Recent Advances in the Treatment of Major Depression
Antidepressant Drugs: Unmet Needs in 2015

- Limited efficacy (~ 10-20% advantage vs PBO in RCTs)
- Intolerable side effects for some
- Inconsistent effects on residual symptoms (insomnia, anxiety, fatigue, cognition)
- Relatively slow onset of action
- Need to identify better alternatives for nonresponders
Rates of Depression in US by Severity (12 and Older)

Percentage of persons aged 12 and over by depressive symptom severity and race and Hispanic origin: United States, 2009–2012

Functional Impairment in Depression in US (12 and Older)

Percentage of persons aged 12 and over reporting difficulty with work, home, or social activities due to depressive symptoms, by severity: United States, 2009–2012

- **Mild**
  - Some Difficulty: 45.7%
  - Serious Difficulty: 3.9%
  - Total: 49.6%

- **Moderate**
  - Some Difficulty: 58.0%
  - Serious Difficulty: 15.8%
  - Total: 73.8%

- **Severe**
  - Some Difficulty: 45.2%
  - Serious Difficulty: 42.8%
  - Total: 88.0%

1 Significant linear trend for “serious difficulty” and “any difficulty”

“Any difficulty” (percentage above the bar in each category) is the sum of the percentages for “some difficulty” and “serious difficulty.”


Access data table at: http://www.cdc.gov/nchs/data/databriefs/db172_table.pdf#4

Remission Is the Goal of Treatment in Major Depression

Euthymia

Symptoms

Syndrome

Treatment phases

Increased severity

Remission = goal

Relapse

Recurrence

Response

Time

Acute (6 wk-12 wk)

Continuation (4 mo-9 mo)

Maintenance (≥1 y)

Definitions of Remission and Response to Treatment

% Reduction in HAM-D Score

- **Remission**: $\geq 75$
- **Response**: $50-74$
- **Partial response**: $25-49$
- **Nonresponse**: $<25$
Obstacles to Attaining Remission in Clinical Practice

- Patients and clinicians are satisfied with partial improvement without remission of symptoms (ie, response, but with residual symptoms)
- Treatments may not be well-tolerated
- Failure to recognize and treat residual symptoms
- Inadequate dosing
- Inadequate duration of therapy
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)
## Doses of First-Line Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose (mg/day)</th>
<th>Usual Dose Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>20-60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50</td>
<td>50-200</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td>12.5</td>
<td>25-75</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>37.5</td>
<td>75-375</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60</td>
<td>60-120</td>
</tr>
<tr>
<td>Desvenlafaxine ER</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Bupropion XL</td>
<td>150</td>
<td>300-450</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15</td>
<td>15-45</td>
</tr>
</tbody>
</table>
Duration of Antidepressant Treatment in Acute Phase: Of Ultimate Remitters, 1/2 Remitted by Week 6

52.9%

N=2876
Remission = QIDS-SR$_{16}$ ≤5
**Antidepressant Treatment Beyond Acute Phase: What is an Adequate Trial Duration?**

<table>
<thead>
<tr>
<th>Episode Features</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{st}) episode, uncomplicated course</td>
<td>9-12 months</td>
</tr>
<tr>
<td>2(^{nd}) episode</td>
<td>24 months or longer-term indefinite use</td>
</tr>
<tr>
<td>3(^{rd}) episode or any presence of suicidality</td>
<td>Longer-term indefinite use</td>
</tr>
</tbody>
</table>
Continued Treatment Reduces Relapse

Continuing Antidepressant Treatment Reduced the Risk of Relapse by 70%

Systematic overview of evidence from randomized trials of continuing treatment with antidepressants in patients with depressive disorders who have responded to acute treatment. Data were pooled from 31 randomized trials (4,410 participants) Geddes JR, et al. *Lancet*. 2003;361;653-661.
Evolution of Antidepressants: 1950-1980s

1950
- Imipramine (1957)
- Isocarboxazid (1959)

1960
- Amitriptyline (1961)
- Phenelzine (1961)
- Desipramine (1964)
- Protriptyline (1967)

1965
- Nortriptyline (1977)
- Trazodone (1981)
- Bupropion (1985)
- Trimipramine (1979)
- Fluoxetine (1987)
- Maprotiline (1987)

1970
- Nortriptyline (1977)

1975
- Trazodone (1981)

1980
- Bupropion (1985)

1985
- Amoxapine (1989)
- Fluoxetine (1987)
- Maprotiline (1987)
Evolution of Antidepressants: 1990s - present

1990
- Sertraline (1991)
- Paroxetine (1992)
- Fluvoxamine (OCD - 1994)
- Venlafaxine (1993)
- Nefazodone (1994)
- Mirtazapine (1996)
- Milnacipran (EU – 1996)
- Nefazodone
- Fluvaxamine
- Mirtazapine
- Milnacipran

1995
- Citalopram (1998)
- Selegiline patch (2005)
- Aripiprazole (MDD – 2007)

2000
- Escitalopram (2002)
- Fluoxetine / Olanzapine (2003)
- Duloxetine (2004)
- L-methylfolate (2006)

2005
- Desvenlafaxine (2008)
- Selegiline patch (2005)
- Aripiprazole (MDD – 2007)

2010
- Quetiapine XR (MDD - 2009)
- Vilazodone (2011)

2014
- Levomilnacipran (2013)
- Vortioxetine (2013)
What’s New for the First-Line Antidepressants?

• New formulations and doses
  – Bupropion HCl → Bupropion HBr extended release
  – Fluoxetine 60 mg tablet
    • Non-AB rated and no generic equivalent
  – Venlafaxine Extended-Release tablet
    • Non-AB rated and no generic equivalent
    • Availability of single 225 mg tablet
  – Bupropion HCL Extended-Release 450mg Tablet
Comparative Efficacy of 12 New-Generation Antidepressants

- 117 RCTs (25,928 patients)
- Mirtazapine, Escitalopram, Venlafaxine, and Sertraline most efficacious
- Escitalopram and Sertraline showed best profile of acceptability

Does Neurotransmitter Selectivity Translate Into Clinical Differences?
### Primary Neurotransmitter Effects of Antidepressants

<table>
<thead>
<tr>
<th></th>
<th>NE</th>
<th>5-HT</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion SR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Desipramine</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Selectivities for SERT vs NET

NET preference | SERT preference

- SSRI
- SNRI
- NRI
- Levomilnacipran
- Desipramine
- Reboxetine
- Duloxetine
- Venlafaxine
- Escitalopram
- Citalopram

Selectivity ratio hNET/hSERT (uptake IC\textsubscript{50})

Venlafaxine versus SSRIs in Major Depression

- 34 randomized studies comparing venlafaxine (n=4,191; mean dose 151 mg/day) versus SSRIs (n=3,621)
- Venlafaxine slightly better than SSRIs as a group (NNT=17) but superior only to fluoxetine individually
- Attrition rates significantly higher with venlafaxine versus SSRIs (11% vs 9%)

Bupropion and SSRIs Have Identical Efficacy: A Pooled Analysis of Seven RCTs

Remission Rate (% HAM-D ≤ 7)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size (N)</th>
<th>Remission Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO (N=524)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI** (N=758)</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>BUP (N=748)</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

*PBO < SSRI = BUP.
**Sertraline (N=358), fluoxetine (N=348), and paroxetine (N=52).
Do TCAs and MAOI's Have a Role in Modern Psychopharmacology?

- Post-ECT relapse prevention (nortriptyline/lithium combination)
- Residual insomnia (low-dose doxepin)
- Comorbid OCD (clomipramine + SSRIs)
- Treatment-resistant depression (SSRI + TCA)
- MAOIs
  - Non-hydrazine (Selegilene patch, tranylcypromine)
  - Hydrazine (phenelzine, isocarboxazid)
  - Role in difficult-to-treat depression (atypical and anxious features; frequent recurrences; treatment-resistance)

Are There Predictors Of Antidepressant Response?
Antidepressant Response Predictors

- Gender
- Atypical Features
- Comorbid Anxiety Disorders
- Endogenous Features
- Severity of Illness
- History of Trauma

90% showed early improvement, 92% showed early improvement.

Early improvement predicts remission.

“Early Improvement” = 20% reduction in HAM-D17 total score within first 2 weeks of antidepressant therapy.
“Stable Response” = reduction in HAM-D17 score of 50% from baseline at 4 wks of treatment and study endpoint.
“Stable Remission” = reduction in HAM-D17 score to -7 points at wk 4 of treatment and all subsequent assessments.

Brain Imaging Biomarker of *Differential* Response to CBT vs SSRI?

McGrath et al *JAMA Psychiatry* 2013
Right Anterior Insula Metabolism: The First Objective Biomarker to Guide Initial Treatment Selection in MDD?

Note: the anterior insula is the only region where the interaction subdivides patients into hypermetabolic (region/whole-brain mean >1.0) and hypometabolic (region/whole-brain mean <1.0) subgroups. McGrath, et al. *JAMA Psychiatry.* 2013.
C-Reactive Protein: Differential Predictor of Response to SSRI vs Tricyclic Antidepressant?

Newer Antidepressants

• Vilazodone (2011)
• Levomilnacipran ER (2013)
• Vortioxetine (2013)
Vilazodone

\[
\text{NC} \quad \text{CONH}_2 \\
\text{NH} \quad \text{O} \\
\text{NC} \quad \text{xHCl}
\]
Vilazodone Blocks Serotonin Transporters and is a Partial Agonist of 5HT$_{1A}$ Receptors

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

• Therapeutic dose = 40 mg/day (requires 3 step titration to minimize nausea)
  – 10 mg tablet for one week
  – 20 mg tablet for one week
• Should be taken with food
• Dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors (e.g. ketoconazole), or increased 2-fold (max dose of 80 mg) when used with strong CYP3A4 inducers (e.g. carbamazepine).
Vilazodone for Major Depression

Pivotal Trials

- **Rickels et al**¹,²
  - 8 weeks
  - **42% IMPROVEMENT from baseline vs 31% for placebo**²
  - **-12.9***
  - Vilazodone (n=198)
  - Placebo (n=199)

- **Khan et al**¹,³
  - 8 weeks
  - **42% IMPROVEMENT from baseline vs 34% for placebo**³
  - **-13.3†
  - Vilazodone (n=232)
  - Placebo (n=231)

Post-marketing Trials

- **MD-03**⁴
  - 8 weeks
  - **53% IMPROVEMENT from baseline vs 36% for placebo**⁴
  - **-16.1‡
  - Vilazodone (n=253)
  - Placebo (n=252)

- **MD-01**⁴
  - 10 weeks
  - **57% IMPROVEMENT from baseline vs 47% for placebo**⁴
  - **-17.6§
  - Vilazodone (n=284)
  - Placebo (n=281)

*P=0.001 vs placebo. Baseline scores: 30.8 for vilazodone; 30.7 for Placebo
†P=0.009 vs placebo. Baseline scores: 31.9 for vilazodone; 32.0 for Placebo
‡P=0.00001 vs placebo. Baseline scores: 30.6 for vilazodone; 30.9 for Placebo
§P<0.01 vs placebo. Baseline scores: 30.8 for vilazodone; 31.3 for Placebo

Goals of the study:
- 8 weeks: Rickels et al
- 8 weeks: Khan et al
- 8 weeks: MD-03
- 10 weeks: MD-01

**Improved outcomes**:
- **42%**
- **53%**
- **57%**

**Results**:
- Vilazodone vs Placebo

**Conclusion**:
Vilazodone is effective in the treatment of major depression, as evidenced by the significant improvements in symptoms compared to Placebo.
# 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-ER

- SNRI with two-fold greater selectivity for NE
- Dose range of 40-120 mg/day in once day dosing
- Starting dose = 20 mg for 2 days (irrespective of meals)
- 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
  - Primarily metabolized by CYP3A4
  - Eliminated primarily by renal excretion

Fetzima, Prescribing Information, Revised July 2014.
Levomilnacipran-ER

- Five double-blind placebo controlled trials (two fixed dose and three flexible dosing), 8-10 weeks in duration
  - All studies were positive, except for one flexible-dose study
- Open-label extension trial over 48 weeks supported long-term safety and tolerability, without clinically relevant weight change
- Most common side effects: nausea, hyperhydrosis, constipation, headache, dry mouth, occasional increased BP and pulse
- Low sexual dysfunction

Levomilnacipran-ER: Impact on functional disability

- 80 mg and 120 mg doses showed superiority over placebo in the Sheehan Disability Scale functional impairment total score.
- Only antidepressant with FDA approval for functional improvement.

Secondary Efficacy Endpoint: SDS Mean Total Score Reduction from Baseline at Week 8

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levo 40 mg/day</td>
<td>41% (P=NS)</td>
</tr>
<tr>
<td>Levo 80 mg/day</td>
<td>45% (*P&lt;0.05 vs placebo)</td>
</tr>
<tr>
<td>Levo 120 mg/day</td>
<td>46% (**P&lt;0.05 vs placebo)</td>
</tr>
<tr>
<td>Placebo</td>
<td>33%</td>
</tr>
</tbody>
</table>

The difference was not statistically significant vs placebo at 40 mg/day and was statistically significant vs placebo at 80 mg and 120 mg/day. The secondary efficacy endpoint was the change in SDS total score from baseline to week 8 in the mITT population.

*P<0.05 vs placebo; †P<0.05 vs placebo
Safety and Efficacy of Levomilnacipran

Number Needed to Treat or Harm vs. Placebo

Efficacy - NNT

Tolerability - NNH

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

- Multimodal mechanism of action: SRI & antagonist of 5-HT$_3$ and 5-HT$_7$, with complex effects on 5-HT$_1$
- Therapeutic dose range: 5-20 mg/day
  - Recommended starting dose is 10 mg, irrespective of meals
- 7/11 positive placebo-controlled trials
- 10-20 mg/day comparable to duloxetineine (5 trials)
# Vortioxetine: Mechanism of Action

<table>
<thead>
<tr>
<th>Target</th>
<th>Type of Activity</th>
<th>Binding Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT3</td>
<td>Antagonist</td>
<td>3.7</td>
</tr>
<tr>
<td>5-HT7</td>
<td>Antagonist</td>
<td>19</td>
</tr>
<tr>
<td>5-HT1D</td>
<td>Antagonist</td>
<td>54</td>
</tr>
<tr>
<td>5-HT1B</td>
<td>Partial agonist</td>
<td>33</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>Agonist</td>
<td>15</td>
</tr>
<tr>
<td>5-HT Transporter¹</td>
<td>Inhibitor</td>
<td>1.6</td>
</tr>
</tbody>
</table>

¹ 80% receptor occupancy at the 20 mg/day dose from clinical PET studies
65% Receptor occupancy at the 10 mg/day dose
50% Receptor occupancy at 5 mg/day dose

Vortioxetine: Pharmacokinetics

- Mean terminal half-life = 66 hours
- Steady state plasma concentrations typically achieved within 2 weeks
- Primary metabolizing enzyme = CYP2D6
  - Poor CYP2D6 metabolizers have ~2x plasma concentration
- With CYP2D6 inhibitors
  - Max recommended dose = 10 mg/day.
- With CYP3A4 inducers
  - Max dose should not exceed 3x original dose
# Vortioxetine: Impact on Weight

<table>
<thead>
<tr>
<th></th>
<th>Short Term Studies (6-8 weeks)</th>
<th>Long-Term Studies (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>(+0.1 kg, N=1536)</td>
<td>Placebo (N=189)</td>
</tr>
<tr>
<td>Vortioxetine 5-20mg</td>
<td>0.0 kg (N=2477)</td>
<td>Vortioxetine 5-10mg (N=199)</td>
</tr>
<tr>
<td>Mean Change in Weight</td>
<td>+0.1 kg</td>
<td>+0.1 kg</td>
</tr>
<tr>
<td></td>
<td>0.0 kg</td>
<td>+0.4 kg</td>
</tr>
</tbody>
</table>
Relative Efficacy/Safety of Vortioxetine

Number Needed to Treat or Harm vs. Placebo

Efficacy - NNT

Tolerability - NNH

Combining Antidepressants: Advanced Practice or Bad Practice?

- Once consider an indicator of bad practice, combining antidepressants is now commonly done for more treatment-resistant patients.
- Bupropion & mirtazapine are preferred co-administered agents.
- No antidepressant has FDA approval for this use and only one (mirtazapine) has the support of two positive studies.
Concurrent Combined Antidepressants – Contrasting Results

Blier et al. 2010

Rush et al. 2011

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

Are Second Generation Antipsychotics 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>Olanzapine trials</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>Subtotal</td>
<td>1.39 (1.05, 1.84); Z=2.30, P=.02</td>
</tr>
<tr>
<td>Risperidone trials</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>Subtotal</td>
<td>1.83 (1.18, 2.82); Z=2.71, P=.007</td>
</tr>
<tr>
<td>Quetiapine trials</td>
<td></td>
</tr>
<tr>
<td>Khullar 2006</td>
<td></td>
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<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>Subtotal</td>
<td>1.61 (1.24, 2.09); Z=3.56, P=.0004</td>
</tr>
<tr>
<td>Aripiprazole studies</td>
<td></td>
</tr>
<tr>
<td>Berman 2007</td>
<td></td>
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<tr>
<td>Marcus 2008</td>
<td></td>
</tr>
<tr>
<td>Berman 2008</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>2.07 (1.58, 2.72); Z=5.28, P=.00001</td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.69 (1.46, 1.95); Z=7.00, P&lt;.00001</td>
</tr>
</tbody>
</table>

Favors Control  Favors Treatment
Lurasidone for Mixed Depression
RESOLVE Study

- 211 MDD patients with 2 or 3 manic symptoms
- Lurasidone 20-60mg/day or placebo (mean 36.2 mg/day)
- MADRS primary efficacy measure
- CGI-S, YMRS, HAM-A secondary efficacy measures
- NNT was 3 and 4 for response and remission resp.
- Lurasidone better than placebo on all measures
- Nausea, insomnia, headache commonest SE

Roger McIntyre MD personal communication
Role of Repetitive Transcranial Magnetic Stimulation (rTMS) and Electroconvulsive Therapy (ECT)

- rTMS is indicated for patients who have failed respond to one prior medication in current episode or any number of antidepressants
- Two current FDA-cleared rTMS devices
  - Neurostar TMS (Neuronetics, approved 2008)
  - Deep TMS (Brainsway, Ltd, approved Jan 2013)
- ECT:
  - Remains gold standard for rapid, definitive response; pharmacotherapy-resistance, and psychotic depression
  - New promising data in treatment-resistant bipolar depression

Rave drug tested against depression
Companies and clinicians turn to ketamine to treat mental-health disorder as pipeline of new drugs dries up.
–Nature, Jan 2015

Comfortably numb
It started life as an anaesthetic, then became a psychedelic club drug. Now researchers think ketamine could hold the key to understanding and treating depression, says Erika Check.
Response at 72 hours Following a Single Ketamine Infusion

Response rates following a single infusion of ketamine in major depressive disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman et al (n=8)</td>
<td>50%</td>
</tr>
<tr>
<td>Zarate et al (n=17)</td>
<td>71%</td>
</tr>
<tr>
<td>Mathew et al (n=26)</td>
<td>66%</td>
</tr>
<tr>
<td>Ibrahim et al (n=42)</td>
<td>62%</td>
</tr>
</tbody>
</table>

Antidepressant effect appears to be large and rapid at 24 hours with efficacy maintained 7 days post infusion.

Unknowns:
- Optimal dose
- Long-term toxicities
- Mechanism of antidepressant effects

“New” Targets in Depression: The Opiate System

- Phase III program of Buprenorphine/SAM (ALKS 5461)
- Selective Kappa Opiate Receptor Antagonists
- Buprenorphine
Efficacy of a Combination Opiate Medication (ALKS 5461) in Major Depressive Disorder


Efficacy of BUP/SAM therapy in MDD. Displayed are mean decreases from baseline in HAM-D17 (left) and MADRS (right) total scores after 7 days of therapy. P-values are from Exact Wilcoxon tests and are based on observed data.

- **BUP:SAM 8:1 (w/w)**
  - (2 mg/0.25 mg \(\rightarrow\) 4 mg/0.5 mg)
  - *p*=0.032 vs. placebo

- **BUP:SAM 1:1 (w/w)**
  - (4 mg/4 mg \(\rightarrow\) 8 mg/8 mg)
  - *p*=0.054 vs. placebo

*BUP*= buprenorphine

*SAM*= samidorphan

(\(\mu\)-opioid receptor antagonist)
Conclusions

• Generic SSRIs, SNRIs & bupropion remain favored first-line therapies
• Greatest unmet needs are speed of onset of benefit and enhanced remission rates
• Uncertain if recently introduced antidepressants will fill these needs
• Promising new directions include glutamatergic (ketamine-like) drugs and drugs impacting opiate systems