OUTLINE

• Do Antidepressants Work?
• Are all Antidepressants the Same?
• Importance of Dose and Treatment Duration
• The Why and How of Measurement Based Care
• Next Steps in Non-responders/Non-remitters
• Alternatives to Pharmacotherapy for Depression
DO ANTIDEPRESSANTS REALLY WORK?

• Criticism of selective publication of industry funded studies--it happened but may not tell us much

• Criticism of small effect sizes of many studies---a likely product of depression heterogeneity and study flaws?

• Criticism of large placebo effect---“anything works”—but why don’t any studies show placebo BEATS drug?

• Criticism of the heterogeneity of "major depression”—are less severe depressions “phenocopies”?

• WHERE DOES THE TRUTH REALLY LIE?
Antidepressant response depends on:

- Initial severity of depression (not really)
- Chronicity of depression (even if not severe)
- Recurrence of depression

So, for a first episode of depression that has not lasted that long, and is not that severe, antidepressants may not be indicated.
GREATER CHANGE IN HDRS WITH HIGHER INITIAL HDRS

Fournier, J. C. et al. JAMA 2010;303:47-53
NO RELATION OF RESPONSE TO SEVERITY

- All available fluoxetine (n=4293) and venlafaxine (n=4882) studies regardless of outcome or publication
- Children, adults, geriatric adults—efficacy in all subgroups
- Change 2.2 vs 2.78 HAMD units (low vs. high severity)
- 17.5% vs. 17.2% drug-placebo response difference (low/high)
- 13.3% vs. 12.7% remission difference (low/high)
- This finding far more valid than previous small sample studies
50% GREATER RESPONSE WITH AD VS PLACEBO

Please note: for NO studies is PLACEBO favored! (for those who doubt efficacy)
CHRONICITY AND AD RESPONSE: DYSTHYMIA

- 11/14 AD Trials in Dysthymia significant
- Entry HAM-D scores 15-22 for most studies
- Overall Response Rates 55% vs 30%
- NNT of 4
- Additional group of 23 studies of "non-major depression" showed identical results

Lin et al Psychol Med 1999 29: 1273-89
ADS IN DYSTHYMIA VS MDD

BETTER AD RESPONSE WITH PRIOR HISTORY

ARE ALL ANTIDEPRESSANTS CREATED EQUAL?

• Extensive data shows very slight advantages for Venlafaxine, Escitalopram, and perhaps Tricyclics

• This data depends on the comparison drug which has usually been various SSRIs

• Mirtazapine clearly shows an earlier onset of effect

• These differences are all quite small and unlikely to be significant for the majority of patients---but perhaps they are for a few?

VENLAFAXINE ADVANTAGE?

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Favors Venlafaxine</th>
<th>Favors Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Dothiepin</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td><strong>Pooled TCA</strong></td>
<td>(7)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td><strong>Pooled SSRI</strong></td>
<td>(19)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td><strong>Pooled “other drug”</strong></td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Overall pooled</td>
<td>(29)</td>
<td></td>
</tr>
</tbody>
</table>

Relative Effect Size

N=5,562 patients; Smith D, et al. Br J Psychiatry. 2002(May);180:396-404
Fig. 2: Exploratory analysis of potentially influential factors (A) for all patients and (B) for severely depressed patients (baseline MADRS ≥ 30). Numbers in parentheses refer to study number (see Table 1). Positive values are in favour of escitalopram, whereas negative values are in favour of comparators. MADRS = Montgomery–Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitors, VLF = venlafaxine XR.
TCA ADVANTAGE?

Relative Effect Size

<table>
<thead>
<tr>
<th></th>
<th>N (Patients)</th>
<th>Favors TCAs</th>
<th>Favors SSRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies 101</td>
<td>(10,496)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatients</td>
<td>25 (1377)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatients</td>
<td>58 (7834)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High HAM-D score</td>
<td>38 (3336)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HAM-D score</td>
<td>39 (4045)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonergic TCAs</td>
<td>48 (5317)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenergic TCAs</td>
<td>53 (5179)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anderson IM. *Depress Anxiety*. 1989;7(suppl 1):11-17.
MIRTAZAPINE ADVANTAGE?

Survival Analysis (Kaplan-Meier, ITT Group) Time to First Response on HAM-D$_{17}$ (Reduction $\geq$50%)

Logrank-Test: $p=0.0014$; NV Organon (Data on file)
SEDATION AND ACTIVATION PROFILES

mirtazapine  paroxetine  trazodone  nefazodone
fluvoxamine     venlafaxine  citalopram  sertraline
paroxetine      fluoxetine  bupropion
IS DOSE IMPORTANT?

- There is limited evidence that venlafaxine, escitalopram and tricyclics have a dose response curve with higher doses yielding slightly better effects (J Psychopharmacol 22:346. 2008)

- The evidence for SSRIs is very weak—at best in some novel analyses the average effect might be one point on the HAM-D scale (drug-placebo differences for marketed antidepressants are usually 3 points) (Hanson et al Med Dec Making 29:91, 2009)

- Still, any non-responder or partial responder should have the dose raised to the highest tolerated—I have personally seen this work dramatically on a few occasions, though often it does not

- Finally, it is clearly true that LOW doses do NOT work as well as average doses—so you must give an “average” dose
ANTIDEPRESSANT DOSE RANGES (AVERAGE)

- Fluoxetine 5-80 mg (20)
- Paroxetine 10-60 mg (20)
- Escitalopram 5-30 mg (10)
- Citalopram 10-60 mg (20)
- Sertraline 25-200 mg (100)
- Fluvoxamine 25-300 mg (150)
- Venlafaxine XR 25-300 mg (150)
- Duloxetine 10-60 mg (60)
- Bupropion SR 75-450 mg (300)
- Mirtazapine 7.5-60 mg (45)
TREATMENT DURATION: 
THE MAJOR PLAYER

• Many studies show that the longer a patient takes an antidepressant, the more likely it is that they respond

• This is true for BOTH depression and various anxiety disorders

• This truth may well extend beyond 12 weeks, up to 24 weeks, depending on the disorder—more data for anxiety

• So, in practice, how long do you have to wait? When can you tell and how certain can you be, that the patient will improve or not?
Table 3. Proportion of Unimproved Subjects at Weeks 4 and 6 Who Ultimately Responded at Week 8

<table>
<thead>
<tr>
<th>Study</th>
<th>Week 4</th>
<th></th>
<th>Week 6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Nierenberg et al, 1995</td>
<td>37</td>
<td>19</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Mulsant et al, 2006</td>
<td>168</td>
<td>31</td>
<td>107</td>
<td>9</td>
</tr>
<tr>
<td>Posternak et al</td>
<td>118</td>
<td>23</td>
<td>61</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 4. Proportion of Unimproved Subjects at Weeks, 4, 6, and 8 Who Ultimately Responded at Week 12

<table>
<thead>
<tr>
<th>Study</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Quitkin et al, (^4) 2003</td>
<td>177</td>
<td>38</td>
<td>120</td>
</tr>
<tr>
<td>Mulsant et al, (^5) 2006</td>
<td>168</td>
<td>30</td>
<td>107</td>
</tr>
<tr>
<td>Posternak et al</td>
<td>117</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

10-20% NON-RESPONDERS RESPOND IN 2 WEEKS

Table 5. Proportion of Unimproved Subjects at Weeks 2, 4, 6, 8, and 10 Who Responded With Exactly 2 More Weeks of Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Mulsant et al⁵</td>
<td>NM</td>
<td>13</td>
<td>168</td>
<td>14</td>
<td>107</td>
</tr>
<tr>
<td>Posternak et al</td>
<td>208</td>
<td>16</td>
<td>117</td>
<td>17</td>
<td>60</td>
</tr>
</tbody>
</table>

Abbreviation: NM = not mentioned.
• If you do not have a metric to gauge how the patient is responding over time, you will be lost

• People rarely respond in an all-or-nothing, or clear-cut qualitative fashion

• Rather response is slow, gradual, punctuated by ebbs and flows

• You have to have something quantitative to gauge response—you can’t rely on general impressions

• Must show 20% improvement to be sure change is not “noise” or random fluctuations—need metric to do this
How to recognize the moods of an Irish setter
WHAT HAPPENS IF YOU DON’T MEASURE?

- Start a drug, patient gets some improvement, feels satisfied, then slips back and has more distress
- Add another drug, patient gets some improvement, feels satisfied, then slips back and has more distress
- Add another drug and….
- You may be on several drugs and actually not much better than at the beginning
- In fact, you have forgotten where you even were at the beginning!
Both scales are based directly on the diagnostic criteria from the DSM-IV

- Patient self-report versions for ease of use

- Excellent psychometric properties

- PHQ-9 relies on frequency judgement (how many days/week)

- QUIDS-SR is more concretely anchored with descriptors

- 1.3X QUIDS-SR score=HAM-D 17 score
Unreliability of self ratings: so many things can bias them

- Placebo Effect (usually positive but can be negative)
- Cognitive Dissonance Reduction (usually positive)
- Loss Aversion (usually negative)
- Measurement Bias (need repeated measurements)
- Weber’s Law (easier to see improvement for severe)
- Social Desirability (usually positive)
- Personal Control

QIDS-16: AN OBJECTIVE SELF RATING SCALE

- Sleep disturbance—initial, middle, terminal insomnia/hypersomnia (pick the worst)
- Feeling sad
- Appetite and weight—increased or decreased (pick the worst)
- Concentration/decision making
- View of myself
- Thoughts of death and suicide
- General interests
- Energy level
- Feeling slowed down or restless (pick the worse)
QUIDS-16—ASSESSING SEVERITY OF ANERGY

1. There is no change in my usual level of energy
2. I get tired more easily than usual
3. I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work)
4. I really cannot carry out most of my usual daily activities because I just don't have the energy
**PHQ-9**

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Minimal depression</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
</tbody>
</table>

### PHQ-9 Questionnaire

**NAME** John Q. Sample  
**DATE**

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th>Question</th>
<th>Never at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2 Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3 Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4 Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5 Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6 Feeling bad about yourself - or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7 Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8 Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9 Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>+</th>
<th>TOTAL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>add columns:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

Available at [http://www.depression-primarycare.org/clinicians/toolkits/](http://www.depression-primarycare.org/clinicians/toolkits/)
WHEN THERE IS INADEQUATE OR NO RESPONSE

• Need to rule out “pseudo-resistance”
• Need to isolate factors associated with poor response
• Need to know what “stage” of resistance you are at
• Ned to proceed carefully and systematically
CAUSES OF “PSEUDO-RESISTANCE”

• Wrong diagnosis (think bipolar?)
• Inadequate treatment—type, dose, duration
• Treatment intolerance (or non-adherence?)

You Must Rule-Out “Pseudo-Resistance”!
• Comorbid medical / psychiatric disorders (especially anxiety but also atypical BP illness!)
• Chronic pain
• Comorbid substance abuse
• Chronic psychosocial stressors/social disadvantage
• History of childhood maltreatment, personality disorder, and maladaptive coping mechanisms
• Therapeutic alliance: Variation in psychiatrists accounts for more depression outcome than variation in medications (McKay et al 2006)
PHARMACOKINETICS IN TREATMENT-RESISTANCE

- CYP450 Enzymes Metabolize ADs
  - “Ultra-Rapid Metabolizers” might receive insufficient AD
  - “Poor metabolizers” might be unusually intolerant

- P-Glycoprotein pumps AD OUT of the brain
  - ADs unaffected by this may work better.
  - Patients with genetic variants providing LESS p-GLY might respond better to p-Gly sensitive ADs
CYP450: CLINICAL RELEVANCE

- Citalopram, Escitalopram, Sertraline, Fluvoxamine not metabolized much by CYP 2D6
- Clozapine, Quetiapine, Ziprasidone not metabolized much by CYP2D6
- Venlafaxine minimally metabolized by 2C19
- There are no RANDOMIZED studies clearly showing that obtaining these genotypes improves outcome (vs. not doing it), though it could help with selective patients who are intolerant or non-responsive
P-GLY: CLINICAL RELEVANCE

- ADs that are affected by p-GLY (get pumped out of the brain back into the blood) may not work as well in some genetically predisposed patients—TCAs, Citalopram, Venlafaxine, Paroxetine

- Mirtazapine, Sertraline, Nefazodone and probably Fluoxetine are NOT as affected by this

- pGLY is elevated in depressed patients either due to the disease, associated inflammatory cytokines or perhaps variation in pGLY gene

- Some atypical APs inhibit pGLY—is this why they are effective “augmenters”? 
• Studies show genetic variants for 5HTT, 5HT2, other “targets” of AD medication provide minimal if any predictability (despite current businesses pushing this)

• Studies of neuroimaging showing structural and “connectivity” correlates of poor response are promising but will likely be very hard to standardize

• Even if the above correlate with “resistance” they would only be of value if they informed specific treatment selection/decisions
IMPORTANCE OF “STAGES” OF RESISTANCE: A BIG DIFFERENCE BETWEEN 1 vs 2 FAILED TRIALS

Psychiatric Services. 2009;60(11):1439-1445. doi:10.1176/appi.ps.60.11.1439
Next step after initial failure?

- Switch or Augment

- Clinical Lore--Switch if no response or intolerance; Augment if some response or no side effects

- However, data shows that there is NO DIFFERENCE in either side effects or efficacy between these two options!

- Switch or augment could always be to psychotherapy rather than another medication

- Most strategies studied have been tested only in patients at “stage 1” of resistance.
George I. Papakostas, Maurizio Fava, Michael E. Thase
Biological Psychiatry Volume 63, Issue 7 2008 699 - 704
Switch Options

- SNRI (some data indicates slight advantage)
- Atypical AD (Mirtazapine or Bupropion)
- TCA (more like SNRI in efficacy but more side effects)
- MAOI—now underutilized as most trainees since 1990 have had little experience using—STAR-D 4th stage switch to tranylcypromine showed response rate 13%
TCA-MAOI NON-RESPONSE CROSSOVER: MAOI BETTER THAN TCA

McGrath et al A J Psych 1993; 150: 118-123
STAR-D REMISSION RATES: AUGMENTATION “LOOKS” BETTER

BUT SWITCH VS AUGMENTATION IS EQUIVALENT!

### TABLE 2  Comparison of Remission, Response, and Quality of Life by Treatment Strategy: Full Study Sample and Propensity-Score-Matched Sample (controls for Rx preference)

<table>
<thead>
<tr>
<th>Measure of Remission</th>
<th>Augment (N = 565)</th>
<th>Switch (N = 727)</th>
<th>Augment vs Switch (N = 1292)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IP</td>
<td>95% CI</td>
<td>IP</td>
</tr>
<tr>
<td>QIDS-SR₁₆</td>
<td>0.33</td>
<td>0.29–0.37</td>
<td>0.23</td>
</tr>
<tr>
<td>HRSD₁₇</td>
<td>0.28</td>
<td>0.25–0.32</td>
<td>0.20</td>
</tr>
<tr>
<td>QIDS-SR₁₆</td>
<td>0.27</td>
<td>0.23–0.30</td>
<td>0.24</td>
</tr>
<tr>
<td>Measures of Quality of Life</td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
</tr>
<tr>
<td>Q-LES-Q</td>
<td>53.3</td>
<td>50.9–55.6</td>
<td>50.9</td>
</tr>
<tr>
<td>SF-12</td>
<td>40.2</td>
<td>38.7–41.7</td>
<td>38.0</td>
</tr>
<tr>
<td>Mental health status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health status</td>
<td>45.9</td>
<td>44.5–47.3</td>
<td>45.1</td>
</tr>
</tbody>
</table>

Remission on the QIDS-SR₁₆ is defined as a level 2 exit score of 5 or less. Remission on the HRSD₁₇ is defined as a level 2 exit score of 7 or less. Response was defined as a decrease of 50% or more in QIDS-SR₁₆ score from level 2 entry to level 2 exit. QIDS-SR₁₆ indicates the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (scores can range from 0 to 27; higher scores indicate increased severity of depressive symptoms); HRSD₁₇, the 17-item Hamilton Rating Scale for Depression (scores can range from 0 to 52; higher scores indicate increased severity of depressive symptoms); Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire (scores can range from 0 to 100; higher scores indicate greater satisfaction); SF-12, Short-Form Health Survey, 2 SF-12 subscales (mental and physical) range from 0 to 100; higher scores indicate increased perceived functioning. The population norm for each is 50 ± 10.

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Treating Depression After Initial Treatment Failure: Directly Comparing Switch and Augmenting Strategies in STAR*D.
Gaynes, Bradley;  MD, MPH;  Dusetzina, Stacie; Ellis, Alan; Hansen, Richard; Farley, Joel; Miller, William;  MD, PhD;  Sturmer, Til;  MD, MPH

DOI: 10.1097/JCP.0b013e31823f705d
Augmentation Options: The Facts

- Atypical Neuroleptics—the absolutely best and most extensive data—31 vs 17% response, with NNT of 7

- Lithium—older data, mostly with TCA, but aggregate response is 41% vs 14% with NNT of 4—better to use with an SNRI (more like TCA?)? But STAR-D 3\textsuperscript{rd} step remission rate was 13%.

- T3—older data, a few studies show similar head to head response with Lithium, better tolerated—STAR-D 3\textsuperscript{rd} step remission rate was 25%

- Combining ADs---poor quality data (5 studies, largest and least biased was totally negative!), actually least well supported yet most often used by clinicians!
Atypical neuroleptic augmentation of ADS: A meta-analysis

LITHIUM AUGMENTATION MAY ALSO WORK WITH SSRIs


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**Figure 2. Meta-Analysis of Lithium Augmentation Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Lithium, N/N</th>
<th>Control, N/N</th>
<th>Fixed Effects OR and 95% CI</th>
<th>Fixed Effects OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heninger et al (1983)²⁶</td>
<td>5/8</td>
<td>0/7</td>
<td></td>
<td>23.57 (1.00 to 556.08)</td>
</tr>
<tr>
<td>Kantor et al (1986)²²</td>
<td>1/4</td>
<td>0/3</td>
<td></td>
<td>3.00 (0.09 to 102.05)</td>
</tr>
<tr>
<td>Zusky et al (1988)²³</td>
<td>3/8</td>
<td>2/8</td>
<td></td>
<td>1.80 (0.21 to 15.41)</td>
</tr>
<tr>
<td>Schöpf et al (1989)²⁸</td>
<td>7/14</td>
<td>0/13</td>
<td></td>
<td>27.00 (1.35 to 541.57)</td>
</tr>
<tr>
<td>Browne et al (1990)²⁹</td>
<td>3/7</td>
<td>2/10</td>
<td></td>
<td>3.00 (0.35 to 25.87)</td>
</tr>
<tr>
<td>Stein and Bernadt (1993)²⁴</td>
<td>2/16</td>
<td>4/18</td>
<td></td>
<td>0.50 (0.08 to 3.19)</td>
</tr>
<tr>
<td>Joffe et al (1993)²⁵</td>
<td>9/17</td>
<td>3/16</td>
<td></td>
<td>4.88 (1.01 to 23.57)</td>
</tr>
<tr>
<td>Katona et al (1995)³⁰</td>
<td>15/29</td>
<td>8/32</td>
<td></td>
<td>3.21 (1.09 to 9.48)</td>
</tr>
<tr>
<td>Baumann et al (1996)²⁷</td>
<td>6/10</td>
<td>2/14</td>
<td></td>
<td>9.00 (1.27 to 63.89)</td>
</tr>
<tr>
<td>Nierenberg et al (2003)⁴</td>
<td>2/18</td>
<td>3/17</td>
<td></td>
<td>0.58 (0.08 to 4.01)</td>
</tr>
<tr>
<td>Total</td>
<td>53/131</td>
<td>24/138</td>
<td></td>
<td>3.11 (1.80 to 5.37)</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: $\chi^2 = 11.90$, df = 9, p = .22, $I^2 = 24.4\%$
Test for Overall Effect: $Z = 4.06$, $p < .0001$

---

*Pooling of patients responding to augmentation therapy. Fixed effects model used.*
T3 AUGMENTATION

- Most studies uncontrolled, without placebo, and with TCAs
- Meta-analysis 4 placebo controlled TCA studies did NOT show significant effect (Aronson et al 1996)
- Only 4 placebo controlled studies with SSRIs—three are not significant; the fourth while significant had the largest proportion of “stage 1” resistance (easiest patients).
RESPONSE TO LI VS T3 AUGMENTATION AFTER TWO FAILED MEDICATION TRIALS IN STAR-D

TIME TO REMIT AFTER AUGMENTATION WITH LI VS THYROID IN THE STAR-D STUDY

Combining AEDs effective as second step strategy?

Carpenter et al; Biol Psychiatry 51:183, 2002
LARGEST AND LEAST BIASED STUDY SHOWS COMBINED AD RX DOES NOT WORK!

N=293

Licht and Qvitzau 2002  Psychopharmacology 161: 143-151
COMBINING MEDICATIONS FROM THE OUTSET IS ALSO NO BETTER THAN A SINGLE SSRI
AUGMENTATION: NEWER OPTIONS

• Deplin
• SAM-E
• Omega-3 Fatty Acids
Pooled Response Rates in Two Trials of L-Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression

Response was defined as a reduction of ≥50% in Hamilton Depression Rating Scale score during treatment or a final score of ≤7. Significant difference between groups in trial 2 (p=0.04). The pooled analysis was conducted as described in Fava et al. (25).

S-Adenosyl Methionine (SAMe) Augmentation of SSRIs for Antidepressant Nonresponders With MDD

Figure Legend:

HAM—D Response and Remission Rates Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo

Data depict last observation carried forward (LOCF) for all patients randomly assigned.

Significant difference between groups (p<0.05, Fisher’s exact test).

Date of download: 9/3/2013
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Figure 1. Standardized Mean Differences and 95% Confidence Intervals for Studies of Depressive Episodes Comparing Antidepressant Effect Between Omega-3 Polyunsaturated Fatty Acids (PUFAs) and Placebo, Arranged by Percentage of Eicosapentaenoic Acid (EPA) in the Supplements

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>% EPA</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.40</td>
</tr>
<tr>
<td>Nemets et al, 2002</td>
<td></td>
<td>100</td>
<td>5.60</td>
</tr>
<tr>
<td>Frangou et al, 2006</td>
<td></td>
<td>100</td>
<td>14.20</td>
</tr>
<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.70</td>
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<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.40</td>
</tr>
<tr>
<td>Mischoulon et al, 2009</td>
<td></td>
<td>100</td>
<td>8.30</td>
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<tr>
<td>Frangou et al, 2006</td>
<td></td>
<td>100</td>
<td>13.90</td>
</tr>
<tr>
<td>Su et al, 2003</td>
<td></td>
<td>66.67</td>
<td>6.80</td>
</tr>
<tr>
<td>Nemets et al, 2006</td>
<td></td>
<td>66.67</td>
<td>5.60</td>
</tr>
<tr>
<td>Su et al, 2008</td>
<td></td>
<td>64.71</td>
<td>9.20</td>
</tr>
<tr>
<td>da Silva et al, 2008</td>
<td></td>
<td>60</td>
<td>3.60</td>
</tr>
<tr>
<td>da Silva et al, 2008</td>
<td></td>
<td>60</td>
<td>4.40</td>
</tr>
</tbody>
</table>

**Overall EPA ≥ 60%**

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>% EPA</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al, 2008</td>
<td></td>
<td>57.89</td>
<td>9.50</td>
</tr>
<tr>
<td>Carney et al, 2009</td>
<td></td>
<td>55.36</td>
<td>20.70</td>
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<td>Rogers et al, 2008</td>
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<td>42.57</td>
<td>35.50</td>
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<td>Grenyer et al, 2007</td>
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<td>21.43</td>
<td>11.50</td>
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<tr>
<td>Rees et al, 2008</td>
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<td>20.18</td>
<td>4.00</td>
</tr>
<tr>
<td>Silvers et al, 2005</td>
<td></td>
<td>20</td>
<td>12.70</td>
</tr>
<tr>
<td>Marangell et al, 2003</td>
<td></td>
<td>0</td>
<td>6.10</td>
</tr>
</tbody>
</table>

**Overall EPA < 60%**
• Quetiapine monotherapy—some UP data

• Pramipexole—8/12 (67%) v 2/10 (20%)—one study; no data in UP Depression—but few Dopamine strategies that don’t confound subjective stimulation

• NAC—no data in UP Depression but works on glutamate, dopamine, and to reduce oxidative stress and increase neurogenesis

• Lamotrigine—negative data in UP Depression

• Lithium Monotherapy?
QUETIAPINE MONOTHERAPY EFFECTIVE IN UP DEPRESSION

LOCF = last observation carried forward; LSM = least squares means;
MADRS = Montgomery Åsberg Depression Rating Scale; MITT, modified intent-to-treat; XR = extended release.
All p values vs add-on lithium.

Michael Bauer, Liliana Dell'Oso, Siegfried Kasper et al: Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on to antidepressants in patients with treatment-resistant major depressive disorder.
Journal of Affective Disorders Volume 151, Issue 1 2013 209 - 219
WHY KETAMINE IS NOT READY FOR PRIME TIME

24 patients got 6 infusions; 17 responded (not remitted); 12 relapsed
So rate of benefit is actually 5/24 or about 20%--Compare with Med Data!

James W. Murrough, Andrew M. Perez, Sarah Pillemer et al: Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression Biological Psychiatry Volume 74, Issue 4 2013 250 - 256
Figure 6. Percentage of treatment responders among infliximab- vs placebo-treated patients with treatment-resistant depression (TRD) and a baseline high-sensitivity C-reactive protein (hs-CRP) concentration of 5 mg/L or less or of greater than 5 mg/L. The percentage of treatment responders, which was defined by a 50% or more drop in the 17-item Hamilton Scale for Depression at any time during treatment, was compared between infliximab- and placebo-treated patients with TRD and a baseline plasma hs-CRP concentration of 5 mg/L or less or of greater than 5 mg/L, as well as combined. Infliximab-treated patients exhibited a higher response rate than placebo-treated patients when the hs-CRP concentration was greater than 5 mg/L, but infliximab-treated patients exhibited a lower response rate than placebo-treated patients when the hs-CRP concentration was 5 mg/L or less. These results did not reach statistical significance ($P=0.19$). No difference was found between the groups when combined ($P=0.99$).
MEDICATIONS THAT DON'T WORK—SHOULD WE TRY?

• Buspirone—placebo controlled trials negative, did worse than combo SSRI + Bupropion in STAR-D

• Stimulants—small trials suggested possibly, but large recent trials totally negative; danger of tolerance

• Modafanil—same as stimulants but did work in several trials in BP illness so possibly useful?
STIMULANT AUGMENTATION INEFFECTIVE IN MDD

WHAT ABOUT PSYCHOTHERAPY FOR RESISTANT DEPRESSION?

• Evidence for Exercise and Behavioral Activation (BA)
• Evidence for Problem Solving Therapy (PST)
• Mindfulness-based therapies are emerging strongly
• IPT and CBT very effective but more complicated to learn and deliver competently
• Psychodynamic therapy even more complicated to do well
• BUT for virtually all of these, there is NO study in treatment resistant populations!!
• EXCEPTION is CoBalT study in Lancet Dec 2012 shows substantial CBT vs UC effect in medication resistant depression (46% vs 22% response rate differences)
Cognitive Therapy (CT) Reduces Relapse Risk Following Incomplete Remission on Antidepressants

Paykel ES, Scott J, Teasdale JD, et al. Arch Gen Psychiatry. 1999(Sept);56(9):829-835
CONCLUSIONS

- Antidepressants work, but probably have greatest advantage in more severe, chronic or recurrent depressions.

- Duration much more important than type or dose.

- Outcome monitoring is crucial for success.

- Multiple second step options have similar effects that are not insignificant, but not overly large.

- Medication trials will have low (<20%) probability of working after the first strategy fails—should we tell patients?

- More effective agents usually have more adverse events!

- “Natural” medications only proven effective in stage 1 resistance!

- Some resistant UP illness could be “biochemically” BP.