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Clozapine in bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Objectives: To assess the clinical efficacy of clozapine in bipolar disorder and its adverse effect profile.
Methods: A literature search with no year and no language restriction was conducted. The search yielded 3858 articles, with 2453 remaining after duplicate removal; 9 were suitable for the systematic review. From the 9 included studies, 3 (100 patients treated with clozapine and 102 patients treated with other antipsychotics) could be included in a meta-analysis to test clozapine efficacy in the treatment of manic episodes.
Results: Clozapine's efficacy was similar to other antipsychotics (Mean difference (MD): 0.03 [95%CI: 0.86-0.92], p = 0.59) in manic episodes. The systematic review also suggested that clozapine is faster at improving symptoms in manic episodes. In addition, two studies included patients with treatment resistant bipolar disorder (TRBD) and showed that clozapine is superior to other treatments for this specific population. Sedation was the most frequent side effect (49.6%), followed by constipation (31.8%) and tachycardia (23.2%).
Conclusion: Clozapine's efficacy was similar to other antipsychotics in manic episodes and is superior to other antipsychotics among TRBD patients.

1. Introduction

Bipolar disorder (BD) is a chronic psychiatric disease with a lifetime prevalence ranging from 0.6% to 2.4% (Grande et al., 2016; Merikangas et al., 2011). Despite the multiple available treatments for BD, around 37% and 60% of patients relapse within 1 and 2 years after recovering from an episode, respectively (Gitlin et al., 1995). Given the high prevalence of incomplete responses to treatment, and the progressive nature of the disorder (Gildengers et al., 2013), new treatments, especially for the non-responders, are needed.

Clozapine was the first produced atypical antipsychotic and its superior efficacy is widely recognized (Crilly, 2007). Its unique receptor interaction profile may explain the superior efficacy but also the most side effects burden among atypical antipsychotics[6]. Although rare, side effects profile could be life-threatening, namely agranulocytosis, myocarditis, venous thromboembolism and seizures (Nucifora et al., 2017). The side-effect profile partly explain why clozapine is not frequently used to treat BD. Of note, adverse effects of clozapine are similar to the side effects of other atypical antipsychotics, namely metabolic syndrome, such as weight gain and diabetes (Iqbal et al., 2003).

Clozapine is the gold standard treatment for treatment resistant schizophrenia (25–30% of schizophrenia patients display no response or partial response to two antipsychotic medication trials at an adequate dose and duration) (Kane, 1996) showing superiority in treating positive and negative symptoms and also at improving cognition, global functioning and quality of life (Meltzer, 2012). Numerous studies showed that clozapine decreases all measures of suicidality being the only FDA-approved medication to prevent suicide behaviours in schizophrenia and schizoaffective disorder (Kang and Simpson, 2010; Meltzer, 2003). In addition, clozapine has been shown to decrease aggressive behaviour (Glazer and Dickson, 1998). Finally, evidence retrieved from meta-analyses, showed that clozapine is the most efficacious treatment for schizophrenia among all available antipsychotics (Leucht et al., 2013; Siskind et al., 2016).

Although atypical antipsychotics have been frequently used in the last decade for the treatment of patients with BD , clozapine remains largely underutilized (Yatham et al., 2018). In 2018 Canadian Network for Mood and Anxiety treatments (CANMAT) (Yatham et al., 2018),

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clozapine is considered a third line treatment for mania and as a potential adjuvant in maintenance treatments (Yatham et al., 2018). However, evidence shows that clozapine is efficacious and well tolerated in severe mood disorders (Frye et al., 1998), and reduces mood related symptoms and rehospitalization rates among these patients (Calabrese et al., 1996; Chang et al., 2006; McElroy et al., 1991; Suppes et al., 1992).

A recent systematic review (Li et al., 2015) showed that clozapine monotherapy or clozapine combined with other treatments were associated with improvement in mood and psychotic symptoms among treatment resistant bipolar disorder (TRBD). Of note, many patients with TRBD achieved remission (Li et al., 2015). However, the existing systematic review included only TRBD patients and because of the heterogeneity among the studies included, authors could not perform a meta-analysis (Li et al., 2015). To the best of our knowledge, there are no meta-analysis assessing the efficacy of clozapine in the treatment of BD.

Therefore, the aim of our study is to perform a systematic review and meta-analysis assessing the clinical efficacy of clozapine in patients with BD.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed for the present review.

2.1. Search strategy

A literature search with no year and no language restriction was conducted on August 26, 2019, using the following databases: Pubmed, PsycInfo, Scopus, Embase, and Cochrane Central. We searched for a combination of the following search items (bipolar disorder OR bipolar disorders OR bipolar depression OR mania OR hypomania OR manic OR hypomanic OR manic-depressive disorder OR manic depressive disorder OR bipolar affective disorder OR mixed) AND (clozapine). The search yielded 3858 articles: (Pubmed = 747, PsycInfo = 601, Scopus = 2027, Embase = 397, Cochrane Central = 86).

To determine whether an article was relevant to our study, we used the following inclusion criteria: the study should (1) present original data, (2) assess the effect of clozapine on bipolar disorder, and (3) compared the effect of clozapine with another intervention. The authors did not add any restrictions related to bipolar disorder subtype, age or therapy. The exclusion criteria were: (1) reviews and meta-analyses, and (2) case reports.

The studies were selected by two blinded reviewers (AD and JV) who determined if studies met inclusion criteria. Manuscripts were assessed independently by the two raters and divergences were resolved by consensus in a meeting with another researcher (TC). Firstly, the raters screened articles by title and abstract, and after by full-text. Duplicates, review articles, and articles not fulfilling the search criteria were removed. The details of the search strategy are depicted in Fig. 1.

2.2. Data extraction

Three researchers (AD, JV and JZ) were involved in the data extraction process. We extracted the following data: authorship, year of publication, country of the study, aim of the study, study design, assessments, and main results.

2.3. Quality assessment

The grading of recommendations assessment, development, and evaluation (GRADE) system was used to rate the quality of studies of this systematic review in line with the Cochrane Collaboration guidelines. The overall quality of the studies was qualified as very low, low, moderate, or high.

2.4. Statistical analysis

We conducted a meta-analysis to assess the differences in the clinical efficacy between clozapine and other interventions in the treatment of BD. We included in the meta-analysis only studies comparing the efficacy of clozapine with other intervention for manic symptoms. For this purpose, the reported means, sample sizes, and standard deviation were used to compute the mean difference in the clinical symptoms at post-intervention. For all the studies included, the authors described no differences regarding the severity of symptoms between groups at baseline. Significance was set as $p < 0.05$. Cochrane's Q test was performed to assess for statistical heterogeneity and the Higgins I2 statistic was used to determine the extent of variation between sample estimates with values ranging from 0 to 100%. If the information was not reported in the paper, we contacted the authors asking for additional information in order to include the paper in the meta-analysis. We contacted two authors, and only one of them answered our question but did not have the data needed for the meta-analysis.

3. Results

The literature search yielded 3858 studies. Of these, 1405 were duplicates, 2438 studies were excluded as the titles and abstracts were not relevant to the research topic, leaving 15 potentially eligible studies for which the full text was reviewed. After this stage, 6 studies did not meet the inclusion criteria. A total of 9 studies met all criteria to be included in the systematic review (Fig. 1). In addition, we hand-searched the references of the included studies and found no additional studies to include. From the 9 included studies, 3 were included in the meta-analysis testing whether clozapine is an efficacious treatment for manic episodes.

3.1. Clozapine treatment in bipolar disorder

3.1.1. Characteristics of included studies

Table 1 shows an overview of the included studies. Among the 9 studies, publication dates ranged from 1997 to 2017. Four studies were conducted in China, 2 in USA, 1 in Italy, 1 in India, 1 in Finland, and 1 in Romania. The total sample size ranged from 27 to 80 patients. All studies assessed the efficacy of clozapine in BD patients. Five studies were open label randomized studies, 1 was an open label naturalistic control trial, 1 was a double-blinded randomized study, 1 a cohort study and 1 a case-control study. For these studies, the time of follow-up assessments ranged from 3 weeks to 2 years. Regarding the outcomes, the majority of the studies used the Bech-Rafaelsen Mania Scale (BRMS) (n = 5).

3.1.2. Clozapine as a treatment for bipolar disorder: efficacy in manic episodes

The systematic review included five clinical trials. All of them assessed the efficacy of clozapine in a manic episode. Barbini et al. (1997) included 30 bipolar patients admitted with a manic episode who have been treated with lithium in the previous six months. These patients were assigned for two treatment groups (clozapine or chlorpromazine) and were followed for 3 weeks. Twenty-seven patients (clozapine n = 15; chlorpromazine n = 12) reached the end point showing that clozapine group had faster improvements in Young Mania Rating Scale (YMRS) than chlorpromazine group. However, there were no significant differences between those groups at the end of the study. Relative to the incidence of side effects, this study showed that hypersialorrhea and white blood cells decrease were higher in the clozapine group. Sedation, hypotension and extrapyramidal side-effects were higher in the chlorpromazine group. Moreover, Liu et al. (2001) in his open label, randomized controlled trial compared the efficacy and side effect profile of clozapine or risperidone both as adjunctive treatment to lithium in the treatment of acute mania. They followed the

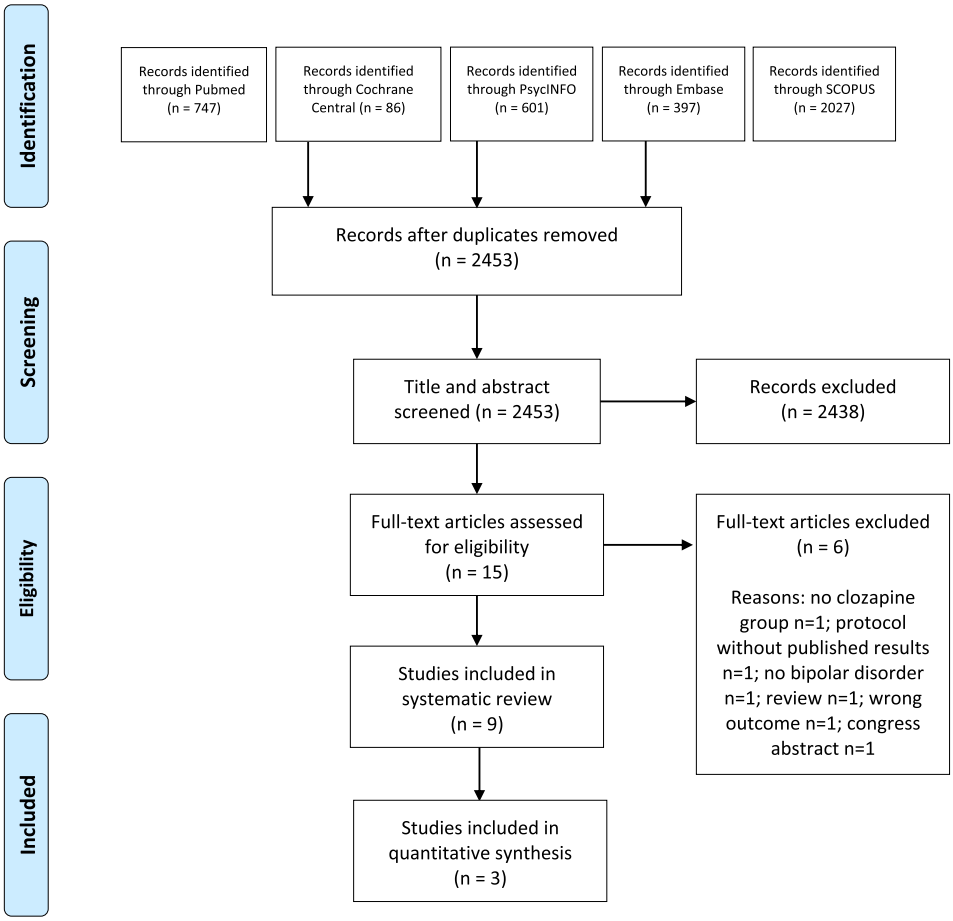

Fig. 1. Flow diagram showing the search, article selection and extraction process.

patients for 8 weeks, assessing the Bech-Rafaelsen Mania Scale (BRMS) and the Treatment emergent symptom scale (TESS) at week 1, 2, 4 and 8. Firstly, they found that clozapine is significantly better on improving the BRMS score at first week, with 55.6% of the patients meeting the response criteria (vs 28.1% in the risperidone group). They also found that both groups improved significantly at endpoint, with no statistically difference between the two groups. The group receiving risperidone had significantly less side-effects than the clozapine group. Furthermore, Wei et al. (2002) conducted a double-blinded randomized controlled trial comparing olanzapine (n = 40) and clozapine (n = 40) effectiveness and side effects in manic patients during 4 weeks. In this study, they showed that olanzapine and clozapine are both equally effective in the treatment of acute mania. On the other hand, clozapine had a higher burden of side effects when compared with olanzapine (21 patients vs 8 patients respectively). Moreover, Ying et al. (2007) in a non-blinded randomized trial dividing patients with BD in two groups – patients taking lithium and quetiapine, and patients taking lithium and clozapine – tested the efficacy of those treatments in 6 weeks of follow-up. The results showed that clozapine is faster on improving clinical symptoms but at the endpoint there are no significant differences between the two treatments and quetiapine has less side-effects leading to a better compliance. Finally, Tang et al. (2011) in a randomized controlled trial evaluated 64 female patients having a manic episode and divided them into two different groups. The first took quetiapine and lithium (n = 32) and the second clozapine and lithium (n = 32). During the 6 weeks of follow-up, greater decreases in BRMS were seen between baseline and week two, as well as between week four and six in both groups. However, no significant differences were found in the time to remission. At the endpoint 87.5% in the quetiapine group and 90.0% in the clozapine group reached the remission criteria (50% drop in BRMS score from baseline). Besides clozapine group had more side-effects, no significant difference was found at the endpoint. The authors concluded that in female patients taking lithium, clinical improvements are equivalent either adding quetiapine or clozapine to the treatment.

3.1.3. Clozapine as a treatment for bipolar disorder: efficacy in treatment resistant patients

The systematic review included two clinical trials. Both assessed the efficacy of clozapine in TRBD patients. Suppes et al. (1999) included 38 patients (26 bipolar disorder and 12 schizoaffective disorder patients) with history of treatment resistance bipolar disorder (TRBD) in this randomized, non-blinded, trial. In this study, clozapine was superior than the treatment as usual in all outcome measures except for the Hamilton Rating Scale for Depression (HRSD) where there were no significant differences between groups. In the treatment as usual group (TAU), 9 patients had to be removed due to partial or absence improvements or intolerable side effects. In a secondary analysis, all of these patients significantly improved in the BPRS scores (> 30% improvement from baseline) when clozapine was introduced. Also, after one year of follow-up, total medication in the clozapine group showed a significant decrease when compared to TAU. Finally, they did not find differences in somatic complaints between the two groups. Furthermore, Kumar et al. (2015) included 40 bipolar disorder patients in a current episode of mania with psychotic symptoms. Twenty of them had history of treatment resistance and started clozapine in the current episode. The control group (no history of treatment resistance, n = 20) started lithium plus an antipsychotic (14 olanzapine, 4 risperidone, 2 haloperidol). They performed baseline and post-treatment assessments at 6–7 weeks with The Brief Psychiatric Rating Scale (BPRS) and YMRS. They found that, although the clozapine group had more episodes and

Table 1
Characteristics of the studies included assessing the clinical efficacy of clozapine in bipolar disorder.

Author, Year, Country	Study Design	Population	Follow-up	Comparator	Assessments	Quality	Main findings
Clozapine efficacy in manic episode							
Barbini et al., 1997, Italy	Open label randomized control trial	Inpatients with a manic episode	3 weeks	Chlorpromazine	DSM-IV; YMRS; DOTES; SARS	Moderate	Clozapine was faster in improving clinical symptoms. Both equally effective.
Liu et al., 2001, China	Open label randomized control trial	Inpatients with a manic episode	8 weeks	Risperidone	CCMD-2-R; BRMS; TESS	Moderate	Both equally effective. Clozapine was faster in improving clinical symptoms. Clozapine had more side effects.
Wei et al., 2002, China	Double blinded randomized control trial	Inpatients with a manic episode	4 weeks	Olanzapine	CCMD-3; BRMS; TESS; GAS; CGI	High	Both treatments showed similar efficacy. Clozapine had more side effects. Clozapine: BRMS base: 28.6 ± 4.2; final: 8.4 ± 3.3 Olanzapine: BRMS base: 29.8 ± 5.1; final: 7.8 ± 3.6
Ying et al., 2007, China	Open label randomized control trial	Inpatients with a manic episode	6 weeks	Quetiapine	CCMD-3; BRMS; TESS	Moderate	Both equally effective. Clozapine was faster in improving clinical symptoms. Clozapine had more side effects. Clozapine: BRMS base: 29.7 ± 8.1; final: 3.1 ± 2.6 Quetiapine: BRMS base: 28.8 ± 8.7; final: 3.2 ± 2.5
Tang et al., 2011, China	Open label randomized control trial	Female inpatients with a manic episode	6 weeks	Quetiapine	ICD-10; BRMS; TESS	Moderate	Both treatments showed similar efficacy. Overall severity of adverse effects was similar. Clozapine: BRMS base: 26.4 ± 4.5; final: 7.6 ± 3.9 Quetiapine: BRMS base: 27.8 ± 4.9; final: 8.3 ± 4.4
Clozapine efficacy in TRBD patients							
Suppes et al., 1999, USA	Open label randomized control trial	TR schizoaffective disorder and BD type I	1 year	TAU	DSM–III–R; DSM-IV; BPRS; BRMS; CGI; HRSD; SAPS; SANS; AIMS	Moderate	Clozapine significantly improves all measures except HRSD when compared with the control group
Kumar et al., 2015, India	Open label naturalistic control trial	Inpatients with psychotic manic episode (TR vs NTR)	6–7 weeks	Lithium + Other antipsychotics	ICD-10; BPRS; YMRS	Low	Both groups equally improved at the endpoint. Clozapine: YMRS base: 27.15 ± 5.26; final: 3.40 ± 7.44 Other: YMRS base: 28.90 ± 7.48; final: 3.25 ± 6.43
Clozapine efficacy in observational studies							
Guille et al., 2000, USA	Case-control study	All BD type I treated	12 weeks	Risperidone Olanzapine	DSM-IV; CGI	Very Low	All are equally effective. No differences between groups for side-effects (except weight gain) Clozapine: CGI base: 4.6 ± 0.5; final: 3.4 ± 0.5 Risperidone: CGI base: 4.1 ± 0.7; final: 2.8 ± 0.9 Olanzapine: CGI base: 3.9 ± 0.9; final: 2.9 ± 0.6
Ifteni et al., 2017, Romania	Naturalistic mirror-image Cohort study	Remitted BD patients after a severe manic episode	2 years	Other antipsychotics	YMRS; CGI-BP; MADRS	Very Low	Switching from clozapine to another antipsychotic may increase the risk of relapse.

DSM, diagnostic statistic manual of mental disorders criteria; YMRS, Young mania rating scale for mania; DOTES, dosage records and treatment emergent symptoms; SARS, Simpson-Angus Rating Scale; TR, treatment resistant: BD, bipolar disorder; TAU, Treatment as usual; BPRS, The Brief Psychiatric Rating Scale; BRMS, Bech-Rafaelsen Mania Scale; CGI, Clinical global impression; HRSD, Hamilton Rating Scale for Depression; SAPS, Scale for the Assessment of Positive symptoms; SANS, Scale for the Assessment of Negative symptoms; AIMS, Abnormal Involuntary Movement Scale; CCMD, Chinese Mental Disorders Classification and Diagnostic Criteria; TESS, Treatment emergent symptom scale; GAS, The Global Assessment Scale; ICD, international statistical classification of diseases and related health problems criteria; NTR, non-treatment resistant; CGI-BP, Clinical global impression for bipolar disorder; MADRS, Montgomery–Åsberg Depression Rating Scale.

more hospitalizations, the BPRS and YMRS significantly improved in both groups when compared to baseline. At the endpoint no significant differences between the two treatment groups were found.

3.1.4. Clozapine as a treatment for bipolar disorder: evidence from observational studies

The systematic review included two observational studies. Both assessed the efficacy of clozapine in BD patients. Guille et al. (2000) in a retrospective study, identified patients with bipolar disorder type I (n = 50) that received at least one dose of clozapine in absence of other antipsychotic medication (n = 5). Then, they compared the clozapine group with another group of BD type I patients receiving either risperidone (n = 25) or olanzapine (n = 20). At the endpoint no differences were found on Clinical Global Impression (CGI) between the three antipsychotics. In the other outcomes, three adverse effects were registered at the clozapine group (1 seizure, 1 parkinsonism, 1 akathisia) in contrast with the risperidone group (eight cases: 1 sedation, 1 acute dystonia, 4 parkinsonism, 2 akathisia) and olanzapine group (five cases: 1 sedation, 3 akathisia, 1 parkinsonism). Higher weight gain was observed in the olanzapine and clozapine group. Also, Ifteni et al. (2017) included 62 asymptomatic bipolar patients treated with clozapine. Of these, 25 switched to another antipsychotic and 37 continued on clozapine. In the switched group, 21 patients had a relapse against 8 in clozapine group, taking the authors to conclude that switching from clozapine to another antipsychotic may augment the risk of relapse.

3.1.5. Clozapine in bipolar disorder: results from the meta-analysis

We included 3 out the 9 studies described above in our meta-analysis. The 3 studies included 100 patients treated with clozapine, and 102 patients treated with other antipsychotics. Our results showed that clozapine treatment is similar to other antipsychotics to the treatment of manic episodes (Mean difference (MD): 0.03 [95%CI: 0.86-0.92], p = 0.59) (Fig. 2).

3.1.6. Clozapine adverse effects: results from the included studies

Clozapine adverse effects are described in Table 2. Sedation was the most frequent side effect (49.6%), followed by constipation (31.8%) and tachycardia (23.2%). Considering the most severe side effects, like white blood cells (WBC) decrease and seizures only 5.3% and 2% were found respectively. The side effect profile of the other antipsychotics are also described in Table 2.

3.2. Quality of assessment of the included studies

We identified one high quality study, five moderate quality studies, one low quality study and two very low studies (Supplementary Table 1). The moderate quality studies lacked blinding and the low and very low studies had methodological issues such as inadequate control of confoundings and differences between the populations.

4. Discussion

To the best of our knowledge this is the first meta-analysis assessing the effect of clozapine in manic episodes . Our results showed that clozapine was similar to other antipsychotics on improving clinical symptoms in manic episodes. Of note, in the systematic review, three studies found that clozapine is faster on improving manic symptoms although no differences were found at endpoint (Barbini et al., 1997; Liu et al., 2001; Ying et al., 2007). Also, in the studies evaluating treatment resistant patients, clozapine was superior in improving clinical symptoms (Kumar et al., 2015; Suppes et al., 1999). Finally, among observational studies, one study found that in remitted BD patients that switched clozapine to other antipsychotics were placed at increased risk of relapse (Ifteni et al., 2017), another study showed that clozapine is equally effective to risperidone and olanzapine in treating bipolar symptoms (Guille et al., 2000).

We also found that clozapine is relatively safe and well tolerated but some adverse effects were frequently described such as sedation, constipation and tachycardia. The existing literature describes severe adverse effects such as agranulocytosis, myocarditis, venous thromboembolism and seizures (Iqbal et al., 2003). Of note, only one study described a case of seizures (Guille et al., 2000). One study also described eight cases of white blood cells decrease, without reaching levels that would require discontinuation of treatment (Barbini et al., 1997).

Although our meta-analysis showed that clozapine had similar clinical efficacy compared to other antipsychotics, it can be argued that the time needed to reach effective dosage, its side effects profile and the need for regular blood assessments are important limitations to be considered. Conversely, besides its slow standard titration, three studies showed that clozapine is faster than other antipsychotics improving manic symptoms (Barbini et al., 1997; Liu et al., 2001; Ying et al., 2007). In our opinion, and based on our meta-analysis results, the combined efficacy, tolerability and safety profile does not recommend clozapine as a first choice treatment for acute manic episodes, which is in line with the CANMAT guidelines (Yatham et al., 2018).

Of note, the literature supports clozapine efficacy in treatment resistant schizophrenia (Kane, 1996; Leucht et al., 2013; Meltzer, 2012; Siskind et al., 2016). In this same vein, clozapine seems to be effective in patients with TRBD (Li et al., 2015). Moreover, patients with BD treated with clozapine showed long-term improvements in symptoms, functioning and quality of life (Li et al., 2015). The use of clozapine in TRBD deserves further investigation, since only two studies included in our systematic review assessed the clozapine use in this specific group of patients (39 patients with TRBD). In a pioneer study conducted by Suppes et al., (1999), patients treated with clozapine showed significant improvements in many clinical outcomes, apart from depressive symptoms. Importantly, in the group using clozapine, the overall number of medications used was reduced, and the medical burden was decreased. In addition, Kumar et al. (2015) showed that TRBD patients treated with clozapine had similar improvements when compared to the non-treatment resistant group which highlights the potential use of clozapine as a first choice in this group. These data are in line with the Li et al. systematic review that showed promising results when clozapine is used in treatment resistant patients with BD (Li et al., 2015).

Our findings should be interpreted in the light of some limitations. Firstly, small trials and/or trials with negative results are often not published and that can increase the risk of publication bias. Secondly,

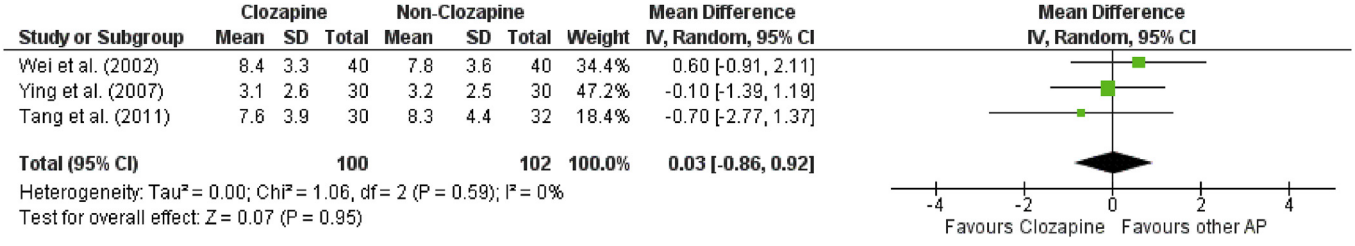

Fig. 2. Forest plot of the meta-analysis.

Table 2
Antipsychotics side effect profiles.

Side Effects	Clozapine NTotal = 151	Risperidone nTotal = 57	Olanzapine nTotal = 60	Quetiapine nTotal = 62	Chlorpromazine nTotal = 12
Sedation	75 (49.6%)	8 (14.0%)	1 (1.7%)	10 (16.2%)	8 (66.7%)
Constipation	48 (31.8%)			4 (6.5%)	
Sialorrhea	45 (29.8%)				3 (25.0%)
Tachycardia	35 (23.2%)		4 (6.7%)		
Abnormal ECG	33 (21.8%)			6 (9.7%)	
Dizziness	28 (18.5%)			5 (8.1%)	
Nausea and vomiting	22 (14.6%)	7 (12.3%)		3 (4.8%)	
Weight gain	16 (10.6%)	12 (21.1%)	8 (13.3%)	4 (6.5%)	
Blurred vision	14 (9.3%)				
WBC decrease	8 (5.3%)				
Others	5 (3.3%)		3 (5.0%)		
Hypotension	5 (3.3%)				5 (41.7%)
EPSE	5 (3.3%)	6 (10.5%)	4 (6.7%)	3 (4.8%)	7 (58.3%)
Diarrhea	4 (2.6%)			1 (1.6%)	
Seizure	1 (2.0%)				
Liver enzyme abnormalities	1 (2.0%)			4 (6.5%)	
Menstrual irregularities	2 (1.3%)				
Hyperglycemia	9 (6.0%)				
Enuresis	6 (4.0%)				
Xerostomia				3 (4.8%)	
Insomnia		9 (15.8%)	3 (5.0%)		
Headache			3 (5.0%)		
Anxiety				2 (3.2%)	

ECG, electrocardiogram; WBC, total white blood cells count; EPSE, Extrapyramidal side effects.

most of the studies included in the present systematic review had important limitations such as lack of blinding, limited sample size and lack of a better description of phase of illness. Also, our search did not find studies in mixed states or bipolar depression and we could not make any assumptions about the clozapine effect in this population. Furthermore (Suppes et al., 1999), did not differentiate patients with schizoaffective disorder from BD patients and results from this trial should be interpreted in the light of this limitation.

An important strength of our study was the possibility to include studies published in Mandarin. Of note, clozapine is frequently used to treat BD in China (Li et al., 2015; Wei et al., 2002). Finally, clozapine was the first atypical antipsychotic showing a positive effect in improving cognitive functioning in patients with schizophrenia (Hagger et al., 1993). It is known that a subset of patients with BD presents a progressive course characterized by episode acceleration, treatment refractoriness, and functional/neurocognitive impairment (Passos et al., 2016). Although the clinical course of BD is heterogeneous and the clinical progression is not a general rule (Burdick et al., 2014; Lima et al., 2019; López-Villarreal et al., 2019; Van Rheenen et al., 2019), functional and cognitive impairment may be important outcomes to be assessed in future trials. In addition, a study assessing the pharmacological maintenance treatment across the clinical stages (I, II, III, and IV) in patients with BD (Goi et al., 2015), showed that patients at later stages (III and IV) needed three or more medications or clozapine. In this sense, clozapine seems important in avoiding polypharmacy among patients at later stage. Despite the greater number of medications in the late stage group, patients on clozapine therapy were using it as monotherapy or with an anticonvulsant. There are no studies assessing the efficacy of clozapine according to the clinical staging of patients with BD, and studies in this field are needed, specially because the effect of clozapine on cognition and functionality was already showed in schizophrenia (Meltzer, 2012), and it is know that patients with BD at later stages demonstrate significantly cognitive and functional impairment.

In conclusion, clozapine is similar to other antipsychotics in the treatment of manic episodes and is superior among patients with treatment-resistant BD. Data from the present review will set the stage for future randomized controlled trials designed to confirm the usefulness of clozapine in the treatment of TRBD. Additional studies investigating the efficacy of clozapine in bipolar depression and longer-term monotherapy as a mood stabilizer in bipolar disorder are warranted.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declaration of competing interest

The authors have no conflict of interest in relation to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.02.026.

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