Selecting a First-line Antidepressant: New Analysis

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Commentary by Michael E. Thase, MD

Many considerations go into the selection of an antidepressant. These include the overall clinical status of the patient, including comorbid disorders, use of other medications, sensitivities to certain side effects, and past history (if any) of treatment with antidepressants. A perennial question involving antidepressants is: Which drug is most effective? As a prescriber and an educator, I am constantly scanning the literature for studies that demonstrate differences in antidepressant efficacy, tolerability, and safety.

Individual studies, usually funded by the companies that market antidepressants, have been of limited value, given what we now know about publication bias. A recent study published in the New England Journal of Medicine reported that among 74 Food and Drug Administration-registered studies, 31% were not published. Moreover, the authors noted:

Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; one study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with three exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11% to 69% for individual drugs and was 32% overall.

With this in mind, a recent news headline caught my eye: “Escitalopram and Sertraline Top Comparison of 12 Newer Antidepressants.” Most other attempts at meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. Most, but not all, showed a slight advantage for drugs that enhanced multiple neurotransmitter systems (notably serotonin and norepinephrine) over those that targeted only one of these systems. The most recent meta-analysis showed no difference among antidepressants.

Of note is a recent study in Lancet by Andrea Cipriani, MD, and an international team of researchers, titled “Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis.” Not an expert at assessing the methodology used in the analysis, I consulted my colleague Michael E. Thase, MD, a professor of psychiatry at the University of Pennsylvania School of Medicine in Philadelphia, to get his opinion on the study. Dr. Thase has published extensively on the subject of antidepressants in general and meta-analyses specifically. Overall, he believes that this is an important study and, because it used a method of indirect comparison, it is probably more informative than other meta-analyses. However, he also noted that it makes the study more subject to potential bias effects than meta-analyses of studies making direct comparisons.

Cipriani and colleagues reviewed 117 randomized controlled trials from 1991 up to November 30, 2007, which compared 12 new-generation antidepressants at therapeutic dose range for the acute treatment of unipolar major depressive disorder (MDD) in adults (see the Table for the drugs and doses). The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was conducted on an intention-to-treat basis. According to the final analysis, mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Reboxetine was significantly less efficacious than all the other antidepressants.
tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. According to the authors:

Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.15

Should these findings be used to help choose among new-generation antidepressants for acute treatment of major depression? The authors claim that:

Some antidepressants differed both statistically and clinically. In terms of response, mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. In terms of acceptability, escitalopram, sertraline, citalopram, and bupropion were better tolerated than other new-generation antidepressants. These results indicate that two of the most efficacious treatments (mirtazapine and venlafaxine) might not be the best for overall acceptability.12

Thus, a useful message from this is that a higher response rate alone needs to be balanced with good tolerability. In that case, sertraline came out the winner. As shown in the Figure, the various drugs have different curves for responses and tolerability.

Reboxetine (not available in the United States), fluvoxamine, paroxetine, and duloxetine were the least efficacious and acceptable drugs, making them less favorable options when prescribing an acute treatment for MDD. According to Dr. Thase, the fact that reboxetine came up last in both efficacy and tolerability may be the post-script to why it did not receive FDA approval for treatment of depression in the US, and is consistent with his clinical experience that noradrenergically selective antidepressants treat a smaller group of depressed people than selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors.

Surprisingly, the authors did not find evidence of sponsorship bias (ie, the bias associated with the commercial interests of industrial sponsors), since many of the studies comparing the newest antidepressants (especially mirtazapine, escitalopram, bupropion, and duloxetine) were conducted by the pharmaceutical companies marketing these compounds. The authors claim to have avoided this pitfall by making indirect and direct comparisons, decreasing the risk for possible sponsorship bias.

“The problem of sponsorship bias continues to receive a lot of discussion,” Dr. Thase said. “The major source of sponsorship bias is actually the file drawer effect—until recently sponsors did not attempt to publish their disappointing studies. Although Cipriani and colleagues discuss this as a potential problem, their results actually indicate that sponsorship did not have much TABLE

STUDIES INCLUDED IN THE MULTIPLE-TREATMENTS META-ANALYSIS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of Trials</th>
<th>Years of Publication</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Earliest Median Latest</td>
<td>Europe North America Africa Asia Multiple Countries</td>
</tr>
<tr>
<td>Bupropion</td>
<td>14</td>
<td>1991 2003 2007</td>
<td>1 10 0 0 2</td>
</tr>
<tr>
<td>Citalopram</td>
<td>16</td>
<td>1993 2002 2007</td>
<td>4 4 0 1 4</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>8</td>
<td>2002 2006 2007</td>
<td>2 5 0 0 1</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>19</td>
<td>2000 2005 2007</td>
<td>5 11 0 0 2</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>54</td>
<td>1991 2000 2007</td>
<td>15 13 1 3 6</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>11</td>
<td>1993 1998 2006</td>
<td>3 2 0 1 2</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>6</td>
<td>1994 2000 2003</td>
<td>2 1 0 2 0</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>13</td>
<td>1997 2002 2005</td>
<td>3 3 1 1 5</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>32</td>
<td>1993 2001 2007</td>
<td>12 13 1 1 2</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>8</td>
<td>1997 2003 2006</td>
<td>2 2 0 0 1</td>
</tr>
<tr>
<td>Sertraline</td>
<td>27</td>
<td>1993 2000 2007</td>
<td>10 9 0 2 1</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>28</td>
<td>1994 2002 2007</td>
<td>7 5 0 1 6</td>
</tr>
</tbody>
</table>

The number of studies across countries in this table does not match the number of trials included in the review. Missing studies scored as other or not known. Two three-arm studies comparing fluoxetine with paroxetine and sertraline were included in the systematic review (the total number of arms is 236 and it corresponds to 115 two-arm and two three-arm studies).

impact on the results. Nevertheless, all but one of the studies of escitalopram were conducted by its sponsors, all of the studies of mirtazapine were conducted by its sponsor, and a large majority of the studies of venlafaxine and sertraline were conducted by the sponsors, so it is hard not to at least ponder the possibility.\textsuperscript{7}

Doubts about some of the generalizations in the conclusions of the paper are raised when one knows the details of some of the studies analyzed. For example, only two trials compared escitalopram to venlafaxine—both designed and sponsored by the manufacturer of escitalopram—and one had a dosing schedule that favored escitalopram. The higher dose escitalopram versus venlafaxine study\textsuperscript{13} was biased in favor of escitalopram, because of the forced upward titration schedule: the venlafaxine dose was tripled over 8 days, whereas the escitalopram dose was only doubled. Escitalopram is acknowledged to be better tolerated than venlafaxine. The rapid dose escalation caused much higher dropout rates in the venlafaxine group.

In a second study\textsuperscript{14} the average doses of both venlafaxine and escitalopram were comparatively low.

According to Dr. Thase, who picked up this kind of potential bias: “In a large data set, with large numbers of studies, these kind of things (ie, a single slanted study) disappear or at least no longer mean that much. However, when the numbers of studies are smaller, one or two slanted studies can be much more meaningful. That may be the bottom line with respect to why duloxetine looked unexpectedly bad in this meta-analysis.”

Dr. Thase commented on possible explanations for the observed differences among the drugs, one of these being that fluoxetine may have a smaller effect than many other newer antidepressants.

“Although not mentioned in the current report,” he observed, “there is likely to be a very simple pharmacokinetic explanation for the poorer showing of fluoxetine: it takes >1 month for the average person to get to steady state norfluoxetine levels follow-

\begin{figure}
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\includegraphics[width=\textwidth]{figure.png}
\caption{RANKING FOR EFFICACY (SOLID LINE) AND ACCEPTABILITY (DOTTED LINE)}
\end{figure}

ing the initiation of therapy or up-titration, which is likely to be a real disadvantage in studies of 6 or 8 weeks duration.”

Dr. Thase is not surprised that venlafaxine, escitalopram, and mirtazapine have higher efficacy ratings, as meta-analyses of head-to-head trials have reported this for each drug.

“The findings for sertraline (one of the more effective in this study) and duloxetine (one of the least effective) are somewhat surprising and, as such, warrant closer inspection,” he said. “Duloxetine may suffer in relative terms because many of the early trials used doses that are today known to be too high, which magnified tolerability problems. Moreover, none of the trials have used the dosing strategies that, we have learned in more recent years, enhance early tolerability (ie, 60 mg with food and, when necessary, reduce to 30 mg with food). That said, duloxetine also suffers in the indirect comparisons because three of the eight comparisons were against escitalopram and six of the eight duloxetine studies were placebo controlled (a relatively high proportion in this data set); placebo-controlled studies tend to report lower response rates than studies that only have an active comparator. I do not have my ‘hands around’ similar explanations for why sertraline did better than I would have expected, though it may simply be a predominance of comparisons versus fluoxetine and other ‘weaker’ antidepressants.”

If nothing else, this latest attempt to determine the true meaning of the accumulating body of research on antidepressant clinical effects serves to underscore the heterogeneity of different classes of antidepressants, and even among the drugs within the SSRI class. Differences in both tolerability and efficacy exist. PP

REFERENCES