Journal Watch

Antidepressant Drugs Effects and Depression Severity: A Patient-Level Meta-analysis

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Abstract
Context Antidepressant medications represent the best established treatment for major depressive disorder, but there is little evidence that they have a specific pharmacological effect relative to pill placebo for patients with less severe depression.
Objective To estimate the relative benefit of medication vs placebo across a wide range of initial symptom severity in patients diagnosed with depression.
Data Sources PubMed, PsycINFO, and the Cochrane Library databases were searched from January 1980 through March 2009, along with references from meta-analyses and reviews.
Study Selection Randomized placebo-controlled trials of antidepressants approved by the Food and Drug Administration in the treatment of major or minor depressive disorder were selected. Studies were included if their authors provided the requisite original data, they comprised adult outpatients, they included a medication vs placebo comparison for at least 6 weeks, they did not exclude patients on the basis of a placebo washout period, and they used the Hamilton Depression Rating Scale (HDRS). Data from 6 studies (718 patients) were included.
Data Extraction Individual patient-level data were obtained from study authors.
Results Medication vs placebo differences varied substantially as a function of baseline severity. Among patients with HDRS scores below 23, Cohen *d* effect sizes for the difference between medication and placebo were estimated to be less than 0.20 (a standard definition of a small effect). Estimates of the magnitude of the superiority of medication over placebo increased with increases in baseline depression severity and crossed the threshold defined by the National Institute for Clinical Excellence for a clinically significant difference at a baseline HDRS score of 25.
Conclusions The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. For patients with very severe depression, the benefit of medications over placebo is substantial.

Strengths

- Substantial sample size (n = 718 patients, combined data from 6 studies)
- Comprehensive and transparent method
- Inclusion of studies involving full range of patients with major or minor depressive disorder
- Clear definition of clinical significance (HDRS point difference ≥ 3)
- Use of patient-level data (i.e. mega-analysis)

Weaknesses

- Limited to adult outpatient samples – may limit generalizability to inpatients and palliative patients
- Only small proportion of patients with HDRS scores of 13 or lower
- Diagnostic assessment and primary outcome measure was limited to severity scores based on Hamilton Depression Rating Scale (HDRS); some criticism of HDRS psychometric properties; different versions of HDRS (modified 17-item vs. 17-item)
- Review was limited to 6 of 23 studies contacted, over a 29-year time period (Jan, 1980 – March, 2009), involving only two antidepressants (paroxetine, imipramine)
- No information regarding patient demographics (e.g. age, treatment history – initial diagnosis vs. recurrence, family history of depression, chronicity of current symptoms, other co-morbidities)

- No information regarding sources of patient recruitment
- Evaluations were partially blinded for 3/6 studies
- Only 2/6 studies used a full intent-to-treat design
- Higher proportion of patients in treatment vs. placebo groups, for some studies
- No information regarding availability of other treatments for depression, including non-pharmacological approaches
- Unable to assess potential role of publication bias (i.e. most published studies involved patients with severe depression and positive treatment effects, negative effects not published)
- Exclusion of patients with dysthymia, yet patients often present with mixed clinical picture
- Exclusion of short-term studies (< 6 weeks) – some evidence to suggest that antidepressants may have a more rapid onset than originally suggested

Relevance to Palliative Care

The diagnosis and treatment of depression in palliative care patients is very complex. The incidence and prevalence of depression in a palliative population may be difficult to determine due to confounding physical factors commonly associated with advancing disease. The treatment of depression with antidepressant therapy is further complicated by the extended time often required for an observed therapeutic effect. The decision of whether or not to treat patients is complex and should not be based solely on depression severity scores, as described in this study. Other factors to consider include, but are not limited to, chronicity of present depressive symptoms, patient's history of prior mood disorders and treatments, and family history. Further research specifically focusing on palliative patients, including both outpatients and inpatients, is warranted.