

## Selecting Antidepressants for Terminally Ill Patients *Clinical Implications and Cost Considerations*

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Depression is a serious disabling illness that affects more than 16% of U.S. adults during their lifetime<sup>1</sup> and is a common problem among terminally ill patients.<sup>2</sup> Prevalence rates of depression among terminally ill patients range widely, depending on diagnostic criteria used and patient population studied. Rates of depression range from 3% to 38% among patients with advanced cancer.<sup>3</sup> Patients with end-stage heart disease are reported to have prevalence rates of 36% for major depression and 22% for minor depression; whereas, those with end-stage renal disease have rates of depression between 5% and 25%.<sup>3</sup> Although the frequency of depression appears to increase as terminally ill patients decline, distinguishing depression that requires treatment from feelings of grief, fear and sadness is challenging.<sup>3</sup>

Suboptimally treated depression is associated with increased hospital readmissions, prolonged hospital stays, and reduced quality of life.<sup>3</sup> Depression influences the will to live and is a major risk factor for requests to hasten death, especially among terminally ill patients.<sup>3</sup> Data indicate that palliative care clinicians usually recognize depression in their patients but tend to underestimate its severity.<sup>4-6</sup> Depression is a treatable illness, even in patients who are terminally ill.<sup>3</sup> However, selecting the most clinically appropriate and cost-effective antidepressant is challenging. This article describes differences in efficacy, effectiveness, tolerability and cost of antidepressants to help palliative care clinicians make more informed choices when selecting an antidepressant for a terminally ill patient.

### How is depression treated?

Depression is treated using a variety of different therapies, such as cognitive behavioral therapy, psychotherapy, and pharmacotherapy.<sup>7</sup> Pharmacotherapy is the treatment most often used and may include first-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) and second-generation antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors, and selective serotonin and norepinephrine reuptake inhibitors).<sup>1</sup> In general, the efficacy and effectiveness of first- and second-generation antidepressants is similar.<sup>1</sup> However, because of their relatively favorable side effect profile and lower toxicity in overdose,

second-generation antidepressants are often preferentially used over first-generation antidepressants.<sup>1,7</sup> The SSRIs are the focus of this article because they are the most commonly prescribed antidepressants for terminally ill patients.<sup>8</sup>

### How do the SSRIs compare in terms of efficacy, effectiveness, and tolerability?

Like most drugs, the SSRIs have not been widely tested in terminally ill patients to determine whether there are clinically meaningful differences in efficacy, effectiveness, and tolerability specific to this patient population. Nonetheless, trials in other patient populations provide valuable information useful in extrapolating to terminally ill patients.

Currently, there is no evidence of substantial differences among the SSRIs in efficacy, effectiveness, or general tolerability for the treatment of depression.<sup>1</sup> Furthermore, depression is often accompanied by symptoms such as anxiety, insomnia, and pain. Several clinical trials of the SSRIs for treating depression accompanied by these symptoms have been reported. Cumulatively, their results show that there are no clinically meaningful differences between the SSRIs in terms of efficacy for treating depression accompanied by anxiety.<sup>1</sup> For depression accompanied by insomnia or pain, their results are inconclusive.<sup>1</sup>

Overall, there is good evidence that the SSRIs are generally well tolerated and have similar side effect profiles, most notably gastrointestinal problems, sexual dysfunction, and sleep disturbances.<sup>1,9</sup> However, the incidence rates of specific side effects and drug interactions differ (Table 1). For example, among the SSRIs, paroxetine has the highest rate of sexual dysfunction and discontinuation syndrome; fluoxetine has the lowest rate of discontinuation syndrome.<sup>1</sup> Paroxetine also has more anticholinergic side effects than other SSRIs.<sup>9</sup> Sertraline has the highest rate of diarrhea,<sup>9</sup> but this side effect does not usually lead to discontinuation and may be a desired feature for some patients with constipation. Fluoxetine, fluvoxamine, and paroxetine are the SSRIs with the greatest likelihood of having a clinically significant drug interaction involving the cytochrome (CYP) P450 system.<sup>9</sup> Because of the long half-life of fluoxetine and its metabolite, norfluoxetine, fluoxetine is more

likely than other SSRIs to result in sustained drug interactions. These differences often influence the choice of an SSRI for specific patients.

### How do the SSRIs compare in terms of cost?

Despite only minor differences in terms of efficacy, effectiveness and general tolerability, the acquisition cost of the SSRIs differ markedly (Table 1). Paroxetine mesylate, for example, is commercially available as a brand-name prescription drug (Pexeva®) and is the most costly of the SSRIs. Although less costly than paroxetine mesylate, escitalopram is also commercially available as a brand-name prescription drug (Lexapro®) and is significantly more costly (+ 5337.2% difference) than citalopram, which is now available generically. Based on cost alone, citalopram and sertraline should be considered the SSRIs of first-choice when initiating treatment of depression. However, when considering both cost and evidence, based on a recent meta-analysis of 117 randomized controlled trials, sertraline should be considered the SSRI of first-choice because it has the most favorable balance between efficacy, effectiveness, tolerability, and acquisition cost.<sup>11</sup>

Cost considerations are especially important in a capitated system, whereby hospices receive a fixed payment for each terminally ill patient

to cover all hospice-related expenses, including drugs. According to industry analysts, drug makers are raising their prices at the fastest rate in nearly 20 years.<sup>12</sup> Last year, for example, drug makers raised the average wholesale prices of brand-name prescription drugs by an estimated 9%.<sup>12</sup> In the last six months, the acquisition cost of escitalopram (Lexapro®), a commonly prescribed SSRI, rose by an estimated 8%. To put this into perspective from the hospice provider viewpoint, the Medicare hospice payment rates increased about 2.1% from fiscal year 2008/2009 to 2009/2010.<sup>13</sup> Thus, the cost of drugs is rising much faster than the Medicare hospice payment rates. Selecting less costly antidepressants could help ease the burden of rising drug cost for hospices.

### What is the take-away message?

Palliative care clinicians routinely care for terminally ill patients with depression. As with all drugs, antidepressants should be used after careful consideration of benefits and risks. Clinicians should select an antidepressant on the basis of the evidence and cost. The SSRIs are fairly well-tolerated and although they differ slightly in terms of specific side effects and drug interactions, they are similar in terms of efficacy and effectiveness. Among the SSRIs, citalopram and sertraline are the least costly.

**Table 1. Differences in Specific Side Effects, Specific Drug Interactions and Acquisition Cost between the SSRIs<sup>1,9,10</sup>**

SSRIs*	Specific Side Effects†	Specific Drug Interactions	Usual Adult Maintenance Dose	% Difference in Acquisition Cost
Sertraline (Zoloft®)	Diarrhea	--	100mg PO QD	--
Citalopram (Celexa®)	--	--	40mg PO QD	+ 5.2%
Fluoxetine IR (Prozac®)	--	CYP450 interactions	20mg PO QD	+ 419.7%
Paroxetine HCl (Paxil®)	Anticholinergic (e.g., blurred vision, constipation, dry mouth) Discontinuation syndrome (e.g., flu-like symptoms, insomnia, sensory disturbances) Sedation Sexual dysfunction Weight gain	CYP450 interactions	20mg PO QD	+ 471.7%
Paroxetine HCl ER (Paxil CR®)	Same as paroxetine HCl but incidence rate may be lower	CYP450 interactions	25mg PO QD	+ 4802.8%
Escitalopram (Lexapro®)	--	--	10mg PO QD	+ 5621.1%
Fluoxetine weekly (Prozac® Weekly™)	--	CYP450 interactions	90mg QW	+ 6378.8%
Paroxetine mesylate (Pexeva®)	Same as paroxetine HCl but incidence rate may be lower	CYP450 interactions	20mg PO QD	+ 9643.0%

CYP450 = cytochrome P450 system; ER = extended-release; HCl = hydrochloride; IR = immediate-release; PO = by mouth (orally); QD = once daily; QW = once weekly; SSRIs = selective serotonin reuptake inhibitors.

\*The SSRIs are expressed as generic name (common brand name) and are listed in ascending order based on acquisition cost (from lowest to highest), with sertraline, the least costly SSRI, used as the comparator (data on file, Hospice Pharmacia, a service of excelleRx, Inc., an Omnicare company; April, 2010). Although sometimes used, fluvoxamine (Luvox®) is not approved by the U.S. Food and Drug Administration for treating depression and, therefore, is omitted from the table.

†Specific side effects are listed if the incidence rate is significantly higher compared with other SSRIs.

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