

# When starting an antidepressant, try either of these 2 drugs first

➡ Most patients find that sertraline and escitalopram are more effective and better tolerated than other antidepressants

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Meta-analysis of 117 high-quality studies found that sertraline and escitalopram are superior to other “new-generation” antidepressants.<sup>1</sup>

**CASE**

**A woman with diabetes who is fatigued but cannot sleep**

Mrs. D., 45 years old, has been your patient for several years. She has type 2 diabetes. On her latest visit, she reports a loss of energy and difficulty sleeping, and wonders if these symptoms could be related to the diabetes.

As you explore further and question Mrs. D. about her symptoms, she becomes tearful, and tells you she has episodes of sadness and no longer enjoys things the way she used to. Although she has no history of depression, when you suggest that her symptoms may be an indication of depression, she readily agrees.

You discuss treatment options, including antidepressants and psychotherapy. Mrs. D. decides to try medication. But with so many antidepressants on the market, how do you choose one?

**M**ajor depression is the fourth leading cause of disease globally, according to the World Health Organization.<sup>2</sup> Depression is common in the United States as well, and primary care physicians, including ObGyns, are often the ones who are diagnosing and treating it. In fact, the US Preventive Services Task Force recently expanded its recommendation that primary care providers screen adults for depression, to include adolescents 12 to 18 years old.<sup>3</sup> When depression is diagnosed, physicians must help patients decide on an initial treatment plan.

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### Not all antidepressants are equal

Options for initial treatment of unipolar major depression include psychotherapy and the use of an antidepressant. For mild and moderate depression, psychotherapy alone is as effective as medication. Combined psychotherapy and antidepressants are more effective than either treatment alone for all degrees of depression.<sup>4</sup>

The ideal medication for depression would be a drug with a high level of effectiveness and a low side-effect profile; until now, however, there has been little evidence to support one antidepressant over another. Previous meta-analyses have concluded that there are no significant differences in either efficacy or acceptability among the various second-generation antidepressants on the market.<sup>5,6</sup> Therefore, physicians have historically made initial monotherapy treatment decisions based on side effects and cost.<sup>7,8</sup> The meta-analysis we report here tells a different story, providing strong evidence that some antidepressants are more effective and better tolerated than others.

### Two “best” drugs revealed

Cipriani and colleagues<sup>1</sup> conducted a systematic review and multiple-treatments meta-analysis of 117 prospective randomized, controlled trials (RCTs). Taken together, the RCTs evaluated the comparative efficacy and acceptability of 12 second-generation antidepressants: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine.

The methodology of this meta-analysis differed from that of traditional meta-analyses by allowing the integration of data from both direct and indirect comparisons. (An indirect comparison is one in which drugs from different trials are assessed by combining the results of their effectiveness and comparing the combined finding with the effectiveness of a drug that all the trials have in common.) Previous studies, based only on direct comparison, yielded inconsistent results.

The studies included in this meta-

analysis were all RCTs in which one of these 12 antidepressants was tested against one, or several, other second-generation antidepressants as monotherapy for the acute treatment phase of unipolar major depression. The authors excluded placebo-controlled trials in order to evaluate efficacy and acceptability of the study medications relative to other commonly used antidepressants. They defined acute treatment as 8 weeks of antidepressant therapy, with a range of 6 to 12 weeks. The primary outcomes studied were response to treatment and dropout rate.

**Response to treatment** (efficacy) was constructed as a Yes or No variable; a positive response was defined as a reduction of  $\geq 50\%$  in symptom score on either the Hamilton Depression Rating Scale or the Montgomery-Asberg Rating Scale, or a rating of “improved” or “very much improved” on the Clinical Global Impression scale at 8 weeks. Efficacy was calculated on an intention-to-treat basis; if data were missing for a participant, that person was classified as a nonresponder.

**Dropout rate** was used to represent acceptability, because the authors believed it to be a more clinically meaningful measure than either side effects or symptom scores. Comparative efficacy and acceptability were analyzed. Fluoxetine—the first of the second-generation antidepressants—was used as the reference medication. The **FIGURE** (page 35) shows the outcomes for nine of the antidepressants, compared with those of fluoxetine. The other two antidepressants, milnacipran and reboxetine, were omitted because they are not available in the United States.

The overall meta-analysis included 25,928 individuals, with 24,595 in the efficacy analysis and 24,693 in the acceptability analysis. Nearly two thirds (64%) of the participants were women. The mean duration of follow-up was 8.1 weeks. The mean sample size per study was 110.

Studies of women with postpartum depression were excluded.

**Escitalopram and sertraline stand out.** Overall, escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than fluoxetine or the other



**Combined psychotherapy and antidepressants are more effective than either treatment alone for all degrees of depression**

medications. Bupropion, citalopram, escitalopram, and sertraline were better tolerated than the other antidepressants. Escitalopram and sertraline were found to have the best combination of efficacy and acceptability.

**Efficacy results.** Fifty-nine percent of participants responded to sertraline, versus a 52% response rate for fluoxetine (number needed to treat [NNT]=14). Similarly, 52% of participants responded to escitalopram, compared with 47% of those taking fluoxetine (NNT=20).

**Acceptability results.** In terms of the dropout rate, 28% of participants discontinued fluoxetine, versus 24% of patients taking sertraline. This means that 25 patients would need to be treated with sertraline, rather than fluoxetine, to avoid one discontinuation. In the comparison of fluoxetine versus escitalopram, 25% discontinued fluoxetine, compared with 24% who discontinued escitalopram.

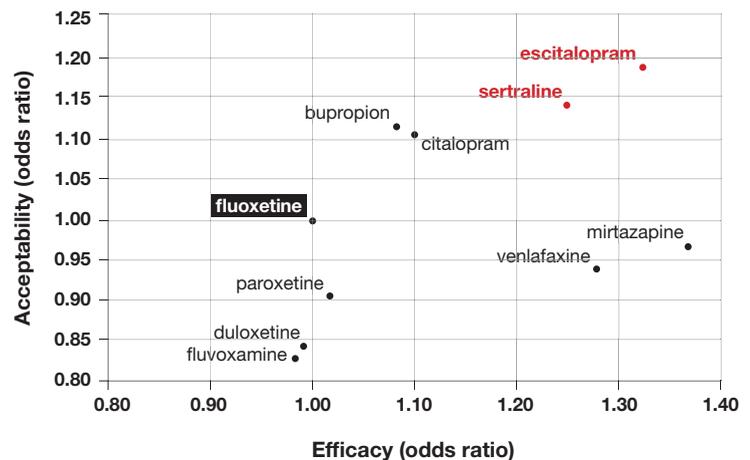
The efficacy and acceptability of sertraline and escitalopram compared with other second-generation antidepressant medications follow similar trends.

**Generic advantage.** The investigators recommend sertraline as the best choice for an initial antidepressant because it is available in generic form and is therefore lower in cost. They further recommend that sertraline, instead of fluoxetine or placebo, be the new standard against which other antidepressants are compared.

### Choice is now evidence-based

We now have solid evidence for choosing sertraline or escitalopram as the first medication to use when treating a patient with newly diagnosed depression. **This represents a practice change because antidepressants that are less effective and less acceptable have been chosen more frequently than either of these medications.** That conclusion is based on our analysis of the National Ambulatory Medical Care Survey database for outpatient and ambulatory clinic visits in 2005-2006 (the most recent data available). We conducted this analysis to determine which of the second-generation antidepressants were prescribed more often for initial monotherapy of major depression.

**FIGURE** Sertraline and escitalopram come out on top in acceptability and efficacy



Researchers analyzed a number of second-generation antidepressants, using fluoxetine as the reference medication. Sertraline and escitalopram provided the best combination of efficacy and acceptability.<sup>1</sup>

Our finding? An estimated 4 million patients 18 years and older given a diagnosis of depression in the course of the study year received new prescriptions for a single antidepressant. Six medications accounted for 90% of prescriptions, in this order:

- fluoxetine (Prozac)
- duloxetine (Cymbalta)
- escitalopram (Lexapro)
- paroxetine (Paxil)
- venlafaxine (Effexor)
- sertraline (Zoloft).

Sertraline and escitalopram, the drugs shown to be most effective and acceptable in the Cipriani meta-analysis, accounted for 11.8% and 14.5% of the prescriptions, respectively.

### Caveats

**This meta-analysis looked at the acute phase of treatment only**

The results of this study are limited to initial therapy as measured at 8 weeks. Few long-term outcome data are available; response to initial therapy may not be a predictor of full remission or long-term success. Current guidelines suggest maintenance of the initial



**Sertraline is the best choice for an initial antidepressant because it is available in generic form**

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

When you initiate an antidepressant for a patient who has not been treated for depression in the past, select either sertraline (Zoloft) or escitalopram (Lexapro).

successful therapy, often with increasing intervals between visits, to prevent relapse.<sup>9</sup>

This study does not add new insight into long-term response rates. Nor does it deal with choice of a replacement or second antidepressant for nonresponders or those who cannot tolerate the initial drug.

What's more, the study covers drug treatment alone, which may not be the best initial treatment for depression. Psychotherapy, in the form of cognitive behavioral therapy or interpersonal therapy, when available, is equally effective, has fewer potential physiologic side effects, and may produce longer-lasting results.<sup>10,11</sup>

**Little is known about study design**

The authors of this study had access only to limited information about inclusion criteria and the composition of initial study populations or settings. There is a difference between a trial designed to evaluate the "efficacy" of an intervention (i.e., "the beneficial and harmful effects of an intervention under controlled circumstances") and the "effectiveness" of an intervention (i.e., the "beneficial and harmful effects of the intervention under usual circumstances").<sup>12</sup> It is not clear which of the 117 studies were efficacy studies and which were effectiveness studies. This

may limit the overall generalizability of the study results to a primary care population.

Studies included in this meta-analysis were selected exclusively from published literature. There is some evidence of a bias toward the publication of studies that have yielded positive results, which may have the effect of overstating the effectiveness of a given antidepressant.<sup>13</sup> However, we have no reason to believe that this bias would favor any particular drug.

Most of the included studies were sponsored by drug companies. Notably, pharmaceutical companies have the option of continuing to conduct trials of medications until a study results in a positive finding for their medication, with no penalty for the suppression of equivocal or negative results (negative publication bias). Under current FDA guidelines, there is little transparency for the consumer as to how many trials have been undertaken and the direction of the results, published or unpublished.<sup>14</sup>

We doubt that either publication bias or the design and sponsorship of the studies included in this meta-analysis present significant threats to the validity of these findings over other sources upon which guidelines rely, given that these issues are common to much of the research on pharmacotherapy. We also doubt that the compensation of the authors by pharmaceutical companies would bias the outcome of the study, in this instance. One of the authors (Furukawa) received compensation from Pfizer, the maker of Zoloft, which is also available as generic sertraline. None of the authors received compensation from Forest Pharmaceuticals, the maker of Lexapro (escitalopram).

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**FAST TRACK**

**Drug therapy may not be the best initial treatment for depression. Psychotherapy is equally effective, has fewer potential side effects, and may produce longer-lasting results**

**About the source of this review**

This article is one of a series of "Priority Updates from the Research Literature" (PURLs), a program of the Family Physicians Inquiries Network (FPIN). It is republished here from the July 2009 issue (volume 58, number 7) of *The Journal of Family Practice*, a Dowden Health Media publication.

The study<sup>1</sup> analyzed in this article was

selected and evaluated using FPIN's PURL Surveillance System methodology. The criteria and findings that led to the selection of this study as a PURL can be found at [www.jfponline.com/purls](http://www.jfponline.com/purls).

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The PURLs editor for *The Journal of Family Practice* is John Hickner, MD, MSc, Chair of the Department of Family Medicine at the Cleveland Clinic, Cleveland, Ohio.

5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

#### E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS**, **WARNINGS** and **PRECAUTIONS**.)

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.24 to 10.3 times the exposure (AUC of drospirenone) of women taking a 1 mg dose, there was an increase in carcinomas of the hardier gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 2.3 to 51.2 times the exposure of women taking a 1 mg dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. (See **WARNINGS** section.)

**F. PREGNANCY**  
ANGELIQ should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

**G. NURSING MOTHERS**  
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when ANGELIQ is administered to a nursing woman.

After administration of an oral contraceptive containing drospirenone about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

**H. PEDIATRIC USE**  
ANGELIQ is not indicated in children.

**I. GERIATRIC USE**  
There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing ANGELIQ to determine whether those over 65 years of age differ from younger subjects in their response to ANGELIQ.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone

acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women who were older than 70. (See **WARNINGS**, **Dementia**.)

#### ADVERSE REACTIONS

See **BOXED WARNINGS**, **WARNINGS**, AND **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following are adverse events reported with ANGELIQ occurring in >5% of subjects:

**Table 4: Adverse Events Regardless of Drug Relationship Reported at a Frequency of >5% in a 1-year Double-blind Clinical Trial**

ADVERSE EVENT	E2 1 MG (N=226) n (%)	ANGELIQ (N=227) n (%)
<b>BODY AS A WHOLE</b>		
Abdominal pain	29 (12.8)	25 (11)
Pain in extremity	15 (6.6)	19 (8.4)
Back pain	11 (4.9)	16 (7)
Flu syndrome	15 (6.6)	16 (7)
Accidental injury	15 (6.6)	13 (5.7)
Abdomen enlarged	17 (7.5)	16 (7)
Surgery	6 (2.7)	12 (5.3)
<b>METABOLIC &amp; NUTRITIONAL DISORDERS</b>		
Peripheral edema	12 (5.3)	4 (1.8)
<b>NERVOUS SYSTEM</b>		
Headache	26 (11.5)	22 (9.7)
<b>RESPIRATORY SYSTEM</b>		
Upper respiratory infection	40 (17.7)	43 (18.9)
Sinusitis	8 (3.5)	12(5.3)
<b>SKIN AND APPENDAGES</b>		
Breast pain	34 (15.0)	43 (18.9)
<b>UROGENITAL</b>		
Vaginal hemorrhage	43 (19.0)	21 (9.3)
Endometrial disorder	22 (9.7)	4 (1.8)
Leukorrhea	14 (6.2)	3 (1.3)

The following additional adverse reactions have been reported with estrogen and/or estrogen/progestin therapy:

**1. Genitourinary system**  
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

**2. Breasts**  
Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

**3. Cardiovascular**  
Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

**4. Gastrointestinal**  
Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increased incidence of gall bladder disease, pancreatitis, enlargement of hepatic hemangiomas.

**5. Skin**  
Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.

**6. Eyes**  
Retinal vascular thrombosis, intolerance to contact lenses.

**7. Central nervous system**  
Headache, migraine, dizziness, mental depression, chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.

**8. Miscellaneous**  
Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, anaphylactoid/anaphylactic reactions including urticaria and angioedema, hypocalcemia, exacerbation of asthma, increased triglycerides.

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## No major barriers anticipated

Both sertraline and escitalopram are covered by most health insurers. As noted, sertraline is available in a generic formulation and is therefore much less expensive than escitalopram.

In a review of drug prices at [www.pharmacychecker.com](http://www.pharmacychecker.com), we found that a prescrip-

tion for a 3-month supply of Lexapro (10 mg) costs about \$250. A 3-month supply of generic sertraline (100 mg) from the same sources costs approximately \$35. Pfizer, maker of Zoloft, and Forest Pharmaceuticals, maker of Lexapro, both administer patient assistance programs to make these medications available to low-income, uninsured patients.

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