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Memantine for Treatment of Moderate to Severe Alzheimer's Disease

Summary

- ✓ **Health Canada has issued a Notice of Compliance with conditions (NOC/c) for memantine in the treatment of moderate to severe Alzheimer's disease (AD).**
- ✓ **The evidence of relative benefit and harm from memantine in this population derives from two randomized controlled trials (RCT) of 24 to 28 weeks duration, in a total of 656 patients; and a post hoc subgroup analysis of 79 patients with severe AD from a third trial of 12 weeks.**
- ✓ **Memantine alone or in combination with donepezil demonstrates improvements in primary outcome scores of activities of daily living and cognition, but not of global performance.**
- ✓ **Memantine's rate of diffusion may be rapid, as it is the only drug available for severe AD and it has a potential for use in unapproved indications.**

The Technology

Memantine is an N-methyl-D-aspartate (NMDA) receptor partial antagonist. In a normal functioning brain, NMDA receptors are activated by glutamate, an excitatory neurotransmitter required for learning and memory. In AD, an excess activation of NMDA receptors by glutamate causes neuronal damage and neuronal death (excitotoxicity). Memantine's ability to bind to NMDA receptors may inhibit glutamate-induced excitotoxicity without interfering with normal physiological function.[1,2]

Regulatory Status

In Canada, memantine (Ebixa® distributed by Lundbeck Canada Inc.) is approved as monotherapy or as adjunctive therapy with cholinesterase inhibitors for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type.[3] It received NOC/c on December 8, 2004.[4,5]

Patient Group

A survey conducted in the early 1990s shows that dementia affects 8% of Canadians older than 65 and 35% of those older than 85. AD accounts for >60% of dementia cases. Among AD patients living in the community, 54% have moderate to severe AD. It is estimated that by 2031, the number of Canadians with dementia will almost triple.[6,7]

AD is a progressive neurodegenerative disorder that is characterized by a gradual loss of cognitive abilities, memory and functional autonomy; and by the development of neuropsychiatric problems and behavioural disturbances.[8] Its etiology is unknown. Risk factors include advanced age, presence of ApoE4 gene, family history and gender (more females are affected, even after adjusting for age).[9,10] A diagnosis of "probable" AD (defined as typical clinical symptoms without histological confirmation) is made if pre-established criteria are met.[8,11]

Current Practice

There is no treatment to prevent or cure AD. Cholinesterase inhibitors (i.e., donepezil, galantamine and rivastigmine) are indicated for the management of mild to moderate AD. There are no treatments for the cognitive and functional deterioration that occurs in the severe stages. Comorbidities, behavioural problems and psychosis are treated according to standards of care. Caregiver support is available through various networks.

The Evidence

In clinical trials, the efficacy of drugs used in AD is evaluated using instruments that measure cognition, function (activities of daily living), behaviour and global performance.

Table 1: Primary outcome measures in memantine trials

Instrument	Description	Interpretation
ADCS-ADL$_{sev}$	Assesses daily activities for patients with severe AD	Maximum score of 54, decrease in score shows deterioration
BGP$_{care\text{-}dependency}$	Assesses cognition, function and behavioural disturbances using care-dependency scale	Maximum score of 46, higher scores means worse function
CIBIC-plus, CGIC	Provides global rating of patient function (general, cognitive, behaviour and activities of daily living)	1=very much improved 4=no change 7=very much worse
SIB	Assesses cognition in advanced AD	Maximum score of 100, lower score shows greater impairment

ADCS-ADLsev=AD Cooperative Study-Activities of Daily Living inventory modified for severe AD; BGP=Behavioural Rating Scale for Geriatric Patients; CGIC=Clinical Global Impression of Change; CIBIC-plus=Clinician's Interview-Based Impression of Change Plus Caregiver Input; SIB= Severe Impairment Battery.

A Cochrane Review has evaluated the efficacy, safety and cost of memantine in patients with dementia (including AD, vascular and mixed dementias).[12] It identifies three published, randomized, double-blind, placebo-controlled, parallel group trials that included patients with moderate to severe AD. No RCTs that studied harms and benefits beyond 28 weeks were identified.

Two trials[13,14] were conducted in outpatients who were 50 years of age or older and had probable AD. In the intent-to-treat analysis, the last observation carried forward method was used. A 12-week, non-randomized post hoc subgroup analysis is also available for 79 inpatients, 60 to 80 years of age, with severe AD.[15] Results for the primary outcome measures appear in Table 2.

One RCT[13] shows that memantine has a statistically significant effect on function, but not on global performance when used alone. In combination with donepezil, memantine has a statistically significant effect on function and cognition.[14] A non-randomized post hoc sub-group analysis shows that there is a statistically significant improvement in global performance scores when memantine treatment is compared with placebo.[15]

Adverse Effects

In the Reisberg *et al*. study, 33.3% of patients in the control group compared with 23.0% patients in the treatment group withdrew from the trial. Of these, 17.4% in the control group versus 10.3% of the treated group withdrew because of adverse effects. In the Tariot *et al.* study, 25.4% of patients in the control group versus 14.8% of patients in the treated group withdrew and 12.4% in the control group versus 7.4% in the treated group withdrew because of adverse effects.

Administration and Cost

The Canadian product monograph recommends that memantine titration occur for several weeks to reduce the risk of side effects. A dose of 5 mg daily is increased by 5 mg increments every week to a maximum of 10 mg twice daily. The medication can be taken with or without food.[3]

The medication price is C$2.295 per 10 mg tablet (Mr. Michel Rousseau, Lundbeck Canada Inc., Montreal: personal communication, 2005 Jan 11).

Concurrent Developments

The use of memantine is being investigated in mild to moderate AD, vascular dementia, neuropathic pain, glaucoma, acquired pendular nystagmus in multiple sclerosis, opioid dependence and alcohol withdrawal. Other drugs being investigated for use in moderate to severe AD include donepezil and neramexane.[16]

Table 2: Benefit and harm observed in memantine versus placebo trials

Reference	Participants	Interventions and Comparators	Primary Outcomes	Most Frequently Reported AE* (%)
Reisberg *et al.*[13,17]	• FAST≥6a • GDS 5 or 6 • MMSE 3 to 14 60% of patients had severe AD	memantine titrated to 20 mg daily (n=126) versus placebo (n=126) for 28 weeks	**ADCS-ADLsev** memantine: -3.1±6.79 SD placebo: -5.2±6.33 SD net treatment effect: 2.1 p=0.022 **CIBIC-plus** memantine: 4.5±1.12 SD placebo: 4.8±1.09 SD p=0.064	**Agitation** memantine: 23/126 (18.2) placebo: 40/126 (31.7) **Diarrhea** memantine: 12/126 (9.5) placebo: 10/126 (7.9) **Insomnia** memantine: 13/126 (10.3) placebo: 10/126 (7.9) **Urinary incontinence** memantine: 14/126 (11.1) placebo: 14/126 (11.1) **Urinary tract infection** memantine: 7/126 (5.6) placebo: 17/126 (13.2)
Tariot *et al.*[14,17]	• MMSE 5 to 14 • on stable dose of donepezil for >6 months before trial entry 59% of patients had moderate AD	memantine titrated to 20 mg daily + donepezil 5 to 10 mg daily (n=203) versus placebo + donepezil 5 to 10 mg daily (n=201) for 24 weeks	**SIB** mem/don: +0.9±0.67 SE placebo/don: −2.5±0.69 SE net treatment effect: 3.4, p<0.001 **ADCS-ADLsev** mem/don: −2.0±0.50 SE placebo/don: −3.4±0.51 SE net treatment effect: 1.4, p=0.03	**Accidental injury** mem/don: 10/202 (5.0) placebo/don: 16/201 (8.0) **Agitation** mem/don: 19/202 (9.4) placebo/don: 24/201 (11.9) **Confusion** mem/don: 16/202 (7.9) placebo/don: 4/201 (2.0) p=0.01 **Diarrhea** mem/don: 9/202 (4.5) placebo/don: 17/201 (8.5) **Dizziness** mem/don: 14/202 (6.9) placebo/don: 16/201 (8.0)
Winblad *et al.* (post hoc subgroup analysis)[15,17]	• GDS 5 to 7 • MMSE<10 all of this subgroup had severe AD	memantine 5 mg daily for one week then 10 mg daily (n=41) versus placebo (n=38)	**CGIC** memantine: 3.1±0.1 SE placebo: 3.5±0.1 SE p=0.003 **BGP-**$_{\text{Care Dependency}}$ memantine: −5.8 placebo: −2.8 p=0.003	Unavailable for subgroup

AE=adverse events, mem/don=memantine with donepezil group, placebo/don=placebo with donepezil group, SD=standard deviation, SE=standard error, *p values not reported, FAST=Functional Assessment Staging scale, GDS=Global Deterioration Scale, MMSE=Mini-Mental State Examination

Rate of Technology Diffusion

The rate of diffusion of memantine may be rapid, as it is the only drug available for severe AD. In the US, memantine was launched in early January 2004. Within a few weeks, 40,000 patients started memantine therapy. Its market share was >17% by the end of the first month.[18]

Implementation Issues

Memantine may be an alternative for patients with moderate AD who cannot tolerate cholinesterase inhibitors.[19] There is no trial that compares memantine with a cholinesterase inhibitor in patients with moderate AD. Memantine's place in therapy for severe AD patients is unclear, because patients were not randomized according to disease severity in the clinical trials.

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