Current PSYCHIATRY

Doxepin for insomnia

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Low-dose doxepin—3 mg and 6 mg—has demonstrated efficacy for insomnia characterized by frequent or early-morning awakenings and an inability to return to sleep ***(Table 1)***.[1] FDA-approved in March 2010, doxepin (3 mg and 6 mg) is only the second insomnia medication not designated as a controlled substance and thus may be of special value in patients with a history of substance abuse.

Clinical implications

Ramelteon, the other hypnotic that is not a controlled substance, is indicated for sleep initiation insomnia (ie, inability to fall asleep). In contrast, low-dose doxepin is for patients with sleep maintenance insomnia, which is waking up frequently or early in the morning and not falling back asleep.[1,2] A tricyclic antidepressant first approved in 1969, doxepin has long been available in larger doses (10-, 25-, 50-, 75-, 100-, and 150-mg capsules) to treat depression and anxiety and as a topical preparation (5% cream) for pruritus, but not in dosages <10 mg. An inexpensive generic doxepin oral solution (10 mg/ml) is available and can be titrated to smaller dosages by a dropper. Liquid doxepin costs 10 to 20 cents per dose. A pharmacist can provide a dropper, and patients should mix the medication in 4 ounces of water, milk, or juice; 0.3 ml of liquid doxepin contains 3 mg of active ingredient and 0.6 ml of solution contains 6 mg of doxepin. These other dosage forms of doxepin, however, are not FDA-approved for insomnia. (The retail price of low-dose doxepin was not available when this article went to press.)

Table 1

Doxepin: Fast facts

Brand name: Silenor
Indication: Insomnia characterized by difficulty with sleep maintenance
Approval date: March 2010
Availability date: September 7, 2010
Manufacturer: Somaxon Pharmaceuticals
Dosage forms: 3 mg and 6 mg tablets
Recommended dosage: 3 mg or 6 mg once daily within 30 minutes of bedtime

How it works

Doxepin's mechanism of action for treating depression and insomnia remains unknown. The antidepressant effect of doxepin is thought to result from inhibition of serotonin and norepinephrine reuptake at the synaptic cleft. Animal studies have shown anticholinergic and antihistaminergic activity with doxepin.[2] Doxepin is a potent histamine antagonist—predominantly at the H1 receptor—and its binding potency to the H1 receptor is approximately 100-times higher than its binding potency for monoamine transporters (serotonin and norepinephrine).[2,3] Brain histamine is believed to be 1 of the key elements in maintaining wakefulness, and the activation of the H1 recep-

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Low-dose doxepin may relieve sleep maintenance insomnia and is not designated as a controlled substance

Clinical Point

Blockade of the H1 receptor by doxepin likely plays a role in reducing wakefulness

tor is thought to play an important role in mediating arousal. Blockade of the H1 receptor by doxepin likely plays a role in reducing wakefulness. Typically, therapeutic doses of antidepressants with antihistaminergic properties, such as doxepin at antidepressant doses, amitriptyline, or desipramine, do not selectively block H1 receptors, but act at cholinergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors, which can cause adverse effects.[3] However, low doses of doxepin (1, 3, and 6 mg) can achieve selective H1 blockade.[4,5] Patients taking >25 mg/d of doxepin may report clinically significant anticholinergic effects.

Pharmacokinetics

When doxepin, 6 mg, was administered to healthy, fasting patients, time to maximum concentration (Tmax) was 3.5 hours. Peak plasma concentration (Cmax) increased in a dose-related fashion when doxepin was increased from 3 mg to 6 mg. Doxepin, 6 mg, taken with a high-fat meal resulted in area under the curve increase of 41%, Cmax increase of 15%, and almost 3-hour delay in Tmax. Therefore, to prevent a delay in onset of action and to minimize the likelihood of daytime sedation, doxepin should not be taken within 3 hours of a meal.[1-3]

Doxepin is metabolized primarily by the liver's cytochrome P450 (CYP) 2C19 and CYP2D6 enzymes; CYP1A2 and CYP2D6 are involved to a lesser extent. If doxepin is coadministered with drugs that inhibit these isoenzymes, such as fluoxetine and paroxetine, doxepin blood levels may increase. Doxepin does not seem to induce CYP isoenzymes. This medication is metabolized by demethylation and oxidation; the primary metabolite is nordoxepin (N-desmethyldoxepin), which later undergoes glucuronide conjugation. The half-life is 15 hours for doxepin and 31 hours for nordoxepin. Doxepin is excreted in urine primarily as glucuronide conjugate.[1-3]

Coadministration with cimetidine, an inhibitor of CYP isoenzymes, could double the doxepin plasma concentration; therefore, patients taking cimetidine should not exceed 3 mg/d of doxepin.

Efficacy

Doxepin reduced insomnia symptoms in 3 pilot studies at doses of 10, 25, and 50 mg, and in 2 phase III randomized, double-blind, placebo-controlled clinical trials using 1, 3, and 6 mg ***(Table 2, page 74)***.[4,5] Clinical studies lasted up to 3 months.[1-3,6-8]

In the first phase III trial, 67 patients, age 18 to 64 with chronic primary insomnia, were randomly assigned to placebo or 1 mg, 3 mg, or 6 mg of doxepin for 2 nights. All patients received all treatments, and each treatment was followed by 8 hours of polysomnography (PSG) evaluation in a sleep laboratory.[4] In this study, patients taking doxepin at all doses achieved improvement in objective (PSG-defined) and subjective (patient-reported) measures of sleep duration and sleep maintenance. Wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE) improved with all doxepin doses, and wake time during sleep (WTDS)—which was the primary study endpoint—decreased with 3 mg and 6 mg doses, but not with 1 mg or placebo. In addition, PSG indicators of early-morning awakenings (terminal insomnia) were reduced, as shown by an increase in SE during the final third of the night and the 7th and 8th hours of sleep (1, 3, and 6 mg doses) and a reduction in wake time after sleep (WTAS) during the final third of the night (6 mg only). The effects on sleep duration and maintenance were more robust with 3 mg and 6 mg doses. Improved sleep onset was seen only with the 6 mg dose. Next-day alertness was assessed using the Visual Analogue Scale (VAS) for sleepiness, and the Digit-Symbol Substitution Test (DSST) and the Symbol-Copying Task (SCT) for psychomotor function. No statistically significant differences were found among placebo and any of the doxepin doses on the VAS, DSST, or SCT.

Doxepin was well tolerated. Reported adverse events were mild or moderate. Headaches and somnolence were report-

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Table 2

Evidence of effectiveness of doxepin for insomnia

Study	Subjects	Dosages	Results
Roth et al, 2007[4]; phase III, randomized, multi-center, double-blind, placebo-controlled, 4-period crossover, dose-response study	67 patients age 18 to 64 with chronic primary insomnia	1, 3, or 6 mg given once daily at bedtime for 2 nights	Improvement vs placebo in PSG-defined WASO, TST, SE, and SE during the final third of the night. 6-mg dose significantly reduced subjective latency to sleep onset. Safety profile of all 3 doses was comparable to placebo. No difference in residual sedation
Scharf et al, 2008[5]; phase III, randomized, multi-center, double-blind, placebo-controlled, 4-period crossover, dose-response study	76 patients age ≥65 with primary insomnia	1, 3, or 6 mg at bedtime for 2 nights	Reduction vs placebo in WTDS and WASO at all 3 doses. Increase in TST and SE at all 3 doses. No difference in number of awakenings after sleep onset and latency to persistent sleep at all 3 doses. WTAS was reduced only at 3 and 6 mg doses. Patient-reported WTAS was decreased at all doses. Patient-reported latency to sleep onset decreased only with 6 mg. Safety profile of all 3 doses was comparable to placebo and there were no differences among placebo and all 3 doses doxepin in next-day sleepiness or psychomotor function

PSG: polysomnography; SE: sleep efficiency; TST: total sleep time; WASO: wake after sleep onset; WTAS: wake time after sleep; WTDS: wake time during sleep

Source: References 4,5

Clinical Point

Doxepin is better tolerated at hypnotic doses than at antidepressant doses, although direct comparative studies are not available

ed by >2% of patients. The incidence of adverse events, including next-day sedation, was similar to that of placebo. Additionally, there were no spontaneous reports of anticholinergic side effects, which are associated with higher doxepin doses.[4]

The second phase III trial examined safety and efficacy of 1, 3, and 6 mg doxepin in patients age ≥65.[5] Seventy-six adults with primary insomnia were randomly assigned to receive placebo or doxepin for 2 nights; all patients received all treatments, and each treatment was followed by an 8-hour PSG. Patients taking any doxepin dose achieved objective and subjective improvement in sleep duration and sleep maintenance, which lasted into the final hours of the night. WTDS (primary study endpoint), WASO, TST, and overall SE improved at all doxepin doses compared with placebo, and WTAS and SE at hours 7 and 8 improved at doxepin doses of 3 mg and 6 mg compared with placebo. These findings suggest that doxepin, 3 mg and 6 mg, can help older insomnia patients with early morning awakenings.

In this study, no statistically significant differences were found among placebo and any doxepin doses on VAS, DSST, or SCT or next-day residual sedation. The incidence of side effects was low and similar to that of placebo. Adverse events were mild or moderate; 1 incident of chest pain was reported, but it was determined not to be of cardiac origin and not related to study drug. There were no spontaneous reports of anticholinergic side effects associated with higher doses of doxepin. There were no reports of memory impairment.[5]

Tolerability

Clinical studies that evaluated the safety of doxepin lasted up to 3 months. Somnolence/sedation, nausea, and upper respiratory tract infection were reported by >2% of patients taking doxepin and were more common than in patients treated with placebo.[1] All reported adverse events were mild to moderate.

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Related Resources

- Doghramji K, Grewal R, Markov D. Evaluation and management of insomnia in the psychiatric setting. Focus. 2009;8(4):441-454.
- Psychiatric Clinics of North America. December 2006. All articles in this issue address sleep disorders encountered in psychiatric practice.
- National Sleep Foundation. www.sleepfoundation.org.

Drug Brand Names

Amitriptyline • Elavil
Cimetidine • Tagamet
Desipramine • Norpramin
Doxepin (3 mg and 6 mg) • Silenor
Doxepin (10 to 150 mg, oral) • Sinequan
Doxepin cream • Prudoxin
Fluoxetine • Prozac
Paroxetine • Paxil
Ramelteon • Rozerem

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

There is no evidence of withdrawal syndrome or rebound insomnia after discontinuing doxepin, 3 mg or 6 mg

Doxepin appears to be better tolerated at hypnotic doses (3 mg and 6 mg) than at antidepressant doses (50 to 300 mg/d), although direct comparative studies are not available.[2,4,5] Additionally, psychomotor function assessed using DSST and SCT and next-day sedation assessed using VAS in patients receiving hypnotic doses of doxepin (1 and 3 mg) were the same as placebo. Two studies noted small-to-modest decreases in DSST, SCT, and VAS when doxepin, 6 mg, was administered.[1] Patients taking doxepin at antidepressant doses report significant anticholinergic side effects, including sedation, confusion, urinary retention, constipation, blurred vision, and dry mouth. Hypotension also has been reported at antidepressant doses, and there seems to be a dose-dependant cardiotoxicity, with higher incidence of adverse effects occurring at higher doses of the drug.

Severe toxicity or death from overdose is presumably less likely with hypnotic doses of doxepin than with higher doses, although this has not been systematically explored. If an insomniac overdosed on a 30-day supply of an hypnotic dose (3 or 6 mg), he or she would take only 90 to 180 mg of doxepin, which would be unlikely to cause severe toxicity or death.[2-4]

Symptoms of withdrawal and rebound insomnia—an increase in WASO compared with baseline after discontinuing the medication—were assessed in a 35-day double-blind study of adults with chronic insomnia.[1] There was no evidence of withdrawal syndrome as measured by Tyler's Symptom Checklist after doxepin 3 mg and 6 mg was discontinued. Discontinuation period-emergent nausea and vomiting was noted in 5% of patients taking 6 mg of doxepin, but not in those taking placebo or 3 mg of doxepin. There was no evidence of rebound insomnia after doxepin 3 mg and 6 mg was discontinued.[1]

Contraindications

Doxepin is contraindicated in patients with hypersensitivity to doxepin hydrochloride, with severe urinary retention, with narrow angle glaucoma, and who have used monoamine oxidase inhibitors (MAOIs) within the previous 2 weeks. Serious adverse effects, including hypertensive crisis and death, have been reported with coadministration of MAOIs and certain drugs, such as serotonergic antidepressants and some opioids derivatives. There are no reports of concomitant use of doxepin with MAOIs.[1]

Bottom Line

Low-dose doxepin may be an effective option for patients with insomnia characterized by difficulties with sleep maintenance. At 3 and 6 mg, doxepin appears to be effective and well tolerated. Doxepin is not designated as a controlled substance. Unlike GABA agonists, low-dose doxepin appears to selectively block histaminergic action; it is essentially inactive at benzodiazepine receptor sites.

Dosing

In adults, the recommended hypnotic dose for doxepin is 6 mg taken 30 minutes before bedtime. For patients age ≥65, the recommended starting hypnotic dose is 3 mg 30 minutes before bedtime, which can be increased to 6 mg if indicated.[1]

References

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