Treatment Resistant Depression: A Systematic Approach to Management

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Within the past 3 years, Dr. Thase has been a consultant to Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Forest Laboratories (PGx), Janssen Pharmaceutica, Lundbeck, Merck (Organon & Schering-Plough), Mylan (Dey), Neuronetics, Novartis, Otsuka, Pfizer, Rexahn, Shire US, Sunovion, Takeda, Teva, and Transcept. He has received honoraria for talks from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Lundbeck, Merck, Mylan, Otsuka, and Pfizer. He has received research funding from AstraZeneca, Eli Lilly and Company, Forest, GlaxoSmithKline, NeoSync, Otsuka, and Pfizer, as well as the National Institute of Mental Health and the Agency for Healthcare Research and Quality. His wife is an employee of Peloton Advantage, which does business with Pfizer.
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.
A Simple System for Staging Antidepressant Resistance

- **Stage I:** failure of an adequate trial of one class of major antidepressant
- **Stage II:** failure of adequate trials of two distinctly different classes of antidepressants
- **Stage III:** stage II plus failure of a third class of antidepressant, including a TCA
- **Stage IV:** stage III plus failure of an adequate trial of MAOI
- **Stage V:** stage IV plus failure of an adequate course of ECT

Should we switch or use adjunctive strategies?

• Parsimony favors switching
• Adjunctive therapies often easier to implement (i.e., avoids washout and cross-titration)
• STAR*D disappointing did not answer this question aside from demonstrating that adjunctive strategies preferred for partial responders and switching preferred for nonresponders
STAR-D Remission Rates Across All 4 Levels

Remission Definition: HAMD-17 ≤7

Level 1
11.9 weeks

Level 2
8-10 weeks

Level 3
≤14 weeks

Level 4
≤14 weeks

Mono, single medication regimen; Augm, combination medication treatment.

The Case for Switching Antidepressants

- Clinically necessary when first drug is poorly tolerated
- Second drug selection is iterative, guided by outcome with first
- Can pick medications with distinctly different MoAs
- Efficacy of second antidepressant clearly established
Should We Switch Within- or Across Classes?

- Across-class switch was the standard until the mid-1990s
- Subsequent study results “muddied the water”
- A second within-class trial with an SSRI or SNRI is now an accepted option
- No consensus on a third within-class trial
Remission rates in patients with treatment-resistant depression after switching drugs

Subjects: 3,097 outpatients at least 18 years old with a diagnosis of major depressive disorder based on DSM-IV classification who had a HAM-D17 total score ≥17 and who showed inadequate response or intolerance to treatment with a conventional antidepressant (e.g., fluoxetine, paroxetine, sertraline, or citalopram) for at least 4 weeks.

Method: An open-label study. Patients were randomly assigned to orally receive venlafaxine or a conventional antidepressant for 24 weeks. Patients in the venlafaxine group received venlafaxine sustained-release capsules at doses of 75 to 225mg/day, and those in conventional antidepressant group received fluoxetine, paroxetine, or citalopram at doses of 20 to 60mg, sertraline at doses of 50 to 200mg/day, or mirtazapine at doses of 15 to 45mg/day.

Safety: 483 adverse events occurred in 274 (15.0%) patients in the venlafaxine group. The number of AEs in the conventional antidepressant group was 472 in 266 patients (17.9%).

Baldomero, E. B. et al.: Depress Anxiety 22 (2): 68, 2005
STAR*D Level 2 Results

- **Monotherapy**
  - Venlafaxine XR: 25%
  - Bupropion SR: 25.5%
  - Sertraline: 26.6%

- **Combination**
  - CIT+Bupropion SR: 39%
  - CIT+Buspirone: 33%

References:
Subjects and methods: Literature searches were performed to obtain randomized comparative studies that investigate antidepressant switching strategies in patients with major depressive disorder and insufficient response to SSRIs. Subsequently, in a meta-analysis, remission and response rates were compared using obtained data. The dosage of venlafaxine was 75 to 375mg/day in 3 studies included in the analysis.

CYP2D6 Status and Response to Venlafaxine: Pooled Analysis of RCTs

Figure 1A. Change in Scores on the HDRS<sub>17</sub> and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status<sup>a</sup>

- HRSD<sub>17</sub> Total Score
- MADRS Total Score

Figure 1B. Response and Remission Rates Based on the HDRS<sub>17</sub> and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status

- EM (Venlafaxine)
- PM (Venlafaxine)
- Placebo

Abbreviations: EM = extensive metabolizer, HDRS<sub>17</sub> = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, PM = poor metabolizer.

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The Case for Adjunctive Therapy

• Builds on partial success of first therapy
• Avoiding washout is a pragmatic benefit for patients
• When effective, benefits may be rapid
• Can choose rx to target specific sx
Adjunctive Strategies (2016): Ranked from Most to Least Likely to be Used

- Lithium & other mood stabilizers
- Thyroid hormones
- Methylfolate (Deplin)
- Modafinil and psychostimulants
- Buspirone and BZs
- 2nd generation antipsychotics (SGAs)
Adjunctive Therapy with Lithium Salts

- More than 60 published studies, but rarely used in the US in 2015
- Definitely effective (meta-analytic p<10^{-6})
- Usual blood level: .4-.8 mEq/L
- Rapid response is rare, so allow 6 weeks for response
- May be both an adjunct and a primary antidepressant

# Placebo Controlled Lithium Augmentation Studies

**Review:** Lithium augmentation  
**Comparison:** 01 Lithium augmentation studies  
**Outcome:** 01 Response rates

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
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<tr>
<td>Bauman 1996</td>
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<td>4.48 [1.27, 63.89]</td>
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<td>Browne 1990</td>
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<td>2/10</td>
<td>6.33 [0.35, 25.87]</td>
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<td>Heninger 1983</td>
<td>5/8</td>
<td>0/7</td>
<td>1.38 [1.00, 556.08]</td>
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<tr>
<td>Joffe 1993</td>
<td>9/17</td>
<td>3/16</td>
<td>9.78 [1.01, 23.57]</td>
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<td>Kantor 1986</td>
<td>1/4</td>
<td>0/3</td>
<td>2.61 [0.09, 102.05]</td>
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<tr>
<td>Katona 1995</td>
<td>15/29</td>
<td>8/32</td>
<td>24.69 [1.09, 9.48]</td>
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<td>Nierenberg 2003</td>
<td>2/18</td>
<td>3/17</td>
<td>18.44 [0.08, 4.01]</td>
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<tr>
<td>Schoepf 1989</td>
<td>7/14</td>
<td>0/13</td>
<td>1.74 [1.35, 541.57]</td>
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<td>Stein 1993</td>
<td>2/16</td>
<td>4/18</td>
<td>22.15 [0.08, 3.19]</td>
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<td>Zusky 1988</td>
<td>3/8</td>
<td>2/8</td>
<td>8.40 [0.21, 15.41]</td>
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<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>131</strong></td>
<td><strong>138</strong></td>
<td>100.00</td>
<td>3.11 [1.80, 5.37]</td>
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</tbody>
</table>

Total events: 53 (Treatment), 24 (Control)  
Test for heterogeneity: Chi² = 11.90, df = 9 (P = 0.22), I² = 24.4%  
Test for overall effect: Z = 4.06 (P < 0.0001)

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Meta-analysis of 10 augmentation studies. Overall pooled rates of response: lithium 53/131 or 40.5% vs 24/138 or 17.4%.  
Crossley and Bauer, J Clin Psychiatry, 2009
Augmentation with Other Mood Stabilizers

- Lamotrigine now most widely used; efficacy unproven for all but lithium
- “Quelching” effect for divalproex and carbamazepine for patients with PTSD?
- Coverage of subtle bipolar or mixed syndromes
- Relief of secondary symptoms such as pain
Adjunctive Thyroid Hormone

- 11 published studies
- $T_3$ preferred over $T_4$
- 25-50 µg/day of $T_3$
- Safe and easy, but inconsistent efficacy for patients with normal thyroid functions
- Significantly easier to implement than lithium in STAR*D
- Treatment of choice for patients with elevated TSH levels?
Meta-Analysis of RCTs of Adjunctive Thyroid Therapy

All 8 Trials, N=298
OR=2.09 (95% CI 1.31-3.32), P=0.002

4 Controlled Trials, N=75
OR= 1.53 (95% CI 0.70-3.35), P=.29

Aronson et al. Arch Gen Psychiatry 1996;53:842-848
Adjunctive Therapy With Lithium or Thyroid Hormone: Results of STAR*D Level 3 Comparison

Potential Pharmacogenetic Relationship with Response to Adjunctive T3?

- There are functional polymorphisms in the genes that code for the enzymes that convert T4 to T3 (deiodinases)
- In a relatively large study of thyroid (T3) acceleration of sertraline response, patients with the DIO1-C785T polymorphism (i.e., lower conversion activity) were more responsive to T3 (Cooper-Kazaz et al., 2009)
Is the benefit of Adjunctive T3 Limited to Women?

Effect Size as a Function of Sample Gender Ratio
(6 Studies, n=125)

$r=.76, p=.041$

Adjunctive Therapy with Modafinil, Armodafinil, and Other Stimulants

- Modafinil and armodafinil (indirectly) dopaminergic agonists with limited abuse potential
- Though proven to relieve sleepiness and fatigue, effects on other depressive symptoms less certain in MDD
- Inconsistent evidence in RCTs of TRD and bipolar depression
Effect of Adjunctive Lisdexamphetamine on Executive Function in MDD

LDX augmentation is not FDA approved for MDD.

*P < .05. †P < .01. ‡P < .001

BRIEF-A = Behavior Rating Inventory of Executive Function-Adult Version;
GEC = Global Executive Composite; LS = least square; EOS = end of study; LDX = lisdexamfetamine.

Other Dopaminergic Options

- Pramipexole
  - dopamine agonist approved for PD
  - some evidence of efficacy in small studies
- Classic psychostimulants
  - subjective benefits for drive, energy, and concentration
  - four contemporary placebo-controlled trials with SSRI nonresponders have yielded mixed results
Buspirone Augmentation

- Popularity has waned despite good overall showing in STAR*D
- Reasonably safe (10 mg - 40 mg/day), but unproven efficacy
- Secondary effects
  - anxiety relief? (failed in STAR*D)
  - reversal of sexual side effects
Other Reasonable Options for Anxious Depression?

- Adjunctive benzodiazepines – effective but concerns about dependence and tolerance
- Adjunctive second generation antipsychotics – effective, but concerns about longer term safety
- MAOIs?
L-methylfolate, not folate, is the necessary cofactor for synthesis of monoamines.

About 2/3rds of the population have a polymorphism of the C677T MTHFR gene that slows synthesis of L-methylfolate.

As a “medical food”, Deplin 15 mg/day is safe, generally well-tolerated and much less expensive than branded SGAs.

Efficacy data starting to emerge.
From: 1-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials

American Journal of Psychiatry

FIGURE 1. Pooled Response Rates in Two Trials of 1-Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression

a Response was defined as a reduction of $\geq 50\%$ in Hamilton Depression Rating Scale score during treatment or a final score of $\leq 7$. Significant difference between groups in trial 2 ($p=0.04$). The pooled analysis was conducted as described in Fava et al..
Combining Antidepressants: Advanced Practice or Fad?

• Once considered indicative 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 of Two RCTs

Blier et al. 2010¹

Rush et al. 2011²

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

Antipsychotic Augmentation

- SGAs now widely used
- Efficacy likely across the class
- Not delimited to psychotic depression or bipolar depression
- Important differences in side effects among drugs
Atypical antipsychotics as adjunctive therapy for MDD

- Adjunctive efficacy has been demonstrated for four SGAs:
  - risperidone (not FDA approved)
  - olanzapine (in combination with fluoxetine)
  - aripiprazole
  - quetiapine XR
  - brexipiprazole
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>
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<tr>
<td><strong>Olanzapine trials</strong></td>
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<td>Shelton 2001</td>
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<tr>
<td>Shelton II 2005</td>
<td></td>
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<tr>
<td>Corya 2006</td>
<td></td>
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<tr>
<td>Thase 2007</td>
<td></td>
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<tr>
<td>Thase II 2007</td>
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</tr>
<tr>
<td>Subtotal</td>
<td>1.39 (1.05, 1.84); Z=2.30, P=.02</td>
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<td><strong>Risperidone trials</strong></td>
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<td>Mahmoud 2007</td>
<td></td>
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<td>Keitner 2009</td>
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<tr>
<td>Reeves 2008</td>
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<tr>
<td>Subtotal</td>
<td>1.83 (1.18, 2.82); Z=2.71, P=.007</td>
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<tr>
<td><strong>Quetiapine trials</strong></td>
<td></td>
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<tr>
<td>Khullar 2006</td>
<td></td>
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<td>Mattingly 2006</td>
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<td>McIntyre 2006</td>
<td></td>
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<td>Earley 2007</td>
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<tr>
<td>El-Khalili 2008</td>
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<tr>
<td>Subtotal</td>
<td>1.61 (1.24, 2.09); Z=3.56, P=.0004</td>
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<td><strong>Aripiprazole studies</strong></td>
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<td>Berman 2007</td>
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<td>Marcus 2008</td>
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<tr>
<td>Berman 2008</td>
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<tr>
<td>Subtotal</td>
<td>2.07 (1.58, 2.72); Z=5.28, P=.00001</td>
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<td>Test for overall effect:</td>
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<tr>
<td></td>
<td>1.69 (1.46, 1.95); Z=7.00, P&lt;.00001</td>
</tr>
</tbody>
</table>

Nelson JC, Papakostas GI; AJP, 2009
Updated Systematic Review and Meta-Analysis of Adjunctive SGAs
Pooled Response, Remission, and Adverse-Event Rates

Response: 44.2% Atypical, 29.9% Placebo
Remission: 30.7% Atypical, 17.3% Placebo
Adverse Event Discontinuations: 9.1% Atypical, 2.3% Placebo

Nelson JC, Papakostas GI; AJP, 2009
Olanzapine Augmentation to Fluoxetine in Treatment-Resistant Depression

**Efficacy (Improvement in MADRS)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Δ from Baseline</th>
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<tbody>
<tr>
<td>FLX</td>
<td>-9</td>
</tr>
<tr>
<td>OLZ</td>
<td>-8.8</td>
</tr>
<tr>
<td>OFC</td>
<td>-12.7</td>
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</table>

*P<.001 vs FLX and OLZ.

**Adverse Events (Weight Increase)**

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<tr>
<th>Group</th>
<th>Mean Δ in Weight (kg)</th>
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<tr>
<td>FLX</td>
<td>0.4</td>
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<tr>
<td>OLZ</td>
<td>5.5</td>
</tr>
<tr>
<td>OFC</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Studies of Newer SGAs

- Brexpiprazole recently approved
- Lurasidone efficacy shown in bipolar depression and MDD with mixed features
- Studies of cariprazine ongoing
Adjunctive Brexipiprazole: Efficacy on Depressive Symptoms (MADRS)

Studies 227 and 228: Primary endpoint – mean change in MADRS total score

- ADT + placebo (n=381)
- ADT + Brex 1 mg (n=211)

LS mean difference from placebo at Week 6
- Brex 1 mg: -2.02, p=0.0018
- Brex 2 mg: -2.35, p=0.0007
- Brex 3 mg: -2.54, p=0.0001

*p<0.05, **p<0.01, ***p<0.001 versus placebo; MMRM analysis; efficacy per final protocol population; pooled placebo group

MADRS baseline: ADT + placebo 26.9, ADT + Brex 1 mg 26.9, ADT + Brex 2 mg 26.9, ADT + Brex 3 mg 26.5

Source: Thase et al. JCP 2015a&b
Adjunctive SGA Therapy: Key Issues & Questions

- Is efficacy sustained?
- Cost effectiveness vs other options?
- Ultimate risks of TD and metabolic complications
- Syndromal indications & possible differences for symptomatic efficacy and metabolic side effects
Treatment Strategy of Choice for Stage III TRD: *Monoamine Oxidase Inhibitors*

- 30%-60% response rates in TCA era
- More effective in:
  - atypical depression (Columbia)
  - anergic depression (Pittsburgh)
  - bipolar depression
- Poor showing for tranylcypromine in STAR*D
- ? role of seligiline patch
Treatment Strategy of Choice for Stage IV TRD: *Electroconvulsive Therapy*

- Most effective treatment available
- Two options: bilateral or ultrahigh energy RUL
- Treatment of choice for delusional and melancholic cases of TRD
- Less effective in TRD than in uncomplicated depression (i.e., 50%-60% vs 90%)
- Majority of TRD cases will relapse within 1 year of successful ECT
High Risk of Relapse Following Successful ECT of TRD

Prevention of Relapse Following ECT: Efficacy of Lithium + Nortriptyline

Other Neuromodulation Strategies

- Transcranial Magnetic Stimulation (rTMS)
- Vagus Nerve Stimulation
- Deep Brain Stimulation
Repetitive Transcranial Magnetic Stimulation (rTMS): Summary

- Better tolerated and safer than ECT
- Definite therapeutic effects (nonpsychotic MDD and less advanced cases of TRD); efficacy confirmed by recent NIMH-funded multi-center trial
- Dose/response/duration characteristics still not well developed
- Labor-intensive and – until coverage issues addressed - expensive
- Perhaps delimited to patients who are too mild for or who refuse or can’t tolerate ECT
Recent Clinical Studies Replicate Antidepressant Effects of TMS

Improved study designs
- Larger samples
- More treatment sessions
- Optimized stimulation parameters

Recent meta-analysis from 2006-7
- Five sham-controlled studies
- N=274 patients
- Effect size = 0.76

Pivotal trial effect size = 0.83 for ATHF 1 group

Uncommon Treatment Strategies

- Chronotherapies (sleep deprivation, phototherapy)
- Other nutriceuticals (e.g., SAM-e)
- Opiates
- Experimental pharmacotherapies (e.g., ketamine infusion)
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= buprenorphine
SAM= samidorphan
(μ-opioid receptor antagonist)
Psychotherapeutic Issues in Refractory Depression

- Reestablishing morale
- Increased activity
- Coping behaviors
- Noncompliance
- Avoid “blaming the victim”

- Focused, specific goals
- Mobilization of resources
- Rehabilitation issues
Conclusions

- Focus first on assessment and staging
- Logical choices are available for careful, sequential trials
- When in doubt, try again
- New developments every year
- Ample room for improvement
- Requires an ongoing systematic nationwide approach