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Molins, C.

2016-12


http://hdl.handle.net/10138/233303
https://doi.org/10.1016/j.schres.2016.09.016

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Invited commentary

Response to antipsychotic drugs in treatment-resistant schizophrenia: Conclusions based on systematic review

C. Molins a,⁎, A. Roldán a, I. Corripio a, M. Isohanni b,c, J. Miettunen b,d,e, J. Seppälä b,f,g, A. Seppälä b, H. Koponen h, J. Molanen c,d,e, E. Jääskeläinen b,d, m-RESIST Group 1

⁎ Corresponding author at: Department of Psychiatry, Institut d’Investigació Biomèdica-Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Barcelona, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
b Center for Life Course Health Research, University of Oulu, Oulu, Finland
c Department of Psychiatry, Oulu University Hospital, Oulu, Finland
d Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
e Research Unit for Clinical Neuroscience, Department of Psychiatry, University of Oulu, Oulu, Finland
f Department of Psychiatry, South-Savo Hospital District, Mikkeli, Finland
g Department of Psychiatry, Carra – Kymenlaakso Social and Health Services, Finland
h University of Helsinki and Helsinki University Hospital, Psychiatry, Finland

A R T I C L E   I N F O

Article history:
Received 19 May 2016
Received in revised form 8 September 2016
Accepted 9 September 2016
Available online 17 September 2016

Keywords:
Treatment-resistant schizophrenia
Antipsychotic
Response
Efficacy
Clozapine
Review

Schizophrenia affects 1% of general population and one of its features is the heterogeneity of response to treatment, 20–30% of individuals with schizophrenia have treatment-resistant schizophrenia (TRS) (Lieberman, 1999). Correctly identifying these patients could contribute to reduce burden in patients themselves, in society and in economy. In fact, TRS constitutes about 60–70% of schizophrenia’s cost burden (Kennedy et al., 2014).

TRS definition was coined by Kane and colleagues in 1988 (Kane et al., 1988). In this groundbreaking trial, they demonstrated superiority in response rate of clozapine over chlorpromazine (30% vs 4%) in well-defined cohort of patients who did not respond to three well-documented antipsychotic trials and one prospective trial with high doses of haloperidol. After that, TRS and treatment response concepts have experienced several variations, as analyzed in the review by Suzuki and colleagues (Suzuki et al., 2012), underlining heterogeneity of definitions and proposing consensus definition.

For these reasons, meta-analyses in this field (Samara et al., 2016; Chakos et al., 2001) could include heterogeneous samples, in part due to unclear or lax TRS definitions. Hence, they are less helpful when searching for evidence based treatment recommendations for TRS (Miyamoto et al., 2015). Another important factors that contribute to this heterogeneity among studies are: dosage differences, investigator bias combined with the difficulty of blinding clozapine treatment assignment, and the effect of prior antipsychotic treatment (Kane and Correll, 2016).

We performed a systematic and critical review of current literature about efficacy of drugs in well-defined TRS. We analyzed key aspects of methodology and quality, definitions of resistance and response, efficacy variables (response rate and mean improvement) and safety outcomes. Here, in this letter, our aim is to present our conclusions about the antipsychotics efficacy and the problems affecting the interpretation of studies on TRS.

Double-blinded randomized trials (DBRT) on TRS were searched by: 1. a systematic search in April 2015 by the following search strategy: schizophrenia[Title] AND (“ultra-resistant”[Title] OR “treatment-refractory”[Title] OR “treatment-resistant”[Title] AND “English”[Language]) from Scopus, PubMed and CINAHL (EBSCO) databases. 2. manual search. We included only studies on treatment efficacy in a clear-defined TRS population according to criteria proposed by Suzuki et al. (2012):

1. History of treatment failure with two or more antipsychotics with different binding profile, clearly documented or prospective validation.

2. Requirement in dose and duration: each treatment with an antipsychotic has continued for six consecutive weeks at chlorpromazine-equivalent doses of ≥600 mg/day.

3. Requirement in rating scales: each treatment has resulted in a failure defined with both Clinical Global Impression (CGI) ≥4 and Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) ≤49 or Global Assessment of Functioning (GAF) ≤50 or Positive and Negative Syndrome Scale (PANSS) ≥75/Brief Psychiatric Rating Scale (BPRS) ≥45.

http://dx.doi.org/10.1016/j.schres.2016.09.016
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Double blinded randomized trials about antipsychotic efficacy in treatment-resistant schizophrenia.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study description</th>
<th>Compared drugs (mg/d)</th>
<th>Response rate</th>
<th>Completion rate</th>
<th>Improvement of symptoms from baseline</th>
<th>Commentaries</th>
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</thead>
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<tr>
<td><strong>FGA vs FGA</strong></td>
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<tr>
<td>Lal et al., 2006 (1)</td>
<td>n = 31 15 weeks ITT Inpatients</td>
<td>Levomepromazine (810)/chlorpromazine (760)</td>
<td>53%/42%</td>
<td>90%/73%</td>
<td>−10/−7</td>
<td>− No differences in efficacy. − Industry sponsored.</td>
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<tr>
<td><strong>SGA vs FGA</strong></td>
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<tr>
<td>Kane et al., 2007 (2)</td>
<td>n = 300 6 weeks PP</td>
<td>Aripiprazole (30)/perphenazine (40)</td>
<td>27%/25%</td>
<td>71%/79%</td>
<td>−10/−10</td>
<td>− No differences in efficacy. − Missing 116 patients between open-trial and BRDT. − TRS definition was incomplete. − Industry sponsored. − No differences in efficacy. − Unclear results, not reported baseline severity. − Trial conducted in India.</td>
</tr>
<tr>
<td>Kane et al., 2006 (3)</td>
<td>n = 306 12 weeks ITT</td>
<td>Ziprasidone (155)/chlorpromazine (740)</td>
<td>58%/55%</td>
<td>90%/88%</td>
<td>NR</td>
<td>− No differences in efficacy. − Industry sponsored. − No differences in efficacy. − Mix TRS and intolerant patients. − Industry sponsored.</td>
</tr>
<tr>
<td>Wirshing et al., 1999 (4)</td>
<td>n = 67 8 weeks PP</td>
<td>Risperidone (7,5)/haloperidol (19)</td>
<td>32%/14%</td>
<td>85%/87%</td>
<td>−10/−12</td>
<td>− No differences in efficacy. − Mix TRS and intolerant patients. − Industry sponsored.</td>
</tr>
<tr>
<td>Conley et al., 1998 (5)</td>
<td>n = 84 8 weeks ITT and CA Inpatients</td>
<td>Olanzapine (25)/chlorpromazine (1173) + BZT</td>
<td>7%/0%</td>
<td>71%/69%</td>
<td>−1/+2</td>
<td>− No differences in efficacy. − Industry sponsored.</td>
</tr>
<tr>
<td><strong>SGA vs SGA</strong></td>
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<tr>
<td>Meltzer et al., 2014 (6)</td>
<td>n = 160 24 weeks</td>
<td>RLAI 50/RLAI 100 (biweekly)</td>
<td>45%/45%</td>
<td>72%/70%</td>
<td>−18/−18</td>
<td>− No significant differences in efficacy. − Mix TRS patients and poor responders. − Mix SAD and SCZ. − Industry sponsored. − Risperidone had more responders. − Modified version of PANSS. − Lax TRS criteria, unclear selection of participants. − Industry sponsored.</td>
</tr>
<tr>
<td>Kane et al., 2011 (7)</td>
<td>n = 321 12 weeks ITT</td>
<td>Risperidone (9)/sertindole (18)</td>
<td>58%/45%</td>
<td>71%/68%</td>
<td>−21/−19</td>
<td>− No differences in efficacy. − Industry sponsored.</td>
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<tr>
<td><strong>Clozapine vs FGA</strong></td>
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<tr>
<td>Kane et al., 2001 (8)</td>
<td>n = 71 6 months ITT In- and outpatient</td>
<td>Clozapine (520)/haloperidol (19) + BZT</td>
<td>57%/25%</td>
<td>65%/33%</td>
<td>−10/−5</td>
<td>− Clozapine had more efficacy. − Favorable discontinuation rate in clozapine. − Industry sponsored.</td>
</tr>
<tr>
<td>Hong et al., 1997 (9)</td>
<td>n = 40 12 weeks CA Inpatients</td>
<td>Clozapine (543)/chlorpromazine (1163)</td>
<td>29%/0%</td>
<td>90%/89%</td>
<td>−8/−1</td>
<td>− Clozapine had more efficacy. − Conducted in China. − Industry sponsored.</td>
</tr>
<tr>
<td>Rosenheck et al., 1997 (10)</td>
<td>n = 423 1 year ITT Inpatients</td>
<td>Clozapine (552)/haloperidol (28) + BZT</td>
<td>37%/32%</td>
<td>57%/28%</td>
<td>−12/−8</td>
<td>− No differences in response rate, but favorable discontinuation rate and total improvement in clozapine. − Industry sponsored. − Clozapine had more efficacy. − Industry sponsored.</td>
</tr>
<tr>
<td>Kane et al., 1988 (11)</td>
<td>n = 268 6 weeks ITT and outpatient</td>
<td>Clozapine (450)/chlorpromazine (900) + BZT</td>
<td>30%/4%</td>
<td>88%/87%</td>
<td>−16/−5</td>
<td>− No differences in efficacy. − Industry sponsored.</td>
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<tr>
<td><strong>Clozapine vs SGA</strong></td>
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<tr>
<td>Meltzer et al., 2008 (13)</td>
<td>n = 40 24 weeks PP Outpatients</td>
<td>Clozapine (564)/olanzapine (34)</td>
<td>60%/50%</td>
<td>48%/74%</td>
<td>−20/−21</td>
<td>− No differences in response rate but clozapine improved more BPRS and CGI. − Industry sponsored.</td>
</tr>
<tr>
<td>Tollefson et al., 2001 (14)</td>
<td>n = 180 18 weeks PP In- and outpatients</td>
<td>Clozapine (304)/olanzapine (20,5)</td>
<td>34%/38%</td>
<td>59%/60%</td>
<td>−14/−15</td>
<td>− No differences in response rate but clozapine improved more BPRS and CGI. − Industry sponsored.</td>
</tr>
<tr>
<td>Azorin et al., 2001 (15)</td>
<td>n = 273 12 weeks PP In- and outpatients</td>
<td>Clozapine (642)/risperidone (9)</td>
<td>48%/43%</td>
<td>72%/74%</td>
<td>−23/−18</td>
<td>− No differences in response rate but clozapine improved more BPRS and CGI. − Industry sponsored.</td>
</tr>
</tbody>
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(continued on next page)
We found sixteen efficacy DBRT in TRS (Table 1), that is notably smaller number compared to the last meta-analysis (Samara et al., 2016). Nine compared clozapine versus non-clozapine antipsychotics and seven compared antipsychotics other than clozapine among themselves.

Among the seven non-clozapine trials, there were only two well-designed studies with applicable results:

- Conley et al. (1998): showing no advantage in efficacy of olanzapine over chlorpromazine at 8 weeks (7% and 0% respectively).
- Lal et al. (2006): showing how high-doses of FGAs produce more neurological adverse events and they can be difficult to distinguish from symptoms associated with psychosis. The improvement in participants' psychopathology could be, at least in part, secondary to dose reduction.

The other five trials had many flaws which may lead to erroneous conclusions (i.e. lax TRS criteria, inclusion of intolerants or schizoaffective patients, unclear results presentation).

Results showed clozapine superiority over first-generation antipsychotics (FGA) in three of four well-designed trials with clear TRS definitions. However, clozapine did not demonstrate superiority over second-generation antipsychotics (SGA): in our meta-analytic calculation there was not statistically significant advantage for clozapine in terms of response (OR 0.94 [95% CI: 0.69–1.27]). The analysis included five studies, including in total 359 clozapine and 347 SGA treated patients. There were no sign of heterogeneity (Chi² = 3.57, I² = 0.0%, p = 0.47) and no indication of publication bias (Egger’s test, z = −0.24, p = 0.999). Our results may be true finding, or be partly explained by 1) unclear eligibility criteria (i.e. mixing schizophrenia and schizoaffective patients), 2) unclear results presentation, 3) broad TRS definitions mixing intolerant patients. In fact, clozapine vs SGA trials achieved higher response rates compared to clozapine vs FGAs (see Table 1). Another important issue was the lower clozapine doses in clozapine vs SGA trials. Regarding this, conclusions of meta-analysis by Samara and colleagues are not supported by evidence. To our knowledge there are no studies in TRS population that compare clozapine monotherapy with non-clozapine polypharmacy, however there are two small open-trials (Kotler et al., 2004; Suzuki et al., 2008) offering discordant results.

Regarding high-dose treatment, there is only one DBRT (Meltzer et al., 2008) comparing high-dose of olanzapine (35 mg/d) versus clozapine (550 mg/d), showing similar response rates at 6 months (50% and 60% respectively). However, this industry supported study excluded patients who did not respond previously to olanzapine. This reveals another problem about inclusion of samples with different severity of treatment-resistance, since the TRS definition does not state exactly how effective antipsychotics should have been tried before clozapine. I.e. the samples with exclusion of patients who had failed trials of olanzapine may be considered less treatment-resistant than samples that have included non-responders to, for example, both olanzapine and risperidone. Underlining this issue, there is NIMH-sponsored study comparing high-dose of olanzapine (50 mg/d) versus clozapine (450 mg/d), that we did not include in the revision because it had a
cross-over design and originally was a safety trial, showing better tolerability and response rate in clozapine (0% vs 30%) (Conley et al., 2003).

In the review we did not include pragmatic studies because usually they applied a more liberal definition of treatment-resistance or they are not double-blinded (e.g. observational studies, population-based register studies, cost-effectiveness trials or open-label effectiveness trials). However, they may provide longitudinal results beyond acute response, they focus in other important outcomes (e.g. quality of life, social functions, discontinuation rate) and they also contribute to enhance our clinical practice. In fact, in many of these studies clozapine was superior to FGA and to SGA (McEvoy, 2006).

To summarize, we know surprisingly little about optimal antipsychotic treatment of TRS. However, clozapine remains as the first-line treatment after a failure of two antipsychotic trials according to treatment guidelines (Gaebel et al., 2005; NICE, 2014) and the results of major pragmatic studies. Varying, and broad definitions of TRS and other issues in methodology mentioned earlier in this Letter may cause problems affecting the interpretation of studies. Indeed, meta-analyses of original studies with low quality methods lead to flawed conclusions. Future efforts must ideally focus on 1. well-characterized TRS samples (e.g. description of symptoms that predominate, onset of resistance, earlier used antipsychotics), 2. consensus definition of TRS to facilitate global interpretation and replication of results (e.g. WHO has produced with an expert panel consensus definition for severe asthma and this is something we need for TRS as well), 3. sample sizes even above 300 participants “to have power to clearly show a difference of 20% between groups for binary outcomes” (Sinclair and Adams, 2014), and 4. studies without industry-sponsorship.

References


Role of funding source

This study was supported by the European Union’s Horizon 2020 research and innovation program under grant agreement No 643552, and in part by grant from the Brain and Behavior Research Foundation. The funding bodies had no role in the study design, in the collection, analysis and interpretation of data, or writing of the paper.

Contributors

C.M. wrote the first draft of the manuscript. E.J. and A.S. managed the literature searches. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interests to declare.

Acknowledgement

None.