The Pathophysiology of Agitation

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Agitation is a nonspecific constellation of relatively unrelated behaviors that can be seen in a number of different clinical conditions, usually presenting a fluctuating course. Multiple underlying pathophysiologic abnormalities are mediated by dysregulations of dopaminergic, serotonergic, noradrenergic, and GABAergic systems. Pathophysiologic mechanisms of agitation that operate in the different clinical disorders where agitation occurs are discussed. These pathophysiologic abnormalities are not associated with distinct clinical features. Although there may be a final common pathway, there is no unifying etiologic pathophysiology. The author suggests that the clinician address the underlying pathophysiology through a treatment intervention that addresses the overarching psychiatric disorder. Generally, agents that reduce dopaminergic or noradrenergic tone or increase serotonergic or GABAergic tone will attenuate agitation, often irrespective of etiology.

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Agitation is a nonspecific constellation of relatively unrelated behaviors that can be seen in a number of different clinical conditions, usually presenting a fluctuating course. Although some data exist on pathophysiologic mechanisms of agitation as part of specific psychiatric disorders, little has been published on its underlying biological mechanisms as a separate and specific syndrome.

On the phenomenological level, agitation is best seen as a transnosologic syndrome, meaning that one can find this cluster of behaviors occurring in a number of psychiatric disorders. Other behavioral syndromes have been described and partly overlap with agitation or are synonymous with it, including akathisia, restlessness, fidgetiness, hyperactivity, and jitteriness. All of these terms describe a state of poorly organized and aimless psychomotor activity stemming from physical or mental unease.[1] Motor restlessness, a heightened responsivity to external or internal stimuli, irritability, and inappropriate and usually purposeless verbal or motor activity are the hallmarks of the syndrome. In addition, vegetative signs exist, such as decreased sleep and an unstable course with symptoms changing very rapidly over time (Table 1).

SUBTYPES OF AGITATION

Attempts have been made to classify subtypes of agitation. One such classification distinguishes between an aggressive physical component (e.g., fighting, throwing, grabbing, destroying items), an aggressive verbal component (e.g., cursing, screaming), a nonaggressive physical component (e.g., pacing), and a nonaggressive verbal component (e.g., constant questioning, chatting).[2] These behaviors are all, by and large, inappropriate by social standards.

INSTRUMENTS FOR THE ASSESSMENT OF AGITATION

A number of instruments have been developed to assess agitation. These can be used more formally when assessing pharmacotherapeutic effects or effects of behavioral interventions. Measures include the Overt Agitation Severity Scale,[3] which is an extension of the Overt Aggression Scale[4]; the Motor Agitation and Retardation Scale[5]; and the Cohen-Mansfield Agitation Inventory.[2] These are relatively well-articulated scales that have been standardized and validated to some degree.[6] They are very useful when investigating effects and outcomes of interventions.

PATHOPHYSIOLOGY OF AGITATION

Neurophysiology of Agitation

The functional neuroanatomy and the neurochemical basis of agitation are not well understood. Clues to specific underlying mechanisms are provided only by our understanding of the mechanisms of some of the disorders that manifest with agitation, by understanding possible mechanisms of drug-related agitation, and by the existence of animal models of hyperactivity.

Among the models suggested has been the hypothesis that similar brain mechanisms operate in the pathophysiology of agitation as in movement disorders with established

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Table 1. Definition of Agitation

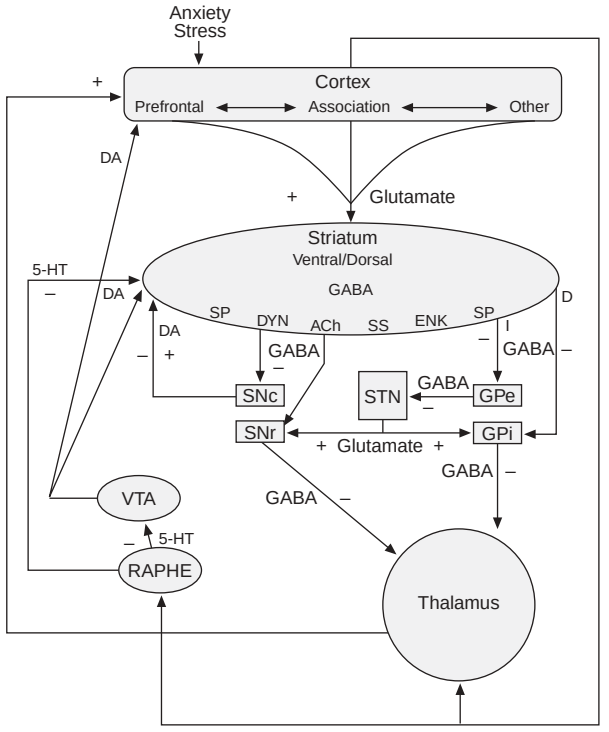
Motor restlessness
Heightened responsivity to stimuli
Irritability
Inappropriate and/or purposeless verbal or motor activity
Decreased sleep
Fluctuation of symptoms over time

neurophysiologic and neuroanatomical basis, such as in ballismus or Huntington's disease.[1]

Restlessness that is part of agitation has been postulated to be the result of disturbances in the segregated parallel pathways that pass through the limbic and sensorimotor limbs of the striatum. According to the model (Figure 1) proposed by Sachdev and Kruk,[1] the cerebral cortex projects into the dorsal striatum (caudate, putamen, and dorsal pallidum) and to the limbic related ventral striatum (nucleus accumbens, ventral pallidum, and substantia nigra pars reticulata [SNr]) in a striato-pallido-thalamic-cortical doubly inhibitory loop. The cortical projections of the circuit are predominantly to the prefrontal and sensorimotor cortex and are excitatory. This suggests that the striatum promotes arousal of the system, allowing movement generated in the cortex to be expressed.[8] The striatal output is mediated through the global pallidus interna (GPi) and SNr, which may be considered as one organ. The striatum projects to the GPi/SNr by 2 pathways: a direct pathway, consisting of neurons containing γ-aminobutyric acid (GABA) and substance P, which is inhibitory; and an indirect pathway beginning with neurons containing GABA and enkephalin.[9] The latter neurons project to the global pallidus externa (GPe), which in turn projects to the subthalamic nucleus and then to the GPi/SNr. The indirect pathway, because of its doubly inhibitory projections, is excitatory for the GPi/SNr. The 2 pathways therefore have opposing effects on the GPi/SNr, and, although the functional significance of such an organization is unclear, it is likely that the interaction between the 2 is important for motor activity. The dominance of the direct pathway on the indirect would facilitate motor activity and vice versa. Figure 1 presents the common features of at least 4 parallel circuits—motor, dorsolateral prefrontal, lateral orbitofrontal, and limbic[7]—which are probably all involved to some degree in the generation of restlessness and agitation. However, the anatomical evidence for this model is still lacking.

The major neurotransmitter of the striatal, pallidal, and SNr projections is GABA, which coexists with a number of neuropeptides in various combinations. The GABAergic fast transmission in the basal ganglia is modulated by neuropeptides, dopamine, acetylcholine, and glutamate in the interneurons.[10] In addition, the striatum receives dopaminergic input from the substantia nigra pars compacta (SNc) and the ventral-tegmental area

Figure 1. The Cortico-Striatal-Thalamic Circuits Important for the Pathogenesis of Restlessness[a]



[a]Reprinted with permission from Sachdev and Kruk.[1] Abbreviations: 5-HT = serotonin, ACh = acetylcholine, D = direct pathway, DA = dopamine, DYN = dynorphin, ENK = enkephalin, GABA = γ-aminobutyric acid, GPe = global pallidus externa, GPi = global pallidus interna, I = indirect pathway, RAPHE = median raphe nuclei, SNc = substantia nigra pars compacta, SNr = substantia nigra pars riticulata, SP = substance P, SS = somatostatin, STN = subthalamic nucleus, VTA = ventral-tegmental area. Symbols: + = excitatory, – = inhibitory.

(VTA) and serotonergic input from the dorsal raphe nuclei. The VTA projects dopamine fibers to the prefrontal cortex as well as to the limbic striatum, and these mesocortical dopamine neurons have inhibitory effects on the cortical neuronal system and the dopaminergic network.[11] The prefronto-mesencephalic neurons in turn influence the midbrain projections to the septum, nucleus accumbens, and the frontal cortex itself. Although the dorsal and ventral striatal circuits are largely parallel, there are prominent connections between the two, involving striatal interneurons principally using acetylcholine, GABA, or somatostatin.[10]

According to Sachdev and Kruk's model,[1] agitation is the consequence of disturbances in the above circuits that finally lead to the loss of excitatory drive to the GPi/SNr and/or disinhibition of the thalamocortical and brain stem neurons. The result can be brought about in a number of ways. Increase in dopaminergic stimulation of the striatum (e.g., by amphetamines or L-dopa) leads to increased excitation by the indirect pathway or increased inhibition by

Table 2. Agitation in the Different Clinical Disorders: An Overview of Underlying Pathophysiologic Mechanisms

Disorder	Mechanism
Agitated depression	Increased serotonergic responsivity; decrease in GABA
Mania	Increase in dopamine
Panic disorder and generalized anxiety disorder	Increase in norepinephrine; decrease in GABA
Dementia	Decrease in GABA
Delirium	Multiple underlying causative mechanisms
Substance-induced agitation	Increase in dopamine
Acute psychosis	Increase in dopamine
Akathisia	Decrease in dopamine; increase in norepinephrine
Aggression	Increase in norepinephrine; decrease in serotonin

the direct pathway. Since the direct pathway is generally predominant, the consequence is motor hyperactivity.

Mechanisms of Agitation in the Different Clinical Disorders

This section will focus specifically on agitation in those disorders where it is clinically significant and where it usually represents a serious management problem. The model described above can then be applied to agitation in a number of these disorders. Specific neurotransmitter dysregulations are associated with these disorders and may be implicated in the pathophysiology of agitation as well as in the following general way (Table 2). In agitated depression, there is increased serotonergic responsivity. Mania with agitation may be akin to agitated psychosis in terms of an increase in dopaminergic activity. In agitation with panic disorder or generalized anxiety disorder, an increase in noradrenergic and a decrease in GABAergic inhibition can be postulated. Because amphetamines can influence the uptake and release of norepinephrine and dopamine, and because norepinephrine has been implicated in the pathogenesis of panic disorders,[12] it has been suggested that agitation may be due to increased norepinephrine activity. In substance-induced psychosis with an agitation component and agitation with acute psychosis, agitation would be associated with an hyperdopaminergic state. In states associated with aggression and agitation, an increase in noradrenergic activity and a decrease in serotonergic activity would be anticipated. Delirium with agitation is a more difficult area to define in terms of underlying mechanisms, because it differs in presentation according to underlying cause, of which several exist. There is probably a final common pathway, which might be a decrease in GABAergic inhibition. Finally, akathisia with agitation is an interesting syndrome in terms of a decrease in dopaminergic activity but also probably an increase in noradrenergic activity. The neuroleptic-induced supersensitivity of noradrenergic receptors and the therapeutic response of akathisia to β-adrenergic antagonists and the α_2-adrenergic agonist clonidine suggest a dysregulation of noradrenergic mechanisms. However, it is uncertain whether the modulation of agitation by reducing adrenergic activity is due to the interaction of dopamine and norepinephrine, especially at the cortical level.[13] Some of these mechanisms are discussed in detail below.

Agitated depression. In agitated depression, 2 phenomenological observations have been made with regard to agitation: the severity of depression tends to correlate with agitation, and a close link exists between anxiety and agitation. This results in a model consisting of 3 psychopathologic overlapping domains: depression, anxiety, and agitation.[14] In terms of pathophysiology, there are probably 2 significant underlying mechanisms: a hyperactive hypothalamic-pituitary-adrenal (HPA) axis (HPA overactivity) and an increased serotonergic responsivity, as demonstrated by some abnormal responses to serotonergic challenges**.**

One of the 2 challenges that have been used in this context is the fenfluramine challenge test, which uses *d*-fenfluramine, a serotonergic agonist. The change in prolactin after fenfluramine challenge is larger in agitated patients with Alzheimer's disease compared with patients without agitation.[15] In another study, patients with affective and personality disorders who were given the challenge test responded with increased prolactin levels as well as with increased anxiety and agitation and psychotic symptoms.[16] The second challenge test that has been used in this context is the *m*-CPP (*m*-chlorophenylpiperazine) challenge test. Also a serotonergic agonist, (*m*-CPP) is a nonspecific agent in terms of serotonergic receptor interaction, just like fenfluramine. These 2 challenge agents activate a number of serotonin (5-HT) receptors (5-HT_{1B}, 5-HT_{1C}, 5-HT_3). Greater anxiety and anger/agitation responses have been observed after *m*-CPP administration in patients with generalized anxiety disorders compared with healthy controls.[17] An increased serotonergic transmission, which can trigger anxiety and agitation in vulnerable individuals, would be one way of understanding these agitated syndromes in depression.

A model of serotonergic sensitivity has been outlined, in either anxiety or depression conditions, by Swann et al.[18] and is modified here (Table 3). In the manic situation with high catecholamine levels and, correspondingly, a low serotonin level related to impulsive aggression, the treatment would seek to increase serotonin function, which would ameliorate the impulsive aggression and agitation component. In this low-serotonin situation, agitation would probably be linked predominantly to aggression.[19,20] This aggression-agitation subsyndrome would respond to treatments that increase serotonergic availability.

In contrast, the serotonin-resistant model, characterized by severe arousal rather than by aggression, would lead to multiple behavioral disturbances including agitation and aggression (see Table 3). In this syndrome, decreased

Table 3. Mechanisms of Agitation in Affective Disorders[a]

Serotonin-sensitive model	
High catecholamines	Manic affective syndrome
Low serotonin	Impulsive aggressive
	Treatment: Increasing serotonin function to ameliorate impulsive aggression/agitation
Serotonin-resistant model	
Severe arousal and manic syndrome	Multiple behavioral disturbances including aggression/agitation
	Treatment: Reduction of arousal through increasing GABA, decreasing noradrenergic transmission

[a]Modified from Swann et al.[18] Abbreviation: GABA = γ-aminobutyric acid.

Table 4. Agitation in Dementia

Nearly 50% of patients with dementia will present with agitation[21]
Possible predisposing factors include deficits in cognitive functions and cerebral impairment
Higher sensitivity to norepinephrine is found in agitated patients with Alzheimer's disease[22]
Significant reduction in serotonin receptors in various brain areas exists in patients with Alzheimer's disease, suggesting reduced serotonergic function[23]
γ-Aminobutyric acid (GABA) deficits found in patients with dementia and agitation[24]

Table 5. Agitation and Psychoses

Hyperdopaminergia in basal ganglia
Increased norepinephrine tone
Reduced GABAergic inhibition

GABAergic function and increased noradrenergic activity are postulated. In this situation, one would try to reduce the arousal through increasing GABAergic inhibition and decreasing noradrenergic transmission. Drugs such as GABAergic agonists (e.g., valproic acid, benzodiazepines), which would increase GABAergic function, and drugs that would decrease noradrenergic transmission would be helpful.

Dementia and agitation. Dementia is very much associated with agitation (Table 4). Nearly 50% of patients with dementia will present with agitation at one point during the course of their disorder.[21] Predisposing factors include deficits in cognitive functions and cerebral impairment.

Generally, a higher sensitivity to norepinephrine has been reported in agitated patients with Alzheimer's disease.[25] Also, a significant reduction in 5-HT receptors has been found in various brain areas in patients with Alzheimer's disease, pointing to reduced serotonergic function.[26] There is also a considerable body of data on GABAergic deficits in patients with dementia and agitation.[24,27]

If these 3 underlying mechanisms represent different clinical syndromes that could be identified clinically, different treatments could be chosen focusing on the identified underlying mechanisms. Patients with higher sensitivity to norepinephrine might be candidates for intervention with dopamine antagonists; dopaminergic antagonists with minimal extrapyramidal symptom (EPS) liability (e.g., atypical antipsychotics) would be indicated. In another situation, drugs that enhance the serotonergic function—for instance, a 5-HT_{1A} agonist (e.g., buspirone)—could be useful. To enhance GABAergic function, drugs such as valproic acid can be used. Interestingly, valproic acid has been widely reported to be an effective antiagitation and antiaggression agent in demented patients with agitation.[28] Another way to enhance GABAergic function is to use benzodiazepines.

Agitated psychosis. Agitation is often part of an acute psychotic episode and phenomenologically is probably related mostly to the positive symptom domain. In terms of critical underlying neurotransmitter systems, dopaminergic, serotonergic, GABAergic, and glutamatergic pathways have been implicated in the pathophysiology of psychotic symptoms (Table 5).

Specifically, mesolimbic dopamine pathways projecting from brain stem to limbic areas mediate positive symptoms. These pathways are referred to as the A10 dopaminergic tracts. Nigrostriatal dopamine pathways project to basal ganglia mediating involuntary movements and are also referred to as A9 tracts. If blocked, these tracts will mediate EPS. In addition, mesocortical dopamine pathways project to cortical areas mediating possibly negative symptoms. The tuberoinfundibular dopamine pathways control prolactin secretion. There are also serotonergic pathways, as represented by 5-HT_{2A} receptors, that show a high density in cortical areas. These pathways modulate nigrostriatal dopaminergic activity, which may explain why 5-HT_{2A} antagonism increases dopamine neurotransmission. This mechanism may underlie the beneficial effects of antipsychotics with pronounced 5-HT_{2A} antagonism on EPS and, possibly, on decreasing negative symptoms (such as the atypical antipsychotics risperidone, olanzapine, clozapine, and quetiapine). 5-HT_3 may modulate mesolimbic dopaminergic activity as well. An indirect support for this hypothesis is the *m*-CPP challenge test, which activates 5-HT_{2C} and 5-HT_3 receptors and increases psychotic symptoms in schizophrenic patients when given acutely.[29]

Another postulated pathophysiologic mechanism underlying psychosis and possibly agitation is related to dysregulated glutamatergic neurotransmission.[30] Glutamatergic activity has been reported to modulate dopaminergic activity in the limbic system. Glutamatergic neurotransmission in the striatum has been suggested as having a primary role in the regulation of psychomotor function,[30] giving prominence to the corticostriatal glutamatergic system. It has been shown that the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist MK-801 causes a pronounced locomotor stimulation in mice depleted of monoaminergic stores.

This may explain restlessness induced by phencyclidine (PCP) and related compounds. Although PCP psychosis does have many similarities with acute psychosis, its usefulness for understanding agitation is not clear at this time.

Put together, acute psychosis can be conceptualized as a mesocortical disconnection syndrome due to limbic dopaminergic hyperactivity with an interruption of glutamatergic modulation of dopaminergic neurotransmission with reduced GABAergic inhibition, which may lead to reduced prefrontal cortical activity, positive and negative symptoms, and cognitive symptoms. An appropriate focus of intervention for antiagitation compounds, therefore, is effective dopaminergic antagonism by antipsychotics with various dopamine-2 (D_2) and 5-HT_2 receptor binding profiles. Compounds with anatomically specific (A10) D_2 receptor binding affinity, high 5-HT_2 receptor affinity to minimize EPS, and additional sedating quality conferred by high histamine-1 (H_1) affinity would be desirable for this purpose. In addition, rapid onset of action is another important feature for compounds useful in the treatment of agitation.

Currently used atypical compounds (risperidone, olanzapine, quetiapine, and clozapine) possess some of these characteristics. Risperidone has been reported in positron emission tomography (PET) studies to show a 5-HT_2 occupancy rate at 2 mg/day of 75%. At 12 mg/day, more than 95% of 5-HT_2 receptors are occupied.[31,32] The occupancy rate for D_2 receptors at 2 mg/day is 63% without EPS, whereas at 12 mg/day (twice as much as the manufacturer's recommended maximum dosage), 88% of D_2 receptors are occupied, a rate that is often associated with the emergence of EPS.[31,32] This finding would indicate that at lower dosages risperidone would be an appropriate antiagitation compound.

Remington et al.[31,32] studied olanzapine using different dosages in the PET experiment. At 5 mg/day, olanzapine showed quick saturation for 5-HT_2 receptors: already 90% of the receptors were bound. At 20 mg/day, the rate was slightly increased to 98%. D_2 receptors showed an occupancy rate of 55% at 5 mg/day and 78% at 20 mg/day with minimal EPS symptoms. Again, this finding would indicate that olanzapine could be an effective agent for patients with psychotic agitation.

Remington et al.[31,32] also looked at 2 different dosages of quetiapine. For the 5-HT_2 receptor, a relatively low occupancy rate of 21% was found at 150 mg/day. At 600 mg/day, the rate reached 80%. At 150 mg/day, quetiapine resulted in only a 2% occupancy rate for D_2 receptors. However, this number may be artificially low, because quetiapine dissociates from D_2 receptors very quickly, and, therefore, this value may not adequately reflect quetiapine's actual receptor occupancy rate. At 600 mg/day, quetiapine's occupancy rate was still rather low at 22%, and no associated EPS were found. It is generally estimated that D_2 receptor occupancy of about 50% to 60% is associated with therapeutic antipsychotic response and that rates above 60% to 70% are associated with EPS. It could be concluded that quetiapine may not be an effective antiagitation compound on the basis of these reported occupancy rates, although its rapid dissociation from D_2 receptor sites casts some doubts on the validity of these numbers. In addition, quetiapine has also potent H_1 receptor affinity, which mediates its sedation property and which may be useful in the treatment of psychotic agitation.

Taking into account pharmacokinetic issues could be useful in reducing absorption time of particular compounds, possibly speeding up their onset of action. An intramuscular administration route could accelerate this absorption rate; however, none of the presently available atypical antipsychotics are available in an intramuscular form. It is hoped that in the near future such administration forms will become available. Another way to bridge the delayed onset of action of antipsychotic compounds is to concomitantly use GABAergic compounds, such as benzodiazepines.

Agitation and akathisia. Another syndrome that causes agitation in a clinically relevant manner is akathisia (Table 6). Its clinical description usually consists of difficulty sitting still, repetitive leg movements, restlessness, subjective feeling of inner agitation, and overall irregular movements.

In terms of underlying pathophysiology, it is thought that the nigrostriatal dopaminergic blockade induced by D_2 antagonism may mediate this syndrome.[33] In addition, increased central norepinephrine may antagonize mesocortical dopamine function even further. Typically, traditional antipsychotics with a low ratio of 5-HT_2 receptor occupancy to D_2 receptor occupancy are associated with the occurrence of akathisia. Treatment, therefore, would consist of reducing nigrostriatal dopamine blockade by reducing the dose of the antipsychotic drug or of using a β-blocker to reduce the central norepinephrine hyperactivity. Also, specific selective 5-HT_2 antagonists seem to

Table 6. Agitation and Akathisia[a]

Symptoms
Difficulty sitting still
Repetitive leg movements
Restlessness
Subjective feeling of inner agitation
Pathophysiology
Mesocortical dopaminergic blockade
Increased central norepinephrine antagonizing mesocortical dopamine function
Low ratio of 5-HT_2 receptor to D_2 receptor blockade
Low D_1 receptor affinity
Treatment
Reduce mesocortical dopaminergic blockade
Use β-blocker to reduce central norepinephrine hyperactivity
Use atypical antipsychotics with high 5-HT_2 receptor and low dopamine receptor antagonism
Use benzodiazepines

[a]Abbreviations: 5-HT = serotonin, D = dopamine.

work in akathisia, such as ritanserin.[34] The use of atypical antipsychotics with a high 5-HT_2 receptor and lower D_2 receptor antagonism would also be helpful. In addition, an increase in GABAergic inhibition by using benzodiazepines would be another way of treating akathisia. The therapeutic effect of benzodiazepines in akathisia supports an additional role for diminished GABA activity in the pathogenesis of akathisia.

CONCLUSION

Agitation is a transnosologic syndrome that is present in a variety of psychiatric disorders. Multiple underlying pathophysiologic abnormalities are found in the dopaminergic, serotonergic, noradrenergic, and GABAergic systems. However, these pathophysiologic abnormalities are not associated with distinct clinical features. Although there may be a final common pathway, there is no unifying etiologic pathophysiology. Therefore, the clinician may want to address the underlying pathophysiology through a treatment intervention addressing the overarching psychiatric disorder. This means that it is important that the diagnosis of the overarching disorder be established early on to allow for specific treatment. Generally, agents that reduce dopaminergic or noradrenergic tone or increase serotonergic or GABAergic tone will attenuate agitation, often irrespective of etiology.

Drug names: buspirone (BuSpar), clonidine (Catapres and others), clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, buspirone, quetiapine, risperidone, and valproic acid are not approved by the U.S. Food and Drug Administration for the treatment of agitation.

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