

A Review of Agitation in Mental Illness: Burden of Illness and Underlying Pathology

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Agitation has been poorly addressed as a unique entity in many psychiatric disorders. Recent medical literature and a range of instruments have measured agitation in various clinical settings. Agitation is a common problem in many patients with schizophrenia, bipolar mania, or dementia. Moreover, agitation adversely impacts many facets of the healing process, including direct patient care, caregiver burden, and community resources. Frontal lobe dysfunction and mutations in the catechol O-methyltransferase (COMT) gene involved in dopamine metabolism and catecholamine inactivation have been linked to agitation in patients with schizophrenia and bipolar disorder. Cerebral impairment and deficits in cognitive function predispose patients with dementia to agitation. In patients with Alzheimer's dementia, both frontal and temporal lobe pathology may be associated with agitation. Addressing agitation as a symptom of psychiatric illness would represent a great opportunity for therapeutic intervention and the alleviation of patient suffering, family burden, and societal costs.

(J Clin Psychiatry 2006;67[suppl 10]:5-12)

Agitation has diverse manifestations across many psychiatric illnesses.¹ Generally recognized component behaviors of agitation may include those that are physically or verbally aggressive (such as fighting, throwing, grabbing, destroying items, verbal outbursts, cursing, and screaming) as well as those that are nonaggressive (restlessness, pacing, wandering, repetitive questioning, chatting, inappropriate disrobing, and verbal outbursts).^{2,3} In addition, there is a social dimension to the perception of agitation, in that the agitated individual is generally considered to be acting inappropriately, as assessed by social standards.²

Despite the fact that agitation is a common component of many psychiatric disorders, few publications in the medical literature address agitation specifically as a unique entity.² As the American Association for Geriatric Psychiatry (AAGP) concluded in 2000,⁴ agitation rarely has been a primary focus of either phenomenological classification or therapeutic intervention. In addition, the study of agitation in mental illness has been complicated by a host of often imprecise and/or conflicting definitions (Table 1),^{2,3,5-9} and the boundaries of agitation have not been elucidated with the precision accorded to other psychiatric symptoms,

such as hallucinations and delusions.⁴ Notwithstanding this apparent lack of attention by the medical community, a broad range of instruments has been developed to measure agitation in various clinical settings (Table 2).¹⁰⁻¹⁸ These scales differ significantly in their assessment approaches and have found their greatest utility in the assessment of interventions rather than in epidemiologic and pathophysiologic research.²

Contrary to the weaknesses and other shortcomings that exist historically with respect to the study of agitation, it is believed that the extant database on the evaluation of agitation, aggression, and related symptoms in psychiatric illness is large enough that rapid progress should be possible in defining the parameters of psychomotor agitation (and related symptoms/syndromes) more specifically than has occurred to date.⁴ The present review represents an attempt to briefly assess the burden of illness and pathophysiology of agitation as evidenced by recent publications in the medical literature, especially with respect to patients with schizophrenia, bipolar disorder, and dementia (Alzheimer's disease).

MANIFESTATIONS OF AGITATION IN PSYCHIATRIC ILLNESS

According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR),¹⁹ agitation is listed as among the following:

- the "grossly disorganized" behavior characteristics of schizophrenia;

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This article was supported by an unrestricted educational grant from Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

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Table 1. An Overview of Definitions for Agitation

Psychiatric Illness	Definition of Agitation	Publication (Year)
Dementia	A heterogeneous group of inappropriate verbal, vocal, or motor behaviors that is not explained by apparent needs or confusion Inappropriate verbal, vocal, or motor activity that does not result from need Nonspecific physical and verbal behaviors that are commonly found in nursing home patients with dementia; these include wandering, pacing, restlessness, inappropriate disrobing, and verbal outbursts	Porsteinsson et al (2001) ⁵ ; Cohen-Mansfield (1986) ⁶ Gray (2004) ⁷ Bartels et al (2003) ³
Broad spectrum of psychiatric illnesses	A state of motor restlessness accompanied by mental tension A nonspecific constellation of relatively unrelated behaviors that can be seen in a number of different clinical conditions, usually presenting a fluctuating course A state of poorly organized and aimless psychomotor activity stemming from physical or mental unease Definition includes the following: motor restlessness, heightened responsivity to external or internal stimuli, irritability, inappropriate and/or purposeless verbal or motor activity, decreased sleep, and fluctuation of symptoms over time Restlessness and agitation are diffuse increases in body movement, usually expressed as fidgeting, rapid and rhythmic leg or hand tapping, and jerky start-and-stop movements of the entire body, accompanied by inner tension; agitation is often accompanied by pacing and hand wringing	Battaglia (2005) ⁸ Lindenmayer (2000) ² Kaplan and Sadock (1995) ⁹

- the diagnostic criteria for a bipolar-manic episode;
- the presenting symptoms of a bipolar-mixed episode; and
- the behavioral disturbances associated with dementia, especially Alzheimer's dementia.

agitation percentages have ranged from as low as 10% to as high as 100%, depending on the specific subtype of dementia and the setting of patient care (in-home vs. nursing home).

Common features of agitation seen in schizophrenia, bipolar disorder, and dementia include: excessive motor and/or verbal activity, irritability, uncooperativeness, vocal outbursts or abuse, threatening gestures or language, physical destruction, and assault.¹

EPIDEMIOLOGY OF AGITATION

Little direct epidemiologic work has been done to assess the prevalence, clinical impact, or financial consequences of agitation, especially with respect to schizophrenia and bipolar disorder. As may be appreciated from the studies summarized in Table 3,^{3,14,20-27} much of the existent epidemiologic data on agitation is derived from patient visits in the psychiatric emergency setting, where agitation has been described as a "common symptom" among emergency patients with psychoses, bipolar disorder, or dementia.^{14,20,21} In the United States, where at least 3.4 million psychiatric emergency visits occur each year, Marco and Vaughan¹⁴ have estimated that 21% (900,000 visits annually) may potentially involve agitated patients with schizophrenia. With the addition of another 560,000 psychiatric emergency visits due to bipolar disorder (13% of all psychiatric emergency visits) and 210,000 due to dementia (5% of all psychiatric emergency visits), the total number of psychiatric emergency visits potentially involving agitated patients approximates 1.7 million annually.²¹ Outside the psychiatric emergency setting, specific epidemiologic data regarding the prevalence of agitation are sparse, except for a few studies addressing agitation as a behavioral symptom of dementia. In these studies (Table 3),^{3,21,26,27}

PATHOPHYSIOLOGY OF AGITATION AND AGGRESSION

The functional neuroanatomy and neurochemical basis of agitation are not well understood.² In patients with psychosis, proposed pathophysiologic mechanisms for agitation have included hyperdopaminergia in the basal ganglia, increased norepinephrine tone, and a reduction of inhibitory γ -aminobutyric acid (GABA) influences.² On the microanatomic level, alterations in inferior frontal white matter microstructure, with resultant frontal lobe dysfunction, have been implicated in the pathophysiology of aggression and impulsivity in patients with schizophrenia.²⁸ In addition, frontal lobe impairment, as determined by comprehensive psychiatric and neurologic assessments, has also been linked to the presence of persistent violence among physically assaultive psychiatric inpatients.²⁹ Among patients with bipolar disorder, multiple neuroimaging studies have likewise pointed to reduced function in the frontal lobes.³⁰

In the realm of genetic research, there has been preliminary evidence regarding a link between aggression in schizophrenic patients and mutations in the catechol O-methyltransferase (COMT) gene, a chromosome 22q gene that codes for the COMT enzyme involved in dopamine metabolism and catecholamine inactivation.^{31,32} Specifically, data from a 1998 study by Lachman and colleagues³² in 55 violent schizophrenic patients (inpatients or residents in community care facilities) suggest that either COMT polymorphism or a gene in linkage disequilibrium with the COMT locus might play a role in violence in schizophrenia. In a more recent 2004 study,³³ COMT

Table 2. Selected Instruments Used in the Assessment of Agitation

Instrument	Technique	Description	Utility	Publication (year)
BEHAVE-AD	Caregiver interview	Documents the presence and severity of 25 behavioral symptoms in 7 symptomatic categories (paranoid and delusional ideation, hallucination, activity disturbances, aggressivity, sleep disturbances, affective symptoms, and anxieties and phobias)	Provides scores for each of the major symptomatic categories, including activity disturbances and aggressivity; also provides scores for overall severity of behavioral disturbance and for caregiver burden	Reisberg et al (1987) ¹⁰ , Sclan and Sallion (1996) ¹¹ , Chen et al (2000) ¹²
Neuropsychiatric Inventory	Caregiver interview	Assesses 12 types of behavioral disturbances, including delusions, hallucinations, agitation, apathy, disinhibition, and sleep disturbances	Each behavioral disturbance is evaluated in terms of its frequency and severity	Norton et al (2001) ¹³
Behavioral Activity Rating Scale	Clinician observation	7-point scale; rates severity of agitation from 1 (difficult or unable to arouse) to 7 (violent, requires restraint)	Measures behavioral activity in acutely agitated patients with psychosis	Marco and Vaughan (2005) ¹⁴ , Swift et al (2002) ¹⁵
Cohen-Mansfield Agitation Inventory	Caregiver observation and evaluation	Assesses frequency of 29 agitated and related behaviors	7-point rating scale; helpful in nursing home setting	Cummings (2005) ¹⁶
PANSS-EC	Clinician's assessment	Assesses severity of the following 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement	Severity of agitation is based on a 1-7 scoring system for each item; helpful in assessing efficacy of anti-agitation medications, especially in clinical trials	Battaglia et al (2003) ¹⁷
Young Mania Rating Scale	Clinician's assessment	Assesses severity of 10 items associated with mania, including: elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech (rate and amount), language-thought disorder, content, disruptive/aggressive behavior, and patient appearance	Severity is graded on a 0-8 scoring system for each item; the YMRS appears to measure the manic "state" as opposed to specific patient traits	Gracious et al (2002) ¹⁸

Abbreviations: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale, PANSS-EC = Positive and Negative Syndrome Scale-excited component.

polymorphism was linked to the presence of significantly higher levels of hostility in patients with schizophrenia or schizoaffective disorder. With respect to patients with bipolar disorder, COMT polymorphism has also been implicated in the etiology of some variants of this illness.³⁴

Among patients with dementia, agitation is believed to be of multifactorial etiology.³⁵ According to a statement by the AAGP,⁴ "agitation may be a final common pathway for the expression of symptoms of depression, anxiety, psychosis, and even pain in dementia . . . and it can clearly be a behavioral response to environmental stressors, unskillful caregiving, or unmet psychosocial needs in patients with cognitive and verbal communication deficits." In patients with Alzheimer's dementia, agitation can be caused or exacerbated by medication, substance intoxication or withdrawal, delirium, pain syndromes, infection, bladder distention, and fecal impaction.³⁶ Potential precipitants for agitation in the patient with dementia may include physical, environmental, social, and psychiatric factors.⁵ While agitation may be of multifactorial etiology in patients with Alzheimer's disease, it is also true that many patients with Alzheimer's disease have only agitation as the target symptom for treatment.³⁵

In patients with dementia, general predisposing factors for agitation may include cerebral impairment and deficits in cognitive function.² With respect to patients with Alzheimer's disease, there is mounting evidence that psychiatric symptoms, including agitation, may be fundamental expressions of underlying cortical dysfunction.³⁷ Specifically, functional neuroimaging studies performed by Sultzer's group³⁷ have suggested that both frontal and temporal lobe pathology may be associated with agitation in patients with the Alzheimer's disease form of dementia. In a population of 21 patients with Alzheimer's disease, these investigators³⁷ compared psychiatric symptoms (as assessed by the Neurobehavioral Rating Scale [NRS]) and regional cerebral metabolic activity (as measured by [18F]fluorodeoxyglucose positron emission tomography). They concluded that patients with Alzheimer's disease showed significant correlations between global cortical metabolic activity and the Agitation/Disinhibition factor score of the NRS. There was also a significant correlation between the Agitation/Disinhibition factor score on the NRS and cerebral metabolism in both the frontal and temporal lobes. Based on retrospective data analysis of 143 patients with Alzheimer's disease, Tekin and colleagues³⁸ concluded that frontal lobe dysfunction may be the common pathologic process that not only mediates agitation in these patients, but also gives rise to executive dysfunction and impairment in pa-

Table 3. Studies Addressing the Epidemiology of Agitation in Psychiatric Illnesses

Psychiatric Illness	Setting	Population	Information (direct or indirect) Regarding the Occurrence of Agitation	Publication (year)
Schizophrenia	Psychiatric emergency setting	Patients with psychiatric emergencies	Agitation is common among emergency patients with psychoses, including schizophrenia; psychoses account for 21% of all psychiatric emergency visits, amounting to 900,000 visits annually	Marco and Vaughan (2005) ¹⁴ ; Hazlett et al (2004) ²⁰
	Psychiatric emergency setting	Patients with psychiatric emergencies	Individuals with psychotic disorders (including schizophrenia and schizoaffective disorder) account for 28% of patients	Allen and Currier (2004) ²¹
	Psychiatric hospital in Munich, Germany	Hospitalized patients with schizophrenia	14% showed aggression on admission	Soyka and Ufer (2002) ²²
	Unspecified	Patients with schizophrenia	In FDA-registration and postmarketing trials involving olanzapine or aripiprazole, approximately 33%–34% of patients had “higher” levels of agitation as defined by test instruments such as the PANSS	Marder et al (in press) ²³
Bipolar disorder	Psychiatric emergency setting	Patients with psychiatric emergencies	Individuals with bipolar disorder account for 13% of patients	Allen and Currier (2004) ²¹
	Psychiatric treatment center in Italy	Outpatients	Of 195 bipolar I patients with a “mixed state” profile, 25.7% were predominately manic	Perugi et al (2001) ²⁴
	Unspecified	Patients with bipolar disorder	In FDA-registration and postmarketing trials involving atypical antipsychotics, the number of patients with “lower agitation” at baseline was roughly equivalent to the number of patients with “higher agitation,” as defined by test instruments including the YMRS, PANSS, or CGI	Sachs et al (in press) ²⁵
Dementia	Psychiatric emergency setting	Patients with psychiatric emergencies	Individuals with dementia account for 5% of patients	Allen and Currier (2004) ²¹
	Nursing home	Elderly residents	Agitation prevalence = 10%–90%; median frequency = 44%	Bartels et al (2003) ³
	Outpatient neurology clinic in India	Outpatients	Agitation frequency: 96.7% overall 93.2% in Alzheimer’s disease 93.5% in vascular dementia 100% in frontotemporal dementia	Srikanth et al (2005) ²⁶
	Home-care setting	Outpatients with dementia	Aggressive behavior in 57%–67%; severe violence in 15.8%/year	Hansberry et al (2005) ²⁷

Abbreviations: CGI = Clinical Global Impressions scale, FDA = Food and Drug Administration, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

tient performance of instrumental activities of daily living. A similar hypothesis was proposed by Norton’s group,¹³ who suggested that frontal deficits not only appear to affect behavioral symptoms, such as agitation, in patients with Alzheimer’s disease, but also impact the extent of patients’ functional disability.

Although there is mounting evidence for a link between cortical dysfunction and dementia at the anatomic and behavioral levels, agitation is poorly understood at the level of cellular physiology.⁸ Underlying mechanisms suggested for the induction of agitation in persons with dementia have included the following: pathologic increases in dopamine and norepinephrine and decreases in GABA, higher sensitivity to norepinephrine, both hyperserotonergic and hyposerotonergic states, low serotonin levels with increased postsynaptic sensitivity, and a significant reduction in serotonin receptors in various brain areas.^{2,8,39} With respect to putative GABA-related mechanisms, it has been theorized that alterations in GABA may have modulating effects on both mesolimbic and nigrostriatal regions in patients with agitation.⁸ In a similar vein, studies supporting the efficacy of valproate (divalproex sodium) in the treatment of agitated patients with dementia have postulated a mechanism of action that involves modulation of GABA transmission, limbic stabilization, modulation of circadian rhythms, and/or possible neuroprotective effects.⁵

AGITATION AND AGGRESSION IN PATIENTS WITH SCHIZOPHRENIA

In 2004, the American Psychiatric Association Steering Committee on Practice Guidelines⁴⁰ emphasized that, although only a minority of patients with schizophrenia are violent, evidence does suggest that schizophrenia is associated with an increase in the risk of aggressive behavior. In a 2002 retrospective European study, Soyka and Ufer²² evaluated the patient files of all schizophrenic patients admitted to the psychiatric hospital of the University of Munich between 1990 and 1995 (N = 2093) and concluded that 14% (292 patients) showed aggressive behavior on admission. In that study,²² aggressive behavior

was most common among the following: male patients with schizophrenia, patients with the disorganized schizophrenia subtype, and psychotic patients who exhibited concomitant symptoms of delusional ideas and disorganized thinking. In another 2002 publication, a review by Flannery⁴¹ of 28 studies involving assaults by psychiatric patients found evidence that repetitively violent patients were most frequently diagnosed with either schizophrenia or personality disorder. In a 2002 selective review of the key literature on the epidemiology of violence and schizophrenia, evidence published in the *British Journal of Psychiatry* by Walsh and coworkers⁴² confirmed the association between violence and schizophrenia, especially in cases of comorbid substance abuse.

Schizophrenic patients posing the greatest risk for violent behavior appear to be those who show more suspiciousness and hostility, have more severe hallucinations, show less insight into their delusions, experience greater thought disorder, and have poorer control of their aggressive impulses than patients who are nonviolent.⁴³ With respect to becoming a target of violence by a person with schizophrenia, documented risk factors have included being a parent or immediate family member of the patient, sharing a residence with the patient for a long time, and having the patient be financially dependent on the family.⁴⁴ Overall, outside the hospital setting, parents and immediate family members of patients with schizophrenia have been the most common targets of aggression by these patients.^{40,44}

AGITATION IN BIPOLAR DISORDER

In patients with bipolar disorder, the DSM-IV-TR lists agitation among the diagnostic criteria for a bipolar-manic episode.¹⁹ In terms of relative percentages, Keck and colleagues⁴⁵ have placed agitation as third among the top 4 symptoms of mania, according to the following order: pressured speech (98%), hyperverboisity (89%), physical hyperactivity and agitation (87%), and decreased need for sleep (81%). From a psychosocial perspective, Alderfer and Allen⁴⁶ have observed that agitation is often seen in bipolar patients during acute manic states, "when increased energy levels and reduced need for sleep lead patients to collide with the limits of others."^{46(p3)} In addition, agitation (characterized by fluctuating energy levels and periods of irritability) also occurs during bipolar-depressive and bipolar-mixed states,⁴⁶ where predominantly manic symptoms may affect over 25% of patients.^{24,30} As may be appreciated from Table 3, specific prevalence data regarding the presence of agitation in bipolar disorder are almost nonexistent.^{21,24,25}

For all patients with bipolar illness who are experiencing agitation and other symptoms of acute mania, rapid and intensive treatment is required to decrease their suffering as quickly as possible, as well as to maintain their

safety and the safety of those around them.⁴⁶ Once acute mania resolves, prevention of future episodes becomes an important goal of long-term therapy, since bipolar disorder is a recurrent illness in 80% to 90% of patients.⁴⁵

AGITATION IN DEMENTIA/ALZHEIMER'S DISEASE

According to Teri and colleagues,⁴⁷ agitation occurs in up to 50% of community-dwelling patients with Alzheimer's disease and 70% to 90% of nursing home residents. Overall, among all patients with Alzheimer's disease, the incidence of agitation is estimated to be 60% to 80% (median = 44%) among all patients with dementia.³ It has been estimated that with respect to patients with Alzheimer's disease, approximately 50% become frankly physically aggressive⁷ and 24% become verbally aggressive³⁵ at some point during their dementia. In a multiethnic community sample of 125 patients with Alzheimer's disease, Chen and coworkers¹² found that behavioral disturbances were extremely common, occurring in 98% of the sample population. Among these behavioral disturbances, the most common was activity disturbance (defined as wandering and purposeless or inappropriate activities), which occurred in 89% of patients, whereas aggression (another agitation-related disturbance) occurred in 64%.¹² Overall, activity disturbances and aggressivity were more common in patients with Alzheimer's disease than were several other common behavioral symptoms, including anxieties, phobias, affective disturbances, sleep disturbances, and hallucinations.¹² Importantly, there is also substantial evidence that agitation tends to increase as Alzheimer's disease progresses, with both aggression and activity disturbances becoming more prevalent during the moderate-to-severe stages of dementia as compared to earlier stages of the illness.¹² For example, as Devanand and colleagues⁴⁸ reported in 1997, the prevalence of agitation increased from 33% to 50% over a 2-year period among patients with mild-to-moderate Alzheimer's disease.

An association has also been demonstrated between behavioral disturbances (such as agitation) and functional deterioration in patients with Alzheimer's disease.¹³ This link between agitation and functional deterioration is evidenced by decreased ability to perform traditional activities of daily living, such as dressing, grooming, and toileting, as well as instrumental activities of daily living, such as medication administration, financial management, and use of transportation.¹³ In addition to being associated with deterioration in a patient's ability for self-care, the onset of agitation and aggression symptomatology may also significantly increase caregiver burden. For example, as Madhusoodanan³⁵ has reported, symptoms associated with agitation (aggression, combativeness, hyperactivity, wandering, hypervocalization, disinhibition) are among the symptoms of Alzheimer's disease that are a major source

of distress for caregivers and often lead to institutionalization of the patient.

Once the patient with Alzheimer's disease is institutionalized, symptoms of agitation and aggression also increase the patient's ongoing burden of illness with respect to nursing home care. In a 2003 study involving almost 2500 physically frail older nursing home residents, Bartels and colleagues³ concluded that patients whose dementia was complicated by mixed agitation and depression had the highest rate of hospitalization (15.6% over a 3-month study period), had the greatest number (mean \pm SD) of medical diagnoses (9.1 ± 4.0), received the most medical drugs (6.7 ± 4.0), and had the greatest use of high-cost medical services. In addition, residents with dementia complicated by agitation had the highest 3-month rate of emergency room visits and the greatest use of physical restraints. Significantly, despite the high use of restraints in this population, over 40% of these agitated patients received no psychiatric medication for their symptoms. The authors³ concluded that the increased use of physical restraint could be an unintended consequence of physicians' efforts to comply with guidelines so as to reduce the use of psychiatric medications in nonspecific agitation.

IMPACT OF AGITATION IN THE EMERGENCY SETTING

Violent or threatening behavior is a common reason for a visit to the emergency department,¹ and among emergency psychiatric services, the prevalence of agitated or frankly violent patients may be as high as 10%.⁴⁹ For both nurses and physicians, agitation is among the most fear-provoking aspects of psychiatry, with an average of 8 assaults occurring per year in a typical psychiatric emergency service.⁵⁰ Nursing staff, in particular, may be especially vulnerable targets, with 6 times as many nurses being assaulted by agitated patients as compared to physicians.⁵⁰ When the American Association for Emergency Psychiatry (AAEP) surveyed medical directors of psychiatric emergency services in 1999, respondents described high numbers of assaults by patients toward staff in psychiatric emergency service facilities, with a mean of 5.8 assaults (range, 0–35) per site annually, of which 56.5% resulted in time lost from work by the psychiatric emergency services staff.²¹

IMPACT OF AGITATION ON INPATIENT AND OUTPATIENT CARE

Among psychiatric inpatients, agitation is a common warning signal that often precedes an act of violence.⁴⁴ In particular, acts of inpatient violence are especially common among manic and demented patients, where the aggressive act usually consists of striking out at random victims or at mere bystanders.⁴⁴ Once a patient commits an act of vio-

lence in the hospital setting, this typically impacts treatment course, resulting in a significantly longer length of stay and its attendant increased financial burden.⁵¹ While it is true that this longer hospital stay may be a logical consequence of the violent patient's more severe psychopathology, it may also reflect the treating physician's reluctance to discharge a patient with a recent violent outburst into the larger community.⁵¹

Following discharge, there is frequently an ongoing risk that agitation and overt violent behavior may recur when the patient leaves the inpatient therapeutic milieu. This is especially true for patients with schizophrenia, who, as a diagnostic population, have a propensity to stop taking their medications, resulting in symptom recurrence.⁴⁰ As a subgroup, nonadherent schizophrenic patients who have a history of psychotic relapses associated with violent behavior constitute a subpopulation of particular concern to caregivers, treating physicians, and civil authorities alike.⁴⁰

For caregivers, the impact of a patient's agitation or outright aggression can be great, often triggering a storm of emotional reactions to the patient's illness, including feelings of guilt, loss, and fear about the future.⁵² In addition, patient agitation or aggression can also increase overall caregiver distress, consequently increasing the need for nursing home placement or other institutionalization.^{7,53} Once the patient is institutionalized, agitation may raise the cost of medical/psychiatric care, increase the need for emergency room visits, and generally have an adverse effect on the patient's quality of life.^{3,7} In addition, the patient and his or her family may face a substantial economic burden related to both support of the patient and to loss of overall productivity of the family unit.⁵²

SUBSTANCE ABUSE AS A COMPLICATING FACTOR IN AGITATION

A patient's concomitant use of alcohol and/or other drugs of abuse is a frequent complicating factor in acute agitation, one with much epidemiologic evidence supporting a relationship between comorbid substance abuse and an increased risk for violent behavior.⁵⁴ In particular, the comorbidity between bipolar disorder and substance use disorders is strong, with data from community-based studies suggesting that drug and alcohol abuse are much more common in persons with bipolar disorder than in either the general population or patients with other mental illnesses, including schizophrenia.⁵⁵ Specifically, population-based studies that have examined the prevalence of substance use disorders in persons with various types of mental illness have found a 48% to 61% lifetime prevalence of substance use disorders in persons with bipolar disorder and a 47% lifetime prevalence in persons with schizophrenia, as compared to a 17% prevalence in the entire community sample.⁵⁵ Among persons with a history of mania, it has

been reported that lifetime odds ratios were 0.3 for alcohol abuse, 9.7 for alcohol dependence, 1.2 for drug abuse, 8.4 for drug dependence, and 6.8 for any substance use disorder.⁵⁵ In a 25-year study of homicide and major mental disorders, Schanda and colleagues⁵⁶ concluded that comorbid alcohol abuse/dependence increased risk for homicide among patients with schizophrenia, major depression, or bipolar disorder. In addition to increasing the risk for violence, intoxication with drugs or alcohol is also a documented risk factor for death or injury if the patient should require restraints for the protection of self or staff.⁵⁷

SUMMARY AND FUTURE DIRECTIONS

As supported by evidence from the medical literature presented in this review, it can be well appreciated that agitation remains a common, yet often unaddressed problem in many patients with psychiatric illness, especially those with schizophrenia, bipolar mania, or dementia. Moreover, agitation is a symptom that adversely impacts many facets of the healing process, including direct patient care, caregiver burden, and community resources (both emergency services and the criminal justice system). Despite these issues, agitation has not been adequately addressed, or even epidemiologically assessed, in the medical literature. At present, addressing agitation as a symptom of psychiatric illness would represent a great opportunity for therapeutic intervention and the alleviation of patient suffering, family burden, and societal costs.⁵⁸

Drug names: aripiprazole (Abilify), divalproex sodium (Depakote), olanzapine (Zyprexa).

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