The safety and tolerability of donepezil in patients with Alzheimer's disease

Stephen Jackson,[1] Richard J. Ham[2] & David Wilkinson[3]

[1]*Department of Health Care of the Elderly, Guy's, King's and St Thomas' (GKT) School of Medicine, Kings College London, London, UK,* [2]*West Virginia University Center on Aging, Morgantown, WV, USA and* [3]*Memory Assessment and Research Centre, Moorgreen Hospital, Southampton, UK*

Correspondence
Stephen Jackson, Department of Health Care of the Elderly, Guy's, King's and St Thomas' (GKT) School of Medicine, Kings College London, London SE5 9RS, UK.
Tel: 0207 3466071
Fax: 0207 3466370
E-mail: stephen.jackson@kcl.ac.uk

Keywords
Alzheimer's disease, donepezil

Cholinesterase (ChE) inhibitors, which prevent the hydrolysis of acetylcholine, have been approved for the symptomatic treatment of Alzheimer's disease (AD) for over a decade. However, the first ChE inhibitors were associated with a high incidence of side-effects and general tolerability concerns, including hepatotoxicity. Side-effects associated with increased cholinergic activity, particularly in the gastrointestinal (GI) system, can prevent patients from achieving effective doses of drug. In addition, the advanced age and frail nature of patients with AD mean that poor tolerability is a serious concern. The potential for drug–drug interactions is also an important consideration, due to the high prevalence of comorbid disease in these patients.

Data both from clinical trials and studies in routine clinical practice have shown that donepezil is associated with a low incidence of GI adverse events (AEs) that is comparable with placebo. Donepezil is a potent, selective inhibitor of acetylcholinesterase, and selective inhibition of central as opposed to peripheral ChEs might be expected to reduce the incidence of AEs, thus this may explain the lower incidence of cholinergic AEs observed following treatment with donepezil, compared with nonselective ChE inhibitors.

There are no differences in cardiovascular AEs, including bradycardia, between placebo and donepezil groups in the clinical trials published to date, even in a very sick vascular dementia population with high rates of comorbidity and concomitant medication use.

Data from single- and multiple-dose studies of donepezil in patients with hepatic impairment and with moderately to severely impaired renal function indicate that donepezil is safe and well tolerated in these groups. Furthermore, both *in vitro* and clinical studies have shown that donepezil is not associated with drug–drug interactions.

The incidence of weight loss is very similar between donepezil- and placebo-treated patients. Although insomnia and other sleep disorders have been reported following administration of donepezil, lengthening the time period before increasing the dose of donepezil from 5 to 10 mg day^{-1} or switching to morning dosing can reduce these events to the levels of placebo-treated patients.

Over 770 million days of patient use and an extensive publication database demonstrate that donepezil has a good tolerability and safety profile.

Introduction

Cholinesterase (ChE) inhibitors, which increase the availability of acetylcholine (ACh) by preventing its hydrolysis, are currently approved for the symptomatic treatment of Alzheimer's disease (AD).

The tolerability of any new drug has a major impact on its utility, and tacrine and physostigmine, the first ChE inhibitors to be used for the treatment of AD, were associated with a high incidence of gastrointestinal (GI) adverse events

(AEs) and other concerns, including hepatotoxicity [1–5].

Poor tolerability is especially relevant for elderly patients, because physiological changes associated with ageing can affect the pharmacokinetics (PK) and pharmacodynamics of medications [6]. Of course, elderly patients are often afflicted with a wide array of medical conditions [7], and the inevitable polypharmacy in these patients increases the potential for drug–drug interactions. A reluctance to add to this polypharmacy may limit the use of novel medications in older patients.

Donepezil, a piperidine-based, reversible and specific inhibitor of acetylcholinesterase (AChE), was the second ChE inhibitor to receive regulatory approval for the symptomatic treatment of mild to moderate AD. Unlike other ChE inhibitors, donepezil has a long half-life, allowing once-daily administration [8, 9]. Although there is a recommended simple one-step titration, treatment begins with an effective dose of 5 mg day^{-1} [10–14]. Since the approval of donepezil, two additional ChE inhibitors (rivastigmine and galantamine) have also been approved for the treatment of mild to moderate AD.

Limited published data at the time of the approvals of the ChE inhibitors led to speculation that these symptomatic treatments demonstrated modest efficacy [15], and this may have initially resulted in a reluctance to use them. However, clinical trials have consistently demonstrated that ChE inhibitors provide benefits in patients with AD; and a wealth of published evidence is now available that demonstrates the efficacy of these agents in reducing the cognitive, functional and behavioural symptoms of AD in the long term, with postponement of dependency, including the need for skilled nursing care [10–14, 16–25].

Recently, the NMDA-receptor antagonist, memantine, has been approved in the European Union and the USA for use in patients with moderately severe to severe AD. Memantine may be used as add-on therapy to donepezil.

ChE inhibitors and cholinergic adverse events

Cholinergic nerves are found throughout the human body, suggesting that inhibition of ChE is likely to have effects on a number of tissues and organs. Following initial experience with the first AChEs, tolerability was clearly an important consideration in the development of new ChE inhibitors for AD in order to improve compliance.

Rapid dose titration

The occurrence of the most common cholinergic AEs (e.g. nausea, diarrhoea, insomnia, vomiting, asthenia/fatigue and anorexia) is most pronounced in the first few weeks after initiating treatment, and most pivotal clinical trials typically use forced titration schedules [12, 18, 20]. For example, during the pivotal trials of donepezil, patients randomized to donepezil 10 mg day^{-1} received donepezil 5 mg day^{-1} for the first 7 days and then 10 mg day^{-1} thereafter. In these studies, AEs such as nausea and diarrhoea were reported by 21% and 16% of patients treated with donepezil 10 mg day^{-1}, respectively, *vs.* 6% and 4% for placebo [26]. Subsequent trials have suggested that the incidence of AEs can be reduced by lengthening the period of time patients receive the lower 5 mg day^{-1} dose before the higher, and more effective, 10 mg day^{-1} [14] dose is initiated, with nausea reported by 11% and diarrhoea by 7% of patients treated with donepezil 10 mg day^{-1} titrated up after 28 days on 5 mg, *vs.* 9% and 7%, respectively, for placebo [22].

Selective inhibition of central cholinesterases

Selective inhibition of central as opposed to peripheral ChEs might be expected to reduce the incidence of AEs associated with ChE inhibitors. The centrally and peripherally mediated cholinergic effects of selective inhibitors of AChE (such as donepezil) and of nonselective inhibitors of both AChE and the predominantly peripherally acting butyrylcholinesterase (BuChE) (such as tacrine and rivastigmine) have been compared in preclinical studies [27, 28]. These effects may indicate the mechanism that explains the lower incidence of cholinergic AEs observed following treatment with selective AChE inhibitors, *vs.* nonselective ChE inhibitors [3, 4, 29–35]. Donepezil is the most potent and selective inhibitor of AChE currently available for the treatment of AD, being over 1252 times more selective for AChE than for BuChE [36].

Pharmacokinetic properties of ChE inhibitors

Pharmacokinetic differences between ChE inhibitors may affect their plasma concentrations and influence the incidence and severity of AEs. Certainly, serum concentrations of tacrine have been observed to predict the risk of AEs [37]. In addition to absolute concentration, rapid fluctuations and rising concentrations as in the initial titration may also be important determinants of cholinergic AEs [38]. If confirmed, these factors may contribute to the reduced incidence of AEs seen with donepezil *vs.* rivastigmine [29].

Gastrointestinal adverse events

The presence of cholinergic innervations in the parasympathetic nervous system means that the GI system

is most commonly affected by the administration of ChE inhibitors. Enhancement of cholinergic neurotransmission increases intestinal propulsion [39] and the secretion of hydrochloric acid, which is controlled by cholinergic vagal postganglionic fibres [40]. Indeed, the peripheral cholinergic origin of GI AEs associated with the ChE inhibitor tacrine was demonstrated in an early trial, when the use of glycopyrrolate (an antimuscarinic drug that does not enter the central nervous system) ameliorated its GI and other side-effects [41].

The low incidence of GI AEs following the use of donepezil in routine clinical practice has confirmed the good tolerability profile observed in earlier pivotal clinical trials [11–13]. For example, in one open-label study where patients were treated with donepezil 5 mg day^{-1} for 6 weeks in a clinical practice setting, the incidences of nausea and diarrhoea were 10% and 6%, respectively [42]. These results are similar to those reported for a pivotal clinical trial of donepezil 5 mg day^{-1}, where incidences of nausea and diarrhoea were 4% and 9%, respectively, compared with 4% and 7%, respectively, for placebo [12]. A further clinical practice study indicated that AEs, which generally occurred within the first few weeks of treatment, were of mild to moderate intensity, and tended to resolve without the need for dose modification [43]. In a German postmarketing surveillance study, the tolerability of donepezil was rated by physicians as 'very good' or 'good' in more than 90% of the 1989 patients assessed [44]. Low drop-out rates due to AEs (5–6%) were reported in this study, in a large multinational experience trial [45], and in a large community-based trial [46].

Despite the wide availability of tolerability data from trials of ChE inhibitors [10–14, 16–20], it is not possible to draw definitive and scientifically valid conclusions regarding the tolerability of one ChE inhibitor compared with another from individual placebo-controlled trials that may have different population characteristics.

Two 12-week, open-label, comparative trials of donepezil *vs.* rivastigmine [29] and donepezil *vs.* galantamine [47], designed to reflect the typical clinical experience, were conducted in accordance with the recommended dosing regimens from the respective product labelling available at the time [30–32]. In the donepezil *vs.* rivastigmine study, significantly more patients in the donepezil group (89%) completed the study compared with the rivastigmine group (69%; $P < 0.01$). Nausea and vomiting were reported in 42% and 24% of rivastigmine-treated *vs.* 11% and 7% of donepezil-treated patients, respectively [29]. These results are consistent with the findings of the pivotal trials of these medications [12,18]. In the donepezil *vs.* galantamine study, a greater proportion of patients receiving galantamine (46%) reported GI AEs compared with donepezil (25%) [47].

Weight loss

Anorexia and weight loss may be relevant in view of the association between weight loss and mortality in AD patients [48]. The effect of donepezil on the body weight of AD patients has been studied in nursing home residents who were older, had more comorbid illnesses, and more concomitant medications than patients in pivotal trials [49], and in patients with moderate to severe AD living in the community or in assisted living settings [45, 46]. In these trials the incidence of weight loss was very similar between donepezil- and placebo-treated patients; a total of 7–9% of donepezil- and 6–8% of placebo-treated patients experienced clinically significant weight loss (≥ 7% from baseline). These results are similar to those in a 1-year, placebo-controlled trial, where 6% of donepezil- and 4% of placebo-treated patients reported weight loss as an AE [23]. Clinically significant weight loss has also been reported in a greater proportion of patients treated with rivastigmine and galantamine compared with placebo [16, 20].

Cardiovascular adverse events

Pacemaker cells of the heart receive autonomic innervation via the vagal fibres releasing ACh to muscarinic receptors, the activation of which may slow heart rate [50]. Particular caution should be used when administering ChE inhibitors to patients with known sick sinus syndrome, but any patient receiving a ChE inhibitor might be at some risk of bradycardia or, rarely, heart block. However, in the pivotal AD trials of donepezil, atrioventricular block (first degree) was described infrequently (in 0.1–1% of patients) [31]. Physicians would be expected to exercise caution when prescribing ChE inhibitors to patients receiving other medications that may reduce heart rate, such as digoxin and beta-blockers.

No consistent patterns of clinically significant treatment effects in cardiovascular indices have been observed in the clinical trials of donepezil published to date, with no increase in serious arrhythmias found [11–13, 21–23, 26]. For example, a low incidence of bradycardia was observed in an analysis of donepezil phase II and III trial results [26] and in later trials, including a 1-year, placebo-controlled study conducted in Northern Europe [22]. The mean decrease in heart rate in donepezil-treated patients from the phase II and III trials

was −1.58 beats per min compared with an increase of 0.47 beats per min in the placebo-treated patients [26]. In addition, in the nursing home study [49], the incidence of clinically significant bradycardia was very similar in the placebo and donepezil treatment groups (5% *vs.* 6%, respectively). Furthermore, the results from two large (> 1200 patients), randomized, placebo-controlled trials of vascular dementia patients who were all on concomitant medication, showed no greater occurrence of bradycardia in the donepezil groups compared with the placebo groups [51, 52].

Syncopal events have been reported to be slightly increased in patients treated with ChE inhibitors. For example, syncope was recorded in 6% of donepezil- and 3% of placebo-treated patients in a 1-year, placebo-controlled trial conducted in Northern Europe [22]. However, none of these cases of syncope was considered related to the study drug, and all patients continued to take the drug [22].

Insomnia and abnormal dreams

Insomnia and other sleep disorders (abnormal dreams, vivid dreams and nightmares) have been reported following the administration of donepezil (8–18% donepezil *vs.* 5% placebo [11], 8% donepezil *vs.* 4% placebo [13], and 9% donepezil *vs.* 6% placebo [26], respectively). The increased incidence of insomnia and abnormal dreams may be related to the half-life and time of administration. Shorter-acting ChE inhibitors may achieve peak plasma levels well before the patient goes to sleep. Donepezil, particularly when administered in the evening, is likely to result in peak plasma concentrations during the night, given that donepezil has a t_{max} of 3–4 h [53]. The cholinergic system is thought to play a role in the regulation of rapid eye movement (REM) sleep, with cholinergic neurones in the laterodorsal and the pedunculopontine tegmental nuclei acting to promote REM sleep [54]. It has also been suggested that donepezil enhances REM sleep [55], which might explain the association of this treatment with abnormal dreams. When insomnia or abnormal dreams occur in donepezil-treated patients, switching to morning dosing may eliminate these events [56, 57]. Lengthening the time period before increasing the dose of donepezil from 5 to 10 mg day^{-1} can also reduce the incidence of insomnia to the levels of placebo-treated patients [31].

The use of donepezil in AD patients with comorbid conditions

Data concerning the tolerability of ChE inhibitors in AD patients with comorbidities are available from two types of clinical trials: firstly, from trials that evaluate the PK parameters and safety of ChE inhibitors in patients suffering from conditions that may affect AD patients (e.g. volunteers with hepatic or renal dysfunction); secondly, from trials investigating the safety and tolerability of ChE inhibitors in AD patients with a variety of comorbid conditions.

Tolerability of donepezil in patients with hepatic impairment

The effect of hepatic impairment on the PK and tolerability of ChE inhibitors is particularly important in the elderly, because liver volume and hepatic blood flow generally decrease with age [58].

Compared with healthy matched controls, data from single-dose studies of donepezil in patients with impaired hepatic function (chronic, compensated cirrhosis of the liver) [59], and from multiple-dose studies of donepezil in patients with hepatic impairment (not to exceed Grade B as defined by the Child-Pugh Classification [60]; reported elsewhere in this supplement) indicate that donepezil 5 mg day^{-1} is a safe and well-tolerated treatment.

Tolerability of donepezil in patients with renal impairment

Renal function also commonly declines with increasing age [61]. Single doses of donepezil can be safely administered to patients with moderately to severely impaired renal function (creatinine clearance < 30 ml min^{-1} (1.73 m^2 body surface area)$^{-1}$ [62]), and multiple doses can be safely administered to patients with moderately impaired renal function (creatinine clearance 17–33 ml min^{-1} (1.73 m^2 body surface area)$^{-1}$) (as described in this supplement).

Trials of AD patients with comorbid disease

AD patients with certain clinically significant, severe or unstable concurrent diseases, such as cardiac disease and severe obstructive pulmonary disease, were excluded from the pivotal trials of ChE inhibitors [12, 18, 20]. However, despite these restrictions, 97% of patients enrolled in the pivotal trials of donepezil had some prior or concurrent medical conditions [26]. Three later trials were designed specifically to evaluate the safety and efficacy of donepezil in 'real-world' patients with numerous comorbid illnesses [44–46]. In one community-based, open-label study conducted in 1035 patients, 70% reported AEs, with 9% reporting nausea and 10% diarrhoea [46]. This compares with 82% of patients reporting AEs (11% reporting nausea and 7% diarrhoea) from a comparable treatment group (donepezil 5 mg day^{-1} increased to 10 mg day^{-1} after 4 weeks) in the 1-year, placebo-controlled clinical trial conducted in Northern Europe [22].

Donepezil and concomitant drug interactions

The high prevalence of comorbid diseases in elderly AD patients inevitably results in patients taking many more prescribed medications than younger adults. In the community-based study mentioned above [46], 93% of patients took at least one concomitant medication. A lack of clinically significant drug–drug interactions is therefore an important consideration when prescribing ChE inhibitors in elderly patients.

Direct drug–drug interaction studies with ChE inhibitors

In vitro studies have shown that while donepezil is metabolized by CYP-3A4 and CYP-2D6, it has a low affinity for these enzymes. In addition, it has been calculated that the therapeutic concentrations of donepezil are more than 280-fold lower than the lowest K_i value obtained for CYP-2D6, and almost 800-fold lower than the K_i observed with CYP-3A4 [62]. This indicates that donepezil has minimal inhibitory activity against these isoenzymes, and is thus unlikely to have clinically significant interactions with other drugs metabolized by or affecting them [64].

Studies conducted in healthy volunteers on cimetidine (a nonspecific CYP inhibitor) [63], and ketoconazole (a specific CYP-3A4 inhibitor) [65], have confirmed that donepezil is not associated with CYP-mediated drug interactions. Furthermore, a similar PK study (reported elsewhere in this supplement) conducted with risperidone [66], which is metabolized by CYP-2D6 and 3A4 [67], has confirmed that donepezil is likely to be devoid of clinically meaningful drug–drug interactions with this and other medications.

In vitro, donepezil does not appear to affect the binding of furosemide, digoxin or warfarin to human albumin. Similarly, these drugs do not affect the binding of donepezil [31]. These findings were confirmed in studies conducted in healthy volunteers, in which donepezil was demonstrated not to interact with digoxin [68] and warfarin [69]. In addition, the PK profile of theophylline, a bronchodilator with a narrow therapeutic index, is also unaffected by the co-administration of donepezil [70]. Thus, despite some concerns regarding the high proportion of donepezil that is protein bound (96%), drug–drug interactions due to inhibition of protein binding are unlikely to occur with donepezil.

Drug–drug interactions in clinical trials of ChE inhibitors

Recent clinical evidence has demonstrated that concomitant medications should not act as a barrier to the use of donepezil in patients with AD. As reported above, in a large community-based US trial, 93% of patients were taking concomitant medications, most commonly aspirin (30%), vitamins (29%), antidepressants (24%), and analgesics other than aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) (21%) [46]. Interestingly, the risk ratios for GI AEs following treatment with donepezil were not significantly increased by the concomitant use of aspirin or other NSAIDs [46].

The action of ChE inhibitors at cholinergic nerve terminals can lead to pharmacodynamic interactions with a variety of medications targeted at cholinergic neurones. Antipsychotics, and particularly 'typical' agents such as haloperidol, which have anticholinergic properties, could antagonize the action of ChE inhibitors.

There is a theoretical risk of increased bradycardia in patients on concomitant beta-blockers and ChE inhibitors; however, an analysis of data from the same US open-label trial of donepezil indicated that the risk of developing clinically significant bradycardia is not significantly increased following the co-administration of beta-blockers, or nondihydropyridine calcium channel blockers or digoxin to donepezil-treated patients with AD [46]. Furthermore, in a very sick vascular dementia population with high rates of comorbidity and concomitant medication use, there was no difference in cardiovascular AEs between placebo and donepezil groups [51, 52].

ChE inhibitors may also prolong the action of neuromuscular blockers such as succinylcholine [71]. A synergistic effect between ChE inhibitors and succinylcholine or other similar neuromuscular blocking agents is a theoretical possibility [72, 73]. It is therefore advised that in ChE inhibitor-treated patients receiving emergency procedures requiring neuromuscular blockade, the anaesthetist should be aware of the potential for prolonged muscle relaxation [73].

Conclusions

Initial reservations over the use of ChE inhibitors in a frail elderly population have largely been overcome and ChE inhibitors are now routinely administered to AD patients, including those with concurrent medical conditions and those receiving numerous concomitant medications. With the greatest clinical experience (more than 770 million days of patient use) among the ChE inhibitors and the most extensive publication database for safety and tolerability (including the PK studies described in this supplement), a good tolerability and safety profile has been convincingly demonstrated for donepezil.

References

1 Ames DJ, Bhathal PS, Davies BM, Fraser JR, Gibson PR, Roberts S. Heterogeneity of adverse hepatic reactions to tetrahydroaminoacridine. Aust N Z J Med 1990; 20: 193–5.

2 Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 1994; 271: 992–8.

3 Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. JAMA 1994; 271: 985–91.

4 Coelho F, Birks J. Physostigmine for Alzheimer's disease. Cochrane Database Syst Rev 2001; 2: CD001499.

5 Kumar V. Introduction to cholinesterase inhibitors used in Alzheimer's disease therapy. In Alzheimer Disease: Therapeutic Strategies, eds Giacobini E, Becker R, Boston: Birkhäuser, 1994: 99–102.

6 Hammerlein A, Derendorf H, Lowenthal DT. Pharmacokinetic and pharmacodynamic changes in the elderly. Clin Pharmacokinet 1998; 35: 49–64.

7 Volicer L, Hurley AC. Physical status and complications in patients with Alzheimer disease: implications for outcome studies. Alzheimer Dis Assoc Disord 1997; 11(Suppl. 6): 60–5.

8 Rogers SL, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following single oral doses. Br J Clin Pharmacol 1998; 46(Suppl. 10): 1–6.

9 Rogers SL, Cooper NM, Sukovaty R, Pederson JE, Lee JN, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following multiple oral doses. Br J Clin Pharmacol 1998; 46(Suppl. 1): 7–12.

10 Rogers SL, Friedhoff LT, the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. Dementia 1996; 7: 293–303.

11 Rogers SL, Doody RS, Mohs RC, Friedhoff LT, the Donepezil Study Group. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. Arch Intern Med 1998; 158: 1021–31.

12 Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, the Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998; 50: 136–45.

13 Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, Rogers SL, Friedhoff LT. The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord 1999; 10: 237–44.

14 Whitehead A, Perdomo C, Pratt R, Birks J, Wilcock G, Grimley-Evans J. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: A meta-analysis of individual patient data from randomised controlled trials. Int J Geriatr Psychiatry 2004; 19: 624–33.

15 O'Brien JT, Ballard CG. Drugs for Alzheimer's disease, cholinesterase inhibitors have passed NICE's hurdle. BMJ 2001; 323: 123–4.

16 Corey-Bloom J, Anand R, Veach J for the ENA713 B352 Study Group. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998; 1: 55–65.

17 Rösler M, Retz W, Retz-Junginger P, Dennler H. Effects of two-year treatment with the cholinesterase inhibitor rivastigmine on behavioural symptoms in Alzheimer's disease. Behav Neurol 1998; 11: 211–16.

18 Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stahelin HB, Hartman R, Gharabawi M. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999; 318: 633–8.

19 Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD – a 6-month randomized, placebo-controlled trial with a 6-month extension. Neurology 2000; 54: 2261–78.

20 Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. Neurology 2000; 54: 2269–76.

21 Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E; Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001; 57: 613–20.

22 Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P; Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001; 57: 489–95.

23 Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD; "312" Study Group. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001; 57: 481–8.

24 Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003; 51: 937–44.

25 Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002; 72: 310–14.

26 Pratt RD, Perdomo CA, Surick IW, Ieni JR. Donepezil: tolerability and safety in Alzheimer's disease. Int J Clin Pract 2002; 56: 710–17.

27 Dronfield S, Egan K, Marsden CA, Green AR. Comparison of donepezil-, tacrine-, rivastigmine- and metrifonate-induced central and peripherally cholinergically mediated responses in the rat. J Psychopharmacol 2000; 14: 275–9.

28 Liston DR, Nielsen JA, Villalobos A, Chapin D, Jones SB, Hubbard ST, Shalaby IA, Ramirez A, Nason D, White WF. Pharmacology of selective acetylcholinesterase inhibitors: implications for use in Alzheimer's disease. Eur J Pharmacol 2004; 486: 9–17.

29 Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, Maud CM, Engelbrecht I, Hock C, Ieni JR, Bahra RS. A multinational, randomised, 12-week, comparative study of

donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. Int J Clin Pract 2002; 56: 441–6.

30 Reminyl® (galantamine HBr). Reminyl® (US package insert), March 2001. Titusville, NJ, USA: Janssen.

31 Aricept® (donepezil hydrochloride tablets). Aricept® (US package insert), December 2001. Teaneck, NJ, USA: Eisai Inc.

32 Exelon® (rivastigmine tartrate). Exelon® (US package insert), June 2001. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation.

33 Gauthier S, Bouchard R, Lamontagne A, Bailey P, Bergman H, Ratner J, Tesfaye Y, Saint-Martin M, Bacher Y, Carrier L, Charbonneau R, Clarfield AMM, Collier B, Dastoor D, Gauthier L, Germain M, Kissel C, Krieger M, Kushnir S, Masson H, Morin J, Nair V, Neirinck L, Suissa S. Tetrahydroaminoacridine-lecithin combination treatment in patients with intermediate-stage Alzheimer's disease. Results of a Canadian double-blind, crossover, multicenter study. N Engl J Med 1990; 322: 1272–6.

34 Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. The Tacrine Study Group. A controlled trial of tacrine in Alzheimer's disease. JAMA 1992; 268: 2523–9.

35 Wood PC, Castleden M. A double-blind, placebo-controlled, multicentre study of tacrine for Alzheimer's disease. Int J Geriatr Psychiatry 1994; 9: 649–54.

36 Sugimoto H, Limura Y, Yamanishi Y, Yamatsu K. Synthesis and anticholinesterase activity of 1-benzyl-4-[(5,6,-dimethoxy-1-indanon-2-yl) methyl]piperidine hydrochloride (E2020) and related compounds. Bioorg Medical Chem Lett 1992; 2: 871–6.

37 Ford JM, Truman CA, Wilcock GK, Roberts CJ. Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. Clin Pharmacol Ther 1993; 53: 691–5.

38 Imbimbo BP. Pharmacodynamic-tolerability relationships of cholinesterase inhibitors for Alzheimer's disease. CNS Drugs 2001; 15: 375–90.

39 Galligan JJ, Burks TF. Cholinergic neurones mediate intestinal propulsion in the rat. J Pharm Exp Ther 1986; 238: 594–8.

40 Lewin MJ. Cellular mechanisms and inhibitors of gastric acid secretion. Drugs Today (Barc) 1999; 35: 743–52.

41 Summers WK, Majovski LV, Marsh GM, Tachiki K, Kling A. Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type. N Engl J Med 1986; 315: 1241–5.

42 Greenberg SM, Tennis MK, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, Walsh KL, Corwin C, Daffner KR, Friedman P, Meadows ME, Sperling RA, Growdon JH. Donepezil therapy in clinical practice — a randomized crossover study. Arch Neurol 2000; 57: 94–9.

43 Matthews HP, Korbey J, Wilkinson DG, Rowden J. Donepezil in Alzheimer's disease: eighteen-month results from Southampton Memory Clinic. Int J Geriatr Psychiatry 2000; 15: 713–20.

44 Hager K, Calabrese P, Frolich L, Gobel C, Berger FM. An observational clinical study of the efficacy and tolerability of donepezil in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2003; 15: 189–98.

45 Boada-Rovira M, Brodaty H, Cras P, Baloyannis S, Emre M, Zhang R, Bahra R; 322 Study Group. Efficacy and safety of donepezil in patients with Alzheimer's disease: results of a global, multinational, clinical experience study. Drugs Aging 2004; 21: 43–53.

46 Relkin NR, Reichman WE, Orazem J, McRae T. A large community based, open-label trial of donepezil in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2003; 16: 15–24.

47 Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, Zhang R, Bahra R. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19: 58–67.

48 White H, Pieper C, Schmader K. The association of weight change in Alzheimer's disease with severity of disease and mortality: a longitudinal analysis. J Am Geriatr Soc 1998; 46: 1223–7.

49 Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM, Whalen E. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001; 49: 1590–9.

50 Dhein S, van Koppen CJ, Brodde OE. Muscarinic receptors in the mammalian heart. Pharmacol Res 2001; 44: 161–82.

51 Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, Pratt RD; Donepezil 308 Study Group. Donepezil in vascular dementia: a randomized, placebo-controlled study. Neurology 2003; 61: 479–86.

52 Black S, Roman GC, Geldmacher DS, Salloway S, Hecker J, Burns A, Perdomo C, Kumar D, Pratt R; Donepezil 307 Vascular Dementia Study Group. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke 2003; 34: 2323–30.

53 Tiseo PJ, Rogers SL, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following evening administration. Br J Clin Pharmacol 1998; 46(Suppl. 1): 13–18.

54 Monti JM, Monti D. Role of dorsal raphe nucleus serotonin 5-HT1A receptor in the regulation of REM sleep. Life Sci 2000; 66: 1999–2012.

55 Ringman JM, Simmons JH. Treatment of REM sleep behavior disorder with donepezil: a report of three cases. Neurology 2000; 55: 870–1.

56 Ross JS, Shua-Haim JR. Aricept-induced nightmares in Alzheimer's disease: 2 case reports. J Am Geriatr Soc 1998; 46: 119–20.

57 Gauthier S. Cholinergic adverse effects of cholinesterase inhibitors in Alzheimer's disease: epidemiology and management. Drugs Aging 2001; 18: 853–62.

58 Woodhouse K, Wynne HA. Age-related changes in hepatic function. Implications for drug therapy. Drugs Aging 1992; 2: 243–55.

59 Tiseo PJ, Vargas R, Perdomo CA, Friedhoff LT. An evaluation of the pharmacokinetics of donepezil HCl in patients with impaired hepatic function. J Clin Pharmacol 1998; 46(Suppl. 1): 51–5.

60 Pugh RNH, Murray-Lyon IM, Danson JL, Pietroni MC, Willians R.

Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973; 40: 646–54.

61 Lubran MM. Renal function in the elderly. Ann Clin Laboratory Sci 1995; 25: 122–33.

62 Tiseo PJ, Foley K, Friedhoff LT. An evaluation of the pharmacokinetics of donepezil HCL in patients with moderately to severely impaired renal function. Br J Clin Pharmacol 1998; 46(Suppl. 1): 56–60.

63 Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and cimetidine: assessment of pharmacokinetic changes following single and multiple doses. Br J Clin Pharmacol 1998; 46(Suppl. 1): 25–9.

64 VanDenBerg CM, Kazmi Y, Jann MW. Cholinesterase inhibitors for the treatment of Alzheimer's disease in the elderly. Drugs Aging 2000; 16: 123–38.

65 Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCL and ketoconazole: assessment of pharmacokinetic changes following single and multiple doses. Br J Clin Pharmacol 1998; 46(Suppl. 1): 30–4.

66 Reyes JF, Preskorn SH, Khan A et al. Concurrent administration of donepezil HCL and risperidone in patients with schizophreria: assessment of pharmacokinetic changes and safety following multiple oral doses. Br J Clin Pharmacol; 58(Suppl. 1): 50–7.

67 Fang J, Bourin M, Baker GB. Metabolism of risperidone to 9-hydroxyrisperidone by human cytochrome P450 2D6 and 3A4. Naunyn Schmiedebergs Arch Pharmacol 1999; 359: 147–51.

68 Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and digoxin: assessment of pharmacokinetic changes. Br J Clin Pharmacol 1998; 46(Suppl. 1): 40–4.

69 Tiseo PJ, Foley K, Friedhoff LT. The effect of multiple doses of donepezil HCl on the pharmacokinetic and pharmacodynamic profile of warfarin. Br J Clin Pharmacol 1998; 46(Suppl. 1): 45–50.

70 Tiseo PJ, Foley K, Friedhoff LT. Concurrent administration of donepezil HCl and theophylline: assessment of pharmacokinetic changes following a multiple-dose administration in healthy volunteers. Br J Clin Pharmacol 1998; 46(Suppl. 1): 35–9.

71 Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. Drug Safety 1996; 15: 261–73.

72 Heath ML. Donepezil, Alzheimer's disease and suxamethonium. Anaesthesia 1997; 52: 1018.

73 Walker C, Perks D. Do you know about donepezil and succinylcholine? Anaesthesia 2002; 57: 1041.