Clinical Trials For Treatment Resistant Neuropsychiatric Conditions: lessons from treatment resistant schizophrenia

Prof Oliver Howes

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Disclosures

• Oliver Howes is a psychiatrist and clinical academic at the Maudsley Hospital NHS Trust & KCL and ICL, UK

• He has received investigator-initiated research grants, and/or spoken at events for:
  • Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen/J&J, Leyden-Delta, Lundbeck, Otsuka, Servier, Sunovion, Roche

• Neither Dr Howes nor his family have shares/other investments in or are employed by biopharmaceutical companies
Acknowledgements


The patients and volunteers
Outline

• Concept of treatment resistance
• Problems with current approach: example of schizophrenia
• TRRIP consensus
• Other issues and recommendations
Concept

Treatment resistance

Correct Diagnosis

Adequate treatment

Non-response

Pillinger & Howes In Sub
Problem 1: clinical guidelines

TABLE 1. Recommendations in International Guidelines for When to Consider a Patient’s Schizophrenia Treatment Resistant

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Minimum Number of Failed Antipsychotic Trials</th>
<th>Specified Antipsychotic</th>
<th>Adequate Treatment Episode Duration</th>
<th>Dosage</th>
<th>Severity of Illness</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA (6)</td>
<td>2</td>
<td>At least one of which is a second-generation antipsychotic*</td>
<td>≥6 weeks</td>
<td>Therapeutic range</td>
<td>A clinically inadequate response* and for patients with persistent suicidal ideation or behavior that has not responded to other treatments</td>
<td></td>
</tr>
<tr>
<td>RANZCP (23)</td>
<td>2</td>
<td>Recommends both first and second trial to be of an atypical antipsychotic</td>
<td>6–8 weeks</td>
<td>Specific dosages specified</td>
<td>Poor response*</td>
<td></td>
</tr>
<tr>
<td>BAP (24)</td>
<td>2</td>
<td>One of the trials should be of an antipsychotic with an established, favourable efficacy profile in comparison with other</td>
<td>Adequate*</td>
<td>Adequate*</td>
<td>Schizophrenic illness has shown a poor response to, or intolerance of the neurological side effects of previous Poor ... adherence, or persistent suicide risk, positively offer trial of clozapine* Poor ... adherence and ... substance use should be excluded as causes of the ... poor response to</td>
<td></td>
</tr>
</tbody>
</table>

Howes et al AJPsych 2017
Problem 2: clinical trial definitions
Lessons from clozapine network meta-analyses
How many defined treatment resistance?

- 50%: no clear definition
- 95%: used different or no clear definition

Howes et al AJPsych 2017
Methods for Defining TRS

Summary of criteria used across 42 clinical trials of treatment resistant schizophrenia

NS – Not specified. CPZ – Chlorpromazine equivalents. Only two studies (5%) utilized the same criteria. Howes et al. Am J Psychiatry. 2017
Patients thought to be treatment resistance....

- 35-44% of patients had sub-therapeutic antipsychotic levels

McCutcheon et al 2015
McCutcheon et al 2017
Can you bring in your medication?
Are they comparing like with like?
In most trials

Treatment resistance

Correct Diagnosis

Adequate treatment

Non-response

Not operationalised

Howes et al 2017
## Similar problems in other disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>GSRD&lt;sup&gt;99&lt;/sup&gt;</th>
<th>APA&lt;sup&gt;91,92&lt;/sup&gt;</th>
<th>Bipolar Affective Disorder</th>
<th>Obsessive Compulsive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td>2</td>
<td>Not defined</td>
<td>Depression: Hidalgo-Mazzei et al., 2019&lt;sup&gt;98&lt;/sup&gt; (consensus definition)</td>
<td>AACAP&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSRD</td>
<td>≥4 weeks</td>
<td>≥8 weeks</td>
<td>2 (antipsychotic/mood-stabiliser)</td>
<td>2 drug trials: either 2 trials of SSRI, or 1 trial of clomipramine 1 trial of CBT</td>
</tr>
<tr>
<td>Optimal dose of the prescribed antidepressant (at least as high as the lowest dose defined as effective in the product data sheet)</td>
<td>'upper limit of a medication dose'</td>
<td>'at the recommended therapeutic dose'</td>
<td>Adequate therapeutic doses</td>
<td>Drug: 10 weeks CBT: 8-10 total sessions, or 6-8 sessions of exposure and response prevention</td>
</tr>
<tr>
<td>Not defined</td>
<td>'assess...treatment adherence'</td>
<td>'ensure that the patient has been taking their medication as prescribed'</td>
<td>'include continuous and rigorous medication adherence'</td>
<td>Maximum recommended or maximum tolerated doses</td>
</tr>
<tr>
<td>Persistent HAM-D-17 score ≥ 17</td>
<td>'minimal or no improvement in symptoms'</td>
<td>'lack of improvement'</td>
<td>'failure to reach sustained remission'</td>
<td>'persistent and substantial OCD symptomatology'</td>
</tr>
</tbody>
</table>

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Review in Pillinger & Howes In Sub
Outline

• Concept of treatment resistance
• Problems with current approach: example of schizophrenia
• TRRIP consensus
• Other issues and recommendations
AIMS

- Operationalise criteria
- Provide reporting benchmarks
- Operationalise reporting criteria

Howes et al AJPsych 2017
TRRIP approach:

Minimum and optimum criteria
Sub-typing by symptom and time course:
positive, negative, cognitive
Early vs late

Correct Diagnosis  Treatment resistance  Adequate treatment

Non-response

Operationalise
• Duration
• Type
• Number
• Dose
• Adherence (PK/PD)

Operationalise
• Duration
• Severity
• Function/impact
Outline

• Concept of treatment resistance
• Problems with current approach: example of schizophrenia
• TRRIP consensus
• Other issues and recommendations
Placebo or active comparator?

Favours active comparator
- Some benefit from treatment
- More representative of practice
- Easier to recruit
- Less risk of unblinding

Favours placebo
- Signal detection may be easier
- Differences in side-effect profile may favour comparator

<table>
<thead>
<tr>
<th>BPRS Score</th>
<th>Baseline Treatment With Typical Antipsychotic</th>
<th>Placebo Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Total</td>
<td>54.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Positive</td>
<td>10.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Negative</td>
<td>11.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Recommendations for future trials

• Operationalise inclusion criteria: non-response and treatment
• Careful attention to prior treatment: prospective run-in
• Active comparator
• Length will probably need to be longer
Example: DAYBREAK LU AF3700 study

Prospective antipsychotic treatment

Randomisation

LU AF3700

Olanzapine/risperidone

single-blind, 6 weeks

double-blind, 10 weeks

ClinicalTrials.gov Identifier: NCT02717195
DAYBREAK study

Correct Diagnosis

Adequate treatment

Treatment resistance

PANSS total > 79
CGI > 3

1 retrospective Rx: over 6 weeks
1 prospective Rx

?adherence

DSM-5: SZ
DAYBREAK study

- Lu AF35700 did not show statistical superiority versus conventional therapy on the primary endpoint (change in Total PANSS) in patients with treatment-resistant schizophrenia (TRS)

Vantage October 26, 2018

Daybreak clouds over for Lundbeck

Elizabeth Cairns

A treatment-resistant schizophrenia drug would have been a blockbuster – but Lundbeck’s high risk, high-reward strategy has not paid off.
LU AF3700 pharmacology and the pathophysiology of TRS

D1 and D2 antagonist

Lu AF35700 is an antagonist at dopaminergic, serotonergic, and α adrenergic receptors. Unlike all currently available antipsychotics, Lu AF35700 has higher affinity for the human dopamine D₁ receptor than it has for the human dopamine D₂ receptor. In TRS, the higher ratio of dopamine D₁ vs. D₂ receptor activity is hypothesized to result in a beneficial efficacy profile and a tolerability profile without the troublesome side effects associated with extensive dopamine D₂ receptor blockade, such as extrapyramidal symptoms.

- No in vivo evidence that D1 signaling is altered in TRS
- Limited in vivo evidence D1 antagonism is involved in therapeutic action of clozapine

DA & treatment resistance

Demjaha et al, AJPsych 2012; Jauhar et al Mol Psych 2018
Recommendations for future trials

• Operationalise inclusion criteria: non-response and treatment
• Careful attention to prior treatment: prospective run-in and adherence monitoring
• Active comparator
• Length of trial likely will need to be longer
  • Understand pathophysiology of treatment resistance
  • Phase Ib trials of target engagement
Summary

Treatment resistance:
• Poorly defined in clinical criteria
• Variably defined in RCTs
• Some RCTs conflate resistance with intolerability
• Inadequate treatment a major issue: definition and choice in some disorders

Potential solutions:
TRRIP approach: operationalize criteria, prospective run-in
Better pharmacodynamic understanding of resistance
Academic and pre-competitive consortia
Consensus approach to definitions and reporting for other disorders
Extra slides
Variation in criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Minimum number of failed APs</th>
<th>Adequate treatment duration</th>
<th>Dose</th>
<th>Current symptoms</th>
<th>Other criteria</th>
<th>Prospective assessment of treatment resistance?</th>
<th>Assessment of post-adherence</th>
<th>Operationalized Criteria used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clayhorn et al., 1987 (3)</td>
<td>2</td>
<td>Yes</td>
<td>≤1000 mg CPZ</td>
<td>Score ≥4 in ≥3 of BPRS items: 3, 4, 10, 12 &amp; 15. DSM-III schizophrenia. Must have had neurological reaction to treatment. Current hospitalization ≥6 months.</td>
<td>“Malignant Illness” for ≥2 years</td>
<td>No</td>
<td>NS</td>
<td>No</td>
</tr>
<tr>
<td>Huang et al., 1997 (89)</td>
<td>2</td>
<td>No</td>
<td>≥66 mg total</td>
<td>Psychotic condition sufficient to require hospitalization</td>
<td>“Malignant Illness” for ≥2 years</td>
<td>Yes</td>
<td>2 weeks haloperidol 60 mg/day</td>
<td>NS</td>
</tr>
<tr>
<td>Kane et al., 1984 (44)</td>
<td>3 within 5 years</td>
<td>Yes</td>
<td>≤1000 mg CPZ</td>
<td>10 item BPRS ≥45 with ≥4 in ≥2 psychotic items. CGI-S≥4</td>
<td>No relief or period of good functioning in previous 5 years</td>
<td>Yes</td>
<td>6 weeks haloperidol treatment up to 60 mg/day</td>
<td>NS</td>
</tr>
<tr>
<td>Breier et al., 1994 (90)</td>
<td>2</td>
<td>No</td>
<td>6 weeks</td>
<td>Score of ≥4 on BPRS positive items or ≥4 on a single item OR score ≥20 on SANS or ≥2 on a global item</td>
<td></td>
<td>Yes</td>
<td>6 weeks trial 20 mg/day fluphenazine</td>
<td>NS</td>
</tr>
<tr>
<td>Vanderzwaag et al., 1998 (91)</td>
<td>2</td>
<td>No</td>
<td>NS</td>
<td>“Failed to respond”</td>
<td></td>
<td>No</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Hong et al., 1997 (92)</td>
<td>2 within 6 months</td>
<td>Yes</td>
<td>≤1000 mg CPZ</td>
<td>≥5 on ≥2 of BPRS positive items: 3, 4, 11, 12, 15</td>
<td></td>
<td>Yes</td>
<td>6 weeks haloperidol 60 mg/day</td>
<td>NS</td>
</tr>
<tr>
<td>Mercer et al., 1997 (93)</td>
<td>NS</td>
<td>No</td>
<td>NS</td>
<td>May et al criteria (94) – scores of 4, 5, or 6 for 26 months and ≥5 years.</td>
<td></td>
<td>No</td>
<td>NS</td>
<td>No</td>
</tr>
<tr>
<td>Meyer-Lindenberg et al., 1997 (95)</td>
<td>2</td>
<td>No</td>
<td>≥3 weeks</td>
<td>“Nonresponse or intolerance”</td>
<td></td>
<td>No</td>
<td>NS</td>
<td>No</td>
</tr>
<tr>
<td>Rosenheck et al., 1997 (96)</td>
<td>2</td>
<td>No</td>
<td>≥4 weeks</td>
<td>Severe symptoms, indicated by scores on the BPRS and the CGI</td>
<td>30-364 days hospitalised during past year. Serious social dysfunction for the previous two years.</td>
<td>No</td>
<td>NS</td>
<td>Yes</td>
</tr>
<tr>
<td>Bondolfi et al., 1998 (97)</td>
<td>2</td>
<td>No</td>
<td>6 weeks</td>
<td>Appropriately treated with CPG-BPRS &gt;100</td>
<td>Intolerance counts as adequate treatment trial</td>
<td>No</td>
<td>NS</td>
<td>No</td>
</tr>
<tr>
<td>Conley et al., 1998 (98)</td>
<td>2 within 5 years</td>
<td>Yes</td>
<td>≤1000 mg CPZ</td>
<td>≥4 on BPRS total AND ≥4 on 2 of the BPRS positive items AND CGI-S≥4</td>
<td></td>
<td>Yes</td>
<td>Haloperidol ≥10-40 mg/day for 6 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>Breier et al., 1999 (99)</td>
<td>1</td>
<td>No</td>
<td>6 weeks</td>
<td>Therapeutic</td>
<td>Score of ≥6 on BPRS positive items OR score ≥20 on SANS or ≥2 on a global item</td>
<td>No good functioning in past 5 years</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Simpson et al., 1999 (100)</td>
<td>3</td>
<td>No</td>
<td>6 weeks</td>
<td>BPRS≥45 with ≥4 in ≥2 psychotic items. CGI-S≥4</td>
<td>Kane et al (101) criteria</td>
<td>Yes</td>
<td>4 week period of normal medication observed as inpatient, then 4 weeks of haloperidol 10 mg</td>
<td>NS</td>
</tr>
<tr>
<td>Wring et al., 1999 (102)</td>
<td>3 in last 5 years</td>
<td>Yes</td>
<td>≤1000 mg CPZ</td>
<td>BPRS≥45, ≥4 in ≥2 psychiatric items. CGI-S≥4</td>
<td>Modified Kane et al (101) criteria</td>
<td>No</td>
<td>NS</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Variation in criteria: including treatment intolerant

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Limitation(s)</th>
<th>Follow-up</th>
<th>Method(s)</th>
<th>ICD-10-diagnosis</th>
<th>Criteria</th>
<th>Duration of treatment</th>
<th>Duration of treatment</th>
<th>Hospitalisation</th>
<th>Treatment failure</th>
<th>Study outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahlbeck et al., 2000 (103)</td>
<td>2 within 5 months, Yes, 6 weeks</td>
<td>≥1000 mg CPZ</td>
<td>Persistent psychotic symptoms**</td>
<td>-</td>
<td>Yes – haloperidol up to 50mg/day for 8 weeks</td>
<td>NS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azorin et al., 2001 (104)</td>
<td>2</td>
<td>Yes, 6 weeks</td>
<td>≥20mg Haloperidol for ≥1 trial</td>
<td>18 item BPRS &gt; 45 with ≥ 24 in 2 psychotic items. CGI-S = 4</td>
<td>Continual antipsychotic treatment for past 6 months without improvement. No period of good functioning for ≥ 24 months despite treatment with ≥ 2 antipsychotics</td>
<td>NS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kane et al., 2001 (105)</td>
<td>2</td>
<td>No, 6 weeks</td>
<td>≥600 mg ≤500mg CPZ</td>
<td>Score of ≥4 on 1 of the positive BPRS items</td>
<td>Continuously hospitalised of ≥1 year</td>
<td>No</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al., 2001 (106)</td>
<td>2</td>
<td>No, Not specified</td>
<td>NS</td>
<td>“Current active positive or severe negative symptoms which impact on functioning and prevent discharge”</td>
<td>Continuously hospitalised of ≥1 year</td>
<td>No</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolleson et al., 2001 (107)</td>
<td>2</td>
<td>Yes, 6 weeks</td>
<td>≥500 mg CPZ</td>
<td>Score of &gt;4 in BPRS total and ≥4 on one of the PANSS positive items</td>
<td>Duration of illness ≥5 years</td>
<td>No</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al., 2001 (108)</td>
<td>3</td>
<td>No, 3 months</td>
<td>≥1000 mg CPZ</td>
<td>CGI-S = 4</td>
<td>No</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alahmadi et al., 2002 (109)</td>
<td>2</td>
<td>Yes, 5 weeks</td>
<td>Therapeutic C**</td>
<td>(Total BPRS positive 2 or ≥4 on individual items) AND (total SANS 2 or ≥2 on a global item)</td>
<td>Intolerance counts as adequate treatment trial</td>
<td>3 weeks of haloperidol 15-30mg/day</td>
<td>NS</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liberman et al., 2002 (110)</td>
<td>3 in past 5 years, Yes, 6 weeks</td>
<td>≥1000 mg CPZ</td>
<td>Modified Kane et al. (101) criteria</td>
<td>Poor functioning ≥ 2 years, defined as lack of competitive employment/enrolment in an academic program and not having age-expected interpersonal relations with someone outside the biological family of origin. Patients described as &quot;sub-optimal responders&quot;</td>
<td>-</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volyakina et al., 2002 (111)</td>
<td>1</td>
<td>No, 6 weeks</td>
<td>≥600 mg CPZ</td>
<td>Persistent positive symptoms, ≥60 on PANSS</td>
<td>-</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conley et al., 2003 (112)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>As in Conley et al. (1998)</td>
<td>-</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fradenberg et al., 2003 (113)</td>
<td>NS, No, NS</td>
<td>NS</td>
<td>Treatment resistant, not otherwise defined</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bitter et al., 2004 (114)</td>
<td>1</td>
<td>No, 4-6 weeks</td>
<td>400-500 mg CPZ</td>
<td>BPRS &gt; 42</td>
<td>Discontinuation due to intolerability</td>
<td>NS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackson et al., 2004 (114)</td>
<td>2</td>
<td>No, 6 weeks</td>
<td>≥1000 mg CPZ</td>
<td>“Failure to respond”</td>
<td>≥ 2 antipsychotics must be a nonphenothiazine. Treatment intolerant patients included. Current hospitalisation ≥ 4 months. Hospitalised for ≥ 2 of past 5 years</td>
<td>No</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moreno et al., 2004 (115)</td>
<td>2</td>
<td>Yes, 6 weeks</td>
<td>≥500mg CPZ</td>
<td>BPRS &gt; 27</td>
<td>-</td>
<td>NS</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Duration

Minimum: At least 12 weeks

Optimum: At least 12 weeks; specify duration of treatment resistance
Functioning

Treatment resistant patients should be determined to be have at least moderate functional impairment, measured using a validated scale (for example, Social and Occupational Functioning Scale).
Dosage

Treatment resistant patients will have been treated with a dose of medication equivalent to at least 600 mg of chlorpromazine per day.

Record minimum and mean(SD) dosage for each drug.
But in non-treatment resistant patients.....