RESPONSE TO ANTIPSYCHOTIC DRUGS IN TREATMENT-RESISTANT SCHIZOPHRENIA: CONCLUSIONS BASED ON SYSTEMATIC REVIEW.

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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) (Liebermann et al 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 ≥600mg/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.

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 no 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 339 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 the selection of less resistant patients in industry-funded trials through: 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 FGA trials (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 very clear: "the underdosing in industry-funded trials could constitute a serious problem that could have affected the results". In addition, only few SGA have been compared with clozapine (i.e. ziprasidone, olanzapine, risperidone) and therefore, the efficacy in TRS-population of another SGAs remains unknown (e.g. amisulpride, aripiprazole, sertindole, quetiapine).

Non-clozapine polypharmacy and high-dose treatment in TRS 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 (35mg/d) versus clozapine (550mg/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 be tried before clozapine (i.e. the exclusion of patients who had failed trials of olanzapine, and these samples could be considered less treatment-resistant than others 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 (50mg/d) versus clozapine (450mg/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 RR 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 et al 2006).

To summarize, we know surprisingly little about optimal antipsychotic treatment of TRS. However clozapine remains as the first-line treatment in TRS according to the majority of guidelines (Gaebel et al 2005) 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 flawed/low quality methods lead to flawed/wrong/confusing 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.

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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 from baseline	Commentaries
FGA vs FGA						
Lal et al., 2006	n = 31 15 weeks ITT Inpatients	Levomepromazine (810) / Chlorpromazine (760)	53% / 42%	90% / 73%	-10 / -7	-No differences in efficacy. -No differences in EPS. -Industry sponsored.
SGA vs FGA						
Kane et al., 2007	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. -Aripiprazole had low EPS. -TRS definition was incomplete. -Industry sponsored.
Kane et al., 2006	n = 306 12 weeks ITT	Ziprasidone (155) / Chlorpromazine (740)	58% / 55%	90% / 88%	NR	-No differences in efficacy. -Ziprasidone had low EPS. -Unclear results, not reported baseline severity. -Trial conducted in India. -TRS definition was incomplete. -Industry sponsored.
Wirshing et al., 1999	n = 67 8 weeks PP	Risperidone (7,5) / Haloperidol (19)	32% / 14%	85% / 87%	-10 / -12	-No differences in efficacy. -Risperidone had low EPS. -Mix TRS and intolerant patients. -Industry sponsored
Conley et al., 1998	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	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	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	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. -No differences in EPS. -Lax response definition. -Industry sponsored.
Hong et al., 1997	n = 40 12 weeks CA Inpatients	Clozapine (543) / Chlorpromazine (1163)	29% / 0%	90% / 89%	-8 / -1	-Clozapine had more efficacy. -Chlorpromazine had more EPS. -Leucopenia in one clozapine-patient. -Conducted in China. -No industry sponsored.
Rosenheck et al., 1997	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. -Haloperidol had more EPS. -Three cases of agranulocytosis in clozapine. -No industry sponsored.
Kane et al., 1988	n = 268 6 weeks ITT Inpatients	Clozapine (450) / Chlorpromazine (900) + BZT	30% / 4%	88% / 87%	-16 / -5	-Clozapine had more efficacy. -Chlorpromazine had more EPS. -No case of agranulocytosis was observed. -Industry sponsored.
Clozapine vs SGA						
Sacchetti et al., 2009	n = 147 18 weeks ITT	Clozapine (365)/ Ziprasidone (137)	55% / 68%	62% / 62%	-24.5 / -25	-Non-inferiority of ziprasidone. -No differences in EPS. -Favorable results in ziprasidone for

						metabolic variables. -No agranulocytosis case was observed. -Mix TRS patients and intolerants. -Non-inferiority trial. -Industry sponsored.
Meltzer et al., 2008	n = 40 24 weeks PP Outpatients	Clozapine (564) / Olanzapine (34)	60% / 50%	48% / 74%	-20 / -21	-No differences in efficacy. -Similar results in two groups for EPS. -Favorable results in clozapine for metabolic variables. -Mix SAD and SCZ. -High-doses of olanzapine were used. -Industry sponsored.
Tollefson et al., 2001	n = 180 18 weeks PP In- and outpatients	Clozapine (304) / Olanzapine (20,5)	34% / 38%	59% / 60%	-14 / -15	-Non-inferiority of olanzapine. -No differences in EPS. -No differences in metabolic variables. -Non-inferiority trial. -Industry sponsored.
Azorin et al., 2001	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. -Risperidone had more EPS -Favorable results for risperidone in metabolic variables. -No agranulocytosis case was observed. -Convulsions were more frequently with clozapine. -Industry sponsored.
Bondolfi et al., 1998	n = 86 8 weeks ITT Inpatients	Clozapine (300) / Risperidone (6)	65% / 67%	79% / 79%	-23 / -27	-No differences in efficacy. -No differences in EPS. -Favorable results for risperidone in metabolic variables. -No agranulocytosis case was observed. -Mix TRS patients and intolerants. -Industry sponsored.

ITT intention to treat analysis, PP per-protocol analysis, CA completers analysis, BZT benzotropine, SAD schizoaffective disorder, SCZ schizophrenia patients, EPS extra-pyramidal symptoms, TRS treatment-resistant schizophrenia, FGA first-generation antipsychotics, SGA second-generation antipsychotics.