Antidepressant Therapy 2016

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Disclosure: Past Three Years

- **Advisory/Consultant**—Alkermes, Allergan (Forest, Naurex), AstraZeneca, Bristol-Myers Squibb, Cerecor, Eli Lilly & Co., Gerson Lehrman Group, Fabre-Kramer, Guidepoint Global, Janssen (J&J, Ortho-McNeil), Lundbeck, Moksha8, MedAvante, Merck, Nestlé (PamLab), Neuronetics, Novartis, Otsuka, Pfizer, Sunovion, Takeda


- **Employment (spouse)**—Peloton Advantage, which does business with Pfizer, Astra Zeneca, and GSK.
Antidepressant Drugs: Unmet Needs Circa 2016

- 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 fictions
- Can new therapies be developed?
- Is growth of combinations a fad?
- Are SGAs antidepressants?
- Does ketamine point the “way forward”
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

Dunlop et al., Neuropsychopharmacol 2012
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

Suicide Rates of US Youth
Antidepressant Pharmacotherapy Lowers Risk of Suicide

Improving Care Improves Outcomes

- In RCTs, more frequent sessions are associated with better outcomes
- Longer sessions also are associated with better outcomes in RCTs
- Combined psychotherapy + pharmacotherapy regimens typically convey a 10-20% advantage in response/remission rates
- Treat to remission & improve functioning
- Sustain treatment to ensure recovery

Thase, Current Psychiatry Reports, 2011; RCTs, randomized controlled trials.
Odds of Remission in Primary Care: Increased Monitoring and Patient Contact

% of Patients Achieving Remission

DPC Intervention:
- Monitoring and support phone calls from nurse or social worker case manager
- Patient education regarding self-management skills
- Monitoring of progress towards individualized self-management goals

DPC, Depression in primary care.

Improving Adherence Improves Outcomes: Depression Care Management

Patients Who Filled Antidepressant Prescriptions

- Intervention:
  - 2 follow-up visits
  - 3 telephone calls

Additive Benefit of Time-Limited Psychotherapy in Major Depression

Enhanced Care Programs Can Improve Outcomes and Satisfaction

![Bar chart showing improved outcomes with enhanced care programs.](chart.png)

- Enhanced care programs significantly improve patient outcomes and satisfaction compared to usual care.

- Figures from Simon GE et al. (2005), JAMA 292(8):935-942

*Significance levels: *p<0.005 vs. usual care; †p<0.05 vs. usual care.
CBASP, Nefazodone, and Their Combination for Treatment of Chronic Depression

Consensus across guidelines that the following are first-line:

- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
- Bupropion (NDRI)
- Mirtazapine (NaSSA) (1st line only for elderly)
Comparative Antidepressant Efficacy (fluoxetine as reference compound)

Efficacy (response rate) odds ratio: drug vs fluoxetine

Odds ratio >1 favours fluoxetine

*p<0.05

Cipriani et al., Lancet 2009
Neurogenesis Is Mediated Through Multiple Mechanisms in Animal Models

Wild Type Mice - HT1α Knockout Mice

BrdU-positive cells

Vehicle Fluoxetine Imipramine

Results following 28-day administration of placebo, fluoxetine or imipramine; Santarelli L et al. (2003), Science 301(5634):805-809

* p<0.01 vs. placebo; † p<0.05 vs. placebo; ‡ BrdU = DNA synthesis marker 5-bromo-21-deoxyuridine
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.

Nemeroff et al., Biological Psychiatry, 2008.
CYP2D6 Status and Response to Venlafaxine

Figure 1A. Change in Scores on the HDRS$_{17}$ and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status$^a$

Figure 1B. Response and Remission Rates Based on the HDRS$_{17}$ and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status

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$^a$Error bars represent the SD.

$^b$P value <.02, EM vs PM.

$^c$P value <.001, EM vs placebo.

$^d$P value <.04, PM vs placebo.

Response is defined as ≥ 50% decrease from baseline score.

HDRS$_{17}$ remission is defined as total score ≤ 7.

MADRS remission is defined as total score ≤ 12.

Abbreviations: EM = extensive metabolizer, HDRS$_{17}$ = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, PM = poor metabolizer.

Newer Antidepressants

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

- Selective inhibition of serotonin reuptake
- Partial agonist at 5-HT$_{1A}$ receptors

Only serotoninergic neurotransmission is depicted here.

1. Selective inhibition of serotonin reuptake
2. Partial agonist at 5-HT$_{1A}$ receptors
Vilazodone (Viibryd)

- Approved for MDD in 2011; positive study but not FDA approved for GAD
- MoA: SRI + 5-HT1a partial agonism
- Therapeutic dose: 20-40 mg/day (requires titration to minimize nausea)
- Low incidence of sexual side effects
- Very little comparative or switching data
Vilazodone Newer Efficacy Studies

- 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.
### 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>Bupropion</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 (Fetzima)
Levomilnacipran-ER

- SNRI with two-fold greater selectivity for NE
- Dose range of 40-120 mg qd
- Starting dose = 20 mg for 2 days
- Minimum therapeutic dose = 40 mg
- Maximum approved dose = 120 mg
- Dose needs to be decreased to 60-80 mg/day in presence of renal impairment

Fetzima, Prescribing Information, Revised July 2014.
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 (Brintellix)
The Targets of Vortioxetine Engaged at Clinically Relevant Doses

Clinical dose range gives 50-90% SERT 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

Pehrson AL et al. Eur Neuropsychopharmacol 2012; May 19: Epub ahead of print;
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 RCTs; efficacy comparable to duloxetine (5 trials)
- Despite Advisory Panel suggestion, FDA did not approve labeling about beneficial cognitive effect (2016)
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
Are SGAs Antidepressants?

- 5 have established efficacy as adjuncts to antidepressants (aripiprazole, brexpiprazole, 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)
- Issues of cost-effectiveness and optimal duration of therapy have not been settled
Ketamine: Important Unknowns

- Will tolerance develop with repeat eddoses?
- 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?
Conclusions: Antidepressant Therapy 2016

- Generic SSRIs, SNRIs & bupropion remain favored 1\textsuperscript{st} line therapies
- Greatest unmet needs are speed of effect and alternate therapies
- Newer antidepressants are “incremental” advances
- For the first time in 20 years, there are promising drugs for future