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Treatment Resistant Depression

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## Learning objectives

<table>
<thead>
<tr>
<th>Clinical characteristics of treatment resistance</th>
<th>Methods to treat TRD &amp; Evidence of their efficacy</th>
</tr>
</thead>
</table>

- Treatment-resistant depression (TRD) is a major public health problem.

**Amresh Srivastava**
Outcome & Treatment resistance

Causes, neurobiology & management of ‘Treatment-Resistance’
WHAT IS THE NATURE & CHARACTERISTICS OF TREATMENT RESISTANCE?
Resistance to What??
## Measuring TRD: Staging Treatment Resistance

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Inadequate response to 1 monotherapy</td>
</tr>
<tr>
<td>Stage II</td>
<td>Inadequate response to 2 adequate monotherapy trials (different classes)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Stage II resistance plus inadequate response to 1 augmentation trial</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Stage III resistance plus inadequate response to a second augmentation trial</td>
</tr>
<tr>
<td>Stage V</td>
<td>Stage IV resistance plus inadequate response to bilateral ECT</td>
</tr>
</tbody>
</table>

Adapted from: Thase ME, Rush AJ. J Clin Psychiatry. 1998;59(suppl 5):5
TRD: chronic, recurrent, debilitating

>50% improvement in depression Scores.
in 4 months F/U

Non-response

Nonremission is Common

Definitions of Response and Remission

The causes of TRD are not fully understood.

% Reduction in Score

<table>
<thead>
<tr>
<th>Level</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Response</td>
<td>50% - 74%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>25% - 49%</td>
</tr>
<tr>
<td>Nonresponse</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>TRD</td>
<td>&gt;40%</td>
</tr>
</tbody>
</table>

12 months Prevalence rate

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>3%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2%</td>
</tr>
</tbody>
</table>

Paradigms Which Contribute to Faulty TRD Labeling
Predictors of Non-Response
Biology:
No specific neurobiology TRD. Exploring newer brain targets

- NT: Dopamine, NMDA,
- Aminoacids: glutamate/glutamine/GABA cycling\(^1\)
- Neuronal nitric oxide synthisase factor (NOS) via Serotonin signaling\(^2\)
- Neuropeptides P/Y\(^3\)
- Endogenous modulators
- Beta 3 – adrenoreceptos (agonist: amibegrone)
- Nicotinic receptors

Biological Changes in treatment Resistant Depression

Biology\(^1, \, 2\)

- N-methyl-D-aspartate (NMDA) receptor\(^4\)

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Reduced global cortical folding\(^5\)

Decreased Neurogenesis
Decision tree for TRD
Diagnosing treatment resistance

- **Was compliance adequate?**
  - Y

- **Was dosage adequate?**
  - Y

- **Was the duration of Tx adequate?**
  - Y

- **Was the assessment comprehensive?**
  - Y

- **Was the diagnosis correct?**
  - Y

- **Was anything interfering with drug-kinetics?**
  - Y
TRD - Common Diagnosis

1. Depressed Mood
2. Suicide ideation or attempt

- Stress
- Physical illness
- Substance
- Psychosis
- Polarity

Organic Depression
Focus on ‘symptoms constellation ’ exclusion of physical & psychiatric conditions

Depression within personality disorder

No manic or hypomanic feature
Differentiate treatment resistance from features of chronicity.
Towards a Comprehensive assessment of Depressive disorder.
What clinical conditions may present as treatment resistant depression?
WHAT CLINICAL CONDITIONS CAN PRESENT AS TREATMENT RESISTANT DEPRESSION?

Bipolar Disorder is a Multidimensional Illness

Lifelong management of this lifelong illness involves targeting all phases of the disorder – atypical antipsychotics can play a major role.

Bipolar II Depression

• Bipolar II disorder is a common disorder, prevalence of approximately 3-5%.
• Distinct clinical features
• The key to diagnosis - recognition of past hypomania,
• This is responsible for a significant rate of missed diagnosis,
• It is unclear if bipolar II disorder is over-represented in TRD

Bipolar diathesis for TRD

MISSED MANIA

BIPOLAR SPECTRUM DISORDER

Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD.

Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, Calabrese JR, Nierenberg AA, Sachs GS.

Am J Psychiatry. 2009 Feb;166(2):173-81
Impact of Bipolar Disorder on Patients’ Lives

Onset is usually during late adolescence and early adulthood, a time at which individuals are establishing their careers and building long-term relationships.

- Healthy life: Reduced by 12 years
- Working life: Reduced by 14 years
- Life expectancy: Reduced by 9 years
- Employment problems: Twice as common
- Divorce / separation: Twice as common

Results for patients developing bipolar disorder in their mid-20s

Coryell et al 1993; Scott 1995
Atypical depression

- 70% of depression with atypical features met with DSM IV criteria for bipolar II
- 60% had antecedents cyclothymic & hyperthymic temperament
- Interpersonal sensitivity & atypical features were found to be powerful prospective predictors of bipolar II

Anxious – bipolar co morbidity

The evolving bipolar spectrum

- Prototype I,II ,III & IV
- Bipolar I – full-blown mania
- Bipolar 1 & ½ : depression with protected hippomania
- Bipolar II : depression with hippomania
Outcome status: What happens when TRD is treated?

- Not very encouraging.
- Nine outcome studies, Total N = 1279; follow-up duration - 1 to 10 years.
- In the short term, TRD was highly recurrent as many as 80% of those requiring multiple treatments relapsing within a year of achieving remission.
- For those with a more protracted illness, the probability of recovery within 10 years was about 40%.
- TRD was also associated with poorer quality of life and increased mortality.

How do we treat the Treatment resistance?? & what is the outcome?
Current (or future) Treatment Options $^{2,3}$

Antidepressants: SSRI, TCA, MAOI, SNRI & others

(Star*D) $^1$ 50% of "real world" - MDD fail to achieve remission, even after four carefully monitored sequenced treatments.

Safety & efficacy of antidepressants
1. Optimization
   inadequate dose & inadequate duration

- Only 11 percent of patients receive adequate therapeutic therapy.
- Inadequate therapy - particularly prevalent in elderly patients.
- The clinician need to maximize the dosage or duration of therapy.
- Higher than recommended dosage: some patients benefit
- An adequate duration has been defined by some - four to six weeks. -- six weeks –10-12 weeks -- to elicit a full ADD response.

**Selecting right ADD**

*Have the cytochrome P450 (CYP450) genotyping test*

Figure 1. Schematic forms of the hormetic dose response. (A) The most common form of the hormetic dose–response curve showing low-dose stimulatory and high-dose inhibitory responses (J- or inverted U-shaped curve). (B) The hormetic dose–response curve depicting low-dose reduction and high-dose enhancement of adverse effects (J- or U-shaped curve).
Selectivity Ratios for Uptake Inhibitor Antidepressants (measured in vitro)

5 – HT selectivity

NA selectivity

Selectivity ratio

Understanding the Illness
Switch to another ADD? Which...??

- 1 in 4 patients on SSRI’s have a response on 2nd drug:
  - Bupropion-SR
  - Sertraline
  - Venlafaxine-XR
- Within class
- 1st SSRI may be ineffective/ intolerable
- 2nd SSRI may be effective/ tolerable
- Out-of-class
- SSRI ----> TCA = 30 to 50%

3. Combination Therapy

- Combination therapy involves the addition of a second antidepressant agent to the therapeutic regimen.
- Concurrent administration of two or more antidepressant agents (e.g., adding trazodone [Desyrel], desipramine [Norpramine] or bupropion [Wellbutrin] to fluoxetine) may result in a different therapeutic response than that produced by use of either drug alone.
- However, no double-blind, placebo-controlled studies recommend the usefulness of this practice.
- In addition, this approach does not allow for adequate evaluation of monotherapy and may lead to significant adverse effects or drug-drug interactions.

4. Augmentation Therapy

- Involves adding a second agent, but one that is not routinely regarded as an antidepressant.

  - Dopaminergic agents, atypical antipsychotics, Psychostimulants, benzodiazepines/hypnotics, hormones and Anticonvulsants.

  - Testosterone
  - Folate
  - Omega
  - Lamotregene
  - Olanzapine/fluoxetine

Shall I persist, increase or add?

Amitriptyline and clomipramine are more effective than SSRIs (but more side effects and more toxic in overdose).

The difference is that these drugs affect both serotonin (5HT) and noradrenaline.

Other drugs that have a similar effect are:
- Venlafaxine
- Mirtazepine
- Duloxetine

Licht & Qvitzau 2002

Are these also more effective?
Combining and Switching
4b. Thyroid hormone: Low dose, short-term

- The thyroid hormone triiodothyronine (T3) appears to be a more effective than tetraiodothyronine (T4).
- Effective in small dosages; for example, 25 to 50 µg per day.
- T3 may be used to augment response to TCA, MAOI, and SSRIs.
- Effective in 50 to 60% of patients.
- Monitoring thyroid function
- T3 potentiates noradrenergic activity.
- Its mechanism of action is not clearly understood.
- Relatively safe, few AE – allergic x 2-3 weeks
4d. Buspirone.

- Anxiolytic.
- No specific/intrinsic antidepressant effects.
- Dosages of 15 to 30 mg /D x 3 Months: improved response – 2/3rd of patients.
- Full agonist at the presynaptic autoreceptor and partial agonist at the postsynaptic autoreceptor.
- Decreases extracellular serotonin concentrations over the short term.
4e. Pramipexole

- Large effect size (0.6-1.1):
- With a low switching in bipolar patients (1% mania, 5% hypomania).
- The pooled discontinuation rate - 9%.
- Neuroprotective
- Effects on sleep architecture.
- SE in Parkinson’s disease
- Sleep attacks,
- Compulsive behaviors
- Pathologic gambling,
- Restless legs syndrome;
- Psychosis


4f. Anticonvulsants

- Lamotregene
- Carbamezapine

- Triple Reuptake Inhibitors (TRI)
- Target all three of brain’s monoamines (serotonin, norepinephrine, dopamine)
- Expected on the market by 2010
- Better efficacy and tolerability, faster acting, less side effects, treats broader range of symptoms
4g. Novel Antipsychotics

1- combination (OFC) 2- Switch to AATPD

- SDA, beneficial
- 50% Response
- 25% Remission
- Olanzapine
- According to results, Aripiprazole, Olanzapine, and Risperidone are reasonable choices as augmentation agents
- With only aripiprazole currently having an FDA (USA) indication for this use.

Clozapine in medication- and electroconvulsive therapy-resistant, depressed inpatients: a case series


# Summary of the Evidence Base for the Efficacy of Atypical Antipsychotics in Bipolar Disorder

## Acute Treatment

<table>
<thead>
<tr>
<th></th>
<th>Mania</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Asenapine</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td>?</td>
</tr>
</tbody>
</table>

## Maintenance / Continuation Treatment

<table>
<thead>
<tr>
<th></th>
<th>Mania</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+?</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Asenapine</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

++ = at least one good RCT showing clinically significant effects  
+ = at least one RCT showing some effect  
- = RCT evidence of a lack of clinically significant effects  
? = uncertain or no controlled data available
<table>
<thead>
<tr>
<th>Agents</th>
<th>Acute Bipolar Depression</th>
<th>Acute Mania</th>
<th>Maintenance Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATYPICALS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td>√</td>
<td>√*</td>
</tr>
<tr>
<td>Quetiapine (SEROQUEL XR)</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Paliperidone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
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<td>√+</td>
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<tr>
<td>Divalproex</td>
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<td>√</td>
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<tr>
<td>Lamotrigine</td>
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</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

+ for use after treatment failure on traditional mood stabilizer

*See PM. Evaluation from 2 “time to relapse” trials with manic or mixed index episode

This chart does not imply comparable efficacy or safety profiles.

All brand names and product names used in this slide are trade names, service marks, trademarks, or registered trademarks of their respective owners.
LSM change from baseline to Week 8

BOLDER & EMBOLDEN (acute phase):
Change in MADRS Total Score

Rapid cycling
(n=393)

Non-rapid cycling
(n=1,814)

*** p<0.001 vs placebo ITT, LOCF
Baseline values: Rapid cycling - quetiapine 300 mg, 29.4; 600 mg, 29.5; placebo, 29.9
Non-rapid-cycling - quetiapine 300 mg, 28.7; 600 mg, 28.3; placebo, 28.9
At Week 1, significant improvement was seen in 6 out of 10 items‡

* Montgomery-Asberg Depression Rating Scale.
† Data combined from two 8-week, multicenter, randomized, double-blind, placebo-controlled, monotherapy bipolar depression trials.

$ P < 0.05 \text{ vs placebo at Week 1}$

$ P < 0.001 \text{ vs placebo at Week 8}$

$ P < 0.05 \text{ vs placebo at Week 8}$

Data on File, DA-SER-45.
How do we explain?

Why do Atypical antipsychotics have Antidepressant action?

A: Regional distribution of 5-HT System in the Brain??

Depression in schizophrenia: perspective in era of ‘atypical antipsychotics’. Siris, S.G. AJP 2000;157
ECT

- ECT in TRD
- average 14.6 months in their current episodes
- 6.2 years of their lifetime in depression.
- Failed to respond to an average of 5.4 different ADD
- (65.8%) responded
- (53.3%) achieved remission.

  - [Khalid N The effectiveness of electroconvulsive therapy in treatment-resistant depression: a naturalistic study. J ECT. 2008 Jun;24(2):141-5.](#)

- The acute effect is well established
  - Continuation Tx is required
  - In 1 study, within 24 weeks of achieving remission, 64% relapsed.¹
  
  - TRD is predictive of post-ECT relapse
    - TRD patients at high risk for relapse: only 32% maintained response in next 12 months²

Deep Brain Stimulation (DBS): The Surgical option

- Five potential targets – identified:
  - Ventral striatum/nucleus accumbens,
  - Subgenual cingulate cortex (area 25),
  - Inferior thalamic peduncle,
  - Rostral cingulate cortex (area 24a), and
  - Lateral habenula.

Deep Brain stimulation

Efficacy: [Subcallosal cingulate gyrus] for treatment-resistant depression

- There were both early and progressive benefits to DBS. One month after surgery,
  - 35% - response
  - 10% - remission.
- Six months after surgery,
  - 60% - responders
  - 35% - remission,
- Benefits maintained at 12 months.

- Reduced activity in this region (shown in blue at bottom) is seen with six months of chronic deep brain stimulation.
- This reduction correlates with the antidepressant effect of the treatment.
- (Images courtesy of Helen Mayberg)
rTMS

• No general anesthesia
• Outpatient procedure
• Lower energy requirement.
• "the magnetic field can be highly focused,"
• No social stigma
• Specific targeted stimulation
• No convulsion requirement
• Minimal side effects such as mild headache and discomfort at the site of stimulation
• No known adverse effects on cognition
• Potential advantages - as an add-on

The long term effectiveness of rTMS for severe depression is unknown.
The use, if any, of continued maintenance therapy is unknown.
Long term pragmatic patient outcomes such as time to further treatment,
TMS add-on on escitalopram
TRD with 2 failed trial of ADD
GR II- 15 sessions
TMS+
20 mg ESCT
Gr !- Sham 15 sessions
TMS+
20 mg ESCT
Follow up of 3 weeks
Outcome assessment by HAM-D shows effects size of 0.7

Vagus Nerve stimulation (VNS)

- Well tolerated
- A safe and feasible procedure, despite its limitations
- Acts via innervation of the nucleus tractus solitarius, with secondary projections to limbic and cortical structures that are involved in mood regulation
- Efficacy data not randomized
- Surgical procedure
- Non-acute antidepressant effect
- MRI contraindication
- Battery

Preventing treatment resistance

Treating treatment resistance