

# Antidep

A surreal image of a hallway with a purple wall covered in numerous small, floating doors and windows. A large wooden door is open on the right side of the frame. The word 'Antidep' is written in large white letters with a purple outline across the top half of the image.

**Referring to certain groups of drugs as antidepressants does them a great disservice; their potential uses range far beyond mood disorders**

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# Antidepressants

## The spectrum beyond depression

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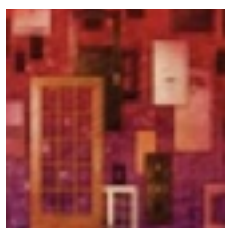
A molecule is a molecule is a molecule—until it becomes identified with a purpose. Consider, for example, (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine. You probably know this molecule as paroxetine—an antidepressant, of course, but it is more than that. If you examine paroxetine's FDA-approved indications, it also has anti-panic, anti-social anxiety, anti-obsessive-compulsive disorder, anti-posttraumatic stress disorder, and anti-premenstrual dysphoric disorder effects.

"Antidepressants" have achieved fame as antidepressants; one could say these molecules' search for meaning has been fulfilled. Yet even within psychiatry, their many other uses (*Table, page 36*) can create semantic misunderstandings. Beyond psychiatry, consider the nondepressed patient with neurocardiogenic syncope who wonders why he's being treated with an antidepressant.

Rather than calling antidepressants "panaceas," the better choice is to educate patients about the drugs' wide spectrum of activity. Let's look broadly across the so-called antidepressants and examine their varied uses in psychiatry and other medical specialties.

### Pain syndromes

**Peripheral neuropathy.** The only antidepressant with an FDA-approved pain indication is duloxetine,



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### Clinical Point

Patients with chronic low back pain (averaging 10 years) seem to benefit from antidepressants, as do patients with chronic migraine

#### Table

### FDA-approved psychiatric indications for serotonin uptake inhibitors\*

Medication	MDD	PD	SAD	PTSD	GAD	OCD	PMDD	BUL
<b>SSRIs</b>								
<b>Citalopram</b>	X							
<b>Escitalopram</b>	X				X			
<b>Fluoxetine</b>	X	X				X	X	X
<b>Fluvoxamine</b>						X		
<b>Paroxetine</b>	X	X	X	X	X	X	X	
<b>Sertraline</b>	X	X	X	X		X	X	
<b>SNRIs</b>								
<b>Duloxetine</b>	X				X			
<b>Venlafaxine</b>	X	X	X		X			

SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; MDD: major depressive disorder; PD: panic disorder; SAD: social anxiety disorder; PTSD: posttraumatic stress disorder; GAD: generalized anxiety disorder; OCD: obsessive-compulsive disorder; PMDD: premenstrual dysphoric disorder; BUL: bulimia

\* The absence of an X does not necessarily imply that a drug is ineffective for a given indication but, more likely, that definitive studies are lacking.

a serotonin-norepinephrine reuptake inhibitor (SNRI). Its approval for diabetic peripheral neuropathic pain (DPNP) was based on two 12-week, randomized, double-blind, placebo-controlled studies using fixed doses of 60 mg once or twice daily.<sup>1,2</sup> Another SNRI—venlafaxine XR, 150 to 225 mg/d, but not 75 mg/d—also was found to be more effective than placebo for this indication in a 6-week, double-blind study (Box 1).<sup>3</sup>

Using antidepressants to treat pain syndromes is neither new nor restricted to SNRIs, however. In combined double-blind, cross-over studies of patients with DPNP, Max et al<sup>4</sup> found:

- moderate or greater pain relief in 74% and 61% of subjects, respectively, from the tricyclics amitriptyline, mean 105 mg/d, and desipramine, mean 111 mg/d—with pain reduced by equal amounts in depressed and nondepressed patients
- no statistically significant difference in pain relief between the selective serotonin reuptake inhibitor (SSRI) fluoxetine, 40 mg/d, and placebo.

Sindrup et al<sup>5</sup> concluded in a 2005 review that antidepressants relieve DPNP according to this hierarchy:

- tricyclics: 1 in every 2 to 3 patients

- SNRIs: 1 in every 4 to 5 patients
- SSRIs: 1 in every 7 patients.

Bupropion SR—a norepinephrine dopamine reuptake inhibitor—also may be more effective than placebo in relieving neuropathic pain, as shown in a small (N=41) 6-week, double-blind study.<sup>6</sup>

**Chronic headache.** A meta-analysis<sup>7</sup> of randomized, placebo-controlled studies found antidepressants more effective than placebo for chronic migraine and tension headache prophylaxis. Although a subgroup meta-analysis found similar effects for tricyclics and SSRIs, the authors characterized the tricyclics' results as well established and the SSRIs' as "less certain."

The results of this meta-analysis might not accurately reflect bona fide antidepressants, however. Some of the 38 studies (25 of migraine, 12 of tension headache, 1 of both) included treatment with serotonin antagonists—most commonly pizotifen, which is not available in the United States and does not appear to be an antidepressant.

**Back pain.** Patients with chronic low back pain (average 10 years) seem to benefit from antidepressants, according to a meta-analysis of 9 randomized, controlled trials



## Dual-action antidepressants ease neuropathic pain

**S**erotonin and norepinephrine are involved in pain modulation via descending inhibitory pathways in the brain and spinal cord. Serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to reduce the severity of diabetic peripheral neuropathic pain (DPNP) in randomized controlled trials.

**Duloxetine.** In 2 double-blind studies,<sup>1,2</sup> nondepressed patients with DPNP received duloxetine, 60 mg once daily; duloxetine, 60 mg bid; or placebo for 12 weeks. They rated the severity of neuropathic pain every 24 hours on an 11-point Likert scale, and weekly mean scores were the primary outcome measure. Average pain scores improved more in both duloxetine groups vs placebo. Duloxetine treatment did not interfere with diabetic control, and both dosages were well tolerated.

The FDA approved an added indication for duloxetine in the management of DPNP.

**Source:** References 1-3

**Venlafaxine.** In a double-blind study,<sup>3</sup> 244 adult outpatients with moderately severe DPNP received venlafaxine ER, 75 or 150 to 225 mg/d, or placebo for 6 weeks. Daily scores on the Visual Analog Pain Intensity (VAS-PI) and Pain Relief (VAS-PR) scales were primary efficacy measures.

Patients receiving the higher venlafaxine dosage—but not 75 mg/d—showed statistically significant less-intensive pain vs placebo. VAS-PI scores were 27% lower than at enrollment with placebo, 32% lower with venlafaxine, 75 mg/d, and 50% lower with venlafaxine, 150 to 225 mg/d ( $P < 0.001$  vs placebo). VAS-PR scores also were significantly greater with venlafaxine, 150 to 225 mg, compared with placebo ( $P < 0.001$ ).

Nausea and somnolence were the most common side effects; clinically important ECG changes occurred in 7 patients treated with venlafaxine, 150 to 225 mg/d.

**Overall,** antidepressants are generally understood to have analgesic effects in the absence of depression. Benefits for patients with pain syndromes are well established for tricyclics (especially amitriptyline) and recently with SNRIs, whereas SSRIs are less effective.

### Smoking cessation

Bupropion SR is FDA-approved to aid smoking cessation, and this effect is independent of the drug's antidepressant activity. Bupropion may act as a nicotine receptor antagonist as well as a norepinephrine dopamine reuptake inhibitor.

Other antidepressants have been studied for smoking cessation, with nortriptyline showing benefit in 2 large placebo-controlled trials. Studies with doxepin, fluoxetine, and moclobemide found little or no benefit for this indication.

### Cardiovascular uses

**Angina.** Monoamine oxidase inhibitor (MAOI) antidepressants were used to treat

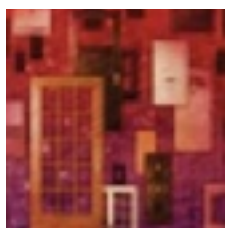
### Clinical Point

Benefits for patients with pain syndromes without depression are well established for tricyclics and SNRIs, whereas SSRIs are less effective

by Salerno et al.<sup>8</sup> The effect on pain in the total 504 patients was “small but significant,” and improvement in function was “small but nonsignificant.” Individual sample sizes also were small, however, and only 2 studies excluded depressed patients.

**Fibromyalgia,** with chronic generalized musculoskeletal pain and tenderness, has been a focus of antidepressant drug therapy. Goldenberg et al<sup>9</sup> concluded from an ambitious literature review (505 articles) that evidence of efficacy was strong for amitriptyline and modest for SSRIs and SNRIs.

On the other hand, Littlejohn and Guymer<sup>10</sup> concluded in a clinical review that trials of SSRIs “have been somewhat disappointing,” that tricyclics are, at best, “only moderately effective,” and that more balanced dual uptake inhibitors such as duloxetine and the investigational agent milnacipran “are showing more promise.” Two placebo-controlled studies by Arnold et al<sup>11,12</sup> of women with fibromyalgia showed benefit from duloxetine that appeared independent from its effect on depression and anxiety.



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### Clinical Point

Paroxetine, 20 mg/d, is considerably more effective than placebo in preventing recurrent vasovagal syncope

### Box 2

## Nondepressed patients with IBS feel better when taking SSRIs

Selective serotonin reuptake inhibitors (SSRIs) often are used to treat irritable bowel syndrome (IBS), though evidence of their effectiveness is scarce. SSRIs can improve IBS patients' quality of life, but effects on abdominal pain and bloating are less clear.

**Paroxetine.** In a randomized, double-blind trial,<sup>16</sup> gastroenterologists tested a high-fiber diet plus paroxetine in nondepressed patients with IBS. Ninety-eight patients ages 18 to 65 who experienced IBS symptoms on low- or average-fiber diets were first put on high-fiber diets and assessed for well-being and abdominal pain and bloating. Of these, 81 symptomatic patients continued high-fiber diets with added paroxetine, 10 to 40 mg/d (n=38) or placebo (n=43).

With paroxetine, patients' overall well-being improved more than with placebo, but abdominal pain and bloating and social functioning did not.

**Fluoxetine.** In a double-blind, randomized trial,<sup>17</sup> 44 patients with pain and constipation-predominant IBS received fluoxetine, 20 mg/d, or placebo for 12 weeks. These patients met Rome II criteria for IBS—

abdominal discomfort/pain for  $\geq 12$  weeks in past year that met 2 of 3 criteria:

- relieved by defecation
- onset associated with change in stool frequency
- onset associated with change in stool appearance.

Patients receiving fluoxetine had less abdominal discomfort, less bloating, more frequent bowel movements, and decreased consistency of stool vs placebo 4 weeks after treatment stopped. Mean number of symptoms per patient decreased from 4.6 to 0.7 in the fluoxetine group vs 4.5 to 2.9 in controls ( $P < 0.001$ ).

**Citalopram.** IBS symptom severity was the primary outcome in a crossover trial comparing citalopram (20 mg for 3 weeks and 40 mg for 3 weeks) with placebo in 23 nondepressed patients.<sup>18</sup> Abdominal pain and bloating, impact of symptoms on daily life, and overall well-being improved significantly more with citalopram than with placebo after 3 and 6 weeks.

Symptom improvements were not related to changes in depression, anxiety, or colonic sensorimotor function.

Source: References 16-18

angina pectoris in the late 1950s and early 1960s. This practice stopped after evidence showed that whereas angina pain may have improved with MAOIs, stress-induced ischemia on ECG did not.

**Antiarrhythmia.** Tricyclics had a brief fling in cardiovascular therapeutics when their quinidine-like class I antiarrhythmic activity was recognized. Imipramine was one of several drugs included in the Cardiac Arrhythmia Pilot Study in the 1980s that involved 502 postmyocardial infarction patients with ventricular arrhythmias. Imipramine was the least effective of the 4 drugs studied and the least well tolerated.<sup>13</sup>

**Syncope.** Neurocardiogenic (vasovagal) syncope—a common cause of fainting—can be treated when necessary with a variety of medications. Options include the vasopressor midodrine, fludrocortisone, beta block-

ers, and SSRIs—none FDA-approved for this indication. Paroxetine, 20 mg/d, was considerably more effective than placebo in preventing recurrent syncope in 68 patients who had been unresponsive to or intolerant of traditional medications. During a mean 25 months of treatment, 82% of patients remained syncope-free on paroxetine vs 47% on placebo.<sup>14</sup>

## Gastrointestinal

**Peptic ulcer disease** was shown in the 1980s to respond to tricyclic antidepressants. At the time, both anticholinergic and antihistaminic effects were thought to be responsible, but the later observation that trimipramine inhibited *Campylobacter pylori* in vitro suggested an additional explanation. Today, tricyclics are only of historic interest as treatments for peptic ulcer.

**Irritable bowel syndrome (IBS)** patients have responded favorably to antidepressants, although it is often difficult to know if the benefit is independent of improved coexisting anxiety or depression. A meta-analysis of 12 randomized, placebo-controlled trials—mostly with tricyclics—found an odds ratio for improvement of 4.2 and a number needed to treat of 3.2.<sup>15</sup>

More recently, a few placebo-controlled studies have shown SSRIs to be beneficial for IBS,<sup>16-18</sup> although not all symptoms improved and some IBS subtypes might be more responsive than others (**Box 2**). In an editorial, Talley<sup>19</sup> concluded that antidepressant therapy of IBS was “at best only a ‘band-aid’ approach to management.”

### Genitourinary

**Nocturnal enuresis.** In the 1960s, imipramine was shown—in some but not all placebo-controlled studies—to be beneficial for nocturnal enuresis in children and adults. Although imipramine is not FDA-approved for this indication, it is thought to work by relaxing bladder muscle and contracting bladder neck smooth muscle. Imipramine appears to have a vasopressin-independent antidiuretic effect in enuretic patients with nocturnal polyuria.

**Stress urinary incontinence.** Placebo-controlled studies have shown duloxetine to be an effective treatment for stress urinary incontinence in women. A Cochrane Database Review of 9 randomized studies in adults (N=3,327) concluded that duloxetine significantly improved patients’ quality of life, although how long the benefits would last was unclear.<sup>20</sup>

Duloxetine is thought to improve stress urinary incontinence by increasing urethral sphincter tone and the force of sphincter contraction. This indication is not FDA-approved for duloxetine but is approved in the European Union.

### Oncology

At one time antidepressants were suggested to promote tumors, based on observations that amitriptyline, fluoxetine, and several antihistamines promoted tumor growth in rodents.<sup>21</sup> In 1995, a few case reports associated these 2 antidepressants with atypical cutaneous lymphoid infiltrates.<sup>22</sup> A review by Sternback in 2003<sup>23</sup> concluded that a link between antidepressants and cancer was questionable but acknowledged the need for very long-term studies.

Recently, a nested case-control study found an association between high-dose SSRI use for ≤5 years

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\*Data from a study comparing driving in 105 young adults with ADHD to 64 community control adults without the disorder.

Reference: 1. Barkley RA, Murphy KR, DuPaul GJ, Bush T. Driving in young adults with attention deficit hyperactivity disorder: knowledge, performance, adverse outcomes, and the role of executive functioning. *J Am Neuropsychol Soc*. 2002;8:655-672.

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## Antidepressants

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Duloxetine is thought to improve stress urinary incontinence by increasing urethral sphincter tone and force of contraction

### Box 3

## A 'beneficial' adverse effect: SSRIs for premature ejaculation

Delayed ejaculation is among the sexual side effects commonly associated with antidepressant medication. In a 6-week trial,<sup>27</sup> 3 selective serotonin reuptake inhibitors (SSRIs)—paroxetine, fluoxetine, and sertraline—were shown to improve intravaginal ejaculatory latency time (IELT) in men with lifelong rapid ejaculation. Compared with baseline, the greatest delay in ejaculation was seen with paroxetine, 20 mg/d, followed by fluoxetine, 20 mg/d, and then sertraline, 50 mg/d, whereas delay with fluvoxamine, 100 mg/d, did not differ significantly from placebo.

**Dapoxetine** is a non-antidepressant SSRI under investigation for on-demand treatment of moderate-to-severe premature ejaculation.<sup>28</sup> In two 12-week, randomized, double-blind, placebo-controlled trials, 870 men took placebo, 874 took 30-mg dapoxetine, and 870 took 60-mg dapoxetine 1 to 3 hours before sexual activity. Efficacy was determined by IELT measured at home by stopwatch.

Both dapoxetine doses improved IELT significantly more than placebo ( $P < 0.0001$ ). Mean IELT at baseline of <1 minute in each group improved to 1.75 minutes with placebo, 2.75 minutes with 30-mg dapoxetine, and 3.32 minutes with 60-mg dapoxetine. Both dapoxetine doses were effective on the first dose.

Nausea, diarrhea, headache, and dizziness occurred in  $\leq 20\%$  of patients and were more common with the 60-mg than 30-mg dapoxetine dose.

Source: References 27, 28

and reduced risk of colorectal cancer, whereas no association was found with tricyclic use.<sup>24</sup> A study of this design does not establish a causal relationship, however, and one can only speculate whether SSRIs might have direct cytotoxic or anti-promoter effects.

At present, it seems reasonable to continue to treat depressed cancer patients with antidepressants without concern that cancer will worsen or hope that it will improve as a result.

## Immunology

The pathogenesis of depression may be linked to pro-inflammatory cytokines—proteins such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and certain interleukins that mediate immune function. Bupropion markedly lowered pro-inflammatory cytokine levels in a mouse inflammation model, prompting the authors to suggest that this anti-inflammatory effect be explored in humans.<sup>25</sup>

Case reports have suggested benefit from bupropion in Crohn's disease, recurrent aphthous ulcerations, psoriasis, atopic dermatitis, and Blau syndrome (a rare autosomal-dominant trait characterized by granulomatous arthritis, iritis, and skin rash). Whether this antidepressant has much anti-inflammatory potential remains to be determined, however.

## Infectious disease

Pathogenic protozoa—such as *Trypanosoma cruzi* (Chagas disease), *Leishmania donovani* (Kala-azar), *Leishmania major* (Oriental sore), and *Giardia lamblia* (Giardiasis)—infect millions of humans worldwide. Clomipramine has been shown in vitro and in mice to inhibit or kill these protozoa, but these potential benefits have not been extended to humans.

Sertraline, on the other hand, might exert antifungal activity. Three patients with recurrent vulvovaginal candidiasis had no episodes while being treated with sertraline for premenstrual dysphoric disorder but relapsed when the drug was discontinued.<sup>26</sup> Although sertraline demonstrated antifungal activity in vitro against several *Candida* species, this SSRI seems unlikely to gain prominence as an antifungal agent.

## Sexual function

**Premature ejaculation.** SSRIs are well-known causes of delayed or absent orgasm, but a perceived liability can become an asset in treating premature ejaculation. By measuring intravaginal ejaculation latency time under double-blind, placebo-controlled conditions, Waldinger et al<sup>27</sup> showed



## Related Resources

- Gorman JM, Kent JM. SSRIs and SMRIs: broad spectrum of efficacy beyond major depression. *J Clin Psychiatry* 1999;60(suppl 4):33-8.
- About.com: Mental Health. Antidepressants for more than depression. <http://mentalhealth.about.com/cs/psychopharmacology/a/antimore.htm>.

### Drug Brand Names

Amitriptyline • Elavil, Endep	Fluvoxamine • Luvox
Bupropion • Wellbutrin, Zyban	Imipramine • Tofranil
Citalopram • Celexa	Midodrine • ProAmitine
Clomipramine • Anafranil	Nortriptyline
Desipramine • Norpramin,	• Pamelor, Aventyl
Pertofrane	Paroxetine • Paxil
Doxepin • Adapin, Sinequan	Phenelzine • Nardil
Duloxetine • Cymbalta	Sertraline • Zoloft
Escitalopram • Lexapro	Trimipramine • Surmontil
Fludrocortisone • Florinef	Venlafaxine • Effexor
Fluoxetine • Prozac	

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pronounced delay in ejaculation with sertraline, fluoxetine, and paroxetine in men with long-standing rapid ejaculation. Dapoxetine—a short-acting non-antidepressant SSRI—is being studied as a treatment for this condition (*Box 3*).<sup>28</sup>

**Spermicidal effect.** SSRIs—including fluoxetine—have demonstrated in vitro spermicidal and antitrichomonas activity<sup>29</sup> but are unlikely to be developed as microbical contraceptives.

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continued



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### Clinical Point

Sertraline has shown antifungal activity in vitro against *Candida* species but is unlikely to gain prominence as an antifungal agent

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## Bottom Line

Antidepressants can have analgesic effects in nondepressed patients with back pain, fibromyalgia, and peripheral neuropathic pain; the efficacy hierarchy appears to be tricyclics, SNRIs, then SSRIs. Irritable bowel symptoms may respond to SSRIs, as may vasovagal syncope, chronic headache, and premature ejaculation. Duloxetine improves stress urinary incontinence, and sertraline may have antifungal effects.