

Review of donepezil, rivastigmine, galantamine and memantine for the treatment of dementia in Alzheimer's disease in adults with Down syndrome: implications for the intellectual disability population[†]

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SUMMARY

The management of dementia in Alzheimer's disease has dramatically changed since the development of anti-dementia drugs. However, there is limited information available regarding the bio-medical aspects of the differing drugs; particularly relating to adults with intellectual disability. Indeed the information available for the intellectual disabled population is limited to adults with Down syndrome. This review highlights the important pharmacological and clinical aspects of donepezil, rivastigmine, galantamine and memantine and supports the view that such drugs play an important part in the management of dementia in adults with intellectual disability. Future clinical and research issues are discussed. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — donepezil; rivastigmine; galantamine; memantine; dementia; mental retardation; learning disability; Down syndrome

INTRODUCTION

Dementia in Alzheimer's disease (DAD) is characterised by multiple cognitive deficits in association with behavioural disorders, mood changes, and deterioration in day-to-day functioning (Berg *et al.*, 1993; WHO, 1993). Alzheimer's disease (AD) is the most common type of senile dementia, and is particularly associated with adults with Down syndrome (Mann, 1988). The onset of DAD has been reported in individuals with Down syndrome aged as young as 30 years, with a dramatic increase in prevalence rates over the subsequent decades; for example 54.5% for age range 60–69 years (Prasher, 1995). Although

the detection of early symptoms of DAD may at times be difficult in individuals with intellectual disabilities, the clinical picture seen is not too dissimilar to that of the general population (Lai and Williams, 1989; Cosgrave *et al.*, 2000). Insidious progression of memory impairment, personality change, dysfunction in language and motor skills, onset seizures and behavioural abnormalities, marked loss of self-care skills and in weight is typical. Death usually occurs within 5 to 10 years of onset. The disease having a devastating impact not only on the individuals themselves but also on carers and the State.

Neuropathological AD is characterised by the formation of amyloid plaques and neurofibrillary tangles, loss of cortical brain matter, synaptic and neuronal loss and presence of inflammatory changes (Esiri, 2001). Neurochemically, there is a deficit in a number of cerebral neurotransmitters, such as acetylcholine, neuroadrenaline and serotonin (Giacobini, 2003; Poirier and Blass, 1999). Findings over the last few decades suggest that the principal chemical deficiency in Alzheimer's disease is that of degeneration

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[†]The term 'intellectual disability' is synonymous with mental retardation, learning disability, mental handicap and intellectual handicap.

of cholinergic neurones, neocortical deficits in choline acetyltransferase, reduced choline uptake and in acetylcholine release. This 'cholinergic hypothesis of Alzheimer's disease' has been the main thrust of drug development in AD (Farlow, 2002). The aim being to enhance selective cholinergic transmission in the brain by increasing the supply of choline, stimulating cholinergic receptors or by reducing acetylcholine metabolism (by inhibiting cholinesterase action). Recently, there has been growing interest in the hypothesis that glutamate mediated neurotoxicity is involved in the pathogenesis of AD (Danysz *et al.*, 2000; Francis, 2003). In this hypothesis, glutamate receptors (N-methyl-D-aspartate [NMDA]) are over-active and may interact with beta-amyloid or tau protein metabolism resulting in the characteristic changes of AD.

It has been 15 years since the publication of the original tacrine study. However, it has been over the last five years that the 'second generation' of cholinesterase inhibitors; donepezil, rivastigmine, and galantamine, have made a significant impact on the clinical management of AD (Dooley and Lamb, 2000; Van Den Berg *et al.*, 2000; Ballard, 2002). In the UK the National Institute for Clinical Excellence (2001) and in the US the American Academy of Neurology (AAN) (Doody *et al.*, 2001) concluded that anti-dementia drugs have a significant benefit in patients with AD and that these agents should be made available. However, both reports limited their recommendations to the general population. This article reviews recent advances in the drug treatments (donepezil, rivastigmine, galantamine and memantine) for DAD in adults with Down syndrome.

PHARMACOLOGICAL PROPERTIES

Donepezil and galantamine are selective inhibitors of acetylcholinesterase (AChE), whilst rivastigmine is a dual inhibitor of AChE and butyrylcholinesterase (AChE). Memantine is a non-competitive antagonist of NMDA (Table 1). All are given orally in tablet/capsule form. Rivastigmine and memantine can be given to individuals with poor compliance or swallowing problems in liquid form. All except donepezil are prescribed twice a day at maintenance dosage. Good clinical practice would suggest that all of the anti-dementia drugs should be started initially at a sub-therapeutic dosage and gradually increased. In the learning disabled population this should be done with greater caution and greater monitoring than that for the general population. All of the cholinesterase inhibitors are licensed for use in mild to moderate

Table 1. Summary of pharmacological parameters of anti-dementia drugs

Drug	Chemical class	Action	Type of inhibition	Route of administration	Frequency of administration	Given with food	Dosage/day	Indications
Donepezil	Piperidine	AChE inhibitor	Rapidly reversible	Oral-tablets	Once a day	No	5–10 mg	Mild-mod AD
Rivastigmine	Carbamate	AChE and BChE inhibitor	Pseudo-reversible	Oral-capsules and oral soln	Twice a day	Yes	6–12 mg	Mild-mod AD
Galantamine	Phenanthrene alkaloid	AChE inhibitor	Rapidly reversible	Oral-tablets	Twice a day	Yes	16–24 mg	Mild-moderately severe AD
Memantine	Glutamatergic modulator	NMDA antagonist	N/A	Oral-tablets and oral soln	Twice a day	No	10–20 mg	Mod severe-severe AD

Table 2. Summary of pharmacological parameters of anti-dementia drugs

Drug	Time to reach maximum concentration (h)	Elimination half-life (h)	Protein binding (%)	Total body clearance* (L/H/kg)	Time to steady state (days)	Excretion
Donepezil	3–5	50–70	96	0.13	14–22	Hepatic
Rivastigmine	0.5–2.0	0.6–2.0	43	N/A	—	Hepatic
Galantamine	1.2	5–7	<20	N/A	2	Hepatic and Renal
Memantine	3–8	60–100	45	N/A	11	Renal

*Drug clearance from plasma.

DAD; memantine is the only drug licensed in the UK for the treatment of moderately-severe to severe DAD. Rivastigmine reaches its maximum concentration and is eliminated the most quickly of the four drugs (Table 2). Memantine, the slowest, has an elimination half-life of up to 4 days. Donepezil and rivastigmine are metabolised by the liver and memantine and galantamine excreted by the kidneys.

Although there are differences in the pharmacokinetics there are still considerable pharmacological similarities between all of the four anti-dementia drugs. They all affect the central cholinergic system either directly as AChE inhibitors or indirectly by acting on related pathways (glutamate receptors). The AChE inhibitors are licensed for mild to moderate DAD. All are given orally, usually twice a day and all should be initiated with a similar degree of caution. Treatment should be withdrawn if tolerance or compliance is poor, if the patient's condition continues to deteriorate at a rate after 3 to 6 months, or if little benefit has been determined during this period.

Therapeutic efficacy

For the general population it has now been established that patients with DAD do benefit clinically both in the short- and long-term (Matthews *et al.*, 2000; Scott and Goa, 2000; Doody *et al.*, 2001; Winblad *et al.*, 2001) with anti-dementia therapy. Mohs *et al.* (2001), in a study of 431 Alzheimer's disease patients randomised to donepezil 10 mg or placebo for 54 weeks found that the former group maintained their function for 72% longer, and were less likely to decline over the year compared to placebo by approximately 40%. Treatment with donepezil delays decline by approximately 5 months. Benefit with active treatment is seen in global functioning, cognitive abilities, neuropsychiatric symptoms, behavioural problems, in day-to-day skills and in the reduction in carer stress (Burns *et al.*, 1999). Limited information is presently available regarding the efficacy of memantine to treat DAD but similar findings

have been reported (Reisberg *et al.*, 2000; Ferris *et al.*, 2001; Wimo *et al.*, 2003).

In contrast to the numerous studies published in the general population, only four significant studies (Kishnani *et al.*, 1999; Lott *et al.*, 2002; Prasher *et al.*, 2002; Prasher *et al.*, 2003) have been reported in the use of donepezil to treat dementia in adults with Down syndrome. These studies are reviewed below. No study to date has been published reporting on the use of rivastigmine, galantamine or memantine in the intellectually disabled population.

Kishnani *et al.* (1999) published findings of four adults with Down syndrome who were treated with up to 10 mg donepezil for between 26 and 68 weeks. Two younger individuals (aged 24 and 27 years) were not demented but two older persons (aged 38 and 64) met DSM-IV criteria for dementia. The report was an open trial of donepezil has been subject to considerable sources of error. On the one objective test used [Vineland Adaptive Behavior Scales, Sparrow *et al.*, 1984] there was improvement in scores for the non-demented individuals but little change for the demented persons.

Prasher *et al.* (2002) published findings from a 24-week, double-blind placebo-controlled trial of donepezil in 30 patients with Down syndrome and DAD. The Dementia Scale for Mentally Retarded Persons (DMR) by Evenhuis *et al.* (1990) was used as the primary outcome measure with secondary outcome measures for cognition, neuropsychiatric features and adaptive behaviour also used. The DMR can be used to give a global impression. The donepezil group had non-statistically significant reduction in deterioration in global functioning, in cognitive skills and in adaptive behaviour. The active group scored worse on the presence of neuropsychiatric symptom profile, which was explained by the authors as being a reflection of drug induced adverse effects being detected by the questionnaire. No life-threatening events occurred during the study period. The authors concluded that donepezil is probably efficacious in the treatment of DAD in adults with Down syndrome.

Lott *et al.* (2002) reported results from an open-label study of donepezil to treat dementia in nine Down syndrome patients. Treatment was for between 83–182 days with dosage up to 10 mg. Findings for the active group were compared to six matched historical control subjects. Dementia was assessed before treatment and after an average interval of 5 months using the Down Syndrome Dementia Scale (DSDS; Geyde, 1995). A significant improvement in dementia scores was seen for the treated group, although the authors highlighted a number of drawbacks with the study.

Prasher *et al.* (2003) went on to report in an open-label study the evaluation of the long-term (104 weeks) safety and efficacy of donepezil in the treatment of DAD. The 25 patients in this study had previously completed the 24-week randomised double-blind placebo-controlled trial (Prasher *et al.*, 2002). Patients were assessed in this study with the same measures as in the 24-week study. The primary outcome measure was the DMR. The mean total DMR score showed initial improvement from baseline for the donepezil group with subsequent deterioration in both the treated and untreated groups over the study period. At 104 weeks the deterioration in global functioning and adaptive behaviour was statistically significantly less for the treated demented Down syndrome subjects. This study demonstrated that donepezil was beneficial in the treatment of DAD in the Down syndrome population for up to two years.

There remains, and will always do so, difficulties in undertaking drug trials in the intellectual disabled population which are of the same standard as those undertaken in the general population. This particularly applies to studies of older adults with DAD. Problems of small sample size, non-blindness of carers and raters, inclusion criteria for DAD, reliability of measures used and type of statistical analysis used are at present inherent sources of error. However, from the limited information available from studies of DAD in the Down syndrome population and the inferences from findings from the general population, it is reasonable to conclude that donepezil can, both in the short-term and long-term, be efficacious in the treatment of DAD in older adults with Down syndrome. In keeping with results for the general population there is a reduction in the deterioration of cognitive skills, neuropsychiatric symptoms and in adaptive skills. No information is available regarding the possible beneficial impact on carers.

All of the other anti-dementia drugs are being used in the clinical setting and there are ongoing assessments on the efficacy of these drugs to treat DAD in

the Down syndrome population (Prasher, personal communication). To date, however, no studies have been published but clinical experience would suggest that intellectually disabled patients with DAD are also likely to benefit from these drugs. Research evidence on the efficacy of these drugs does remain an important omission of scientific knowledge.

TOLERABILITY

(i) Side-effects

All of the anti-dementia drugs discussed are generally well tolerated, and most of the adverse events that may occur are mild and transient. In the case of the AChE inhibitors these are related to the cholinergic system. The rate of adverse events are often similar to placebo (Inglis, 2002; Prasher *et al.*, 2002) and are dose-related. The commonly reported adverse events are listed in Table 3. In drug trials approximately 5% of individuals withdraw from studies because of adverse events. Many of the side-effects listed in Table 3 are relatively minor, transient and can be stopped by reducing the dose of medication used.

In the studies involving adults with Down syndrome, Kishnani *et al.* (1999) found that none of the 4 study individuals experienced any serious adverse effect. Transient agitation and loose stools were the only side-effect noted. Prasher *et al.* (2002, 2003) found fatigue (44%), diarrhoea (38%), insomnia (25%), nausea (25%), dizziness (19%) and anorexia (19%) as the most common treatment-emergent features. Hemingway-Eltomey and Lerner (1999) reported three cases of Down syndrome patients with dementia who developed adverse effects of agitation, aggression, urinary incontinence and deteriorating memory loss whilst being treated with donepezil.

Clinicians should be aware of the more serious side-effects, e.g. reduced heart rate (which can be significant in a individual with Down syndrome who may already have a low resting heart rate), stomach ulcer with bleeding, seizures, and depression. Starting at a low dose and slower titration of dosage can reduce the frequency of side-effects, particularly in an ageing population.

(ii) Contra-indications

There are a number of medical conditions where the use of the anti-dementia drugs are contra-indicated. These conditions are generally similar for all four of the drugs. They include sick-sinus syndrome, supra-ventricular conduction abnormalities, history of peptic ulcer, chronic airway disease, anaesthesia,

Table 3. Commonly occurring Side-effects of the Anti-dementia drugs

Adverse event	Donepezil	Rivastigmine	Galantamine	Memantine
Nausea	+	+	+	
Diarrhoea	+	+	+	+
Insomnia	+	+	+	+
Fatigue	+	+	+	+
Vomiting	+	+	+	+
Muscle cramps	+			
Anorexia	+	+	+	
Headache	+	+	+	+
Dizziness	+	+	+	+
Syncope	+	+	+	
Urinary incontinence	+			
Psychiatric disturbances	+	+	+	+
Rash	+	+	+	
Pruritus	+			
Weight loss		+	+	
Abdominal pain		+		
Drowsiness		+		
Hallucinations				+
Cardiac changes	+		+	+
Cystitis			+	+
Increased libido			+	

Table 4. Conditions where anti-dementia therapy should be used with caution

Drug	Condition
Donepezil	Sick sinus syndrome, supraventricular conduction abnormalities, history of peptic ulcers, asthma, chronic obstructive airway disease, hepatic impairment
Rivastigmine	Renal impairment, hepatic impairment, sick sinus syndrome, supraventricular conduction abnormalities, history of peptic ulcers, asthma, chronic obstructive airway disease
Galantamine	Sick sinus syndrome, supraventricular conduction abnormalities, history of peptic ulcers, asthma, chronic obstructive airway disease, hepatic impairment, urinary obstruction
Memantine	Renal impairment. Caution in patients with epilepsy, cardiovascular disorders

hepatic and renal impairment. Older adults with Down syndrome are more vulnerable than their general population counterparts to presenting with concurrent medical conditions and a detailed review of their physical health status is necessary prior to prescribing the drugs for DAD.

(iii) Drug interactions

Rivastigmine and galantamine are removed from the blood circulation rapidly (half-life of 1–2 h and 5–7 h respectively) and therefore are at low risk for interactions with other drugs. They have low binding to plasma protein and are eliminated by the kidneys (Table 1) and are, therefore, also of low risk for long-term accumulation. Donepezil, however, is high risk for accumulation due to its high protein binding (particular concern in overdose) and its long half life (50–70 h) may be of concern in patients who develop

serious adverse events, e.g. bradycardia where rapid elimination would be desirable. Drug interactions can occur with all the anti-dementia drugs with other drugs that share metabolic pathways, particularly relating to the liver (Inglis, 2002). Drugs which may give cause for concern include phenytoin, carbamazepine, paroxetine and fluoxetine. As elderly persons with and without intellectual disability are often on poly-pharmacy, clinicians need to be fully aware of known and possible drug interactions that may occur.

OTHER ISSUES

Due to the considerable absence of evidence-based research findings for the intellectually disabled population, there remain several unresolved issues. Do adults with intellectual disability other than persons with Down syndrome also benefit from anti-dementia therapy? Concerns remain regarding the maximum

dose and exact dosage schedule to be used. Is efficacy dose-related? There remains considerable clinical uncertainty regarding when anti-dementia drugs should be stopped. Medication should be withdrawn if significant adverse effects occur, compliance is poor or a significant contra-indication occurs. NICE recommend that a repeat assessment should take place 2–4 months after the maintenance dose has been reached and only if there has not been a decrease in assessment scores (Mini-mental State Examination for the general population) together with improvements in behaviour and/or functioning.

Other issues are, could AChE inhibitors be beneficial to individuals with Down syndrome who have the neuropathological changes of Alzheimer's disease but as yet not presented with clinical dementia? As for the general population, are there particular predictors of response, are there any significant differences between the drugs, can an AChE inhibitor be used in combination with a NMDA antagonist and can the drugs be used for forms of dementia other than DAD?

The health economics of the prescribing of anti-dementia therapy has been researched in the general population (Wimo *et al.*, 2003). No information is available for people with intellectual disability. Yearly healthcare costs for providing care for adults with dementia are a significant proportion of the State budget. Such costs are usually related to provision of residential/nursing home care. It is argued, therefore, maintaining a person with DAD in their family home by using drugs which delay severe deterioration of DAD or improve functional abilities would significantly impact on healthcare costs. Many older adults with Down syndrome are often, prior to the onset of DAD, already living in residential-type accommodation and cared for by paid carers. The economic benefit will, therefore, be markedly less as compared to those for the general population. Nevertheless further health economic analyses evaluating the cost benefits of all the anti-dementia drugs for adults with intellectual disability is recommended. Further, considerable emotional and financial stress is put upon family carers.

DISCUSSION

The use of anti-dementia drugs (donepezil, rivastigmine, galantamine and memantine) has now become the gold standard for the treatment of DAD in the general population. In the field of intellectual disability there has been a greater degree of hesitance to prescribe these drugs. With growing research evidence

and growing clinical experience, it is likely that the above drugs will also become first-line treatment for DAD in older adults with intellectual disability with or without Down syndrome. Research evidence in the field of intellectual disabilities is limited to donepezil. Information regarding the clinical use of other anti-dementia drugs is much needed. Whether adults with Down syndrome can tolerate higher doses remains uncertain but the initiation of drug therapy at low dose with gradual titration will reduce adverse effects and lead to greater compliance.

There are many other drug therapies which are being developed as alternatives or supplements to the present medications. These include metal chelators (e.g. clioquinol), non-steroidal anti-inflammatory drugs (e.g. indomethacin) antioxidants (e.g. vitamin E), hormones (e.g. oestradiol), herbs (e.g. Gingo biloba), and vitamins (e.g. folic acid). Irrespective of the type of drug, it remains important that drug therapy is used as part of a wider management plan with carer support, psychological and behavioural treatment and ongoing assessments of physical health status.

In the field of intellectual disability, the decision regarding when to stop medication can be difficult, e.g. anticonvulsant medication. This particularly applies to the use of anti-dementia therapy. There is limited information available regarding the natural progression of DAD in adults with Down syndrome. For clinicians the ongoing prescribing of a drug that modifies deterioration over a short period of time, continues to be a dilemma. Ideally, an objective measure is required. Several potential markers, such as red blood cell cholinesterase inhibition, cerebrospinal fluid monoamine or beta-amyloid measurement and platelet amyloid precursor protein, are being investigated but as yet have not been established.

There remain several areas of further research. How do the different drugs compare? Can they be combined? Do any significantly improve the quality of life? Is there a cost-benefit to the State? Are they any outcome predictors (e.g. apolipoprotein status)? Do people with intellectual disability but without Down syndrome respond differently?

The development of drug therapy for DAD, a devastating medical illness, is a major advance in medical care. Adults with Down syndrome should be allowed access to the same types of treatments as the general population but with caution and modification in the management plan as appropriate. At present it is recommended that treatment should follow, in principle, NICE guidelines with initiation of therapy and responsibility for monitoring of the patient by a specialist.

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