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Evaluation and Management of Behavioral Conditions (19-Nov-2001)

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Introduction

Psychiatric disorders - whether in humans or in domestic animals where they are called behavioral disorders - are among the most complex and incapacitating of all pathological conditions. In the USA 20 million patients suffer from depression, manic depression, and schizophrenia. The direct and indirect cost for the treatment of schizophrenia, alone, is $33 billion per year, similar to the combined costs of the treatment of arthritis and coronary artery disease [1].

The data from the literature on canine and feline behavioral disorders are equally impressive. Behavioral disorders are responsible for the relinquishment and death of more pet animals per year than infectious, neoplastic, and metabolic disease, combined. In the early 1990s, the average veterinary practice in the USA was estimated to lose in excess of $17,500 in income annually for services that were not delivered because the pets were relinquished due to behavioral concerns [2]. More recent estimates of behavioral problems suggest that this may be a gross under-estimate [3,4].

Until the 1990s became the decade of the brain and neuroscience in the USA, the tendency was to neatly cluster "neurological" conditions as separate from those considered "behavioral". Neurological conditions tended to be considered as those with discrete somatic pathologies, whereas behavioral conditions, by definition, were viewed as nebulous phenomenon that were the result of an often stated but poorly understood interaction between the physical and genetic environments. Such an absolute and simplistic view had as logical sequelae the views that:

1. all dogs and cats were inherently normal, but their behaviors could be inappropriate or undesirable,
2. if the dog or cat exhibited inappropriate or undesirable behaviors, such behaviors were the result of inadequate guidance from the owner, and
3. appropriate training could fix all concerns about dog behaviors, whereas cats were best left to their own devices as outdoor cats where they could revert to their "normal" state.

Without exception, none of these views is true, and they are - mostly - not often uttered now, although there is still substantial support for the stated views regarding cats. Veterinarians who are general practitioners are committed to providing total patient care. They should be in the position to evaluate deviations from normal behavior and to suggest solutions before the problem worsens. The activities of trainers and handlers are predicated on normal behavior and on the assumption that all problems are management related. While management may play a role in both the expression of behavioral problems and their resolutions, it would be inexcusable and irresponsible to advance poor management as the primary etiology of behavioral disorders. The vast majority of animals with behavioral problems are not poorly managed or misbehaved; they are abnormal or are responding to an abnormal social system [5]. In this context these problems are "organic" in nature - the "organic cause" is a dynamic one, and now encompasses disorders of neurochemical metabolism that underlie many, if not most, behavior problems.

The decade of the brain and of neuroscience forced us to confront the fact that we and our patients are functionally bags of interacting genes and chemicals, and that the nature versus nurture question may be sufficiently simplistic to no longer be heuristically useful.

In light of the findings of regional brain activity and neurotransmitter interaction and dysregulation, it may be a more useful paradigm to consider neurology and behavioral medicine as different points on the same continuum/response surface, or as functions of the scale at which the diagnosis is made and treatment addressed. This position is supported by data from both humans and animals indicating that behavioral changes are the function of, or result in altered regulation of neurochemical function, or dysregulation of neurochemical function. Given this, the pathologies in behavioral medicine are just as organic, although possibly harder to evaluate, as those involved in brain tumors.

Diagnosis in Behavioral Medicine - The Importance of Terminology

Behavioral medicine, unlike other specialties in veterinary medicine, does not have a protected vocabulary. Words that are in common daily usage are often used within the framework of the diagnosis. This has advantages in that the clients are speaking the same language as the veterinarian.The disadvantage is that without a protected vocabulary there is no guarantee that the same definition or context is agreed upon for any of the terms used. Accordingly, it is essential that anyone engaging at any level in the practice of behavioral medicine be very careful about the words they use and their perceived meanings. Associated difficulties can be avoided by defining all terms that are used. The intent here is to ensure that, regardless of anyone's personal definition, the criteria for contextual discussion of the problem at hand are clear.

Also, if the words you choose as labels affect your interpretation and thinking about processes for which you have incomplete information, the actual words become very important. Nowhere is this more important than in behavioral medicine - a field for which signs have (usually erroneously) been viewed as "soft", and for which few simple tools that permit reasonably unambiguous comparison (e.g., a gas chromatograph or refractometer) are available. In fact, only after one is assured that all workers in the field are using the same diagnostic criteria, can any comparisons be made at the population level. The fraction of animals afflicted by a specific behavioral problem is real, but the labels we place on those animals may not be consistent across populations, so that demographic data may not, in fact, reflect the underlying frequency or occurrence of the problem. If this is true, comparisons of efficacy of treatment across populations may be suspect. Cultural patterns of human impact of the behavioral problems of pets can only be assayed using multicenter studies. When well done, such studies can detect underlying sources of variation that suggest causal mechanisms for disorders that may not have been previously appreciated, but such comparisons are invalid if the same rules were not used to formulate the diagnoses (e.g., the "data" here) [5].

In humans, a label like "depression" may refer to a symptom, a syndrome, or a nosological entity [6-9]. Because we assess what we have come to define as depression in humans largely by a series of verbal responses, we use data that are, at best, correlates of underlying pathology. Observable changes in behavior that occur in rodents, which serve as models for human depression, are treated as secondary symptoms in humans, and little effort is made to characterize either human or rodent behaviors in a manner that would allow assessment of analogy or homology. These concerns are central to diagnostic conundrum in both human psychiatry and veterinary behavioral medicine, and have implications for understanding the underlying mechanism of the pathology and for treatment [5,9-12].

The Case for the Use of Necessary and Sufficient Conditions

Implicit in all diagnostic categories, unless explicitly stated, is that there is no known underlying gross physical or physiological reason for the behavioral problem, and that gross physical and physiological "causes" have been ruled out. It is also important to remember that as they are listed here these classifications represent diagnoses of problem behaviors, not just descriptions of a behavioral event (i.e., dominance aggression can **only** be a diagnosis for an abnormal behavior, but interdog aggression can be both a diagnosis and description).

The implementation of "necessary and sufficient" criteria, using the terms as they are used in logical and mathematical applications, is a refinement over descriptive definitions of terms. The imposition of necessary and sufficient diagnostic criteria act as qualitative, and potentially quantitative, exclusion criteria. They allow for uniform and unambiguous assessment of aberrant, abnormal, and undesirable behaviors [13].

A **necessary** criterion or condition is one that must be present for the listed diagnosis to be made. A **sufficient** criteria or condition is one that will stand alone to singularly identify the condition. Sufficiency is an outcome of knowledge: the more we learn about the genetics, molecular response, neurochemistry, and neuroanatomy of any condition and its behavioral correlates the more succinctly and accurately we will be able to define a sufficient condition. Definition of necessary and sufficient conditions is not synonymous with a compendium of signs associated with the condition. The number of signs present and the intensity of those may be a gauge for the severity of the condition, or act as a flag when there can be variable, non-overlapping presentations of the same condition [5]. This approach is similar to that taken by the American Psychiatric Association for the Diagnostic and Statistical Manual (most recent edition = DSM-IV). The conditions that are of interest in veterinary behavioral medicine do not have to be exact analogues of human conditions for this type of classification to be meritorious. In veterinary behavioral medicine we do not yet have the data on large numbers of patients from varied centers that allow human psychiatrists to use clusters of signs to help with diagnosis; however, the criteria for human psychiatric disorders are not based on non-specific signs, either. They are based on definitional criteria that are descriptive, and the non-specific signs are nested within the stipulation made by those criteria [14].

The approach endorsed here provides for a mechanism to collect behavioral data from a variety of populations across time, and to compare those data. Comparisons of data predicated on this classification scheme should engender revisions and refinements of the classification. The classification, itself, is not important: the extent to which it provides a structured, logical, heuristic tool for the development of thought in the field **is** important [13].

Any joint theoretical/clinical approach to studying abnormal behavior should include the following goals:

- a description of the specific behavioral profiles and response surfaces (multi-dimensional) of those profiles;
- postulated levels of mechanism in which to examine potential profiles and response surfaces;
- tests of these postulates by a) breeding for the behavior, b) cataloging response to treatments in controlled and double blind fashions, and imaging of patients (CT, MRI, functional MRI, PET and SPECT scans).

Diagnosis in Behavioral Medicine - The Importance of Mechanism of Level of Resolution

When one makes a behavioral diagnosis one is usually making the diagnosis on the basis of some descriptor of the behavior. Such diagnoses are functional, phenotypic, or phenomenological diagnoses. They are based on the patterns of the behaviors or on profiles of behavioral sequences. Diagnosis at this level may hint at underlying neuroanatomical, neurochemical, molecular, or genetic forces or mechanisms driving the abnormality, but phenotypic diagnoses are not pathognomonic for any of these further discrete, mechanistic levels.

The most common error made in diagnostic approaches that rely on description is to confuse or confound levels of mechanism within descriptions of diagnosis. It is important to realize that tests for mechanistic hypotheses must occur within the level for which the mechanism is specified. For example, tests of a putative neurochemical basis for a behavioral problem must be tested at that level, not only at the more gross level of changes in behavior, although the result of the test may be changed behavior. This approach is outlined in Table 1.

Part of the problem in identifying the relative contributions of the different mechanistic levels to overall behavioral presentation is that most of the data available (e.g., behaviors associated with specific environmental stimuli; alterations in behavior in response to drug therapy) are only correlations. Correlational data can suggest tests of potential hypotheses of causality, but such data are not synonymous with "cause" or mechanism, itself. Diagnoses are not diseases; correlation is not causality. The assumption that they are equivalent is epistemologically insufficient. This assumption is the most common error made in thought about most processes, including normal and abnormal behavior.

Conditions for which there is putative etiologic and pathophysiologic heterogeneity (multi-factorial disorders) are complex. Diagnosis and treatment will be complex. For example, not all tail-chasing is due to the same underlying neurophysiological mechanism (See Table 1), but unless there are criteria for diagnosis and description, and a heuristic framework within which to separate various causal or mechanistic aspects of diagnosis, we will not able to distinguish between different causes of tail chasing.

Phenotypic (functional, phenomenological) diagnoses are open to various mechanistic bases at all lower levels. Some of these more reductionistic levels can be partially tested using treatment (specific pharmacologic agents), but few phenotypic diagnoses can be specifically tested using behavior modification. Regardless, the logic for using very specific phenomenological diagnoses is to (a) enumerate and identify the particular behavioral manifestation that needs to be altered or assessed, and (b) to identify areas where specific behavioral intervention can be useful.

Table 1. Understanding Patterns of Behavior within Levels of a Mechanistic Approach

I. Phenomenological, phenotypic, functional diagnoses: must meet necessary and sufficient terminological criteria

A. Demographic patterns

1. Global patterns of behavioral change with age and neutering (must follow individuals through time)

B. Suites of behavioral patterns

1. Specific behaviors that occur
   a. Number of behaviors that occur (range, mean, predictive value)
   b. Covariation in behaviors to define subtypes or subpopulations (Venn diagrams, r values) - must avoid spurious correlations
   c. Ontogenetic development of specific behavioral suites (ethograms) (must follow individuals)
2. Elemental behaviors that are shared across diagnoses (may hint at underlying reductionist mechanism - i.e., the neurochemistry of stress)

II. Neuroanatomical diagnoses

A. Region activated during normal versus abnormal behavior

1. Level of activity
2. Variants in patterns of activity

B. Neuron behavior

1. Types
2. Densities
3. Overall activity

III. Neurochemical/Neurophysiological diagnoses

A. Types of neurochemicals

1. Activities
2. Receptor types associated with these
   a. Activity of receptor gates
   b. "Metabolism" of receptors
   c. Conformation of receptors

B. Interactions of neurochemicals

1. Neuron recruitment
   a. Regional activity
   b. Responses to behavioral changes

IV. Molecular diagnoses

A. Molecular/conformational chemistry of receptors and neurotransmission

B. Gene product regulators of expression

C. Gene product regulators of function

V. Genetic diagnoses

A. At the level of gene/locus

1. Overall heritability (Mendelian pattern)
   a. Codon shifts
   b. Errors (loss or addition of part of chromosome - e.g., Marshall's disease, Down Syndrome)
   c. Coding for different proteins
2. Multi-factorial effects

B. At the level of genome

1. Gene products
2. Regulator genes
3. Local environmental receptor effects

Note: tests of mechanistic hypotheses must occur at the level of focus.

Inherent in the nature of a functional or phenotypic diagnosis is the association of a compilation of what are relatively non-specific signs. Growling is no more specific a sign than is an elevation in temperature, yet the distinction between compilations of signs and diagnosis has often been blurred in behavioral medicine. Some of the difficulty is the result of the fact that behavior is so complex. Behavior can be both an event and a process, and observable behaviors are the result of the integration of all of the processes ongoing in underlying organ systems, in interaction with the external social and physical environments. The integration of processes inadvertently encourages tautological diagnoses. Careful thought is necessary to avoid tautology. One mechanism whereby tautology can be avoided is to specify necessary and specific conditions for diagnosis, separately from compendia of non-specific signs. Once these conditions are specified, lists of signs and frequencies with which those signs occur can be compiled for each diagnosis, allowing within and between level population comparisons. Differences could reflect cultural or environmental effects on the manifestation of frequencies of constellations of signs, and would allow comparisons of intensity or relatedness of individual diagnoses when they occur singly compared to when they occur in tandem with other diagnoses. Knowledge of the frequency of specific behaviors is useful for:

1. establishing an overall pattern of the behavior [a. suites of behavioral patterns, b. determining heterogeneity of condition (how variable is it?), c. mechanistic tests of causality];
2. intervention;
3. danger assessment, and
4. prognosis. These components are not synonymous with a diagnosis.

Finally, it is essential to understand that the model presented in Table 1 is **not** merely a behavioral recapitulation of the standard paradigm of diagnostic pursuit (e.g., first a clinical diagnosis is made, then a laboratory or radiographic diagnosis is made, then a pathological diagnosis, etc.). In behavioral medicine the "levels" of diagnoses interact in a dynamic and complex manner. How an animal behaves affects which areas of the brain are active and the degree to which they are active, which, in turn, affects regional neurochemistry. The behavior can also affect the neurochemistry directly, and both the behavior and the neurochemistry can have an effect on the molecular effects on receptor configuration. Rather than view these as nested diagnostic levels, each of these levels should be viewed as dynamic, variable, interactive response surfaces. In this model the genomic response surface sets boundary conditions that define the extent to which the other responses surfaces can respond in a fluid manner and can be plastic in their interactions with other levels of response surfaces.
The approach discussed tracks the number and type of diagnoses, number and type of signs, and population level and temporal differences, without confounding these as occurs when diagnosis is indistinguishable from lists of signs. This approach generates data that could then provide hypotheses for which tests could be directed at each individual level. For example, if two diagnoses were phenotypically different, but neurochemically indistinct, this suggests that the differences in the phenotypic presentation are due to environmental, social, or cultural effects. If, on the other hand, one diagnosis is shown to have two neurochemical bases, the resultant behavior can be due to underlying differences in physiology and genetics plus any overlying effects of the environment (See Table 2A & Table 2B for examples).

Table 2A. Example for Consideration of Interaction of Phenotypic Level of Mechanism with others

Phenotype	Abnormal Variant A	Abnormal Variant B	Abnormal Variant C	"Normal" D
Neuroanatomical Variant	I	I	I	I
Neurochemistry	a	b	a	b
Molecular Products	I'	II'	II'	II'
Genotype	a'	b'	b'	b'

In this example the variants in the condition are due to some difference in environmental response. This could be a purely phenotypic effect (Abnormal variant B). Alternatively, the effect could be due to learning and long-term potentiation (in which case the molecular level is affected - Abnormal variant A); this molecular effect also affects neurochemistry. The effect could also be one of neurochemistry, without affecting the molecular level (Abnormal variant C).

Table 2B. Example for Consideration of Interaction of Phenotypic Level of Mechanism with Others

Phenotype	Abnormal Variant A	Abnormal Variant B	"Normal" C
Neuroanatomical Variant	I	I	I
Neurochemistry	a**	b	b
Molecular Products	I'**	II'	II'
Genotype	a'	b'	b'

In this example the variants in the condition are due to some difference in environmental response. This could be a purely phenotypic effect, as presented. Alternatively, the effect could be due to learning and long-term potentiation (in which case the molecular level is affected) or the effect could be one of neurochemistry. The two latter choices are reflected as (**).

Fears, phobias, anxieties, and obsessive-compulsive disorders (OCDs) are among the most difficult behavioral problems to diagnose and treat. There is probably no other area in behavioral medicine that is fraught with such confusion and opinion. Historically, many anxiety-related conditions, including those involving impulsive aggression, have been viewed as neurological conditions involving seizure activity. This assumption has lead to treatment with barbiturates, as for a seizure disorder, which has often initially mitigated the clinical signs experienced by the patient. It would be a mistake to think that response treatment with any medication commonly used to control any kind of epilepsy or seizure activity confirmed the presence of such activity. Rather, it is necessary to understand the gross neurochemical pathways involved in these conditions, their locations and interactions, and how they are affected by medications used to treat them.
Fear and anxiety are probably closely related, but may not be identical at the neurophysiological level. It is worth remembering that when one diagnoses a problem related to fear or anxiety one is doing so at the level of the phenotypic or functional diagnosis, but such conditions are treated at this level and, when psychotropic medication is used, at the neurophysiological level.

Definitions of Common Conditions that may be Concerns for those Evaluating Neurological Diagnoses
As already discussed, diagnosis may not be as simple or clear-cut as a definition. Given that we do not understand the manner in which the "causal" levels interact to produce the problem, we can only evaluate the form that interactions take phenotypically. Clear use of terminology can help to make apparent the parts that are consistent and that we can understand and separate them from those that are more complex. While these definitions are clear, the conditions for which they are relevant may be multi-factorial and heterogenous. Table 3 contains the preferred and accepted definitions of general behavioral descriptors that are used in both neurology and behavioral medicine, as well as psychiatry. Table 4 contains the necessary and sufficient diagnostic criteria for behavioral diagnoses that may frequently be considered as differential diagnoses for the putative neurological patient. One can see by the definitions of epilepsy and seizure that these terms could be used to describe virtually all behavioral conditions, without actually providing any information about them. Again, such inexactitude is an historical artifact related to how we began to understand neurological and behavioral conditions that has virtually no relevance for modern approaches to behavior. In part, the diagnostic scheme discussed and demonstrated in Table 4 was created in response to an informational vacuum with respect to phenotypic behavioral characterization.

Table 3. Preferred and Accepted Definitions of often Discussed General Behavioral Conditions
Abnormal behavior: Activities which show dysfunction in action and behavior. **Anxiety:** Anxiety is the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria (in humans) and, or somatic symptoms of tension (vigilance and scanning, autonomic hyperactivity, increased motor activity and tension). The focus of the anxiety can be internal or external. **Convulsion:** Seizure with generalized motor impairment. **Displacement activity:** An activity which is performed out-of-context, or "displaced", because the animal is "frustrated" in its attempt to execute another activity or otherwise occupy itself. This is considerably less specific than redirected activity which implies a substitution of behavior "in kind", but towards another target. In cases where displacement activity is involved the activity may not be "in kind". **Epilepsy:** A disorder of the brain that is characterized by recurring seizures. **Fear:** A feeling of apprehension associated with the presence or proximity of an object, individual, social situation, or class of the above. Fear is part of normal behavior and can be an adaptive response. The determination of whether the fear or fearful response is abnormal or inappropriate must be determined by context. For example, fire is a useful tool, but fear of being consumed by it, if the house is one fire, is an adaptive response. If the house is not on fire, such fear would be irrational, and, if it was constant or recurrent, probably maladaptive. Normal and abnormal fears are usually manifest as graded responses, with the intensity of the response proportional to the proximity (or the perception of the proximity) of the stimulus. A sudden, all-or-nothing, profound, abnormal response that results in extremely fearful behaviors (catatonia, panic) is usually called a phobia.

Table 3. Preferred and Accepted Definitions of often Discussed General Behavioral Conditions

Mental disorder (not generally used in veterinary behavioral medicine):

Clinically significant behavior of psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or a loss of freedom." [14]. Regardless of cause, the disorder is a "manifestation of a behavioral, psychological, or biological dysfunction in the individual." [14].

Obsessive-compulsive disorder:

An APA classification of abnormal behaviors that have as characteristics recurrent, frequent thoughts or actions that are out-of-context to the situations in which they occur. These behaviors can involve cognitive or physical rituals, and are deemed excessive (given the context) in duration, frequency, and intensity of the behavior. One of the hallmarks of this condition that distinguishes it from motor tics, etc., is that OCD behaviors follow a set of rules created by the patient. The condition in domestic animals is probably similar and analogous through descent, and probably includes stereotypies, self-directed behaviors, etc. Regardless, the behavior must be sufficiently pronounced to interfere with normal functioning.

Phobia:

A sudden, all-or-nothing, profound, abnormal response that results in extremely fearful behaviors (catatonia, panic) is usually called a phobia. An immediate, excessive anxiety response is characteristic of phobias. Phobias usually appear to develop quickly, with little change in their presentation between bouts; fears may develop more gradually, and within a bout of fearful behavior, there may be more variation in response than would be seen in a phobic event. It has been postulated that once a phobic event has been experienced, any event associated with it or the memory of it is sufficient to generate the response. Phobic situations are either avoided at all costs, or if unavoidable, are endured with intense anxiety or distress.

Redirected activity:

Direction of an activity away from the principal target and toward another, less appropriate target. This is usually best identified when the recognized activity is interrupted by the less appropriate target or by a third party, and, in contrast to displacement activity, redirected activity appears to be a substitution "in kind" of the interrupted behavior.

Separation anxiety:

When animals exhibit symptoms of anxiety or excessive distress when they are left alone the condition is called separation anxiety; however, the most commonly exhibited behaviors (elimination, destruction, excessive vocalization) are only the most visible signs of anxiety. Drooling, panting, and cognitive signs of anxiety will not be diagnosed but probably occur.

Seizure:

Synonymously used with fits and convulsions, a term used to describe the manifestations of abnormal brain function that are characterized by paroxysmal stereotyped alterations in behavior.

Stereotypy:

A repetitious, relatively unvaried sequence of movements which have no obvious purpose or function, but that are usually derived from contextually normal maintenance behaviors (e.g., grooming, eating, walking). Inherent in the classification of dysfunction is that the behavior interferes with normal behavioral functioning.

Vacuum activity:

An activity involving an instinctive, unconscious, or response behavior in the absence of the stimulus that would elicit that behavior. Such activity seemingly has no apparent, contextual, useful purpose.

Table 4. Necessary and Sufficient Conditions for Selected Behavioral Diagnoses Associated with Anxiety in Small Animals, and with Relevance to Patients for whom Neurological Diagnoses may be a Concern (adapted from [15].)

Behavioral Diagnosis: **Cognitive dysfunction**
Necessary and Sufficient Conditions: Change in interactive, elimination, or navigational behaviors, attendant with aging, that are explicitly not due to primary failure of any organ system.

Behavioral Diagnosis: **Dominance aggression** (perhaps better labeled canine impulse control aggression)
Necessary Condition: Abnormal, inappropriate, out-of-context aggression (threat, challenge, or attack) consistently exhibited by dogs towards people under any circumstance involving passive or active control of the dog's behavior or the dog's access to the behavior.
Sufficient Condition: Intensification of any aggressive response from the dog upon any passive or active correction or interruption of the dog's behavior or the dog's access to the behavior.

Table 4. Necessary and Sufficient Conditions for Selected Behavioral Diagnoses Associated with Anxiety in Small Animals, and with Relevance to Patients for whom Neurological Diagnoses may be a Concern (adapted from [15].)

Behavioral Diagnosis: **Noise phobia**
Necessary and Sufficient Conditions: Sudden and profound, non-graded, extreme response to noise, manifest as intense, active avoidance, escape, or anxiety behaviors associated with the activities of the sympathetic branch of the autonomic nervous system; behaviors can include catatonia or mania concomitant with decreased sensitivity to pain or social stimuli; repeated exposure results in an invariant pattern of response.

Behavioral Diagnosis: **Obsessive-compulsive disorder**
Necessary Condition: Repetitive, stereotypic motor, locomotory, grooming, ingestive, or hallucinogenic behaviors that occur out-of-context to their "normal" occurrence, or in a frequency or duration that is in excess of that required to accomplish the ostensible goal.
Sufficient Condition: As above, in a manner that interferes with the animal's ability to otherwise function in his or her social environment.

Behavioral Diagnosis: **Panic disorder**
Necessary condition: sufficient, profound, non-graded, extreme response exhibited out-of-context to the provocative environment, manifest as active avoidance, escape, or anxiety associated with the activities of the sympathetic branch of the autonomic nervous system.
Sufficient condition: as above but includes mania or catatonia concomitant with decreased sensitivity to pain or social stimuli; once established repeated exposure results in an invariant pattern of response.

Behavioral Diagnosis: **Separation anxiety**
Necessary Conditions: Physical or behavioral signs of distress exhibited by the animal only in the absence of, or lack of access to the client.
Sufficient Conditions: Consistent, intensive destruction, elimination, vocalization, or salivation exhibited only in the virtual or actual absence of the client; behaviors are most severe close to the separation, and many anxiety-related behaviors (autonomic hyperactivity, increased motor activity, and increased vigilance and scanning) may become apparent as the client exhibits behaviors associated with leaving.

The Conundrum Posed by the Neurological/Behavioral Continuum

Most of the ways in which clients recognize that something is wrong with their pets or that their pets are ill involves behavior. Clients may not be able to define "normal" behavior for their pet under non-provocative circumstances, but they are excellent at recognizing when their pet deviates from this. Accordingly, a limp which is the result of a purely somatic condition is first understood and recognized by the client because the dog ceases to run and walks oddly.

The standard DAMNIT scheme for grouping of conditions actually originates in perceived behavioral changes, and then seeks underlying somatic "causes" for the dysfunction. Unfortunately, this heuristic model is inadequate to deal with behavioral conditions that may reflect altered or dysegulated neurochemistry in the absence of any organic or somatic dysfunction. Even the "anomalous" grouping refers primarily to structural developmental defects. The heuristic failure of this classification scheme in behavioral medicine is demonstrated by how often algorithms designed to identify neurological pathology lead to "behavior" or "non-neurogenic X" as a path of last resort [16].
Furthermore, if we wish to explore more refined mechanisms of the behavioral conditions we would have to redefine the accepted terminology in the DAMNIT mnemonic to reflex complex interactions at the cell, molecular, and genomic levels. This is unlikely to happen, and would not necessarily increase our understanding even if it were done.

In part, the difficulty with behavioral medicine is due to the fact that the diagnostic paradigms used in veterinary (and human) medicine have changed little in the last 100+ years, and are inadequate to describe or discuss conditions that are the result of genomic, molecular, or neurochemical dysfunction in the absence of structural or mechanical defects that can be directly measured. To understand behavioral conditions at a level more sophisticated than that of general and broad gene x environment interactions, a paradigm shift is required. In addition to the structured thought process previously discussed, a new paradigm should require that we are careful with our terminology and define the conditions by which phenotypic diagnoses can be made, and that we understand that the behaviors we see are, at some level, the results in complex interactions between DNA, RNA, 2nd messenger systems, trophic factors, receptors, neurochemicals, and tracts and pathways that help define the possibilities for neurochemical interaction. The rest of this chapter will focus on these complex interactions as they are presently understood.
Nowhere is the resultant compromise of our understanding about the behavioral condition more clear than for various behavioral conditions that are termed "seizure disorders". The most common of the behavioral conditions that are often

classified as "seizure disorders" are obsessive-compulsive disorder (OCD), panic disorder, and dominance aggression or canine impulse and control disorder. A short discussion of dominance aggression, OCD, and cognitive dysfunction will indicate the problems faced.

Considerations for the Neurobiology of Canine Dominance Aggression

When considering the application of the necessary and sufficient conditions listed in Table 4 for dominance aggression, it is critical to consider the entire context of the interaction in which the behavior occurs. The classic afflicted dog growls, lunges, snaps or bites if they are stared at, physically manipulated - often when reaching over their head to put on a leash, physically disrupted or moved from a resting site - no matter how gently this is done, and when they are physically or verbally corrected. Otherwise, owners report that these are perfectly wonderful and charming dogs for well over 95% of the time. Owners are further puzzled by the observation that the dog often seeks them out for attention and then bites them when they give it. As for most other behavioral conditions, this one develops or becomes enhanced during social maturity, further confusing owners because the dog was "perfect" for the first 1 - 1.5 years of life. Unfortunately, the age at which the condition most frequently becomes apparent is also the age at which most dogs develop idiopathic epilepsy, further confounding the problem. Most dogs exhibiting dominance aggression/impulse - control disorder are male, although there is a female group that exhibits the behavior beginning in puppyhood, leading to questions of *in utero* androgenization of the brain [17]. Unlike for fear aggression, where the animal intensifies his or her response when escape becomes impossible, dogs with a control disorder take a proactive role in precipitating the events. They do so because of underlying anxiety about contextually appropriate responses in situations involving humans. These dogs are unable to take a more passive role and to obtain, from context, what would be considered acceptable behavior. There are 2 broad classes of this condition: the impulsive or explosive form, and the more common, consistent form where the dog’s response and behavior are variable depending on the circumstances and the behavior of the humans involved.

In type 1 of this canine impulse control disorder, the dog appears to fire quickly and without warning, leading may authors to describe "rage" like behaviors [16] or to consider this to be a form of temporal or frontal lobe epilepsy [18]. Again, based on the definition of epilepsy, little information is gained by such a label and much might be lost because we think that we know something when, in fact, we do not. Rage is undefined for domestic animals, and also implies some human value judgement/emotion that may be compromised in its evaluation in animals.

Instead, perhaps we should think of canine impulse-control disorder, in general, as a pathology involving both control and anxiety; the control is a direct result of the anxiety and is the rule structure by which the patient attempts to deal with and address the anxiety. In type 1 the patient is working every second to keep their reactivity level below their explosive threshold. Behaviors exhibited by humans involving manipulating the patient or the patient’s access to their own behaviors function to induce the patient’s reactivity to approach the threshold. Once the threshold is reached the patient fully, and often indiscriminately, "fires". In this case the "firing" results in full-blown attack. The dilation of the pupils described by the clients is a sympathetic response. That the dogs often withdraw afterwards is logical: the response is physically exhausting, as is long-standing anxiety, itself. Also, although these dogs may be uncertain about appropriate contextual responses, they are certain that their response is viewed by the humans as "wrong". These dogs may even realize that they are out of control; humans with impulse-control disorders realize that something is wrong and that their response was wrong, although they feel helpless to stop it, once started.

In type 2 of this condition the dogs use somewhat threatening behaviors to deform their social interactions involving humans. In this way the dog gets information about the individual person’s response and whether the dog should worry or feel threatened, given the context. People who give the dogs clear, unambiguous signals that do not scare, injure, hurt, or threaten the dog tend to have a good relationship with the dog. People who are unclear, timid, or truly threatening are at risk from the dog because the dog has now, by deforming the social environment and getting information, confirmed the individual’s unreliability. This is a rule structure that ideally should address the anxiety by telling the dog when there is a threat, but backfires because the humans don’t understand what the dog is doing. All attempts to lead by physical intimidation ("dominate the dog") are teleologically doomed to failure, worsen the dog, cause increased risk of injury to humans, and may result in the dog’s death.

A New Look at Canine Dominance Aggression - The Neurobehavioral Genetics Paradigm

Canine dominance aggression is a control disorder that has impulsive and non-impulsive forms. Both forms involve access to control in direct social situations involving humans. The range of behaviors manifest in this condition includes postural threats and stares to sudden stiffening and bites [13,19,20]. This is the primary category of canine aggression in which no warning is given [21].

Impulsivity in humans has been relatively well studied from the behavioral aspect because of the public safety and legal concerns associated with the attendant aggression [11]; however, any behavior that is considered unduly risky or inappropriate has a tendency to be labeled "impulsive". Impulse-control disorders in humans are characterized phenotypically. Intermittent explosive disorder is characterized by failure to resist aggressive impulses that then result in explosive attacks [14]. The aggression is grossly out of proportion or out of context with any ostensible provocative stimulus. Individuals are remorseful after the event. While it is difficult or impossible to evaluate "resistance" or "remorse" in dogs, those affected with dominance aggression exhibit out-of-context, inappropriate, abnormal - whether in scope or form - behaviors under relatively non-provocative circumstances. After the outbursts these dogs often withdraw and may be avoided by other family pets.

Little work has been done either post-mortem on neuroanatomy or cytoarchitectural facets of these conditions, or ante-mortem using imaging studies of dominance aggression or impulsivity,*per se*. Limbic system structures, in general, have been related to impulsive risk-taking, behavioral timing, and time judgements [22].

The serotonin system has been implicated in both canine impulse - control disorder/dominance aggression and in human impulsivity. Affected dogs have been reported to have both lower [23] and equivalent [24] CSF levels of 5-hydroxyindol acetic acid (5-HIAA) and homovanillic acid (HVA), metabolites of serotonin and dopamine, respectively, post-mortem when compated with control dogs. Clearly, any conclusions regarding CSF levels of neurotansmitter and the condition are premature.

In a screening study seeking to examine urinary metabolites, dominantly aggressive dogs were statistically over-represented, compared with unaffected controls and all other canine patients evaluated for behavioral problems for excess excretion of certain amino acids that may be related to excitatory amino acids [25]. Further refinement of amino acid identification is still needed to interpret these findings. Afflicted dogs respond to treatment with TCAs (tricyclic antidepressants) and SSRIs (selective serotonin re-uptake inhibitors) when combined with behavior modification, supporting at some level an association between improvement and serotonin levels.

These neurochemical finding are interesting in light of the putative role of serotonin in impulsivity [26]. Linnoila et al., [27] found that CSF 5-HIAA was reduced in aggressive human patients only for those who were impulsive. This correlation between serotonin metabolites and impulsivity has been noted in further studies [28-30] that implicate low serotonin turnover rate in impulsive aggression. Treatment for many of these patients involves augmentation of serotonin through use of TCAs and SSRIs, as for dogs. Part of the problem in assessing the relative importance of such changes is that monoamine levels appear to change over the course of development in humans and over the course of the condition [31], so these data may be more relevant than they seem. Finally, monoamine levels may not accurately reflect functioning of receptors or neurons, and, as discussed below, serotonin may not be the relevant target. Instead, serotonin may be the messenger by which trophic compounds that remodel receptors are stimulated to act.

Considerations for the Neurobiology of Canine Obsessive-Compulsive Disorder

The behavior changes that occur with seizures include, one or more of the following involuntary phenomenon:

1. loss or derangement of consciousness or memory (amnesia),
2. alteration of muscle tone or movement,
3. alterations of sensation and special senses including visual, auditory, and olfactory hallucinations,
4. disturbances of the autonomic nervous system (e.g., salivation, urination, defecation), and
5. other "psychic" manifestations, abnormal thought processes or moods recognized as behavioral changes (e.g., fear, rage) [16].

Unfortunately, in the absence of criteria that also require abnormal brain function characterized by paroxysmal, stereotyped alterations in behavior, and the aural, ictal, and postictal phases, these 5 suites of behavioral descriptions are sufficiently broad that all behavioral conditions could be considered related to "seizure disorders". This observation suggests, again, that the extant paradigms for understanding neurobehavioral conditions are inadequate to describe the elegant interacting neurochemical, receptor, and genomic mechanisms that specify brain function in normal and abnormal states.

Obsessive-compulsive disorder (OCD) in dogs is usually recognized because of the presence of the compulsive component - the ritualistic, stereotypic behaviors. Obsessive compulsive behaviors can include those characterized by circling, tail-chasing, flank sucking (particularly in Dobermans), fence running, fly-biting, self-mutilation (acral lick granuloma, neurotic dermatitis), hair/air biting, pica, pacing/spinning, staring and vocalizing, some aggressions, self-directed vocalizing, and wool/fabric-sucking/chewing (particularly in cats) [32,33]. Because behaviors manifest in OCD are often normal behaviors exhibited in an inappropriate, excessive, or out-of-context manner, history becomes particularly important in elucidating whether the patient truly has OCD. Parallel examples of stereotypic behaviors are found in human medicine. These include trichotillomania (hair-pulling), hand washing, and checking (lights, gas jets, locks) [34].

Although the underlying etiology of these disorders is unclear for both dogs and humans, the symptomology and pathophysiology are striking. OCD is characterized by repetitive, ritualistic behaviors, in excess of any required for normal function, the execution of which interferes with normal, daily activities and functioning. Inherent in this description is a behavior that is exaggerated in form as well as duration. Furthermore, the behavior can be perceived by the human patient as abnormal and may be controlled to the extent that the behavior is performed only minimally, or not at all, in the presence of others. This is probably also true for domestic animals. Dogs who flank suck or tail chase may, after frequent reprimands and corrections, remove themselves from view of the owners, then commit the behavior elsewhere. Upon approach, the behavior ceases, to be begun again when no one is watching or when the animal removes himself from view. The presence of a cognitive component is not sufficient to rule out OCD, but it does suggest that the problem is rooted at a higher level than the behavior, alone, may indicate (i.e., the Doberman is flank-sucking, but not because anything is wrong with its flank). This particular class of OCD makes the case for obsessions being a valid component of OCD. We evaluate obsessions in humans by asking them about ruminant, invasive thoughts. The verbal or written component of the response is a translation of the rumination - it is not identical to the ruminant thought, itself. It is inappropriate to apply a criteria to one species that has a divergent phylogeny that prohibits the use of that tool or criteria.

Not all dogs and cats fit a volitional pattern where they can at least temporarily stop their compulsive behaviors. Some dogs show continuous stereotypic and ritualistic behavior regardless of distraction or companionship. It is not necessary that the behavior be continuously witnessed for the animal to have OCD, but it is requisite that the offending behavior substantially interfere with normal functioning in the absence of physical restraint. If the desire to exhibit the behavior is present, despite restraint because of punishment, training, or physical incarceration, the condition is present. The key is that if such control is removed and the animal could commit the behavior he will commit the behavior. Ignoring this crucial point will result in under-diagnosis of OCD and under-estimation of its frequency in canine and feline populations.

Obsessive-compulsive disorder in humans frequently appears in adolescence, and continues through mid-life. Human patients are generally clustered into four major groups: washers, checkers, ruminators, and an indistinct group of primary obsessive slowness. In dogs, OCD also appears during social maturity, and left untreated, whether by behavioral or pharmacologic intervention, it worsens.

In the case of OCD, the facets of a seizure disorder that are often concordant with the behaviors can include apparent loss or derangement of consciousness or memory (amnesia) or the appearence of confusion that the animal may perceive associated with the recurrent urges or obsessions to act in their own, peculiar stereotypic manner, alteration of movement, visual, auditory, and olfactory hallucinations, and abnormal thought processes or moods recognized as behavioral changes (e.g., fear, rage). Caution is urged here in associating unspecified and non-specific signs with either a descriptor (e.g., "rage") or a diagnosis (e.g., "fear"). Furthermore, we are severely handicapped in our ability to measure or assess auditory or olfactory alteration; we are utterly incapable of defining "psychic" manifestations in pets. Such terminology adds nothing to our knowledge and actually interferes with our ability to understand the problem by allowing us to dismiss it with a label. Disturbances of the autonomic nervous system function (e.g., salivation, urination, defecation) may be secondary to other behaviors, and should not be considered diagnostic or pathonogmonic, alone. In fact, these physical, measurable, and visual non-specific signs are shared by a number of conditions, and the extent to which the animal exhibits multiple signs may hint about underlying mechanism of the disorder and about prognosis [5]. Because non-specific signs associated with all forms of OCD in both dogs and cats appear out of context to the owner and stereotyped they are often incorrectly grouped with seizure disorders.

Lick granulomas have been variously attributed to neuropathies or atopy, but we should consider that these attributions be the result of correlations of non-specific signs. Some lick granulomas have been attibuted to a neuropathy/radiculopathy [137]. In these cases it is unclear if the radiculopathy is primary or secondary to the damage and lesion. This is an important point because in studies involving nerve conduction function, although some dogs with lick granulomas appeared to have aberrant nerve conduction function, the leg with the lesion was not the only leg that was affected [138]. Such data strongly suggest that problems with nerve conduction velocities are not causal in a solitary manner. At some point in their pathology these lesions appear to change in an almost chaotic way at some point and what leads to that change should be the mechanism for the pathology. The SSRIs and specific TCAs are fantastic analgesics - particularly for myopathic and neuropathic pain - because they have some effects on the dorsal root ganglia and some complex and poorly understood interaction between serotonin, nitric oxide and substance P, in addition to a host of kinin agents [139]. It is possible that when we have a lick granuloma we are actually seeing a manifestation of a bizarre migration of dysfunctional cells that, during gastrulation, experienced some regulatory inductive effects, or that are affected post-development by other neuroregulatory dysfunction

[140,141]. Hence, the behavioral (central) and peripheral signs are co-morbid. If people would begin to collect good behavioral history data so that we could more discretely define the phenotypic subgroups we might be able to test that hypothesis.

If this classification is so egregious, why does a drug commonly used to treat seizure disorders, phenobarbital, often initially aid in or mitigate the treatment of OCD?
This question elucidates the crux of the entire argument in favor of a paradigm shift to further our understanding of neurobehavioral genetics. GABA (gamma amino butyric acid) is formed from the excitatory amino acid (EEA) glutamate via glutamic acid decarboxylase (GAD), catalyzed by GABA-transaminase (GABA-T) and destroyed by transamination. There are two main groupings of GABA receptors: GABA-A and GABA-B. GABA-A receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing chloride influx. Barbiturates and benzodiazepines are potentiators of GABA-A [35]. Both barbiturates and progesterone suppress excitatory responses to glutamate [36]. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate [37]. Accordingly, if both OCD and seizure activity involve dysregulation of GABA and glutamate at some level, it would not be surprising that barbiturates can affect both. OCD is a progressive disorder. It is possible that as the condition progresses other neurochemical tracts (e.g., those in the dorsal raphé affecting serotonin) become involved with resultant dysfunction of serotonin metabolism. At this point, barbiturates, which provided an initial, relatively non-specific neuromodulatory role, are insufficient to address the level and form of neurochemical pathology. The barbiturates would then be said to work "some of the time" or "early". Uncritical acceptance of such statements tricks us to thinking we understand something when, in fact, the chance for further understanding has been obscured.

A New Look at Canine OCD - The Neurobehavioral Genetics Paradigm
Studies involving computed tomography have implicated the basal ganglia, particularly in the region of the basal ganglia and the caudate nucleus [38-41]. These regions have also been implicated in animal models [42,43]. Changes in cerebral glucose metabolism in the orbitofrontal region have been found to correlate response to treatment [25]. The pathology of OCD appears to be partially attributable to aberrant serotonin metabolism, although some have postulated a tandem role for abnormal endorphin metabolism [44]. Neuropharmacological approaches to therapy have sought to address these abnormalities by augmenting serotonin through the use of TCAs and SSRIs [45]. A complete understanding of the integrated anatomical and neurophysiological mechanisms of OCD is not yet a reality.
As is true for humans, OCD appears to be rooted in a neurophysiological abnormality [33], and dogs respond well to the tricyclic antidepressant clomipramine [33,46-49] and to the SSRI, fluoxetine [50]. In dogs, as in humans, in the absence of behavioral and pharmacological treatment, OCD rarely resolves. Should the medication be discontinued, the patient relapses in many cases [13]. Symptoms may be worse or more pronounced in stressful or anxiety producing circumstances [14,15].

It has been hypothesized that there is a genetic and heritable component to the condition since it appears to run in some family lines; at least 2 - 3% of the general human population is afflicted with obsessive-compulsive disorders. First degree relatives have a greater risk for the condition than do members of families in the unaffected human population. Given that dog breeds represent genetic canalization that is further compounded by inbreeding schemes, we would expect the incidence in the canine population to be higher than that in the human population. The breeds in which OCD appears to run in family lines that are commonly seen in the Behavior Clinic at VHUP are: great Danes, German short-haired pointers, German shepherd dogs, bull terriers [48], English bull dogs, Jack Russell terriers, Dalmatians, Bouvier de Flanders, Salukis, Cairn terriers, basset hounds, and soft-coated Wheaton terriers [51]. As is true for humans, first degree relatives usually have a different manifestation of OCD than does the proband. These features support the above hypotheses of a neurochemical/neurogenetic basis for OCD. Again, it is important to remember that although this condition responds to TCAs and SSRIs (e.g., compounds affecting serotonin), augmentation of serotonin may not be the end point. Serotonin may function only to trigger 2nd messenger systems that then affect transcription and translation of proteins that comprise receptors, as discussed later.

Considerations for the Neurobiology of Canine Cognitive Dysfunction
Cognitive dysfunction is broadly defined in animals to represent geriatric behavioral changes not attributable to a general medical condition [13,52]. This definition encompasses all of the human geriatric dementias and is not sufficiently specific to delineate a sub-population that may be a good phenotypic model for anxiety. The commonly noted signs of cognitive dysfunction are similar to those noted for canine separation anxiety: elimination in the house and alterations in activity level. The pattern of these changes differs from that seen in true separation anxiety dogs, and the dogs also exhibit behaviors consistent with disorientation that may share similarities with some of the behavioral changes associated with seizure disorders.

Finally, in dogs such signs can be difficult to separate from non-specific changes associated with decreasing function of the visual, auditory, or locomotor systems that occurs with aging. There are currently few published assessment scales that permit objective evaluation of behavioral changes either with the progress of the condition(s) or with treatment (but see [53]). Thus far, the majority of data have been collected from opinion surveys of owners. This is an inadequate and insufficient tool, and is neither reliable nor repeatable. Future work in the field needs to address quantification and qualification of the specific behaviors noted in cognitive dysfunction.
Age-related memory dysfunction is extraordinarily difficult to assess in dogs, but it can and has been done using longitudinal studies of actual behavioral progressions and changes and responses to provocative memory tests are required to enhance specificity of behavioral correlates and diagnosis [54-56].

A New Look at Canine Cognitive Dysfunction - The Neurobehavioral Genetics Paradigm
As is true with human Alzheimer's disease, definitive diagnosis may be ascertainable only post-mortem [57]. Aged dogs with cognitive changes show similar lesions, including the deposition of β-amyloid plaques to those seen in human patients [58]. The hippocampus and the cerebral cortex are primarily affected [58,59], as is true for most humans. Additional changes include ventricular dilation, thickening of the meninges, vascular changes, and reactive gliosis [60,61]. Caution is urged about attributing too much weight to such changes: they can be non-specific and may occur in a number of neurodegenerative disorders, as well as in unaffected patients without cognitive signs [62-64]. A study of cognitively unimpaired aged humans found that 51 of 59 subjects had neurofibrillary tangles post-mortem and 46 of 59 subjects had diffuse neuritic, senile plaques throughout the neocortex and entorhinal cortex, and vascular amyloid was present in 44 subject [63].
Imaging studies in humans have also produced somewhat non-specific results. Ventricle-to-brain ratio appears to be larger in manic geriatric patients compared with controls [65], but this is not directly associated with age nor does it correlate well with cortical sulcal widening. Cortical sulcal widening was larger in geriatric manic patients when compared with age-matched controls [65,66]. Again, a strong argument can be made for further, more specific investigation.

Treatment with selegiline (L-deprenyl) has a beneficial effect in laboratory tests of aged canine cognitive performance [67,68] that mirrors improvements similar to those seen in the treatment of Parkinson's disease [69,70]. This effect may be a non-specific and related to augmentation of dopamine via direct effects in the pre-synaptic neuron, or indirect effects on other biogenic amines and neuromodulation.
Apolipoprotein studies suggest than some forms of human Alzheimer's disease may be genetically affected. There are no comparable studies in dogs currently; however, in laboratory beagles a congruence of pathology was found within 15/16 litters [71]. There are few data available for dogs concerning regulatory or structural proteins that have been implicated in normal or pathological brain or in neurological or neuropsychiatric conditions. In humans, synaptic proteins involved in structural plasticity and remodeling of axons and dendrites, debrin [post-synaptic] and GAP-43 [~neuromodulin; pre-synaptic] decline significantly with normal aging [72]. We know that neuroregulatory proteins are involved in the pathology of both human [73] and canine narcolepsy, and that the molecular genetics of the defect associated with neuromodulatory/neuroregulatory dysfunction differs between afflicted breeds [74,75]. This system, in turn, is affected by activation of the histaminergic system. Obviously, regulatory issues are complex and have complex effects on phenotypes, including those associated with cognition, in general, and its various declines. Paradigms seeking to understand associations between neurological attributes and behaviors must accomodate these complex issues.

General Associations Between Neurobehavioral Genetics, Neuroanatomy, and Fears and Anxieties
The specific neuroanatomy of a fear response involves the locus coeruleus (LC), the principal norepinephrinergic (noradrenergic) nucleus in the brain. Dysregulation of the LC appears to lead to panic and phobias in humans [77]. The LC directly supplies the limbic systems and may be responsible for many correlated "limbic" signs. Patients with true panic and phobic responses are more sensitive to pharmacologic stimulation and suppression of the LC than controls [77-79].
The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in anxiety and other disorders. Researchers have variously reported hypercortisolemia and flattening of responses in patients with panic [80-82], suggesting that this is another condition that is heterogenous.
Positive emission tomography (PET) scans have been used to study regional brain blood flow: increases in blood flow in bilateral temporal poles during anticipatory anxiety have been noted, as has an asymmetry of cerebral blood flow (left < right) in the parahippocampal gyrus [83,84]. The lactate test is an accepted test to provoke (and diagnose) panic attacks in people, but until recently it had not been evaluated in dogs [85]. In human lactate-responsive/susceptible patients, parahippocampal blood flow (a marker of neuronal activity), blood volume, and oxygen metabolism are asymmetric when evaluated by PET scans under resting, non-panic conditions. This suggests that the abnormality is both biochemical and structural. The biochemical abnormality is postulated to be due to an increase in norepinephrine output from the locus coeruleus, which, in turn, stimulates parahippocampal "over-responsiveness". The behavioral and phyiological responses to

the lactate test are sufficiently promising that similar imaging studies should be done in animals.

Recently, a role for abnormal serotonin function has been substantiated, in part, based on the shared ontogeny and amygdaloid projections of serotonin neurons and those associated with the LC [86]. In this system serotonin is postulated to have a modulatory role that directly or indirectly affects discharge of brain stem nuclei, limbic activation, and prefrontal cortex activation. Such models of complexity and inter-regulation are likely to more closely explain the mechanistic variability underlying population heterogeneity in conditions like panic disorder. Further evidence implicating both serotonergic neurons and benzodiazepine receptors comes from the clinical literature demonstrating the efficacy of TCAs, SSRIs, and benzodiazepines in the treatment of panic disorder and related anxieties [87-97].

Hints About Genetics of Anxiety from Rodents

Rats bred for high (HAB) or low anxiety-related behaviors (LAB) have provided some insight into possible genetic mechanisms involved in panic disorder. Despite similar basal levels of ACTH and corticosterone HAB rats show higher plasma concentrations at both 5 and 15 minutes after provocative testing and have higher basal and stimulated levels of prolactin than do LAB rats [98]. Transgenic mice that over-produce corticotropic releasing factor (CRF) show increased anxiety-related behaviors that are reversed by central administration of a specific CRF antagonist, suggesting a neuromodulatory role for CRF in the regulation of stress and anxiety [99]. The *Drosophila* white gene shares significant sequence similarity to a gene regulating tryptophan found on human chromosome 21 (21q22.3); associations between gene polymorphism and mood and panic disorders were significant for human males, suggesting that this gene may at least partially control mood, anxiety, and panic disorders [100].

Anxiety and Related Psychopharmacology - A Preliminary Caution

The use of medication should occur and is most effective as part of an integrated treatment program. There is no substitute for the hard work involved in behavior modification; however, some medications may be able to make it easier to implement the modification [101]. Those seeking "quick fix" solutions will doubtless be disappointed: inappropriate drug use will only blunt or mask a behavior without alteration of processes or environments that produced the behavior. Furthermore, the newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior. This delay is due to the mechanism of action of the TCAs and SSRIs which employ second messenger systems to alter transcription of receptor proteins. The primary focus is on the main groups of drugs now recommended for use: those drugs affecting serotonin and GABA.

Neurotransmitters and Neurochemical Tracts

The neurotransmitters affected by behavioral medications are acetylcholine, serotonin, norepinephrine (noradrenaline), dopamine, GABA, and excitatory amino acids. Common adverse effects of psychotherapeutic drugs are usually caused by a blockage of the muscarinic acetylcholine receptors, which have diffuse connections throughout the brain.

<u>Serotonin (5-hydroxy-tryptamine [5-HT])</u> - Serotonin receptors are all G-protein-coupled receptors. There are 14 identified classes of serotonin receptors. The 5-HT1 receptors are linked to the inhibition of adenylate cyclase and affect mood and behavior. Presynaptic 5-HT-1A receptors predominate in dorsal and median raphé nuclei; post-synaptic 5-HT-1A receptors are predominant in limbic regions (hippocampus and septum) and some cortical layers. Activation of pre-synaptic receptors by agonists results in decreased firing of serotonergic neurons leading to transient suppression of 5-HT synthesis and decreased 5-HT release; activation of post-synaptic receptors decreases firing of post-synaptic cells. These are thermostatic effects, not integrated outcomes of receptor activation. The overall effect depends on regulation of second messengers (cAMP, Ca++, cGMP, IP3) and their effects on protein kinases which then alter neuronal metabolism and receptor protein transcription. The subclasses of 5-HT receptors vary in their affects. 5-HT-1A receptors affect mood and behavior. 5-HT-1D receptors affect cerebral blood vessels and appear to be involved in the development of migraine.

<u>Noradrenaline/norepinephrine (NE)</u> - The most prominent collection of noradrenergic neurons is found in the locus coeruleus of the gray matter of the pons and in the lateral tegmental nuclei. There is also a cluster in the medulla. NE has been postulated to affect:

1. mood (decreases in depression and increases in mania),
2. functional reward systems, and
3. arousal.

Dopamine - The distribution of dopamine in the brain is non-uniform, but is more restrictive than that of NE. Dopaminergic nuclei are found primarily in:

1. the substantia nigra pars compacta which projects to the striatum and is largely concerned with coordinated movement;
2. the ventral tegmental area which projects to the frontal and cingulate cortex, nucleus accumbens, and other limbic structures; and
3. the arcuate nucleus of the hypothalamus which projects to the pituitary. A large proportion of the brain's dopamine is found in the corpus striatum, the part of the extrapyramidal system concerned with coordinated movement.

Dopamine is metabolized by monamine oxidase (MAO) and catechol-O-methyl transferase (COMT) into dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA). HVA is used as a peripheral index of central dopamine turnover in humans, but this use has been little explored in veterinary medicine. All dopaminergic receptors are G-protein-coupled transmembrane receptors. The D-1 receptors exhibit their post-synaptic inhibition in the limbic system and are affected in mood disorders and stereotypies. The D-2, D-3, and D-4 receptors are all affected in mood disorders and stereotypies. Excess dopamine, as produced by dopamine releasing agents (amphetamines and dopamine agonists, like apomorphine) is associated with the development of stereotypies.

Gamma Amino Butyric Acid (GABA) - GABA, the inhibitory neurotransmitter found in short interneurons, is produced in large amounts only in the brain and serves as a neurotransmitter in ~30% of the synapses in the human CNS. The only long GABA-ergic tracts run to the cerebellum and striatum. GABA, formed from the EEA glutamate, has two main groupings of receptors: GABA-A and GABA-B. GABA-A receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing Cl-influx. Barbiturates and benzodiazepines are a potentiators of GABA-A. GABA-B receptors are involved in the fine-tuning of inhibitory synaptic tansmission: presynaptic GABA-B receptors inhibit neurotransmitter release via high voltage activated Ca++ channels; postsynaptic GABA-B receptors decrease neuronal excitability by activating inwardly rectifying K+ conductance underlying the late inhibitory post synaptic potential [36].
GABA also has a variety of tropic effects on developing brain cells [102]. During ontogeny GABA-ergic axons move through areas where other neurotransmitter phenotypes are being produced, and so may be related to later monoaminergic imbalances [36]. Whether the extent of such ontogenic effects are relevant for behavioral conditions is currently unknown but bears investigating.

EAAs (glutamate, aspartate, and, possibly, homocysteate) - EEAs have a role as central neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders. The main fast excitatory transmitters in the CNS are EEAs. Glutamate, widely and uniformly distributed in the CNS, is involved in carbohydrate and nitrogen metabolism. It is stored in synaptic vesicles and released by Ca++ dependent exocytosis, so calcium channel blockers may affect conditions associated with increased glutamate. Both barbiturates and progesterone suppress excitatory responses to glutamate [37]. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate [38].

Other Chemical Mediators - Nitric oxide (NO) and arachidonic acid metabolites (e.g., prostaglandins) can mediate neurotransmitter release. These are synthesized on demand and released by diffusion, requiring no specialized vesicles or receptors. Like encapsulated neurotransmitters (i.e., ACh) that are extruded through exocytosis after binding with the synaptic membrane, these chemical mediators are activated by an increase in calcium, so may be affected by calcium channel blockers.

Classes of Drugs Used and Misused in Behavioral Medicine
Anti-histamines, anti-convulsants, progestins/estrogens, sympathomimetics/stimulants, narcotic agonists/antagonists, and mood stabilizers/antipsychotics have been discussed elsewhere [15]. With the exception of the last class they have limited use in modern behavioral medicine. The focus here is on the medications affecting GABA and 5-HT: the benzodiazepine tranquilizers, MAO-Is, TCAs, SSRIs, and 5-HT agonists.

Tranquilizers - Tranquilizers decrease spontaneous activity, resulting in decreased response to external or social stimuli. They interfere profoundly with any behavioral modification. Neuroleptic butyrophenones like haloperidol decrease both appropriate and inappropriate activity, and because of side effects associated with the most effective mode of delivery (i.e., IV), have limited use. Use of phenothiazines (e.g., chlorpromazine, promazine, acetylpromazine, and thioridazine), which target the dopamine receptor, is outdated, the level and duration of tranquilization varies and both normal and abnormal behaviors are blunted. All phenothiazines have side effects from long standing use (e.g., cardiovascular disturbance, extrapyramidal signs). Acetylpromazine makes animals more reactive to noises and startle, and so is wholly inappropriate for use in noise phobic patients.

The exact mechanism of action of the benzodiazepines (e.g., diazepam, chlordiazepoxide, clorazepate, lorazepam, alprazolam, and clonazepam) is poorly understood. Calming effects may be due to limbic system and reticular formation effects. Compared with barbiturates, cortical function is relatively unimpaired by benzodiazepines. All benzodiazepines potentiate the effects of GABA by increasing binding affinity of the GABA receptor for GABA and increasing the flow of chloride ions into the neuron, affecting primarily GABA-A receptors. Barbiturates also affect the GABA receptor-benzodiazepine receptor-chloride ion channel complex, but because of detrimental effects on cognition barbiturates have been superseded by benzodiazepines and TCAs in the treatment of aggression. Binding of diazepam is highest in the cerebral cortex compared with the limbic system and midbrain, which are, in turn, higher than the brainstem and the spinal cord, paralleling the distribution of GABA-A receptors.

At low dosages, benzodiazepines act as mild sedatives, facilitating daytime activity by tempering excitement. At moderate dosages they act as anti-anxiety agents, facilitating social interaction in a more proactive manner. At high dosages they act as hypnotics, facilitating sleep. Ataxia and profound sedation usually only occur at dosages beyond those needed for anxiolytic effects. Benzodiazepines decrease muscle tone by a central action that is independent of the sedative effect, but may function as a non-specific anxiolytic effect. Some newer benzodiazepines like clonazepam have muscle relaxation effects at smaller dosages than those needed for behavioral effects. Many of the long-term effects and side effects of benzodiazepines are the result of intermediate metabolite function. Parent compound and intermediate metabolite $t_{1/2}$ are found in Table 5 for humans and Table 6 for domestic species [103,104].

Table 5. Half-lives of Parent Compounds and Intermediate Metabolites of Target Benzodiazepines in Humans

Parent Compound	**$t_{1/2}$ Parent Compound**	**$t_{1/2}$ Intermediate Metabolite**	**Overall Duration of Action**
Triazolam	2 - 4 h	2 h	Ultra Short: 6 h
Oxazepam	8 - 12 h	---	Short: 12 - 18 h
Alprazolam	6 - 12 h	6 h	Medium: 24 h
Diazepam	24 - 40 h	60 h	Long: 24 - 48 h
Clonazepam	50 h	---	Long: 24 - 48 h

Table 6. Duration of Action of Parent Compound, Diazepam, and its Intermediate Metabolite, Nordiazepam (N-desmethyl Diazepam) in Selected Domestic Animals [104]

Species	**Diazepam**	**N-desmethyl diazepam**	**Oxazepam [103]**
Horse	24 - 48 h	51 - 120 h	---
Cat	5.5 h	21 h	---
Dog	3.2 h (if given PO) 0.258 h (if given IV)	3 - 6 h (if given PO) 2.20 h (if given IV) 2.83 h (if given rectally)	3.83 h (if given IV) 5.13 (if given rectally)

Benzodiazepines are essential for treatment of sporadic events involving profound anxiety or panic (e.g., thunderstorms, fireworks, panic associated with departures of humans signaled by an outside indicator, e.g., an alarm clock). For these drugs to be efficacious they must be given to the patient at least an hour before the anticipated stimulus, and minimally before the patients exhibit signs of distress. This timing allows repeat dosing that makes use of the $t_{1/2}$ of parent compounds and intermediate metabolites and permits concomitant use with daily TCA or SSRI treatment.

Monoamine oxidase inhibitors (MAO-Is) - MAO-Is act by blocking oxidative deamination of brain amines (dopamine, norepinephrine, epinephrine, 5-HT), increasing these substances, and elevating mood. The MAO-B inhibitor, selegiline is used to treat "cognitive dysfunction" in aged cats and dogs, but in dogs deamination of catecholamines is controlled by MAO-A. Selegiline is fairly specific for dopamine and slows destruction of synaptic knobs of presynaptic neurons.

TCAs - TCAs are structurally related to the phenothiazine antipsychotics. In humans they are commonly used to treat endogenous depression, panic attacks, phobic and obsessive states, neuropathic pain states, and pediatric enuresis. The antidepressant effect is due to inhibition of prejunctional re-uptake of norepinephrine and serotonin. There are three major effects of TCAs that vary in degree depending on the individual drug:

1. sedation,
2. peripheral and central anticholinergic action, and
3. potentiation of CNS biogenic amines by blocking their re-uptake presynaptically.

The ability of TCAs to inhibit prejunctional re-uptake of norepinephrine and serotonin is largely responsible for their antidepressant effect. Many TCAs also have potent muscarinic, α1-adrenergic, and H-1 and H-2 blocking activity, which can account for their common side effects (dry mouth, sedation, hypotension). The H-1 and H-2 effects, however, may be useful in treating pruritic conditions (e.g., doxepin).

The tertiary amines (amitriptyline, imipramine, doxepin, trimipramine, and clomipramine) are metabolized to secondary amines (desipramine, nortriptyline, and protriptyline). These classes of anti-depressants are among the most widely and safely (compared with benzodiazepines, phenothiazines, barbiturates, and sympathomimetic agents) used drugs in companion animal behavioral medicine.

In general, TCA metabolites are more potent inhibitors of NE uptake, while parent compounds are more potent inhibitors of 5-HT uptake; metabolites usually have similar or longer half-lives compared with the parent compound. Imipramine's intermediate metabolite, norimipramine, is a more potent inhibitor of NE uptake than is imipramine (it is also an active intermediate metabolite of other anti-anxiety agents) and has its own active intermediate metabolite. Doxepin's intermediate metabolite, nordoxepin, fully retains the pharmacological properties of the parent compound, and its $t_{1/2}$ is 33 - 88 h in humans compared with a $t_{1/2}$ of 8 - 25 h with doxepin. Norclomipramine (N-desmethylclomipramine), one of the active intermediate metabolites of clomipramine, is also a more potent inhibitor of NE than is clomipramine and has an elimination $t_{1/2}$ 1.5 times longer than that of clomipramine [105]. Not only does this have profound implications for calculating how long one expects effects to last, but it is interesting to note that the ability to formulate intermediate metabolites is subject to genetic polymorphism in the human population. One can only imagine the complexity for the canine and feline populations. Most dogs treated with clomipramine (Clomicalm, Novartis Animal Health) reach steady state levels in 3 - 5 days, attain peak plasma concentrations in approximately 1 - 3 h, and experience $t_{1/2}$ of 1 - 16 h of the parent compound and 1 - 2 h of the active intermediate metabolites [101,106], suggesting that dogs may require higher dosages or more frequent dosing than do humans treated with such medications.

Knowledge of intermediate metabolites can be important: animals experiencing sedation or other side effects with the parent compound may do quite well when treated with the intermediate metabolite, alone. For example, cats that become sedated or nauseous when treated with amitriptyline may respond well when treated with nortriptyline at the same dose. Table 7 lists parent compounds, intermediate metabolites, and their relative effects on NE and 5-HT. Side effects in humans can include a dry mouth, constipation, urinary retention, tachycardias and other arrhythmias, syncope associated with orthostatic hypotension and α-adrenergic blockade, ataxia, disorientation, and generalized depression and inappetence [107]. Symptoms usually abate upon decrease or cessation of drug administration.

Use of TCAs is contraindicated in animals with a history of urinary retention and severe, uncontrolled cardiac arrhythmias [109] and a cardiac consult, including a rhythm strip, should be a part of standard, pre-dispensation work-up. The common side-effects of TCAs as manifest on ECG include: flattened T waves, prolonged Q-T intervals, and depressed S-T segments. In high doses TCAs have been implicated in sick euthyroid syndrome. In older or compromised animals complete laboratory evaluations are urged since high doses of TCAs are known to alter liver enzyme levels. Extremely high doses are associated with convulsions, cardiac abnormalities, and hepatotoxicity. TCAs can interfere with thyroid medication necessitating conscientious monitoring if administration of both medications is concurrent. Cats are likely to be more sensitive to all TCAs than are dogs because TCAs are metabolized through glucuronidation.

TCAs are extremely successful in treating many canine and feline conditions including separation anxiety, generalized anxiety that may be a precursor to some elimination and aggressive behaviors, pruritic conditions that may be involved in acral lick dermatitis (ALD), compulsive grooming, and some narcoleptic disorders. Amitriptyline is very successful in treating separation anxiety and generalized anxiety. Imipramine has been useful in treating mild attention deficit disorders in people, and may be useful in dogs since it has been used to treat mild narcolepsy. Clomipramine has been inordinantly successful in the treatment of human and canine obsessive compulsive disorders [34,46-48,110-115]. Clomipramine has one active, intermediate metabolite, clomipramine, that acts as a serotonin re-uptake inhibitor [46,115].

Table 7. Relative Effects of TCA Parent Compounds and Intermediate Metabolites on NE and 5-HT Re-uptake [108]

Parent Compound	Intermediate Metabolite	NE	5-HT
Desipramine	---	++	+
Imipramine	Desipramine	+++	++
Amitriptyline	Nortriptyline	++	++
Nortriptyline	---	+	+
Clomipramine	N-desmethyl Clomipramine + Clomipramine*	++	+++

* does not include the specific effect of the intermediate metabolite as a selective serotonin reuptake inhibitor (SSRI).

Serotonin Agonists - Partial 5-HT-1A/B agonists (e.g., buspirone) have few side effects, do not negatively affect cognition, allow rehabilitation by influencing cognition, attention, arousal, and mood regulation, and may aid in treating aggression associated with impaired social interaction. Buspirone has been used with varying, but unimpressive success, in the treatment of canine aggression of dominance or idiopathic origins, canine and feline ritualistic or stereotypic behaviors, self-mutilation and possible obsessive compulsive disorders, thunderstorm phobias, and feline spraying, in a multi-cat household. Its best use is for the treatment of spraying if one of the intents is to make a victimized cat more assertive.

SSRIs - The SSRIs (fluoxetine, paroxetine, sertraline, and fluvoxamine) are derivatives of TCAs. These drugs have a long half-life, and after 2 - 3 weeks plasma levels peak within 4 - 8 hours. Treatment must continue for a minimum of 6 - 8 weeks before a determination about efficacy can be made since these drugs act to induce receptor conformation changes, an action that can take 3 - 5 weeks. Most of the SSRI effects are due to highly selective blockade of the re-uptake of 5-HT1-A into pre-synaptic neurons without effects on NE, dopamine, acetylcholine, histaminic, and alpha-adrenergic receptors. The SSRIs should not be used with MAO-Is because of risks of serotonin syndrome [116].
Fluoxetine is efficacious in the treatment of profound aggressions, animal models of obsessive-compulsive disorders (wheel running, anorexia, weight loss) [117], companion animal separation anxiety [118], panic, avoidance disorders, including post-traumatic stress disorder [119], and obsessive-compulsive disorders. Paroxetine is efficacious in the treatment of depression, social anxiety, and agitation associated with depression [120]. Sertraline is useful particularly for generalized anxiety and panic disorder [121].

Most of the effect of fluoxetine seems to be via a highly selective blockade of the re-uptake of 5-HT into pre-synaptic neurons. Fluoxetine appears to have no effects on NE or dopamine, no anticholinergic, no antihistaminic, and no anti-α-adrenergic activities, so most of the side effects associated with anti-depressants are absent or minimized. Concomitant use of TCAs or benzodiazepines increases the plasma levels of these and may prolong the excretion of fluoxetine. Co-administration of buspirone may decrease the efficacy of buspirone and potentiate extrapyramidal symptoms, but there have also been reports of synergistic effects. Fluoxetine should not be used with MAO-Is. Table 8 contains an algorithm for the "gestalt" of TCA and SSRI use. This algorithm is extrapolated from the human literature based on the similarity of dogs and humans with respect to pharmacokinetics and pharmacodynamics when treated with TCAs or SSRIs.
Acceleration of the treatment effect of TCAs and SSRIs can be accomplished by the addition of the β-adrenergic antagonists, pindolol, which blocks the pre-synaptic/somatodentrictic autoreceptor thereby aborting the initial down-regulation phase of monoamine release [115,122].

Table 8. "Gestalt" of TCA and SSRI Use Based on t-1/2 of Parent Compounds and Active Intermediate Metabolites, Relative Effects on NE and 5-HT, and Extrapolations from Multi-center Human Studies	
Diagnosis/Type of condition	**First drug of choice**
Narcolepsy	Imipramine
Milder, relatively non-specific anxieties	Amitriptyline
Milder, relatively non-specific anxieties with avoidance of sedation	Nortriptyline
Social phobias/anxieties concerning social interaction	Paroxetine
Panic/generalized anxiety	Sertraline
Outburst aggression/related anxieties	Fluoxetine
Ritualistic behavior associated with anxiety, including OCD	Clomipramine

Mechanism of Action of Serotonergic Agents - Why a Mechanistic Paradigm Shift is Necessary

What makes TCAs and SSRIs special and why are they so useful for anxiety disorders? The key to the success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to "learn" something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) - particularly Src - which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus [123-125].

There are two phases of TCA and SSRI treatment: short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendric autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a thermostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the β-adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the post-synaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (e.g., trkB) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the post-synaptic receptors renders serotonin stimulation and signal transduction more efficient [115,122].

Long-term treatment, particularly with the more specific TCAs (e.g., clomipramine) and SSRIs, employs the same pathway used in LTP to alter reception function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of in vivo "gene therapy" that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued "normal" functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying heterogeneity of the patient population considered to have the same diagnosis.

Pre-medication Considerations

Prior to incorporating behavioral pharmacology into any treatment program the following conditions must be met:

1. A reasonable diagnosis or a list of diagnoses should be formulated. This is different from a list of non-specific signs.
2. The clinician should have some insight into the neurochemistry relevant to the condition.
3. The clinician should have an appreciation for the putative mechanism of action of the chosen medication.
4. The clinician should have a clear understanding of any potential side effects.
5. The clinician and client should have some clear concept of how the prescribed drug will alter the behavior in question. The latter is critical because it will help clients to watch for side-effects and improvements and can help the clinician confirm or reject the diagnosis.

Without these five guidelines, behavioral drugs may not be given long enough or at a sufficient dosage to attain the desired effect, the clients will be unable to participate in the evaluation process, there will be no objective behavioral criteria that will allow the veterinarian to assess improvement, and drug selection is liable to be similar to alchemy.

Prior to prescribing any drug a complete behavioral and medical history should be taken. Should the animal be older, suffer from any metabolic or cardiac abnormalities, or be on any concurrent medical therapy, caution is urged. All animals should have complete laboratory and physical examinations. Most behavioral drugs are metabolized through renal and hepatic pathways so knowledge of baseline values is essential. For example, SSRIs are often considered "safer" than many TCAs, but because of the small sizes of clinical trials necessary to bring drugs to market the exact incidence of potential side effects is often unknown in the absence of post-marketing surveillance.

Baseline ECGs are recommended for in any patient who has had a history of any arrhythmia, heart disease, prior drug reactions, is on more than one medication, and who may be undergoing anesthesia or sedation [109]. Liver dyscrasias and cardiac arrhythmias may not rule out the use of a drug, but knowing that they exist can serve as a guide to dosage and anticipated side effects. Once alerted to potential adverse reactions clients are extremely willing to comply with all monitoring and with the extensive communication needs of behavioral cases. Clients should receive a complete list of all potential adverse responses and should be encouraged to communicate with the clinician at the first sign of any problem. Clients are often very distressed after a behavioral consultation and need a written reminder of situations for which they should be alert.

In the USA, extra-label use of human drugs, including psychopharmacological agents, for the treatment of pets hinges on a valid client/veterinarian/patient relationship. This means that a behavioral history was taken, a tentative diagnosis was formulated, and a treatment plan was developed. If any veterinarian is uncomfortable with complying with these guidelines, they should refer their behavioral cases to a specialist in behavioral medicine. Consultations directly with a client by fax, phone, mail, or e-mail, in the absence of actual visual inspection of the patient, most often do not meet the criteria of a valid client/veterinarian/patient relationship. Caution is urged. The preferred mode of consultation if the clinician can not have a visual inspection of the patient is for the consultation to take place directly with the specialist and the referring clinician, who is then responsible for treatment and follow-up.

Finally, the client household must be considered when the decision to use behavioral drugs is made. Substance abuse is rampant in humans and many drugs used for behavioral pharmacology have high abuse potential.

Monitoring

Monitoring of side-effects is critical for any practitioner dispensing behavioral medication. The first tier of this involves the same tests mandated in the pre-medication physical and laboratory evaluation. Age-related changes in hepatic mass, function, blood flow, plasma drug binding, etc., cause a decrease in clearance of some TCAs, so it is prudent to monitor hepatic and renal enzymes annually in younger animals, biannually in older, and always as warranted by clinical signs. Adjustment in drug dosages may be necessary with age.

Withdrawal from Medication

It is preferable to withdraw most patients from one class of drug before starting another. For changing between SSRIs and MAO-Is the recommended drug-free time in humans and dogs is two weeks (2 + half-lives: the general rule of thumb for withdrawal of any drug). SSRIs can be added to TCAs and may then exhibit a faster onset of action than when they are given alone. This is due to the shared molecular effects on second messenger systems of both TCAs and SSRIs. Combination treatment allows the clinician to use the lower end of the dosage for both compounds which minimizes side effects while maximizing efficacy. Furthermore, benzodiazepines can be used to blunt or prevent acute anxiety-related outbursts on an as needed basis in patients for whom daily treatment with a TCA or an SSRI is ongoing. Together, the combination of benzodiazepines and TCAs/SSRIs may hasten improvement and prevent acute anxiety-provoking stimuli from interfering with treatment of more regularly occurring anxieties.

When stopping a drug, weaning is preferred to stopping abruptly. A model for how to do this is found in Table 9. Weaning minimizes potential central withdrawal signs, and allows determination of the lowest dosage that is still effective [5,15]. Long-term treatment may be the rule with many of these medications and conditions, however, maintenance may be at a considerably lower level of drug than was prescribed at the outset. The only way the practitioner will discover if this is so, is to withdraw the medication slowly.

Table 9. Algorithm for Treatment Length and Weaning Schedule
1- Treat for as long as it takes to begin to assess effects 7 - 10 days for relatively non-specific TCAs 3 - 5 weeks minimum for SSRIs and more specific TCAs **PLUS** **2-** Treat until "well" and either have no signs associated with diagnosis or some low, consistent level Minimum of another 1 - 2 months **PLUS** **3-** Treat for the amount of time it took you to attain the level discussed in (2) so that reliability of assessment is reasonably assured Minimum of another 1 - 2 months **PLUS** **4-** Wean over the amount of time it took to get to (1) or more slowly. Remember, if receptor conformation reverts it may take 1+ months to notice the signs of this. While there are no acute side effects associated with sudden cessation of medication, a recidivistic event is a profound "side effect". Full-blown recidivistic events may not be responsive to re-initiated treatment with the same drug and, or the same dose. 7 - 10 days for relatively non-specific TCAs 3 - 5 weeks minimum for SSRIs and more specific TCAs **TOTAL**: Treat for a minimum of 4 - 6 months

Conclusions - Lessons from Schizophrenia - Humans as Models for Complex Neurobehavioral Conditions in Dogs
Advances in treatment in behavioral medicine will be genetic, molecular, and pharmacological. We can best learn some of the pitfalls of trying to understand multi-factorial, heterogeneous disorders by comparison with the human experience with schizophrenia. Schizophrenia has been increasingly recognized as a neurodevelopmental brain disorder with a strong genetic vulnerability component and some underlying neuroanatomic and neurochemical dysfunction [126-128]. Recent structural and functional neuroimaging studies have implicated tissue loss in fronto-temporal regions and abnormally increased activity in temporal regions [129]. Studies with magnetic resonance spectroscopy (MRS) have revealed distinct abnormalities in the frontal and temporal regions, the former characterized by decreased n-acetyl-aspartate ratio to creatine (NAA/Cr), increased choline ratios (Cho/Cr) and normal amino acid ratios (AA/Cr), while the latter showed decreased NAA/Cr associated with decreased Cho/Cr and markedly increased AA/Cr. Consistent with the fronto-temporal abnormalities in brain structure and function, neuropsychological studies have shown differential deficits in executive and memory functions linked to frontal and temporal networks, respectively [129-135]. Neuroanatomical findings alone are not sufficiently consistent to be diagnostic for schizophrenia.

Examination of the pathology at the cytoarchitectural and cell protein level has been illuminating. Proteins like synaptophysin (synaptic vesicle protein) are unique molecular components of neurons. Selective lesions in lab animals can establish the presence of a significant correlation between quantitative assessments of synaptic terminals and levels of immunoreactivity of synaptophysin and SNAP-25 (synaptosomal-associated protein-25). Other proteins like neural cell adhesion molecule (N-CAM) promote cell-cell interactions during development and appear to have important functions in synapses of adult brain. Ratio of N-CAM to synaptophysin may provide an index of synaptic maturity: increased N-CAM to synaptophysin ratios are observed in animal models of synaptic formation or proliferation including experimental lesions, genetic models, and during studies of learning and behavior. During long-term potentiation (LTP) initial down-regulation or resorption of N-CAM and related adhesion molecules seems to occur followed by a period of increased synthesis. In cingulate gyrus samples from patients with schizophrenia N-CAM immunoreactivity is increased about 22% [136].

At least 4 modes of heritability have been postulated for various "kinds" of schizophrenia [127]:

1. liability threshold model or polygenic threshold or oligogenic inheritance,
2. single gene models,
3. mixed model - gene of major effect acting in combination with a background of polygenes,
4. genomic imprinting and mutations involving unstable DNA sequences in the form of expanded trinucleotide repeats.

These repeats form dynamic mutations that can expand from one generation to the next. This would account for underlying variability in symptoms and intensity. The first threshold or polygenic model is problematic because we don't know if patients actually meet the postulated normal distribution, but there is heuristic value to this type of model. Single gene models have been largely disavowed across the board, but their main point has been to differentiate mechanisms for early-onset profound cases. The mixed model has only produced inconclusive practical and statistical results to date. The genomic imprinting/mutation model looks appealing and has potential for the future. We ought to be viewing the behavioral neurogenetics of domestic animals in the same context.

To what extent are we impaired in our understanding of neurobehavioral disorders because of our inability to fully evaluate some of the cognitive signs? How would we know if dogs heard the canine equivalent of voices? Pathologies in behavior have been attributed to genetics, some to environmental conditions, and some to the interaction. We are likely to be less hampered by our inability to ask and receive verbal responses from dogs than by the shackles bestowed by simplistic and out-dated diagnostic and treatment approaches.

Appendixes

- Appendix 1 - Selected Psychopharmacological Agents that may be Useful in the Treatment of Feline Behavioral Diagnoses.
- Appendix 2 - Selected Psychopharmacological Agents that may be Useful in the Treatment of Canine Behavioral Diagnoses.

Appendix 1 -

Selected Psychopharmacological Agents that may be Useful in the Treatment of Feline Behavioral Diagnoses	
Alprazolam	0.125 - 0.25 mg/kg po q 12 h
Amitriptyline	0.5 - 2.0 mg/kg po q 12 - 24 h; start at 0.5 mg/kg po q 12 h
Clomipramine*	0.5 mg/kg po q 24 h
Clonazepam	0.1 - 0.2 mg/kg po q 12 - 24 h
Clorazepate	0.5 - 2.2 mg/kg po prn for profound distress; 0.2 - 0.4 mg/kg q 12 - 24 h
Diazepam	0.2 - 0.4 mg/kg po q 12 - 24 h (start at 0.2 mg/kg po q 12 h)
Doxepin	0.5 - 1.0 mg/kg po q 12 - 24 h (start with a low dose)
Fluoxetine	0.5 - 1.0 mg/kg po q 24 h
Fluvoxamine	0.25 - 0.5 mg/kg po q 24 h
Imipramine	0.5 - 1.0 mg/kg po q 12 - 24 h (start at 0.5 mg/kg po q 12 h)
Nortriptyline	0.5 - 2.0 mg/kg po q 12 - 24 h
Oxazepam	0.2 - 0.5 mg/kg po q 12 - 24 h; high dose:1.0 - 2.5 mg/kg po q 12 - 24 h; 3 mg/kg po as a bolus for appetite stimulation
Paroxetine	0.5 mg/kg po q 24 h for 6 - 8 weeks to start

Appendix 1 -

Selected Psychopharmacological Agents that may be Useful in the Treatment of Feline Behavioral Diagnoses	
Protriptyline	0.5 - 1.0 mg/kg po q 12 - 24 h (start at 0.5 mg/kg po q 12 h)
Selegiline*	0.25 - 0.5 mg/kg po q 12 - 24 h (start with a low dose)
Sertraline	0.5 mg/kg po q 24 h for 6 - 8 weeks to start
Triazolam	2.5 - 5 mg/cat po q 8 h

* Veterinary label for some canine and feline conditions; label depends on country and species.

Appendix 2 -

Psychopharmacological Agents that may be Useful in the Treatment of Canine Behavioral Diagnoses	
Alprazolam	0.125 - 1.0 mg/kg po q 12 h; range: 0.01 - 0.1 mg/kg po prn for phobic or panic attacks, not to exceed 4 mg/dog/day - profound lethargy and incoordination may result (0.75 - 4.0 mg/dog/day; may increase slowly over 4.0 mg/dog/day if obtaining some effect at a lower dose) (start with 1 - 2 mg for a 25 kg dog)
Amitriptyline	1 - 2 mg/kg po q 12 h to start
Buspirone	1 mg/kg po q 8 - 24 h (mild anxiety) 2.5 - 10 mg/dog q 8 - 24 h (mild anxiety) 10 - 15 mg/dog po q 8 - 12 h (more severe anxiety; use high dose for thunderstorm phobia)
Carbamazepine	4 - 8 mg/kg po q 12 h; 0.5 - 1.25 mg/kg po q 8 h; 4 - 10 mg/kg/day divided q 8 h
Chlordiazepoxide	2.2 - 6.6 mg/kg po prn (start with a low dose)
Clomipramine*	1 mg/kg po q 12 h for 2 weeks, then 2 mg/kg po q 12 h for 2 weeks, then 3 mg/kg po q 12 h for 4 weeks and then as maintenance dose - or - 2 mg/kg po q 12 h for 8 weeks to start. May need higher maintenance dose. Constant dosage associated with slight increase in GI side effects. nb: q 24 h dosing insufficient for vast majority of animals, particularly those with multiple signs, early age onset, or long-standing complaint.
Clonazepam	0.125 - 1.0 mg/kg po q 12 h; range: 0.01 - 0.1 mg/kg po prn for phobic or panic attacks, profound lethargy and incoordination may result at dosages over 4.0 mg/day, but higher dosages may be used incrementally if there has been some effect at a lower dose (start with 1 - 2 mg for a 25 kg dog)
Clorazepate	0.5 - 2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q 4 - 6 h prn; 11.25 - 22.5 mg/dog po q 24 h (~22.5 mg/large dogs; ~11.25 mg/medium dogs; ~5.6 mg/small dogs)
Diazepam	0.5 - 2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q 4 - 6 h prn
Doxepin	3 - 5 mg/kg po q 8 - 12 h
Fluoxetine	1 mg/kg po q 12 - 24 h for 6 - 8 weeks to start
Fluvoxamine	1 mg/kg po q 12-24 h for 6 - 8 weeks to start
Imipramine	2.2 - 4.4 mg/kg po q 12 - 24 h; 1 - 2 or 2 - 4 mg/kg po q 12 - 24 h (start with a low dose)

Appendix 2 -

Psychopharmacological Agents that may be Useful in the Treatment of Canine Behavioral Diagnoses	
Nortriptyline	1 - 2 mg/kg po q 12 h
Oxazepam	0.2 - 1.0 mg/kg po q 12 - 24 h
Paroxetine	1 mg/kg po q 24 h for 6 - 8 weeks to start
Protriptyline	5 - 10 mg/dog po q 12 - 24 h (narcolepsy)
Selegiline*	0.5 - 1.0 mg/kg po q 24 h for 6 - 8 weeks to start
Sertraline	1.0 mg/kg po q 24 h to start
Triazolam	0.125 - 1.0 mg/kg po q 12 h; range: 0.01 - 0.1 mg/kg po prn

* Veterinary label for some canine and feline conditions; label depends on country and species.

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