Use of ultra-low-dose (≤6 mg) doxepin for treatment of insomnia in older people

Carlos H. Rojas-Fernandez, BSc(Pharm), PharmD; Yannan Chen, BMSc, BSc(Pharm)

CARLOS H. ROJAS-FERNANDEZ

ABSTRACT

Background: Insomnia is one of the most frequent complaints encountered in primary care practice, one that results in significant clinical consequences and cost burden to the public health system. It is more common in elderly adults (≥65 years of age), with frequent complaints regarding sleep maintenance and early morning wakening. Current treatment options have limitations. This review was conducted to evaluate the evidence behind ultra-low-dose doxepin in insomnia and to discuss its potential advantages, its place in therapy and its implications in practice in the treatment of older patients.

Methods: A systematic literature search was conducted of MEDLINE via Ovid, PubMed and EMBASE using the MeSH and key terms "doxepin," "sleep initiation and maintenance disorders," "insomnia," and "low dose." Only randomized controlled trials comparing 3 mg and/or 6 mg of doxepin to placebo and involving participants diagnosed with primary insomnia were included. Primary outcomes for this review were objective sleep study parameters.

Results: Five studies were identified, 3 of which (n = 571) were conducted in older adults. Doxepin 3 mg and 6 mg significantly reduced waking after sleep onset and increased total sleep time. There was no significant difference between the 2 doses of doxepin. Latency to persistent sleep did not differ significantly compared with placebo for any doses of doxepin. The most frequent adverse events reported were somnolence and headache. Adverse events did not appear to be dose-related, and studies reported the incidence of adverse effects to be comparable to placebo.

Conclusion: Doxepin 3 mg and 6 mg significantly improved and sustained sleep maintenance and sleep duration into the last third of the night but did not significantly affect sleep onset. Sleep benefits were achieved without next-day residual or discontinuation effects. Doxepin appears to be well suited for managing insomnia in older people. *Can Pharm J (Ott)* 2014;147:281-289.

Introduction

Insomnia disorder is defined as a predominant complaint of dissatisfaction with sleep quantity or quality, associated with 1 or more of the following symptoms: difficulty initiating and/or maintaining sleep and early morning awakening (with inability to return to sleep), all of which cause clinically significant distress or impairment in daily functioning (e.g., social, academic, vocational, etc.). It occurs at least 3 nights per week, has been present for at least 3 months and occurs despite adequate opportunity for sleep.[1,2] Estimates of its prevalence vary, and according to the Canadian Community Health Survey conducted in 2002, an estimated 13.4% of Canadians aged 15 or older have experienced insomnia.[3] In other words, 1 in 7 people experience difficulties initiating or maintaining sleep or have nonrestorative sleep. Insomnia leads to significant clinical consequences and cost burden on the public health

Insomnia pharmacotherapy can be challenging in older people, and until recently there has been a lack of new medications that might represent desirable alternatives. We therefore sought to evaluate the evidence for ultra-low-dose doxepin in the management of insomnia, with a particular focus on its use in older patients.

La pharmacothérapie contre l'insomnie chez les personnes âgées est un défi. Jusqu'à tout récemment, peu de nouveaux médicaments constituaient des alternatives intéressantes. Nous avons donc évaluer les données concernant l'usage de la doxépine à dose ultra faible pour la prise en charge de l'insomnie, avec une attention particulière aux personnes âgées.

DOI: 10.1177/1715163514543856

KNOWLEDGE INTO PRACTICE

- Doxepin 3 mg and 6 mg significantly improves and sustains sleep maintenance and sleep duration into the last quarter of the night but does not significantly affect sleep onset.
- Sleep benefits are achieved without next-day residual effects or discontinuation effects. The most frequent side effects with doxepin were headache and somnolence/sedation.
- Doxepin appears to be well tolerated in older people.
- Doxepin may be initiated starting at 6 mg nightly for adults and 3 mg for older (≥65 years) people.

system, and the indirect costs from absenteeism and lost productivity are higher than the direct costs of its treatment.[4] Due to the high prevalence and concurrent presentation of insomnia with other comorbid conditions, it is important not to underestimate the negative impact of insomnia on long-term health outcomes and to initiate treatment when indicated.

Insomnia in the elderly and limits of current medications

Compared with younger adults, older people (≥65 years of age) are more likely to suffer from insomnia, with prevalence estimates doubling from 10% at ages 15 to 24 to about 20% at age 75 or older.[2,3] With an aging population, an increase in the percentage of Canadians suffering from insomnia can be expected in the future. Insomnia has also been found to be more severe in this population, with frequent complaints regarding problems with sleep maintenance and early morning awakening.[5,6] Consequences of disturbed sleep in older people include impairments in memory, concentration, daytime performance at work or while driving and increased risk of falls.[7,8]

While nonpharmacological approaches are important for managing insomnia, pharmacotherapy is often necessary in treating patients with insomnia.[7,9] Benzodiazepine receptor agonists and benzodiazepines are typically considered first-line agents for the management of insomnia.[7,8] These drugs are associated with important adverse effects in older people, such as falls and fractures, cognitive impairment, withdrawal symptoms, rebound insomnia, carryover sedation and increased risk of drug dependence and abuse.[10] Other commonly used drugs in this population include trazodone, mirtazapine and melatonin, and while the latter is thought to be safe, evidence of efficacy for these agents is inconsistent and additional pharmacotherapeutic options are welcome and necessary.[7,8]

Rationale for ultra-low-dose doxepin

Histamine is one of the key neurotransmitters of wakefulness, so it is not surprising that doxepin, a drug with selective histamine H_1 receptor blockade, has been recently introduced as a new agent for insomnia in Canada.[11] Historically, doxepin has been used to treat depression and anxiety disorders, with its sedative effects improving disrupted sleep.[12] At antidepressant doses (25-300 mg per day), however, doxepin possesses significant anticholinergic and antinoradrenergic properties, leading to dose-limiting side effects.[12] This may be explained by its pharmacology, because at doses exceeding 25 mg, doxepin's selectivity for H_1 receptors is lost and additional receptors (e.g., muscarinic, noradrenergic) are affected.[13] In contrast, ultralow doses of doxepin (3 mg and 6 mg per day) appear to exhibit potent and highly selective H_1 receptor antagonism and are nearly free from antimuscarinic effects.[5,6,10,12,13,14] Marketed as Silenor, ultra-low-dose doxepin has been available in the United States to treat insomnia since 2010 and is currently available in Canada for insomnia characterized by frequent nocturnal awakening and/or early morning awakenings.[15,16]

The objective of this clinical review is to evaluate the evidence supporting the use of ultra-low-dose doxepin in insomnia and in particular to discuss its potential advantages as an alternative to currently available sedative hypnotics in elderly people.

Methods

Search strategy

A literature search was performed using MEDLINE (1966 to August 2013, terms used: "doxepin" AND "Sleep Initiation and Maintenance Disorders"), International Pharmaceutical Abstracts (1970 to August 2013) and All Ovid MEDLINE (1946-August 2013), using the terms doxepin AND insomnia AND low dose. No additional filters were applied.

Study selection

Titles and abstracts from the search results were independently screened by the 2 authors. Selection of studies was based on the following

TABLE 1 Summary of study characteristics of ultra-low-dose doxepin in randomized placebo-controlled trials in chronic primary insomnia

Studies	Sample size	% completed (No. of dropouts)	Mean age, years (range)	Design	Placebo wash-in	Doxepin doses, mg	Duration, days	Outcomes	
								Self-report	PSG
Adults (age <65 years)									
Roth et al. 2007[13]	67	98.5 (1)	42.4 (18-64)	Cross-over	Yes	1, 3, 6	*	Yes	Yes
Krystal et al. 2011[14]	229	89 (26)	44.5 (18-64)	Parallel	Yes	3, 6	35	Yes	Yes
Older adults (age ≥65 years)									
Scharf et al. 2008[10]	76	96.1 (3)	71	Cross-over	Yes	1, 3, 6	*	Yes	Yes
Krystal et al. 2010[5]	240	89 (26)	71.4 (64-93)	Parallel	Yes	1, 3	84	Yes	Yes
Lankford et al. 2012[6]	254	93 (18)	72.5 (64-91)	Parallel	Yes	6	28	Yes	No

PSG, polysomnogram.
*Five 2-day treatment periods with a 5- or 12-day drug-free interval between treatment periods.

inclusion criteria: randomized, placebo or active-controlled trials; participants with primary insomnia; and doxepin doses not exceeding 6 mg nightly. Given the paucity of studies, we did not exclude studies conducted in nonelderly populations, in order to provide a complete dataset of efficacy and safety. Studies were excluded if they involved healthy subjects with normal sleep habits or if they classified low-dose doxepin as 25 to 50 mg. All studies included for this review were agreed upon by the 2 authors.

Data extraction, synthesis and analysis

Data were extracted from the studies based on standard polysomnographic (PSG) measured and patient-reported/subjective sleep outcomes, which include wake after sleep onset (WASO), sWASO (the subjective WASO), total sleep time (TST), subjective total sleep time (sTST), latency to persistent sleep (LPS), latency to sleep onset (LSO) and sleep quality.[2] Standardized effect sizes were calculated wherever possible.[17] All available data regarding adverse effects were extracted.

Results

Study characteristics

Five randomized controlled trials (RCTs) met the inclusion criteria and were included in this review (Table 1). Two studies involved adult patients (aged 18-64 years; mean age 42-45 years) and 3 involved elderly patients (aged ≥65 years; mean age 71-73 years). All studies used DSM-IV-TR to diagnose primary insomnia in a total 867 study participants. No active control trials were identified.

Efficacy

In adult patients (Table 2), WASO was significantly reduced (on average) by 14.4 minutes, 20.15 minutes and 23 minutes for doxepin 1 mg, 3 mg and 6 mg, respectively. TST was significantly increased on average by 17.9 minutes, 24.6 minutes and 30.4 minutes for doxepin 1 mg, 3 mg and 6 mg, respectively. At the 6 mg dose, LPS was significantly reduced by 5.7 minutes in 1 study.[13]

Results for subjective measures among adult patients were somewhat varied, with statistically significant findings for sWASO in 1 study for doxepin 3 mg and 6 mg and significant reductions in LSO in 2 studies for 6 mg doxepin and 1 study for doxepin 3 mg.[13,14] Sleep quality was significantly better in both studies for doxepin at the 6 mg dose ($p < 0.05$).

In older patients (Table 2), WASO was significantly reduced on average by 15.3, 28.2 and 34 minutes for 1 mg, 3 mg and 6 mg, respectively. TST was significantly increased on average by 14.4, 30.2 and 37.7 minutes for 1 mg, 3 mg and 6 mg, respectively. LPS was not significantly different than placebo for any doxepin doses across adult or elderly studies (Table 2). Patient-reported measures were significantly better for sWASO and sTST at the 1, 3 and 6 mg doses, while LSO results were significant for doxepin 6 mg in one of the studies and for doxepin 1 mg

TABLE 2 Summary of mean polysomnographic (PSG) and subjective sleep measures

	PSG				Subjective			
Study outcomes	PBO, min	DXP 1 mg, min (%)	DXP 3 mg, min (%)	DXP 6 mg, min (%)	PBO, min	DXP 1 mg, min (%)	DXP 3 mg, min (%)	DXP 6 mg, min (%)
Sleep onset	LPS % reduction compared with PBO				LSO % reduction compared with PBO			
Roth et al. 2007[13]	33	29.6 (10.3)	30.1 (8.8)	27.3 (17.3)	49.6	46.5	45.3	43*
Krystal et al. 2011[14]	36.9	NA	31 (16)	27.8 (24.7)	NR	NA	NR	NR†
Scharf et al. 2008[10‡]	26.8	28 (4.5)	23.2 (13.4)	22.4 (16.4)	45.5	42.4 (6.8)	42.7 (6.2)	33.8* (25.7)
Krystal et al. 2010[5‡]	34.9	29 (16.9)	37.5 (2.6)	NA	55.5	37.5* (32)	39.9* (28)	NA
Lankford et al. 2012[6‡§]	NA	NA	NA	NA	NS	NA	NA	NS
Sleep maintenance	WASO % reduction compared with PBO				sWASO % reduction compared with PBO			
Roth et al. 2007[13]	61.1	46.7* (23.6)	38.9* (36.3)	38.1* (37.6)	54.4	56.4	49.4	45.1
Krystal et al. 2011[14]	62.5	NA	44.4* (28.9)	39.5* (36.8)	NR	NA	NR†	NR†
Scharf et al. 2008[10‡]	98	80* (18.4)	71* (27.6)	64* (34.7)	89.3	74.1 (17)*	69.3 (22.4)*	70.2 (21.4)*
Krystal et al. 2010[5‡]	109.2	97* (11)	75.7* (31)	NA	NA	NA	NA	NA
Lankford et al. 2012[6‡§]	NA	NA	NA	NA	78.9	NA	NA	66.5 (15.7)*
Sleep duration	TST % increase compared with PBO				sTST % increase compared with PBO			
Roth et al. 2007[13]	389.6	407.5* (4.6)	415.4* (6.6)	418.4* (7.4)	364.2	364.8	380.0	380.7*
Krystal et al. 2011[14]	385	NA	408.5* (6.1)	417* (8.3)	NR	N/A	NR†	NR†
Scharf et al. 2008[10‡]	360.7	377.4* (4.6)	390.6* (8.3)	398.4* (10.5)	340	356.6* (4.9)	364.2* (7.1)	370.8 (9.1)*
Krystal et al. 2010[5‡]	343.7	360.5* (4.9)	373.3* (8.6)	NA	326	371.5* (14)	389.4* (19)	NA
Lankford et al. 2012[6‡§]	NA	NA	NA	NA	336.4	NA	NA	346.1* (2.9)

DXP, doxepin; LPS, latency to persistent sleep; LSO, latency to sleep onset; NA, not applicable; NR, not reported; NS, nonsignificant; PBO, placebo; sWASO, subjective WASO; TST, total sleep time; WASO, wake after sleep onset.

*$p < 0.05$.

†Study only reported that findings were statistically significant but did not provide absolute values.

‡Studies conducted in elderly patients.

§Study only collected subjective efficacy measures (i.e., patient-reported outcomes).

and 3 mg in a second study (reductions of 18 and 16 minutes, respectively).[5,6,10] Sleep quality was noted to be better for doxepin at 1, 3 and 6 mg doses ($p < 0.05$).[5,6,10]

Last, 4 of the 5 studies documented better sleep efficiency for doxepin 3 mg and 6 mg overall and during the last third of the night.[5,10,13,14] Specifically, for the last third of the night, studies in adults revealed sleep efficiencies of 86% to 88% for doxepin 3 mg, 89% for doxepin 6 mg and 80% for placebo; studies in older people documented sleep efficiency of 76% to 79% for doxepin 3 mg, 81% for doxepin 6 mg and 65% to 69% for placebo.

Standardized effect size results

Standardized mean differences can be found in Table 3. As can be seen, doxepin's effect on sleep latency (LPS) tended to be small and dose-related, while its effects on sleep maintenance (WASO) and total sleep duration (TST) were larger and consistent with the proposed mode of action of this medication.[5,10,13]

Safety

The most frequently reported adverse events (Table 3) among patients taking doxepin were somnolence (2%-9% vs 3%-5% for placebo) and headache (1%-6% vs 5%-14% for placebo).

TABLE 3 Standardized mean difference of doxepin compared with placebo

Mean effect size *d*	PSG (Objective)			Subjective		
	DXP 1 mg vs PBO	DXP 3 mg vs PBO	DXP 6 mg vs PBO	DXP 1 mg vs PBO	DXP 3 mg vs PBO	DXP 6 mg vs PBO
Sleep onset	LPS (95% CI)			LSO (95% CI)		
Roth et al. 2007[13]	−0.16 (−0.50 to 0.19)	−0.14 (−0.48 to 0.21)	−0.27 (−0.61 to 0.07)	*	*	*
Krystal et al. 2011[14]	*	0.2	0.32	*	*	*
Scharf et al. 2008[10†]	0.056 (−0.26 to 0.38)	−0.2 (−0.52 to 0.13)	−0.26 (−0.59 to 0.06)	−0.09 (−0.42 to 0.23)	−0.07 (−0.40 to 0.25)	−0.38 (−0.71 to −0.06)
Krystal et al. 2010[5†]	−0.2 (−0.51 to 0.12)	0.08 (−0.23 to 0.39)	*	−0.55 (−0.87 to −0.24)	−0.32 (−0.63 to −0.01)	*
Lankford et al. 2011[6†]	*	*	*	*	*	*
Sleep maintenance	WASO (95% CI)			sWASO (95% CI)		
Roth et al. 2007[13]	−0.372 (−0.72 to −0.03)	−0.59 (−0.94 to −0.24)	−0.62 (−0.97 to −0.28)	*	*	*
Krystal et al. 2011[14]	*	0.58	0.72	*	*	*
Scharf et al. 2008[10†]	*	*	*	−0.26 (−0.58 to 0.07)	−0.34 (−0.66 to −0.01)	−0.32 (−0.65 to 0)
Krystal et al. 2010[5†]	−0.26 (−0.57 to 0.06)	−0.75 (−1.07 to −0.43)	*	*	*	*
Lankford et al. 2011[6†]	*	*	*	*	*	−0.25 (−0.49 to 0)
Sleep duration	TST (95% CI)			sTST (95% CI)		
Roth et al. 2007[13]	0.42 (0.073 to 0.76)	0.61 (0.26 to 0.96)	0.70 (0.35 to 1.05)	*	*	*
Krystal et al. 2011[14]	*	0.48	0.72	*	*	*
Scharf et al. 2008[10†]	0.41 (0.08 to 0.73)	0.7 (0.37 to 1.04)	0.98 (0.64 to 1.32)	0.25 (−0.08 to 0.57)	0.35 (0.03 to 0.68)	0.45 (0.12 to 0.78)
Krystal et al. 2010[5†]	0.32 (0 to 0.63)	0.59 (0.28 to 0.91)	*	0.65 (0.33 to 0.97)	0.88 (0.56 to 1.20)	*
Lankford et al. 2011[6†]	*	*	*	*	*	0.15 (−0.01 to 0.39)

d ~ 0.2 = small effect, *d* ~ 0.5 = moderate effect, *d* ~ 0.8 = large effect. Negative sign signifies decrease and positive number signifies increase. DXP, doxepin; LPS, latency to persistent sleep; LSO, latency to sleep onset; PBO, placebo; sWASO, subjective WASO; TST, total sleep time; WASO, wake after sleep onset;.

*Unable to calculate due to missing information.

†Studies conducted in older adults.

Adverse events did not appear to be dose-related, and all adverse effects were comparable to placebo in terms of frequency.[6,13,14] No clinically relevant changes were noted in laboratory parameters, vital signs or electrocardiograms.[5,6,13,14] Discontinuation rates due to adverse events for doxepin were comparable to placebo and ranged from 1% to 4%.[5,13,14] No next-day residual sedation/

TABLE 4 Summary of adverse events reported in more than 2% of patients

Adverse events	PBO	DXP 1 mg	DXP 3 mg	DXP 6 mg
Any adverse event (%)*				
Roth et al. 2007[13]	9	14	8	12
Krystal et al. 2011[14]	27	NR	35	32
Scharf et al. 2008[10†]	10	12	8	7
Krystal et al. 2010[5†]	52	40	38	NR
Lankford et al. 2011[6†]	27	NR	NR	31
Somnolence/sedation (%)				
Roth et al. 2007[13]	0	2	2	4
Krystal et al. 2011[14]	5	NR	9	8
Scharf et al. 2008[10†]	NA	NA	NA	NA
Krystal et al. 2010[5†]	5	5	2	NR
Lankford et al. 2011[6†]	3	NR	NR	9
Headache (%)				
Roth et al. 2007[13]	5	5	0	1
Krystal et al. 2011[14]	10	NR	5	0
Scharf et al. 2008[10†]	NA	NA	NA	NA
Krystal et al. 2010[5†]	14	3	6	NR
Lankford et al. 2011[6†]	4	NR	NR	0

DXP, doxepin; NA, not available; NR, data not reported; PBO, placebo.
*"Any adverse event" included nausea, diarrhea and dizziness.
†Studies conducted in older adults.

impairment was noted as assessed by psychomotor testing using digit symbol substitution test, symbol coping test and visual analog scale.[5,10,13] Withdrawal effects and rebound/worsening insomnia were not significantly different compared with placebo for all doses of doxepin, although this was only assessed in 1 study.[14] Last, in 2 of the studies in older people,[6,10] there were no reports of adverse effects that might be attributable to anticholinergic effects, while in the third study, it was noted that these side effects were rare and occurred at a similar incidence across the placebo and 2 doxepin doses (1 and 3 mg).[5]

Discussion

Results from the studies reviewed here support the notion that in low doses, doxepin has promising advantages over current pharmacotherapies for insomnia and in particular for older adults. At 3 mg and 6 mg, doxepin significantly reduced WASO, increased TST and improved sleep efficiency and sleep quality. The clinical relevance of improving sleep efficiency, improving sleep maintenance and reducing early awakenings with no next-day residual effects is particularly germane for older people, as they most frequently report nocturnal and early awakenings and typically have reduced total sleep time.[5,6,10] Sustained sleep maintenance and longer sleep duration that persisted into the last quarter of the night were observed in all studies.[5,6,10,13,14] These findings may be explained by histamine's role in sleep regulation, as histamine activity is higher toward the latter half of the night, while upon wakening a substantial surge in histamine release and other arousal neurotransmitters would be expected to overwhelm doxepin-induced H_1

antagonism, thus preventing major carryover sedative effects.[10,18] The fact that doxepin did not significantly decrease sleep onset latency compared with placebo may be due to the slower absorption of doxepin.[19]

The absolute effects of –28 to –34 minutes for WASO, +30 to +38 minutes for TST and improved sleep efficiency from PSG data are clinically relevant as defined in sleep medicine but, perhaps more important, are also corroborated by patient-reported subjective outcomes, including sleep quality. Whether these findings translate into effects on overall quality of life, lower rates of falls and other iatrogenic complications will require further study.[2,7]

The most frequent complaints reported with doxepin in the clinical trials were headache and somnolence/sedation. Data from all 5 trials support the conclusion that at all dosages studied (1-6 mg per night), the incidence of doxepin-related adverse effects was comparable to placebo.[5,6,10,13,14] Furthermore, doxepin was not associated with anticholinergic effects, cognitive impairment or discontinuation effects such as rebound insomnia or withdrawal symptoms.[5,6,10,13,14]

Indirect comparison of efficacy to current treatments

A meta-analysis of the effectiveness of nonbenzodiazepines in treatment of adult insomnia reported a small effect on sleep onset, LPS or LSO (PSG: –0.36, 95% CI –0.57 to –0.16; subjective: –0.33, 95% CI –0.62 to –0.04); a small effect on sleep maintenance, WASO (PSG: –0.24, 95% CI –0.72 to 0.24; subjective: –0.16, 95% CI –0.60 to 0.28); and a moderate effect on sleep duration, TST (PSG: 0.41, 95% CI –0.51 to 1.32; subjective: 0.45, 95% CI –0.08 to 0.98).[19] Similarly, a recent meta-analysis involving benzodiazepines for chronic insomnia reported a moderate effect on sleep onset (0.56, 95% CI 0.41 to 0.71) and a large effect on total sleep duration (0.71, 95% CI 0.55 to 0.87).[20] A comparison of effect sizes (albeit an imperfect and indirect comparison) between doxepin, benzodiazepines and nonbenzodiazepines would suggest that doxepin may be better than nonbenzodiazepines at improving sleep maintenance and sleep duration and may be similar to benzodiazepines at increasing sleep duration. Nonbenzodiazepines and benzodiazepines would appear to be more effective than doxepin in reducing sleep onset latency, with a larger effect size noted with benzodiazepines. The current review suggests that doxepin's efficacy is comparable (at least by indirect comparisons) and possibly better than current therapeutic options for patients with sleep maintenance problems.

MISE EN PRATIQUE DES CONNAISSANCES

- Les doses de 3 mg et de 6 mg de doxépine améliorent de façon considérable et durable le maintien et la durée du sommeil dans le dernier quart de la nuit, mais n'a pas d'effet notable sur l'endormissement.
- Les bénéfices pour le sommeil se produisent sans effets résiduels le lendemain ni après l'arrêt du traitement. Les effets secondaires les plus fréquents sont les maux de tête et la somnolence ou la sédation.
- La doxépine semble bien tolérée chez les personnes âgées.
- On peut commencer le traitement à 6 mg chaque soir chez l'adulte et 3 mg chez les personnes âgées (de 65 ans et plus).

Geriatric considerations

While the pharmacokinetics of doxepin at low doses have not been evaluated in older people, it is plausible that its metabolism may be diminished in these patients, leading to a longer terminal half-life and possibly a longer duration of action.[15] It is also possible that some older people may be more sensitive to the effects of doxepin, although this has not been studied. In either of these cases, it may be necessary to consider lower doses by splitting the 3 mg tablet. It is currently unknown how frail older adults or those with cognitive impairment will tolerate low doses of doxepin. It is possible that in these patients, doxepin might be more tolerable than benzodiazepines or benzodiazepine receptor agonist drugs or other commonly used agents such as trazodone or mirtazapine, because at low doses, doxepin has a high affinity for H_1 receptors, with negligible effects at other receptors.[21]

Administration, potential drug-drug interactions and proposed place in therapy

The manufacturer suggests a dose of 6 mg for adults and 3 mg for older adults (which may be increased to 6 mg if necessary). Doxepin should be taken within 30 minutes of bedtime, and it should not be taken within 3 hours of a meal (administration with food delays absorption and increases exposure to doxepin) to minimize the risk of carryover effects. With regard to drug-drug interactions, doxepin is metabolized by cytochrome P-450 2D6 and 2C19; thus, coadministration of inhibitors of these isozymes (e.g., paroxetine and

cimetidine, respectively) may increase systemic exposure to doxepin. In such cases, the dose of doxepin should not exceed 3 mg.[15] Doxepin could be considered as first-line therapy for adults and older people with sleep maintenance insomnia. In addition, ultra-low-dose doxepin has not been demonstrated to produce physical tolerance or dependence, nor has it been associated with abuse potential, making it a potential option for those with a history of the same.[15]

Conclusion

Available data support the use of ultra-low-dose doxepin for sleep maintenance insomnia in adults as well as older adults. Further research should be aimed at directly comparing doxepin with other currently used sedative hypnotics for efficacy and safety. Additional studies are also necessary to further investigate the efficacy and safety in frail older adults and those with cognitive impairment. ■

From the Schlegel-UW Research Institute for Aging (Rojas-Fernandez) and School of Pharmacy (Rojas-Fernandez, Chen), University of Waterloo, Waterloo; the School of Public Health and Health Systems (Rojas-Fernandez), Faculty of Applied Health Sciences, University of Waterloo; and the Michael G. DeGroote School of Medicine (Rojas-Fernandez), Dept. of Family Medicine, McMaster University, Hamilton, Ontario. Contact carlos.rojas-fernandez@uwaterloo.ca.

Author Contributions: *Dr. Rojas-Fernandez had full access to all of the data and takes responsibility for the integrity of the data in this paper and the accuracy of the data analysis. Dr. Rojas-Fernandez created the study concept and design, critically revised the manuscript and supervised the study. Dr. Rojas-Fernandez and Ms. Chen both acquired, analyzed and interpreted the data and drafted the manuscript.*

Declaration of Conflicting Interests: *The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.*

Funding: *The authors received no financial support for the research, authorship, and/or publication of this article.*

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* DSM-V, 5th ed. Washington (DC): American Psychiatric Publishing; 2013.
2. Hirshkowitz M, Seplowitz-Hafkin RG, Sharafkhaneh A. *Sleep disorders.* 9th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2009.
3. Tjepkema M. Insomnia. *Health Rep* 2005;17:9-25.
4. Daley M, Morin CM, LeBlanc M, et al. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms and good sleepers. *Sleep* 2009;32:55-64.
5. Krystal AD, Durrence HH, Scharf M, et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. *Sleep* 2010;33:1553-61.
6. Lankford A, Rogowski R, Essink B, et al. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. *Sleep Med* 2012;13:133-8.
7. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol* 2010;24:1577-601.
8. Hall-Porter JM, Curry DT, Walsh JK. Pharmacologic treatment of primary insomnia. *Sleep Med Clin* 2010;5:609-25.
9. Morin AK, Jarvis CJ, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy* 2007;27:89-110.
10. Scharf M, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2008;69:1557-64.
11. Swick TJ. The neurology of sleep. *Sleep Med Clin* 2011:1-14.
12. Goforth HW. Low-dose doxepin for the treatment of insomnia: emerging data. *Expert Opin Pharmacother* 2009;10:1649-55.
13. Roth T, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg and 6 mg in adults with primary insomnia. *Sleep* 2007;30:1555-61.
14. Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep* 2011;34:1433-42.
15. Paladin Pharmaceuticals Inc. Silenor (doxepin) tablets for oral administration: Canadian prescribing information. Available: www.paladin-labs.com/our_products/PM_Silenor_EN.pdf (accessed Oct. 25, 2013).
16. Paladin Labs announces Canadian approval for Silenor. *Marketwire* 2012 December 17. Available: http://paladin-labs.mwnewsroom.com/press-releases/paladin-

labs-announces-canadian-approval-for-silen-tsx-plb-20121217084234000l (accessed May 18, 2013).
17. Wilson DB. Practical meta-analysis effect size calculator. The Campbell Collaboration. Available: www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD1.php (accessed Sept. 22, 2013).
18. Stahl SM. Selective histamine H1 antagonism: novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. *CNS Spectr* 2008;13:1027-38.
19. Huedo-Medina TB, Kirsch I, Middlemass J, et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ* 2012;345:e8343.
20. Nowell PD, Mazumdar S, Buysse DJ, et al. Benzodiazepines and zolpidem for chronic insomnia: meta-analysis of treatment efficacy. *JAMA* 1997;278:2170-7.
21. Weber J, Siddiqui MA, Wagstaff AJ, et al. Low-dose doxepin: in the treatment of insomnia. *CNS Drugs* 2010;24:713-20.