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Characteristics and definitions of ultra-treatment-resistant schizophrenia – A systematic review and meta-analysis

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1. Introduction

First mentioned in 2006 (Mouaffak et al., 2006), ultra-treatment-resistant or clozapine-resistant schizophrenia (CRS) is defined by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group as persistence of either positive, negative, or cognitive symptoms of schizophrenia of at least moderate severity after an adequate trial of clozapine (Howes et al., 2017). Up to 60% of treatment-resistant schizophrenia patients do not respond to an adequate trial of clozapine (Siskind et al., 2017). One of the most relevant questions in the clinical care of people with schizophrenia is how to treat CRS. Evidence from current meta-analyses and meta-reviews indicates only marginal and/or low-quality benefits for pharmacological clozapine combination or augmentation strategies after insufficient response to clozapine-monotherapy (Correll et al., 2017; Wagner et al., 2019). Despite the marginal benefits for pharmacological combination strategies, the augmentation of clozapine with another pharmacological agent is commonly used in clinical practice (Morrato et al., 2007). Among non-pharmacological augmentation strategies, cognitive-behavioral therapy (CBT) has been investigated in multiple randomized controlled trials (RCTs) (Barretto et al., 2009; Morrison et al., 2018; Pinto et al., 1999) including a recent large RCT (Morrison et al., 2018). These studies yielded mixed results regarding the efficacy of CBT as a CRS treatment augmentation strategy. On the contrary, electroconvulsive therapy (ECT) is reported in recent systematic reviews and meta-analysis (Lally et al., 2016; Wang et al., 2018; Arumugham et al., 2016) to be an efficacious treatment option for clozapine-refractory positive symptoms, although characterized by limited evidence regarding its safety. Finally, a novel intervention method has been offered by repetitive transcranial magnetic

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stimulation (rTMS). However, this augmentation strategy did not provide a high level of evidence due to a lack of high-quality RCTs (de Jesus et al., 2011) and the absence of meta-analyses involving studies with CRS populations. Overall, the evidence for clozapine augmentation is sparse and at times with conflicting evidence (Wagner et al., 2019), which is likely due to a lack of high-quality trials and co-occurring inconsistent definitions of CRS. With our approach, we aim at extending the evidence by assessing 1) baseline characteristics of enrolled patients (i.e. symptom severity), 2) whether and to which extent CRS definitions differ between studies and whether they aligned to multiple schizophrenia guidelines definition of CRS, 3) differences in baseline characteristics of enrolled patients between multiple sub-groups of studies based either on study design, intervention strategy or geographical study location.

2. Methods

The methods are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.1. Search strategy

Systematic searches of articles indexed in PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO using the search terms (clozapin* OR clozaril OR zaponex OR denzapin* OR clopine) AND (add-on OR added OR augment* OR combin*) were conducted. The abstracts and titles of articles identified through electronic searches were independently screened by two reviewers (EW, MC). No language restrictions were applied.

2.2. Inclusion criteria

Randomized and non-randomized (including prospective observational and open-label) clozapine add-on trials were included if they reported psychopathological (including cognitive) outcome(s) (mean and standard deviation, SD) at baseline, irrespective of the used scale (e.g. Positive and Negative Syndrome Scale (PANSS) total scores (Kay et al., 1987), Brief Psychiatric Rating Scale (BPRS) scores (Overall and Gorham, 1962)).

2.3. Exclusion criteria

Case reports, case series, studies without any psychopathological assessments, studies including patients on any other antipsychotic medication than clozapine at baseline, and studies from mainland China were excluded.

2.4. Data extraction

Two reviewers (EW, MC) independently extracted the data into an electronic spreadsheet and disagreements were resolved by joint examination of the papers. The following data were extracted:

1. Number of study arms
2. Sample size of subjects on clozapine in intervention and control or total group at baseline
3. Mean (and SD) age (in years) at baseline
4. Gender distribution
5. Mean (and SD) duration of illness (in years) at baseline
6. Mean (and SD) clozapine dose (in mg/day) at baseline
7. Mean (and SD) clozapine plasma level (in ng/ml) at baseline
8. Mean (and SD) of PANSS total score / BPRS total score at baseline
9. Geographical location of the study (Europe, North America, non-Europe and non-north America)
10. CRS definitions.

2.5. Data synthesis

The primary outcome was the overall symptom score at baseline, measured with PANSS total or BPRS total scores. Meta-analyses were conducted using Comprehensive Meta-Analysis (Version 3.3).

2.6. Subgroup and sensitivity analyses

Subgroup analyses were undertaken on randomized vs. non-randomized (including prospective observational and open-label) studies, ECT vs. drug studies and vs. rTMS studies and vs. psychotherapy/psychosocial support studies and European vs. North American vs. non-European and non-North American based studies.

2.7. Quality analysis

Quality analyses were undertaken to assess and compare the quality of CRS definitions between studies. In line with schizophrenia guideline recommendations (Howes et al., 2017; Kreyenbuhl et al., 2010; Remington et al., 2017; Hasan et al., 2012) we developed a "Guidelines Affinity Score (GAS)" to quantify the implementation in each single study of a best practice CRS definition modeled on the aforementioned schizophrenia guidelines and adapted to also include a standardized clinical score (in this case PANSS) to define "inadequate response" more consistently. GAS is based on 5 items with a maximum value of 5 points. Each study was given:

1. 1 point for inclusion of a temporal criterion (at least 8 weeks of clozapine trial before enrollment)
2. 1 point for the use of the highest tolerable clozapine dose before assessing clozapine-resistance
   - o OR
3. 2 points for clozapine plasma levels measurement with a cut-off set at 350 ng/ml before enrollment
4. 1 point for the use of a clinical scale to define inadequate response to clozapine
   - o OR
5. 2 points if inadequate response was defined as a PANSS total score of minimum 58 or a BPRS score of minimum 32. A value of PANSS equal or higher than 58 was chosen as it is considered to correspond to a "mildly ill" Clinical Global Impression (CGI) score (Leucht et al., 2005), a value of BPRS equal or higher than 32 was chosen as it is equivalent to a PANSS value of 58 (Leucht et al., 2013).

Finally, we evaluated the study quality of RCTs using the Cochrane Risk of Bias tool (Higgins et al., 2011).

2.8. Data analyses

The included studies were divided in single study arms based on their designs for a total of 120 different arms. Each study arm was considered as independent in all analyses, with the exception of GAS values comparisons where study arms within a study shared the same value (for GAS values comparisons N=number of studies, for all other analyses N=number of study arms; i.e. a two-arm RCT study was considered as N=2). Baseline data were extracted and then pooled performing a weighted mean analysis for all included study arms resulting in: N, mean and SD. Additionally, baseline data from different study subgroups (Randomized, Non-randomized, Drugs, Psychotherapy/Psychosocial, ECT, rTMS, European, North American, non-European and non-north American) were extracted and pooled with weighted mean analyses. Differences in continuous outcomes between subgroups were compared with summary independent *t*-tests (weighted means) and independent t-tests (non-weighted means). To compare differences in GAS values between subgroups

we used Mann-Whitney-*U* tests. Weighted means were computed using Comprehensive Meta-Analysis Version 3.3. All weighted means were calculated using a random effects model. IBM SPSS Version 26.0.0.1 was used for all analyses. Significance threshold was set at 0.05. Equality of variances was checked with Hartley's Test for variance homogeneity in summary independent *t*-tests or with Levene's Test in independent t-tests and in cases of $p < 0.05$, respective corrections were performed. Due to the limited availability of certain data (i.e. clozapine plasma levels) there was a difference in the degrees of freedom between different tests.

3. Results

3.1. General study information

In total, 1541 articles were independently screened on title/abstract and 99 articles on full-text level. A total of 28 articles were excluded after full text review (see Supplementary Table S1 for the list of excluded studies) and N=71 articles were included in the meta-analyses (see Fig. 1). For detailed study information, see Supplementary Table S2.

3.2. Study characteristics and quality

The majority of a total of N=71 included studies were pharmacological clozapine augmentation studies (87%, N=62) (Afshar et al., 2008; Anghelescu et al., 1997; Anil Yağcioğlu et al., 2005; Assion et al., 2007; Barbui et al., 2011; Barnes et al., 2017; Behdani et al., 2011; Bruno et al., 2016; Bruno et al., 2014a; Bruno et al., 2014b; Buchanan et al., 1996; Chang et al., 2008; Chiaie et al., 2007; de Groot et al., 2001; De Lucena, 2011; Diaz et al., 2005; Doruk et al., 2008; Evins et al., 2000; Fleischhacker et al., 2010; Freudenreich et al., 2009; Freudenreich et al., 2007; Friedman et al., 1997; Friedman et al., 2011; Genç et al., 2007; Goff et al., 2001; Goff et al., 1996; Gunduz-Bruce et al., 2012; Hahn et al., 2010; Heck et al., 2005; Henderson and Goff, 1996; Henderson et al., 2006; Honer et al., 2006; Josiassen et al., 2005; Kelly et al., 2015; Koen et al., 2006; Lane et al., 2006; Lin et al., 2017; Lu

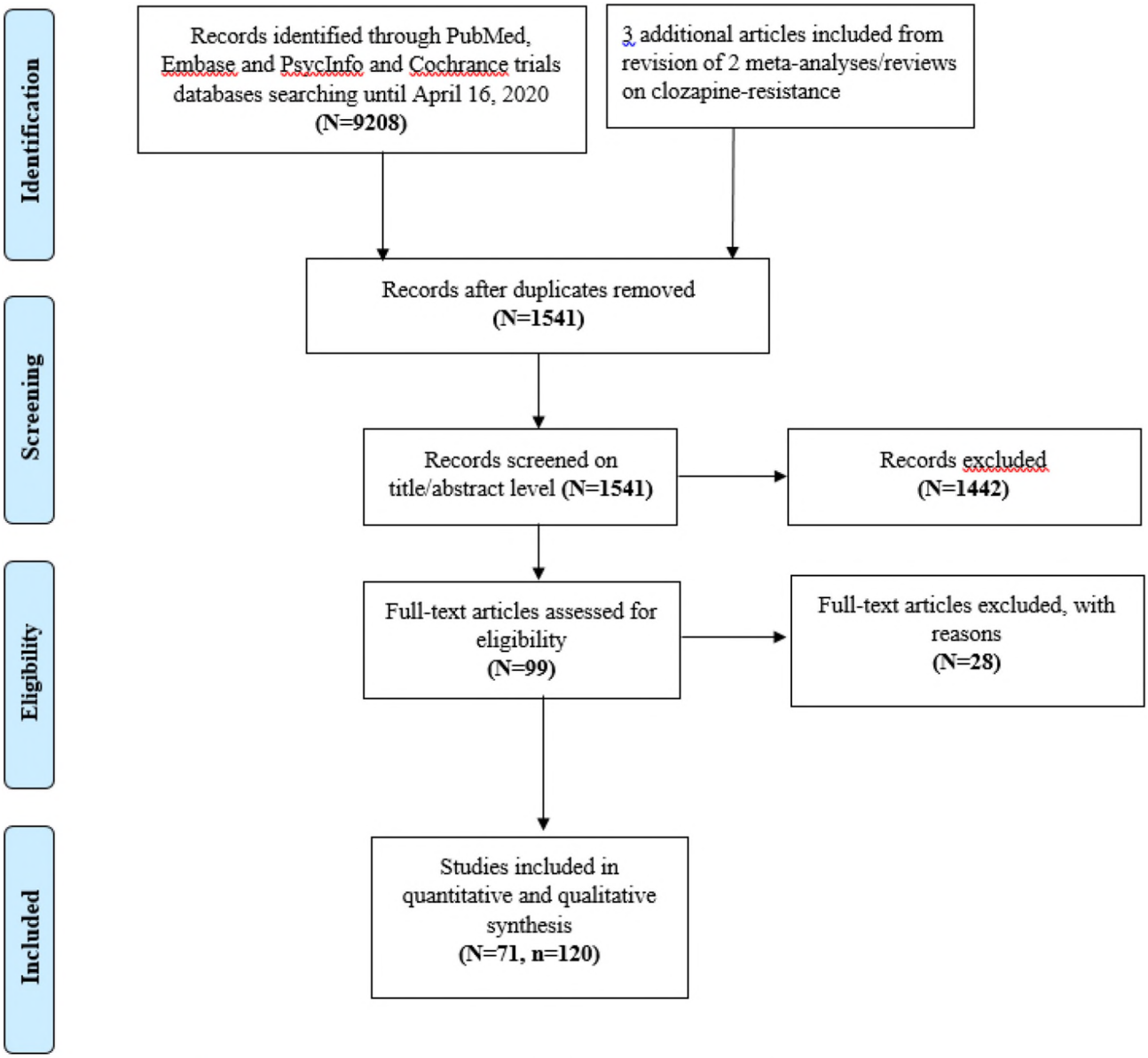

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Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. N: number of studies, n: number of study arms.

et al., 2018; Mico et al., 2011; Mitsonis et al., 2007; Munro et al., 2004; Muscatello et al., 2010; Muscatello et al., 2014; Muscatello et al., 2011; Nielsen et al., 2012; Potkin et al., 1999; Repo-Tiihonen et al., 2012; Shiloh et al., 1996; Shiloh et al., 1997; Stryjer et al., 2004; Taylor et al., 2001; Tiihonen et al., 2003; Tsai et al., 1999; Vayisoglu et al., 2012; Veerman et al., 2016; Weiner et al., 2010; Ziegenbein et al., 2005; Ziegenbein et al., 2006a; Ziegenbein et al., 2006b; Zink et al., 2009; Zoccali et al., 2007; Zoccali et al., 2003). The remainder of non-pharmacological studies were relatively equally distributed between psychotherapy/psychosocial (3%, N=2) (Cardoso Buchain et al., 2003; Morrison et al., 2018), ECT (7%, N=5) (Braga et al., 2019; Kho et al., 2004; Melzer-Ribeiro et al., 2017; Petrides et al., 2015; Tang and Ungvari, 2002) and rTMS augmentation studies (3%, N=2) (de Jesus et al., 2011; Rosa et al., 2007). Among the included psychotherapy/psychosocial studies, one investigated cognitive behavioral therapy (CBT) administered on an individual basis over a period of 9 months and included up to 26 h of treatment on an approximately weekly basis in addition to clozapine, whereas the other investigated occupational therapy over a period of 6 months as a clozapine add-on treatment. N=48 out of 71 (68%) were randomized studies (with N=24 being evaluated as high risk of bias and N=24 low risk of bias studies) and N=23 (32%) non-randomized studies. 42% (N=30) of the studies were conducted in Europe, 30% (N=21) in North America and 28% (N=20) neither in Europe nor in North America. For detailed information, see Table 1.

3.3. Patient characteristics

Overall, data from a total of n=2731 patients were collected. The mean age of the total population (n=2467) was 38.42 years (SD=± 3.92 years). 69.57% of the population were male. The mean duration of illness (n=1141) was 14.64 years (SD=±4.14 years). The mean clozapine dose (n=1642) was 436.94 mg/day (SD=±87.47 mg/day) with an average clozapine plasma level (n=682) of 500.98 ng/ml (SD=± 127.49 ng/ml). The mean PANSS total score at baseline (n=1554) was 79.16 (SD=±7.52) (moderately ill (Leucht et al., 2005)), and the mean BPRS score (n=826) was 40.90 (SD=±4.62). For detailed information see Table 2.

3.4. Subgroup comparisons

Subgroups baseline data, in form of both weighted and non-weighted means, from each study and study arm were compared using summary independent *t*-tests for weighted means, independent t-tests for non-weighted means and Mann-Whitney-*U* tests for GAS value comparisons. Since weighted and non-weighted data differed only minimally, the resulting independent t-tests comparisons yielded the same results as the weighted means comparisons with only one exception. For conciseness reasons we report here only weighted mean analyses. For non-weighted analyses please see Supplement tables from S5.1 to S5.7.

Table 2
Overall characteristics of enrolled patients. Abbreviations: n = number of patients, SD = standard deviation, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale. Mean values are weighted means and were computed with CMA (Comprehensive Meta-Analysis Software) using a random effect model.

Patients characteristics	n	Mean	SD±
Age (years)	2467	38.42	3.92
Duration of illness (years)	1141	14.64	4.14
Clozapine dose (mg/day)	1642	436.94	87.47
Clozapine plasma level (ng/ml)	682	500.98	127.49
PANSS total	1554	79.16	7.52
BPRS total	826	40.90	4.62

3.4.1. Randomized vs. non-randomized studies, weighted mean analyses

When randomized studies were compared with non-randomized studies, no significant differences were detected for the variables age ($t_{(50.5)}=-0.01$, p=0.991), duration of illness ($t_{(54)}=0.35$, p=0.725), clozapine dose ($t_{(19.5)}=-0.88$, p=0.388), clozapine plasma levels ($t_{(32)}=1.34$, p=0.191) and PANSS total scores between the two groups ($t_{(53)}=1.05$, p=0.300). BPRS total scores were significantly higher in randomized studies ($t_{(47)}=3.53$, p<0.001). For all results and complete test statistics see Supplement Table S4.1, for non-weighted analyses, see Supplement Table S5.1.

3.4.2. Drug studies vs. ECT studies, weighted mean analyses

Clozapine plasma levels were significantly higher in ECT studies compared to drug studies (776.81 ng/ml vs. 466.98 ng/ml respectively, $t_{(32)}=-3.94$, p<0.001). All the remaining variables did not significantly differ between the two groups (age, duration of illness, clozapine dose, PANSS total score, BPRS score) (see Supplement Table S4.2, for non-weighted analyses, see Supplement Table S5.2).

3.4.3. Drug studies vs. psychotherapy/psychosocial studies, weighted mean analyses

No significant differences were detected for all variables (age, duration of illness, PANSS total score). Data for all other variables (clozapine dose, clozapine plasma levels, BPRS total score) were not available (see Supplement Table S4.3, for non-weighted analyses, see Supplement Table S5.3).

3.4.4. ECT studies vs. rTMS studies, weighted mean analyses

A significantly longer duration of illness and higher BPRS scores could be observed in the ECT population ($t_{(2)}=5.80$, p=0.028 and $t_{(3)}=3.23$, p=0.048, respectively). Of note, there was no significant difference in BPRS scores when comparing non-weighted data ($t_{(3)}=0.71$, p=0.529) and the limited N needs to be considered when interpreting these contrasts. No significant difference was observed for the remaining tested variables (age, clozapine dose, PANSS total score) (see Supplement Table S4.4, for non-weighted analyses, see Supplement Table S5.4).

Table 1
Characteristics of included studies. Abbreviations: N = number of studies, ECT = electroconvulsive Therapy, rTMS = repetitive transcranial magnetic stimulation, PT = psychotherapy. Percentage refers to a total of 71 studies. Because risk of bias was assessed only in randomized studies, percentage refers only in this case to a total of 48 studies.

Study Characteristics			
	N(%)		***N(%)***
Total	71(100)	**Pharmacological**	62(87)
Randomized	48(68)	**ECT**	5(7)
Non-randomized	23(32)	**PT/ Psychosocial**	2(3)
European	30(42)	**rTMS**	2(3)
North American	21(30)	**High risk of bias**	24(50)
Non-European, non-north American	20(28)	**Low risk of bias**	24(50)

Table 3
Comparisons of weighted baseline parameters between European and North American studies. Abbreviations: n = number of cohorts (each study arm is considered as a single cohort, i.e. studies with two study arms are given n=2), t = t-value, p = p-value, df = degrees of freedom, SD = standard deviation, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale. Summary independent *t*-tests were corrected if Hartley's tests for equal variance were significant.

	European studies			North American studies			Group comparisons		
	n	Mean	SD±	n	Mean	SD±	t	df	p
Age (years)	40	37.26	4.90	26	40.38	4.34	−2.64	64	**0.010**
Duration of illness (years)	20	11.09	4.38	11	17.38	5.05	−3.63	29	**0.001**
Clozapine dose (mg/day)	34	417.35	116.10	20	466.87	52.37	−2.14	49.5	**0.037**
Clozapine plasma level (ng/ml)	11	372.91	126.71	19	562.01	126.90	−3.94	28	**<0.001**
PANSS total	24	77.15	8.07	15	76.03	15.26	0.26	19.0	0.796
BPRS total	18	36.10	5.27	17	42.97	3.08	−4.74	27.7	**<0.001**

In bold statistically significant results, that is p <=0,05.

3.4.5. Geographical location, weighted mean analyses

In North American studies, participants were significantly older ($t_{(64)}=-2.64$, p=0.010) and had a longer duration of illness ($t_{(29)}=-3.63$, p=0.001) compared to European studies. Furthermore, in North American studies, significantly higher clozapine dose, clozapine plasma levels and BPRS scores were observed ($t_{(49.5)}=-2.14$, p=0.037, $t_{(28)}=-3.94$, p<0.001 and $t_{(27.7)}=-4.74$, p<0.001 respectively). No significant differences were found for PANSS total scores ($t_{(19.0)}=0.26$, p=0.796) (see Table 3). Furthermore, a similar pattern was found when comparing European studies with non-European and non-north American studies. Participants enrolled in European studies showed a shorter duration of illness ($t_{(43)}=-3.55$, p=0.001), lower clozapine plasma levels ($t_{(13)}=-2.81$, p=0.015) as well as lower severity of illness measured with PANSS and BPRS scores ($t_{(38)}=-2.79$, p=0.008 and $t_{(30)}=-4.09$, p<0.001 respectively). No significant differences were found for age and clozapine dose ($t_{(76)}=-0.81$, p=0.421 and $t_{(59)}=-0.69$, p=0.492 respectively). Additionally, no significant differences were found when comparing North American studies with non-European and non-north American studies. (see Supplement Tables S4.6 and S4.7, for non-weighted analyses, see Supplement Tables S5.5, S5.6 and S5.7).

3.4.6. GAS values comparisons

No significant differences were found when comparing GAS values across all study sub-groups. For detailed information see Supplement Table S5.8.

3.4.7. Qualitative analysis

When assessing guidelines implementation of CRS definitions by mean of the Guidelines Affinity Score, a substantial variety of scores was observed among all included studies. The total mean GAS value from all the included studies was 2.28 (SD=±1.30). The majority of studies (N=28) reached a score of 2 points, with only 4 studies reaching the maximum of 5 points and 6 studies scoring 0 points (see Fig. 2).

4. Discussion

4.1. Main findings

4.1.1. Patient baseline characteristics

In this first systematic review and meta-analysis to date evaluating baseline data of participants with CRS and comparing CRS definitions across studies, key differences were found both on patient- and study-

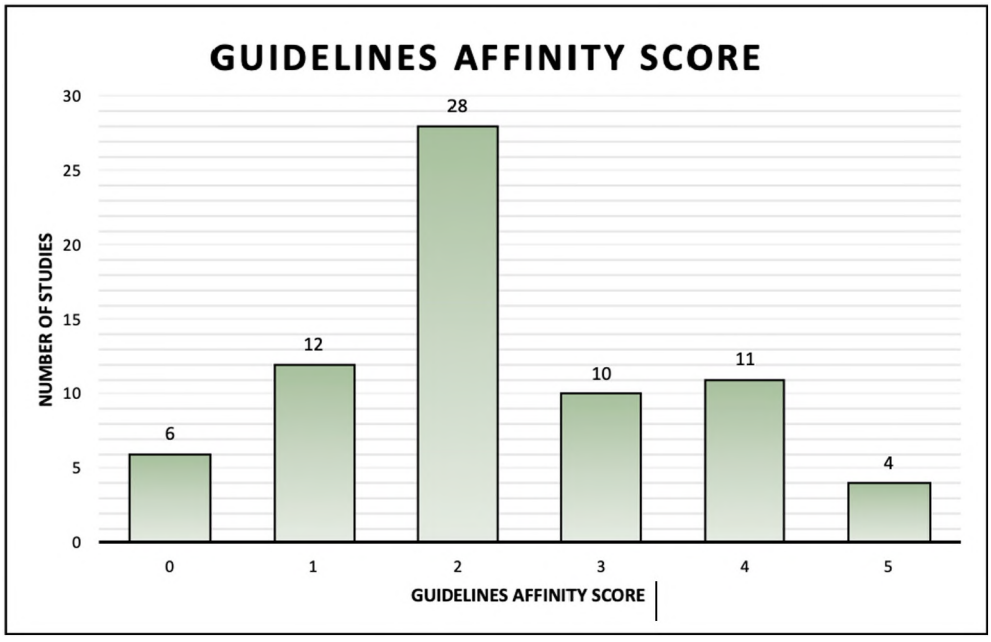

Fig. 2. Guidelines Affinity Score. X axis: Score (0 to 5 points); Y axis: Number of studies (N=71). GAS is based on 5 items with a maximum value of 5 points. Each study was given: 1 point for inclusion of a temporal criterion (at least 8 weeks of clozapine trial before enrollment); 1 point for the use of the highest tolerable clozapine dose before assessing clozapine-resistance OR 2 points for clozapine plasma levels measurement with a cut-off set at 350 ng/ml before enrollment; 1 point for the use of a clinical scale to define inadequate response to clozapine OR 2 points if inadequate response was defined as a PANSS total score of minimum 58 or a BPRS score of minimum 32.

level. We characterized CRS patients by focusing on demographical, psychopathological and clinical data, stratifying the results according to augmentation strategies, study design, and geographical study location. Moreover, we assessed the various definitions of CRS applied in the included studies and put them into perspective with national and international schizophrenia guidelines in order to check for consistency and gain a viewpoint on the level of guideline implementation in clinical trials.

Evaluating baseline parameters of our pooled CRS cohort, we encountered a moderately ill population. The average baseline parameters (see Table 2), despite the heterogeneity of CRS definitions among the included studies, show high mean clozapine plasma levels well above the 350 ng/ml threshold mentioned in various guidelines (Howes et al., 2017; Kreyenbuhl et al., 2010; Remington et al., 2017; Hasan et al., 2012). Moreover, the long duration of illness together with the moderately high PANSS total score hint at the fact that the examined cohort might nevertheless represent a CRS cohort. Among the baseline parameters, the duration of clozapine treatment is undoubtedly an important assessment in that it could help discerning correlational strength between length of clozapine treatment and CRS insurgence as well as length of treatment in general and CRS onset, thus helping discerning between early- and late-onset treatment-resistance (Howes et al., 2017). Unfortunately, only 10 out of 71 studies specified duration of clozapine treatment.

4.1.2. Subgroups comparisons

Comparing baseline parameters in the different subgroups we found relatively homogeneous populations. Interestingly, significant differences in symptom severity were only found when comparing subgroups with regard to BPRS scores but not with regard to PANSS scores, suggesting a potential lack of comparability of the two scores when applied in the setting of a clinical trial. Notably, when considering the different interventions, no significant differences were found between psychotherapy/psychosocial intervention studies and drug studies even though it could be assumed that patients with a higher symptom load would less likely participate in non-pharmacological (except ECT) studies than pharmacological studies (or ECT studies). Interestingly, those results differed from a recent similar comparison of the two subgroups (drugs vs. psychotherapy interventions) in people with schizophrenia, although not explicitly CRS, where patients enrolled in drug studies were markedly longer and more severely ill than patients enrolled in psychotherapy studies (Bighelli et al., 2020). Multiple significant differences were found when data were compared based on geographical study-site location. Of note, patients enrolled in North America, when compared to European studies, have been ill for a longer time, received higher doses of clozapine, also reflected in their higher clozapine plasma levels and yet exhibited more severe symptoms measured with BPRS. Furthermore, patients enrolled in European study sites showed less severe symptoms compared with patients enrolled in areas other than North America. These data reveal a geographically rooted heterogeneity in CRS study populations, which could presumably in part be explained by the lack of implementation of standardized CRS definitions. Another explanation for these geographical differences, especially for the stark contrast between European and North American studies, could lie in the course of CRS itself. Patients in Europe had been enrolled earlier in their illness, thus showing a shorter duration of illness than patients in other areas outside Europe. A longer duration of illness could have led to a chronification of the disease with consequently higher clozapine dose and plasma levels as well as more severe symptoms. The reported geographically rooted heterogeneity has a complex nature. Important factors that might strongly influence both the course and burden of the disease as well as the outcomes of therapeutic interventions may include, but not be limited to, the presence of a welfare system (paid medical leave, affordable therapeutic community homes), a free and universal healthcare coverage (easier access to treatment, coverage of most treatment-related costs), individual social factors like family structure as well as larger socioeconomically relevant factors like unemployment rates.

4.1.3. CRS definitions

CRS definitions appear in guidelines, but are underrepresented in clinical trials. However, it is important to acknowledge that a number of studies included in this meta-analysis were conducted prior to the publication of the following guidelines. Overall various schizophrenia guidelines (the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations of 2009 (Kreyenbuhl et al., 2010), the TRRIP working group guidelines (Howes et al., 2017), the World Federation of Societies of Biological Psychiatry (WFSBP) (Hasan et al., 2012) as well as the Canadian guidelines for the Pharmacotherapy of Schizophrenia in Adults (Remington et al., 2017)) defined CRS as a failure to demonstrate an adequate response to the drug with clozapine plasma levels above 350 ng/ml and a duration of clozapine treatment of a minimum of 8–12 weeks after reaching therapeutic plasma levels. Details on the different definition criteria of an adequate trial of clozapine from the aforementioned guidelines could be seen in Table S6. All the guidelines suggest a minimum clozapine trial of 8 weeks with the TRRIP and Canadian guidelines suggesting a minimum of 12 weeks. The recommended dosage of clozapine differs between guidelines ranging from 100 to 900 mg/day. Finally, all of the considered guidelines recommend, if possible, to reach clozapine plasma levels of 350 ng/ml. To better quantify guidelines affinity, while at the same time providing an easy tool for standardization and quality improvement of future clinical trials we created a Guidelines Affinity Score. The low scores for studies on our GAS, and the lack of correlation between GAS and study design, augmentation strategy or geographical location suggests that the problem of poorly standardized definitions of CRS is widespread in the literature. This hinders the replicability of these studies as well as the applicability of their results.

4.2. Limitations and strengths

To our knowledge this is the only systematic analysis to date evaluating baseline data of participants with CRS and comparing CRS definitions across studies. This approach entails some limitations: although the evaluated 71 studies cover data from a relatively large population of 2731 patients, some baseline parameters were measured only in a limited amount of studies. Due to a lack of data with regard to specific symptom domain scales such as negative symptoms (e.g. SANS), we focused on overall symptom scores, such as PANSS and BPRS total scores since they were the ones most frequently used. As mentioned above only 10 out of 71 studies specified duration of clozapine treatment, thus hampering a comparison of treatment's outcomes between the included studies. Although more than 20 studies measured clozapine plasma levels among participants, only 7 studies measured those levels more than twice, meaning more than at baseline and at endpoint. Moreover, even in those studies where plasma levels were measured multiple times, the exact levels were rarely reported in the publications, and available overall data was very scarce. For future studies, we would recommend to measure clozapine levels using a double-blind procedure at least twice (e.g. beginning, when the target dose is reached) or even multiple time (also when primary outcome is reached) and to report these findings. Moreover, investigators should receive a blinded information whether optimal clozapine levels were reached during a clinical trial or not bearing in mind that several guidelines (e.g. PORT, WFSBP) recommend clozapine levels above 350 ng/ml in the case of pharmacological treatment resistance (Kreyenbuhl et al., 2010; Hasan et al., 2012). From a statistical point of view, patients with treatment resistance who did not reach the optimal serum level may be excluded in the per-protocol analyses. Such algorithms as part of the protocols of double-blind clozapine trials may help to evaluate the true efficacy of clozapine in the future.

Noteworthy, comparing studies with regard to geographical regions might help put into perspective future data and results as a potential confounder in guideline development. In this context, the exclusion of studies from mainland China reduces the applicability of the results to this country. Nevertheless, multiple publications suggest that study

quality of Chinese trials continue to be of low quality (Parry, 2017; Tong et al., 2018; Woodhead, 2016).

Of note, an individual study's adherence to guidelines is not an automatic evaluation of its validity. Nonetheless our approach aims at harmonizing evidence-based medicine approaches in psychiatry. For this reason at the core of this study is both the systematic evaluation of CRS definitions in the literature as well as the creation of a quality score to be easily referred to and implemented in future trials. Inclusion criteria recommendations (Fig. S4) could help future CRS trials standardizing inclusion criteria, hence increasing their comparability. Since obtaining high-level evidence in the treatment of CRS is hampered by different or absent definitions of CRS across publications, we hope that this manuscript could raise awareness on this problem while providing key elements to help with its solution.

4.3. Future perspective

An approach supporting clinical evidence from DSM-V with genetic and biological findings (Goldstein et al., 2015; Iwata et al., 2019) seems promising to understand underlying mechanisms and response predictors of CRS. Since schizophrenia entails different subtypes, these can show resistance to antipsychotics as early as illness onset (Demjaha et al., 2017). In the future, a strategy based on mapping the cognitive, circuit, and genetic aspects of mental disorders could yield a novel classification of diseases, providing a better frame for clinical studies and possibly better treatment targets. It could be argued that a new, more accurate, CRS definition could lead to an earlier and better treatment strategy ultimately resulting in a decreased burden that schizophrenia imposes on both economics and quality of life (Jin and Mosweu, 2017).

5. Conclusions

This systematic review and meta-analysis offers a first overview of characteristics of patients with CRS. The findings of this work have implications both for research and clinical practice. Overall, unstandardized implementations of CRS definitions in clinical studies together with notable geographical differences regarding enrolled patients make future meta-analysis of CRS more complex to evaluate while raising concerns on the interpretability of previously published works (Samara et al., 2016; Siskind et al., 2016). The systematic assessment of CRS definitions between studies with the Guidelines Affinity Score could work as a base framework for future trials. Future projects involving the evaluation of CRS patients could set the quality of their trials by referring to the results showed here. This, on one hand, could standardize the design of future clinical trials, thus enhancing the homogeneity of patients enrolled. On the other hand, results from coherent clinical trials could be translated into clinical practice more easily and effectively.

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CRediT authorship contribution statement

None other than the authors.

Declaration of competing interest

M. Campana and E. Wagner report no conflicts of interest. A. Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakerships from Desitin, Janssen-Cilag, Otsuka and Lundbeck. He was member of Roche, Otsuka, Lundbeck and Janssen-Cilag advisory boards. D. Siskind reports no conflict of interest. P. Falkai was honorary speaker for Janssen-Cilag, Astra-Zeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. Presently, he is a member of the advisory boards of Richter Pharma, Abbot and Otsuka.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.12.002.

References

Afshar, H., Roohafza, H., Mousavi, G., Golchin, S., Toghianifar, N., Sadeghi, M., Talaei, M., 2008. Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. J. Psychopharmacol. 23 (2), 157–162 (Mar).

Anghelescu, I., Szegedi, A., Schlegel, S., Weigmann, H., Hiemke, C., Wetzel, H., 1997. Combination treatment with clozapine and paroxetine in schizophrenia: safety and tolerability data from a prospective open clinical trial. Eur. Neuropsychopharmacol. 8 (4), 315–320 (Dec).

Anil Yağcioğlu, A.E., Kivircik Akdede, B.B., Turgut, T.I., et al., 2005. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. Journal of clinical psychiatry 66 (1), 63–72.

Arumugham, S.S., Thirthalli, J., Andrade, C., 2016. Efficacy and safety of combining clozapine with electrical or magnetic brain stimulation in treatment-refractory schizophrenia. Expert Rev Clin Pharmacol Sep 9 (9), 1245–1252.

Assion, H.J., Reinbold, H., Lemanski, S., Basilowski, M., Juckel, G., 2007. Amisulpride augmentation in patients with schizophrenia partially responsive or unresponsive to clozapine. A randomized, double-blind, placebo-controlled trial. Pharmacopsychiatry 41 (1), 24–28 (Jan).

Barbui, C., Accordini, S., Nose, M., et al., 2011. Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia in routine clinical care: a randomized, controlled trial. J. Clin. Psychopharmacol. 31 (3), 266–273 (Jun).

Barnes, T.R., Leeson, V.C., Paton, C., et al., 2017. Amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS): a double-blind, placebo-controlled, randomised trial of clinical effectiveness and cost-effectiveness. Health technology assessment (Winchester, England) 21 (49), 1–56.

Barretto, E.M., Kayo, M., Avrichir, B.S., et al., 2009. A preliminary controlled trial of cognitive behavioral therapy in clozapine-resistant schizophrenia. J Nerv Ment Dis Nov 197 (11), 865–868.

Behdani, F., Hebrani, P., Rezaei Ardani, A., Rafee, E., 2011. Effect of topiramate augmentation in chronic schizophrenia: a placebo-controlled trial. Arch. Iran. Med. 14 (4), 270–275 (Jul).

Bighelli, I., Leucht, C., Huhn, M., Reitmeir, C., Schwermann, F., Wallis, S., Davis, J.M., Leucht, S., 2020. Are randomized controlled trials on pharmacotherapy and psychotherapy for positive symptoms of schizophrenia comparable? A systematic review of patient and study characteristics. Schizophr Bull 46 (3), 496–504 (Apr 10).

Braga, R.J., John, M., Schooler, N.R., Bailine, S.H., Malur, C., Mendelowitz, A., Petrides, G., 2019. Continuation electroconvulsive therapy for patients with clozapine-resistant schizophrenia: a pilot study. J. ECT 35 (3), 156–160 (Sep).

Bruno, A., olfo, G., Crucitti, M., Lorusso, S., Zoccali, R.A., Muscatello, M.R., 2016. Acetyl-L-Carnitine augmentation of Clozapine in partial-responder schizophrenia: a 12-Week, open-label uncontrolled preliminary study. Clin. Neuropharmacol. 39 (6), 277–280 (Nov-Dec).

Bruno, A., Zoccali, R., Bellinghieri, P.M., olfo, G., De Fazio, P., Spina, E., Muscatello, M.R., 2014a. Reboxetine adjuvant therapy in patients with schizophrenia showing a suboptimal response to clozapine: a 12-week, open-label, pilot study. J. Clin. Psychopharmacol. 34 (5), 620–623 (Oct).

Bruno, A., Zoccali, R.A., Abenavoli, E., olfo, G., Scimeca, G., Spina, E., Muscatello, M.R., 2014b. Augmentation of clozapine with agomelatine in partial-responder schizophrenia: a 16-week, open-label, uncontrolled pilot study. J. Clin. Psychopharmacol. 34 (4), 491–494 (Aug).

Buchanan, R.W., Kirkpatrick, B., Bryant, N., Ball, P., 1996. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. The American Journal of Psychiatry 153 (12), 1625–1627.

Cardoso Buchain, P., Dias Barbosa Vizzotto, A., Henna Neto, J., Elkis, H., 2003. Randomized controlled trial of occupational therapy in patients with treatment-resistant schizophrenia. Revista Brasileira de Psiquiatria 25 (1), 26–30.

Chang, J.S., Ahn, Y.M., Park, H.J., Lee, K.Y., Kim, S.H., Kang, U.G., Kim, Y.S., 2008. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 69 (5), 720–731 (May).

Chiaie, R.D., Salviati, M., Fiorentini, S., Biondi, M., 2007. Add-on mirtazapine enhances effects on cognition in schizophrenic patients under stabilized treatment with clozapine. Exp. Clin. Psychopharmacol. 15 (6), 563–568 (December).

Correll, C.U., Rubio, J.M., Inczedy-Farkas, G., Birnbaum, M.L., Kane, J.M., Leucht, S., 2017. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. JAMA Psychiatry 74 (7), 675–684 (Jul 1).

De Lucena, D., 2011. Improvement of negative and positive symptoms in treatment-refractory schizophrenia: a double-blind, randomized, placebo-controlled trial with memantine as add-on therapy to clozapine (Journal of Clinical Psychiatry (2009) 70, 10 (1416–1423)). Journal of clinical psychiatry 72 (8), 1157.

Demjaha, A., Lappin, J.M., Stahl, D., et al., 2017. Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. Psychol Med Aug 47 (11), 1981–1989.

Diaz, P., Bhaskara, S., Dursun, S.M., Deakin, B., 2005. Double-blind, placebo-controlled, crossover trial of clozapine plus glycine in refractory schizophrenia negative results. J. Clin. Psychopharmacol. 25 (3), 277–278 (Jun).

Doruk, A., Uzun, O., Ozşahin, A., 2008. A placebo-controlled study of extract of Ginkgo biloba added to clozapine in patients with treatment-resistant schizophrenia. International clinical psychopharmacology 23 (4), 223–227.

Evins, A.E., Fitzgerald, S.M., Wine, L., Rosselli, R., Goff, D.C., 2000. Placebo-controlled trial of glycine added to clozapine in schizophrenia. Am. J. Psychiatry 157 (5), 826–828 (May).

Fleischhacker, W.W., Heikkinen, M.E., Olie, J.-P., et al., 2010. Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. International Journal of Neuropsychopharmacology 13 (8), 1115–1125.

Freudenreich, O., Henderson, D.C., Macklin, E.A., Evins, A.E., Fan, X., Cather, C., Walsh, J.P., Goff, D.C., 2009. Modafinil for clozapine-treated schizophrenia patients: a double-blind, placebo-controlled pilot trial. J. Clin. Psychiatry 70 (12), 1674–1680 (Dec).

Freudenreich, O., Henderson, D.C., Walsh, J.P., Culhane, M.A., Goff, D.C., 2007. Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial. Schizophr. Res. 92 (1), 90–94 (May).

Friedman, J., Ault, K., Powchik, P., 1997. Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. Biol. Psychiatry 42 (6), 522–523 (Sep-15).

Friedman, J.I., Lindenmayer, J.-P., Alcantara, F., et al., 2011. Pimozide augmentation of clozapine inpatients with schizophrenia and schizoaffective disorder unresponsive to clozapine monotherapy. Neuropsychopharmacology 36 (6), 1289–1295.

Genç, Y., Taner, E., Ansayar, S., 2007. Comparison of clozapine-amisulpride and clozapine-quetiapine combinations for patients with schizophrenia who are partially responsive to clozapine: a single-blind randomized study. Advances in therapy 24 (1), 1–13.

Goff, D.C., Tsai, G., Manoach, D.S., Flood, J., Darby, D.G., Coyle, J.T., 1996. D-cycloserine added to clozapine for patients with schizophrenia. Am. J. Psychiatry 153 (12), 1628–1630 (Dec).

Goff, D.C., Leahy, L., Berman, I., Posever, T., Herz, L., Leon, A.C., Johnson, S.A., Lynch, G., 2001. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. J. Clin. Psychopharmacol. 21 (5), 484–487 (Oct).

Goldstein, M.E., Anderson, V.M., Pillai, A., Kydd, R.R., Russell, B.R., 2015. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. Int J Neuropsychopharmacol 18 (6) (Jan 20).

de Groot, I.W., Heck, A.H., van Harten, P.N., 2001. Addition of risperidone to clozapine therapy in chronically psychotic inpatients. The Journal of Clinical Psychiatry 62 (2), 129–130.

Gunduz-Bruce, H., Oliver, S., Gueorguieva, R., et al., 2012. Efficacy of pimozide augmentation for clozapine partial responders with schizophrenia. Schizophr. Res. 143 (2), 344–347 (Feb).

Hahn, M.K., Remington, G., Bois, D., Cohn, T., 2010. Topiramate augmentation in clozapine-treated patients with schizophrenia: clinical and metabolic effects. J. Clin. Psychopharmacol. 30 (6), 706–710 (Dec).

Hasan, A., Falkai, P., Wobrock, T., et al., 2012. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry Jul 13 (5), 318–378.

Heck, A.H., de Groot, I.W., van Harten, P.N., 2005. Addition of lamotrigine to clozapine in inpatients with chronic psychosis. J. Clin. Psychiatry 66 (10), 1333 (Oct).

Henderson, D.C., Goff, D.C., 1996. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. J. Clin. Psychiatry 57 (9), 395–397 (Sep).

Henderson, D.C., Kunkel, L., Nguyen, D.D., et al., 2006. An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. Acta Psychiatr. Scand. 113 (2), 142–147 (Feb).

Higgins, J.P., Altman, D.G., Gotzsche, P.C., et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928 (Oct 18).

Honer, W.G., Thornton, A.E., Chen, E.Y., et al., 2006. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. New England journal of medicine 354 (5), 472–482.

Howes, O.D., McCutcheon, R., Agid, O., et al., 2017. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. Am J Psychiatry 174 (3), 216–229 (Mar 1).

Iwata, Y., Nakajima, S., Plitman, E., et al., 2019. Glutamatergic neurometabolite levels in patients with ultra-treatment-resistant schizophrenia: a cross-sectional 3T proton magnetic resonance spectroscopy study. Biol Psychiatry 85 (7), 596–605 (Apr 1).

de Jesus DR, Gil A, Barbosa L, et al. A pilot double-blind sham-controlled trial of repetitive transcranial magnetic stimulation for patients with refractory schizophrenia treated with clozapine. Psychiatry Res 2011;188(2):203–207 (Jul 30).

Jin, H., Mosweu, I., 2017. The societal cost of schizophrenia: a systematic review. Pharmacoeconomics Jan 35 (1), 25–42.

Josiassen, R.C., Joseph, A., Kohegyi, E., Stokes, S., Dadv, M., Paing, W.W., Shaughnessy, R.A., 2005. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Am. J. Psychiatry 162 (1), 130–136 (Jan).

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kelly, D.L., Sullivan, K.M., McEvoy, J.P., et al., 2015. Adjunctive minocycline in clozapine-treated schizophrenia patients with persistent symptoms. Journal of clinical psychopharmacology 35 (4), 374–381.

Kho, K.H., Blansjaar, B.A., De Vries, S., Babuskova, D., Zwinderman, A.H., Linszen, D.H., 2004. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia: an open label study. Eur. Arch. Psychiatry Clin. Neurosci. 254 (6), 372–379 (December).

Koen, L., Niehaus, D.J., Schulte, A., Muller, J., Emsley, R., Oosthulzen, P., 2006. Amisulpride as adjunct to clozapine in treatment-resistant schizophrenia and schizoaffective disorder: an open-label pilot study. S. Afr. J. Psychiatry 12 (1), 17–20 (March).

Kreyenbuhl, J., Buchanan, R.W., Dickerson, F.B., Dixon, L.B., Schizophrenia Patient Outcomes Research T, 2010. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull Jan 36 (1), 94–103.

Lally, J., Tully, J., Robertson, D., Stubbs, B., Gaughran, F., MacCabe, J.H., 2016. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. Schizophr Res Mar 171 (1–3), 215–224.

Lane, H.-Y., Huang, C.-L., Wu, P.-L., Liu, Y.-C., Chang, Y.-C., Lin, P.-Y., Chen, P.-W., Tsai, G., 2006. Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to clozapine for the treatment of schizophrenia. Biological Psychiatry 60 (6), 645–649.

Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean? Schizophr Res 79 (2–3), 231–238 (Nov 15).

Leucht, S., Rothe, P., Davis, J.M., Engel, R.R., 2013. Equipercentile linking of the BPRS and the PANSS. Eur Neuropsychopharmacol Aug 23 (8), 956–959.

Lin, C.H., Lin, C.H., Chang, Y.C., Huang, Y.J., Chen, P.W., Yang, H.T., Lane, H.Y., 2017. Sodium benzoate, a D-amino acid oxidase inhibitor, added to clozapine for the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Biol. Psychiatry 84 (6), 422–432 (Sep-15).

Lu, M.-L., Chen, T.-T., Kuo, P.-H., Hsu, C.-C., Chen, C.-H., 2018. Effects of adjunctive fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia: a 12-week, randomized, double-blind, placebo-controlled study. Schizophrenia Research 193, 126–133.

Melzer-Ribeiro, D.L., Rigonatti, S.P., Kayo, M., Avrichir, B.S., Ribeiro, R.B., Dos Santos, B., Fortes, M., Elkis, H., 2017. Efficacy of electroconvulsive therapy augmentation for partial response to clozapine: a pilot randomized ECT – sham controlled trial. Revista de psiquiatria clinica 44 (2), 45–50.

Mico, U., Bruno, A., Pandolfo, G., et al., 2011. Duloxetine as adjunctive treatment to clozapine in patients with schizophrenia: a randomized, placebo-controlled trial. International Clinical Psychopharmacology 26 (6), 303–310.

Mitsonis, C.I., Dimopoulos, N.P., Mitropoulos, P.A., Kararizou, E.G., Katsa, A.N., Tsakiris, F.E., Katsanou, M.N., 2007. Aripiprazole augmentation in the management of residual symptoms in clozapine-treated outpatients with chronic schizophrenia: an open-label pilot study. Prog. Neuropsychopharmacol. Biol. Psychiatry 31 (2), 373–377 (Mar-30).

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of clinical epidemiology Oct 62 (10), 1006–1012.

Morrato, E.H., Dodd, S., Oderda, G., Haxby, D.G., Allen, R., Valuck, R.J., 2007. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998–2003. Clin Ther Jan 29 (1), 183–195.

Morrison, A.P., Pyle, M., Gumley, A., et al., 2018. Cognitive behavioural therapy in clozapine-resistant schizophrenia (FOCUS): an assessor-blinded, randomised controlled trial. Lancet Psychiatry Aug 5 (8), 633–643.

Mouaffak, F., Tranulis, C., Gourevitch, R., Poirier, M.F., Douki, S., Olie, J.P., Loo, H., Gourion, D., 2006. Augmentation strategies of clozapine with antipsychotics in the treatment of ultraresistant schizophrenia. Clin Neuropharmacol Jan-Feb 29 (1), 28–33.

Munro, J., Matthiasson, P., Osborne, S., et al., 2004. Amisulpride augmentation of clozapine: an open non-randomized study in patients with schizophrenia partially responsive to clozapine. Acta Psychiatr. Scand. 110 (4), 292–298 (Oct).

Muscatello, M., Bruno, A., olfo, G., et al., 2010. Topiramate augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. J. Psychopharmacol. 25 (5), 667–674 (May).

Muscatello, M.R.A., Bruno, A., Pandolfo, G., et al., 2011. Effect of aripiprazole augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. Schizophrenia Research 127 (1), 93–99.

Muscatello, M.R., Pandolfo, G., Micò, U., et al., 2014. Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study. Journal of clinical psychopharmacology 34 (1), 129–133.

Nielsen, J., Emborg, C., Gydesen, S., et al., 2012. Augmenting clozapine with sertindole: a double-blind, randomized, placebo-controlled study. J. Clin. Psychopharmacol. 32 (2), 173–178 (Apr).

Overall, J.E., Gorham, D.R., 1962. The Brief Psychiatric Rating Scale. Psychol. Rep. 10 (3), 799–812.

Parry, J., 2017. China vows to clamp down on academic fraud amid medical journal scandal. BMJ 357, j2970 (Jun 19).

Petrides, G., Malur, C., Braga, R.J., et al., 2015. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. American journal of psychiatry 172 (1), 52–58.

Pinto, A., La Pia, S., Mennella, R., Giorgio, D., DeSimone, L., 1999. Cognitive-behavioral therapy and clozapine for clients with treatment-refractory schizophrenia. Psychiatr Serv Jul 50 (7), 901–904.

Potkin, S.G., Jin, Y., Bunney, B.G., Costa, J., Gulasekaram, B., 1999. Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia. Am. J. Psychiatry 156 (1), 145–147 (Jan).

Remington, G., Addington, D., Honer, W., Ismail, Z., Raedler, T., Teehan, M., 2017. Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry Sep 62 (9), 604–616.

Repo-Tiihonen, E., Hallikainen, T., Kivisto, P., Tiihonen, J., 2012. Antipsychotic polypharmacy in clozapine resistant schizophrenia: a randomized controlled trial of tapering antipsychotic co-treatment. Ment Illn 4 (1), e1 (Jul-26).

Rosa, M.O., Gattaz, W.F., Rosa, M.A., et al., 2007. Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. J Clin Psychiatry Oct 68 (10), 1528–1532.

Samara, M.T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G., Leucht, S., 2016. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. JAMA Psychiatry Mar 73 (3), 199–210.

Shiloh, R., Zemishlany, Z., Aizenberg, D., Weizman, A., 1997. Sulpiride adjunction to clozapine in treatment-resistant schizophrenic patients: a preliminary case series study. Eur Psychiatry 12 (3), 152–155.
Shiloh, R., Zemishlany, Z., Aizenberg, D., et al., 1996. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. Br. J. Psychiatry 171, 569–573 (Dec).
Siskind, D., McCartney, L., Goldschlager, R., Kisely, S., 2016. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry Nov 209 (5), 385–392.
Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can J Psychiatry Nov 62 (11), 772–777.
Stryjer, R., Strous, R., Bar, F., et al., 2004. Donepezil augmentation of clozapine monotherapy in schizophrenia patients: a double blind cross-over study. Human psychopharmacology 19 (5), 343–346.
Tang, W.K., Ungvari, G.S., 2002. Efficacy of electroconvulsive therapy combined with antipsychotic medication in treatment-resistant schizophrenia: a prospective, open trial. Journal of ECT 18 (2), 90–94.
Taylor, C.G., Flynn, S.W., Altman, S., Ehmann, T., MacEwan, G.W., Honer, W.G., 2001. An open trial of risperidone augmentation of partial response to clozapine. Schizophr. Res. 48 (1), 155–158 (Mar-1).
Tiihonen, J., Hallikainen, T., Ryynänen, O.-P., et al., 2003. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. Biological Psychiatry 54 (11), 1241–1248.
Tong, Z., Li, F., Ogawa, Y., Watanabe, N., Furukawa, T.A., 2018. Quality of randomized controlled trials of new generation antidepressants and antipsychotics identified in the China National Knowledge Infrastructure (CNKI): a literature and telephone interview study. BMC Med Res Methodol 18 (1), 96 (Sep 24).
Tsai, G.E., Yang, P., Chung, L.C., Tsai, I.C., Tsai, C.W., Coyle, J.T., 1999. D-serine added to clozapine for the treatment of schizophrenia. Am. J. Psychiatry 156 (11), 1822–1825 (Nov).
Vayisoglu, S., Anil Yagcioglu, A.E., Yagcioglu, S., Karahan, S., Karci, O., Gurel, S.C., Yazici, M.K., 2012. Lamotrigine augmentation in patients with schizophrenia who show partial response to clozapine treatment. Schizophr. Res. 143 (1), 207–214 (Jan).
Veerman, S.R.T., Schulte, P.F.J., Smith, J.D., de Haan, L., 2016. Memantine augmentation in clozapine-refractory schizophrenia: a randomized, double-blind, placebo-controlled crossover study. Psychological Medicine 46 (9), 1909–1921.
Wagner, E., Lohrs, L., Siskind, D., Honer, W.G., Falkai, P., Hasan, A., 2019. Clozapine augmentation strategies - a systematic meta-review of available evidence. Treatment options for clozapine resistance. J Psychopharmacol Apr 33 (4), 423–435.
Wang, G., Zheng, W., Li, X.B., et al., 2018. ECT augmentation of clozapine for clozapine-resistant schizophrenia: a meta-analysis of randomized controlled trials. J Psychiatr Res Oct 105, 23–32.
Weiner, E., Conley, R.R., Ball, M.P., et al., 2010. Adjunctive risperidone for partially responsive people with schizophrenia treated with clozapine. Neuropsychopharmacology 35 (11), 2274–2283 (October).
Woodhead, M., 2016. 80% of China's clinical trial data are fraudulent, investigation finds. BMJ 355, i5396 (Oct 5).
Ziegenbein, M., Sieberer, M., Kuenzel, H.E., Kropp, S., 2006a. Augmentation of Clozapine with amisulpride in patients with treatment-resistant schizophrenia an open clinical study. German Journal of Psychiatry 9 (1), 17–22.
Ziegenbein, M., Wittmann, G., Kropp, S., 2006b. Aripiprazole augmentation of clozapine in treatment-resistant schizophrenia: a clinical observation. Clin Drug Investig 26 (3), 117–124.
Ziegenbein, M., Kropp, S., Kuenzel, H.E., 2005. Combination of clozapine and ziprasidone in treatment-resistant schizophrenia: an open clinical study. Clin. Neuropharmacol. 28 (5), 220–224 (Sep-Oct).
Zink, M., Kuwilsky, A., Krumm, B., Dressing, H., 2009. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. J. Psychopharmacol. 23 (3), 305–314 (May).
Zoccali, R., Muscatello, M.R., Cedro, C., Neri, P., La Torre, D., Spina, E., Di Rosa, A.E., Meduri, M., 2003. The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: a double-blind, placebo-controlled study. Int. Clin. Psychopharmacol. 19 (2), 71–76 (Mar).
Zoccali, R., Muscatello, M.R., Bruno, A., Cambria, R., Micò, U., Spina, E., Meduri, M., 2007. The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. Schizophrenia Research 93 (1), 109–116.

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