

## Agitated dementia

(APRIL 1998)

**TO THE EDITOR:** I read with interest the review on the drug and nondrug treatment of agitation in dementia by Dr. Pozuelo and colleagues.<sup>1</sup>

Perhaps another treatment to be considered for their case presentation of agitation in a patient with Alzheimer disease is the use of cholinergic agents, ie, tacrine, donepezil, metrifonate, and rivastigmine. Past studies have shown that cholinergic agents improve not only cognition, but also behaviors such as agitation, apathy, anxiety, aberrant motor behaviors, irritability, withdrawal, and hallucinations.<sup>2,3</sup> The basis for these findings seems to be the correction of the cholinergic deficiency that underlies Alzheimer disease.<sup>3,4</sup>

The therapeutic implication of this observation is that the cholinergic agents have psychotropic effects, and the initiation of cholinergic therapy should probably be preferred over the conventional or novel psychotropic agents. Psychotropic agents can then be used to treat any residual behavior disorder.<sup>5</sup>

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### REFERENCES

1. Pozuelo L, Franco K, Palmer R. Agitated dementia: drug vs nondrug treatment. *Cleve Clin J Med* 1998; 65:191-199.
2. Hashmi FH, Grossberg GT. Diagnosis and management of agitation in the long-term care setting. *Nurs Home Med: Ann Long-Term Care* 1998; 6:(Suppl B):1-9.
3. Mintzer JE, Hoernig KS, Mirski DF. Treatment of agitation in patients with dementia. *Clin Geriatr Med* 1998; 14(1):147-175.
4. Kumar V, Durai NB, Jobe T. Pharmacologic management of Alzheimer's disease. *Clin Geriatr Med* 1998; 14(1):129-146.
5. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *Am J Geriatr Psychiatry* 1998; 6:S64-S78.

**TO THE EDITOR:** Dr. Pozuelo et al are to be commended for their excellent article "Agitated dementia: Drug vs nondrug treatment,"<sup>1</sup> which details management of this extremely important condition. I would like to add a fundamental complementary insight on behalf of clinicians who treat agitated demented patients.

The algorithm provided by the authors appropriately stresses the merit of initially optimizing the internal and external environments via amelioration of potential stressful stimuli. This step must include a section dedicated to identifying cognitively offensive medications and specifying alternative agents which less adversely intrude on cognition and predispose to agitation.

Clonidine, methyl dopa, and lipophilic beta-blockers such as propranolol should be replaced by less cognitively injurious antihypertensives such as ACE inhibitors, calcium channel blockers, and hydrophilic beta-blockers which less effectively penetrate the blood-brain barrier. For gastritis, H<sub>2</sub> receptor blockers can be cognitively offensive,<sup>2</sup> and should be changed to sucralfate or antacids. Analgesia may be more favorably achieved with respect to cognition with acetaminophen, NSAIDs, liniments, ice, heat, or massage than with narcotics. Mood depression is better treated with paroxetine and other selective serotonin reuptake inhibitors than with tricyclic antidepressants, which have anticholinergic properties. Benzodiazepines should also be avoided, as these agents contribute to sedation, impaired memory and attention, and consequent agitation.

Spasticity is a common sequela of dementia associated with multiple infarcts. Phenol or botulinum toxin injections are entirely bereft of cognitive side effects, and control spastic hypertonus well without the sedation and confusion that not uncommonly accompany the antispasticity drugs diazepam and clonidine. If spasms are the principal manifestation of the triad of hypertonus, hyperreflexia, and spasms, then a systemically active agent may be most efficacious. Dantrolene is the least cognitively offensive. Baclofen started at 5 mg at night or tizanidine are also usually well-tolerated antispasticity agents. For treatment of nausea, metoclopramide and prochlorperazine are proconvulsant and suppress cognition, and should be changed to trimethobenzamide. If the indication for metoclopramide was to promote gastric emptying, then the cholinergic agonist cisapride should be used instead. Metoclopramide can cause irreversible tardive dyskinesia after a single dose.<sup>3</sup>

The clinician must reassess the indication for anticonvulsants. If drugs are necessary, sedating agents such as phenobarbital, primidone, and phenytoin should be tapered after therapeutic levels of less offensive agents such as carbamazepine or valproate are achieved.<sup>4</sup> Monotherapy should be pursued to obviate the cumulative toxicity of polytherapy. Dosing should approximate the lowest level in the therapeutic window, as anticonvulsants impair speed of thought processing, attention, and memory more extensively at higher therapeutic window levels. If antiseizure efficacy is appreciated with negligible cognitive side effects despite "subtherapeutic" serum levels, then clinicians should seek informed consent to maintain patients "subtherapeutic" yet seizure-free and free of untoward cognitive effects.

Potential side effects of drugs are suboptimally discussed in the article. The negative inotropy of beta-blockers and potential to iatrogenically initiate fulminant congestive heart failure in the premorbidly predisposed must be appreciated, as the FDA has not approved beta-blockers for the indication of management of disinhibited agitation, despite well-documented efficacy. Similarly, trazodone is well tolerated in females, but is relatively contraindicated in males in light of risks of iatrogenic priapism,<sup>5</sup> which may require emergent surgical reduction with accompanying risks for irreversible impotence.

Neuroleptics impair attention, memory, and other aspects of cognition. Antipsychotics are also proconvulsant, and cause akathisia, which predisposes to behavioral disinhibition. Not infrequently they are prescribed to control agitation. These agents globally sedate patients, and it is preferable to selectively extinguish the disinhibition without compromising mental acuity. This can frequently be achieved with atypical agents such as the anticonvulsants, as identified by the authors. However, additional agents also warrant description, as does a more precise classification of agitated behavior.

Aggressive agitation may be ameliorated with psychostimulants such as amantadine and methylphenidate.<sup>6</sup> Emotional disinhibition agitation, unrelated to mood depression

and manifested by unsuppressible crying or laughing, may be selectively extinguished with amitriptyline.<sup>7</sup> Sexual disinhibition may respond to lithium and other agents used to address physical agitation, but medroxyprogesterone and other hormonal interventions should also be considered in the efficacious but limited armamentarium available to the clinician.<sup>8</sup> Tacrine has been described as being efficacious to enhance memory in dementia as well as to ameliorate disinhibited behavior.<sup>9</sup> Donepezil is a benign agent which is well tolerated and merits further investigation in randomized controlled trials in agitated dementia.

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#### ■ REFERENCES

1. Pozuelo L, Franco K, Palmer R. Agitated dementia: drug vs nondrug treatment. *Cleve Clin J Med* 1998; 65:191-199.
2. Gualtieri CT. *Neuropsychiatry and Behavioral Pharmacology*. New York: Springer-Verlag, 1991:37-88.
3. Miller LG, Jankovic J. Metoclopramide-induced movement disorders. *Arch Intern Med* 1989; 149:2486-2492.
4. Dodrill CB, Troupin AS. Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. *Neurology* 1977; 27:1023-1028.
5. Saenz de Tejada I, Ware JC, Blanco R, et al. Pathophysiology of prolonged penile erection associated with trazodone use. *J Urol* 1991; 145:60-64.
6. Kaplitz SE. Withdrawn, apathetic geriatric patients responsive to methylphenidate. *J Am Geriatr Soc* 1975; 23:271-276.
7. Schiffer R, Herndon RM, Rudick RA. Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985; 312: 1480-1482.
8. Blumer D, Migeon C. Hormone and hormonal agents in the treatment of aggression. *J Nerv Ment Dis* 1973; 160:127-137.
9. Raskind MA, Sadowski CH, Sigmund WR, Beitler PJ, Auster SB. Effect of tacrine on language, praxis, and noncognitive behavioral problems in Alzheimer disease. *Arch Neurol* 1997; 54:836-840.

**IN RESPONSE:** We thank Dr. Geller for his comments regarding the cognitive effects of medications. Changes in drug disposition and sensitivity with aging, polypharmacy, drug-drug, and drug-disease interactions predispose elderly patients to adverse drug reactions.<sup>1</sup>



Although many of Dr. Geller's recommendations for alternative drug therapies have merit, they need to be supported by clinical trials that establish the safety and effectiveness of these treatments in elderly patients. In the meantime, physicians are well advised to introduce new medications cautiously to old patients, and to "start low and go slow" when the therapeutic dose of a drug is unknown or the patient has complex medical problems.

Our interpretation of the value of certain drugs in this group of patients varies from Dr. Geller's in some areas. There are certainly pros and cons to any group of drugs, such as antihypertensives, but we would urge careful consideration before adding some of these drugs. For example, beta-blockers can cause blood pressure drops, resulting in falls or fractures as well as in dysphoria.

Carbamazepine and valproate come with their own concerns, such as weight gain and tremor in the elderly. Patients may have received these for mood stabilization as opposed to "antiseizure" medication. Serum level issues can be bypassed in some cases by using gabapentin if kidney function is adequate and simply monitoring for side effects and clinical progress.

Neuroleptics, although not appropriate for all patients, have advanced significantly from those described in the past. For example, risperidone, now the antipsychotic most often selected in the elderly, has fewer negative cognitive effects, fewer extrapyramidal concerns, and good tolerability at low dosages. Various other newer agents such as

olanzapine and clozapine offer advantages in the agitated patient with Parkinson disease.<sup>2</sup>

Amantadine, a dopamine agonist, often causes increased psychotic behavior. The same is true for the psychostimulant methylphenidate, which is more appropriate for depression in the non-demented elderly patient.

Pseudobulbar emotional incontinence can be treated with selective serotonin reuptake inhibitors as well as tricyclic antidepressants. For the latter group secondary amines (ie, nortriptyline) are clearly preferred to the tertiary amines (ie, amitriptyline), which carry greater risk for anticholinergic confusion and orthostasis.

As Dr. Chan and Dr. Geller point out, new cholinergic agents, which slow the progression of memory loss, may promote improved judgment and resultant behavior. Although the recent treatment guidelines did not comment on cholinergic agents for agitated patients with dementia, we realize clinical studies in this area are only beginning. We look forward to the future research in this area.

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#### ■ REFERENCES

1. Vestal RE. Aging and pharmacology. *Cancer* 1997; 80:1302-1310.
2. Alexopoulos G, Silver J, Kahn D, Frances A, Carpenter D. Treatment of agitation in older persons with dementia. *Postgrad Med* 1998; 103(Suppl) April:9-80.

#### CORRECTION

Two errors appeared in the article by Ana Vann, PharmD, "The herbal medicine boom: Understanding what patients are taking," which was published in the March 1998 issue of the *Cleveland Clinic Journal of Medicine*.<sup>1</sup>

The first paragraph on page 129 incorrectly cited a survey<sup>2</sup> as saying one in three respondents took an herbal medication. In fact, one in three received some form of alternative therapy, but not necessarily an herbal medication.

The first paragraph on page 130 incorrectly cited a test from *Consumer Reports*<sup>3</sup> as finding that 7 of 10

ginseng products contained no ginseng at all. In fact, *Consumer Reports* measured the amounts of 6 ginsenosides (the putative active ingredients in ginseng) in 10 ginseng products. Some products had 10 to 20 times as much ginsenoside as others, and one product had very little.

#### ■ REFERENCES

1. Vann A. The herbal medicine boom: Understanding what patients are taking. *Cleve Clin J Med* 1998; 65:129-134.
2. Eisenberg DM, Kessler RC, Roster C, et al. Unconventional medicine in the United States. prevalence, costs, and patterns of use. *N Engl J Med* 1993; 328:246-252.
3. Consumers Union. Herbal roulette. *Consumer Reports* November 1995:698.