Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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. Moilanen [c,d,e], E. Jääskeläinen [b,d], m-RESIST Group [1]

[a] 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, Carea – Kymenlaakso Social and Health Services, Finland
[h] University of Helsinki and Helsinki University Hospital, Psychiatry, Finland

ARTICLE INFO

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

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.

* Corresponding author at: Department of Psychiatry, Institut d'Investigació Biomèdica-Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Carrer Sant Antoni Maria Claret 167, 08025 Barcelona, Spain.
E-mail address: cmolins.zambotti@gmail.com (C. Molins).
[1] A full list of m-RESIST Group authors and affiliations appears in www.mresist.eu.

http://dx.doi.org/10.1016/j.schres.2016.09.016
0920-9964/

Table 1
Double blinded randomized trials about antipsychotic efficacy in treatment-resistant schizophrenia.

Trial	Study description	Compared drugs (mg/d)	Response rate	Completion rate	Improvement of symptoms from baseline	Commentaries
FGA vs FGA						
Lal et al., 2006 (1)	n = 31 15 weeks ITT Inpatients	Levomepromazine (810)/chlorpromazine (760)	53%/42%	90%/73%	−10/−7	– No differences in efficacy. – Industry sponsored.
SGA vs FGA						
Kane et al., 2007 (2)	n = 300 6 weeks PP	Aripiprazole (30)/perphenazine (40)	27%/25%	71%/79%	−10/−10	– No differences in efficacy. – Missing 116 patients between open-trial and BRDT. – TRS definition was incomplete. – Industry sponsored.
Kane et al., 2006 (3)	n = 306 12 weeks ITT	Ziprasidone (155)/chlorpromazine (740)	58%/55%	90%/88%	NR	– No differences in efficacy. – Unclear results, not reported baseline severity. – Trial conducted in India. – TRS definition was incomplete. – Industry sponsored.
Wirshing et al., 1999 (4)	n = 67 8 weeks PP	Risperidone (7,5)/haloperidol (19)	32%/14%	85%/87%	−10/−12	– No differences in efficacy. – Mix TRS and intolerant patients. – Industry sponsored
Conley et al., 1998 (5)	n = 84 8 weeks ITT and CA Inpatients	Olanzapine (25)/chlorpromazine (1173) + BZT	7%/0%	71%/69%	−1/+2	– No differences in efficacy. – No industry sponsored.
SGA vs SGA						
Meltzer et al., 2014 (6)	n = 160 24 weeks	RLAI 50/RLAI 100 (biweekly)	45%/45%	72%/70%	−18/−18	– No significant differences in efficacy. – Mix TRS patients and poor responders. – Mix SAD and SCZ. – Industry sponsored.
Kane et al., 2011 (7)	n = 321 12 weeks ITT	Risperidone (9)/sertindole (18)	58%/45%	71%/68%	−21/−19	– Risperidone had more responders. – Modified version of PANSS. – Lax TRS criteria, unclear selection of participants. – Industry sponsored.
Clozapine vs FGA						
Kane et al., 2001 (8)	n = 71 6 months ITT In- and outpatient	Clozapine (520)/haloperidol (19) + BZT	57%/25%	65%/33%	−10/−5	– Clozapine had more efficacy. – Favorable discontinuation rate in clozapine. – Lax response definition. – Industry sponsored.
Hong et al., 1997 (9)	n = 40 12 weeks CA Inpatients	Clozapine (543)/chlorpromazine (1163)	29%/0%	90%/89%	−8/−1	– Clozapine had more efficacy. – Conducted in China. – No industry sponsored.
Rosenheck et al., 1997 (10)	n = 423 1 year ITT Inpatients	Clozapine (552)/haloperidol (28) + BZT	37%/32%	57%/28%	−12/−8	– No differences in response rate, but favorable discontinuation rate and total improvement in clozapine. – No industry sponsored.
Kane et al., 1988 (11)	n = 268 6 weeks ITT Inpatients	Clozapine (450)/chlorpromazine (900) + BZT	30%/4%	88%/87%	−16/−5	– Clozapine had more efficacy. – Industry sponsored.
Clozapine vs SGA						
Sacchetti et al., 2010 (12)	n = 147 18 weeks ITT	Clozapine (365)/ziprasidone (137)	55%/68%	62%/62%	−24.5/−25	– Non-inferiority of ziprasidone. – No differences in EPS. – Mix TRS patients and intolerants. – Non-inferiority trial. – Industry sponsored.
Meltzer et al., 2008 (13)	n = 40 24 weeks PP Outpatients	Clozapine (564)/olanzapine (34)	60%/50%	48%/74%	−20/−21	– No differences in efficacy. – Mix SAD and SCZ. – High-doses of olanzapine were used. – Industry sponsored.
Tollefson et al., 2001 (14)	n = 180 18 weeks PP In- and outpatients	Clozapine (304)/olanzapine (20,5)	34%/38%	59%/60%	−14/−15	– Non-inferiority of olanzapine. – Non-inferiority trial. – Industry sponsored.
Azorin et al., 2001 (15)	n = 273 12 weeks PP In- and outpatients	Clozapine (642)/risperidone (9)	48%/43%	72%/74%	−23/−18	– No differences in response rate but clozapine improved more BPRS and CGI. – Industry sponsored.

Please cite this article as: Molins, C., et al., , Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.09.016