Review Article Open Acces

Introduction

Pharmacokinetics: Donepezil is metabolized by the hepatic enzymes, CYP 450 isoenzymes 2D6 and 3A4, and undergoes hepatic glucuronidation. Donepezil may interact with drugs that inhibit these enzymes, such as cimetidine, ketoconazol, paroxetine, uoxetine and uvoxamine. Cimetidine and ketoconazol increase donepezil plasma concentrations. ese interactions were not considered clinically signi cant according to the United States Food and Drug Administration (FDA) guidelines. Formal pharmacokinetic studies have shown that donepezil does not inhibit the metabolism of theophylline, warfarin, cimetidine, or digoxin in healthy subjects [9-14]. e metabolites of donepezil are excreted in urine (5-O-desmethyl donepezil, 6-O-desmethyl donepezil, donepezil-cis-N-oxide, etc), about 11-17% of which are unchanged [15]. Pharmacokinetic properties have been assessed mainly in patients with AD. Tmax and elimination half-life (t1/2) are longer in elderly than in younger volunteers, the volume of distribution (Vd), larger than in younger volunteers [15]. e longer t1/2 in the elderly may be attributed to the increase in the steady state volume of distribution throughout the whole body since drug clearance is similar in the elderly and the young [15].

Tolerability: Cholinergic nerves are found throughout the human body, suggesting that a number of tissues and organs could be a ected with inhibition of ChE. e most common donepezil-related adverse events are gastrointestinal symptoms, including diarrhea, nausea, vomiting, abdominal pain or abdominal distention, and can be attributed to the cholinergic action of the drug.

e occurrence of the predominant cholinergic adverse events is most pronounced in the rst few weeks a er initiating treatment. e incidence of side e ects is higher during initiating to treatment or when doses are increased before steady-state is achieved. Rapid dose titration schedules had typically been used in most pivotal clinical trials of donepezil, in that patients randomized to donepezil 10 mg per day received donepezil 5 mg per day for the rst 7 days and then 10 mg per day therea er. However, in those trials, donepezil has been generally well tolerated and most of the adverse events are transient and generally mild in severity [16-19]. Subsequent trials have suggested that the rate of adverse events can be reduced by lengthening the period of time patients receive the lower dose before the higher dose initiated, with nausea reported by 11% and diarrhea by 7% of patients treated with donepezil 10 mg per day titrated up a er 28 days on 5 mg, vs. 9% and 7%, respectively, for placebo [19,20]. Clinical physicians would be expected to exercise caution when prescribing ChEIs particularly to patients with known sick sinus syndrome, or who receiving other medications that may reduce heart rate, such as digoxin and beta-blocker. Any patient receiving ChEIs can be at some risk of bradycardia or cardiac block. However, in the pivotal clinical trials of donepezil, no consistent patterns of clinically signi cant treatment e ects in cardiovascular indices have been reported to date, with no increase in serious arrhythmias found [16, 18,20-23].

Dosage and administrationIn the treatment of mild to moderate AD, donepezil is given once daily in a dose of 5-10 mg, beginning with a dosage of 5 mg per day. An initial dose should be maintained for 4-6 weeks before increasing to 10 mg. A dose of 23 mg once daily can be administered once patients with severe AD have taken a dose of 10 mg once daily for at least 3 months. In Japan, the recommended dose are lower than in other countries (3 mg daily increasing to 5 mg a er 2-3 weeks), because of retrospective pharmacokinetic analysis and population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with AD. However, according to an extension of the donepezil label to severe AD in 2007, a dose of 5-10 mg have been approved in Japan.

Clinical evidence supporting the use of donepezil against dementia with Lewy bodies

e rst trial of a ChEI for the treatment of DLB or Parkinson's disease dementia (PDD) was a small, open-label study of patients treated with tacrine, who showed improvement in cognition and visual hallucinations [24]. e similar case report and case series literature suggested that donepezil was also an e ective treatment for DLB, particularly with respect to neuropsychiatric symptoms, and several reports highlighting improvements in uctuating confusion [25-30]. Shea et al. reported in 1998, that treatment of nine DLB patients with donepezil for 12 weeks most commonly improved hallucinations, and sometimes improved cognition and overall function [30] (Table 1).

Other preliminary study showed that patients with DLB exhibited greater cognitive improvement on the Mini-Mental State Examination (MMSE) scale than patients with AD [29]. Both DLB and AD patients were prescribed donepezil 5 mg per day and, at baseline and at 6 months, underwent cognitive testing with the MMSE and assessment of psychological assessment using the Behavioral Symptoms in Alzheimer's Disease (BEHAVE-AD) scale. AD patients had only a slight increase in cognitive scores, while DLB patients' mean MMSE scores increased to a signi cantly greater degree. An increase in MMSE scores across 6 months of treatment correlated with an improvement in BEHAVE-AD scores [29].

In 2004, Aarsland et al. reviewed 14 small studies that focused on ChEI treatment in patients with DLB or PDD [31]. ese studies had an

placebo-controlled study [33]. In this study, PDD patients (n=550) were randomized to donepezil (5 or 10 mg) or placebo for 24 weeks. Two scales, the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) and Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC1; global function), were originally de ned as coprimary end points. CIBIC1 mean changes from baseline to week 24 showed signi cant bene t for the 10-mg group, but not 5-mg group. ADAS-cog did not revealed signi cant bene ts for both donepezil doses compared with placebo. A few years later, the authors reanalyzed the results removing the treatment-by-country interaction term from the model and suggested that the alternative ADAS-cog analysis revealed dose dependent bene t with donepezil [34].

More recently, Mori et al. reported a randomized, placebo-controlled trial of 140 DLB patients who received placebo or 3, 5 or 10 mg of donepezil daily for 12 weeks [35]. is exploratory study had no prespeci ed primary endpoint but rather examined a variety of cognitive, behavioral, global function, and caregiver outcomes. E cacy was assessed at baseline and at weeks 4, 8, and 12. At the nal evaluation, 5 or 10 mg donepezil treated patients bene ted from a 2.0 to 3.8 points on the MMSE, which is a larger di erence than that reported in other studies of ChEIs in DLB, AD and PDD. e Neuropsychiatric Inventory (NPI) scores were signi cantly more improved over the course of the study in the 5 mg and 10 mg donepezil groups compared with placebo. Signi cant improvements were also seen in several neuropsychiatric domains a ected by DLB, especially delusions, hallucinations and cognitive uctuations, for patients receiving donepezil. Global function scores also were signi cantly higher in all active treatment groups compared with placebo. Caregiver scores were improved in the 10-mg group only compared with placebo, and that di erence was not signi cant a er baseline adjustments.

Furthermore, the same research group reported the safety and e cacy of long-term administration of donepezil in patients with DLB [36]. 108 patients enrolled in the 52-week, multicenter, open-label extension study, showed improvements in cognitive function and dementia-related behavioral symptoms, including cognitive uctuations, a er the start of donepezil treatment, and improvement was maintained for 52 weeks. Reduction in caregiver burden observed in the preceding RCT returned to the baseline level at 52 weeks.

ere is some evidence that di erent types of anti-dementia drugs also may be e ective in the treatment of DLB. A multicenter trial of rivastigmine in 120 DLB patients for 20 weeks, published in 2000, reported that rivastigmine (mean 7 mg/day) provided signi cantly greater bene t than placebo [37]. In this study, 30% improvements were shown in a four-item NPI subscore(delusions, hallucinations, apathy, anxiety) as the primary outcome measure. Although not statistically signi cant, attentional performance in the rivastigmine treated patients also improved with a mean one-point advantage on the MMSE. e preliminary literature relating to use of rivastigmine in DLB emphasized the need for an RCT, which culminated in a large, parallel-group RCT of rivastigmine in 541 patients with DLB for 24 weeks [38]. Over the treatment period, rivastigmine-treated patients bene ted from a mean one-point advantage on the MMSE, an almost three-point mean advantage on the ADAS-cog. e mean total NPI score also improved signi cantly, albeit modestly, by two points, although no speci c breakdown of bene ts in speci c subscores was reported. ere was no overall signi cant worsening of parkinsonism, but, compared with placebo, there was a signi cant increase in tremor as a reported adverse event in the rivastigmine-treated patients and an increased likelihood of nausea and vomiting. Mortality rates were signi cantly lower te 0 0 9 42.5(s)-8(e)-6(a a)9(o)11.9(m 3.9(d v)(e r)Dw 9 0 0 9 42.5197 1 Tf 0.3

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