Clinical Perspective on Conducting Trials in Major Depressive Disorder

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Utility of the “partial” response construct

- In general, published clinical guidelines do not differentiate between partial and minimal responders when deciding upon augmentation therapy, deferring to clinical judgment (APA 2010, Anderson 2008, CANMAT 2009, NICE 2009)

- Distinguishing between “partial” and “minimal” responders is done through an arbitrary cut-off on a prospectively administered rating scale during an observation (run-in) period,
  - “partial” response: 25-49% response on primary outcome measure
  - “minimal” response: <25% response on primary outcome measure

- Two concepts are important when evaluating this construct:
  - How is “partial” response defined in clinical practice? (i.e., how does it translate into real world practice?)
  - What is the clinical relevance of “partial” response?
Clinicians use clinical judgment/medication history to determine partial response, not rating scales.

<12% of UK and <20% of US psychiatrists routinely use rating scales:
- Not clinically useful
- Overly simplistic
- Burdensome
- Not trained to use

Psychiatrists in the UK do not use outcomes measures: National survey
### Efficacy of Adjunctive Aripiprazole in Patients with MDD with an Inadequate Response to Antidepressant Monotherapy: Data from 3 Pooled 6-Week Double-blind, Placebo-controlled Trials

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline MADRS Total Score</th>
<th>Change from Baseline to Week 6 Endpoint in MADRS Total Score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjunctive aripiprazole</td>
<td>Adjunctive placebo</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>292</td>
<td>21.1</td>
<td>21.1</td>
<td>-7.9</td>
</tr>
<tr>
<td>Responders*</td>
<td></td>
<td></td>
<td></td>
<td>-6.1</td>
</tr>
<tr>
<td>Minimal</td>
<td>746</td>
<td>28.6</td>
<td>28.8</td>
<td>-10.3</td>
</tr>
<tr>
<td>Responders**</td>
<td></td>
<td></td>
<td></td>
<td>-6.5</td>
</tr>
<tr>
<td>Nonresponders***</td>
<td>160</td>
<td>32.1</td>
<td>31.5</td>
<td>-12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-8.7</td>
</tr>
</tbody>
</table>

**NOTE:** data reflects pooling of 3 similarly designed, randomized, double-blind, placebo controlled trials examining the efficacy of adjunctive aripiprazole in patients with MDD with an inadequate response to antidepressant monotherapy.

From Nelson 2012 and 2014
Conclusions regarding the “partial” response construct

- Regulatory Guidance definition of “partial” response is not shared by practitioners, who rarely use formal rating scales
- Risk ratio of responding to an adjunctive drug versus placebo is not substantially influenced by whether a subject is categorized as a "partial responder" or "minimal responder"
- Excluding “minimal” responders from clinical trials excludes subjects who may benefit from treatment, and are representative of those seen and treated with augmentation strategies in clinical practice
“Suboptimal” response as an alternative construct

- A more comprehensive term, "suboptimal" responder, indicates a patient who has not achieved significant clinical improvement with monotherapy treatment, necessitating an augmentation treatment..
  - “Suboptimal” includes those patients defined in clinical trials through use of a prospective lead-in period as “partial” and “minimal” responders
  - Might also include those patients who have responded but not remitted

- Once defined, “suboptimal” response may be determined through clinical assessment, self-report, medical records, and a validated measure (*Antidepressant Treatment History Form (ATHF)*\(^1\), *Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ)*\(^2\)) to determine:
  - dosage,
  - duration of treatment, and
  - treatment response

- An alternative approach is to focus an adjunctive treatment trial on specific residual symptoms or on remission as the primary endpoint

\(^1\) Oquendo et al., 2003
\(^2\) Desseilles et al., 2011
Use of a Prospective Run-in Period

• Guidance concerning clinical trial design should allow the necessary flexibility to address the specific research questions at hand

• Use of prospective lead-in has not shown predictive value in determining efficacy

• Possibly more productive and efficient means of establishing suboptimal response:
  – Historical determination
  – current and emerging technologies that confirm adequacy of compliance/dose, blood sampling, etc
### Prospective Antidepressant Lead-in: Effect on outcomes in augmentation/combination trials in MDD

<table>
<thead>
<tr>
<th></th>
<th>With Prospective Lead-in</th>
<th>Without Prospective Lead-in</th>
<th>Mean Active-PBO difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>42.6%</td>
<td>47.4%</td>
<td>11.2%</td>
</tr>
<tr>
<td>PBO</td>
<td>29.7%</td>
<td>36.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Remitters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>31.0%</td>
<td>37.3%</td>
<td>12.6%</td>
</tr>
<tr>
<td>PBO</td>
<td>18.1%</td>
<td>24.7%</td>
<td></td>
</tr>
</tbody>
</table>

Data pooled from 40 adjunctive treatment trials in MDD; N = 4676
Example: Sample size estimates for a Phase 3 adjunctive treatment trial with and without lead-in

General Assumptions:
- Parallel group design
- Primary Outcome Measure, HDRS_{17} (Delta=3, S.D. = 8)
- Placebo v. 2 Doses
- Power=90%, 2-sided alpha=0.025, for comparison of each dose with placebo

<table>
<thead>
<tr>
<th></th>
<th>NO LEAD-IN</th>
<th>LEAD-IN Randomize “Suboptimal” responders (Partial + Minimal-Responders)</th>
<th>LEAD-IN Randomize only Partial-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>669</td>
<td>1,488</td>
<td>2,232</td>
</tr>
<tr>
<td>Specific Assumptions</td>
<td>20% attrition rate</td>
<td>45% partial +minimal responders to SSRI lead-in</td>
<td>30% partial responders to SSRI lead-in</td>
</tr>
</tbody>
</table>
Prospective lead-in and enrollment of “partial” responders only results in 334% increase in sample size

Ethical concerns:
• Results in exposing many more patients to experimental medicinal products or placebo which they may not benefit from or may experience harm from
• Increases the timelines for development, potentially delaying an effective treatment from coming to market

Feasibility concerns:
• Subject numbers required will result in intense competition for subjects within one program and across programs, delaying development timelines and potentially resulting in programs closing due to incomplete enrollment

Potential to create a great discrepancy between the number of subjects required to develop a monotherapy versus an adjunctive treatment in MDD, potentially deterring sponsors from pursuing needed adjunctive therapies or resulting in compounds being developed for a treatment paradigm (i.e. monotherapy) that may not afford the best benefit:risk for the population concerned.
Monotherapy investigation – should this be required for adjunctive treatment trials?

- For new MOAs, current understanding of the neurobiology may indicate that a specific drug is likely to be most effective as an adjunctive treatment.
- Requirement for a monotherapy study (in cases where the sponsor cites valid scientific rationale for expected efficacy as an adjunctive treatment) raises ethical issues: washout from current treatment, reinstatement of treatment.
- MDD is a serious and potentially fatal disorder, making it difficult to justify exposure for the sole purpose of obtaining information on the activity of the drug as monotherapy – information that is non-essential in a trial designed to demonstrate efficacy in the adjunctive setting.
- Individual sponsors, with extensive knowledge of the compound’s potential, should be allowed to decide on the utility of including a monotherapy study.
Summary

• Academia, Industry and Regulators would benefit from consensus surrounding how to define patients to be enrolled in adjunctive treatment trials in depression.
  – Risk ratio of responding to an adjunctive drug versus placebo is not substantially influenced by whether a subject is categorized as a "partial responder" or "minimal responder”
  – “Suboptimal” responder may be a construct with greater clinical meaning and utility
• Use of a prospective lead-in period is not supported by current data and adds unnecessary burden to conducting clinical trials for adjunctive treatments.
• The utility of a monotherapy study (in cases where the sponsor cites valid scientific rationale for expected efficacy as an adjunctive treatment) should be at the discretion of the Sponsor.
BACK UP SLIDES
Switching doesn’t offer benefits over continuation

- Meta-analysis suggests no benefit in response rates and marginal benefit in remission rates of switching from one class of AD to another \(^1\)
- Several studies report no advantage to switching to another antidepressant class \(^2\)\(^-\)\(^4\)
- Response rates following *within class* switches are low, although variable: TCAs 9-30%, SSRIs 27-72% \(^1\)
- No advantage was seen for switching versus continuing in a systematic meta-analysis. \(^3\) A recent, carefully designed study confirmed these findings, with continuation with the same treatment associated with a higher remission rate than switching to another class \(^5\)

\(^1\) Ruhe et al., 2006; \(^2\) Rush et al., 2006; \(^3\) Bschor and Baethge 2010, \(^4\) Souery et al., 2011a; \(^5\) Souery et al., 2011b
Treatment continuation versus switch: response and remission rates

Example: Sample size estimates for a Phase 2b adjunctive treatment trial

General Assumptions:
- Design includes a randomization at start of Lead-in (Placebo:SSRI, 1:5), as per the CHMP Guideline
- Primary Outcome Measure, HDRS sub
  - Delta=3, S.D. = 8
  - Power=90%, 1-sided alpha=0.05
- PBO v. 3 Doses

<table>
<thead>
<tr>
<th></th>
<th>No Lead in Parallel Group</th>
<th>Lead-in Randomize Suboptimal Responders (Partial + Non-Responders)</th>
<th>Lead-in Randomize only Partial-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>480</td>
<td>1,236</td>
<td>1,848</td>
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Final CHMP Guidance Differed Substantially from Draft Guidance Subject to Public Consultation for Design of Adjunctive Studies

Additions to the section on **adjunctive therapy studies** include:

- **As there is no established consensus on the definition and thresholds of partial responders.** Applicants are encouraged to adjust these criteria via scientific advice before starting a program.

- **It is of critical importance that the applicant can establish that the population recruited to the trial are true partial responders.** A run-in period alone with assessment of response to standard intervention may not be sufficient since partial response may be driven by other factors than the actual pharmacological treatment in this population. Instead, an **initial randomisation to standard medication or placebo** would be the best way to characterise the proportion of the population that were partial responders for reasons other than the actual pharmacological treatment.

  *In any case criteria for inclusion should be carefully defined to best identify “true” partial responders, and relevant data properly documented and critically appraised. Medical history and use of and response to non-pharmacological interventions may help identify the appropriate patient population.*