavior modification and ensuring all these can be answered with yes before initiating treatment.

1. Has a thorough behavioral and medical work-up been performed to identify the potential underlying causes for the problem behavior? Has a working diagnosis or differential diagnoses been established?
2. Have the potential underlying medical issues and environmental stressors been adequately dealt with? Has or will an appropriate behavior modification plan be(en) put into place?
3. Is it possible for the owner to medicate the bird without causing additional stress that may exacerbate the existing problems?
4. Does the drug of choice's mechanism of action correspond with the hypothesized neuropathophysiologic processes that underlie the behavioral problem (eg, reduction of anxiety, compulsiveness, or hormonal influence)?
5. Did the medical work-up reveal no contraindications for use of the medication? If the bird is receiving any other medication, is there no interaction with these drugs that warrants caution or adjustment of the dose?
6. Has the owner been informed properly with regard to effects of the therapy and the potential risks (ie, side effects) of the treatment?
7. Has a proper monitoring and follow-up protocol been set in place (eg, frequency of rechecks, monitoring of plasma concentrations, evaluation for presence of side effects)?

themselves with the indications and contraindications, mechanisms of action, and potential side effects of the various classes of behavior modification drugs (discussed later). In general, drug selection primarily depends on the type of behavior problem that is present, whereby the preferred drug comes from the drug class that is most likely to be effective in treating the behavioral problem but poses the least risk of adverse side effects. Given the drug class, the drug selection subsequently depends on the experience with the drug in the given species, whereby the choice falls on the drug with the best-known efficacy.

Unfortunately, for many of the behavior modifying drugs, the absorption, distribution, metabolism, excretion profiles (ie, pharmacokinetic properties of the drug); dose-response curves (ie, pharmacodynamics properties); and therapeutic indices (ie, safety of the drug) in birds are lacking. Placebo-controlled clinical trials demonstrating the effectiveness of behavior modification drugs in birds are also few in number. As a result, data are often extrapolated from studies on other animals or humans. Species differences, however, may be present, which could result in a lack of efficacy or onset of unexpected adverse events. Thus, starting at a low dose and gradual titration of the drug are recommended to determine the optimal dose for individual patients (ie, the dose at which clinical effects are seen without side effects noted). Should (unexpected) side effects be encountered, adjustment of the dose or switching to a different drug or drug class should be considered. Seeming therapeutic failure, on the other hand, first warrants re-evaluation of the original diagnosis and the conditions of drug use (eg, Has the drug been used sufficiently long for it to exert an effect?) before adjusting, switching, or combining medication.

Aside from the behavioral indication, other factors may also play a role in drug selection. For example, in humans, age, gender, and health status of patients have been shown to significantly affect therapeutic efficacy and safety of certain drugs.[31,40–44] Similar

findings are therefore to be expected in birds. A study on pharmacokinetics of paroxetine in gray parrots indicated presence of gender-based differences in plasma concentrations.[45] This emphasizes the need to further study the effects of aforementioned patient parameters on the drug's action. Information from studies in humans and other animals may provide initial clues on whether and how these factors may affect the efficacy and tolerability of a drug in a given situation. Presence of health problems (eg, liver or renal disease and arrhythmias) does not necessarily rule out use of a drug but does warrant extra caution with regard to the used dosage and monitoring of potential side effects.

Other issues related to drug selection pertain to the cost, availability, and ease of administration of the medication. Many of the psychoactive drugs need compounding to enable their use in avian patients. This may pose additional challenges, because the effects of compounding on storage and stability of drugs are largely unknown. Moreover, formulation may significantly alter the absorption (and, therefore, clinical efficacy) of drugs as shown in gray parrots, where a commercial suspension of paroxetine resulted in little to no absorption after oral administration compared with a water-based solution of paroxetine.[45] Similarly, challenges may be encountered with intake of medication because of an owner being unable to administer the drugs and/or the bird resisting medication (eg, due to taste aversion of bitter-tasting drugs [Fig. 3]).

PSYCHOACTIVE DRUG CLASSES AND THEIR MODE OF ACTION

Psychoactive drugs typically work by changing or balancing the amount of 1 or more neurotransmitters in the brain. Of the various neurotransmitters that have been identified, the following play a pertinent role in regulation of behavior and behavior problems: acetylcholine, dopamine, endorphins, γ-aminobutyric acid (GABA), glutamate, norepinephrine, and serotonin (Table 1). Psychoactive drugs exert their effect on one or more of these neurotransmitters, thereby inducing alterations in mood, perception, consciousness, cognition, and behavior. Historically, behavioral drugs have been classified into 6 categories according to their first clinical application in humans:[31]

Fig. 3. One of the challenges when attempting behavior modification with drugs is to ensure that the medication is properly administered to the bird. Unfortunately, many owners are not experienced in administering medications to their birds, which can subsequently result in poor therapeutic compliance but also exacerbate an already existent behavior problem (eg, fear or aggression). Operant learning techniques, such as shaping and positive reinforcement, can help teach the birds to voluntarily take in their medication, as demonstrated by this gray parrot (*Psittacus erithacus*). (*Courtesy of* Nico Schoemaker, DVM, PhD, DECZM, DABVP-Avian, Utrecht University, Utrecht, The Netherlands; Yvonne van Zeeland, DVM, MVR, PhD, DECZM, CPBC, Utrecht University, Utrecht, The Netherlands.)

Table 1
Neurotransmitters and their respective functions and associated pathologies

Neurotransmitter	Function	Pathology Resulting from Depletion	Pathology Resulting from Excess
Acetylcholine	Voluntary movement, attention, memory and learning, reward, arousal, and sleep; major neurotransmitter in the autonomic nervous system	Cognitive decline, dementia, Alzheimer disease, myasthenia gravis; blocking of muscarinic receptors results in anticholinergic effects (eg, dry mouth, dry eye, pupillary dilation, tachycardia, constipation, and urinary retention)	Depression
β-Endorphin	Pain relief, feelings of pleasure and contentment	Pain, addiction	Depersonalization disorder, catalepsy
Dopamine	Coordination of motor activities, attention, and learning; modulation of mood (D_1–D_4 receptors), pleasures related to motivation	Behavioral quieting, depression, extrapyramidal motor symptoms (muscle tremors, tics, motor restlessness, and Parkinson disease)	Compulsive and stereotypical behaviors, schizophrenia (in humans)
Epinephrine	Affects sleep, mood, memory and learning, focus and alertness; fight-or-flight response		Fear, agitation; sympathetic effects, leading to, for example, vasoconstriction (α-adrenergic receptors) or vasodilation β_2-adrenergic receptors), increased cardiac contractility (α-adrenergic and β_1-adrenergic receptors), bronchodilation and/or changes in gastrointestinal tract motility (intestinal relaxation, contraction of bladder, and intestinal sphincters)
GABA	Inhibition of excitation and anxiety, behavioral quieting	Seizure activity, Parkinson disease, fear, and phobias	Sleepiness, drowsiness

(*continued on next page*)

Table 1
(*continued*)

Neurotransmitter	Function	Pathology Resulting from Depletion	Pathology Resulting from Excess
Glutamate	Excitation; cognitive functions, such as memory and learning	Insomnia, problems with concentration, mental exhaustion, energy depletion	Seizure activity; hyperalgesia; neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson disease, Alzheimer disease
Histamine	Sleep-wake cycle, appetite, sexual behavior, temperature, nociception, gastric acid release, vasodilation, bronchoconstriction, secretory functions (eg, nasal mucous membranes); involved in cognition (memory loss)		Hypersensitivity response, anaphylactic shock
Norepinephrine	Affects mood, functional reward systems, sleep patterns, focus, and arousal/alertness	Depression	Schizophrenia, mania, sympathomimetic effects
Serotonin	Modulation of sleep-wake cycle, temperature, appetite, mood (emotional response), sexual behavior, memory and learning, and impulse control (particularly through serotonin binding to serotonin 1 receptors); also involved in regulation of cardiovascular and endocrine function	Depression, anxiety, irritability, aggression, impulse control and obsessive-compulsive disorders	Agitation, irritability, tremors, hyperreflexia, hyperthermia, sweating, dilated pupils, and diarrhea

1. Anxiolytics, which are primarily used to treat anxiety and anxiety-related disorders
2. Antidepressants, which are used to treat clinical depression as well as some other disorders (eg, anxiety disorders, obsessive compulsive disorders, impulse control disorders, and chronic or neuropathic pain)
3. Antipsychotics, which are predominantly used to treat psychotic symptoms (such as seen in schizophrenia or mania) but also can be used as adjunct therapy to relieve clinical depression

4. Mood stabilizers, which are used to facilitate mood regulation in people experiencing intense, repeated shifts in their mood, as can be seen with bipolar disorder and schizoaffective disorder
5. Stimulants, which are used to help regulate disorganized thought processes and are as such used in the treatment of attention deficit hyperactivity disorder; they furthermore have sympathomimetic activity and increase bodily activity and are therefore also used to treat narcolepsy and for weight reduction.
6. Depressants, which include all hypnotics, sedatives, and anesthetics. This group also includes the opioid antagonists, which can help to overcome endorphin-related or opioid-related addictions by blocking their euphoric effects.

The aforementioned classification is based mainly on a drug's initial clinical application in humans and does not necessarily imply similar functionality in animals. For example, some of the drugs that have traditionally been used as antidepressants in humans have also been found to exert significant anxiolytic effects in animals.[46]

Aside from the classification based on clinical use, drugs are also classified according to their chemical structure and neurochemical activity, whereby drugs in the same category share a similar mechanism of action and side effects.

In veterinary medicine, the most commonly used psychoactive medications include drugs from the antidepressant (ie, TCAs and SSRIs) and anxiolytic (ie, BZPs and azapirones) classes. Of these, however, only 3 have been specifically licensed for use in animals, that is,:

- Fluoxetine (Reconcile), which is licensed for the treatment of dogs with separation anxiety when used in combination with behavior modification
- Clomipramine (Clomicalm), which is also licensed for treatment of separation anxiety in dogs when used in combination with behavior modification
- Selegiline (Anipryl), which is licensed to treat dogs suffering from behavioral problems with an emotional underlying origin

Other uses of these drugs, including the use in other species as well as use of other psychoactive agents, constitutes extralabel use that in the United States falls under the Animal Medicinal Drug Use Clarification Act of 1994. This act requires presence of a valid client-patient-veterinarian relationship as well as an established diagnosis (based on a complete medical and behavioral evaluation) and sound scientific rationale for prescribing the drug made by the veterinarian prescribing the drug (discussed later). If and when a veterinarian feels uncomfortable or insecure about his/her ability to comply with these guidelines, referral of the case to a specialist in behavioral medicine is advised.

In birds, the following classes of psychoactive drugs have been used (**Table 2**):

1. BZPs (eg, diazepam and lorazepam)[47–49]
2. Azapirones (eg, buspirone)[50]
3. TCAs (eg, amitriptyline, clomipramine, and doxepin)[51–56]
4. SSRIs (eg, paroxetine and fluoxetine)[45,51,55,57–62]
5. (Typical) antipsychotics or neuroleptics, which include the phenothiazine derivatives (eg, chlorpromazine),[49] and butyrophenones (eg, haloperidol)[63–65]
6. Opioid antagonists (eg, naltrexone and naloxone)[66,67]

Benzodiazepines

BZPs (eg, diazepam, midazolam, lorazepam, alprazolam, oxazepam, and clorazepate) act by binding to GABA-receptors (primarily $GABA_A$), thereby increasing binding

Table 2
Classes of medications (including mode of action and dosing regimen) that may be considered for behavior modification in birds[a]

Drug Class	Drugs	Mechanism of Action	Indications	Potential Side Effects	Reported Dosing Ranges for Selected Drugs in Birds	Comments
Anticonvulsants	Carbamazepine Gabapentin Levetiracetam Phenobarbital Potassium bromide Zonisamide	Carbamazepine: blocks voltage-gated sodium channels preventing repetitive action potentials Gabapentin: increases synaptic levels of GABA in the CNS Levetiracetam: reduces neurotransmitter release by binding inhibiting presynaptic calcium channels Phenobarbital: potentiates GABA and blocks AMPA-receptor resulting in reduced neuronal excitability Potassium bromide: potentiates the effect of GABA by competing with the transmembrane chloride transport Zonisamide: is thought to block sodium and T-type calcium channels. It has some GABA-ergic activity	Behavior problems arising from seizure activity; potentially beneficial to treat compulsive behaviors (including feather-damaging behavior) and anxiety- or frustration-related aggression, and depression	Mild sedation, lethargy, ataxia, polyuria, polydipsia, polyphagia, anticholinergic effects, bone marrow suppression	Carbamazepine: 3–10 mg/kg q24h; PO, or 166 mg/L drinking water Gabapentin: 10–15 mg/kg q12h PO Levetiracetam: 50–100 mg/kg q8–12h PO Phenobarbital: 1–7 mg/kg q12–24h PO (gray parrots may need dosages of at least 20 mg/kg) Potassium bromide: 25–75 mg/kg Zonisamide: 20–80 mg/kg q12h PO	Can be combined with antipsychotics, such as haloperidol Barbiturates contraindicated in patients with liver disease Carbamazepine contraindicated in patients with renal, hepatic, cardiovascular, or hematologic disorders, including bone marrow suppression Do not combine with antipsychotics or antidepressants; combined use with paroxetine may lower availability of the latter Potassium bromide works synergistically with drugs that have a GABA-ergic effect

Antihistamines	Diphenhydramine Hydroxyzine	Antihistamine; inverse H_1 receptor agonist, thereby blocking effects of histamine	Treatment of allergies; pruritus and pruritus-associated behavioral disorders	Sedation, local anesthesia, antinausea, anticholinergic, antiserotonergic effects	Diphenhydramine: 2–4 mg/kg q12h PO or 2 mg/L drinking water Hydroxyzine: 2 mg/kg q8-12h; PO, or 30–40 mg/L drinking water	Caution is warranted when using these drugs together with anticholinergic agents or CNS depressants or when using these drugs in patients with hepatic disease
Antipsychotics (neuroleptics)	Chlorpromazine (phenothiaze derivative) Haloperidol (butyrophenone derivative)	Dopamine receptor antagonist	Low-potency antipsychotics (eg, chlorpromazine): mild sedation, tranquilizer; high-potency antipsychotics: treatment of obsessive-compulsive behaviors, including feather-damaging behavior, self-injurious behavior and stereotypic behaviors	Hypotension, bradycardia, decreased seizure threshold, ataxia, sedation, extrapyramidal motor signs, such as muscle tremors and ticks, motor restlessness, agitation and excitability, depression, decreased appetite, regurgitation	Chlorpromazine: 0.1–0.2 mg/kg once; PO, 0.2–1 mL stock solution[b]/kg q12–24h; PO, or 1 mL stock solution/120 mL drinking water Haloperidol: 0.1–0.9 mg/kg q12–24h; PO or 1–2 mg/kg q14–21d; IM	Distinction between typical (eg, chlorpromazine, haloperidol) and atypical antipsychotics (eg, clozapine, risperidone), of which the latter have less side effects Chlorpromazine is less specific then haloperidol and mainly results in sedation Low-potency antipsychotics may be combined with BZPs or SSRIs; use with other antipsychotics or TCAs is contraindicated.
Azapirones	Buspirone	Acts as a serotonin agonist	Anxiolytic, treatment of anxiety disorders	A large range of side effects are reported in people ranging from dizziness to gastrointestinal signs, alterations in social behavior, and pruritus. Generally, these are mild and noted soon after initiation of therapy.	Buspirone: 0.5 mg/kg q12h; PO	Combined use with either itraconazole, rifampicin and haloperidol may increase the plasma concentration of buspirone. Carbamazepine, on the other hand decreases plasma concentrations of buspirone.

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Table 2
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Drug Class	Drugs	Mechanism of Action	Indications	Potential Side Effects	Reported Dosing Ranges for Selected Drugs in Birds	Comments
BZPs	Diazepam, lorazepam	Binds to $GABA_A$ receptor thereby potentiating the inhibitory effects of GABA	Anticonvulsant; skeletal muscle relaxant; appetite stimulant; short-term management of acute and intermittent behavior problems, in particular those involving fear, anxiety, and phobia, feather picking or aggression. Also useful to facilitate collar placement	Sedation, ataxia, muscle weakness, hyperphagia, disinhibition of aggression, paradoxic excitation, memory deficits (also: inhibition of learning); potentially fatal hepatic necrosis after oral dosing in cats; neutropenia, jaundice, and anemia have been reported after long-term use in humans.	Diazepam: 0.25–1.5 mg/kg q8–24h; IM, 0.5–4 mg/kg q6–24h; PO, or 10–20 mg/L drinking water Lorazepam: 0.1 mg/kg q12h; PO Midazolam: 0.1–2 mg/kg IM or IV, 1–2 mg/kg intranasally	BZPs act as sedatives at low dosages, as anxiolytics at moderate dosages; and as hypnotics at high dosages Risk of drug dependence has been reported in humans, therefore recommending gradual withdrawal after chronic dosing BZPs can be used concurrently with other psychoactive drugs (eg, antipsychotics, TCAs and SSRIs) to help to overcome the delayed efficacy of the other drugs. Concurrent dosing requires lowering of the dose to prevent CNS depression. Avoid in patients with CNS or respiratory depression, obesity, renal or hepatic failure
β-Blockers	Propranolol	Selectively prohibits the reconsolidation of the fear memory	Treatment of anxiety disorders	Bradycardia, lethargy, hypotension, syncope	No dose reported in birds	Has been reported effective for treating anxiety in dogs, but a meta-analysis of its use in humans provided insufficient support for the use of propranolol in the treatment of anxiety disorders

GnRH agonists	Deslorelin Leuprolide acetate	Down-regulation of GnRH, after initial increase, and thereby LH (and FSH)	Treatment of sexual-related behavior disorders	None reported	Deslorelin: 4.7 and 9.4 mg (slow-release implant); q3–6 mo Leuprolide acetate: 100–800 μg/kg q2–3 wk	A delayed response of up to 2 wk may be seen, due to the initial rise of GnRH Because both GnRH agonists have the same mode of action, deslorelin has a longer duration of action and is also registered for use in animals, there is no reason to still use leuprolide acetate.
Melatonin	Melatonin	Stimulates release of GnIH thereby down-regulating GnRH	Treatment of aggression, undesired sexual related behavior, and anxiety disorders	Mild sedation may occur in dosages >1 mg/kg	0.5–3 mg/kg	Further studies are needed to determine optimal dosage and indication
NSAIDs	Meloxicam Carprofen Piroxicam	Analgesic, anti-inflammatory and antipyretic action through inhibition of prostaglandin synthesis	Treatment of pain-related behaviors	May cause gastrointestinal bleeding and renal failure	Meloxicam: 0.5–1.5 mg/kg q12–24h PO Carprofen: 1–10 mg/kg q12–24h IM Piroxicam: 0.5 mg/kg q12h PO	Only COX-2 specific drugs are mentioned because these have the lowest risk of side effects. Great species variation in dose. For meloxicam: gray parrot 0.5 mg/kg q24h; Amazon parrot 1.5 mg/kg q12h
Opiate receptor antagonists	Naloxone Naltrexone	Block effects of endogenous endorphins	Treatment of stereotypies and other compulsive or self-injurious behavior, including feather-damaging behavior and self-injurious behavior; analgesia	Increased anxiety, gastrointestinal problems, such as abdominal cramps, nausea, vomiting, and constipation	Naloxone: 2 mg/kg; IV Naltrexone: 1.5 mg/kg q8–12h; PO	Is expected to work predominantly in the early phases, when behavior is not ritualized. Reduction in feather-damaging behavior can be observed within 20 min postinjection (for naloxone) Contraindicated in patients with liver disease

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Table 2
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Drug Class	Drugs	Mechanism of Action	Indications	Potential Side Effects	Reported Dosing Ranges for Selected Drugs in Birds	Comments
SSRIs	Fluoxetine Paroxetine Zimelidine	Selective block of serotonin reuptake at presynaptic membrane, leading to an increased availability of serotonin; increased sensitivity to serotonin, with secondary down-regulation of postsynaptic receptors	Compulsive and impulsive disorders (including feather-damaging behavior and self-injurious behavior), fear, phobias, and anxiety-related disorders, aggression	Generally mild side effects, including lethargy, sedation, insomnia, loss of appetite, weight loss, nausea, diarrhea, mild ataxia, and potential lowering of seizure threshold; serotonin syndrome can occur on sudden withdrawal from medication.[c] In pigeons, the use of an SSRI has been shown to result in a decrease of time spent on rapid-eye-movment sleep.	Fluoxetine: 1–5 mg/kg q24h; PO Paroxetine: 1–4 mg/kg q12–24h; PO Zimelidine: 7.5 mg/kg IM (10 mg/kg may cause regurgitation)	Preferred treatment of affective- and anxiety-related disorders Delayed onset of action of approximately 2–6 wk (clinical effects seen in cats within 1–2 wk) Caution warranted in patients with seizures and altered blood glucose (monitoring of blood glucose is advised) Do not use in combination with MAOIs, TCAs, anticonvulsant drugs, and antipsychotics

TCAs	Amitriptyline Clomipramine Doxepin Nortriptyline	Block norepinephrine and serotonin reuptake; act as competitive antagonists at muscarinic acetylcholine, histaminergic H_1, and α_1-adrenergic or α_2-adrenergic receptors	Treatment of fear, phobia, anxiety, and aggression; depression; impulsive and obsessive compulsive disorders (including feather-damaging behavior and self-injurious behavior); alleviation of chronic neuropathic pain; treatment of pruritic conditions (including feather-damaging behavior) due to antihistamine action	Sedation, lethargy, hyperactivity, paradoxic anxiety, agitation, ataxia, seizures, hallucinations, tachycardia, mydriasis, decreased tear production, dry mouth, gastrointestinal upset, regurgitation, constipation, change in appetite, increased thirst, urinary retention	Amitriptyline: 1–5 mg/kg q12–24h; PO; 9 mg/kg may be needed to achieve serum concentrations within the human therapeutic range (although this may be toxic to some birds) Clomipramine: 0.5–9.5 mg/kg q12–24h; PO Doxepin 0.5–5 mg/kg q12–24h; PO Nortriptyline: 16 mg/L drinking water	Clinical effects and improvement generally not seen until 2–4 wk after start of treatment Clomipramine most selective for serotonin reuptake inhibition; doxepin and amitriptyline have strongest antihistamine effects Recommended to start with low dose and gradually titrate to effect; gradual tapering off to minimize risk of withdrawal syndrome Can be combined with anxiolytics (eg, buspirone, BZPs); do not use in combination with MAOIs, antipsychotics, anticholinergics, antidepressants, barbiturates, anticonvulsants, thyroid supplements or antithyroid medication Contraindicated in patients with blood glucose alterations, adrenal disorders, glaucoma, seizures, hepathopathy, or cardiac disease.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; IM, intramuscular; IV, intravenous; MAOI, monoamine oxidase inhibitor.

[a] Note: most of the dosages in this table have been derived from case reports and/or anecdotal evidence. Because information on pharmacokinetics, pharmacodynamics, efficacy and toxicity are currently lacking for most of these drugs, no specific recommendations can be made at this stage.

[b] Stock solution: 125-mg chlorpromazine in 31-mL simple syrup.

[c] A potentially fatal condition that is characterized by onset of 1 or more of the following symptoms: diarrhea; restlessness; extreme agitation, hyperreflexia, and autonomic instability with possible rapid fluctuations in vital signs; myoclonus, seizures, hyperthermia, uncontrollable shivering, and rigidity; and delirium, coma, status epilepticus, cardiovascular collapse, and death.

affinity of the receptor for GABA. As a result, these drugs potentiate the inhibitory effects of GABA, whereby their effects are dose dependent: at low dosages, BZPs act as sedatives; at moderate dosages, they act as anxiolytics; and at high dosages, they act as hypnotics, facilitating sleep.[68] Because of their rapid onset of action, BZPs are considered particularly beneficial for short-term treatment of acute and intermittent fear and anxiety-related behaviors (including fear-related aggression). In addition, BZPs can be useful in the treatment of (acute episodes of) fear-related or stress-related feather damaging and self-injurious behaviors. BZPs furthermore have sedative, appetite-stimulating, and anticonvulsant effects (with a rapid onset of action) and, therefore, can also be considered useful in the treatment of acute seizures or anorexia; to facilitate social interaction and in situations where (temporary) sedation may be necessary, for example, to facilitate the acceptance of (Elizabethan) collars by the bird.[38,55,69] For the drugs to be effective, they must generally be given at least an hour before the anticipated stimulus (if administered orally) and at least before the bird starts displaying signs of distress. BZPs can be used in conjunction with other psychoactive drugs (eg, TCAs and SSRIs) to help overcome the period needed for onset of action of these drugs. Main disadvantages include long-term dependence and tolerance, necessitating the dose to be increased.[70] Moreover, BZPs interfere with the ability to learn and thus may negatively affect the outcome of a behavior modification plan (except in situations where formation of aversive associations is preferred [eg, when visiting a veterinarian]). Withdrawal signs may also occur after cessation of treatment.[71]

Azapirones

Azapirones (of which buspirone is the only one commercially available) are serotonin 1A agonists that act as full agonists at the presynaptic serotonin 1A receptors (resulting in decreased serotonin synthesis and inhibition of neuronal firing) and as partial agonists at postsynaptic serotonin 1A receptors.[72,73] In humans, buspirone has been used in the treatment of generalized anxiety disorder and the treatment of aggression associated with impaired social interaction but has been found ineffective for the treatment of panic disorder.[74–76] In animal models, buspirone has also shown efficacy in treatment of conditioned avoidance responses[77] and has anecdotally been used to treat paradoxic anxiety caused by clomipramine.[50] Compared with BZPs, buspirone produces no sedation, no cognitive impairment, and low risk of side effects.[72,73,78] Moreover, it has low abuse potential and low risk of withdrawal concerns, thereby rendering it favorable to BZPs for long-term treatment of anxiety. To evaluate its effect, buspirone needs to be administered for several weeks because no immediate behavioral effects are produced.[72,73]

Tricyclic Antidepressants

TCAs, including amitriptyline, imipramine, clomipramine, nortriptyline, and doxepin, potentiate the effects of biogenic amines (ie, norepinephrine, epinephrine, dopamine, serotonin, and histamine) to varying degrees. TCAs may either block the neurotransmitter reuptake (norepinephrine, serotonin, and — to a lesser extent — dopamine) or act as competitive antagonists at the respective muscarinic acetylcholine, histaminergic H_1, and α_1-adrenergic or α_2-adrenergic receptors (acetylcholine, histamine, and norepinephrine).[79] Therapeutic effects are believed to result primarily from inhibition of norepinephrine and serotonin reuptake, whereas blockage of α-adrenergic, antihistaminic, and anticholinergic activities is believed to account for the various side effects seen after administration of these drugs.[79]

Because TCAs exert their effect (in part) through down-regulation of the receptors, their onset of action is delayed (ie, improvement may not be noticeable until 2–4 weeks after initiation of the treatment).[79]

In humans, TCAs are commonly used to treat depression, panic disorders, phobias, neuropathic pain and obsessive-compulsive behaviors. Clomipramine, in particular, which has the highest selectivity for serotonin reuptake inhibition, is used widely in veterinary medicine for treating compulsive disorders, including feather-damaging behavior.[38,52,54,80,81] Similar to humans, TCAs may also be indicated in the treatment of fear, phobia, anxiety, and aggression or to alleviate chronic neuropathic pain.[38,79] Amitriptyline and doxepin, which produce the strongest antihistaminergic effects, may furthermore be useful to treat pruritus resulting from allergic conditions based on favorable efficacy in birds suspected of an allergy-related form of feather-damaging behavior.[38,53,82]

Because of their anticholinergic, antihistaminergic, and adrenergic effects, TCAs are generally considered to have narrow therapeutic safety, with no specific antidotes available in case of overdosing.[79] Side effects seen after TCA administration in birds include increased wariness, anxiety, agitation, depression, increased appetite, and neurologic signs (including hallucinations, dystonia, ataxia, and tremors).[50,53,55,56,82,83] Many of these side effects were only seen afer administration of higher dosages (ie, >4 mg/kg clomipramine every 12 hours orally; 9 mg/kg amytriptiline orally, single dose).[50,56] In two birds (a green-winged macaw and Moluccan cockatoo), however, severe neurologic signs and death were seen at lower dosages (ie, 3 mg/kg clomipramine every 12 hours orally; 2 mg/kg imipramine every 12 hours orally),[55] emphasizing that caution should be exercised when administering these drugs as species or individuals may respond differently to the treatment. Gradual dose titration and careful, continued monitoring for the presence of side effects are, therefore, recommended when starting a patient on TCAs.

Selective Serotonin Reuptake Inhibitors

SSRIs, including fluoxetine, fluvoxamine, sertraline, paroxetine, and zimelidine, selectively block the reuptake of serotonin into the presynaptic membrane, thereby increasing availability of serotonin. In addition, SSRIs can increase the sensitivity of the postsynaptic receptors to serotonin.[84] SSRIs usually need to be administered for at least 2 weeks to 6 weeks to induce down-regulation of postsynaptic receptors and the associated clinical effects.[84] Common behavioral indications include compulsive and impulsive disorders (including feather-damaging behavior and self-injurious behaviors), fear, phobias, and anxiety-related disorders, and aggression.[38,84] Because of their mood-stabilizing effect, SSRIs are also considered the preferred drugs for treating affective or anxiety-related disorders.

Of the various SSRIs that are available, paroxetine is one of the most potent and selective, thereby posing minimal risk of central and autonomous side effects.[85] Paroxetine has been found beneficial in treating phobias and feather-damaging behavior in birds.[10,38,55,60] Reports concerning its efficacy, however, are sparse and limited to case reports and anecdotal evidence, with no controlled clinical trials available to support these findings. A study in gray parrots demonstrated a dose of 4-mg/kg paroxetine hydrochloride, every12 hours orally, to result in plasma concentrations within the therapeutic range recommended for the treatment of depression in humans.[45] Large interindividual differences were present, however, in plasma concentrations, indicating the need for further clinical trials into its efficacy, whereby therapeutic drug monitoring may potentially help establish the correct dosing regimen for individual patients. In addition to paroxetine, fluoxetine has also been shown promising in birds

with feather-damaging behavior and toe-chewing, although relapses were commonly seen.[57,63]

Because of their selectivity, which results in fewer side effects compared with TCAs, SSRIs are considered the safer choice in humans.[86,87] Gradual withdrawal is recommended to prevent serotonin syndrome.[84]

Antipsychotics

Antipsychotics or neuroleptics are classified as low-potency agents (eg, acepromazine and chlorpromazine) and high-potency agents (eg, haloperidol and risperidone). These drugs act as dopamine receptor antagonists, resulting in behavioral quieting or ataraxia (ie, decreased emotional reactivity and relative indifference to stressful situations) and suppression of spontaneous movements without affecting spinal and pain reflexes.[88] In veterinary medicine, low-potency antipsychotics are commonly used as tranquilizers, whereas high-potency antipsychotics have been used to reduce compulsive behaviors in various animal species, including compulsive feather-damaging and self-injurious behaviors in parrots.[63–65,88,89]

Of the high-potency antipsychotics available, haloperidol is the most commonly used. Haloperidol is available as both long-acting injectable and oral formulations. Although the long-acting injectable can be advantageous to use in birds because of reduced dosing frequency and omitting the need for an owner to administer the medication, to the author's knowledge there currently is no information available on the pharmacokinetics of this drug in birds. Due to the greater risks associated with overdosing of long-acting formulations, the author therefore recommends against the use of these in the treatment of avian patients.

Compared with high-potency agents, low-potency antipsychotics generally require larger doses and result in more sedation and greater anticholinergic and cardiovascular effects but have a lower incidence of neurologic side effects (ie, extrapyramidal side effects, including Parkinson-like symptoms, dystonia, dyskinesia, and akathisia).[88] Such neurologic side effects have also been reported in birds.[64,65] Most of these side effects are primarily encountered within the first few days after initiation of treatment, with only few occurring in the long term (ie, after treatment of several months up to years).[63–65] Anecdotally, haloperidol has been reported to result in sudden death in a hyacinth macaw and a red-bellied macaw.[64] Similarly, evidence suggests that Quaker parakeets and cockatoo species may be more sensitive to side effects. Caution and lowering of the dose may thus be warranted in these species.[64] Besides species differences in side effects, conflicting results also have been reported concerning the efficacy of antipsychotic drugs in the treatment of psittacine behavior problems. For example, favorable results were achieved after the use of haloperidol in automutilating cockatoos,[51,64,65] whereas no obvious improvement was seen in others.[63] Thus, further studies into dosing regimen and efficacy (including species differences therein) are needed to enable evidence-based decisions to be made on the use of antipsychotics in birds. It should be remembered, however, that these drugs exert their effect (at least in part) through generalized behavioral quieting because of their sedative effects and, therefore, may not specifically address the underlying neuropathophysiology. This is also the reason why this group of drugs has lost a great deal of its popularity in the veterinary and behavior fields.

Opioid Antagonists

Opioid or narcotic antagonists (eg, naloxone and naltrexone) counteract the effects of endogenous opioids that are released during stress. Endogenous opioids activate the dopaminergic system, induce analgesia, and block pain, which are all factors

believed to contribute in the onset of stereotypical and self-injurious behaviors.[90] By reversing the opioid-induced analgesia, opioid antagonists have the potential to block the reinforcing effects of self-injurious behaviors and might, therefore, be useful in the diagnosis and treatment of stereotypic and other compulsive or self-injurious behaviors in zoo and companion animals.[91–95] The suppression of these behaviors, however, may only last for a short while, thereby rendering these drugs primarily beneficial in acute presentations when the behavior is not yet ritualized (ie, shortly after their onset). In parrots, opioid antagonists, such as naltrexone, might be helpful to treat early-stage feather-damaging and self-injurious behaviors, with a positive response seen in more than 75% of treated birds.[67] More than half of these birds, however, wore collars or restraint devices, thereby potentially biasing the outcomes, although in several individuals the collar was removed prior to the end of the trial.

HORMONE THERAPY FOR TREATMENT OF REPRODUCTIVE-RELATED BEHAVIORS

Reproduction-related behaviors (eg, territoriality, aggression toward humans in the house, courtship activity, masturbation, and some forms of feather-damaging behavior) can be seen in birds of both genders during the breeding season. Although reproduction-related behaviors should be considered normal behaviors, they can become a problem when they are directed toward humans or result in medical conditions, such as a cloacal prolapse. Most commonly, birds displaying unwanted reproduction-related behaviors have been reared by humans and lack an avian companion.[96] Measurement of plasma sex steroids and endoscopic evaluation of the gonads can be used to assess the reproductive status of the bird, thereby aiding in the diagnosis.[35,97]

Historically, medroxyprogesterone acetate has been used in the management of reproductive-related conditions in birds. Due to the abundance of side-effects seen with this hormone and with the introduction of other effective therapies, this treatment option has effectively become obsolete.[10] Nowadays, slow-release depot gonadotropin-releasing hormone (GnRH) agonists, such as deslorelin or leuprolide acetate, are the primary drug of choice to be used in patients with suspected reproductive-related behavior problems.[10,96] These depot GnRH agonists have a similar mode of action and result in an initial increase of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH),[98,99] which is followed within the next weeks with a decrease in gonadotropin production to levels under the detection limit of the assay. It is hypothesized that either a down-regulation of gonadotropin receptors in the pituitary gland occurs or that the release of gonadotropins no longer occurs due to the loss of pulsatile release of GnRH. Before the deslorelin-containing implants came onto the market for use in animals, leuprolide acetate — an injectable depot GnRH-agonist registered for use in humans —was considered the drug of choice. Because slow-release deslorelin implants are registered for use in animals (**Fig. 4**), have a longer duration of action, and do not need off-label storage, however, as is required after dissolving the leuprolide acetate, the use of these implants is favored over the use of leuprolide acetate. Anecdotal reports have shown both drugs to be effective in treatment of reproductive-related behaviors, with leuprolide acetate providing 73% overall improvement, with temporary resolution in 89% of chronic egg-laying psittacines,[100] and deslorelin resulting in an overall improvement of 50% (varying from 34% in case of masturbation to 62% in case of territorial aggression) of birds with reproductive-related behavioral problems.[96] If the environment retains the triggers for reproductive stimulation, however, the problems are likely to recur despite

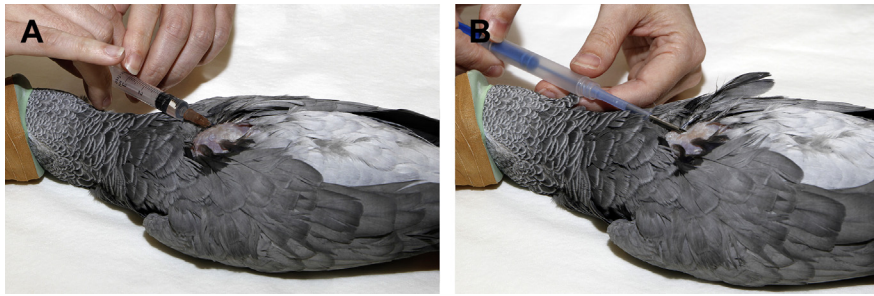

Fig. 4. To reduce reproductive-related behaviors, long-acting depot deslorelin-containing implants can be used. These implants are best placed subcutaneously in between the shoulder blades. To facilitate placement, a small amount of fluid can be injected subcutaneously prior to placement of the implant (*A*). The needle can then be inserted into the fluid bubble to place the implant (*B*). Analgesics (eg lidocaine, bupivacaine) can be added to the fluid for additional pain relief. (*Courtesy of* Nico Schoemaker, DVM, PhD, DECZM, DABVP-Avian, Utrecht University, Utrecht, The Netherlands; Yvonne van Zeeland, DVM, MVR, PhD, DECZM, CPBC, Utrecht University, Utrecht, The Netherlands.)

hormone therapy. Thus, environmental triggers must effectively be dealt with before long-term effects can be achieved.

Recently, a study also reported favorable outcomes after administration of melatonin, with efficacy reported in 3 of 4 birds treated for aggression, 1 of 3 birds treated for undesired hormonal behavior, and 2 of 4 birds treated for anxiety-related behavior problems.[101] Its action is hypothesized to be similar to the depot GnRH-agonists, whereby the melatonin-induced release of gonadotropin-inhibiting hormone (GnIH) down-regulates the synthesis and release of GnRH, thereby inhibiting the synthesis and release of the gonadotropins LH and FSH.[102] In birds with feather-damaging behavior, melatonin yielded no clinical improvement.[101]

THERAPY FOR PAIN-RELATED BEHAVIORS

Any painful condition may initiate a change in behavior, resulting in defensive forms of aggression (biting), feather-damaging, and/or self-injurious behavior. It is, therefore, important to determine under what preceding circumstances the behavior occurs to aid in localizing the origin/location of the pain. The painful area is usually located in the region that is targeted by the bird or the region that evokes a biting response in the bird once it is approached or touched.

When suspecting pain as the underlying cause for the behavior problem(s), a trial with 1 or more analgesics may be warranted. The analgesic effects can particularly be beneficial in patients with self-injurious behaviors that is caused by pain or those that are experiencing pain as a result of the self-injurious behaviors.[38] The drugs' duration of action, however, may be a limiting factor in successful, long-lasting pain relief, because some (eg, butorphanol) need to be given a frequently as 6 times per day. However, sustained release formulations, which have been reported to provide analgesia in Amazon parrots for up to 5 days,[103] may provide a practical solution once they become commercially available.

Different classes of analgesic drugs can be used to prevent, eliminate, or reduce the nociceptive input at different stages, forming the basis of a multimodal approach to pain management.[104] Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects by inhibiting the enzymes cyclooxygenase (COX)-1 and COX-2. The COX enzymes are responsible for the production of prostaglandins, which play an important

role in inflammatory processes and in regulating renal and gastrointestinal mucosal perfusion. In addition, they have an antipyretic activity. Meloxicam and carprofen, both potent COX-2 inhibitors, are currently the most frequently used NSAIDs in birds. Because COX-2 inhibitors supposedly have less effect on the gastrointestinal mucosa and kidney function, these drugs are considered safer compared with other NSAIDs.[104]

Opioids are used for the management of moderate to severe pain. They exert their analgesic effects by binding to the opioid receptors. Butorphanol is most commonly used in birds because it has a high affinity for the κ-opioid receptor, which is considered the predominant receptor in birds.[104] TCAs have also been indicated as potential treatment agents to ameliorate chronic neuropathic pain.[38,55]

Gabapentin, a structural analog of the neurotransmitter GABA, has also anecdotally been used in the treatment of (presumed) neuropathic pain in birds.[105–107] Although the mechanism of action of gabapentin is not completely understood, the drug is thought to bind to the α2-δ subunit of voltage-gated calcium channels, thereby decreasing the release of excitatory neurotransmitters.[108] In a recent pharmacokinetic study in Amazon parrots, a dose of 15 mg/kg, every 8 hours, was found to result in therapeutic plasma levels,[8,109] whereas in great horned owls, sufficient plasma concentrations were achieved after giving 11 mg/kg every 8 hours.[110] These dosages are higher than the previously recommended dose of 10 mg/kg every 12 hours[49] and show that the recommended dose may be dependent on the species. Overdosing may result in diarrhea, ataxia, decreased mental alertness, agitation, and hyperesthesia.[111]

THERAPY FOR PRURITUS-ASSOCIATED BEHAVIORS

Similar to pain, pruritus may be at the basis of many self-injurious behaviors, including feather-damaging behavior. This pruritus may be the end result of various types of infections or inflammatory or neoplastic skin diseases. Although hypersensitivity responses have been suspected in avian patients, diagnosis of disease is difficult due to the diminished response of birds to histamine after intradermal testing.[112] As a result, clinicians have to rely on histopathologic results of skin and/or feather follicle biopsy to make a tentative diagnosis of allergic skin disease, while ruling out other causes of pruritus.[113,114]

In cases of a tentative diagnosis of allergic skin disease, treatment should be aimed at eliminating the potential (food and contact) allergens from the bird's environment. This can prove difficult, however. In cases of extreme pruritus, treatment can also be initiated with antihistaminergic drugs (eg, diphenhydramine or hydroxyzine), which block the physiologic effects of histamine by preventing it from binding to the postsynaptic H_1 receptors.[115] The experience with the use of antihistaminergic drugs is limited, however, with only 1 case report reporting successful resolution of feather-damaging behavior and pruritus in a parrot after a combination treatment with hydroxyzine and eicosapentaenoic acid.[116] Other options for alleviation of pruritus and pruritus-associated behaviors include TCAs (amitryptiline and doxepin)[38,53,82] and corticosteroids, although the latter should be used with caution due to their immunosuppressive effects.[117]

THERAPEUTIC OPTIONS IN CASES OF CONVULSIVE BEHAVIORS

Anticonvulsant drugs are not commonly used in behavioral medicine, unless idiopathic epilepsy warrants long-term treatment. When confronted with a parrot with acute seizures, BZPs (eg, diazepam and midazolam) in particular are considered useful because they have an anticonvulsant effect with a rapid onset of action.[118] The duration of action, however, is short and they have a sedative effect. For long-term management of seizure activity, phenobarbital (a drug belonging to the class of

barbiturates that enhance the action of GABA) is commonly used.[118] Barbiturate use is contraindicated, however, in patients with hepatic disease and those receiving other central nervous system (CNS) drugs (eg, antipsychotics and/or antidepressants) because concurrent administration of these drugs may result in CNS depression.[119] In addition, combined administration of, for example, paroxetine and phenobarbital, may decrease plasma concentrations of paroxetine, thereby limiting its effects.[120] A study in gray parrots has shown that much higher and frequent dosages are needed to achieve similar plasma concentrations as those found effective in humans.[121] It is, therefore, important to measure plasma concentrations of phenobarbital to evaluate the treatment of any bird with epilepsy.

Carbamazepine is an anticonvulsant drug with mood-stabilizing properties. This drug is, therefore, considered useful in the treatment of humans with depression, mania, and/or explosive aggression. In birds, carbamazepine may likewise be useful to treat compulsive disorders (including feather-damaging behavior) and fear-related or frustration-related aggression.[10] In the treatment of birds with compulsive feather-damaging behavior or self-mutilation, it has been proposed to combine the administration of carbamazepine with chlorpromazine or haloperidol, particularly during the initial first 2 weeks of treatment.[38]

Gabapentin, levetiracetam, and zonisamide have also been proposed as potential anticonvulsant drugs in birds.[118,122–124] The advantage of these drugs is that they are not metabolized in the liver and therefore may be used in birds with hepatic disease. Pharmacokinetic studies have revealed similar findings as with phenobarbital in that higher dosages are needed compared with mammals. Because large variations in plasma concentrations were found with these drugs, individual drug monitoring is recommended during treatment with these drugs.[124]

MONITORING AND FOLLOW-UP

To evaluate whether the treatment has the desired (and no adverse) effects, regular monitoring and follow-up of patients are recommended. Regular contact with the owner is needed to discuss alterations in the behavior, including presence of side effects. To obtain objective, meaningful assessments, owners need to be educated to be observant and recognize signs indicative of potential adverse effects. Moreover, they should be encouraged to immediately contact a clinician if suspecting a problem. Regular rechecks in the clinic are also advised during which a physical examination and laboratory tests may be performed. Whether and which tests to perform depends on the type of drug that is used. For most drugs, evaluation of renal and liver function (ie, annually in younger birds and biannually in older birds) is indicated because alteration of the function of these organs can affect the metabolism and clearance of the drugs, thereby warranting adjustment of the dose.[32] Similarly, ECGs should be considered in patients treated with psychoactive medications with known cardiac side effects (eg, SSRIs and phenothiazines).[32] Ideally, therapeutic drug monitoring is performed by a qualified laboratory because this can help guide the course of action in cases of poor clinical response or observation of side effects. Although some initial studies have been performed into plasma concentrations of specific psychoactive agents (ie, amitriptyline and paroxetine) after single or repeated dosing,[45,56] no studies have yet been performed to link plasma concentrations to clinical effects in birds. As a result, clinicians primarily have to rely on data regarding therapeutic windows established in humans and other species. Species, age, and gender differences may exist, however, emphasizing that adequate clinical response are not always achieved by giving the same dose of the same drug to any patient.

In general, starting at a low dose and gradual titration until a clinical effect or adverse effects are observed is recommended. Unless a patient exhibits adverse effects, treatment should be attempted for at least the time period that is needed for the drugs to take effect (ie, 1 week for BZPs and 1 month for most other drugs [**Box 3**]). If, after this period, insufficient response but no adverse effects are seen, the dose can be gradually increased. Should the maximum dose be reached or adverse effects encountered without the problem behavior adequately resolved, switching to another drug (either one from the same family or one from a different family) can be attempted.

Because combined use of psychoactive drugs can potentially result in undesired interactions, withdrawal of 1 drug before starting the next is generally recommended (although some drugs, such as TCAs and SSRIs, can be combined with BZPs to obtain faster results). For example, in humans, the recommended drug-free time for SSRIs is 2 weeks (ie, at least 2 drug-free dosing intervals or 2+ half-lives—the general rule of thumb for withdrawal of any drug).[32] Rather than stopping abruptly, drugs should be weaned to minimize the risk of withdrawal symptoms as well as enable determination of the least effective dose (should long-term maintenance therapy be required). Gradual tapering of the dose is generally accomplished over the same period of time as needed for the onset of clinical effect, or more slower (if possible). Weaning can generally be done rapidly (ie, a reduction of the total daily dose by 25% every week) in patients with minor problems and a rapid response to therapy, whereas slower weaning (ie, over a period of months [eg, reducing the total daily dose by 25% every 3 weeks]) is recommended for patients with major problems and/or a long recovery time.[32,38] Should serious side effects be encountered, immediate discontinuation of the drugs can be attempted. Acute discontinuance, however,

Box 3
Algorithm for treatment length and weaning schedule

For most psychoactive medications, a treatment period of at least 4 months to 6 months is required, in which the following 4 steps or phases can be distinguished:

1. Treat for the minimum period needed for the drugs to take effect, so that their effect can be assessed. Note that some drugs may have a delayed onset of action, for example:
   - Nonspecific TCAs: minimum 7 days to 10 days
   - More specific TCAs and SSRIs: minimum 3 weeks to 5 weeks
2. Treat until the clinical signs related to the behavior problem have been resolved or at least have been reduced to a low, consistent level
   - Requires an additional period of at least 1 month to 2 months
3. Extend treatment of a similar amount of time it took to attain the level as discussed in (2) to reasonably assure reliability of the assessment.
   - Requires an additional period of at least 1 month to 2 months
4. Taper the drugs off gradually over at least the same amount of time needed for the drugs to take effect (more slowly is also possible, eg, 10–20 days for short-acting psychoactive drugs; 6–8 weeks for longer acting ones).

Note: because reversion of receptor conformation may take 1 month or more, it can take longer before signs are noticed. Although acute weaning off does not necessarily have to result in side effects, full-blown recurrence can occur and is a profound side effect, which is preferably prevented because signs may not resolve after reinitiation of treatment with the same drug and/or the same dose.

Adapted from Overall KL. Pharmacologic treatment in behavioral medicine: the importance of neurochemistry, molecular biology, and mechanistic hypotheses. Vet J 2001;62:18; with permission.

may increase the risk of adverse effects (ie, withdrawal or discontinuation syndrome characterized by rebound anxiety and aggression or reoccurrence of the behavioral problem).[38,56]

Should a favorable response be seen to the medication, weaning of the drug can also be attempted (because ultimately the goal is to not have to use drugs permanently). Prior to attempting to wean a patient off medication, however, it is generally recommended to maintain patients on medication for at least 2 months to 3 months to assure that the effects are long lasting (see **Box 3**). If and when sufficient response to therapy has been ascertained, weaning can be attempted in a similar manner as described previously.

SUMMARY

Although behavior modifying drugs can be useful in the treatment of behavior problems in birds, they are not expected to provide a cure on their own. As a rule, beneficial outcomes can be achieved when using symptom-relieving medication as an adjunct therapy to appropriate behavior modification therapy, environmental adjustments, and adequate treatment of any concurrent medical illnesses. If and when thoughtfully applied, medications are likely to benefit the treatment plan because they can help attenuate an animal's response and increase its receptiveness to the environment. Nevertheless, it is important to remember that each patient is unique and no simple test or specific set of clinical signs exists to determine which drug benefits a patient most. As a result, establishing efficacy of a given treatment regimen in an individual patient largely is based on trial-and-error testing, whereby the initial treatment chosen should always be based on sound rationale regarding the origin of the problem behavior and the prescribed drug's mechanism of action. Moreover, despite the potential added value that hormone therapies and psychoactive drugs can have in the treatment of problem behaviors, it should be considered that drugs can also potentially do harm to a patient when having a negative impact on the treatment plan and/or inducing potential adverse effects. Especially for drugs of which the use has been extrapolated from dogs and cats and on which little information is available in birds, risks of potential side effects are great because a drug's pharmacokinetic and pharmacodynamics profile can vary greatly from that in mammals. As a result, veterinarians are warranted to carefully consider whether medication will benefit the individual patient or not and only consider its use if a beneficial outcome is to be expected.

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