Efficacy, Safety, and Tolerability of Desvenlafaxine 50 mg/d for the Treatment of Major Depressive Disorder: A Systematic Review of Clinical Trials

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Objective: Desvenlafaxine is the third serotonin-norepinephrine reuptake inhibitor (SNRI) approved by the US Food and Drug Administration for major depressive disorder (MDD). This article summarizes data on the clinical pharmacology, efficacy, safety, and tolerability of desvenlafaxine (administered as desvenlafaxine succinate) for MDD with a focus on the 50-mg/d therapeutic dose. Additionally, the article discusses clinical practice considerations and future directions in desvenlafaxine research.

Data sources: Data relating to desvenlafaxine 50 mg/d were identified through searches of MEDLINE and publication databases of Pfizer for articles in English published before January 2009. Keywords were *desvenlafaxine*, *O-desmethylvenlafaxine*, *ODV*, and *50 mg*.

Study selection: Three randomized, placebo- and/or active comparator–controlled, 8-week clinical trials reported the efficacy of desvenlafaxine 50 mg/d for the treatment of MDD. The third of these studies included a post hoc pooled analysis of data from all 3 of these trials. In addition, the search retrieved an article examining pooled data from 9 trials, including 50-mg data from 2 of the 3 retrieved trials.

Data synthesis: Desvenlafaxine is the major active metabolite of the SNRI venlafaxine. Significant improvements compared with placebo were observed on the primary efficacy measure (17-item Hamilton Depression Rating Scale total score) and most secondary measures in 2 of 3 clinical trials. An integrated analysis of registration data from 9 randomized, double-blind, placebo-controlled, 8-week studies of desvenlafaxine (50 to 400 mg/d) for MDD demonstrated no evidence of greater efficacy with doses higher than 50 mg/d. Safety results indicate that desvenlafaxine treatment is generally safe and well tolerated; findings were consistent with those for the SNRI class. The 50-mg/d dose of desvenlafaxine was associated with low rates of discontinuation due to treatment-emergent adverse events, which were similar to placebo.

Conclusions: Desvenlafaxine 50 mg/d has demonstrated efficacy, safety, and tolerability for the treatment of MDD in placebo-controlled trials. A long-term study is underway to further explore desvenlafaxine 50 mg/d for MDD.

Prim Care Companion J Clin Psychiatry 2010;12(3):e1–e10

Submitted: *June 3, 2009; accepted October 21, 2009.*
Published online: *June 24, 2010 (doi:10.4088/PCC.09r00845blu).*
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Major depressive disorder (MDD) is a common illness associated with serious impairment and substantial disability. An estimated 33 to 35 million Americans experience MDD during their lifetime, and 13 to 14 million are affected by MDD in a 12-month period.[1] World Health Organization data from 60 countries worldwide indicate that depression impairs health to a greater degree than the chronic diseases angina, arthritis, asthma, and diabetes.[2] Depression also is frequently comorbid with chronic diseases and physical conditions.[2] World Health Organization projections of future mortality and disability rank MDD as a leading cause of disease burden worldwide by 2020, second only to ischemic heart disease.[3]

A range of effective antidepressants are available for the treatment of MDD[4]; however, an estimated 50% of patients do not receive adequate treatment for MDD,[1] and many respond partially or not at all to treatment.[5] For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, approximately one-half of patients with MDD failed to respond to adequate first-line antidepressant monotherapy, and more than 65% failed to achieve remission.[6] Thus, there remains a need for new agents that maximize efficacy and minimize side effects.[4]

The availability of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) has improved the treatment of MDD owing to safety and tolerability advantages over older tricyclic and heterocyclic agents.[7] SSRIs primarily inhibit only serotonin reuptake, while dual-acting agents such as venlafaxine extended release (ER) and duloxetine, which also have demonstrated efficacy and safety for the treatment of MDD,[8–11] are unique because they block the reuptake of both serotonin and norepinephrine.[4] Serotonin and norepinephrine are implicated in the pathophysiology of MDD, since the functioning of the serotonin and norepinephrine systems appears to be dysregulated during depressive episodes.[12] Complex interactions between serotonin and norepinephrine neurotransmitter systems, such as the inhibitory effect of serotonin on norepinephrine neurons, may mediate the wide range of psychological, physical, and functional symptoms of MDD.[12,13]

Clinical Points

- The recommended therapeutic dosage for desvenlafaxine is 50 mg/d.
- The recommended dose can be started without titration.
- Most side effects occur in the first week of treatment and resolve shortly thereafter.

Desvenlafaxine (administered as desvenlafaxine succinate) is the third SNRI approved in the United States by the US Food and Drug Administration (FDA) for the treatment of MDD.[14–16] Desvenlafaxine is formulated as an ER, film-coated tablet for once-daily, oral administration.[14] A pooled analysis of all short-term, randomized, double-blind, placebo-controlled, fixed-dose registration trials has demonstrated the efficacy, safety, and tolerability of desvenlafaxine 50-, 100-, 200-, and 400-mg/d doses for the treatment of MDD.[17–21] Across the dose range studied, treatment with desvenlafaxine was generally safe and well tolerated, with an adverse event (AE) profile consistent with other SNRI agents.[17–20]

Mechanism of Action

Desvenlafaxine, as desvenlafaxine succinate, is a novel salt form of the isolated major active metabolite (*O*-desmethylvenlafaxine) of the SNRI venlafaxine.[22] Preclinical studies using competitive radioligand binding assays indicate that desvenlafaxine exhibits selective inhibitory activity of neurotransmitter uptake at the human serotonin and norepinephrine transporters.[22] Higher affinity was found for the human serotonin transporter compared with the norepinephrine transporter, and weak affinity was observed for the human dopamine transporter.[22] The assays indicate that desvenlafaxine is approximately 10-fold more potent at inhibiting serotonin uptake than norepinephrine uptake.[22] All currently available SNRIs in the United States are more potent for serotonin than norepinephrine reuptake inhibition. The estimated sequential engagement ratio of serotonin inhibition relative to norepinephrine inhibition is approximately 9 for duloxetine,[23] 11 for desvenlafaxine,[22] and 30 for venlafaxine ER.[23] Of note, the ratios are based on in vitro studies performed with different assays; different methodologies may impact results. In addition, the relevance of in vitro findings to clinical outcomes is unknown; the in vivo effect is determined by various factors, such as pharmacokinetics and protein binding.[22] Desvenlafaxine appears to have no monoamine oxidase inhibitory activity, and it shows virtually no affinity for muscarinic, cholinergic, H_1-histaminergic, or α_1-adrenergic receptors in vitro.[14]

Pharmacokinetics and Metabolism

Desvenlafaxine appears to be well absorbed after oral administration, and it has a large volume of distribution. Desvenlafaxine can be taken without regard to meals, and the absolute oral bioavailability after oral administration is approximately 80%.[14] The mean terminal half-life ($t_{1/2}$) is approximately 11 hours, and mean time to peak plasma concentrations (T_{max}) after oral administration is approximately 7.5 hours.[14] The pharmacokinetics of desvenlafaxine are minimally affected by food.[14] Plasma protein binding of desvenlafaxine is low (30%) and independent of drug concentration.[14]

Studies of healthy volunteers indicate that desvenlafaxine undergoes extensive metabolism and is primarily renally excreted.[14] Desvenlafaxine is metabolized primarily by conjugation in the liver (mediated by uridine-diphosphate glucuronosyltransferase isoforms) and, to a minor extent, through oxidative metabolism.[14] The cytochrome P450 (CYP) isozyme 3A4 mediates the oxidative metabolism (*N*-demethylation).[14] Desvenlafaxine metabolism is independent of the CYP2D6 metabolic pathway in the liver.[14] The pharmacokinetics of desvenlafaxine have been shown to be similar in patients with CYP2D6 poor and extensive metabolizer phenotypes, and in vitro data have shown minimal inhibitory effects of desvenlafaxine on CYP2D6, suggesting low potential for drug-drug interactions with other CYP2D6 substrates.[14,24] In vitro data also have shown that desvenlafaxine is not a substrate or an inhibitor of the P-glycoprotein (P-gp) transporter.[25] Therefore, the pharmacokinetics of desvenlafaxine are unlikely to be affected by drugs that inhibit the P-gp transporter, and desvenlafaxine is not likely to alter the pharmacokinetics of drugs that are P-gp substrates.[14]

Elimination of desvenlafaxine is primarily as an unchanged compound or as a glucuronide metabolite. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration.[14] Approximately 19% of the administered dose is excreted as the glucuronide metabolite, and less than 5% is excreted as the oxidative metabolite (*N,O*-didesmethylvenlafaxine).[14]

METHOD

The objectives of the current report are to summarize data on the clinical pharmacology, efficacy, safety, and tolerability of desvenlafaxine for the treatment of MDD with a focus on the 50-mg/d therapeutic dose. In addition, this article discusses clinical practice considerations as well as future directions in desvenlafaxine research.

Data relating to desvenlafaxine 50 mg/d were identified through searches of MEDLINE and publication

Table 1. Summary of Clinical Data Relating to Desvenlafaxine 50 mg/d for MDD

Study	Title of Study/Methods	Efficacy Results
Primary studies		
Liebowitz et al (332)[19]	Efficacy, safety, and tolerability of desvenlafaxine 50 and 100 mg/d in outpatients with MDD. Phase III, fixed-dose, 8 weeks. ITT: placebo, n = 159; desvenlafaxine 50 mg/d, n = 158; desvenlafaxine 100 mg/d, n = 157. Primary efficacy measure: $HDRS_{17}$ total score. Secondary efficacy measures: CGI-I, CGI-S, MADRS, SDS, and $HDRS_{17}$ response (≥ 50% reduction from baseline total score) and remission (total score ≤ 7).	The global *F* test used for controlling multiplicity of the desvenlafaxine doses for the primary efficacy endpoint, the $HDRS_{17}$ total score, reached statistical significance at the .05 level ($P = .046$). The desvenlafaxine 50-mg/d group had significantly lower $HDRS_{17}$ total scores compared with placebo starting at week 4 ($P = .019$) and continuing through endpoint ($P = .018$); the 100-mg dose group did not reach statistical significance ($P = .065$). On secondary measures, there were no significant differences observed vs placebo in CGI-I and CGI-S scores for either the 50- or 100-mg/d groups. The 50-mg dose achieved significantly better outcomes than placebo on the MADRS and SDS total and 3 of 4 subscale scores; the 100-mg/d group did not separate significantly from placebo on the MADRS or SDS. Response rates did not differ statistically among treatment groups (53%, 51%, and 44% for desvenlafaxine 50 mg/d, desvenlafaxine 100 mg/d, and placebo, respectively). Remission rates were significantly different for the desvenlafaxine 50-mg group compared with placebo (34% vs 24%; $P = .03$); the difference was not significant vs placebo for the 100 mg-dose group (31%; $P = .09$).
Boyer et al (333)[17]	Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/d for MDD in a placebo-controlled trial. Phase III, fixed-dose, 8 weeks. ITT, placebo, n = 161; desvenlafaxine 50 mg/d, n = 164; desvenlafaxine 100 mg/d, n = 158. Primary efficacy measure: $HDRS_{17}$ total score. Secondary efficacy measures: CGI-I, CGI-S, MADRS, SDS, and $HDRS_{17}$ response (≥ 50% reduction from baseline total score) and remission (total score ≤ 7).	The global *F* test used for controlling multiplicity of the desvenlafaxine doses for the primary efficacy endpoint, the $HDRS_{17}$ total score, reached statistical significance at the .05 level ($P < .001$). The desvenlafaxine 50-mg/d group had significantly lower $HDRS_{17}$ total scores compared with placebo starting at week 6 ($P = .002$) and continuing through endpoint ($P = .002$); the 100-mg dose had significantly lower $HDRS_{17}$ total scores vs placebo starting at week 4 ($P < .05$) and also continuing through endpoint ($P < .001$). On secondary measures, CGI-I scores differed significantly for the desvenlafaxine 50-mg/d ($P = .002$) and 100-mg/d ($P < .001$) groups vs placebo. Similarly, desvenlafaxine 50 and 100 mg/d were significantly better than placebo on the CGI-S, MADRS, and SDS total and subscale scores. Rates of response were significantly better than placebo (50%) for both the desvenlafaxine 50-mg/d (65%; $P = .005$) and 100-mg/d (63%; $P = .018$) groups. Remission rates were significantly better than placebo (29%) for the 100-mg/d group (45%; $P = .003$); the 50-mg dose did not separate from placebo (37%; $P = .100$).
Tourian et al (335)[26]	Desvenlafaxine 50 and 100 mg/d in the treatment of MDD: a multicenter, randomized, double-blind, placebo-controlled trial and a pooled analysis. Phase III, fixed-dose, duloxetine-referenced, 8 weeks; duloxetine 60 mg/d was included for assay sensitivity, and the study was not designed or powered to compare desvenlafaxine with duloxetine. ITT: placebo, n = 160; desvenlafaxine 50 mg/d, n = 148; desvenlafaxine 100 mg/d, n = 150; duloxetine 60 mg/d, n = 157. Primary efficacy measure: $HDRS_{17}$ total score. Secondary efficacy measures: CGI-I, CGI-S, MADRS, SDS, and $HDRS_{17}$ response (≥ 50% reduction from baseline total score) and remission (total score ≤ 7). A post hoc pooled analysis evaluated the overall efficacy of desvenlafaxine 50 and 100 mg/d using the current trial and similarly designed, completed trials (Boyer et al[17] and Liebowitz et al[19]) of both desvenlafaxine 50 and 100 mg/d. Placebo, n = 471; desvenlafaxine 50 mg/d, n = 462; desvenlafaxine 100 mg/d, n = 455. Pooled analysis efficacy measures: $HDRS_{17}$ total score (primary), CGI-I, MADRS, and $HDRS_6$.	In the individual trial, the global *F* test used for controlling multiplicity of desvenlafaxine doses for the primary endpoint, change from baseline in $HDRS_{17}$ total score at the final evaluation, did not reach significance ($P = .086$). Based on pairwise comparison, significantly greater improvements on the $HDRS_{17}$ were observed for desvenlafaxine 100 mg/d ($P = .028$), unadjusted for multiple comparisons, and duloxetine 60 mg/d ($P = .047$) vs placebo. No significant differences were observed for desvenlafaxine 50 mg/d vs placebo on primary and secondary outcomes. Desvenlafaxine 100 mg/d and duloxetine 60 mg/d were significantly better than placebo on the CGI-I, CGI-S, and MADRS. On the SDS, desvenlafaxine 100 mg/d and duloxetine 60 mg/d separated from placebo on the total and 3 of 4 subscale scores. There were no significant differences vs placebo for any treatment group in rates of response (38%, 39%, 49%, and 47% for the placebo, desvenlafaxine 50-mg/d, desvenlafaxine 100-mg/d, and duloxetine 60-mg/d groups, respectively) and remission (21%, 20%, 28%, and 29% for the placebo, desvenlafaxine 50-mg/d, desvenlafaxine 100-mg/d, and duloxetine 60-mg/d groups, respectively). In the post hoc pooled analysis, significantly greater improvements in $HDRS_{17}$ total scores were observed for desvenlafaxine 50 mg/d ($P < .001$) and 100 mg/d ($P < .001$) vs placebo; separation from placebo started at week 3 for both doses and continued through endpoint. Both doses also were significantly better than placebo on the CGI-I, MADRS, and $HDRS_6$.

(continued)

Table 1 (continued). Summary of Clinical Data Relating to Desvenlafaxine 50 mg/d for MDD

Study	Title of Study/Methods	Efficacy Results
Pooled studies		
Thase et al[21]	An integrated analysis of the efficacy of desvenlafaxine compared with placebo in patients with MDD. An integrated analysis of individual data performed on the complete set of registration data from 9 randomized, double-blind, placebo-controlled, 8-week studies of desvenlafaxine (5 fixed-dose and 4 flexible-dose studies). Overall (full) data set ITT: placebo, n = 1,108; desvenlafaxine, n = 1,805. 5 fixed-dose studies: placebo, n = 631; desvenlafaxine 50 mg/d, n = 314; 100 mg/d, n = 419; 200 mg/d, n = 300; 400 mg/d, n = 309. Four flexible-dose studies: placebo, n = 447; desvenlafaxine (100-400 mg/d), n = 463. Primary efficacy measure: $HDRS_{17}$ total score. Secondary efficacy measures: CGI-I, CGI-S, MADRS, and $HDRS_{17}$ response (≥ 50% reduction from baseline total score) and remission (total score ≤ 7).	Significantly greater improvement with desvenlafaxine vs placebo on the $HDRS_{17}$ total score was observed for the overall (full) data set ($P < .001$); the 50-, 100-, 200-, and 400-mg fixed-dose groups (all $P < .001$); and the flexible-dose group ($P = .024$). On secondary measures, significant differences vs placebo also were observed on the CGI-I, CGI-S, and MADRS for the overall desvenlafaxine group ($P < .001$), the 4 dose groups (all $P < .001$), and the flexible-dose data set ($P < .05$). Rates of $HDRS_{17}$ response were significantly better for desvenlafaxine than placebo for the overall desvenlafaxine group (53% vs 41%; $P < .001$), the 4 dose groups (50 [60% vs 47%; $P = .002$], 100 [56% vs 44%; $P < .001$], 200 [52% vs 38%; $P < .001$], and 400 mg [51% vs 38%; $P = .002$]), and the flexible-dose set (48% vs 40%; $P = .013$). $HDRS_{17}$ remission rates were significantly better for desvenlafaxine vs placebo for the overall data set (32% vs 23%; $P < .001$) and all individual dose groups (50 [36% vs 26%; $P = .012$], 100 [36% vs 25%; $P < .001$], 200 [33% vs 23%; $P = .007$], and 400 mg [32% vs 23%; $P = .008$]); the flexible-dose group did not separate from placebo (26% vs 21%; $P = .091$).
Clayton et al[32]	An integrated analysis of the safety and tolerability of desvenlafaxine compared with placebo in the treatment of MDD. A pooled analysis of the complete set of registration data from 9 randomized, double-blind, placebo-controlled, 8-week studies of desvenlafaxine (4 flexible-dose and 5 fixed-dose studies). Overall data set (9 short-term studies): placebo, n = 1,116; desvenlafaxine, n = 1,834. 5 fixed-dose studies: placebo, n = 636; desvenlafaxine: 50 mg/d, n = 317; 100 mg/d, n = 424; 200 mg/d, n = 307; 400 mg/d, n = 317. TEAEs, laboratory values, vital signs, and discontinuation symptoms evaluated for the overall population; dose-related effects analyzed in the subset of fixed-dose studies.	In the overall population, discontinuations due to AEs were 3% and 12% for the placebo and desvenlafaxine groups, respectively. In fixed-dose studies, discontinuations due to AEs were 4% for placebo and increased with desvenlafaxine dose (4% with 50 mg/d to 18% with 400 mg/d). In the pooled population from all 9 studies, the most commonly reported TEAEs (≥ 5% and at least 2 times greater with desvenlafaxine than placebo) were nausea, dry mouth, hyperhidrosis, dizziness, insomnia, constipation, somnolence, decreased appetite, fatigue, erectile dysfunction (≥ 5% males), vomiting, tremor, mydriasis, and anorgasmia. Overall, the incidence of TEAEs was dose-related. In the 50-mg group, the most commonly reported TEAEs were nausea, dizziness, hyperhidrosis, constipation, and decreased appetite. In all treatment groups, the most common TEAE was transient nausea, and the incidence was highest in the first treatment week (5% in placebo and 16%, 20%, 30%, and 34% in the desvenlafaxine 50-, 100-, 200-, and 400-mg/d groups, respectively) and returned to placebo levels during the second treatment week at all doses except the 400 mg/d group, which returned to placebo levels during the third week. Clinically important changes in laboratory values, vital signs, and ECG findings were infrequent at all desvenlafaxine doses (50 to 400 mg/d).

Abbreviations: AEs = adverse events, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ECG = electrocardiogram, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, SDS = Sheehan Disability Scale, TEAEs = treatment-emergent adverse events.

databases of Pfizer for articles in English published before January 2009. Key words were *desvenlafaxine*, *O-desmethylvenlafaxine*, and *ODV.* Three randomized, placebo- and/or active comparator–controlled, 8-week clinical trials reported the efficacy of desvenlafaxine 50- mg/d for the treatment of MDD.

RESULTS

Efficacy

Table 1 summarizes clinical data relating to desvenlafaxine 50 mg/d for MDD. The individual studies[17,19,26] included in this review were 8-week, randomized, placebo- and/or active comparator-controlled clinical trials that included desvenlafaxine 50 mg/d for the treatment of MDD. The 3 individual studies[17,19,26] with the 50-mg/d dose also were analyzed via a post hoc pooled efficacy analysis included in the Tourian et al[26] report. The post hoc analysis was designed to evaluate the efficacy of desvenlafaxine 50 and 100 mg/d in the context of all similarly designed, completed studies that included both the 50- and 100-mg/d doses for the treatment of MDD.[26]

In addition to individual studies, pooled data from studies with the 50-mg/d dose and higher doses are presented in Table 1. Thase et al[21] performed an integrated analysis of individual patient data from the complete set of registration data of desvenlafaxine for the treatment of MDD. Nine double-blind, placebo-controlled, 8-week phase II and III clinical trials of desvenlafaxine comprised the complete portfolio of FDA registration studies for MDD. Of the 9 studies in the analysis, 5 were fixed-dose in which patients were treated with desvenlafaxine 50 to 400 mg/d: 50 mg/d (2

studies), 100 mg/d (3 studies), 200 mg/d (3 studies), and 400 mg/d (3 studies).[21] In the 4 flexible-dose studies, patients were treated with desvenlafaxine 100 to 400 mg/d: 100 to 200 mg/d (1 study) and 200 to 400 mg/d (3 studies).[21] The Tourian et al[26] study, completed later, was not included in the registration data set and was therefore not included in the integrated analysis.

In all studies in this review, participants were outpatient men and women ≥ 18 years of age with a primary diagnosis of MDD based on the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[27] and in a single or recurrent episode, without psychotic features for at least 30 days before the screening visit. Minimum scores required at screening and baseline included a total score ≥ 20 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[28] (≥ 20 or ≥ 22 in the Thase et al integrated analysis[21]), ≥ 2 on the $HDRS_{17}$ item 1 (depressed mood), and ≥ 4 on the Clinical Global Impressions-Severity of Illness (CGI-S) scale.[29] Major exclusion criteria included previous treatment with desvenlafaxine or known hypersensitivity to venlafaxine, significant risk of suicide based on clinical judgment, current Axis I disorder (other than MDD) or anxiety disorder, or any clinically important medical disease.[17,19,26]

Overall, baseline characteristics were largely similar in the 3 studies using 50 mg/d of desvenlafaxine.[17,19,26] Mean $HDRS_{17}$ total scores at baseline ranged from 23 to 24.[17,19,26] In the Liebowitz et al[19] trial, patient characteristics were similar among treatment groups, with the exception of baseline weight for desvenlafaxine 50 mg/d ($P = .046$) versus placebo; this difference was not expected to impact efficacy results. In the studies by Boyer et al[17] and Tourian et al,[26] there were no significant differences in either trial among treatment groups in pretreatment demographic and clinical characteristics.

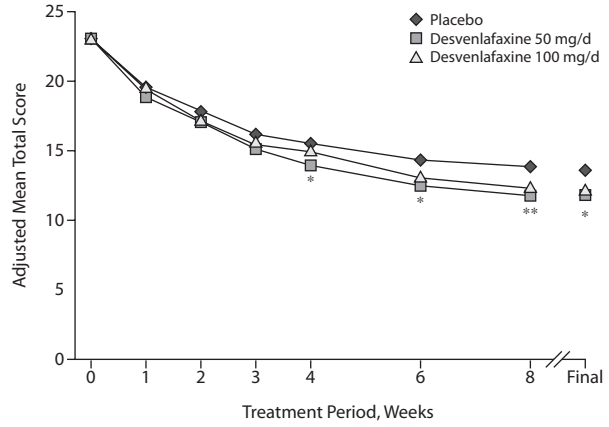
The primary efficacy outcome for the 3 studies using 50 mg/d of desvenlafaxine[17,19,26] as well as in all the studies in the Thase et al 9-study pooled efficacy analysis,[21] was mean change from baseline to endpoint on the $HDRS_{17}$ total score. Secondary outcomes included mean scores at endpoint on the Clinical Global Impressions-Improvement (CGI-I)[29] scale and the CGI-S and mean changes from baseline to endpoint on the Montgomery-Asberg Depression Rating Scale[30] (MADRS) and the patient-rated Sheehan Disability Scale[31] ([SDS]; not analyzed in the 9-study pooled efficacy analysis[21]). Rates of $HDRS_{17}$ response (≥ 50% reduction from baseline) and remission (total score ≤ 7) also were analyzed. In the 3-study, post hoc, pooled analysis presented in the Tourian et al[26] report, efficacy measures were the $HDRS_{17}$ total score (primary), CGI-I (adjusted means), MADRS, and $HDRS_6$. The CGI-S, SDS, and rates of $HDRS_{17}$ response and remission were not assessed in the post hoc analysis.

In all studies, the primary population for the efficacy analyses was the intent-to-treat (ITT) population, which included all patients who were randomly assigned to treatment, had a baseline primary efficacy evaluation, took at least 1 dose of study medication, and had at least 1 primary efficacy evaluation after the first dose of double-blind test medication. The primary endpoint for all efficacy analyses was the last-observation-carried-forward (LOCF) final evaluation; the LOCF method was used to account for missing data. Treatment effects were tested at a 2-sided significance level of .05. Multiplicity adjustment in the primary studies included closed testing procedures for the primary efficacy variable (the $HDRS_{17}$ change from baseline at the LOCF final evaluation) that was performed to compare 2 doses of desvenlafaxine (50 and 100 mg/d) with placebo. A sequential testing method was used to control for multiplicity in the primary ($HDRS_{17}$ total score) and 1 secondary efficacy variable (CGI-I). No adjustment for multiplicity was made for other secondary efficacy variables.[17,19,26]

Table 1 presents study designs and efficacy results for the individual studies and pooled analyses which included desvenlafaxine 50 mg/d. On the primary efficacy measure, the desvenlafaxine 50-mg/d dose group had significantly lower $HDRS_{17}$ total scores at endpoint compared with placebo in 2 studies,[17,19] the 3-study post hoc pooled analysis,[26] and the 9-study pooled efficacy analysis.[21] Adjusted mean $HDRS_{17}$ total scores over time (LOCF, ITT) for all studies are shown in Figures 1, 2, 3A, and 3B. In the Tourian et al[26] trial, $HDRS_{17}$ total scores were not significantly different for desvenlafaxine 50 mg/d versus placebo. The global *F* test used for controlling multiplicity of the desvenlafaxine doses for the primary efficacy endpoint, the change from baseline in the $HDRS_{17}$ total score at the final evaluation, did not reach significance at the .05 level ($P = .086$); based on pairwise comparison (unadjusted for multiple comparisons), no significant differences were observed for desvenlafaxine 50 mg/d versus placebo on primary and secondary outcomes. The global *F* test used for controlling multiplicity of the desvenlafaxine doses for the primary efficacy endpoint, the $HDRS_{17}$ total score, reached statistical significance at the .05 level in both the Liebowitz et al trial[19] ($P = .046$) and the Boyer et al trial[17] ($P < .001$). Results of the Thase et al[21] integrated analysis of individual patient data from the all-inclusive set of 9 short-term, placebo-controlled trials demonstrated efficacy across the range of desvenlafaxine doses studied; all 4 doses (50, 100, 200, and 400 mg/d) had significantly greater improvement on the $HDRS_{17}$, with no evidence of greater efficacy at doses higher than 50 mg/d.

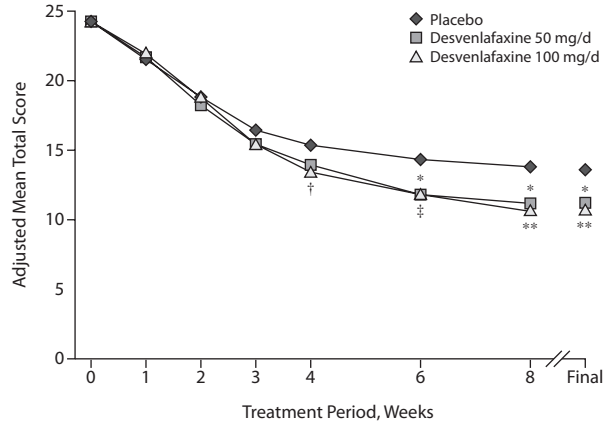
Most secondary measures showed significant separation from placebo. CGI-I scores (adjusted means) differed significantly for desvenlafaxine 50 mg/d versus placebo in 1 trial (Boyer et al[17]), the 3-study post hoc pooled analysis,[26] and the 9-study pooled efficacy

Figure 1. Study 332: $HDRS_{17}$ Adjusted Mean Total Scores Over Time (ITT, LOCF)[a]



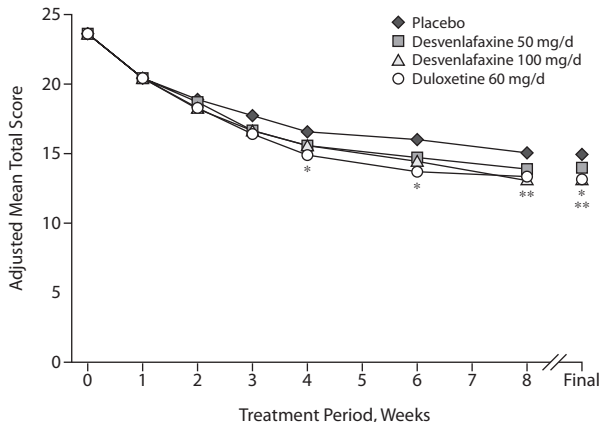
[a]Reprinted with permission from Liebowitz et al.[19]
*$P < .05$ desvenlafaxine 50 mg/d vs placebo.
**$P < .01$ desvenlafaxine 50 mg/d vs placebo.
Abbreviations: Final = LOCF final evaluation, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward.

Figure 2. Study 333: $HDRS_{17}$ Adjusted Mean Total Scores Over Time (ITT, LOCF)[a]



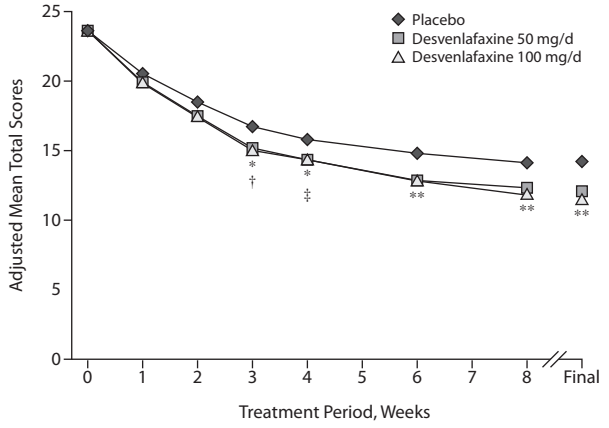
[a]Adapted with permission from Boyer et al.[17]
*$P < .01$ desvenlafaxine 50 mg/d vs placebo.
†$P < .05$ desvenlafaxine 100 mg/d vs placebo.
‡$P < .01$ desvenlafaxine 100 mg/d vs placebo.
**$P < .001$ desvenlafaxine 100 mg/d vs placebo.
Abbreviations: Final = LOCF final evaluation, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward.

Figure 3A. Study 335: $HDRS_{17}$ Adjusted Mean Total Scores Over Time (ITT, LOCF)[a]



[a]Reprinted with permission from Tourian et al.[26]
*$P < .05$ duloxetine 60 mg/d vs placebo.
**$P < .05$ desvenlafaxine 100 mg/d vs placebo.
Abbreviations: Final = LOCF final evaluation, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward.

Figure 3B. Post Hoc Pooled Analysis: $HDRS_{17}$ Adjusted Mean Total Scores Over Time (ITT, LOCF)[a]



[a]Reprinted with permission from Tourian et al.[26]
*$P < .01$ desvenlafaxine 50 mg/d vs placebo.
†$P < .05$ desvenlafaxine 100 mg/d vs placebo.
‡$P < .01$ desvenlafaxine 100 mg/d vs placebo.
**$P < .001$ desvenlafaxine 50 mg/d vs placebo and desvenlafaxine 100 mg/d vs placebo.
Abbreviations: Final = LOCF final evaluation, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward.

analysis[21]; nonsignificant results were observed in 2 trials (Liebowitz et al[19] and Tourian et al[26]). CGI-S scores were significantly better for desvenlafaxine 50 mg/d versus placebo in 1 trial (Boyer et al[17]) and the 9-study, pooled efficacy analysis[21]; nonsignificant results were observed in 2 trials (Liebowitz et al[19] and Tourian et al[26]). CGI-S scores were not assessed in the 3-study, post hoc, pooled analysis.[26] MADRS scores differed significantly for desvenlafaxine 50 mg/d versus placebo in 2 trials (Boyer et al[17] and Liebowitz et al[19]); the 3-study, post hoc, pooled analysis[26]; and the 9-study, pooled efficacy analysis[21]; nonsignificant results were observed in 1 trial.[26] SDS total and subscale scores showed significant improvements for desvenlafaxine 50 mg/d versus placebo in 2 trials (Boyer et al[17] and Liebowitz et al[19]) but not in the Tourian et al[26] trial. SDS total and subscale scores were not assessed in the 3-study, post hoc, pooled analysis[26] or in the 9-study, efficacy pooled analysis.[21]

Rates of $HDRS_{17}$ response (≥ 50% reduction from baseline total score) were significantly greater for desvenlafaxine 50 mg/d versus placebo in 1 trial (Boyer et al[17]) and the 9-study, pooled efficacy analysis.[21] Specifically, response rates for placebo and desvenlafaxine 50 mg/d were 44% and 53% ($P = .098$), respectively, in the Liebowitz et al trial[19]; 50% and 65% ($P = .005$), respectively, in the Boyer et al[17] trial; 38% and 39% ($P = .961$), respectively, in the Tourian et al[26] trial; and 47% and 60% ($P = .002$), respectively, in the 9-study, pooled efficacy analysis.[21] $HDRS_{17}$ response was not assessed in the 3-study, post hoc, pooled analysis.[26]

Rates of $HDRS_{17}$ remission (total score ≤ 7) were significantly greater for desvenlafaxine 50 mg/d versus placebo in 1 trial (Liebowitz et al[19]) and the 9-study pooled efficacy analysis.[21] Remission rates for placebo and desvenlafaxine 50 mg/d were 24% and 34% ($P = .03$), respectively, in the Liebowitz et al trial[19]; 29% and 37% ($P = .10$ vs placebo), respectively, in the Boyer et al[17] trial; 21% and 20% ($P = .82$), respectively, in the Tourian et al trial[26]; and 26% and 36% ($P = .012$), respectively, in the 9-study, pooled efficacy analysis (odds ratio [95% CI]: 1.55 [1.10–2.18]).[21] $HDRS_{17}$ remission was not assessed in the 3-study, post hoc, pooled analysis.[26]

Overall, the results demonstrate the efficacy of desvenlafaxine 50 mg/d for the treatment of MDD. Significant improvements compared with placebo were observed on the primary efficacy measure ($HDRS_{17}$) in all but 1 trial[26] as well as on most secondary measures in all but 1 trial.[26] Efficacy was demonstrated on both clinician- and patient-rated measures of depression. Remission rates in the individual studies and the 9-study post hoc analysis (range, 20%–37%) were generally consistent with the rate of HDRS remission (27.5%) reported for patients treated with open-label citalopram in the STAR*D study[6]; however, the remission rate in the STAR*D study may be somewhat inflated compared with those in the desvenlafaxine studies, as a placebo control group was not included in STAR*D.[6] The post hoc pooled efficacy analysis of the 3 completed, similarly designed clinical trials, including the Tourian et al trial,[26] with both desvenlafaxine 50- and 100-mg/d doses, supported the overall similar efficacy of both desvenlafaxine doses for MDD.[26] Based on the pooled integrated analysis of 9 registration studies, desvenlafaxine demonstrated efficacy on both standard rating scales and categorical outcomes across the entire range of doses studied; no evidence of greater efficacy was observed with doses higher than 50 mg/d.[21]

Table 2. Number (%) of Patients Reporting Treatment-Emergent Adverse Events[a] During the On-Therapy Period of 3 Short-Term, Double-Blind, Placebo-Controlled Studies of Desvenlafaxine 50 and 100 mg/d for MDD, by Most Common Event

		Desvenlafaxine	
Adverse Event[b]	Placebo	50 mg/d	100 mg/d
From Liebowitz et al,[19] Study 332			
	(n = 152)	(n = 151)	(n = 148)
Dizziness	6 (4)	25 (17)	10 (7)
Dry mouth	6 (4)	15 (10)	23 (16)
Constipation	5 (3)	14 (9)	16 (11)
Insomnia	4 (3)	14 (9)	15 (10)
Decreased appetite	7 (5)	8 (5)	15 (10)
Hyperhidrosis	4 (3)	10 (7)	14 (10)
Fatigue	5 (3)	9 (6)	10 (7)
Abdominal pain	4 (3)	9 (6)	5 (3)
Anxiety	1 (1)	5 (3)	7 (5)
Vision blurred	2 (1)	7 (5)	5 (3)
From Boyer et al,[17] Study 333			
	(n = 161)	(n = 166)	(n = 158)
Nausea	17 (11)	44 (27)	48 (30)
Dizziness	6 (4)	17 (10)	11 (7)
Insomnia	7 (4)	13 (8)	14 (9)
Constipation	7 (4)	13 (8)	8 (5)
Fatigue	5 (3)	12 (7)	11 (7)
Anxiety	5 (3)	4 (2)	9 (6)
Decreased appetite	1 (1)	8 (5)	7 (4)
From Tourian et al,[26] Study 335			
		Desvenlafaxine	Duloxetine,
Adverse Event[b]	Placebo (n = 161)	50 mg/d (n = 148)	100 mg/d (n = 150)	60 mg/d (n = 157)
Nausea	14 (9)	33 (22)	35 (23)	49 (31)
Insomnia	5 (3)	16 (11)	21 (14)	29 (19)
Decreased appetite	5 (3)	14 (10)	14 (9)	29 (19)
Somnolence	4 (3)	9 (6)	17 (11)	23 (15)
Fatigue	6 (4)	12 (8)	15 (10)	19 (12)
Constipation	4 (3)	9 (6)	10 (7)	17 (11)
Hyperhidrosis	3 (2)	7 (5)	9 (6)	16 (10)
Vomiting	3 (2)	2 (1)	6 (4)	13 (8)
Vision blurred	1 (1)	6 (4)	7 (5)	2 (1)
Abnormal dreams	2 (1)	2 (1)	3 (2)	8 (5)
Yawning	0	2 (1)	1 (1)	7 (5)

[a]Events reported by at least 5% of patients at twice the rate of placebo in any active treatment group during the double-blind period, excluding taper, safety population (all randomly assigned patients who took at least 1 dose of double-blind test medication).
[b]Classification of adverse events is based on the *Medical Dictionary for Regulatory Activities*.[33]

Safety

In the individual studies, safety assessments included monitoring of spontaneously reported treatment-emergent adverse events (TEAEs) and assessment of vital signs, laboratory tests, physical examinations, and electrocardiograms (ECGs). Safety was evaluated in the safety population, defined as all randomly assigned patients who took at least 1 dose of double-blind test medication. The most common TEAEs observed in each of the 3 placebo-controlled trials are presented in Table 2.

The pooled safety analysis with the 50-mg/d dose by Clayton et al[32] is included in Table 1. Clayton et al conducted a pooled safety analysis of the 9 short-term, randomized, double-blind, placebo-controlled registration

Table 3. Most Common Treatment-Emergent Adverse Events During the On-Therapy Period of All Short-Term, Double-Blind, Placebo-Controlled Studies of Desvenlafaxine for MDD, Safety Population[a]

	All Short-Term Studies		All 5 Fixed-Dose Studies				
				Desvenlafaxine			
Adverse Event[b]	Placebo (n = 1,116)	Desvenlafaxine, 50 to 400 mg/d (n = 1,834)	Placebo (n = 636)	50 mg/d (n = 317)	100 mg/d (n = 424)	200 mg/d (n = 307)	400 mg/d (n = 317)
Nausea	117 (11)	585 (32)	66 (10)	69 (22)	112 (26)	110 (36)	129 (41)
Dry mouth	93 (8)	361 (20)	57 (9)	36 (11)	70 (17)	63 (21)	78 (25)
Hyperhidrosis	46 (4)	276 (15)	28 (4)	30 (10)	47 (11)	56 (18)	66 (21)
Dizziness	71 (6)	241 (13)	33 (5)	42 (13)	41 (10)	47 (15)	50 (16)
Insomnia	71 (6)	226 (12)	40 (6)	27 (9)	49 (12)	42 (14)	47 (15)
Constipation	41 (4)	197 (11)	24 (4)	27 (9)	37 (9)	31 (10)	43 (14)
Somnolence	43 (4)	161 (9)	23 (4)	11 (4)	36 (9)	37 (12)	37 (12)
Decreased appetite	18 (2)	167 (9)	13 (2)	16 (5)	34 (8)	30 (10)	33 (10)
Fatigue	47 (4)	152 (8)	22 (4)	21 (7)	28 (7)	30 (10)	35 (11)
Erectile dysfunction[c]	4 (1)	53 (7)	3 (1)	3 (3)	9 (6)	10 (8)	17 (11)
Vomiting	26 (2)	105 (6)	18 (3)	9 (3)	15 (4)	19 (6)	27 (9)
Tremor	17 (2)	105 (6)	11 (2)	6 (2)	13 (3)	26 (9)	28 (9)
Mydriasis	1 (< 1)	68 (4)	1 (< 1)	5 (2)	7 (2)	19 (6)	18 (6)
Anorgasmia	0	41 (2)	0	1 (< 1)	7 (2)	6 (2)	18 (6)

[a]Data from Clayton et al.[32]
[b]Events reported by at least 5% of patients at twice the rate of placebo in any active treatment group during the double-blind period, excluding taper, safety population (all randomly assigned patients who took at least 1 dose of double-blind test medication). Classification of adverse events is based on the *Medical Dictionary for Regulatory Activities*.[33]
[c]Percentage based on number of men. All studies: placebo, n = 403; desvenlafaxine, n = 723; fixed-dose studies: placebo, n = 239; desvenlafaxine 50 mg/d, n = 108; 100 mg/d, n = 157; 200 mg/d, n = 131; 400 mg/d, n = 154.
Abbreviations: MDD = major depressive disorder, TEAEs = treatment-emergent adverse events.

studies for MDD. Treatment-emergent adverse events, laboratory values, vital signs, and discontinuation symptoms were assessed in the safety population. Data were analyzed from all 9 registration studies combined (4 flexible-dose and 5 fixed-dose studies) to assess the overall safety and tolerability of desvenlafaxine. Additionally, data were analyzed from the 5 fixed-dose studies to evaluate safety and tolerability outcomes in relation to dose.[32]

In the pooled safety analysis, desvenlafaxine exhibited a safety and tolerability profile generally consistent with that of the SNRI class. Overall, discontinuations due to AEs were dose related and occurred most often in the first week of treatment. In the subgroup of fixed-dose studies, discontinuation rates in the placebo and 50-mg/d desvenlafaxine groups were both 4%, with no single AE accounting for ≥ 1% of patients' stopping study medication.[32]

Table 3 summarizes the most common TEAEs observed in the pooled safety analysis. Overall, the incidence of TEAEs was dose related. The most common TEAE observed across all doses was transient nausea, which was generally mild to moderate in severity. In the 50-mg/d group, the incidence of nausea was highest in the first treatment week (5% and 16% in the placebo and desvenlafaxine 50-mg/d groups, respectively), and it decreased to placebo levels during the second treatment week.[32]

In the pooled safety analysis,[32] the most common taper/poststudy-emergent AEs (TPAEs) occurring in ≥ 5% of patients and ≥ 2 times more frequently with desvenlafaxine than with placebo) in the total set of 9 registration studies were nausea (2% and 7% for placebo and desvenlafaxine, respectively) and dizziness (2% and 9% for placebo and desvenlafaxine, respectively). In the 5 fixed-dose studies, the incidence of TPAEs was 27% with placebo and 47% (50 mg), 43% (100 mg), 32% (200 mg), and 38% (400 mg) with desvenlafaxine. A dose-response relationship was not observed for any of the most-common TPAEs.[32]

Across all studies, few clinically significant changes were observed in laboratory, vital sign, weight, and ECG assessments. Overall, the results demonstrated that desvenlafaxine treatment was generally safe and well tolerated.[17,19,26,32] Across the dose range, findings were consistent with those of the SNRI class.[32]

Clinical Practice Considerations

The recommended therapeutic dose for desvenlafaxine is 50 mg once daily, with or without food, and the 50-mg/d dose can be initiated without titration.[14] Most side effects with desvenlafaxine, including the 50 mg/d dose, occur in the first week of treatment and resolve shortly thereafter.[14] Specifically, discontinuations due to AEs occur most often in the first week of treatment, and the incidence of nausea, which is the most common side effect observed across all desvenlafaxine doses, is highest during the first week of treatment.[32] In clinical trials, nausea was generally mild to moderate in severity, and it resolved without treatment.[32]

Counseling patients about side effects is important, since research shows that, among adults who initiate antidepressant treatment, 42% discontinue during the first 30 days of treatment, and 72% discontinue during the first 90 days.[34] In addition, patients who discuss side effects with

their physicians are less likely to discontinue treatment than patients who do not discuss side effects and also are more likely to switch medications.[35] Women in particular may be more sensitive to gastrointestinal-related side effects than men, and they should be advised accordingly.[36,37]

Considerations for special populations include patients with renal or hepatic impairment.[14] Dosage adjustment is not necessary in patients with mild renal impairment, defined as a 24-hour creatinine clearance (CrCl) of 50 to 80 mL/min. The recommended desvenlafaxine dose is 50 mg/d in patients with moderate renal impairment, defined as a 24-hour CrCl of 30 to 50 mL/min. In patients with severe renal impairment (24-hr CrCl of 30 mL/min) or end-stage renal disease, the recommended dose is 50 mg every other day; doses should not be escalated in patients with moderate or severe renal impairment or end-stage renal disease. In addition, supplemental doses should not be given to patients after dialysis. For patients with hepatic impairment, no adjustment of the starting dosage is necessary; however, dose escalation greater than 100 mg/d is not recommended.[14]

Higher doses of desvenlafaxine (ie, 100, 200, and 400 mg/d) have been examined in several studies of healthy patients with MDD. The efficacy, safety, and tolerability of desvenlafaxine for MDD have been demonstrated in 4 double-blind, randomized, fixed-dose, placebo-controlled trials of desvenlafaxine doses ranging from 50 to 400 mg/d.[17–20] Additionally, as mentioned earlier, Thase et al[21] performed an integrated analysis on the complete set of registration data from 9 randomized, double-blind, placebo-controlled, 8-week studies of desvenlafaxine. Patients received fixed- (50, 100, 200, or 400 mg/d; n = 1,342) or flexible-dose (100 to 400 mg/d, n = 463) desvenlafaxine or placebo (n = 1,108). Significantly greater improvement was observed for desvenlafaxine versus placebo on the primary ($HDRS_{17}$) and secondary (CGI-I, CGI-S, and MADRS) outcomes for the overall desvenlafaxine group, the 4 dose groups, and the flexible-dose data set.[21] In general, desvenlafaxine doses up to 400 mg/d have been shown to be effective for MDD, although no additional benefit has been demonstrated at doses greater than 50 mg/d, and AEs and discontinuations are more frequent at higher doses.[14]

Future Directions

Future studies of desvenlafaxine for MDD are planned. At this time, the lowest effective dose of desvenlafaxine has not yet been identified. Two phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials were scheduled to be initiated in 2009 to evaluate the efficacy, safety, and tolerability of desvenlafaxine at doses lower than 50 mg/d for the treatment of MDD in adult outpatients. In addition, a long-term clinical trial of desvenlafaxine 50 mg/d in adult outpatients with MDD will be initiated to evaluate the efficacy of desvenlafaxine for reducing relapse rates of MDD. The study will be conducted in the United States, Europe, and Latin America. Patients will first receive 8-week, open-label desvenlafaxine treatment, after which responders will be eligible to enter a 12-week, open-label treatment phase for stabilization (to maintain response); patients who respond to open-label treatment will then be randomly assigned to double-blind desvenlafaxine 50 mg/d or placebo in a 6-month, relapse-assessment phase.

CONCLUSION

Desvenlafaxine is the third SNRI approved in the United States for the treatment of MDD.[14] Overall, desvenlafaxine 50 mg/d demonstrated efficacy for the treatment of MDD in placebo-controlled trials. No additional benefit was demonstrated at doses higher than 50 mg/d. However, studies of higher doses in patients not responding to adequate trials of 50 mg/d have not been done. The overall safety results from placebo-controlled trials indicate that treatment with desvenlafaxine is generally safe and well tolerated, and the findings are consistent with the SNRI class. Desvenlafaxine can be initiated with the 50-mg/d therapeutic dose without titration, and it provides efficacy with low rates of discontinuation due to TEAEs, particularly for the 50-mg/d dose. Desvenlafaxine has minimal interaction with the CYP450 system, which may minimize potential drug-drug interactions. Additional lower-dose and long-term studies are underway to further explore the efficacy, safety, and tolerability of desvenlafaxine for MDD.

Drug names: citalopram (Celexa, Lexapro, and others), desvenlafaxine (Pristiq), duloxetine (Cymbalta), venlafaxine (Effexor and others).

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Potential conflicts of interest: **Dr Liebowitz** reports equity ownership in ChiMatrix LLC and the Liebowitz Social Anxiety Scale (LSAS); is a consultant to AstraZeneca, Tikvah, Wyeth, Eli Lilly, Pherin, and Jazz; has licensed LSAS software to GlaxoSmithKline, Pfizer, Avera, Tikvah, Eli Lilly, Indevus, and Servier; is on the speakers bureaus for Wyeth, AstraZeneca, Bristol-Myers Squibb, and Jazz; and has received grant/research support from Pfizer, GlaxoSmithKline, AstraZeneca, Forest, Tikvah, Avera, Eli Lilly, Novartis, Sepracor, Horizon, Johnson & Johnson, Pherin, PGX Health, Abbott, Jazz, MAP, Takeda, Wyeth, Cephalon, Allergan, Indevus, Endo, Ortho-McNeil, and Grunthal. **Dr Tourian** is an employee and stock shareholder of Wyeth, a Company of the Pfizer Group, Division Wyeth Research, Paris, France.

Funding/support: This analysis was sponsored by Wyeth Research, Collegeville, Pennsylvania, which was acquired by Pfizer Inc in October 2009. Medical writing support was funded by Wyeth and was provided by Sherri Jones, PharmD, of Embryon, LLC, a Division of Advanced Health Media, LLC (formerly Medesta Publications Group, a Business of Advogent).

Previous presentation: Information presented in this manuscript has been presented as a poster at the International Society for Affective Disorders Regional Meeting, February 28–March 2, 2009, Brisbane, Australia; the College of Psychiatric and Neurologic Pharmacists 12th Annual Meeting, April 19–22, 2009, Jacksonville, Florida; and the 9th World Congress of Biological Psychiatry, June 28–July 2, 2009, Paris, France.

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