Treatment of Agitation in Dementia

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Behavioral and psychological signs and symptoms associated with dementia are common and often confusing because they do not meet criteria for typical discrete psychiatric disorders. Although the symptoms tend to occur in clusters, the clusters often vary with time and between patients. Recognizing the behavioral pathology associated with dementia is important because it can be distressing to the patient, lead to dangerous interactions with others or the environment, and result in the use of inappropriate psychotropic medications. A practical, general approach to the evaluation and management of agitation in dementia for psychiatric consultants confronted with such problems is proposed.

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It has been estimated that up to 90% of patients with dementia will develop significant behavioral problems at some point in the course of their illness.[1] The scope of the problem was illustrated in a recent study of a rating scale assessing behavioral pathology in dementia.[2] More than 300 outpatients with probable Alzheimer's disease were assessed with the Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease (BRSD CERAD). As assessed by this scale, none of these patients had been free of behavioral signs or symptoms in the preceding month, while the average number of behavioral problems present during that time was 15, with some patients exhibiting 30 or more identified problems. These findings were generally consistent with those of prior studies,[1] confirming Merriam and colleagues' assertion that Alzheimer's disease is "the most widely encountered cause of psychiatric pathology associated with a specific neuropathologic substrate."[3]

Behavioral signs and symptoms in dementia are protean and, to the uninitiated, often confusing. One reason for confusion is that these features often do not meet criteria for typical discrete psychiatric disorders. Rather, they tend to occur in subsyndromal clusters that vary with time and between patients.[1] With experience, clinicians can learn to identify these clusters, which can serve as a guide to therapy. These clusters are summarized in Table 1, which is a schematic summary of the incidence of behavioral disturbances in dementia, based on published values. The clusters include features suggestive of depression or, less commonly, of mania (i.e., disturbed affect/mood), psychosis (i.e., disturbed ideation and perception), agitation, aggression, anxiety, and withdrawn/passive behavior. Vegetative features are included in this Table because they are often used in psychiatric nosology and influence therapeutic decision making.

With the exception of "agitation," most of the behavioral terms in Table 1 are self-explanatory. Cohen-Mansfield and Billig defined agitation as inappropriate verbal, vocal, or motor activity unexplained by apparent needs or confusion.[4] This excellent operational definition emphasizes the point that disturbed behavior very often has meaning that can be discerned. We should be hesitant to label such behaviors as "agitated" or "merely related to dementia," until we are reasonably sure that there is no underlying explanation or need being expressed.

In broad terms, agitated behaviors in dementia can be characterized as disruptive but nonaggressive (i.e., physical and verbal), socially inappropriate, or aggressive.[4] Aggression constitutes an important subset of agitation in this construct, defined as hostile actions directed toward others, self, or objects. Aggressive behaviors could be physical, verbal, or sexual. As the values in Table 1 suggest, nearly 50% of patients with dementia would be expected to demonstrate agitation at some point in the course of their illness, and 25% to 33% might exhibit aggressive behaviors. Examples of physically agitated behaviors include actions such as inappropriate robing and disrobing, pacing, handling things inappropriately, and restlessness, while verbal behaviors could include complaining, requests for attention, and negativism.[4] Examples of physically aggressive behaviors include hitting, kicking, pushing, and scratching, while verbally aggressive behaviors include actions such as threats, accusations, name-calling, and obscenities.[4]

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Table 1. Summary of Psychopathology of Dementia Based on a Review of the Literature[a]

Cluster	% of Patients Affected Among Studies Reviewed	
	Range	Median
1. Disturbed affect/mood	0–86	19
2. Disturbed ideation	10–73	33.5
3. Altered perception		
Hallucinations	21–49	28
Misperceptions	1–49	23
4. Agitation		
Global	10–90	44
Wandering	0–50	18
5. Aggression		
Verbal	11–51	24
Physical	0–46	14.3
Resistive/uncooperative	27–65	14
6. Anxiety	0–50	31.8
7. Withdrawn/passive behavior	21–88	61
8. Vegetative behaviors		
Sleep	0–47	27
Diet/appetite	12.5–77	34

[a]Adapted from Tariot and Blazina,[1] with permission.

Table 2. Summary of General Principles to the Approach of Agitation and Aggression in Patients With Dementia[a]

1. Define target symptoms
2. Establish or revisit medical diagnoses
3. Establish or revisit neuropsychiatric diagnoses
4. Assess and reverse aggravating factors
5. Adapt to specific cognitive deficits
6. Identify relevant psychosocial factors
7. Educate caregivers
8. Employ behavior management principles
9. Use psychotropic medications for specific psychiatric syndromes
10. For remaining problems, consider symptomatic pharmacotherapy
    - Use psychobehavioral metaphor
    - Use medication class relevant to metaphor and with empirical evidence of efficacy
    - Start low, go slow
    - Avoid toxicity
    - Use lowest effective dose
    - Withdraw after appropriate period, observe for relapse
    - Serial trials sometimes needed

[a]Adapted from Tariot,[7–9] Tariot et al.,[10] and Leibovici and Tariot.[11]

Behavioral pathology associated with dementia is important for a number of reasons. It can be distressing to the patient, lead to dangerous interactions with others or the environment, and result in the use of appropriate or even inappropriate psychotropic medications. Caregivers frequently suffer serious psychological and physical consequences from their attempts to deal with these behaviors. Disruptive behaviors, especially agitation and aggression, are a common precipitant of institutionalization. Kalunian and colleagues found that dementia and other organic mental disorders were the most frequent diagnoses among older patients needing to be hospitalized for aggression.[5] Similarly, Nilsson and coworkers found these diagnoses most often were associated with aggression in hospitalized geropsychiatric patients.[6] Our own experience in a home-visit program, which targeted homebound elderly in need of psychiatric assessment, has been consistent with this finding; the majority of the patients have had a dementia and about 60% experienced some form of agitation (P.N.T., unpublished data). Behavioral problems in dementia are common in the community as well as in health care institutions. They are morbid for all concerned, but patients' function, autonomy, and quality of life can improve with effective treatment, which can prove beneficial for caregivers as well.

Our group at the University of Rochester follows a systematic general approach to the evaluation and management of agitation in dementia, which we propose might be adopted by psychiatric consultants confronted with such problems. The stepwise approach is by itself therapeutic, offering reassurance to families and caregivers that a confusing situation may be able to be clarified, understood, and helped. The approach is summarized in Table 2 and Figure 1 and is based on prior work.[7–11] Table 3 offers supplemental suggestions for patient management, which have been drawn chiefly from nursing literature, that families and caregivers may find useful. Taking the time to listen to the problem, validating the difficulty of caregiving, and offering some concrete suggestions can have a calming and reassuring effect.

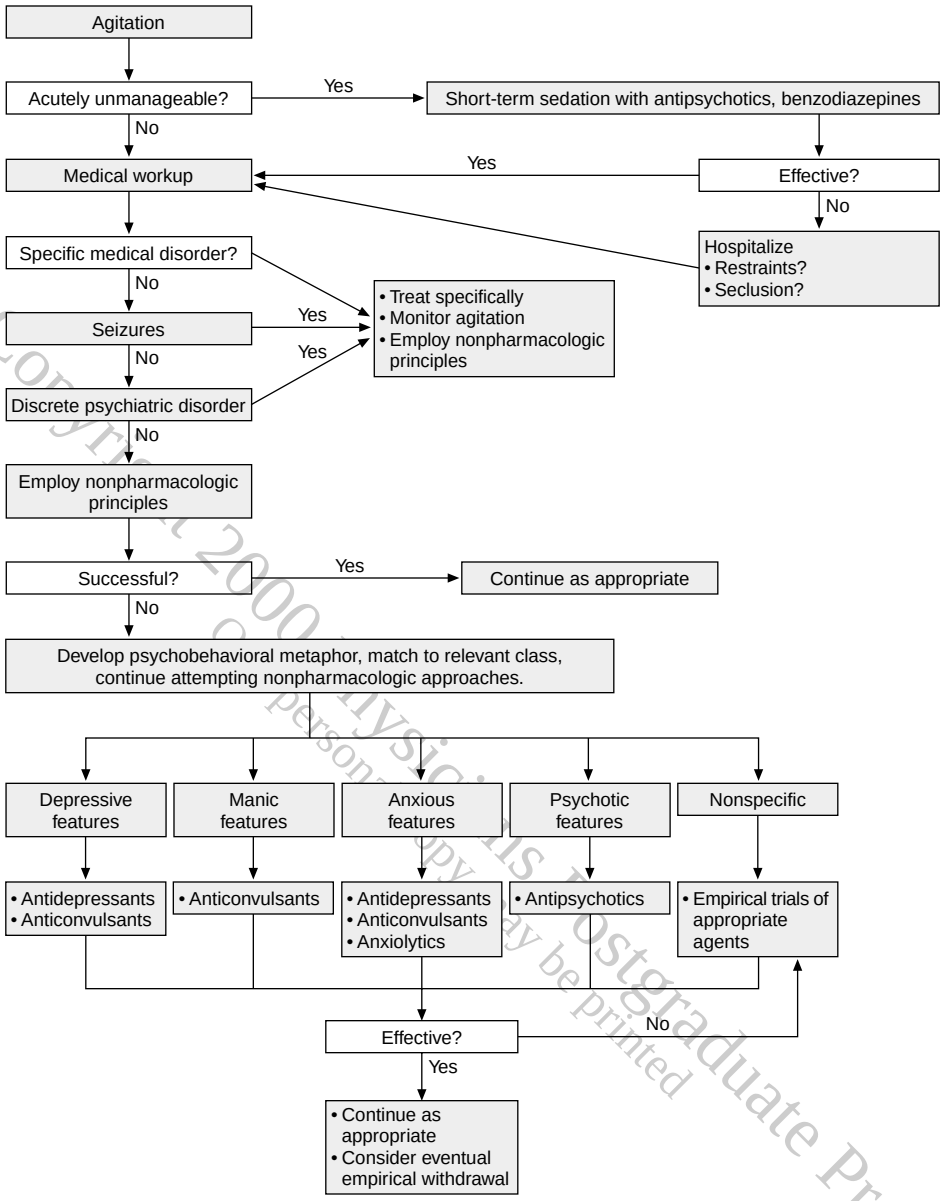
DEFINE TARGET SYMPTOMS

It is important to delineate patients' behavior patterns. For example, the patient might constantly bang on the table, call out loudly, resist personal care, weep intermittently, or exhibit self-deprecatory ideation. Noting these acts will guide the clinician-patient interaction and may help track progress. Because of the variability in signs and symptoms over time, it is usually prudent to check with multiple sources and to coach the most reliable informant about appropriate ways of observing and reporting symptoms. These observations can be critical in monitoring therapy.

ESTABLISH OR REVISIT MEDICAL DIAGNOSES

Among elderly patients, it is common for problem behaviors like agitation to result in the first detailed medical evaluation in some time. We generally presume that the patient is medically ill until proven otherwise, and we train families and caregivers to think along similar lines. The most dreaded medical explanation for a new-onset disturbed behavior is delirium, which is commonly caused by inappropriate medications, infectious disorders (especially genitourinary and respiratory), dehydration, trauma, or electrolyte disturbances. In patients who lack language abilities, savvy clinicians have learned that constipation or an occult hip fracture may be the precipitant of screaming or repeated requests for help. These medical problems should be specifically treated, and the patient should be monitored to see whether the behavioral problems are improved. The level of distress exhibited or the disruptive-

Figure 1. Flow Chart for Management of Agitation in Dementia[a]



[a]Adapted from Tariot,[7–9] Tariot et al.,[10] and Leibovici and Tariot.[11]

ness of the behavior associated with an intercurrent medical problem would dictate the need for additional short-term interventions apart from the particular remedies needed for this problem. For example, in a nonurgent situation where the agitation is associated with a urinary tract infection, psychotropic medication may be avoidable and antibiotics alone might be the definitive therapy.

ESTABLISH OR REVISIT NEUROPSYCHIATRIC DIAGNOSES

The behavioral disturbance may reflect a long-standing, recurrent, or even new-onset psychiatric disorder and bears investigation through an examination of the patient's current symptomatology, medical and psychiatric history (including prior response to therapy), and family history. If such a disorder is present, it should be specifically treated and the patient should be monitored.

ASSESS AND REVERSE AGGRAVATING FACTORS

A variety of aggravating factors that can contribute to agitation can often be identified and ameliorated. Caregivers often overlook deficits in hearing or vision, although these can lead to perceptual distortion as well as to what may appear to be bizarre behavior. Further, patients

Table 3. Practical Recommendations for Caregivers to Decrease Agitation and Aggression and Improve Communication With Demented Patients[a]

Decrease escalation
Decrease environmental stimuli and modify the environment
Approach in a calm manner
Use distraction—food, drink, music
Maintain eye contact and comfortable posture with arms/hands relaxed
Use more than one sensory modality to send a calm message
Match verbal and nonverbal signals
Identify the affect observed in the patient; verbalize this for him/her
Do not add more demands at the time
Slow down pace and simplify your actions
Maintain physical comfort
Identify what is fueling the fire (eg, triggers and reactions)
Maintain safety
Communicate effectively
Capture the patient's attention; stay in view
Use simple, direct statements
Limit choices
Use gestures to assist with verbal directions
Use one-step command
Speak clearly and slowly; allow time for response
Lower tone if voice needs to be raised
Communicate your desire to help
Review the basics
Behavior is symptomatic of the illness; separate the behavior from the person
A damaged mind gets stuck in one activity and has trouble shifting gears—what worked an hour ago may not work now
The caregiver is the only security in a shrinking world
Persons with dementia lose the ability to plan
Know the person and structure his/her environment accordingly
Having a daily pattern of repetitive behaviors at predictable times and by familiar persons helps those with memory impairment to help themselves
A loving voice, attentiveness, touch, and consistency are enormously important
Remember, a caregiver is not always an angel; there are times when frustration and anger are expressed—no one is perfect
The caregiver's needs must also be recognized and respected
Maintain the patient's religious/spiritual identity
Humor can help

[a]Adapted from Roberts and Algase, 1988[13]; Beck and Heacock, 1988[40]; Smith et al., 1993[41]; Gwyther and Rabins, 1996.[42]

may fail to comprehend the current situation because of a language barrier. In these circumstances, simplifying and clarifying communication, improving vision or hearing, or employing an interpreter can be extremely helpful. Sometimes environmental disturbances aggravate behavior, including excessive heat or cold, noise, or the disruptive behavior of other patients. Altered daily routines can also result in significant agitation. Clarifying triggers and defining consequences of disturbed behaviors can help delineate effective interventions such as using distraction, increasing personal space, and limiting environmental disturbances.[12]

ADAPT TO SPECIFIC COGNITIVE DEFICITS

Agitated behaviors may reflect disruptive efforts to communicate or adapt. Pacing might indicate a need for exercise or stimulation, and "wandering" may stem from a false but firm belief that the patient needs to be somewhere else. Verbally disruptive behaviors could reflect efforts to obtain help or to express pain, discomfort, or emotional distress. Suspiciousness may stem from the false but understandable perception that another person has taken the patient's possessions, since the patient cannot recall putting them somewhere and is attempting to make sense of why they disappeared.

A variety of different interventions could be considered for these kinds of problems and may prove to be sufficient in some cases. Patients who are disoriented but have some ability to respond to pictures or words may benefit from the use of labels. Some patients do better with less stimulation; others do better with more. Reducing the clutter in the environment and simplifying the environmental cues may also help. The physical layout and the organization of the environment can have a therapeutic impact on agitated behavior by providing orienting cues to the patient through stimulation from sound, lighting, colors, and textures. Further, dedicating rooms for specific purposes or minimizing the rearrangement of furniture can decrease disorientation.[13] Placing visual or physical barriers to unsafe egress may be helpful, along with making an effort to promote safe walking and exploring for those who need to pace.

IDENTIFY RELEVANT PSYCHOSOCIAL FACTORS

It is perhaps obvious that a patient with dementia may experience sadness, anger, or even denial in response to life events. Reviewing and acknowledging losses and stressors can help reduce agitation and aggression, as can support, encouragement, and validation. Likewise, learning from the family about the patient's basic personality, interests, likes, and dislikes can aid in the determination of helpful responses to disruptive behaviors as the patient becomes increasingly demented. It is usually advantageous to optimize physical, social, and emotional stimulation (e.g., participation in therapeutic group activities; retention of a religious identity; and involvement with family, an exercise program, or musical activity). It makes sense to tailor such activities to individual proclivities when possible. This process can be facilitated by a documented psychosocial history.

EDUCATE CAREGIVERS

Patients with language and cognitive impairment communicate distress through behavior. Such behaviors can occur in patterns. Understanding that this is the case can be beneficial for caregivers by helping them to interact in a more supportive manner. Caregivers can learn to obtain clues from feelings displayed and from reactions to recent changes in the environment, and they can help patients identify their feelings. For instance, irritability may be the

manifestation of sadness at the loss of a family member or pet or of anger because of reduced visits by family members or friends. In the process of understanding, attending, and communicating more accurately, the caregiver may be trained to employ basic behavioral management principles. In simplistic terms, this refers to the concept that the caregiver's demeanor, that is, affect, tone of voice, and posture, has a major impact on the patient's behavior—"it is not what you say but how you say it." Caregivers can be trained to identify common triggers and consequences of agitation and try to minimize triggers and maximize positive outcomes. Other practical points to convey to caregivers drawn from other authors are summarized in Table 3.

USE OF PSYCHOTROPICS: GENERAL CONSIDERATIONS

For agitation that persists after nonpharmacologic steps are undertaken, it is usual to consider medicating the patient. In many cases, it is appropriate to conceptualize this as a process of trial and error. While evidence is mounting that psychopharmacologic interventions are safe and effective, prediction of response in individual cases remains an elusive goal.

The choice of medication may be influenced by the urgency of the situation. If rapid control of grossly disturbed or unsafe behaviors is necessary, antipsychotics or benzodiazepines are the treatments of choice. In some cases, the patient may need to be admitted to an acute care hospital. Once the emergency is addressed, attention can be paid to the basic principles listed in Table 2.

For nonemergent problems, our group has developed an approach that has been termed the development of a "psychobehavioral metaphor" (Figure 1).[11] The goal is to specify the disturbed behaviors and then attempt to cluster the most salient signs and symptoms into a pattern that is roughly analogous to a drug-responsive syndrome. The term *metaphor* refers to atypical features of classic syndromes rather than to discrete psychiatric disorders. This distinction is important, since patients with dementia who are agitated can present a confusing picture with no other discrete psychiatric diagnosis. It is possible, as we more fully understand behavior patterns in dementia, that we will be able to successfully identify specific syndromes such as depression, mania, or psychosis. Until that clarity is achieved, we have chosen to adopt the more general term *metaphor*.

Once the metaphor has been articulated, the next issue is selecting a class of appropriate medications. Consider the agitated patient who is withdrawn, negativistic, irritable, or dysphoric, even in the absence of an overt syndromal depression. In such cases, an empirical trial of antidepressant medication might be considered first. Alternatively, for a patient with agitation and hyperactivity, pressured speech, expansive or irritable mood, or sexual preoccupation, a mood stabilizer might be the more appropriate initial medication. A patient with impaired verbal abilities may nonetheless express fragmented, poorly articulated fears or inappropriate accusations or may only respond fearfully when someone approaches. This is suggestive of a forme fruste of paranoia and might provide a logical basis for the initial use of an antipsychotic.

It is important to note at this juncture that there is no pharmacotherapy for agitation or aggression associated with dementia, or indeed any diagnosis, that has been approved by the U.S. Food and Drug Administration (FDA). Further, the Omnibus Budget Reconciliation Act (OBRA) guidelines of 1987[14] place restrictions on the use of psychopharmacologic agents in patients with dementia in the nursing home. For example, the use of antipsychotics for restlessness, anxiety, agitation, and fidgeting was deemed inappropriate according to OBRA guidelines. Nonetheless, even in the absence of regulatory approval and the type of consensus regarding treatment that this implies, concerned clinicians deal with difficult agitation as best as they can on a case-by-case basis, trying to find an approach that works. The magnitude of the problem and the fact that there are emerging data to guide clinicians are reflected in a variety of recent consensus statements regarding this issue (e.g., APA 1997), which support the use of psychotropic medications when other approaches fail.[15,16]

Our approach, which admittedly goes beyond regulatory guidelines and consensus statements, is to select a medication class relevant to the psychobehavioral metaphor with at least some empirical evidence of efficacy and with the highest likelihood of tolerability and safety. The choice is sometimes influenced by the likelihood of a particular side effect. In implementing therapy, we observe some other general rules such as starting with low doses and escalating slowly, assessing both target symptoms and toxicity, and discontinuing the medication if it is harmful or ineffective. When a medication is helpful, the dose is maintained at subtoxic levels for an appropriate period after which the empirical trial is performed in reverse, that is, the medication is tapered and the patient is monitored for a recurrence of the problem. Sometimes several medications need to be tried before the problem is ameliorated; sometimes all medication trials fail.

SPECIFIC CLASSES OF PSYCHOTROPICS

Individual agents and representative starting doses are shown in Table 4. The doses are based primarily on our clinical experience, as the literature is limited. Hence, they must be viewed as guidelines only.

Antipsychotics

Conventional antipsychotics. According to the approach adopted in this article, antipsychotics would be

Table 4. Classes of Agents and Representative Starting Doses

Drug	Suggested Dose	Suggested Maximal Dose[a] (mg/day)
Anticonvulsants		
Carbamazepine	50–100 mg/day	300–500
Divalproex sodium	125 mg b.i.d.	500–1500
Antidepressants		
Trazodone	25 mg/day	150–300
Sertraline	25–50 mg/day	100–200
Fluoxetine	10 mg/day	20
Paroxetine	5 mg	20–40
Antipsychotics		
Haloperidol	0.25–0.5 mg/day	2–4
Thioridazine	10 mg/day	50–100
Clozapine	12.5 mg/day	25–100
Risperidone	0.5 mg/day	2–4
Quetiapine	25 mg	100–300
Anxiolytics		
Lorazepam	0.5 mg/day	2–4
Buspirone	5 mg b.i.d.	40–60
β-Blockers		
Propranolol	10 mg b.i.d.	50–100
Selegiline	5 mg b.i.d.	10

[a]Lower doses often effective.

Table 5. Side Effects of Typical Antipsychotics

1. Anticholinergic effects
   - Peripheral
   - Central (eg, confusion, delirium)
2. Cardiovascular
   - Postural hypotension
   - Conduction effects
3. Parkinsonism
   - Bradykinesia
   - Rigidity
   - Tremor
   - Gait disturbance
   - Decreased postural reflexes
   - Masked faces
   - Drooling
4. Sedation
5. Acute dystonic reaction
6. Akathisia
7. Tardive dyskinesia
8. Neuroleptic malignant syndrome
9. Falls/fractures

chosen first only in agitated patients with psychotic "metaphors." Historically, however, antipsychotics have been used for virtually all forms of psychopathology associated with dementia, including all manifestations of agitation. They have also been studied more intensively than any other class of psychotropic medications. Wragg and Jeste reviewed the controlled studies of typical antipsychotics in agitation and confirmed that the effects of antipsychotics were modest but consistent, and that no single agent was better than another.[17] In a meta-analysis of controlled trials of neuroleptics, Schneider and colleagues found that conventional antipsychotics improved agitation better than placebo in 18% of patients with dementia.[18] Not all studies were clear about exactly what behaviors changed.[18] Nonpsychotic symptoms that were reported to improve in some studies included suspiciousness, sleeplessness, excitability, hostility, belligerence, emotional lability, restlessness, tension, agitation, aggression, uncooperativeness, and irritability.[9,18] Some reports indicated that psychotic symptoms also improved, supporting the use of these target symptoms in the framework of the therapeutic metaphor. Certain other symptoms, such as wandering, apathy, withdrawal, and hypersexuality generally did not improve. Low doses of the antipsychotics were usually effective. Side effects associated with typical antipsychotics (Table 5) are well known and are of particular concern in older patients and those with dementia and include peripheral and central anticholinergic effects, hypotension, cardiac conduction changes, sedation, falls, and a host of motor signs and symptoms.[19] For practical purposes, side effects dictate the selection of a particular agent in this population.

Atypical antipsychotics. There is little published literature regarding the efficacy, safety, and tolerability of atypical antipsychotics for treatment of agitation or aggression in patients with dementia. There is anecdotal evidence suggesting at least partial benefit with clozapine therapy in patients with agitation. Side effects associated with clozapine include sedation and anticholinergic effects. Concern about agranulocytosis is also a consideration in using clozapine for any diagnosis.[9] The usual starting dose is 12.5 mg/day.

There are several case reports of patients treated with risperidone who showed decreased aggression and agitation.[9,20] However, side effects were reported to occur in some patients, including dose-related extrapyramidal symptoms, sedation, and postural hypotension, and there is some evidence of increased prolactin plasma concentrations of uncertain significance. There are also abstracts summarizing results of 2 multicenter trials of risperidone in nursing home patients.[21,22] One study compared fixed daily doses (0.5 mg, 1 mg, 2 mg) with placebo in 625 patients and found reduced measures of agitation, aggression, and psychosis at the higher doses using predetermined response criteria. Approximately 50% of patients taking placebo responded, versus about 60% and 65% of patients at 1 and 2 mg/day.[21] The drug was described as generally well tolerated, with extrapyramidal features more likely to occur at the 2-mg/day dose. The other study compared flexible doses of risperidone and haloperidol (up to 4 mg/day each) and placebo in 344 patients. Similar but less robust results were reported.[22] It will be important to review the full details of these studies, the first publicly presented results from large multicenter trials in nursing home patients, when they become available.

A recently approved atypical antipsychotic, quetiapine fumarate, is currently being evaluated in a controlled, multicenter trial in nursing home patients for its effect on agitation and aggression. A year-long, open trial of quetiapine in a large (N = 106) population of elderly patients with dementia and mixed behavioral problems, including

psychotic features, has been completed.[23] Abstracts of the 3-month data have been presented.[24] These data indicate improved measures of agitation and psychosis. Reported side effects included sedation, orthostatic hypotension, and dizziness, which typically occurred early in the course of treatment. As with younger patients, very low rates of extrapyramidal symptoms, including akathisia, were reported among patients taking a wide range of quetiapine dosages (median dosage = 100 mg/day; range, 25–800 mg/day).[23,25] No clinically important effects on hematology, other laboratory values, ECG evaluations, or vital signs were associated with quetiapine use in this patient population. Once again, it will be important to review the full reports from this study and the controlled study when they become available.

Other atypical agents that have been evaluated for agitation, or are under study now, include olanzapine and ziprasidone. Extensive data from these trials have not yet been presented. Early impressions of the effectiveness of atypical antipsychotics in treating agitation and aggression have been encouraging; complete presentation will be necessary in order to be more certain about their role. It is conceivable that favorable results from these clinical trials will have a major impact on current patterns of antipsychotic use for agitation in patients with dementia.

Anxiolytics

In the context of the target symptom approach that we advocate, anxiolytics as a class would be the agents of choice for patients with prominent anxious features. Since geriatric psychiatrists often "bundle" anxious and depressive features, antidepressants are sometimes used first in cases in which anxious features predominate. Anxiolytics have nonetheless been widely used for agitation in dementia, although they have not been studied as extensively as the antipsychotics. Some reports show a reduction in agitation with short-term use of benzodiazepines, especially agitation associated with anxiety, sleep problems, and tension.[9] Side effects with the benzodiazepines include sedation, ataxia, falls, paradoxical increases in agitation, and anterograde amnesia, as well as tolerance and withdrawal syndromes. It is often asserted that lorazepam and oxazepam are the preferred choices in older patients because these agents are less likely to accumulate after repeated dosing. Currently, there is only anecdotal evidence regarding the use of clonazepam for agitation and aggression.[9]

The anxiolytic buspirone has considerably fewer side effects compared with the benzodiazepines, the most common being headache and dizziness. Anecdotal reports suggest that buspirone might be effective in reducing some target symptoms such as anxiety, aggression, and depression; however, no controlled data are currently available.[9] One blinded study comparing low-dose buspirone with low-dose haloperidol failed to show improvement, leaving open the question of what might have happened with higher doses.[26] There are no other data available about this agent.

Antidepressants

Theoretically, antidepressants would be the drug class of choice in patients with depressive features accompanying agitation. Regrettably, baseline target symptoms (beyond agitation) have not been routinely delineated in clinical trials with antidepressants.

Several case reports and open studies have reported antiagitation efficacy with trazodone, a serotonergic antidepressant with α_2-adrenergic blocking activity. This literature is summarized in a review article by the author.[9] The only blinded study, which compared trazodone (50–250 mg/day; mean = 218 mg/day) with haloperidol (1–5 mg/day), found equal improvement in agitation in both groups, but the side effect profile reported for the group treated with trazodone was more benign.[27]

There are several reports regarding the use of other serotonergic agents in the modulation of agitation in dementia, although most of the data are anecdotal or come from studies of agents not yet available in this country.[9] A retrospective analysis of a study of citalopram showed improved emotional bluntness, confusion, irritability, anxiety, fearfulness, depressed mood, and restlessness in patients with Alzheimer's but not for patients with vascular-type dementia.[28] Currently, only anecdotal reports of beneficial effects for fluvoxamine, fluoxetine, and sertraline are available.[9] To confirm the impressions proffered, confirmatory controlled trials will be needed. Side effects associated with these drugs can include sedation, restlessness, increased agitation, sexual dysfunction, and gastrointestinal distress.

Anticonvulsants

Certain anticonvulsants are used in psychiatry for the treatment of acute mania and have been assessed by clinicians for their effectiveness in a variety of other psychiatric disorders. Strict adherence to our metaphor approach would dictate the use of these agents for agitation in patients with affective features (in particular, manic features, but also depressive features), or possibly in those with prominent impulsivity, lability, or nonspecific agitation. In reality, clinicians appear to be using anticonvulsants for agitation with increasing frequency. For instance, in a recent survey of a large long-term care facility, we found that more than 10% of all patients were receiving anticonvulsants for behavioral indications; most had dementia.[29]

The anticonvulsant carbamazepine has psychotropic properties that are similar to lithium when it is used in mania. However, carbamazepine is associated with less neurotoxicity than lithium. Extrapolations from data in studies of other clinical populations also led to the suggestion that carbamazepine may have beneficial effects for agitation associated with dementia.[30] Numerous pilot studies and

case reports subsequently suggested that carbamazepine may be effective in the treatment of some agitated behaviors in patients with dementia. One small placebo-controlled, crossover study in 19 women who were also treated with as-needed thioridazine was negative.[31] In contrast, markedly different results were obtained from a preliminary study of agitation in 25 nursing home patients with dementia.[30] In that study, carbamazepine (average dose = 300 mg/day) was associated with significantly reduced agitation compared with placebo. With the exception of 1 case of tics, minimal side effects were reported. A follow-up, confirmatory, randomized, placebo-controlled study has been conducted in 51 patients at 4 nursing homes in Rochester, New York. Equally robust benefits were noted, and tolerability of the carbamazepine was generally good.[10] Interestingly, nursing home staff reported spending less time taking care of behavioral problems for patients who were receiving carbamazepine in this study. Findings such as those regarding reduced need for staff time would help illuminate some of the potential indirect benefits of the appropriate use of psychotropic medications for agitation.

While the preliminary data regarding carbamazepine for agitation are encouraging, its role is not fully established as no multicenter studies have been performed. Further, while side effects have been mild in our controlled studies, they would be more likely to occur with uncontrolled use. These adverse effects can include rash, sedation, ataxia, hematologic abnormalities, hepatic dysfunction, and electrolyte disturbances.[32] Additionally, there are numerous known drug-drug interactions associated with the use of carbamazepine. Alternative, potentially safer, anticonvulsant agents would be valuable additions to the armamentarium for agitation.

Valproic acid, along with its better tolerated and more frequently used enteric-coated derivative, divalproex sodium, is another anticonvulsant, but one that is structurally dissimilar to carbamazepine. Compared with carbamazepine, it has similar psychotropic effects in mania, a reduced potential for drug-drug interactions, and fewer serious side effects. Divalproex is FDA-approved for the treatment of mania associated with bipolar disorder as well as for the prophylactic treatment of migraine. In a variety of clinical populations studied in detail thus far, it has a more favorable side effect profile in comparison to the alternative antimanic agents. Based on a number of open trials or chart reviews that have been conducted in patients with agitation and aggression associated with dementia, divalproex appears to show promise as an antiagitation agent as well.[7,8] All of these reports, including one from our group,[33] indicated reduced agitation in the majority of patients, with generally good tolerability of the divalproex. Potential side effects include sedation, weight gain, hair loss, thrombocytopenia, and hepatic dysfunction. It is perhaps because of experience in mania that psychiatrists and other clinicians often choose divalproex for the treatment of agitation.[33] Several controlled trials are underway that will help clarify its importance as a therapeutic tool.

The potential role for the newest anticonvulsant agents (i.e., lamotrigine, gabapentin, and topiramate) is not yet established. Because anticonvulsants as a class have a relatively benign side effect profile based on years of experience in multiple clinical populations, evidence of significant efficacy of one or more individual anticonvulsants will very likely influence practice.

Miscellaneous Therapies

Limited studies for lithium and propranolol are available in the treatment of agitation.[7] The data suggest minimal efficacy with considerable potential for side effects.

Selegiline has also been suggested in some reports to be beneficial.[34] In contrast, no evidence in support of significant behavioral benefit was found in a prolonged outpatient trial of selegiline by Sano and colleagues.[35]

A brief report regarding electroconvulsant therapy (ECT) in screaming, demented patients suggested some beneficial effects with this procedure.[36] Benefits were also noted in a detailed case report of ECT for a patient with life-threatening agitation.[37]

Estrogen and progestin therapies have occasionally been reported to be beneficial in reducing physical and sexual aggression in men.[9]

Interesting work by Satlin and colleagues has also suggested that bright light pulses may be beneficial for the treatment of behavioral disturbances in Alzheimer's patients.[38]

Cholinergic agents have been suggested to have unanticipated behavioral benefits, which bears further examination.[39]

Small series or individual case reports have suggested that even more unconventional therapies may be effective; these will not be reviewed here.

SUMMARY

Agitation occurs commonly in dementia. Before symptomatic pharmacotherapy is undertaken, it is imperative to follow a sequence of evaluations and interventions to establish whether simpler and safer nonpharmacologic approaches will be beneficial. When psychotropic medications are used, they should be used judiciously, in the lowest effective doses and for the shortest period of time necessary. Ineffective medications should be stopped, and even effective medications should be empirically tapered in most patients to learn whether treatment is still necessary. Antipsychotics show the most benefit for the treatment of agitation associated with psychotic features. The adverse side effects of typical agents is legion; data are pending regarding the atypical agents risperidone, olanzapine, and quetiapine.

The available evidence regarding non-neuroleptic medication ranges from case reports to well-designed, double-blind, placebo-controlled, randomized, parallel-group studies. Literature exists describing the use of anticonvulsants, anxiolytics, serotonergic antidepressants, and other agents to manage agitation. Carbamazepine and divalproex have demonstrated efficacy in uncontrolled studies, while the use of carbamazepine has produced negative results in 1 small controlled study and positive results in 2 controlled studies. Buspirone has shown benefit in some open trials. Encouraging early findings have been reported for trazodone, including from 1 controlled trial. Varied results have been obtained in studies using selective serotonin reuptake inhibitors, but with consistently encouraging anecdotes.

In the aggregate, the evidence suggests but does not prove that alternatives to traditional antipsychotics exist. Again, none of these agents has yet been approved for this purpose by the FDA. As more studies become available, we will have a better idea about which classes of agents are most efficacious, as well as about relative effectiveness. It is likely that there may be a role for "rational polypharmacy" in the management of this distressing complication of dementia. However, we know of no published controlled studies that address combination therapy, forcing the clinician to contemplate this option on a case-by-case basis. Clinical trial data are pending from studies with divalproex, haloperidol versus trazodone versus placebo, risperidone, olanzapine, quetiapine, donepezil, donepezil plus sertraline, and buspirone, at the very least. These data will undoubtedly have a major impact on how we as psychiatrists care for our patients, and lead to revisions of current practice guidelines.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), citalopram (Celexa), clonazepam (Klonopin), clozapine (Clozaril), divalproex sodium (Depakote), donepezil (Aricept), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), lorazepam (Ativan and others), olanzapine (Zyprexa), oxazepam (Serax), paroxetine (Paxil), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), selegiline (Eldepryl), sertraline (Zoloft), thioridazine (Mellaril and others), topiramate (Topamax), trazodone (Desyrel and others), valproic acid (Depakene and others).

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