ANTIDEPRESSANT UPDATE:
What’s New?
The Cardiac Debate
The Efficacy Debate
Pharmacogenomics?

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WHAT’S NEW

Short Answer????

Vilazodone (Viibryd®)

- SSRI with partial agonist activity at 5HT1A receptors.
- Pharmacology of buspirone “built in”
- CYP3A4 Substrate
- No clinically significant CYP inhibition

Vilazodone - Dosing

- Initiate at 10 mg/day X 7 days, then 20 mg/day X 7 days
- Target dose = 40 mg/day
- Reduce dose by 50% if co-medication with potent CYP3A4 inhibitors (ketoconazole, some macrolide antibiotics)
- QD dosing – 25 hour half-life
Vilazodone – Pluses / Minuses

• Potential Pluses:
  – Less sexual dysfunction than other SSRI’s?
  – Enhanced anti-anxiety activity (NOT FDA labeled for anxiety)?
• Potential Minuses: Still an SSRI
  – GI side effects
  – Sleep disturbance
  – Cost

Ketamine

• NMDA Receptor Antagonist
• THEORY:
  – NMDA Antagonism → ↑ Glutamate release (??compensatory??)
  – Stimulation of AMPA glutamate receptors, AND
  – Repair / regeneration of glutamate-related circuits.

Ketamine

• IV Sub-anesthetic doses
  – 0.5 mg/kg IV infused over ~40 min
  – One study of repeated doses (6)
• RAPID (hours) remission of depression symptoms in treatment-resistant patients
• Possible significant reduction in suicidality
• “Moderate” to “Large” Statistical Effect Sizes
• SHORT duration of effect days - weeks

Ketamine – Relevant PK

• $T_{1/2} = \sim 2.5$ hours
• Distribution $T_{1/2} = \sim 10$ min
• Hepatic Metabolism: CYP 450
  – 2B6, 3A4
  – 2C9 (minor)
• Bioavailability:
  – IM: 93%
  – Intranasal: 25 – 50%
  – Oral: 16 – 20%

Mathew et. CNS Drugs.2012;26:189-204
Ketamine: Adverse Effects

- Relatively well-tolerated at studied doses
- Side effects generally transient
- Transient BP elevations
- Mild dissociative effects (short-lived)
- Non-specific psychiatric/neurlogic
  - “Heady” or “Muzzy” feelings
  - Visual distortions
  - Dizziness

FDA Warning

- Post-marketing reports of QTc interval prolongation and Torsade de Pointes
- Thorough QT study of 20 mg and 60 mg of citalopram in 119 patients showing dose-related QTc prolongation
- “Thou shalt no longer Rx 60 mg doses and thou shalt not use > 20 mg in those over 60 or those on CYP2C19 inhibitors”
- Doses above 40 mg “confer no added benefit”
The Clinical Evidence??

- Published cases of citalopram-related cardiotoxicity (TdP) are extremely rare
- CIT was the most widely Rx’d antidepressant in the U.S.
- Prudence

- Is it true that 60 mg offers no additional benefit over 40 mg?
  - Population phenomenon? vs Individual Patient Phenomenon?


The Efficacy Debate

Do Antidepressants Work in Other than Very Severe Depression?
How Well do Antidepressants Work?

Negative Publications - ADs

- **PUBLISHED** AD Trials
  - 94% positive outcomes
- **UNPUBLISHED** AD Trials (FDA)
  - 51% positive outcomes
  - Statistical Effect Sizes were 25% smaller in entire FDA AD Study database than in published literature

> EH Turner, Matthews AM, Linardatos E et al. NEJM 2008;358:252-260
Are ADs better than placebo?
Multiple Meta-analyses

- Pooled data; mean changes in rating scale scores
  - Kirsch: AD 9.6 vs 7.8 placebo, difference 1.8
  - Fountoulakis reanalysis: AD 10.04 vs 7.85, difference 2.15
  - Overall drug versus placebo difference = ~2 points
  - NICE criterion for clinical significance = 3 points
    - Is NICE right?
    - Mean not valid in skewed distribution
    - Severe depression – about 5 point benefit
- “ADs are INEFFECTIVE in all but most severe”


Floor Effect

- Comparing absolute rating scale score changes or differences ignores this - Scores can’t go below Zero
- 50% drug improvement
- 25% placebo improvement
- Severe depression
  - Drug vs. placebo is 10 pts
- Mild depression
  - Drug vs placebo is 5 pts

Ghaemi SN. Making Sense of Antidepressants. CPNP Annual Meeting 2012

Relative Effect Size Difference
(Hamilton Depression Rating Scale – HDRS)

<table>
<thead>
<tr>
<th>Depression Severity *</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline HDRS score</td>
<td>Mean final change in HDRS score</td>
<td>Mean Baseline HDRS score</td>
</tr>
<tr>
<td>Mild (23%)</td>
<td>22.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Moderate (54%)</td>
<td>25.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Severe (23%)</td>
<td>28.75</td>
<td>12.0</td>
</tr>
</tbody>
</table>

* Mild= At least one arm (drug or placebo) is rated <24 on HDRS
Moderate= At least one arm is rated >24 and <28 on HDRS
Severe= At least one arm (drug or placebo) is rated ≥28 on HDRS
** Relative effect size = absolute mean HDRS change/mean baseline HDRS score

Efficacy Debate: Conclusions

- Antidepressants are not placebos
- Not accurate that ADs are less effective in mild depression
  - ADs appear about equally effective in all severity of depression
- PBO is less effective in more severe depressions

Pharmacogenomics & Depression

- ACTIVE Research Effort
- Pharmacodynamic Effects
  - Serotonin Transporter Gene variability
    - 5HTTLPR-promoter region
    - Long (l) allele associated with twice the expression of serotonin transporter & improved outcomes with SSRI antidepressant therapy
- Pharmacokinetic Effects
  - CYP450 metabolizer status
    - Poor metabolizers of 2D6 substrates experience more side effects.

CYP2D6 & Antidepressants

- **CYP2D6 Substrates**
  - Most TCAs (amitriptyline, nortriptyline, imipramine, etc.)
  - Duloxetine, venlafaxine, paroxetine

- **CYP2D6 Inhibitors**
  - Paroxetine, Bupropion & Fluoxetine ++++
  - Duloxetine +++

CYP2D6 & Antidepressants: PK Interactions

- Genetic Range:
  - Poor Ultra-Rapid Metabolizers
  - PM’s
    - Lower dose requirements
    - Poor tolerance to med
  - UM’s
    - Higher dose requirements
    - Improved tolerance to med
- Phenoconversion: 2D6 inhibitors can convert “good” metabolizers to poor metabolizers.

CYP2D6 & Antidepressants: More of the Story

- Pooled data from four DBPC clinical trials of venlafaxine
- Desvenlafaxine/venlafaxine ratios >1
  - Extensive 2D6 metabolizers
  - Significantly higher rates of response & remission compared to both placebo AND poor 2D6 metabolizers.
- Why? Pharmacology of desvenlafaxine and venlafaxine is the same.


CYP2D6 & Antidepressants: More of the Story (cont.)

- CYP2D6 significantly expressed in CNS
  - role in serotonin metabolism
  - Metabolizer status may correlate with some personality subtypes
- CYP2D6 Poor metabolizer status MAY be a genetic marker for poor or non-responders to noradrenergic or serotonergic antidepressants (≤ 40% per STAR*D)
- And there may be more..............

CYP2D6 & Antidepressants: The Rest of the Story???

- Relationship between CYP2D6 metabolizer status and antidepressant response MAY also explain:
  - Curvilinear “Therapeutic Window” for nortriptyline plasma concentrations
  - Population phenomenon vs. individual patient phenomenon
- NOT known if drug-induced phenoconversion is problematic