Antidepressants: Do They "Work" or Don't They?

A new study finds little difference between pill and placebo

By John Kelley on March 2, 2010
WHY ANTIDEPRESSANTS ARE NO BETTER THAN PLACEBOS

BY SHARON BEGLEY ON 1/28/10 AT 7:00 PM
Antidepressants No Better Than Placebo?

Study Shows Only Most Depressed Patients Benefit; Expert Is Critical of Study's Method

By Salynn Boyle
Anti-depressants' 'little effect'

New generation anti-depressants have little clinical benefit for most patients, research suggests.
Severity and the Treatment of Depression: A Review of Two Controversies

Mark Zimmerman, MD
Director of Outpatient Psychiatry
Director of the Partial Hospital Program
Rhode Island Hospital
Professor of Psychiatry
Brown Medical School
Providence, Rhode Island
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Overview

• What does it mean to say that someone has a severe illness?
• Severity of medical illnesses
• Severity in DSM-5
• Severity of depression in DSM-5 and ICD-10
• Depression scales
• Depression severity and treatment of depression: Official guidelines
• Depression severity and pharmacology
• Depression severity and medication or psychotherapy as first-line treatment
Conceptualizing Severity
Clinical Implications of Severity

• Decisions to seek treatment
• Type and intensity of treatment
• Whether to continue or stop treatment
• Expectations in the fulfillment of role function
• Disability determinations
• Evaluations of treatment impact
What Does Severity Refer To?

- Number of symptoms
- Intensity of symptoms
- Frequency or persistence of symptoms
- Impact of symptoms on functioning or quality of life
- Likelihood of permanent disability
- Likelihood of death
  - Imminence of death
  - Death only if untreated
Conceptualizing Severity across Disorders

• Should severity be conceptualized the same for all illnesses?
  – eg, Heart failure vs upper respiratory tract infection
Severity of Physical Illness: Some Examples

• Degree of damage to the diseased organ
  – Rheumatoid arthritis: X-rays of joint damage
  – Diabetic retinopathy: Degree of retinal damage
• Physiological measures indicating degree of damage to the diseased organ
  – Cardiac disease: Left ventricular ejection fraction
  – Cystic fibrosis: Forced expiratory volume
  – Hepatitis: Aminotransferase and bilirubin levels
• Disorder-specific clinical exam
  – Rheumatoid arthritis: Number of swollen and painful joints
• Impact
  – Cardiac disease: New York Heart Association Functional Classification based on limitations in physical activities and physical symptoms with varying degrees of activity
Severity of Physical Illness: Some More Examples

• Composite measures of overall illness severity
  – Acute Physiology and Chronic Health Evaluation (APACHE) scores: based on nonspecific clinical and biological indicators of health status (eg, age, body temperature, electrolytes, hematocrit)

• Self-report scales
  – Benign prostatic hypertrophy: American Urological Association Symptom Index
  – Tinnitus Severity Index
  – Irritable Bowel Syndrome Symptom Severity Scale
  – Headache Impact Test
  – Liverpool Seizure Severity Scale
Severity of Psychiatric Disorders
Severity in *DSM-5*

- Defines severity for some, but not all, disorders
- Severity defined differently for different disorders
  - Some definitions emphasize number of criteria met (eg, alcohol use disorder)
  - Some emphasize the core criterion of the disorder (eg, binge eating disorder)
  - Some based on level of distress (eg, sexual disorders)
  - Some focus on response to intervention (eg, narcolepsy)
  - Some refer to prediction of course (eg, learning disorders)
Severity of Depression in *DSM-5*

- **Mild**
  - Few, if any, symptoms in excess of those required to make the diagnosis
  - The intensity of the symptoms is distressing but manageable
  - The symptoms result in minor impairment in social or occupational functioning

- **Severe**
  - Number of symptoms is substantially in excess of that required to make the diagnosis
  - The intensity of the symptoms is seriously distressing and unmanageable
  - The symptoms markedly interfere with social and occupational functioning

- **Moderate**
  - Lying between mild and severe in symptoms, distress, and/or impairment

- **Note**
  - No mention of suicidality or need for hospitalization

Using Scales to Evaluate Severity

• Numerous scales
• Different content
• Different rating instructions
• Problems
  – Different scales classify patients into different severity groups
  – Uncertain validity of cutoffs to define severity groupings
Prevalence of Severity Subtypes According to Different Measures of Depression

• Patients
  – 245 depressed outpatients in ongoing treatment in the Rhode Island Hospital outpatient practice

• Methods
  – Evaluated with the 17-item HAM-D
  – Completed the CUDOS, PHQ-9, and QIDS

• Definitions
  – Severity categorization based on the scale developers’ recommended thresholds

Prevalence of Severity Subtypes According to Different Measures of Depression

Use of Different Cutoffs to Define Severe Depression

- DeRubeis et al— mega-analysis of 4 studies comparing CBT to medication
  - Severe depression: HAM-D ≥ 20
- Gibbons et al— mega-analysis of placebo-controlled studies of fluoxetine and venlafaxine
  - Severe depression: HAM-D ≥ 20
- Khan et al— meta-analysis of placebo-controlled studies of antidepressants
  - Severe depression: HAM-D ≥ 28
- APA Handbook of Psychiatric Measures:
  - Mild to moderate: < 18; severe: 19 to 22; very severe: > 23

CBT = cognitive-behavioral therapy.
Severity and the Treatment of Depression: *Controversy 1*
Do Antidepressants Only Work for Severely Depressed Patients?
Do Antidepressants Work?
Official Treatment Guidelines’ Recommendations Related to the Severity of Depression

- **American Psychiatric Association**
  - Mild depression: Medication or psychotherapy
  - Moderate depression: Medication or psychotherapy
  - Severe depression: Medication

- **National Institute for Health and Clinical Excellence (NICE)**
  - Mild depression: Psychotherapy
  - Moderate depression: Medication and psychotherapy
  - Severe depression: Medication and psychotherapy

- **British Association for Psychopharmacology**
  - Mild depression: Psychotherapy or medication
  - Moderate depression: Psychotherapy or medication
  - Severe depression: Medication

---


Severity of Depression and Pharmacotherapy—
A Change in the Debate

• 1990s
  – Are SSRIs effective in treating severe depression?
  – Are SSRIs as effective as tricyclic antidepressants in treating severe depression?

SSRI = selective serotonin reuptake inhibitor.
The First Meta-Analysis of the FDA Data Base

- 45 studies in FDA data base
- Subdivided studies based on mean baseline 17-item HAM-D score
- Results
  - HAM-D \leq 24—little difference between medication and placebo (1/10)
  - HAM-D 25–27—half the comparisons between medication and placebo differed (20/41)
  - HAM-D \geq 28—most medication-placebo comparisons differed (5/7)

Conclusions

• Antidepressants’ effects seem more robust and placebos’ less so among patients with more severe depression
• These data may help inform the design of future antidepressant clinical trials
• These data are of immediate relevance to the design of antidepressant clinical trials but cannot be directly applied to clinical practice. Research participants meet stringent exclusion and inclusion criteria and are not representative of the general population of patients with depression.

The Second Meta-Analysis of the FDA Data Base

- 35 trials in FDA data base
- Results
  - Overall difference between active drug and placebo: 1.80 points on HAM-D
  - Drug-placebo differences increased as function of severity

The Second Meta-Analysis of the FDA Data Base

Figure 4. Mean Drug–Placebo Difference Scores as a Function of Initial Severity

The Fascinating Link Between Placebo and Antidepressants
Antidepressants: Do They "Work" or Don't They?

A new study finds little difference between pill and placebo

By John Kelley on March 2, 2010
Antidepressants No Better Than Placebo?

Study Shows Only Most Depressed Patients Benefit; Expert Is Critical of Study's Method

By Salynn Boyle
Anti-depressants' 'little effect'

New generation anti-depressants have little clinical benefit for most patients, research suggests.
The drugs don’t work

A new assault by a leading psychologist on Prozac-style antidepressants claims they are worse than useless. Try telling that to the many people who believe they are life-saving

by John Cornwell / September 23, 2009 / Leave a comment
Published in October 2009 issue of Prospect Magazine
Do Anti-Depressants Really Work?

Depression affects many Americans but are we reaching for the wrong treatment?

Carolyn C. Ross M.D., M.P.H.
Real Healing

Posted Feb 20, 2012
TREATING DEPRESSION: IS THERE A PLACEBO EFFECT?

A Harvard scientist says the drugs used to treat depression are effective, but for many, it's not the active ingredient that's making people feel better. It's the placebo effect.
The Second Meta-analysis of the FDA Data Base: Conclusions

• Interpreted results in context of the criterion proposed in the NICE guidelines as an indicator of a clinically meaningful effect—a difference in mean change scores between drug and placebo of 3 points on the HAM-D

• “… there seems little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients, unless alternative treatments have failed to provide benefit.”

Comments on Kirsch et al in the Peer Review Literature

– Bech (2010)
– Broich (2009)
– Hegerl and Mergl (2010)
– Horder et al (2011)
– Mathew and Charney (2009)

– McAllister-Williams (2008)
– Nutt and Malizia (2008)
– Parker (2009)
– Vöhringer and Ghaemi (2011)
Limitations of Khan and Kirsch Studies

- Mean values vs individual patient data
- Examined mean change rather than percent of patients who improved
- Severity of patient samples studied
  - All but 2 studies in Kirsch study had mean baseline HAM-D score > 23
- Generalizability
Generalizability of Treatment Studies

Have Treatment Studies of Depression Become Even Less Generalizable? A Review of the Inclusion and Exclusion Criteria Used in Placebo-Controlled Antidepressant Efficacy Trials Published During the Past 20 Years

Mark Zimmerman, MD; Heather L. Clark, BS; Matthew D. Miltach, BA; Emily Walsh, BA; Lia K. Rosenstein, BA; and Douglas Gazarian, BA

<table>
<thead>
<tr>
<th>Exclusion criterion</th>
<th>All studies (N=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity scale score below the cutoff</td>
<td>170 (100.0)</td>
</tr>
<tr>
<td>Severity scale score above the cutoff</td>
<td>14 (8.2)</td>
</tr>
<tr>
<td>Psychotic disorder and current psychotic features</td>
<td>143 (84.1)</td>
</tr>
<tr>
<td>Substance abuse and dependence</td>
<td>137 (80.6)</td>
</tr>
<tr>
<td>Significant suicidal ideation</td>
<td>128 (75.3)</td>
</tr>
<tr>
<td>History of suicide attempt(s)</td>
<td>35 (20.6)</td>
</tr>
<tr>
<td>Significant homicidal ideation or violence risk</td>
<td>28 (16.5)</td>
</tr>
<tr>
<td>Other nondepressive/nonsubstance use disorders</td>
<td>92 (54.1)</td>
</tr>
<tr>
<td>Episode duration too long</td>
<td>34 (20.0)</td>
</tr>
<tr>
<td>Episode duration too short</td>
<td>81 (47.6)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>128 (75.3)</td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>46 (27.1)</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>70 (41.2)</td>
</tr>
<tr>
<td>Item 1 of the Hamilton Rating Scale below the cutoff</td>
<td>33 (19.4)</td>
</tr>
<tr>
<td>Any Axis I disorder</td>
<td>46 (27.1)</td>
</tr>
</tbody>
</table>
Symptom Severity and Exclusion From Antidepressant Efficacy Trials

MARK ZIMMERMAN, MD, MICHAEL A. POSTERNAK, MD, AND IWONA CHELMINSKI, PHD

J Clin Psychopharmacol, Vol 22/No 6, December 2002

- Mean extracted 21-item HAM-D = 20.4 (SD = 6.0)
- At the 2 most common cutoffs of 20 on the 21-item HAM-D and 18 on the 17-item version, 47.3% and 44.5%, respectively, would have been excluded
The JAMA Study (2010)

- Pooled analysis of individual data from 6 studies (5 MDD, 1 minor depression; N=718)

- Results
  - HAM-D ≤ 18, effect size (d)=0.11
  - HAM-D 19–22, HAM-D < 18, effect size (d)=0.17
  - HAM-D ≥ 23, effect size (d)=0.47

- Conclusions
  - “…efforts should be made to clarify to providers and prospective patients that whereas ADMs can [have a substantial effect] with more severe depressions, there is little evidence to suggest that they produce specific pharmacological benefit for the majority of patients with less severe acute depressions.”

MDD = major depressive disorder; ADM = antidepressant medication.
Large Scale, Recent, Pooled Analyses #1

- All company sponsored studies of fluoxetine and venlafaxine (41 studies; > 9000 patients)
- Compared participants scoring 19 ≤ vs ≥ 20 on the HAM-D
- Low/high severity

<table>
<thead>
<tr>
<th></th>
<th>Mean Change</th>
<th>Response Rate</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>9.40/12.85</td>
<td>54.8%/57.7%</td>
<td>49.9%/37.8%</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.20/10.07</td>
<td>37.3%/40.5%</td>
<td>36.6%/25.1%</td>
</tr>
<tr>
<td>Difference</td>
<td>2.20/2.75</td>
<td>17.5%/17.2%</td>
<td>13.3%/12.7%</td>
</tr>
</tbody>
</table>

Large Scale, Recent, Pooled Analyses #2

- All company sponsored studies of desvenlafaxine (9 studies, 4271 patients)
- Compared drug–placebo differences in 3 severity cohorts defined by baseline scores on the 17-item HAM-D
  - mild, HAM-D ≤ 18
  - moderate, HAM-D 19 to 24
  - severe, HAM-D ≥ 25
- Note: 7/9 studies required minimum HAM-D of 20 (only 3% of the patients were in the mild group)

Results

HAM-D17 Remission

- Placebo
- Desvenlafaxine 50 mg
- Desvenlafaxine 100 mg

Percentage of Remitters

Baseline Severity of Depression

Mild | Moderate | Severe

Results (cont’d)

B

MADRS Remission

- Placebo
- Desvenlafaxine 50 mg
- Desvenlafaxine 100 mg

Percentage of Remitters

Baseline Severity of depression

MADRS = Montgomery-Åsberg Depression Rating Scale.
Large Scale, Recent, Pooled Analyses #3

• All company sponsored studies of citalopram, duloxetine, escitalopram, quetiapine, and sertraline (34 studies, 10,737 patients)
• Compared drug–placebo differences in 3 severity cohorts defined by baseline scores on the 17-item HAM-D
  – mild, HAM-D ≤ 21
  – moderate, HAM-D 22 to 25
  – severe, HAM-D ≥ 26
• 2 types of analyses: pooled analysis, trial level data

### Results

#### Table 1 Placebo–active differences in Hamilton Rating Scale for Depression (HRSD) scores and drop-out rates by group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>HRSD score, mean (s.d.)</th>
<th>Drug-placebo difference, a mean (95% CI), s.e.</th>
<th>Drop-out, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 3258)</td>
<td>23.0 (4.1)</td>
<td>-8.8 (8.1)</td>
<td>-2.05 (-2.38 to -1.72) 0.17</td>
</tr>
<tr>
<td>Active (n = 7323)</td>
<td>23.1 (4.2)</td>
<td>-10.8 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Baseline severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (less than 22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 1328)</td>
<td>19.3 (2.7)</td>
<td>-7.1 (7.2)</td>
<td>-2.04 (-2.50 to -1.53) 0.24</td>
</tr>
<tr>
<td>Active (n = 3046)</td>
<td>19.4 (2.8)</td>
<td>-9.1 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Medium (22–25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 1102)</td>
<td>23.8 (0.8)</td>
<td>-9.2 (8.0)</td>
<td>-1.82 (-2.40 to -1.24) 0.30</td>
</tr>
<tr>
<td>Active (n = 2345)</td>
<td>23.8 (0.8)</td>
<td>-11.0 (8.1)</td>
<td></td>
</tr>
<tr>
<td>High (above 25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 828)</td>
<td>28.0 (2.4)</td>
<td>-10.7 (9.1)</td>
<td>-2.41 (-3.17 to -1.64) 0.39</td>
</tr>
<tr>
<td>Active (n = 1932)</td>
<td>28.1 (2.6)</td>
<td>-13.1 (9.4)</td>
<td></td>
</tr>
</tbody>
</table>

a. Largest pairwise difference high -2.41 v. medium -1.82, t = 1.16, d.f. = 6205, P = 0.25.

Summary of Pooled Analysis Studies

- Antidepressants are effective across a range of severity
- Efficacy is **not** limited to a narrow band of severely depressed patients
- Caveat: Symptom severity inclusion criterion limits generalizability
  - The lower bound of symptom severity associated with efficacy has not been well studied
Severity and the Treatment of Depression: *Controversy 2*
Should patients with severe depression preferentially be treated with medication?
Is psychotherapy alone beneficial for severely depressed patients?
Official Treatment Guidelines’ Recommendations Related to the Severity of Depression

• American Psychiatric Association
  – Mild depression: Medication or psychotherapy
  – Moderate depression: Medication or psychotherapy
  – Severe depression: Medication

• National Institute for Health and Clinical Excellence (NICE)
  – Mild depression: Psychotherapy
  – Moderate depression: Medication and psychotherapy
  – Severe depression: Medication and psychotherapy

• British Association for Psychopharmacology
  – Mild depression: Psychotherapy or medication
  – Moderate depression: Psychotherapy or medication
  – Severe depression: Medication

NIMH Treatment of Depression Collaborative Study (1989)

- Comparison of 4 treatments
  - Placebo
  - Imipramine
  - CBT
  - IPT

- Sample size
  - 239 patients entered treatment
  - 204 patients completed at least 3.5 weeks of treatment
  - 162 patients completed 15 weeks of treatment

- Severity
  - Less severe: < 20 on HAM-D
  - More severe: ≥ 20 on HAM-D

IPT = interpersonal therapy.
PLA = placebo; IMI = imipramine; CM = clinical management.

Psychotherapy vs Medication: Meta-Analysis

- 30 studies
- > 3000 patients
- Differential treatment outcome not associated with mean baseline symptom severity
- Compared studies with baseline HAM-D scores below 20 vs 20—no association with differential treatment response

Psychotherapy vs Medication: Pooled Analysis

- 16 studies comparing medication and CBT

### Table 1. Sample Size by Baseline Depression Severity at Posttest

<table>
<thead>
<tr>
<th>Baseline Severity</th>
<th>CBT</th>
<th>Posttreatment, Mean (SE)</th>
<th>ADM</th>
<th>Posttreatment, Mean (SE)</th>
<th>Cohen's d (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;14</td>
<td>62</td>
<td>7.89 (0.83)</td>
<td>74</td>
<td>6.08 (0.71)</td>
<td>0.29 (-0.13 to 0.05)</td>
</tr>
<tr>
<td>14 to &lt;19</td>
<td>245</td>
<td>7.98 (0.41)</td>
<td>292</td>
<td>7.21 (0.45)</td>
<td>0.11 (-0.28 to 0.06)</td>
</tr>
<tr>
<td>≥19</td>
<td>344</td>
<td>9.89 (0.42)</td>
<td>450</td>
<td>9.07 (0.40)</td>
<td>0.10 (-0.24 to 0.04)</td>
</tr>
<tr>
<td>&gt;23</td>
<td>104</td>
<td>10.62 (0.82)</td>
<td>152</td>
<td>9.79 (0.69)</td>
<td>0.10 (-0.35 to 0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;29</td>
<td>233</td>
<td>10.07 (0.58)</td>
<td>254</td>
<td>9.28 (0.62)</td>
<td>0.08 (-0.25 to 0.09)</td>
</tr>
<tr>
<td>≥29</td>
<td>243</td>
<td>13.03 (0.73)</td>
<td>314</td>
<td>11.58 (0.67)</td>
<td>0.14 (-0.30 to 0.03)</td>
</tr>
</tbody>
</table>

Meta-Analysis of Psychotherapy Studies

- 132 studies
- > 10,000 patients
- Mean baseline symptom severity did not predict poorer response
- 6 studies that presented outcome data separately for higher and lower severity groups
  - Effect size in the low severity groups was not significantly different than the effect size in the high severity groups
- Authors noted that few studies had a mean pretreatment depression level in the severe range and the mean pretreatment scores were generally lower than the mean pretreatment scores in pharmacology studies

# Generalizability of Psychotherapy Studies

## Table 1

Frequency of commonly-used psychiatric inclusion and exclusion criteria in randomized controlled trials of antidepressants (n = 170) or psychotherapy (n = 16).

<table>
<thead>
<tr>
<th>Criteria</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity scale score below cutoff</td>
<td>170</td>
<td>100%</td>
<td>13</td>
<td>81%</td>
<td>0.00</td>
</tr>
<tr>
<td>Psychotic disorder/current psychotic features</td>
<td>143</td>
<td>84%</td>
<td>14</td>
<td>88%</td>
<td>1.00</td>
</tr>
<tr>
<td>Substance abuse/dependence</td>
<td>137</td>
<td>81%</td>
<td>12</td>
<td>75%</td>
<td>0.53</td>
</tr>
<tr>
<td>Significant suicidal ideation</td>
<td>128</td>
<td>75%</td>
<td>9</td>
<td>56%</td>
<td>0.13</td>
</tr>
<tr>
<td>Episode duration too short</td>
<td>81</td>
<td>48%</td>
<td>2</td>
<td>13%</td>
<td>0.00</td>
</tr>
<tr>
<td>Any Axis II disorder</td>
<td>60</td>
<td>35%</td>
<td>3</td>
<td>19%</td>
<td>0.27</td>
</tr>
<tr>
<td>Any Axis I disorder</td>
<td>46</td>
<td>27%</td>
<td>1</td>
<td>6%</td>
<td>0.08</td>
</tr>
<tr>
<td>History of suicide attempt(s)</td>
<td>35</td>
<td>21%</td>
<td>2</td>
<td>13%</td>
<td>0.74</td>
</tr>
<tr>
<td>Episode duration too long</td>
<td>34</td>
<td>20%</td>
<td>2</td>
<td>13%</td>
<td>0.74</td>
</tr>
<tr>
<td>Significant homicidal ideation/violence risk</td>
<td>28</td>
<td>16%</td>
<td>6</td>
<td>9%</td>
<td>0.14</td>
</tr>
<tr>
<td>Severity scale score above cutoff</td>
<td>14</td>
<td>8%</td>
<td>6</td>
<td>38%</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Conclusions
Conclusions

- Conclusions regarding the impact of severity on treatment outcome are limited by the exclusion of patients with insufficient or high levels of severity.
- The efficacy of antidepressants is not limited to severely depressed patients.
- The efficacy of psychotherapy is not limited to mildly and moderately depressed patients.
- Empirical support for treatment guidelines recommending medication as the first-line treatment for severe depression is limited.