Drug Class Review

Second Generation Antidepressants

Final Report Update 4
Executive Summary

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The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, mirtazapine, venlafaxine, bupropion, and nefazodone are often described as second-generation antidepressants. These drugs are used to treat a variety of psychiatric disorders, including major depressive disorder, dysthymia, anxiety disorders, and premenstrual dysphoric disorder. The first of the second-generation drugs was introduced to the US market in 1985, when the US Food and Drug Administration (FDA) approved bupropion for the treatment of major depressive disorder.

The mechanism of action of most second-generation antidepressants is poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. Several second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), known as selective serotonin reuptake inhibitors (SSRIs), act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. Other second-generation antidepressants commonly are described by their prominent mechanism of action. Venlafaxine, characterized as a serotonin and norepineprine reuptake inhibitor (SNRI), is a potent inhibitor of serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake. Mirtazapine is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist. Nefazodone, sometimes referred to as a 5-HT2 receptor antagonist, is believed to inhibit neuronal uptake of serotonin and norepineprhine. One manufacturer recently withdrew nefazodone from the US market, but generic versions are still available. Although sometimes referred to as a dopamine reuptake inhibitor (DopRI), bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), was approved for the treatment of major depressive disorder and diabetic peripheral neuropathic pain in 2004.

Since their introduction, the second-generation antidepressants have established a prominent role in the medical management of axis I psychiatric disorders. In addition to FDA-approved use, these drugs are prescribed for several off-label (non-FDA-approved) indications. Despite widespread use, drawing conclusions about comparative efficacy and tolerability among these drugs is difficult.

The purpose of this report is to examine the role of these agents in treating patients with conditions in diagnostic categories classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM); these include depressive disorders (major depressive disorder [MDD] and dysthymic disorder), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), premenstrual dysphoric disorder (PMDD) or late luteal phase dysphoric disorder (LLPDD), and depressed mood subtype, and others. We focus this review on these disorders in adult and geriatric outpatient populations; pediatric populations are examined only for MDD.

This report addresses only the initial use of antidepressants, i.e., beginning an antidepressant treatment for a current depressive episode. It does not address which antidepressants are better for approximately 50 percent of patients who do not remit after initial treatment. Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria and longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the average patient than results from highly selected populations in efficacy studies.

Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and tolerability (adverse events) of second-generation antidepressant medications. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in efficacy or effectiveness?
2. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, and sex), other medications, or comorbidities for which one second-generation antidepressant is more effective or associated with fewer adverse events than another?

METHODS

To identify articles relevant to each key question, we searched MEDLINE, Embase, The Cochrane Library, PsychLit, and the International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications, drug interactions, and adverse events with a list of 11 specific second-generation antidepressants. We searched sources from 1980 to April 2008 to capture literature relevant to the scope of our topic.

Furthermore the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Final_Submission_Protocol_Ver1_1.pdf). We received dossiers from six pharmaceutical companies. We imported all citations into an electronic database (Endnote® v. X.02).

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events. RCTs of at least 6 weeks' duration and an outpatient study population with a sample size greater than 40 participants were eligible for inclusion. Trained reviewers abstracted data from each study; a senior reviewer evaluated the completeness of data abstraction and confirmed the quality rating. We assessed the internal validity (quality) of trials based on predefined criteria. These criteria are based on those developed by the US Preventive Services Task Force (ratings: good-fair-poor),[3] and the National Health Service Centre for Reviews and Dissemination.

RESULTS

Key Question 1.

For outpatients with depressive, anxiety, adjustment, and/or premenstrual dysphoric disorder, do second-generation antidepressants differ in efficacy?

We included 125 randomized controlled trials, 18 meta-analyses, and 1 study of other design. Of the randomized controlled trials, 91 were head-to-head trials; 34 were placebo-controlled trials.

I. For adult outpatients with depressive disorder (major depressive disorder and dysthymia subtypes) and pediatric outpatients with major depressive disorder, do second-generation antidepressants differ in efficacy?

Major Depressive Disorder in Adults

Seventy-two head-to-head trials and multiple meta-analyses compared the effectiveness and efficacy of one second-generation antidepressant to another for treating adults with MDD. All studies addressed initial use of antidepressants.

Overall, effectiveness and efficacy were similar; the majority of trials did not identify substantial differences among drugs. Response and remission rates assessed on multiple diagnostic scales did not differ substantially when taking all the evidence into consideration. Overall, we did not find any evidence that one group had a greater benefit from an individual drug than another. Statistically significant differences of response rates of some metaanalyses are likely not clinically significant. This assessment based on direct head-to-head evidence was augmented by a comprehensive meta-analysis using indirect statistical methods for comparisons where no or little direct evidence was available. In this study no substantial differences in efficacy were found among second-generation antidepressants.

Additionally, second-generation antidepressants are similar in tolerability. Pooled results of our meta-analyses did not identify statistically significant differences in overall discontinuation rates. Only discontinuation rates because of adverse events were significantly higher for venlafaxine than for SSRIs (RR: 1.36; 95% CI: 1.09, 1.69). However, this was compensated by higher discontinuation rates because of lack of efficacy for SSRIs than for venlafaxine (RR: 0.73; 95% CI: 0.52, 1.02). Differences among some medications exist in adverse events, speed of response, and some aspects of health-related quality of life. Specifically, bupropion has fewer sexual side effects than sertraline and fluoxetine; mirtazapine has a faster onset of action than paroxetine and sertraline; venlafaxine and sertraline have higher response rates than fluoxetine but venlafaxine also has a higher incidence of nausea and vomiting and a higher risk of seizures in overdose than fluoxetine.

Few studies assessed the efficacy of second-generation antidepressants in comorbid patients with other psychiatric disorders. Patients with other axis I disorders were generally excluded from study participation. Secondary outcome measures often included anxiety scales. Overall, no substantial differences in improvements on anxiety scales exist. However, mixed results or findings limited to a single trial make the body of evidence inconclusive if any of the second generation antidepressants has a higher efficacy in comorbid patients with high anxiety, recurrent depression, or somatization. Generally, high rates of loss to follow-up limit the validity of many studies.

Dysthymia in adults

We identified no head-to head trials. Five placebo-controlled studies assessed efficacy and tolerability of fluoxetine, paroxetine and sertraline in a population with dysthymia. In these trials, significant differences in population characteristics make this evidence insufficient to identify differences between treatments. The strength of the evidence for comparing second-generation antidepressants in adult patients with dysthymia is poor.

Subsyndromal depression in adults

We identified no head-to head RCT. The only available head-to-head evidence was a nonrandomized, open-label trial comparing citalopram with sertraline that did not detect any differences in efficacy between the 2 drugs. In one effectiveness study, effectiveness did not differ significantly between paroxetine and placebo for the treatment of minor depression. In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments.

Seasonal affective disorder

Currently, only bupropion has FDA-approval for the treatment of seasonal affective disorder. No head-to-head evidence was available. We identified two trials, one comparing sertraline to placebo, and one comparing fluoxetine to light therapy. The placebo controlled RCT offered statistically significant evidence for the efficacy of sertraline in seasonal effective disorder, while a good RCT of fluoxetine compared with light therapy demonstrated no difference in efficacy between the two therapies.

Major Depressive Disorder in Children and Adolescents

Currently, fluoxetine is the only second-generation antidepressant approved by the FDA for treating MDD in children (2 to 12 years) and adolescents (13 to 18 years).

We identified no head-to head trials. FDA-approved evidence supports the efficacy of fluoxetine in treating major depressive disorder in children and adolescents; additional evidence supports greater efficacy of fluoxetine when combined with CBT. The existing evidence, summarized in three systematic reviews of published and unpublished RCTs, provides fair evidence that efficacy to improve health outcomes does not differ between placebo and citalopram, escitalopram, sertraline, paroxetine, and venlafaxine. These studies support a greater efficacy for fluoxetine compared to placebo. No evidence exists for duloxetine, fluvoxamine, mirtazapine, bupropion, or nefazodone.

II. For adult outpatients with anxiety disorders (generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder), do second-generation antidepressants differ in efficacy?

Generalized Anxiety Disorder

Currently, only duloxetine, escitalopram, paroxetine, and venlafaxine have FDA are approval for the treatment of generalized anxiety disorder (GAD).

We identified four head-to-head trials. One fair study compared paroxetine with sertraline; another fair study compared duloxetine with venlafaxine. Both studies reported no differences in efficacy and adverse events. Two additional poor head-to-head trials compared

paroxetine with escitalopram or venlafaxine. Both studies found no differences in efficacy between treatments, although we rated both studies poor due to high attrition.

Additional evidence supports the general efficacy of sertraline. Evidence is insufficient about efficacy of citalopram, fluoxetine, fluvoxamine, mirtazapine, bupropion, and nefazodone for treating GAD. The strength of the evidence for comparing second-generation antidepressants in adult patients with GAD is poor.

Obsessive-compulsive disorder

FDA-approved evidence exists for the general efficacy of fluoxetine, fluvoxamine, paroxetine, and sertraline for treating OCD.

Three head-to-head trials and four meta-analyses provide fair evidence that evaluated second-generation antidepressants do not differ in efficacy and adverse events. Additionally, one study provides fair evidence supporting a greater efficacy of citalopram than placebo. In a second study, citalopram-treated patients augmented with mirtazapine had a faster response than patients treated with citalopram alone, although differences did not persist past 6 weeks. One head-to-head trial provides fair evidence that venlafaxine XR and paroxetine do not differ in improving health outcomes; in a follow-up study, 42% of nonresponders switched to the alternative treatment achieved a response. The strength of the evidence for comparing second-generation antidepressants in adult patients with OCD is fair.

Panic disorder

We identified four head-to-head trials; these provide fair evidence that citalopram and escitalopram, citalopram and paroxetine, as well as paroxetine and sertraline do not differ significantly in efficacy and adverse events in outpatients with panic disorder. Two fair trials provide mixed evidence about the comparative efficacy of venlafaxine ER and paroxetine.

Three placebo-controlled trials provide fair evidence of significantly greater efficacy of fluvoxamine than placebo. Evidence is insufficient about the efficacy of mirtazapine, bupropion, and nefazodone for treating panic disorder. The strength of the evidence for comparing second-generation antidepressants in adult patients with panic disorder is fair to poor.

Post-traumatic stress disorder

For PTSD, we found four head-to-head studies; one comparing citalopram to sertraline, two comparing nefazodone to sertraline, and one comparing venlafaxine to sertraline. No other second-generation antidepressants were compared to one another. Results presented no significant differences between compared drugs.

Three placebo-controlled RCTs provide conflicting results on the general efficacy of fluoxetine for the treatment of PTSD. One RCT supported the general efficacy of venlafaxine compared with placebo for the treatment of PTSD. Significant differences in population characteristics make this evidence insufficient to identify differences between treatments. Evidence is insufficient about the efficacy of citalopram, escitalopram, fluvoxamine, mirtazapine, bupropion, and nefazodone for treating PTSD. The strength of the evidence for comparing second-generation antidepressants in adult patients with PTSD is fair to poor.

Social anxiety disorder

We did not identify any study with a high degree of generalizability. One comparative trial provided fair evidence of comparable efficacy between escitalopram and paroxetine for the

treatment of social anxiety disorder. Two comparative trials provided fair evidence of comparable efficacy between venlafaxine ER and paroxetine. One meta-analysis of placebo-controlled studies provides fair evidence of comparable efficacies of fluvoxamine, paroxetine, and sertraline for the treatment of social anxiety disorder. Six trials and one systematic review provided fair evidence that selective serotonin reuptake inhibitors significantly improve health outcomes compared to placebo.

Two placebo-controlled trials did not support the efficacy of fluoxetine and nefazodone Evidence from three placebo-controlled trials supports the efficacy of escitalopram, and evidence from one placebo-controlled trial supports the efficacy of mirtazapine in women. Evidence is insufficient about the efficacy of citalopram, duloxetine, mirtazapine, bupropion, and nefazodone for treating social anxiety disorder.

III. For adult outpatients with premenstrual dysphoric disorder or late luteal phase dysphoric disorder, do selective serotonin reuptake inhibitors or second generation antidepressants differ in efficacy?

FDA-approved evidence supports the efficacy of fluoxetine, paroxetine, and sertraline in the treatment of premenstrual dysphoric disorder (PMDD) and late luteal phase dysphoric disorder (LLPDD).

We identified no head-to-head trials. One meta-analysis provides good evidence that SSRIs as a class have a significantly greater efficacy than placebo in the treatment of PMDD and LLPDD. One RCT provides fair evidence that the efficacy is significantly greater for venlafaxine than for placebo. One RCT provides evidence that intermittent dosing with paroxetine CR improves mood and daily functioning. Two RCTs provides fair evidence that sertraline improves quality of life and daily functioning significantly more than placebo does. Lastly, fair evidence from one RCT indicates that nefazodone does not have greater efficacy than placebo in the treatment of PMDD or LLPDD. We could not identify sufficient evidence on the efficacy of escitalopram, mirtazapine, and bupropion for treating either PMDD or LLPDD. The strength of the evidence for comparing second-generation antidepressants in adult patients with PMDD and LLPDD is poor.

Key Question 2.

For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorder, do second-generation antidepressants differ in safety, tolerability, or adverse events?

Fair to good evidence from multiple randomized controlled head-to-head trials and retrospective data analyses of prescription event monitoring documents that adverse events profiles are similar among reviewed drugs. Frequencies of some adverse events, however, differ among drugs. In general, venlafaxine had a significantly higher rate of nausea and vomiting in multiple trials; paroxetine frequently led to higher sexual side effects; mirtazapine to higher weight gains; and sertraline to a higher rate of diarrhea than comparable second-generation antidepressants. A retrospective review of prescription event monitoring data provides fair evidence that, among selective serotonin reuptake inhibitors, fluvoxamine has the highest mean incidence of adverse events. Pooled estimates from efficacy trials suggest that venlafaxine has a statistically significantly higher rate of discontinuation because of adverse events than do selective serotonin

reuptake inhibitors as a class (relative risk 1.36; 95% CI 1.09 to 1.69). However, overall discontinuation rates do not differ significantly between venlafaxine and selective serotonin reuptake inhibitors.

Venlafaxine had a consistently higher rate of nausea and vomiting than SSRIs. The rate of patients reporting nausea or vomiting ranged from 25 percent to 36 percent. A pooled analysis of published and unpublished trials of duloxetine did not find significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d), and between duloxetine (120mg/d) and fluoxetine (20mg/d). Three trials reported a significantly higher rate of dizziness in the venlafaxine group than in the fluoxetine group. Three other studies reported significantly higher rates of diarrhea in sertraline-treated patients than in comparison drugs. Mirtazapine and paroxetine frequently led to greater weight gains than fluoxetine and sertraline.

RCTs were powered primarily to detect differences in adverse events between fluvoxamine and citalopram and fluvoxamine and paroxetine. Significantly more patients treated with fluvoxamine than with citalopram had an excess incidence of diarrhea (+13%; $p = 0.026$) or nausea (+16%; $p = 0.017$). Sweating was the only significantly higher adverse event in paroxetine patients (30%) compared to fluvoxamine patients (10%; $p = 0.028$).

Suicidality

We identified no trial comparing the risk of suicidality (suicidal acts and ideation) of SSRIs, SNRIs, or other second-generation antidepressant to each other. Evidence from controlled trials and observational studies is mixed about a higher risk of suicidality in patients treated with second-generation antidepressants. Data is insufficient to draw conclusions about the comparative risk among second-generation antidepressants.

An Expert Working Group of the UK Committee on Safety in Medicines (CSM) studied data from 477 published and unpublished randomized controlled trials on more than 40,000 individuals. The Expert Group concluded that the balance of risks and benefits for the treatment of depression in children less than 18 years is unfavorable for citalopram, escitalopram, mirtazapine, paroxetine, sertraline, and venlafaxine. Only fluoxetine appeared to have a favorable risk-benefit ratio. Fluvoxamine could not be assessed for pediatric use because of lack of data. Conclusions were based on the fact that, with the exception of fluoxetine, clinical trial data failed to demonstrate efficacy in a pediatric population. In addition, an increased risk of suicidal thoughts and self-harm was observed consistently across drugs.

For adults, clinical trial data consistently showed that the risk of suicide-related events in patients receiving second-generation antidepressants is higher than in patients on placebo. However, none of the pooled estimates for individual drugs reached statistical significance. The risk of suicide-related events was similar between second-generation antidepressants and active comparators.

Findings of the CSM Expert Group on suicidality in children are consistent with results from an earlier NICE report. Results of other studies on suicidality in adults are mixed.

Sexual dysfunction

Fair evidence from three RCTs indicates that the rate of sexual side effects is significantly lower for bupropion than for sertraline. The combined NNT to yield one additional person who is satisfied with the overall sexual function is 7. Two additional studies reported fewer sexual side effects in bupropion-treated patients than in paroxetine- or fluoxetine-treated patients.

A cross-sectional survey supports this evidence by reporting the lowest rates of sexual side effects for bupropion and nefazodone in patients treated with SSRIs or other second-generation antidepressants. Multiple trials give fair evidence that paroxetine, sertraline, and mirtazapine tend to have higher rates of sexual side effects than other second-generation antidepressants.

Weight changes

Multiple studies provide fair evidence that mirtazapine and paroxetine lead to a greater weight gain than do fluoxetine and sertraline. Additionally, one study presents fair evidence that bupropion treatment leads to a moderate loss of body weight. An open-label, non-randomized, 2.5-year long study on OCD patients treated with SSRIs reported the lowest increase in weight gain for fluoxetine (+0.5 kg). Other SSRIs lead to greater weight gains (sertraline +1.0 kg; citalopram +1.5kg; paroxetine +1.7kg; fluvoxamine +1.7 kg), however, differences are neither statistically nor clinically significant. The strength of the evidence for comparing second-generation antidepressants is fair.

Cardiovascular adverse events

A post hoc analysis of pooled data reports that venlafaxine significantly increases the supine DBP. None of the controlled efficacy trials reported significant changes in heart rates or an increase in arrhythmias during treatment with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or other second-generation antidepressants. Another post hoc analysis reports that duloxetine lead to higher heart rates than fluoxetine and paroxetine. One fair randomized controlled trial did not detect any differences in supine blood pressure between duloxetine and placebo.

Other serious adverse events

Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but potentially fatal adverse events such as hyponatremia or liver toxicity.

Key Question 3.

Are there subgroups of patients based on demographics (age, racial groups, sex), other medications, or co-morbidities for which one second-generation antidepressant is more effective or associated with fewer adverse events?

We did not find any studies directly comparing the efficacy and tolerability of second-generation antidepressants between subgroups and the general population. However, multiple studies conducted subgroup analysis or used subgroups as the study population. Results can provide indirect evidence. Overall, the strength of the evidence for comparing second-generation antidepressants in terms of a variety of variables that define important subgroups is fair to poor.

Age

A fair pooled analysis did not find significant associations between age and outcomes or age and treatment.

No study directly compared efficacy and safety of treatments in an elderly population to those in a younger population. Eight studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ. Results of these studies, all conducted in patients with MDD or dysthymia, are generally consistent with results of trials conducted in younger populations. Only one small study, rated poor for efficacy outcomes, reported a significantly higher loss to follow-up because of adverse events in venlafaxine-treated, frail elderly patients than in sertraline-treated participants.

No study directly compared efficacy and safety of treatments in a pediatric or adolescent population to those in an adult population. Two systematic reviews found that only fluoxetine had a favorable risk-benefit profile in children and adolescents with MDD.

Ethnicity

Fair evidence from a pooled data analysis on paroxetine and a single RCT on fluoxetine suggest that response rates, loss to follow-up, and response to placebo treatment might differ between groups of different ethnic background. Hispanics tend to have lower response rates than Blacks and Whites. However, two pooled data analyses (of the same seven placebo-controlled duloxetine trials) found no significant differences between Whites and Hispanics[125] or between Whites and African Americans.

Sex

A fair pooled data analysis did not find significant associations between sex and either outcomes or treatment. Another pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder, however, reported better responses of female patients on some outcome measures. A subgroup analysis of a RCT comparing bupropion with paroxetine revealed that anti-depressant related sexual dysfunction was significantly higher in men than in women.

Comorbidities

No prospective study directly compared the efficacy and tolerability of SSRIs, SNRIs, and other second-generation antidepressants in a population with a specific comorbid condition to a population without that same condition. Two retrospective data analyses provide fair evidence that efficacy does not differ between patients with vascular disease and somatizing depressions and patients without these comorbidities.

Various trials conducted in populations with different comorbidities provide indirect evidence about subgroups. Most of these studies were placebo-controlled trials conducted in patients with an underlying disease (e.g., Alzheimer's disease, myocardial infarction, substance abuse, cancer, and others) and accompanying depression. Findings about the general efficacy of second-generation antidepressants to treat depression in such populations are mixed, particularly in patients with serious diseases such as cancer, multiple sclerosis, and HIV/AIDS. Overall, findings about the general efficacy of second-generation antidepressants in these subpopulations were limited. We found no evidence about the comparative efficacy of second-generation antidepressants in patients with comorbidities.

Addendum

On February 29, the FDA approved desvenlafaxine extended-release tablets (*Pristiq*; Wyeth Pharmaceuticals, Inc) for the treatment of major depressive disorder in adult patients. Because this approval took place after finalizing the key questions, we were unable to integrate data on desvenlafaxine in this report.

Desvenlafaxine is a serotonin-norepinephrine reuptake inhibitor and the major active metabolite of venlafaxine XR, which will lose patent protection in 2010. The manufacturer argues that the avoidance of the cytochrome P450 isoenzyme 2D6 could be beneficial in patients requiring concomitant therapy with medications that use this metabolic pathway, such as certain beta-blockers and class I antiarrhythmics. Desvenlafaxine is approved at a once-daily 50 mg dose that does not require titration.

The FDA approval was based on four, 8-week placebo controlled RCTs. No head-to-head trials comparing the efficacy and safety of desvenlafaxine to any other second-generation antidepressants appear to be available to date. Like all second-generation antidepressants, desvenlafaxine has a black box warning regarding suicidality.