

Trazodone extended release for major depressive disorder

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Once-daily dosing eliminates peaks and troughs in serum concentration seen with the immediate release formulation

Extended-release (ER) trazodone—FDA-approved in February 2010—improves symptoms of major depressive disorder (MDD) and allows once-daily dosing (*Table 1*). Trazodone immediate release (IR) was developed in 1960 and approved by the FDA for treatment of MDD in December 1981. Trazodone IR is now mainly prescribed off-label as a hypnotic at lower-than-antidepressant doses, such as 50 to 100 mg/d at bedtime. The dose needed to achieve antidepressant effect is believed to be ≥ 300 mg/d. Use of the IR formulation for treating depression has been limited by the need for 3-times-a-day dosing and daytime sedation associated with peaks in serum concentration.

Clinical implications

Trazodone ER was designed to eliminate the peaks and troughs in serum concentration seen with trazodone IR. It was hypothesized that by reducing the maximum concentration (C_{max}) peaks, trazodone ER would permit higher doses to be better tolerated and help patients to more easily reach target antidepressant doses (≥ 300 mg/d). Trazodone ER's once-daily dosing also may increase patient adherence.

How it works

The exact mechanism of action through which trazodone treats depression is not completely understood, but is likely related to enhancing serotonergic activity in the CNS. Trazodone is a triazolopyridine antide-

Table 1

Trazodone extended release: Fast facts

Brand name: Oleptro
Class: Triazolopyridine-derived antidepressant
Indication: Major depressive disorder
Approval date: February 2, 2010
Availability date: August 10, 2010
Manufacturer: Labopharm, Inc.
Dosage forms: 150 mg and 300 mg bisectable tablets
Starting dose: 150 mg at bedtime
Target dose: 300 mg/d; maximum dose 375 mg/d

pressant, inhibits the serotonin transporter, and is a 5-HT_{2A} and 5-HT_{2C} antagonist. This is why it is sometimes referred as a serotonin antagonist/reuptake inhibitor, but regulatory agencies do not accept this class name. Trazodone is an antagonist at both histamine (H₁) and α -adrenergic receptors, which may mediate trazodone's sedating properties (H₁) and hypotensive (α -adrenergic) effects.

The ER formulation employs a cross-linked, high-amylose starch excipient that provides controlled release of trazodone over an extended period.

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Pharmacokinetics

Trazodone ER has linear pharmacokinetics in doses from 75 to 375 mg. Trazodone ER, 300 mg/d, provides a steady-state exposure equivalent to 100 mg of trazodone IR given 3 times daily, while having a lower C_{max} . A high-fat meal can increase C_{max} of trazodone ER by 1.9-fold. Trazodone is extensively biotransformed in the liver via the cytochrome P450 (CYP) 3A4 pathway and its metabolites are eliminated within 72 hours. Elimination is predominantly renal, with 70% to 75% of an oral dose being recovered in the urine within 72 hours.¹ This formulation maintains its controlled-release properties if bisected.

Because trazodone is a substrate of the CYP3A4 enzyme, its metabolism can be inhibited by CYP3A4 inhibitors. Exercise caution when coadministering medications that cause CYP3A4 inhibition with trazodone ER. The effect of short-term administration of ritonavir (4 doses of 200 mg) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10 healthy subjects.² The C_{max} of trazodone increased by 34%, area under the curve increased 2.4-fold, half-life increased by 2.2-fold, and clearance decreased by 52%. There is no difference in the half-life between the IR and ER formulations because the ER formulation influences only the release kinetics of the drug, not the half-life of the medication.

Efficacy

Efficacy of trazodone for MDD initially was established in trials conducted with trazodone IR.³⁻¹⁰ The efficacy of the ER formulation was established in a multi-center randomized, double-blind, placebo-controlled trial with 412 patients (age 18 to 80). Patients who met DSM-IV criteria for MDD were randomly assigned to trazodone ER ($n=206$) or placebo ($n=206$) for 8 weeks.¹¹ This study showed a statistically significant difference between trazodone ER and placebo after 8 weeks of treatment on the primary outcome measure, which was a change in score on the 17-item Hamilton Depression Rating scale (HAM-D-17). HAM-D-17 scores decreased 11.4

points in the trazodone ER group and 9.3 points in the placebo group ($P = .012$ in the modified intent to treat [ITT] population; $P = .009$ in the completer analysis). This difference was seen from week 1 and throughout the study. Efficacy of trazodone ER was further supported by statistically significant differences between the drug and placebo in 7 of 13 secondary efficacy endpoints in both the modified ITT and per protocol (PP) populations (HAM-D-17 mood item, mean Montgomery-Åsberg Depression Rating Scale [MADRS] total score, mean Clinical Global Impressions Severity of Illness [CGI-S] score, percentage of HAM-D-17 responders, and 3 quality of sleep items [overall quality of sleep, trouble falling asleep, and awakening during the night]). Overall effect sizes for the HAM-D-17 were -0.26 (modified ITT-last observation carried forward [LOCF] dataset) and -0.33 (PP/observed cases [OC] dataset). The effect sizes in MADRS scores were -0.22 and -0.29 for the modified ITT-LOCF and the PP/OC analyses, respectively.¹²

Sleep measures. In the study sample >90% of patients had insomnia at baseline (defined as a score ≥ 2 in any HAM-D-17 sleep item or sum of all 3 sleep items of ≥ 4). Patients receiving trazodone ER had significant improvement in all 3 HAM-D-17 sleep items. Subjects reported improvement in the overall quality of sleep and awakening during the night after the first week of treatment. Investigators found no significant interaction between improvements in core symptoms of depression and baseline MADRS reduced sleep item or early changes in the HAM-D-17 sleep items. This suggests that the antidepressant effect of trazodone ER was independent of severity of sleep difficulties at baseline and of improvement in insomnia during the study.¹²

Researchers observed improvement in suicidal ideation on MADRS (item 10) and HAM-D-17 (item 3) after 8 weeks of treatment (effect size -0.2 favoring trazodone ER over placebo).¹²

Clinical Point

Compared with placebo, trazodone ER resulted in a statistically significant difference in change in HAM-D-17 score

continued

Clinical Point

The most common side effects leading to discontinuation were dizziness, sedation, and somnolence

Table 2

Trazodone extended release treatment-emergent adverse events*

	Trazodone ER (n=202)	Placebo (n=204)
Headache	67 (33%)	55 (27%)
Somnolence	63 (31%)	32 (16%)
Dry mouth	51 (25%)	26 (13%)
Dizziness	50 (25%)	25 (12%)
Nausea	42 (21%)	26 (13%)
Sedation	34 (17%)	7 (3%)
Fatigue	30 (15%)	17 (8%)
Diarrhea	19 (9%)	23 (11%)
Constipation	16 (8%)	4 (2%)
Back pain	11 (5%)	7 (3%)
Blurred vision	11 (5%)	0 (0%)

*Reported by $\geq 5\%$ of patients

Source: Reference 11

In 2 European comparative, randomized, double-blind trials, trazodone prolonged release showed similar antidepressant efficacy as paroxetine⁴ and setraline⁵ as measured by HAM-D, MADRS, and CGI-S. This prolonged release formulation made in Europe is not the same technology as the ER formulation recently approved by the FDA.

Tolerability

In the pivotal registration study, trazodone ER was well tolerated at a mean dose of 310 mg/d.¹¹ Twenty-five patients (12.4%) in the trazodone ER group discontinued the drug because of side effects. The most common side effects leading to discontinuation in the active treatment group were dizziness (n=7), sedation (n=5), and somnolence (n=3).¹¹ The most frequent adverse events reported at any study time point were headache (33%), somnolence (31%), dry mouth (25%), dizziness (25%), nausea (21%), sedation (17%), and fatigue (15%) (Table 2).¹¹ In general, these adverse events were mild to moderate and short-lived; most side effects resolved within the first 2 to 3 weeks of treatment with trazodone ER.¹¹

Sexual side effects—delayed ejaculation, delayed time to orgasm, or orgasmic blockade—are common with many antidepressants. In the pivotal registration study, the incidence of sexual side effects was low (4.9% with trazodone ER vs 2.5% with placebo).¹¹ This is much lower than the rates typically found with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, which range from 17% to 41%.^{13,14} This benefit is thought to be mediated through 5-HT_{2A} and 5-HT_{2C} antagonism. Priapism has been reported in trazodone IR at rates ranging from 1 in 1,000 to 1 in 10,000 and does not appear to be dose-related.¹⁵ The rate of priapism in persons using agents for erectile dysfunction ranges from .05% to 6%.¹⁵ No case of priapism was seen in the trazodone ER study; however, with its sample size of 412 patients this study was not powered to adequately detect this adverse event.¹¹

There was no significant weight gain difference between the active drug and placebo groups over 8 weeks of treatment.

Safety. Trazodone ER should not be used within 14 days of taking a monoamine oxidase inhibitor.¹ Trazodone carries a pregnancy category C, meaning that it should

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Related Resource

• Extended-release trazodone (Olepro) prescribing information. www.olepro.com/images/9379.pdf.

Drug Brand Names

Paroxetine • Paxil	Trazodone • Desyrel
Ritonavir • Norvir	Trazodone extended-release • Olepro
Sertraline • Zoloft	

Disclosures

Dr. Hidalgo receives grant/research support from AstraZeneca, CeNeRx Biopharma, Centers for Disease Control and Prevention, Dainippon Sumitomo Pharma America, Inc., Eli Lilly and Company, Forest Laboratories, Indevus Pharmaceuticals, Janssen Pharmaceuticals, Labopharm, Otsuka, Pfizer, Inc., Repligen Corp., Sanofi-Synthelabo, Sepracor, and the University of South Florida, and is consultant to the MAPI Institute.

Dr. Sheehan has received grant funding support from, been affiliated with, or received honoraria and travel expenses related to lectures/presentations or consultant activities from the following organizations: Abbott Laboratories,^{1,2,3} Ad Hoc Committee, Treatment Drug and Assessment Research Review,¹ Alexza,¹ Alza Pharmaceuticals, Palo Alto, CA,¹ the American Medical Association,² American Psychiatric Association Task Force on Benzodiazepine Dependency,¹ American Psychiatric Association Task Force on Treatments of Psychiatric Disorders,¹ American Psychiatric Association Working Group to Revise DSM III Anxiety Disorders Section,¹ Anclote Foundation,² Anxiety Disorders Resource Center,¹ Anxiety Drug Efficacy Case, the FDA,¹ Applied Health Outcomes/Xcenda,¹ AstraZeneca,^{1,2,3} Avera Pharmaceuticals,^{1,2} Boehringer Ingelheim,³ Boots Pharmaceuticals,³ Bristol-Myers Squibb,^{1,2,3} Burroughs Wellcome,^{2,3} Cephalon,¹ Charter Hospitals,³ Ciba Geigy,³ Committee (RRC) of the National Institute for Mental Health on Anxiety and Phobic Disorder Projects,¹ Connecticut and Ohio Academies of Family Physicians,¹ Cortex Pharmaceutical,¹ Council on Anxiety Disorders,¹ CPC Coliseum Medical Center,¹ Cypress

Bioscience,¹ Dista Products Company,³ Division of Drugs and Technology, American Medical Association,¹ Eisai,^{1,2} Eli Lilly and Company,^{2,3} Excerpta Medica Asia,³ Faxed, Inc.,¹ Forest Laboratories,^{1,2} Glaxo Pharmaceuticals,³ GlaxoSmithKline,^{1,2,3} Glaxo-Wellcome,² Hospital Corporation of America,³ Humana,³ ICI,³ INC Research,¹ International Clinical Research (ICR),² International Society for CNS Drug Development (ISCD),¹ Janssen Pharmaceuticals,^{1,2,3} Jazz Pharmaceuticals,^{1,2} Kali-Duphar,^{2,3} Labopharm,¹ Layton Bioscience,¹ Lilly Research Laboratories,¹ Lundbeck, Denmark,¹ Marion Merrell Dow,³ McNeil Pharmaceuticals,³ Mead Johnson,^{2,3} Medical Outcome Systems,⁴ MediciNova,^{1,2} Merck Sharp & Dohme,^{2,3} National Anxiety Awareness Program,¹ National Anxiety Foundation,¹ National Depressive and Manic Depressive Association,¹ National Institute on Drug Abuse,² National Institute of Health,² Neuronetics,¹ Novartis Pharmaceuticals Corp.,² Novo Nordisk,³ Organon,^{1,3} Orion Pharma,¹ Parexel International Corporation,¹ Parke-Davis,^{2,3} Pfizer, Inc.,^{1,2,3} Pharmacia,¹ Pharmacia and Upjohn,^{1,3} Philadelphia College of Pharmacy and Science,¹ Pierre Fabre, France,¹ Quintiles,² Rhone Laboratories,³ Rhone-Poulenc Rorer Pharmaceuticals,³ Roche,¹ Roerig,³ Sandoz Pharmaceuticals,^{2,3} sanofi-aventis,^{1,2,3} Sanofi-Synthelabo Recherche,^{1,2} Schering Corporation,³ Sepracor,¹ Shire Laboratories, Inc.,¹ SmithKline Beecham,^{1,2,3} Solvay Pharmaceuticals,^{1,3} Takeda Pharmaceuticals,¹ Tampa General Hospital,¹ University of South Florida Psychiatry Center,² University of South Florida College of Medicine, TAP Pharmaceuticals,^{2,3} Targacept,¹ Tampa General Hospital-University Psychiatry Center,³ Tikvah Therapeutics,¹ Titan Pharmaceuticals,¹ United Bioscience,² The Upjohn Company,^{1,2,3} U.S. Congress-House of Representatives Committee,¹ University of South Florida Friends of Research in Psychiatry, Board of Trustees,¹ Warner Chilcott,^{2,3} World Health Organization,¹ Worldwide Clinical Trials,² Wyeth-Ayerst,^{1,2,3} ZARS,¹ and Zeneca Pharmaceuticals.¹

1: Consultant; 2: Grant/Research Support; 3: Lectures/Presentations; 4: Stock Holder

Clinical Point

The recommended starting dose is 150 mg/d at bedtime; it may be increased by 75 mg/d every 3 days, but should not exceed 375 mg/d

be used only if the potential benefit justifies potential risk to the fetus. In animal studies, trazodone has been shown to cause increased fetal resorption and congenital anomalies with doses up to 50 times the maximum human dose (375 mg/d). Trazodone may be secreted in breast milk. The drug is best avoided in patients with recent myocardial infarction.

Dosing

The recommended starting dose is 150 mg/d at bedtime. The dose may be increased by 75 mg/d every 3 days, but the maximum dose should not exceed 375 mg/d.¹ Trazodone ER is available in 150 mg or 300 mg bisectable tablets. Breaking the tablets in half does not affect the controlled release, but they should not be chewed or crushed.

Bottom Line

Trazodone ER is an effective treatment for major depressive disorder (MDD), has an acceptable tolerability profile, and allows once-daily dosing. The most common adverse events are somnolence, sedation, headache, dry mouth, and dizziness. The beneficial effect on sleep quality may be helpful in patients with MDD who have insomnia, making it less necessary to coadminister hypnotics and anxiolytics.

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