DRUG EFFECTIVENESS REVIEW PROJECT

P&T Committee Brief
Drug Class Review on Second Generation Antidepressants Update 3

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P & T COMMITTEE BRIEF
Second Generation Anti-depressants: Comparative Drug Class Review Summary

Background:
Axis I psychiatric disorders such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual disorders are serious disabling illnesses. Combined, they affect approximately one in five Americans. Major depressive disorder (MDD) is the most prevalent, affecting more than 16 percent (lifetime) of US adults.

Pharmacotherapy dominates the medical management of Axis I psychiatric disease. Before the late 1980s, pharmacologic treatment was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). TCAs and MAOIs sometimes are referred to as traditional or first generation antidepressants. Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs.

The mechanism of action of most second-generation antidepressants (SGAD) is only poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. With the exception of fluvoxamine, which is approved only for the treatment of obsessive compulsive disorder (OCD), all of the other second-generation antidepressants are approved for the treatment of MDD. The products included in this review are listed below by mechanism of action:

SSRI (selective serotonin reuptake inhibitor)
- fluoxetine (Prozac, Sarafem)
- sertraline (Zoloft)
- paroxetine (Paxil)
- citalopram (Celexa)
- fluvoxamine (Luvox)
- escitalopram (Lexapro, Cipralex - Canada)

SSNRI (selective serotonin and norepinephrine reuptake inhibitor)
- venlafaxine (Effexor)

SNRI (serotonin and norepinephrine reuptake inhibitors)
- duloxetine (Cymbalta – US only)

Other mechanisms
- buproprion (Wellbutrin)
- mirtazapine (Remeron)
- nefazodone (Serzone – US only)

Purpose:
The purpose of this review is to summarize the comparative data on the efficacy, tolerability, and safety of newer antidepressants when used for the following conditions in adult outpatients: depressive disorders (MDD and dysthymic disorder), generalized anxiety disorder (GAD), OCD, panic disorder, post-traumatic stress disorder (PTSD), social anxiety disorder and premenstrual dysphoric disorder (PMDD) (also known as late luteal phase dysphoric disorder (LLPDD)). In

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addition, the use of these drugs in the treatment of MDD in pediatric outpatient populations is evaluated.

Methodology:
The Drug Effectiveness Review Project reviews all pertinent studies, solicits and accepts public input and updates reviews frequently. The original SGAD review, completed November 2004, has been updated three times. Literature searches identified 2,449 citations. Study eligibility is determined by pre-set criteria. Studies which did not meet these criteria with respect to study design or duration, patient population, interventions, or outcomes were excluded. Additionally, studies published in ineligible publications or not in English were excluded. The quality of all included studies was appraised.

Evidence Available:
Relevant information for this topic consists of 158 studies, including 118 randomized controlled trials (RCT), 14 meta-analyses, 15 observational studies and 11 studies of other design. Another 72 studies were included for background information. Fourty-seven studies that met the eligibility criteria were later rated as poor quality and excluded, primarily because of high loss to follow up (more than 40% or lack of double blinding). Outcomes were evaluated using a wide variety of diagnostic scales and health status or quality of life instruments (45 in total).

Key Questions and Findings:

Question # 1: For outpatients with depressive, anxiety, adjustment, and/or premenstrual dysphoric disorder, do second-generation antidepressants differ in efficacy?

Major Depressive Disorder in Adults

- Overall, effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs, based on 55 head-to-head trials.
- The only exception is the comparison of citalopram to escitalopram, for which four fair trials indicate consistently that escitalopram has a greater efficacy for the treatment of MDD than citalopram. Meta-analyses of these studies led to statistically significantly greater response rates and effect sizes for escitalopram than citalopram. Although statistically significant, the clinical significance of the actual difference remains unclear. Potential funding bias is also a concern as all available studies for these drugs were funded by the brandname manufacturer, which is the same for both citalopram and escitalopram. Citalopram is now available as a generic product whereas escitalopram is still patented.
- Differences among medications exist in adverse events, speed of response, and some aspects of health-related quality of life.
    - Mirtazapine has a faster onset of action than paroxetine and sertraline
    - Bupropion has fewer sexual side effects than fluoxetine, paroxetine, and sertraline
    - Nefazodone improves sleep quality
    - Venlafaxine has a slightly higher response rate than sertraline and fluoxetine but a higher incidence of nausea and vomiting and a risk of seizures in overdose.
- Few studies assessed the efficacy of SGAD in patients with other psychiatric disorders. Secondary outcome measures often included anxiety scales, and overall, no substantial differences in improvements on anxiety scales were found. However, mixed results or findings limited to a single trial make the body of evidence inconclusive whether any of the SGAD has a higher efficacy in patients with high anxiety, recurrent depression, or

somatization. A recent systematic review did not detect any differences in efficacy between SSRIs and other SGAD for the treatment of MDD with anxiety.

Dysthymia in Adults

No head-to head trials were identified. In other trials, significant differences in population characteristics make this evidence insufficient to identify differences between treatments.

Major Depressive Disorder in Children and Adolescents

No head-to-head trials were identified. Published evidence is insufficient to compare one SGAD to another in pediatric outpatients with MDD. Recent evidence from a systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk-benefit profile in pediatric populations.

Generalized Anxiety Disorder

Evidence is insufficient to compare one SGAD to another for treating GAD. One fair rated head-to-head trial did not detect any significant differences in efficacy between paroxetine and sertraline. Evidence supports the general efficacy of escitalopram, paroxetine, venlafaxine and sertraline for treating GAD. Evidence is insufficient about the efficacy of citalopram, fluoxetine, fluvoxamine, mirtazapine, duloxetine, bupropion, and nefazodone for treating GAD.

Obsessive-Compulsive Disorder

Two fair head-to-head studies provide evidence that there is no difference in efficacy between fluoxetine and sertraline or venlafaxine and paroxetine. Other evidence is insufficient to draw conclusions about comparative efficacy between one SGAD and another.

Panic Disorder

One fair head-to-head study provides evidence that there is no difference in efficacy between citalopram and escitalopram for the treatment of panic disorder. In other trials, lack of correspondence in study designs and primary outcomes provide insufficient evidence to identify differences between other SGAD.

Post-Traumatic Stress Disorder

Two head-to-head trials did not detect any differences in efficacy between citalopram and sertraline and sertraline and nefazodone. Placebo-controlled trials report general efficacy of fluoxetine, paroxetine, and sertraline in the treatment of PTSD. Significant differences in population characteristics make this evidence insufficient to identify differences between treatments based on placebo-controlled evidence.

Social Anxiety Disorder

Three fair rated head-to-head trials compared one SGAD to another for the treatment of social anxiety disorder. These trials suggest no differences in efficacy for escitalopram and paroxetine or venlafaxine ER and paroxetine. Additionally, indirect evidence from a meta-analysis of placebo-controlled trials provides evidence that there is no difference in efficacy between fluvoxamine, paroxetine, and sertraline.

Premenstrual dysphoric disorder

No head-to-head trials were identified. Good to fair evidence exists from 2 meta-analyses that the efficacy of SSRIs as a class is significantly greater than placebo. Five additional trials provide fair evidence that the efficacies of paroxetine, sertraline, and venlafaxine are significantly greater than the efficacy of placebo. Another study reported no significant treatment effect for nefazodone

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compared to placebo. Significant differences in study characteristics make this evidence insufficient to identify differences among treatments.

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 side-effect profiles differ significantly among reviewed drugs.

- Venlafaxine had a significantly higher rate of nausea and vomiting in multiple trials than comparable SGAD.
- Paroxetine frequently leads to a higher frequency of sexual side effects than comparable SGAD.
- Mirtazapine results in greater weight gains than comparable SGAD.
- Sertraline has a higher rate of diarrhea than comparable SGAD.
- Among SSRIs, fluvoxamine has the highest mean incidence of adverse events.
- Venlafaxine has a statistically significant higher rate of discontinuation because of adverse events than do SSRIs as a class based on pooled data, although overall discontinuation rates do not differ significantly between venlafaxine and SSRIs.

Regarding specific adverse events, the following evidence exists:

- Suicidality: Evidence is mixed about a higher risk of suicidality in patients treated with SGAD and is insufficient to draw conclusions about their comparative risk.
- 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. An additional study reports fewer sexual side effects in bupropion-treated patients than in 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 SGAD. 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 fair study presents evidence that bupropion treatment leads to a moderate loss of body weight.
- Cardiovascular adverse events: A post hoc analysis of pooled data reports that venlafaxine significantly increases supine diastolic blood pressure. None of the controlled efficacy trials reported significant changes in heart rates or an increase in arrhythmias during treatment with SSRIs, SNRIs, or other SGAD. Another post hoc analysis reports that duloxetine leads to higher heart rates than fluoxetine and paroxetine.

Question #3: Are there subgroups of patients based on demographics (age, racial groups, sex), other medications, or co-morbidities for which one SGAD is more effective or associated with fewer adverse events?

- Age: No study directly compared the efficacy and safety of treatments in an elderly population compared to a younger population. A fair to poor meta-analysis did not find significant associations between age and outcomes or age and treatment. Findings from a pooled data analysis, however, suggested that older women had a poorer response to SSRIs than younger women. Eight studies provide fair to good indirect evidence that

efficacy and tolerability for patients older than 60 years and those younger do not differ. In children and adolescents, placebo-controlled evidence supports the efficacy of fluoxetine and sertraline for MDD, but does not support the efficacy of other SGAD. Based on a systematic review of published and unpublished studies comparing SGAD to placebo, only fluoxetine was shown to be safe and effective in the treatment of MDD in children and adolescents. This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

- Ethnicity: Fair evidence from a pooled data study 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.
- Gender: A meta-analysis rated fair to poor did not find significant associations between sex and outcomes or sex and treatment. A fair pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder reported better responses of female patients on some outcome measures.
- Concomitant medications: Evidence is insufficient to determine the influence of concomitant medications on the effectiveness of SSRIs, SNRIs, or other SGAD.
- Comorbidities: No prospective study directly compared the efficacy and tolerability of SSRIs, SNRIs, and other SGAD 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 co-morbidities. Various other trials conducted in populations with different comorbidities provide indirect evidence that efficacy does not differ.

Conclusion:
Fair to good evidence exists that the overall effectiveness, efficacy, and tolerability of SGAD do not differ substantially for the treatment of MDD in adults. For all comparisons, overall outcomes in terms of clinical improvement and rates of overall discontinuation were similar across agents. In efficacy trials, about 40 percent of patients with MDD did not achieve a response, and about 60 percent did not achieve remission. However, fair evidence supports some differences between individual drugs with respect to onset of action, adverse events, response rates on individual scales, and some measures of health-related quality of life; these are of modest magnitude but statistically significant. Specifically, consistent evidence from multiple trials demonstrates that mirtazapine has a faster onset of action than fluoxetine, paroxetine, and sertraline and that bupropion has fewer sexual side effects than fluoxetine, paroxetine, and sertraline. In addition, weaker evidence indicates fewer sexual side effects from nefazodone than from sertraline, and a better sleep profile with nefazodone compared to fluoxetine.

Evidence is insufficient to conclude on the comparative efficacy and tolerability of SGAD for the treatment of dysthymia, GAD, OCD, panic disorder, PTSD, social anxiety disorder and PMDD. Similarly, evidence is insufficient to draw conclusions about comparative efficacy and tolerability of SGAD in various subgroups.

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