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Managing discontinuation syndrome in patients with dementia

Evidence for a loss of symptomatic benefit 6 weeks after stopping donepezil has been clearly established in a 6-month randomized placebo-controlled study in patients with probable mild-to-moderate Alzheimer's disease (Rogers et al, *Neurology* 1998;50:136-45). The loss of benefit was assessed using cognitive measures (Mini Mental State Examination [MMSE], the cognitive portion of the Alzheimer's Disease Assessment Scale [ADAS-cog]) and global measures (Clinical Interview Based Impression of Change — plus caregiver input [CIBIC plus], Clinical Dementia Rating — Sum of Boxes [CDR-SB]).

What became evident in clinical practice was that the loss of benefit could be functional as well as behavioural and could be apparent as early as 1 week after cessation of a cholinesterase inhibitor (AChEI) in Alzheimer's disease, as well as related dementias. Singh and Dudley (*Int J Geriatr Psychiatry* 2003;18:282-4) reported the following 2 cases of discontinuation syndrome. One patient with Alzheimer's disease and cerebrovascular disease developed severe agitation, difficulty with concentration and sleep, and rapid mood changes from day 6 to day 10 off donepezil. A patient with dementia with Lewy bodies (DLB) developed similar symptoms starting on day 6 after donepezil was stopped until treatment with the same drug was started again.

Another circumstance when discontinuation syndrome can be observed is during a switch from one AChEI to another: for 2–4 weeks the second AChEI is given at subtherapeutic doses to avoid gastrointestinal side effects (Gauthier et al, *Curr Med Res Opin* 2003;19:707-14). The most serious reported observation has been in 3 patients with DLB whose treatment was being switched from donepezil to galantamine: although their MMSE scores deteriorated only slightly, the 3 patients developed restlessness and concentration difficulties, nighttime agitation and insomnia, or delirium requiring admission to hospital (Bhanji and Gauthier, *Int Psychogeriatr* 2003: 15[Suppl 2]:179).

Recommendations for practice would thus be the following: (1) do not stop a well-tolerated AChEI without discussing the risk of discontinuation syndrome with the patient and his or her family, (2) look for emerging neuropsychiatric symptoms as well as loss of cognitive and functional benefit and (3) patients with DLB may be more at risk than those with probable Alzheimer's disease.

A new factor in the management of dementia is the availability of the *N*-methyl-D-aspartate receptor partial antagonist memantine, which has shown benefits on a spectrum of outcomes as monotherapy (Reisberg et al, *N Engl J Med* 2003;348:1333-41) or in combination with an AChEI (Tariot et al, *JAMA* 2004;291:317-24). It has also shown specific effects on agitation (Gauthier et al, *Int J Geriatr Psychiatry* 2005; 20:459-64) in moderate-to-severe stages of probable Alzheimer's disease. It would, however, be prudent not to withdraw a well-tolerated AChEI when starting memantine.

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The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.