Use of memantine to treat Alzheimer's disease

The regulatory approval of memantine for use in the symptomatic treatment of moderate to severe Alzheimer's disease has led to high hopes among patients and their families. However, many physicians are still unsure about how best to use this medication. This letter summarizes the available evidence.

Persistent activation of *N*-methyl-D-aspartate (NMDA) in the central nervous system has been considered to contribute to chronic neurodegeneration in Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a moderate-affinity, uncompetitive NMDA receptor antagonist.[1]

Memantine has been used for more than 10 years in Europe and more recently in the United States. In randomized controlled trials (RCTs)[2–5] comparing the drug with usual care or placebo (see Table 1), memantine treatment has been associated with reduced rate of deterioration on global, cognitive and functional (activities of daily living [ADLs]) measures and also with behavioural improvements (particularly related to agitation). It has been suggested that memantine's properties related to agitation and aggression might reduce the need for antipsychotics.[2] To evaluate this antipsychotic-sparing effect, a Canadian placebo-controlled RCT is under way in which outcomes such as cognition, ADLs and behaviour are being examined in patients with baseline agitation and/or aggression. Alternatively, combination therapy with memantine and cholinesterase inhibitors has been shown to increase the cognitive benefits.[4,6] These results have been attributed to the distinct therapeutic mechanisms of these drugs.

In Canada, memantine is licensed for use in the treatment of symptoms associated with moderate to severe Alzheimer's disease. Although licensed, memantine is currently reimbursed only in Quebec and there only as monotherapy. The dose recommended in the approved product monograph[7] is 20 mg/d (10 mg twice a day). Memantine is mostly excreted through the kidneys; therefore, if creatinine clearance is known to be less than 60 mL • min^{-1} • 1.73 m^{-2}, the dose prescribed should be no more than 10 mg/d. Furthermore, memantine is not recommended for patients with severe renal impairment. Data from prior use of memantine in Europe and the United States suggest a good safety profile, using a titration of 5 mg per week up to 20 mg/d in 2 divided doses. The most common side effects (occurring in 5% or more of patients) are dizziness, constipation, confusion and headaches; less common side effects (occurring in less than 5% of patients) are hypertension, somnolence and visual hallucinations. Families have reported that higher doses (e.g., 10 mg twice a day) can lead to worsening of confusion, which disappears at lower doses. There are no apparent additive side effects when memantine is combined with cholinesterase inhibitors.

For most patients who are receiving cholinesterase inhibitors and whose condition progresses to a more severe stage, the cholinesterase inhibitor is discontinued when memantine is started. Because of a risk of discontinuation syndrome (or withdrawal reaction) when cholinesterase inhibitors are stopped, a 1-month overlap between these 2 drug classes is suggested.[9,10]

Clinical efficacy may be evaluated by directly observing patients and questioning caregivers about the 5 do-

Table 1: Pivotal studies comparing memantine to placebo in moderate-to-severe Alzheimer's disease (AD)

Study	Patients	Memantine dose and duration	Positive results for drug over placebo
Winblad and Poritis 1999[5]	Nursing home MMSE <10 *n* = 166 (49% with AD)	10 mg/d for 3 mo	Clinical global impression of change, behavioural rating scale for geriatric patients
Reisberg et al. 2003[3]	Community MMSE 3—14 *n* = 252	20 mg/d for 6 mo	Clinical interview-based impression of change, ADCS—ADL scale, severe impairment battery
Tariot et al. 2004[4]	Community MMSE 5—14 *n* = 404 (all receiving donepezil)	20 mg/d for 6 mo	Clinical interview-based impression of change, ADCS—ADL scale, severe impairment battery, neuropsychiatric inventory, behavioural rating scale for geriatric patients

Note: MMSE = Mini mental state examination, ADCS-ADL = Alzheimer Disease cooperative study — activities of daily living.

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mains of cognition, mood, behaviour, ADLs and social interaction. Caregivers can be asked to focus on the ability to participate in conversations, anxiety, and the behaviours of agitation and aggression.

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Competing interests: Dr. Gauthier and Dr. Herrmann are the principal investigators in the ongoing Canadian randomized study comparing memantine with placebo, sponsored by Lundbeck Canada. Seven years ago, Dr. Gauthier was awarded (through a peer-reviewed process) a research chair funded by the Canadian Institutes of Health Research and Rx&D Canada's Research-Based Pharmaceutical Companies (via a pool of funds from different companies, including Lundbeck Canada). Both Dr. Gauthier and Dr. Herrmann have received speakers' honoraria and consultant fees from Lundbeck Canada. No competing interests declared for Florian Ferreri or Catherine Agbokou. None of the authors received any honoraria for writing this letter.

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Dealing with alcoholism

Stephen Hwang, in his commentary on homelessness and harm reduction,[1] notes the severe limitations of the study by Tiina Podymow and colleagues,[2] including the small number of subjects and the unreliability of self-reported evidence. As an addictions counsellor for many years, I have yet to encounter anyone meeting the DSM-IV criteria for alcoholism who accurately reports consumption levels; either they lie deliberately or, alas, they are too befuddled to recall. In addition, people with alcoholism tend to be "people-pleasers," telling the researcher or counsellor what they think he or she wants to hear, which compounds the problems of self-reporting.

If you want to get at the truth about attempts to cut down, consider attending 3 or 4 "open" meetings of Alcoholics Anonymous a week for a year. Although the evidence provided at AA meetings is also self-reported, it has 2 advantages: the people involved are likely to be sober and therefore less fearful of telling the truth, and there will be considerably more "subjects," which should also increase the reliability.

One thing that I have discovered is that until and unless a person with alcoholism discovers what he or she would rather do than drink, there will be considerable difficulty in abstaining or maintaining abstinence. There is also the frequently unspoken terror of stopping. It can take an awful lot of time and effort to bring any addict to that point, but at least by working within the framework of the transtheoretical model,[3] the process can be started.

The idea of giving a person with alcoholism a drink every hour on demand because it will help him "cut down" or reduce harm appalls me. If it's such a good idea, why don't we suggest the same for smokers?

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[Dr. Hwang responds:]

The main finding of the study by Tiina Podymow and colleagues[1] was that the homeless participants in their harm reduction program had significantly fewer numbers of emergency department visits and police encounters after entry into the program, as determined by a review of hospital and police records. Data on these service utilization outcomes were no doubt more reliable than the self-reported data on alcohol consumption.

Few would argue that one of our duties as physicians is to encourage patients with alcoholism to strive to abstain from alcohol. Many of these individuals may find it helpful to participate in programs such as Alcoholics Anonymous. But what do we recommend to someone who drinks 8 bottles of wine a day, sleeps on the street and expresses an unwillingness to contemplate abstinence? Harm reduction programs such as the one described provide a means of engaging these people in a way that may ultimately lead to