Methodological issues in treating Treatment-Resistant Affective Disorders

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Epidemiology

- 6.7% of adults in the US experience a depressive episode every year.
- Only 30% of patients with a depressive episode reach full recovery or remission.
- More than 30% of patients with bipolar disorder in the depressed phase receiving treatment do not experience remission of depressive symptoms.
- Patients with treatment-resistant depression are twice as likely to be hospitalized.
### Epidemiological factors associated with treatment resistance

#### Factors associated with treatment resistance (N = 702)

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>p value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>&lt; 0.001</td>
<td>2.6</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>&lt; 0.001</td>
<td>3.2</td>
</tr>
<tr>
<td>Social phobia</td>
<td>0.008</td>
<td>2.1</td>
</tr>
<tr>
<td>Melancholia</td>
<td>0.018</td>
<td>1.5</td>
</tr>
<tr>
<td>Suicide risk</td>
<td>0.001</td>
<td>2.2</td>
</tr>
<tr>
<td>Severity</td>
<td>0.001</td>
<td>1.7</td>
</tr>
<tr>
<td>Failure of first AD</td>
<td>0.019</td>
<td>1.6</td>
</tr>
<tr>
<td>Early age of onset</td>
<td>0.009</td>
<td>2.0</td>
</tr>
</tbody>
</table>

#### Risk factors for treatment resistance (N = 230,801)

<table>
<thead>
<tr>
<th>General conditions</th>
<th>Specific condition</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age group: 18–15 years</td>
<td></td>
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<tr>
<td></td>
<td>Age group: 20–24 years</td>
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<td></td>
<td>Age group: 25–29 years</td>
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<td></td>
<td>Age group: 30–34 years</td>
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<tr>
<td></td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>Opioid dependence</td>
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<tr>
<td></td>
<td>Drug abuse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poisoning by CNS drug</td>
<td></td>
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<tr>
<td></td>
<td>Tobacco dependence syndrome</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>OCDs and symptoms</td>
<td></td>
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<tr>
<td></td>
<td>Social phobia</td>
<td></td>
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<tr>
<td></td>
<td>Posttraumatic stress disorder</td>
<td></td>
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<tr>
<td></td>
<td>Panic disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety disorders and symptoms</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Eating disorders</td>
<td></td>
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<tr>
<td></td>
<td>Insomnia</td>
<td></td>
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<tr>
<td></td>
<td>Attention-deficit disorder</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Pain of head and neck</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal pain</td>
<td></td>
</tr>
</tbody>
</table>

AD, antidepressant; CI, confidence interval; CNS, central nervous system; OCD, obsessive-compulsive disorder; OR, odds ratio.

Burden of TRD vs MDD

• Direct costs from TRD are 40% higher than from MDD
  • Likely due to increased risk of hospitalization, more outpatient visits, and greater use of psychotropic medication

• Patients with TRD are 1.7 times more likely to die following a MI than those with MDD

• TRD is associated with a greater suicide risk

• MI, myocardial infarction.

Slide Courtesy of Prof. Eduardo Vieta
Definitions

• TREATMENT RESISTANT DEPRESSION:
  • Defined most commonly by the number of prior antidepressant failures of treating depression.
  • Failures can range from a single treatment failure (relating to any drug) to three or more failures using three different classes of antidepressants.

• TREATMENT RESISTANT BIPOLAR DISORDER:
  • Specific number of failed medication trials, incomplete or unsatisfactory response to treatment, unsuccessful response for a specified duration of treatment, failure to respond to a phase of bipolar disorder.
### Definition of Treatment-Resistant Depression in the Medicare Population

#### Table 3. Four categories of definitions of treatment-resistant depression by number of treatment failures

<table>
<thead>
<tr>
<th>Number of Treatment on TRD Treatments, Failures</th>
<th>Type of Publication on TRD Treatments, Date</th>
<th>Ways to Define Failure</th>
<th>Specify Current Episode?</th>
<th>Define Adequate Dose?</th>
<th>Define Adequate Duration?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more</td>
<td>Seminal article on defining TRD, 2003b</td>
<td>Nonresponse (&lt;25%) partial response (≥25% to &lt;30%) responses without remission (30% or greater symptom reduction)</td>
<td>During current episode</td>
<td>Within therapeutic range but conflicting dosages recommended for same drug by different authors</td>
<td>25 weeks</td>
</tr>
<tr>
<td></td>
<td>International Workshop on &quot;Future and Future of TMS, Safety and Ethical Guidelines&quot;</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td></td>
<td>Gaynes et al., 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SR - smokable augmentation, 2015**

- Nonresponse (<50% decrease in HAM-D after 1 failed treatment or equivalent)
- Not described
- Not described
- 4 weeks

**SR - psychotherapy, 2011**

- Nonresponse, partial response, or no remission (not further defined)
- Not described
- Most studies in the review provided the accepted dose range
- 25 weeks

**Nonsyntomatic review defining TRD, 2015**

- Nonresponse, partial response, or no remission (not further defined)
- Majority of studies in the review referred to adequacy as therapeutic leverage
- 6 to 8 weeks

**SR - TMS, 2015**

- Nonresponse, inadequate response, insufficient response (not further defined)
- During current episode
- Not described
- 4 to 6 weeks

**SR - predictors of nonresponse, 2016**

- Nonresponse, no remission (not further defined)
- Not described
- Not described
- Not described

**SR and MA of clonazapine/fluoxetine combination, Luan et al., 2017**

- Nonresponse, no remission (not further defined)
- Not described
- Not described
- Not described

**SR - pharmacologic treatments, 2007**

- Majority of studies in the review using 2 or more failures incorporated nonresponse or remission in the definition
- During current episode
- At least two thirds of the maximal PDR dose
- 24 weeks

**SR - antidepressant treatments, 2007**

- Lack of clinically meaningful response or remission or lack of decrease in symptom severity
- In HAM-D of less than 5 points (a 3-point difference is considered clinically meaningful)
- In the current episode
- At least one of the treatment trials must have been administered at an adequate course of mono- or poly-drug therapy
- Not described

**SR - augmenting treatment, 2015**

- Failure to respond (not further defined)
- Minimum dosage that will produce the expected effect or the maximum dosage within the therapeutic range that the patient can tolerate until the expected effect is achieved
- 4-6 weeks is considered an adequate period to see clinical response, although recent research suggests that longer periods (up to 8 or 12 weeks) may be needed to achieve remission
- Not described

**SR - lithium or atypical antipsychotics, 2015**

- Failure to respond (not further defined)
- Few studies in the review specified in the current episode of depression
- Not described
- 34 weeks for augmentation
### Table 3. Four categories of definitions of treatment-resistant depression by number of treatment failures (continued)

<table>
<thead>
<tr>
<th>Number of Treatment Failures</th>
<th>Type of Publication on TRD Treatments</th>
<th>Ways to Define Failure</th>
<th>Specify Current Episode?</th>
<th>Define Adequate Dose?</th>
<th>Define Adequate Duration?</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>Small randomized trials</td>
<td>Failure to respond (not further defined)</td>
<td>Not described</td>
<td>Maximal dosage (or blood level achieved)</td>
<td>44 weeks</td>
</tr>
</tbody>
</table>

**BIDH**

- **Nonpharmacological, 2014**
  - No standard definition of AD failure, but a variety of TRD staging tools provide different ways of assessing the adequacy of prior treatment so that the clinician can determine treatment failure.

- **Australian/New Zealand Clinical Practice Guideline, 2015**
  - Failure to respond (not further defined)
  - Not described
  - Maximal dosage (or blood level achieved)
  - 44 weeks

- **BIDH**
  - Lack of improvement defined as a reduction of 10% from baseline in HAM-D (in different studies) at 4 and 6 weeks, only 20% and 10%, respectively, go on to eventual response (50% improvement) at 8 weeks.

- **BIDH**
  - Partial response defined as a reduction of 10% in symptom scores or no response (<25% reduction).

- **BIDH**
  - Nonresponse defined as at least one failure in the current episode of depression.

- **BIDH**
  - Nonresponse defined from baseline less than 50% at study endpoint.

- **BIDH**
  - Nonresponse mostly defined as MADRS score greater than 7 at study endpoint.

### Table 4. Four categories of definitions of treatment-resistant depression by number of treatment failures (continued)

<table>
<thead>
<tr>
<th>Number of Treatment Failures</th>
<th>Type of Publication on TRD Treatments</th>
<th>Ways to Define Failure</th>
<th>Specify Current Episode?</th>
<th>Define Adequate Dose?</th>
<th>Define Adequate Duration?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more</td>
<td>ISCTM Adult Depression in Primary Care Guidelines, 2018b</td>
<td>Failure to achieve remission with an adequate trial of at least three different classes of ADs at adequate duration and dosage</td>
<td>Not described for TRD</td>
<td>Not described for TRD</td>
<td>Not described for TRD</td>
</tr>
</tbody>
</table>

**BIPOLAR TRD:**

- **Washington State Health Care Authority, 2014**
  - Defined as a significant reduction in score on a depression symptom scale rather than in terms of the number of treatment failures.

- **International Society for Bipolar Disorders, 2018**
  - Recommends using no significant reduction in Montgomery-Asberg Depression Rating Scale (MADS) or Hamilton Rating Scale for Depression (HAM-D) score.

- **International Society for Bipolar Disorders, 2018**
  - Time frame required for an adequate trial of AD may need to be longer than with unipolar depression because of the greater natural fluctuation of the disease, which suggests that clinicians may need to observe a patient 2 to 4 weeks beyond the time frame usually considered adequate for an AD trial.
C. European Staging Model (ESM)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Duration of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Non-responder</td>
<td>Non-response to one adequate trial of TCA, SSRI, MAOI, SNRI, ECT or other antidepressants</td>
<td>6-8 weeks</td>
</tr>
</tbody>
</table>
| b. TRD | Resistance to two or more adequate antidepressant trials of different classes | TRD1: 12-16 weeks  
TRD2: 18-24 weeks  
TRD3: 24-32 weeks  
TRD4: 30-40 weeks  
TRD5: 36 weeks to 1 year | |
| c. CRD | Resistant to several antidepressant trials, including augmentation strategy | At least 12 months |

Table 1 Thase and Rush Staging Method

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Any medication trials, to date, judged to be inadequate</td>
</tr>
<tr>
<td>Stage I</td>
<td>Failure of at least 1 adequate trial of 1 major class of antidepressants</td>
</tr>
<tr>
<td>Stage II</td>
<td>Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants</td>
</tr>
<tr>
<td>Stage III</td>
<td>Stage II resistance plus failure of an adequate trial of a TCA</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Stage III resistance plus failure of an adequate trial of an MAOI</td>
</tr>
<tr>
<td>Stage V</td>
<td>Stage IV resistance plus a course of bilateral electroconvulsive therapy</td>
</tr>
</tbody>
</table>

*Adapted from Thase and Rush 32

McIntyre et al., J. Affective Disorders, 2013

Berlim & Turecki, Canadian Review of Psychiatry, 2007
Regulatory definition of the EMA

• European Union’s CPMP guidelines (currently under revision)
  • “A patient is considered therapy-resistant when consecutive treatment with 2 products of different classes, used for a sufficient length of time at an adequate dose, fails to induce an acceptable effect”
  • Key guideline for the approval of new therapies

• Design of monotherapy trials in treatment-resistant patients
  • Perform a separate TRD-specific trial rather than a subgroup analysis of the MDD population
  • Use an active comparator and power for superiority (more on this later)
  • TRD is defined as
    • 2 failures (lack of clinically meaningful improvement, inadequate response), regardless of class and mechanism of action


Slide courtesy of: Prof. Eduardo Vieta
CPMP, Committee for Proprietary Medicinal Products; MDD, major depressive disorder.
A substantial number of patients with MDD are resistant to treatment

STAR*D study: lower acute remission rates when more treatment steps are required

CT, cognitive therapy; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self-Report; T3, triiodothyronine/liothyronine.

Slide courtesy of Prof. Eduardo Vieta
SMRI

- The Stanley Medical Research Institute (www.stanleyresearch.org) is a non-profit, charitable organization focused on developing novel treatments for severe mental diseases. Since 1995, SMRI has funded 410 treatment trials, of which 175 were focused on affective disorders.

- By definition, almost all of these trials were on treatment resistant patients.

- Will present methods of pre-screening, treatment strategies used,

- Placebo vs active comparators, add-on vs monotherapy, creative research designs.
Pre-screening

- Hormonal Levels: FSH >20 → for raloxifene
- Smoking status: CO of 8 ppm or more → for varenicline
- Glucose Levels: fasting glucose >100 or treatment for hyperglycemia → for pioglitazone
- Immune response: Lipopolysaccharide Binding Protein to test for Integrity of the intestinal epithelial barrier → for a study on probiotics
- Inflammation: CRP > 0.5 mg/dL → for Withania somnifera (WSE), or aspirin
Pre-screening: is it practical?

Study funded by SMRI for mesenchymal stem cells for the treatment of bipolar depression

- Justification: mesenchymal stem cells secrete compounds which decrease immune activity
- Inclusion criteria:
  - TRD
  - Willingness to stop medication
  - CRP >3.0
- 21 patients with TRD were approached, 8 refused to stop their medication, 13 were screened, 12 had low CRP, only 1 patient was recruited → the study was discontinued.
- Other studies have used prescreening of immunological measures and also had such difficulties → often decreased the threshold level of prescreened compound in order to include patients.
- What is the appropriate marker of inflammation? CRP? Cytokines? NIMH mandates a single marker (imaging) for funding
PLACEBO-CONTROLLED OR ACTIVE COMPARATOR?

Are Placebo-Controlled, Relapse Prevention Trials in Schizophrenia Research Still Necessary or Ethical?

increased. Consequently, we believe the time has come to cease the use of placebo in relapse prevention studies and encourage the use of active comparators that would protect patients from relapse and provide information on the comparative effectiveness of the drugs studied. We recommend that pharmaceutical companies not seek maintenance labeling if it would require placebo-controlled, relapse prevention trials. However, for putative antipsychotics with a novel mechanism of action, placebo-controlled, relapse prevention trials may still be justifiable.

Lawrence et al., JAMA Psych, 2019
ARE PLACEBO-CONTROLLED TRIALS IN TRD NECESSARY?

**Efficacy:** no antidepressant has been shown to be more effective than others in improving depressive symptoms in TRD,

In the absence of a gold standard, mono-therapy, placebo-controlled studies are justified
What is the appropriate comparator for IV Ketamine trials?
The issue of functional un-blinding

Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial

A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression

Murrough et al., 2013

Singh et al., 2016
**MONOTHERAPY OR ADD-ON?**

- For novel anti-depressants/novel mechanisms, always preferable to test with mono-therapy design vs placebo

- Non-antidepressants: anti-psychotics, mood stabilizers, hormones, if proven efficacious, will probably be administered together with anti-depressants, justifying add-on designs

- Problem with add-on: hard to differentiate effect of added on drug from effect of baseline drug, and drug-drug interactions
**ADD-ON STUDIES**

**Combined Treatment With Sertraline and Liothyronine in Major Depression**

*A Randomized, Double-blind, Placebo-Controlled Trial*

Cooper-Kazaz et al., Arch Gen. Psychiatry, 2007

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**Rapid and Sustained Antidepressant Response with Sleep Deprivation and Chronotherapy in Bipolar Disorder**

Wu et al., Biol Psychiatry, 2009

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**Figure 1.** Significant reduction in mean depression (19-item Hamilton Rating Scale for Depression [HRSD]) ratings over baseline in subjects treated with chronotherapeutic augmentation treatment (CAT) within 48 hours of sleep deprivation (SD) compared with medication-only (MED) subjects. Significant improvement was maintained for Weeks 1–7 (with the exception of Day 6). *p < .05; **p < .01; ***p < .001.

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ISCTM-ECNP Joint Autumn Conference  ▪  6 September 2019  ▪  Copenhagen, Denmark
ADD-ON STUDIES

A Placebo-Controlled Evaluation of Adjunctive Modafinil in the Treatment of Bipolar Depression

Frye et al., Am. J. Psychiatry, 2007

Ropinirole Augmentation for Depression

A Randomized Controlled Trial Pilot Study

Abstract:

Objective: Evidence both from animal and human studies suggests a role for dopaminergic pathways in the treatment of depression. Ropinirole, a selective agonist of dopamine D2/D3, is in use for the treatment of parkinsonism. Preliminary evidence suggests that such agonists might be useful as antidepressants. We tested whether an add-on ropinirole is effective in depressed patients.

Methods: We conducted a double-blind, randomized, placebo-controlled trial of add-on ropinirole in depressed patients unresponsive to at least one antidepressant. We recruited 32 unipolar and bipolar patients who remained depressed (modified 21-item Hamilton Depression Rating Scale) despite at least 4 weeks of treatment with an adequate dose of antidepressant medication. Patients received either 2 mg of oral ropinirole or placebo twice daily added on to their current medication and were evaluated weekly for 7 weeks using the Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale.

Results: No difference in primary or secondary outcome measures was detected between the treatment and control groups.

Discussion: These results differ from previous studies and are unexpected in light of theoretical considerations. This may indicate that there are differences in pharmacological activity between ropinirole and other dopaminergic agents such as pramipexole.

Gershon et al., J Clin Psychopharmacol, 2019
MONOTHERAPY

Efficacy of Adjunctive Infliximab vs Placebo in the Treatment of Adults With Bipolar I/II Depression
A Randomized Clinical Trial

McIntyre et al., JAMA Psychiatry, 2019
MONOTHERAPY: NEUROSTIMULATION

Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy

International randomized-controlled trial of transcranial Direct Current Stimulation in depression

Fig. 1. The immediate mean change in subjective mood ratings (post- minus pre-TMS treatment) for subjects receiving active and sham is graphed by treatment day. There does not appear to be a trend for change in immediate mood differences across the treatment days.

Nahas et al., Bipolar Disorders, 2003
Loo et al., Brain Stimul., 2018
Valnoctamide as a valproate substitute with low teratogenic potential in mania: a double-blind, controlled, add-on clinical trial


ACTIVE CONTROL OR PLACEBO? ADD-ON OR MONOTHERAPY?

Table 2: Efficacy of valnoctamide (n = 15) versus placebo (n = 17) as add-on to risperidone in acute mania

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment effect</th>
<th>Time effect</th>
<th>Time x treatment interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
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<td>Week 2</td>
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<tr>
<td>Week 3*</td>
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<td></td>
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<tr>
<td>Week 4*</td>
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<td></td>
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<tr>
<td>Week 5*</td>
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<tr>
<td>YMRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valnoctamide</td>
<td>35.1 ± 6.5</td>
<td>26.4 ± 6.0</td>
<td>20.0 ± 7.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>33.7 ± 5.9</td>
<td>30.1 ± 7.4</td>
<td>25.9 ± 10.0</td>
</tr>
<tr>
<td>BPRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valnoctamide</td>
<td>49.4 ± 6.9</td>
<td>44.3 ± 7.2</td>
<td>37.0 ± 6.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>49.3 ± 8.1</td>
<td>44.4 ± 8.7</td>
<td>41.2 ± 9.5</td>
</tr>
<tr>
<td>CGI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valnoctamide</td>
<td>5.0 ± 0.5</td>
<td>4.3 ± 0.6</td>
<td>3.5 ± 0.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.1 ± 0.7</td>
<td>4.6 ± 0.9</td>
<td>4.3 ± 1.2</td>
</tr>
</tbody>
</table>

Values indicated as mean ± SD. YMRS = Young Mania Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression.

* Differences between valnoctamide and placebo groups were significant from week 3 to week 5 (least significant difference (LSD) post-hoc, p < 0.05).
Active control or placebo? Add-on or monotherapy?

Use of both placebo and active control allows examination of assay sensitivity. Design allows ruling-out issues of drug-drug interactions.

Bipolar Disorders 2017
Tried to encourage the use of sequential parallel comparison design (SPCD)