REVIEW

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Agitated dementia: Drug vs nondrug treatment

ABSTRACT

When an elderly patient with Alzheimer's disease or other form of dementia exhibits agitated behavior, the caregiver often wants the physician to "do something"—ie, give a neuroleptic drug. Yet, an individualized, rational approach to identify and treat the cause of the agitation is more effective. We present an algorithm that emphasizes environmental and behavioral therapy.

KEY POINTS

Ask the caregiver to identify the patient's most troublesome behavior and to keep a log to document how often this behavior occurs, the events leading up to it, and how the caregiver responds.

If treatable physical causes of agitation have been ruled out, behavioral and environmental interventions are the first line of treatment.

Drug therapy is reserved for patients with potentially dangerous behavior or for whom nonpharmacologic therapy has failed. Antidepressant drugs are finding increased use in this situation.

Caregivers should avail themselves of resources in the community, particularly the Alzheimer's Association.

A 72-YEAR-OLD MAN with Alzheimer's disease is seen in the office at his wife's request. For the past 2 or 3 months he has become increasingly belligerent and argumentative. When told to get dressed or bathe he becomes angry and shouts at her. On several occasions he has made threatening gestures; at other times he shouts or curses for no apparent reason. He accuses his wife of having an affair with his brother and of stealing his clothes. At night he paces for hours, disturbing her sleep. However, he is physically well with a normal appetite and weight. He takes no daily medications.

The patient's wife is exhausted. Friends have advised her to place her husband in a nursing home. Their two daughters live out of state and are not aware of their father's behavioral changes.

Physical examination reveals nothing remarkable. The patient is alert, cooperative, and euthymic. He scores 15 on the Mini-Mental State Examination (normal: > 23). He appears suspicious of the purpose of the office visit. A complete blood count, chemistry panel, and electrocardiogram are normal.

What should the physician do?

AGITATED DEMENTIA: A COMMON AND VEXING PROBLEM

Agitation is a frequent clinical problem in elderly patients with dementing conditions such as Alzheimer's disease, and poses difficulties for patients, caregivers, and physicians.

The prevalence of dementia is sobering: 1% at age 60 and doubling every 5 years, reaching 30% to 50% by age 85.[1] And at least 50% of outpatients with dementia exhibit

TABLE 1

Management of agitation

Behavioral interventions
- Provide a structured and calm environment
- Teach the caregiver effective communication
- Provide an area in which the patient can wander safely
- Establish a daily routine that includes exercise
- Correct the sleep/wake cycle

Medications
- Neuroleptics
- Anxiolytics
- Antidepressants
- Mood stabilizers
- Beta-blockers

Caregiver support
- Support groups (eg, Alzheimer's Association)
- Home care and adult day care
- Respite care

behavioral disturbances—as do 42% to 62% of *all* nursing home residents.[2] In fact, it is a behavioral disturbance such as agitation rather than dementia per se that most often precipitates the transition from home care to institutional care.[3,4]

Behaviors such as wandering and stealing usually do not respond to drugs

A common definition of agitation, based on nursing home studies, is inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion per se.[5] It includes behaviors such as aimless wandering, pacing, cursing, screaming, biting, and fighting.[6]

Family members and caregivers commonly ask physicians to treat these behaviors, often requesting medications. Yet, certain behaviors such as wandering, insulting, repetitive banging, hoarding, stealing, and having a "difficult personality" usually do not respond to drug therapy.[7] They may, however, respond to behavioral or environmental interventions.

AN ALGORITHMIC APPROACH TO TREATING AGITATION

Physicians can use various tools and resources when treating agitation (TABLE 1); the key is to use them in a systematic way. Treatment should be individualized with environmental, behavioral, and pharmacologic approaches, and should take into account that the caregiver may need support and respite. An algorithmic approach is detailed in FIGURE 1.

Is there a physical cause of the agitation?

Physical illness is a common cause of agitation. Often, the most appropriate approach to treating agitation is to treat the physical problem that is provoking it, if a physical problem can be identified. A comprehensive evaluation is therefore needed. However, elderly patients with dementia are difficult to assess, since they often cannot verbalize the reasons for their behaviors, rendering a typical self-reporting interview of limited utility.[8]

A change in behavior may be the cardinal feature of delirium (acute confusion) resulting from virtually any acute illness. Delirium occurs in 14% to 56% of elderly hospitalized medical patients; yet, their physicians fail to recognize delirium in 32% to 67% of cases.[9]

Common causes of delirium that should be excluded are:
- Primary cerebral disease
- Systemic disease
- Intoxication
- Withdrawal syndromes (TABLE 2).[10]

Sensory impairment and pain can also contribute to behavioral problems.[11] Patients with hearing and visual impairment can have misperceptions of the environment, resulting in threatening illusions and behavioral disruptions. Assist devices such as corrective lenses, hearing aids, and headset microphone amplifiers can help overcome sensory impairments.

Patients with verbal impairment may have difficulty communicating complaints about their pain, accounting for increased irritability. To improve communication, such patients can be encouraged to respond to yes-or-no questions by nodding their head, squeezing your hand, or blinking.

Does an environmental stressor trigger the agitation?

The physician should ask the patient and caregiver to select the one behavior that is most troublesome in terms of safety and daily functioning. By maintaining a behavior log, the caregiver can document when the behavior occurs, what events precede it, and how the patient and caregiver react to it. Reviewing this log can reveal patterns of envi-

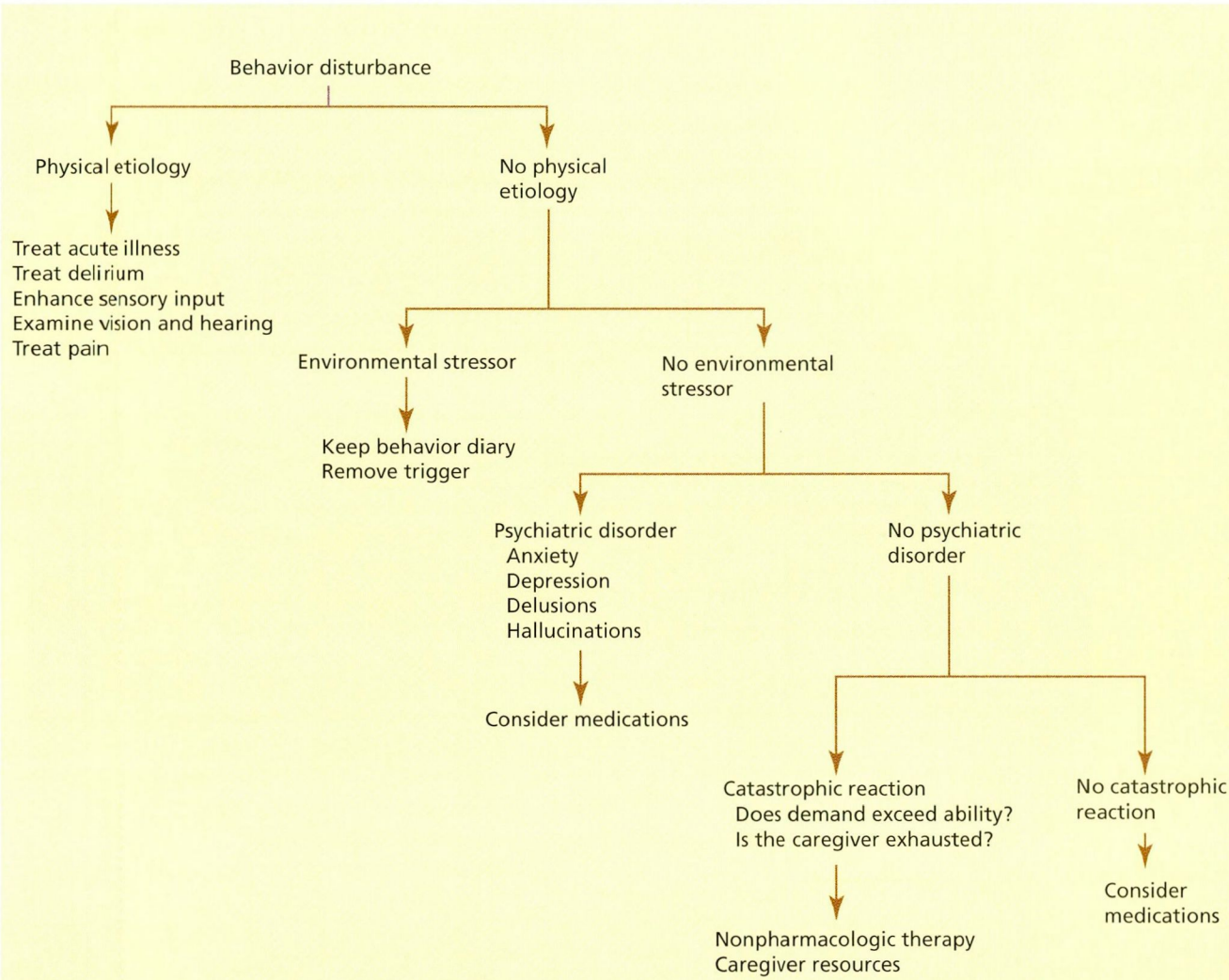

FIGURE 1. Algorithmic approach to behavioral disturbance.

ronmental stimuli that act as triggers, as well as patterns of caregiver response.[11]

Does the patient have a psychiatric disorder?

Anxiety affects up to 40% of patients with dementia, often manifesting itself as excessive anticipatory concern about upcoming events or by behaviors such as wandering and screaming. Medical illness, depression, abuse, social losses, cognitive impairment, and functional decline (loss of self-care ability) can contribute to anxiety.[12]

Depressive symptoms occur in up to 50% of patients with Alzheimer's disease.[13] Common manifestations include worsening cognitive impairment, social withdrawal, weight loss, tearfulness, thoughts of worthlessness, and concerns about being a burden to caregivers.

The rate of depression is also high in patients with other forms of dementia, such as vascular dementia, Huntington's disease, and Parkinsonism.[14] An "emotional incontinence" (ie, rapid fluctuation of anger, tears, or laughter) can be seen in vascular dementia.

TABLE 2

Causes of delirium in the elderly

- **Systemic illnesses**
  - Infections
    - Pneumonia
    - Urinary tract infections
    - Sepsis
  - Electrolyte or metabolic imbalance
    - Hyponatremia
    - Hypoglycemia
    - Vitamin deficiencies
    - Hypoxia
    - Hypercalcemia
    - Hyperthyroidism or hypothyroidism
  - Cardiopulmonary diseases
    - Congestive heart failure
    - Arrhythmias
    - Pulmonary embolism
  - Anemia
- **Central nervous system disorders**
  - Seizures
  - Stroke
  - Subdural hematoma
  - Subarachnoid hemorrhage
  - Vasculitis
- **Medications**
  - H_2 blockers
  - Antiarrhythmics
  - Anticholinergics
  - Nonsteroidal anti-inflammatory drugs
  - Narcotics
  - Benzodiazepines
  - Alcohol
- **Withdrawal syndromes**
  - Benzodiazepines and other sedatives
  - Alcohol

Delirium occurs in up to half of elderly hospitalized patients

Delusions occur in 30% to 57% of patients with Alzheimer's disease, and patients with delusions have a more rapid cognitive decline and exhibit more disruptive behavior than do patients without delusions.[12] Common delusions are accusations of infidelity and of theft, beliefs of personal harm, and fear of abandonment. Not surprisingly, institutionalization is much more frequent among delusional demented patients than nondelusional patients (54% vs 15%).[15]

Occasionally there really are problems of abuse and theft in institutions and home care. In deciding whether any accusations are delusional or grounded in reality, physicians can explore the complaint with one or more staff members to clarify whether there is any basis of reality for the expressed concern.

Hallucinations and illusions occur in 10% to 28% of patients with Alzheimer's disease. Visual hallucinations are more common than auditory ones and often involve people or animals. Before starting treatment, examine the patient's vision and hearing to determine if these symptoms can be environmentally modified, and ask whether the hallucinations are distressing and harmful to the patient or are harmless and acceptable.[12]

Is the patient reacting catastrophically to excessive demands?

An environment that is overstimulating or that places excessive demands on the patient may trigger a "catastrophic" reaction, in which the patient lashes out with anger and frustration, manifested by agitated behavior.[16] Feelings of frustration and resignation, resulting from progressive losses, can be minimized by having caregivers structure patient tasks in ways that reduce the likelihood of failure and increase opportunities for success.[12] Caregivers frequently need to adjust their expectations and make them commensurate with the patient's ability to perform. Since many family caregivers are thrust into a role they had not expected and are quite unprepared for, educational material about dementia and behavioral problems are invaluable.[3]

NONPHARMACOLOGIC MANAGEMENT

Behavioral interventions should be the first-line treatment for agitation.[3] A structured daily routine is helpful. Patients need a consistent schedule that includes time for physical activity and socializing. Brief, repetitive social contacts can benefit some patients. Daily staff greetings to the individual patients by name, conversations at mealtimes, or asking questions about their old interests are helpful in stimulating appropriate patterns of socialization.

Caregivers can use a number of specific strategies when confronted with a particular behavioral problem. For instance, if a patient

wanders, caregivers should use familiar objects, pictures and signs when communicating with the patient, and should make sure the patient has a safe wandering path in the home.

If the patient has memory deficits, the caregivers should avoid quizzing the patient, start each day with a reminder of the date and weather, and use calendars, clocks, and written lists as reminders. TABLE 3 suggests strategies for managing a variety of behavior problems in patients with dementia.[12,16,17]

Factors that can lead to agitation and which caregivers should try to avoid include[18]:

- Sensory impairments (eg, glare from kitchen lights).
- Environmental disruption (eg, disembodied voices from the radio).
- Altered daily routines (eg, shifting time of meals).
- Overreacting to the patient's behavior.

Overreaction on the part of caregivers accounts for many of the phone calls primary physicians receive. The key principle is not to argue with the patient and for the caregiver to understand how his or her emotions and reactions can adversely influence the patient's behavior. To aid in this understanding, caregiver education and respite are helpful.

TABLE 3

Advice to family and caregivers of patients with agitated dementia

BEHAVIOR PROBLEM	STRATEGIES
Wandering	Use familiar objects, pictures, signs Provide a safe wandering path at home Label doors of commonly used rooms
Memory deficit	Avoid quizzing Start day with reminder of date, weather Use calendars, clocks, and written lists
Task difficulty	Give ample time Split task into small steps Allow participation Grooming, eating at same time of day; use same sequence
Suspiciousness	Offer to help find lost objects Do not take suspicion personally Tell the patient who you are, why you are there, and what you are going to do In new environment, quickly establish a routine Distract to alternative activity
Catastrophic reaction	Do not argue Reduce noise and level of stimulation Use calming music; use television sparingly Use soft, smooth textures Pose one question at a time Speak softly and slowly and control affect Use support system and respite care
Sleep deprivation	Limit alcohol and caffeine For naps, use recliner instead of bed; limit time Use indirect bright light during daytime Use night-lights

PHARMACOLOGIC MANAGEMENT: FOR DANGEROUS OR RECALCITRANT BEHAVIOR

Patients who exhibit potentially dangerous behavior or for whom environmental and behavioral interventions have failed warrant a trial of medication, although nonpharmacologic means should always be continued or improved. Historically, antipsychotic agents have been used for this purpose.[19] More recently, nonneuroleptic medications such as anticonvulsants, anxiolytics, and antidepressants have been reported as useful (TABLE 4).

Neuroleptic agents

Psychotic symptoms (delusions and hallucinations) and nonpsychotic symptoms of suspiciousness, sleeplessness, belligerence, and aggression warrant treatment with neuroleptic drugs. However, wandering, apathy, and hypersexuality generally do not improve with neuroleptic treatment.[19]

In a meta-analysis of trials of neuroleptic therapy in elderly patients with dementia, Schneider et al[20] calculated that 59% of patients who received neuroleptic drugs showed some improvement in their symptoms of agitation, compared with 41% of patients who received placebo, an absolute difference of 18 percentage points ($P = .004$). However, the high rate of response to placebo indicates that many factors influence the outcome of medication treatment.

No antipsychotic drug appears to be more effective than any other.[21] Nevertheless,

TABLE 4

Psychotropic drugs for elderly agitated patients: dosage and observations

CLASS OF MEDICATION	INITIAL DAILY DOSE	TOTAL DAILY DOSE RANGE	ADVERSE EFFECTS AND COMMENTS
Neuroleptics			
Haloperidol	0.5–1.0 mg	0.5–3 mg	Parkinsonism
Risperidone	0.5–1.0 mg	0.5–2 mg	Postural hypotension
Olanzapine	2.5 mg	2.5–5.0 mg	Postural hypotension, sedation
Anxiolytics			
Lorazepam	0.5 mg	0.5–2 mg	Confusion, falls
Oxazepam	10 mg	10–30 mg	Confusion, falls
Temazepam	7.5 mg	7.5–15 mg	Confusion, falls
Buspirone	5 mg twice daily	10–60 mg	Delayed onset
Antidepressants			
Trazodone	25 mg twice daily	50–300 mg	Sedation, hypotension
Fluoxetine	5 mg	5–20 mg	Anxiety, insomnia
Sertraline	25 mg	25–100 mg	Nausea, diarrhea
Paroxetine	5 mg	5–20 mg	Nausea, sedation
Mood stabilizers			
Carbamazepine	200 mg twice daily	400–800 mg	Monitor white blood cell count, liver function, and serum levels
Valproic acid	250 mg twice daily	500–1000 mg	Monitor white blood cell count, liver function, and serum levels
Beta-blockers			
Pindolol	5 mg twice daily	10–20 mg	Monitor blood pressure
Propranolol	10 mg twice daily	20–160 mg	Monitor blood pressure

Reserve drug treatment for dangerous or recalcitrant behavior

highly potent neuroleptics such as haloperidol, in low doses, are preferred to less potent agents such as chlorpromazine in higher doses, because they produce fewer anticholinergic and postural side effects. Since memory deficits in patients with Alzheimer's dementia are associated with deficiencies in the cholinergic system, highly potent agents should be less likely to cause further memory impairment.[22] However, the highly potent neuroleptics may cause more extrapyramidal side effects.

Elderly patients, especially older women, are at higher risk for developing tardive dyskinesia and other extrapyramidal side effects of neuroleptic drugs and need close observation and physical examination. Newer agents such as risperidone and olanzapine may have better side effect profiles, but data are limited comparing these newer agents with older ones.[3]

Anxiolytic agents

Benzodiazepines have been used short-term for reducing agitation associated with anxiety, fearfulness, and sleep problems.[19] Side effects such as ataxia, a paradoxical increase in agitation, memory impairment, sedation, and an increased risk of falling limit their use. Short-acting agents that pass only once through the liver before being metabolized, such as lorazepam, oxazepam, and temazepam, are preferred because they accumulate less after repeated dosing than do other agents.

Buspirone has been used in non-urgent cases of agitation syndromes, in part owing to its serotonergic effects and favorable side-effect profile.[23] This drug does not produce sedation, and its most common adverse effects are headache, nausea, and dizziness. It needs to be given in adequate doses and for 6 weeks to determine its benefit.[3]

Antidepressant drugs

Because serotonin production in the brain is reduced in patients with Alzheimer's disease, and neuroleptic agents have limited efficacy, a trial of a selective serotonin reuptake inhibitor should be considered in patients with behavioral problems, especially if depressive symptoms are present.[24] Their side-effect profile, with little anticholinergic or hypotensive effects, has caused them to displace tricyclic antidepressants as first-line antidepressants.

Trazodone, a serotonergic antidepressant, is helpful in low doses (eg, 25–50 mg) at bedtime for insomnia. At higher dosages (TABLE 4), this agent has been reported to decrease physical aggression and verbal outbursts.[23] Orthostatic hypotension and oversedation, however, may occur with higher doses.

Mood stabilizers

Mood stabilizers can be useful when agitation occurs in vascular dementia.[3]

Lithium carbonate is limited in its use by concerns of neurotoxicity, nephrotoxicity, drug interactions, and clearance, coupled with a narrow therapeutic window. Patients with underlying neurological diseases such as Alzheimer's disease or stroke have been reported to fare poorly with lithium.[18]

Carbamazepine and valproate are increasingly being used as alternative agents to treat agitation. Even though effective plasma levels for agitation have not been established, lower levels than those used for anticonvulsant effects are used. Increased sedation and ataxia are seen at higher levels.[3] Hepatotoxicity, rash, cardiac interval prolongation, and leukopenia are adverse effects of carbamazepine. Liver and platelet function must be monitored with valproate use.

In one study, valproate (also known as divalproex) produced a response rate similar to those previously reported for neuroleptics in the treatment of behavioral disturbances in dementia.[25] In patients receiving neuroleptics, adding valproate may permit the neuroleptic dose to be reduced without worsening the behavioral disturbance.

Beta-blockers

Beta-blockers have been used in patients with traumatic brain injuries to control aggressive outbursts; however, only two agents, propranolol and pindolol, have been studied in the demented elderly.[23] Before prescribing a beta-blocker, the physician should consider the potential side effects of these drugs, including bradycardia, hypotension, lethargy, and exacerbation of respiratory conditions such as asthma. Beta-blockers are recommended only for chronic aggression. Psychosis, depression, and anxiety should be treated with other agents.[23]

CAREGIVER RESOURCES

Caregivers for persons with dementia, especially elderly spouses, are at risk for increased physical and psychological morbidity.[26] The most useful resource for family support, education, and referral is the Alzheimer's Association (1-800-272-3900, http://www.alz.org), which provides support groups, training classes, and access to local resources. Publications such as *The 36-Hour Day* are excellent resource texts on behavior in dementia for caregivers and physicians alike.[27]

The Alzheimer's Association (800-272-3900) is a valuable resource

Caregivers often need assistance from various community services, ranging from adult day care and home care programs to overnight respite services. Long-term assistance is available through retirement communities and assisted living facilities. These services can enable patients with dementia to remain independent longer and improve the caregiver's well-being.

RESOLUTION OF OUR CASE

The physician explained the nature of the symptoms (agitation) to the patient's wife, at whose request nondrug therapies were started. A social worker helped her get in touch with an adult day care center, respite services, and an Alzheimer's Association support group. She was also advised to accept help from family, friends, and home care supports. The daughters were asked to meet with the wife and physician and were informed of their mother's need for support and respite.

A daily routine for the patient was instituted, with walks in the morning, lunch and afternoons at an adult day care center, quiet

evenings, and music before bedtime. These interventions noticeably decreased the patient's agitation. At follow-up visits, it was agreed to use 0.5 mg of risperidone at bedtime for any escalating suspiciousness or violent outbursts.

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