Management of Depression After Stroke
A Systematic Review of Pharmacological Therapies

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Background and Purpose—Although depression may affect recovery and outcome after stroke, it is often overlooked or inadequately managed, and there is uncertainty regarding the benefits of antidepressant therapy in this setting. We aimed to assess the effectiveness of antidepressants for the treatment and prevention of depression after stroke.

Methods—We undertook a systematic review using Cochrane methods of randomized placebo-controlled trials of antidepressants for the treatment or prevention of depressive illness and “abnormal mood” after stroke. Treatment effects on physical and other outcomes were also examined.

Results—Outcome data were available for 7 treatment trials including 615 patients and 9 prevention trials including 479 patients. Because of the considerable variation in research design, trial quality, and method of reporting across studies, we did not pool all the outcome data. In the treatment trials, antidepressants reduced mood symptoms but had no clear effect on producing a remission of diagnosable depressive illness. There was no definitive evidence that antidepressants prevent depression or improve recovery after stroke.

Conclusions—There is insufficient randomized evidence to support the routine use of antidepressants for the prevention of depression or to improve recovery from stroke. Although antidepressants may improve mood in stroke patients with depression, it is unclear how clinically significant such modest effects are in patients other than those with major depression. There is a pressing need for further research to better define the role of antidepressants in stroke management. (Stroke. 2005;36:1092-1097.)

Key Words: clinical trials  ■ depression

Depression is an important complication of stroke that may impede rehabilitation, recovery, quality of life, and caregiver health.1-4 Furthermore, stroke-associated depression may reduce survival and increase the risks of recurrent vascular events.5,6 Yet many stroke patients may not receive effective treatment because their mood disorder goes undiagnosed or their doctor is uncertain about the most appropriate therapy.7 This can be attributed to the complexities in determining the significance of abnormal mood in patients with stroke-related disability, but it could also be related to continued uncertainty about the balance of benefits and risks of antidepressants in this setting. We wished to evaluate whether pharmacological agents used either selectively for treatment or more generally for prevention of depression in stroke patients improve outcomes.

Methods
These analyses were done using Cochrane Review methodology8 and appear as 2 separate expanded versions in the Cochrane Library.9,10 In addition to the Cochrane Stroke Group trials register (last searched in June 2003), we searched various scientific and medical databases (to 2002) for all randomized (or quasi-randomized), placebo-controlled trials of a pharmacological agent used specifically for either the treatment or prevention of depression in patients with a clinical diagnosis of stroke. There were no restrictions on the basis of age, sex, or other patient characteristic, but we excluded trials with a cross-over design or in which ≥2 agents were compared with each other rather than a placebo. We also excluded trials that included mixed patient groups (eg, inclusion of patients with head injury or another neurological disorder) unless separate results for the stroke patients were identified. We also searched Digital Dissertations, a database of abstracts from doctoral theses from the United States, Canada, Scandinavia, and the United Kingdom, conference abstracts, book chapters on the treatment of depression and stroke management, and we wrote to all active researchers in the area of stroke-associated mood disorders from the last 10 years, asking them to verify that we had identified all relevant trials. Finally, we wrote to 22 major pharmaceutical companies and asked whether they had any unpublished trials that should be included in the review.

Specific pharmacological agents included tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). Trials of an agent that was being compared with another agent were included in the review, but we excluded trials with a cross-over design or in which ≥2 agents were compared with each other rather than a placebo. We also excluded trials that included mixed patient groups (eg, inclusion of patients with head injury or another neurological disorder) unless separate results for the stroke patients were identified. We also searched Digital Dissertations, a database of abstracts from doctoral theses from the United States, Canada, Scandinavia, and the United Kingdom, conference abstracts, book chapters on the treatment of depression and stroke management, and we wrote to all active researchers in the area of stroke-associated mood disorders from the last 10 years, asking them to verify that we had identified all relevant trials. Finally, we wrote to 22 major pharmaceutical companies and asked whether they had any unpublished trials that should be included in the review.

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of psychostimulants, mood stabilizers, benzodiazepines, and combined preparations were included but analyzed separately.

Included trials were considered in 2 groups: treatment trials included patients with diagnosed depression at entry, and in prevention trials, patients were free of depression at entry. The diagnostic categories of depression considered were: (1) depressive disorder, as defined by symptom scores on standard screening instruments; (2) major depression; and (3) minor depression or dysthymia, as defined by standard diagnostic criteria.

The primary end point was the proportion of patients who met diagnostic criteria for depression as applied at the end of follow-up in a trial. Secondary outcomes included depression as a continuous end point, as measured on a standardized mood rating scale, as well as anxiety, general health, cognition, social activities, activities of daily living (ADL), and disability, according to standard measures as outlined previously. Disadvantages to treatment were recorded as adverse events grouped as deaths, all events, and premature exit from the study (including death).

One reviewer (M.H.) extracted data, which were cross-checked by another reviewer (C.A.), and any discrepancies were resolved by consensus. Missing information was obtained from the primary investigators whenever possible. Responses were received regarding 9 trials (Downes et al, unpublished data, 1995; Murray et al, unpublished data, 2003) and a response without data for another trial. Ten replies were received from pharmaceutical companies known to produce, or have a license to produce, antidepressants, but this did not identify any new trials.

We analyzed binary outcomes with a fixed-effects model, as Peto odds ratios (ORs) with 95% CIs, where appropriate. For continuous outcomes, we used mean differences with 95% CIs. We used Review Manager software, version 4.2.1. In view of the large number and heterogeneous nature of the outcome measures and the reporting of results, we did not pool outcome data for all end points.

**Results**

**Characteristics**

Seven trials with 615 patients at entry and 9 trials with 479 patients at entry were identified for inclusion in the treatment and prevention groups, respectively as shown in the Table. Two trials compared 2 active treatments with placebo. Data from both treatment arms in these trials were compared with data from half the number of patients in the control groups and the results presented as 2 separate trials. Eight trials were identified for which no outcome data are available at the time of writing (Davis et al, unpublished data, 1995; Downes et al, unpublished data, 2003; Graffagnino et al, unpublished data, 2002). Further details are presented in the Cochrane Library version of these reviews.

The mean or median age of patients ranged from 56 to 73 years; 1 trial included women only. The average time from stroke onset to entry into a trial ranged from “within a few days” to 195 days, but most trials included patients recruited within 1 month of stroke onset. Most trials reported specific exclusion criteria usually consisting of communication or cognitive difficulties or other coexisting conditions that would interfere with the assessments or adherence to the treatment. Other reasons for exclusion included a history of depression in the last year, recent or current use of antidepressant medication, and concurrent psychiatric disorders or deterioration.

**Pharmacological Agents**

Among the 7 treatment trials, 4 trials used an SSRI, 1 trial used a TCA, and other agents with antidepressant effects were used in 2 trials. Five trials used a flexible dose regimen, with a lower dose in older people or dose escalation for persistently elevated mood scores during follow-up. The duration of treatment was generally short, ranging from several weeks to 12 weeks, with the exception of Murray et al. Among the 9 prevention trials, 3 used an SSRI, and 2 a serotonin antagonist and reuptake inhibitor. Other agents with antidepressant effects were used in 5 trials, and a psychostimulant in 1 trial. Treatment duration varied from 2 weeks to 12 months.

**Assessment Procedures and Analyses**

A wide variety of criteria and methods was used to diagnose depression, including: standard depression scales such as the Hamilton Depression Rating Scale (HDRS); the Montgomery Åsberg Depression Rating Scale (MADRS), depressive illness diagnosis by psychiatric interview using standard psychiatric criteria; and a combination of psychiatric interview and high scores on a depression scale. One trial included patients based on the “physician’s impression.” Ten methods were used to assess depression, or change in depression, at the end of treatment. The most commonly used measure was the HDRS, but not all trials described adequate concealment of allocation. Among the 7 treatment trials, 4 trials used an SSRI, 1 trial used a TCA, and other agents with antidepressant effects were used in 2 trials. Five trials stated a double-blind method but did not state who was blinded. Six trials reported per protocol analyses. Three trials provided only intention-to-treat (ITT) analyses, and 4 reported ITT in addition to per protocol analyses. The method of analysis was unclear in 2 trials. The drop-out rate varied from 6% to 51%.

**Treatment of Depression**

Outcome data were available for 7 trials of antidepressants including 615 patients. No consistent treatment effects were reported across the trials or the end points measured. There was no clear benefit of pharmacotherapy in treating diagnosable depression (Figure 1), but there was some evidence of an effect of pharmacotherapy in reducing symptoms, as shown by the general skewed distribution of reduced (improved) scores on mood rating scales across studies (Figure 2). More limited pooled data from 3 of the studies, which included a ≥50% reduction in mood scores as an end point, showed a significant overall beneficial
effect of treatment (OR, 2.28; 95% CI, 1.31 to 3.97). However, the 95% CIs were wide around all mood score end points, and positive effects were seen in treatment and control groups in most of the studies. There was no evidence of benefit of pharmacotherapy in improving cognitive function, or in reducing disability according to ADL or other measure, as shown previously.9,10 However, in 1 trial,24 more control patients experienced an improvement (reduction) in anxiety symptoms (OR, 0.48; 95% CI 0.26 to 0.88) than patients on active treatment. There was no clear evidence of harm associated with pharmacotherapy through the reporting of adverse events (OR, 1.23; 95% CI, 0.62 to 2.46).

Prevention of Depression
Outcome data were available for 9 trials of antidepressants including 479 patients.19,20,22,26–31 Five small trials reported lower numbers meeting criteria for depression in antidepressant-treated patients at the end of treatment (OR, 0.41; 95% CI, 0.24 to 0.7), although 2 of these trials used “clinician impression” as the measure of this end point (Figure 1). There was no evidence that pharmacotherapy improved mood scores, cognitive function, or disability, as demonstrated by the heterogeneous results and wide CIs around these estimates.9,10 However, no evidence of harm was demonstrated in the analysis of adverse events.

Outcome data were available for 1 trial of a psychostimulant that included 21 people;28 no consistent treatment effects were demonstrated. Patients in the control group reported large reductions in mood scores and smaller improvements in disability over the course of the trial, but there were wide 95% CIs around these estimates. No benefit of treatment was seen for cognition or in patients leaving early in this study.

Discussion
We were unable to find any strong evidence that pharmacotherapy is effective in either producing a remission or in preventing the onset of diagnosable depressive illness in stroke patients. Although such treatment may, on average, be more effective than placebo in reducing depressive symptoms, it is uncertain how clinically significant such modest changes in mood scores are for stroke patients who would be considered to have depressive symptoms within the mild–moderate range of “abnormality.” Moreover, it is uncertain how well such effects translate into other substantive outcomes such as improvements in physical functioning, health service use, and quality of life.

There were major challenges to this review in addressing the methodological heterogeneity of included trials, such as the variation in patient characteristics, methods of diagnosis and assessment of depression, multiple end points, and the
The difficulty of defining depression as an outcome in clinical trials is well exemplified by the varying methods of assessment, at entry and follow-up, in the included trials. Few treatment trials clearly stated that the primary goal of therapy was “remission” (ie, no longer meeting baseline diagnostic criteria), “recovery” (eg, defined as a 50% reduction in mood scores from baseline), or simply a greater reduction in mood scores in one of the randomized groups. There is clearly a lack of agreement on what can be considered useful criteria for improvement in patients with mood disorders.40

A key requirement for assessing the effects of treatment, in clinical practice and research, is for patients to achieve a therapeutic dose of medication for an adequate period of time. As outlined in guidelines of the American College of Physicians, antidepressants should be continued for only brief (usually 6 weeks) time periods and only if no response has been shown by 6 weeks.41 It is interesting then that most of the trials included in this review used agents for only brief (usually 6 weeks) time periods and only followed up patients in the short term.

Given the problems inherent with the diagnosis of a significant mood state in the setting of stroke and that stroke patients are at high risk of developing depression (and anxiety disorders), an attractive therapeutic option to consider is the provision of antidepressants along with vascular preventative strategies in the majority of stroke patients. Moreover, there is increasing evidence that antidepressants may have benefits over and above the stabilization of mood via neurotrophic or neuronal plasticity effects.27,42–44 However, the current direct randomized evidence available for this review provides little support for such routine use of antidepressants (or psycho-stimulants), either for “depression prevention” or to enhance frequent lack of a clearly defined a priori measurable primary outcome. As such, we felt it inappropriate to perform a meta-analysis of all end points. The aggregation of data in this way might lead to overinterpretation (simplification) of the findings and encourage the reader to overlook the multiple assessments and selective reporting of depression end points within individual trials.

One key factor that limits the generalizability of these data are that up to one half of all potentially eligible stroke patients were excluded from the individual trials38 because of communication problems, cognitive loss, or previous psychiatric illness, thus reinforcing a common criticism of depression research that patients are often not representative of those provision of antidepressants along with vascular preventative strategies in the majority of stroke patients. Moreover, there is increasing evidence that antidepressants may have benefits over and above the stabilization of mood via neurotrophic or neuronal plasticity effects.27,42–44 However, the current direct randomized evidence available for this review provides little support for such routine use of antidepressants (or psycho-stimulants), either for “depression prevention” or to enhance

### Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>No. of Randomized Patients</th>
<th>Men, %</th>
<th>Mean Age, y</th>
<th>Primary Outcome</th>
<th>Additional Scales</th>
<th>Medication (mg)</th>
<th>Duration, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen, 199419</td>
<td>Denmark</td>
<td>33</td>
<td>33</td>
<td>66</td>
<td>HDRS, &lt; 13</td>
<td>Melancholia Scale</td>
<td>Citiploram, 10–20</td>
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<td>Fruehwald, 200317</td>
<td>Austria</td>
<td>28</td>
<td>26</td>
<td>64</td>
<td>HDRS, &lt; 13</td>
<td>BDI</td>
<td>Fluoxetine, 20–40</td>
<td>12</td>
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<tr>
<td>Lispay, 198423</td>
<td>USA</td>
<td>17</td>
<td>22</td>
<td>64</td>
<td>DSM-III</td>
<td>HDRS</td>
<td>Nortioptil, 20–100</td>
<td>4–6</td>
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<td>Murray, 200218</td>
<td>Sweden</td>
<td>62</td>
<td>61</td>
<td>52</td>
<td>MADRS</td>
<td>Sertraline, 50–100</td>
<td>26</td>
<td></td>
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<tr>
<td>Dhwombo, 199524</td>
<td>Japan</td>
<td>150</td>
<td>135</td>
<td>u</td>
<td>u</td>
<td>Physician assessment</td>
<td>Anratiam, 600</td>
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<tr>
<td>Reding, 198619</td>
<td>USA</td>
<td>11</td>
<td>6</td>
<td>66</td>
<td>ZDS</td>
<td>ZDS</td>
<td>Trazodone-HCl, 50–200</td>
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<td>16</td>
<td>15</td>
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<td>25</td>
<td>25</td>
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<tr>
<td>Dam, 1996a27</td>
<td>Italy</td>
<td>18</td>
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<td>44</td>
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<td>Fluoxetine, 20</td>
<td>10</td>
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<tr>
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<td>Mianserin, 10–60, e</td>
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<td>ZDS</td>
<td>Trazodone-HCl, 300</td>
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<td>CGI</td>
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<td>2</td>
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<td>Trazodone-HCl, 50–200</td>
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<td>USA and Argentina</td>
<td>17</td>
<td>8</td>
<td>88</td>
<td>HDRS</td>
<td>Fluoxetine, 10–40, e</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Robinson, 2000b32</td>
<td>USA and Argentina</td>
<td>15</td>
<td>8</td>
<td>47</td>
<td>HDRS</td>
<td>Nortioptil, 25–100, e</td>
<td>12</td>
<td></td>
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<tr>
<td>Roh, 199631</td>
<td>Korea</td>
<td>32</td>
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<td>90</td>
<td>HDRS</td>
<td>CGI</td>
<td>Indeloxazine, 20</td>
<td>12</td>
</tr>
</tbody>
</table>

*Psychostimulant; BDI indicates Beck Depression Inventory; CGI, Clinical Global Impression of Depression; DSM: Diagnostic and Statistical Manual of Mental Disorders; e, escalating or flexible dose strategy; GDS, Geriatric Depression Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; SGRS, Stockton Geriatric Rating Scale; u, unclear; USA, United States of America; ZDS, Zung Depression Scale.40
physical recovery. Although indirect evidence of the benefits of antidepressants is available in other clinical situations, and most physicians would consider it unethical to deny treatment in a stroke patient with an overt major depressive episode, the data about the effects of pharmacological therapies on which to guide practice for a broad range of stroke patients with different degrees and characteristics of abnormal mood are very limited. As well as the potential to increase anxiety symptoms, antidepressants may present other risks, especially with regard to seizures, falls, and delirium in stroke patients. Because the benefits of antidepressant therapy are potentially large and widely applicable, there is a pressing need for further research in this important but somewhat neglected area of stroke medicine.

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References


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