Pharmacotherapy of Depression: State of the Art and Future Directions

Michael E. Thase, MD
University of Pennsylvania School of Medicine
Philadelphia Veterans Affairs Medical Center
University of Pittsburgh Medical Center
thase@mail.med.upenn.edu
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Antidepressant Drugs: Unmet Needs Circa 2015

- Limited efficacy (~ 10-20% advantage vs PBO in RCTs)
- Intolerable side effects for 10%
- Inconsistent effects on key symptoms (insomnia, anxiety)
- Relatively slow onset of action
- Better alternatives for nonresponders
Areas of Controversy and Debate

- Questions about the small specific effect of ADs & magnitude of placebo response: do ADs really work?
- ADs and suicide: facts and fiction
- Can new therapies be developed?
- Is growth of combinations a fad?
- Are second generation antipsychotics also antidepressants?
ANTIDEPRESSANTS DON'T WORK
The debate over the nation's most popular pills
By Sharen Begley

Antidepressants Do Not Work

NEWSWEEK
Do Antidepressants Really Work? 
Controversy Chronology

• 2002 & 2008: Kirsch “Emperor’s New Drugs” meta-analyses (ADs have small effects)
• 2003: UK regulatory authority concludes that ADs do not have proven efficacy for youth
• 2008: Turner et al. NEJM paper (publication bias inflates apparent efficacy)
• 2010: Fournier et al. JAMA paper (ADs only effective in very severe depression) & Newsweek has a feature article about topic
Kirsch et al.: Mean Drug–Placebo Differences as a Function of Initial Severity

Plotted values are sized according to sample sizes (n); the green line represents the NICE clinical significance criterion. The solid blue regression line represents the trend across all 35 trials; the dashed red line excludes outlier.
Fournier et al. JAMA Meta-analysis: Pretreatment Severity and Response to Antidepressant and Placebo
Why Are These Observations So Controversial?

• The percentage of persons treated with antidepressant drugs (ADs) in the US increased from 5.8% to 10.1% between 1996-2005; 11-13% of US adults now take ADs
• The rate of ADs use increased for anxiety and adjustment disorders in addition to depressive disorders
• Increasing use of ADs corresponded to decreasing rates of counseling and psychotherapy
• ADs are about twice as likely to be prescribed by primary care providers than psychiatrists

Effect Sizes of Placebo & Drug–Placebo Differences Over Time

Standardised mean change from baseline, placebo only

Standardised mean difference in change scores, drug vs placebo

MADRS scores improved by 15.9 points in patients with a true treatment effect; NNT for escitalopram is 5 (19.5%)

Antidepressants and Suicidality

- Increased risk of suicidal behaviors, broadly defined, in meta-analyses of RCTs of youth; also in young adults up to ~24 years old
- Small risk (~2% above placebo) for youth; even smaller risk (~1%) for young adults
- No evidence of increase in risk of suicide
- Reduced AD use increased youth suicide rates
- Mechanism: neurodevelopmental vs agitated mixed states vs akathisia

RCTs, randomized controlled trials.
Suicide Rates of US Youth

Antidepressant Pharmacotherapy Lowers Risk of Suicide

First Line Antidepressants: 2015

- Consensus across guidelines is that the following antidepressants are first-line:
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
  - Bupropion (NDRI)
Efficacy (Response Rate) Odds Ratio – Fluoxetine as Reference Compound

Odds ratio >1 favors fluoxetine
*p<0.05
Neurogenesis Is Mediated Through Multiple Mechanisms in Animal Models

†p<0.05 vs. placebo; †p<0.01 vs. placebo; 
‡BrdU = DNA synthesis marker 5-bromo-21-deoxyuridine; 
Results following 28-day administration of placebo, fluoxetine or imipramine; 

- Wild Type Mice
- 5-HT$_{1\alpha}$ Knockout Mice

![Bar chart showing BrdU-positive cells](chart.png)
Funnel Plot Analysis: 46 Randomized Studies Comparing VEN and SSRIs

*The funnel plot trim and fill method identifies excess statistical outliers on either side and "fills" the opposite side with theoretical studies accordingly to balance the funnel.

CYP2D6 Status and Response to Venlafaxine

Figure 1A. Change in Scores on the HDRS17 and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status

Figure 1B. Response and Remission Rates Based on the HDRS17 and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status

Abbreviations: EM = extensive metabolizer; HDRS17 = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; PM = poor metabolizer.

Error bars represent the SD.

P value <.02, EM vs PM.
P value <.001, EM vs placebo.
P value <.04, PM vs placebo.

Response is defined as ≥ 50% decrease from baseline score.
MADRS remission is defined as total score ≤ 12.

P value <.02, EM vs PM.
P value <.001, EM vs placebo.
P value <.04, PM vs placebo.

Newer Antidepressants

• Vilazodone (2011)
• Levomilnacipran ER (2013)
• Vortioxetine (2013)
Vilazodone
Vilazodone Blocks Serotonin Transporters and is a Partial Agonist of $5\text{HT}_{1\text{A}}$ Receptors

1. Selective inhibition of serotonin reuptake
2. Partial agonist at $5\text{HT}_{1\text{A}}$ receptors
Vilazodone

- Approved for MDD in 2011
- MoA: SRI + 5-HT1a partial agonism
- Therapeutic dose: 40 mg/day (requires 3 step titration to minimize nausea)
- Low incidence of sexual side effects
- Still no comparative or switch data
Vilazodone Additional Efficacy Studies

**MD-03**

**MD-01**

Baseline scores: 30.6 for VIIBRYD and 30.9 for placebo

Baseline scores: 30.8 for VIIBRYD and 31.3 for placebo

- Whether the statistically significant differences observed at time points earlier than 8 or 10 weeks represent clinically relevant treatment effects is unknown.
- VIIBRYD should be taken with food. Taking VIIBRYD on an empty stomach can reduce plasma concentrations by approximately 50% and may diminish effectiveness.¹
## Sexual Side Effects of Vilazodone

### Relative frequency of sexual dysfunction by antidepressant

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sexual Desire</th>
<th>Sexual Arousal</th>
<th>Orgasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprion</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Levomilnacipran ER
Efficacy (Response Rate) Odds Ratio – Fluoxetine as Reference Compound

Odds ratio >1 favors fluoxetine
*p<0.05
Safety and Efficacy of Levomilnacipran

Figure 1 NNT for response/remission, NNH for adverse events where incidence with levomilnacipran ≥ 5% and ≥ 2 times the rate for placebo as identified in product labelling (3), and NNH for discontinuation because of an adverse event, with 95% CIs, for pooled short-term studies comparing levomilnacipran vs. placebo. AE, adverse event; D/C, discontinuation; NNH, number needed to harm; NNT, number needed to treat
Vortioxetine
Vortioxetine

- Serotonin modulator introduced 11/13: SRI & antagonist of 5-HT3 and 5-HT7, complex effects on 5-HT1
- Therapeutic dose range: 5-20mg/day
- 7/11 positive placebo controlled trials; at 10-20 mg/day comparable to duloxetine (5 trials)
- Availability: Introduced 11/13
The Targets of Vortioxetine Engaged at Clinically Relevant Doses

Clinical dose range gives 50-90% SERT occupancy

**Receptor occupancy (%)**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Rat</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₃</td>
<td>1.1</td>
<td>3.7</td>
</tr>
<tr>
<td>5-HT₇</td>
<td>190</td>
<td>19</td>
</tr>
<tr>
<td>5-HT₁B</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>5-HT₁A</td>
<td>230</td>
<td>15</td>
</tr>
<tr>
<td>SERT</td>
<td>8.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**Simulated human affinity**

Relative Efficacy/Safety of Vortioxetine

Figure 1 NNT (and 95% CIs) for response vs. placebo for vortioxetine and active controls, NNH for discontinuation because of an AE vs. placebo, and NNH vs. placebo for AEs for vortioxetine 5–20 mg/day with incidence ≥ 5% and ≥ 2 times the rate for placebo, as identified in product labelling. AE, adverse event; CI, confidence interval; D/C, discontinuation; NNH, number needed to harm; NNT, number needed to treat

Path Analysis: Direct Effects of Vortioxetine on Cognitive Domains During MDD Treatment

<table>
<thead>
<tr>
<th>Domain</th>
<th>Vortioxetine 10 mg vs Placebo</th>
<th>Vortioxetine 20 mg vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroop Incongruent</td>
<td>70%</td>
<td>58%</td>
</tr>
<tr>
<td>Stroop Congruent</td>
<td>84%</td>
<td>80%</td>
</tr>
<tr>
<td>TMT-A</td>
<td>60%</td>
<td>51%</td>
</tr>
<tr>
<td>TMT-B</td>
<td>71%</td>
<td>67%</td>
</tr>
<tr>
<td>Simple Reaction Time</td>
<td>66%</td>
<td>26%</td>
</tr>
<tr>
<td>Choice Reaction Time</td>
<td>67%</td>
<td>Not calculable*</td>
</tr>
</tbody>
</table>

(* tx effects had different signs)
Combining Antidepressants: Advanced Practice or Fad?

- Once consider an indicator of bad practice, combining antidepressants is now commonly done for TRD
- Bupropion & mirtazapine now preferred
- No antidepressant has FDA approval for this use and only one (mirtazapine) has the support of two positive studies
- Most newer combos safe; caveats
Concurrent Combined Antidepressants – Contrasting Results

**Blier et al. 2010**

- **FLU** (n=28)
- **FLU + MIRT** (n=26)
- **VEN + MIRT** (n=25)
- **BUP + MIRT** (n=25)

**Rush et al. 2011**

- **ESC + PBO** (n=224)
- **BUP + ESC** (n=221)
- **VEN + MIRT** (n=220)

* *p<0.05; FLU=fluoxetine; MIRT=mirtazapine; VEN=venlafaxine; BUP=bupropion; ESC=escitalopram

Are SGAs Antidepressants?

- 4 have established efficacy as adjuncts to antidepressants (aripiprazole, olanzapine, quetiapine, & risperidone)
- 3 have established efficacy as monotherapies in bipolar depression (olanzapine, quetiapine, & lurasidone)
- 1 has established efficacy as a monotherapy in MDD (quetiapine)
Meta-Analysis of Response Rates in Double-Blind, Placebo-Controlled, Atypical Augmentation Trials

Odds Ratios of Response Rates With Atypicals and Placebo

<table>
<thead>
<tr>
<th>Trials Nested by Drug</th>
<th>OR (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olanzapine trials</strong></td>
<td></td>
</tr>
<tr>
<td>Shelton 2001</td>
<td></td>
</tr>
<tr>
<td>Shelton II 2005</td>
<td></td>
</tr>
<tr>
<td>Corya 2006</td>
<td></td>
</tr>
<tr>
<td>Thase 2007</td>
<td></td>
</tr>
<tr>
<td>Thase II 2007</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.39 (1.05, 1.84); Z=2.30, P=.02</td>
</tr>
<tr>
<td><strong>Risperidone trials</strong></td>
<td></td>
</tr>
<tr>
<td>Mahmoud 2007</td>
<td></td>
</tr>
<tr>
<td>Keitner 2009</td>
<td></td>
</tr>
<tr>
<td>Reeves 2008</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.83 (1.18, 2.82); Z=2.71, P=.007</td>
</tr>
<tr>
<td><strong>Quetiapine trials</strong></td>
<td></td>
</tr>
<tr>
<td>Khullar 2006</td>
<td></td>
</tr>
<tr>
<td>Mattingly 2006</td>
<td></td>
</tr>
<tr>
<td>McIntyre 2006</td>
<td></td>
</tr>
<tr>
<td>Earley 2007</td>
<td></td>
</tr>
<tr>
<td>El-Khalili 2008</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.61 (1.24, 2.09); Z=3.56, P=.0004</td>
</tr>
<tr>
<td><strong>Aripiprazole studies</strong></td>
<td></td>
</tr>
<tr>
<td>Berman 2007</td>
<td></td>
</tr>
<tr>
<td>Marcus 2008</td>
<td></td>
</tr>
<tr>
<td>Berman 2008</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>2.07 (1.58, 2.72); Z=5.28, P=.00001</td>
</tr>
</tbody>
</table>

Test for overall effect:

<table>
<thead>
<tr>
<th>Favors Control</th>
<th>Favors Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.69 (1.46, 1.95); Z=7.00, P&lt;.00001</td>
<td></td>
</tr>
</tbody>
</table>

• Statistical significant outcome on both primary and secondary endpoints in favor brexpiprazole over placebo
• More than 90% of patient participants completed trial
• Brexpiprazole well-tolerated; Most common (>5% and more than twice placebo) AEs reported included weight gain and akathisia

Augmentation with SGAs: Important Issues

- Is efficacy sustained?
- Cost effectiveness vs other options?
- Ultimate risks of TD and metabolic complications
- Within-class differences:
  - Anxiety?
  - Utility for reverse neurovegetative symptoms?
  - Metabolic risks?
Conventional and Novel Targets to Modulate Signaling Cascades

Chemical Structure of Ketamine
Ketamine

- Dissociative anesthetic with significant psychomimetic properties
- An NMDA antagonist, related to PCP and controlled substance because of recreational abuse potential
- Dramatic, rapid antidepressant effects first observed serendipitously in a study of its psychotomimetic effects
How Might Ketamine Work?
Ketamine Infusion Rapidly Enhances Neuronal Connectivity
Ketamine in MDD: An Evolving Story

- NMDA receptor antagonist
- Antidepressant effect appears to be large and rapid at 24 hours with efficacy maintained 7 days post infusion
- Rapid antidepressant effects appear to be independent of transient psychoactive effects
Ketamine: Important Unknowns?

- Will tolerance develop with repeated doses?
- Will repeated doses be neurotoxic?
- Complexity of NMDA receptor suggests antidepressant effect can be uncoupled from psychotomimetic effects: studies underway with novel compounds
- Can effect be maintained by other, less problematic compounds?
## NMDAR Antagonists Studied for MDD

<table>
<thead>
<tr>
<th>Compound/Company</th>
<th>Phase</th>
<th>Route</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLYX-13/Naurex</td>
<td>Ph2 completed</td>
<td>IV</td>
<td>EOPII Aug 2014</td>
</tr>
<tr>
<td>NRX-1074/Naurex</td>
<td>SD IV Ph2 data 4Q2014</td>
<td>IV, oral</td>
<td>Ph1 IV/oral ongoing; Ph3 to begin 2016</td>
</tr>
<tr>
<td>CERC-301/Cerecor</td>
<td>Ph2</td>
<td>Oral</td>
<td>Ph2 expected by 2014 end</td>
</tr>
<tr>
<td>Esketamine/JNJ</td>
<td>Ph2</td>
<td>IV, IN</td>
<td>Rapid acting (primary EPs 2-3 days after admin)</td>
</tr>
<tr>
<td>CP-101606 (traxoprodil)/JNJ</td>
<td>D/C</td>
<td>IV</td>
<td>D/C in Ph2; dissociative AEs seen</td>
</tr>
<tr>
<td>AZD-6765/6423/8108/Astra Z</td>
<td>D/C</td>
<td>IV</td>
<td>D/C for lack of efficacy</td>
</tr>
</tbody>
</table>
Glyx-13 Phase 2a Single Dose Study

**GLYX-13 at 5 and 10 mg/kg:**
- Drug Effect \( p<0.05 \)
- Time Effect \( p<0.0001 \)
- Drug x Time \( p<0.0001 \)

**Effect size of GLYX-13 after a single dose was roughly double that of SSRIs after weeks of repeated dosing**

GLYX-13 (one 5 mg/kg dose) = 0.41-0.49
Abilify (6 wks daily dosing) = 0.36
Conclusions: Antidepressant Therapy 2015

• Generic SSRIs, SNRIs & bupropion remain favored 1st line therapies
• Greatest unmet needs are speed of effect and alternate therapies
• Uncertain if recently introduced antidepressants will fill these needs
• Glutamatergic (ketamine-like) drugs now most promising