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## Clozapine for Treatment-Resistant Bipolar Disorder: A Systematic Review

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# Clozapine for Treatment-Resistant Bipolar Disorder: A Systematic Review

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X-BL and Y-LT contributed equally to the review of the articles and to the writing of the first draft. C-YW and JdL contributed by improving the first and later drafts. All authors have contributed to and have approved the final manuscript.

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**Abstract**

**Objective:** To evaluate the efficacy and safety of clozapine for treatment-resistant bipolar disorder (TRBD).

**Methods:** A systematic review of randomized controlled studies, open-label perspective and retrospective studies. Samples were patients with TRBD. Interventions included clozapine monotherapy or clozapine combined with other medications. Outcome measures were efficacy and adverse drug reactions (ADRs)

**Results:** Fifteen clinical trials including a total of 1044 patients met the inclusion criteria. Clozapine monotherapy or clozapine combined with other treatments for TRBD were associated with improvement in: 1) symptoms of mania, depression, rapid cycling and psychotic symptoms, with many TRBD patients achieving a remission or response; 2) the number and duration of hospitalizations, the number of psychotropic co-medications and hospital visits due to somatic reasons for intentional self-harm/overdose; 3) suicidal ideation and aggressive behavior; and 4) social functioning. In addition, patients with TRBD showed greater clinical improvement in long-term follow-up when compared with published schizophrenia data. Sedation (12%), constipation (5.0%), sialorrhea (5.2%), weight gain (4%), and body ache/pain (2%) were the commonly reported ADRs; usually not requiring drug discontinuation. The percentage of severe ADRs reported, such as leukopenia (2%), agranulocytosis (0.3%), and seizure (0.5%) appeared to be lower than those reported in published schizophrenia literature.

**Conclusion:** The limited current evidence supports the concept that clozapine may be both an effective and relatively safe medication for TRBD.

**Key words:** clozapine, treatment-resistant, bipolar disorder

## Introduction

Clozapine, an atypical antipsychotic, is primarily used for the treatment of treatment-resistant schizophrenia in most parts of the world (1, 2). Long-term use of clozapine is associated with improvement in clinical symptoms, measurable social and functional gains, and decreased hospitalization as compared with typical antipsychotic agents (3, 4). Furthermore, meta-analyses of randomized clinical trials (RCTs) (5, 6) and a recent review of effectiveness trials (7) supported the greater efficacy of clozapine among antipsychotics in schizophrenia.

A growing number of reports, however, suggest that clozapine may also have a role in other treatment-resistant psychotic conditions (8-10), such as schizoaffective disorder (SAD) and psychotic mood disorders (11-13). Furthermore, case reports and retrospective studies suggest that clozapine may be particularly effective in the treatment of medication-resistant unipolar depression and bipolar disorder; some even suggested it is more effective than it is for schizophrenia (12, 14-16).

Compared with unipolar depression, bipolar disorder (BD) is a more serious type of mood disorder. BD is a recurrent, potentially disabling, sometimes even fatal psychiatric illness (17-19), and the estimated lifetime prevalence of various types of BD is over 2.0% (20, 21). BD is often associated with high levels of unfavorable outcomes or treatment-resistance (22-24). In contrast to schizophrenia, definitions of TRBD vary greatly (17, 25-27). However, a failure to respond to at least two trials of dissimilar treatments, involving an adequate dose and duration, could serve as a conservative definition (28-31).

Although mood disorder (MD) was traditionally considered as a rather rare condition in China, recently-conducted epidemiological studies in the country showed that it is one of the common mental disorders (32, 33), with a 1-month prevalence of 6.1% (32). Unlike other countries, clozapine has been widely used for BD in China despite not having been approved for mood disorders (34-36), and it is indeed one of the most commonly used antipsychotics in the treatment of BD (34, 37, 38). Some psychiatrists even preferred it as a first-line treatment for

mania (38-40). Similar to findings from studies in Western countries, RCTs showed that clozapine was an effective add-on treatment to antidepressants for treatment-resistant depression (41). Clozapine was also effective for treatment-resistant mania in a case report (42) and a RCT (43).

Clozapine is a drug of choice for TRBD in China but the evidence for its use in Western countries remains sparse, and the studies are limited to case reports (44), open-label trials (11), and only one RCT with fewer than 20 patients in each group (45). As China has the largest population on clozapine (46-48), the Chinese experience and studies may be of keen interest to Western psychiatrists (49). So far, no exhaustive systematic review on clozapine for TRBD has been published.

The primary aim of this review was to evaluate the efficacy and safety of clozapine for TRBD. As previously mentioned, in addition to international databases, we also included Chinese databases that are not usually reviewed in articles written by Western psychiatrists. Particular attention was paid to safety and tolerability, as the potentially severe adverse drug reactions (ADRs) associated with clozapine are commonly a factor discouraging clinicians from prescribing it.

## **Methods**

Before we conducted this systematic review, our protocol of reviewing clozapine use for TRBD was published online (<http://www.crd.york.ac.uk/prospero/>); the registration number was CRD42013004322 at the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA provides an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (50).

### *Types of studies*

All types of trials evaluating the efficacy and safety of clozapine for TRBD were eligible for inclusion. We included RCTs (Table 1), open-label retrospective studies (Table 2) and prospective trials (Table 3). We excluded meta-analyses and systematic reviews. We also excluded from the comprehensive review the case series and reports since they offer lower level of evidence, and

high suspicion of publication biases. However, we included them in Table 4 and provided a brief statement on them for the sake of entirety. The retrospective open study by Nielsen et al. (51) was included in this review (Table 2), although the sample also included patients with non-TRBD; it was not possible to exclude them. All tables provided details of the contamination of the studies by other diagnoses when it was not possible to separate the patients.

### *Study selection*

We searched PubMed, Embase, and Cochrane Library databases and the Cochrane Controlled Trials Register of clozapine for TRBD. We also searched the Chinese databases (CBM and CNKI databases) using the same key words. The search included all studies published between January 1979 and June 2014, regardless of language. The keywords used for the searches included: clozapine, bipolar disorder, manic, depression, resistant/resistance/refractory, drug therapy, and trial. The keywords were used in combination with the Boolean operators AND, OR, and NOT. We supplemented the search by using the “related article” function. We also manually searched bibliographies of RCTs, meta-analyses, and systematic reviews for studies that were missed in the initial electronic search (52).

One author (X-BL) independently inspected citations from the searches and identified relevant abstracts. A random 20% of the samples were independently re-inspected by author Y-LT to ensure reliability. When disagreements arose, the full report was acquired for more detailed scrutiny. Full reports of the abstracts meeting the review criteria were obtained and inspected by X-BL. Again, a random 20% of reports were re-inspected by Y-LT in order to ensure reliable selection. Where it was not possible to resolve disagreement by discussion, a third author (C-YW) mediated the decision. If the matter was unresolved, an attempt was made to contact the authors of the original study for clarification (53).

### *Data Extraction*

Review authors X-BL and Y-LT considered all included studies initially, without seeing comparison data, to judge clinical, methodological and statistical heterogeneity and thereby decide whether each study would be included for meta-analysis or other data synthesis. We then extracted data into standard, simple forms. X-BL extracted data from all included studies. In addition, to ensure reliability, Y-LT independently extracted data from a random sample of these studies, comprising 30% of the total. Again, any disagreement was discussed, decisions documented, and, if necessary, authors of studies were contacted for clarification. Data presented only in graphs and figures was extracted whenever possible, but included only if two authors independently had the same result. We also attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever deemed necessary. If studies were multi-center, we extracted data relevant to each component center separately (53).

#### *Assessment of reporting biases*

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. We tried to locate the research protocols of included RCTs. If the protocol was available, outcomes in the protocol and in the published report were compared. If the protocol was not available, outcomes listed in the methods section of the trial report were compared with the actually-reported results (54).

#### *Grading recommendations*

We used the grading of recommendations assessment, development, and evaluation (GRADE) system to rate the quality of evidence and strength of recommendations of this system review following the guidelines of the Cochrane Collaboration. GRADE included systematic assessments of all included trials across six main domains for each outcome: limitations of the study design and execution, inconsistency, indirectness, and imprecision of results, publication bias, and large treatment effect. Accordingly, we graded the recommendation for outcome measure of clozapine for BPD as very low, low, moderate, or high (Table 5).

## Results

The various combinations of the following search “clozapine, bipolar disorder, manic, depression, resistant or resistance, refractory” yielded 342 articles, of which 15 studies met the criteria. In total, 1044 TRBD patients had received clozapine treatment (Figure 1). There were 2 RCTs (Table 1); 3 retrospective studies (Table 2), and 10 open-label perspective trials (Table 3). These studies were equally distributed across the years between 1991 and 2012, which indicates that clozapine for TRBD has been a rather long-lasting, clinically important topic for the last 25 years.

It was not possible to conduct a meta-analysis because of the study's heterogeneity including differences in illness phase (mania, depression, or rapid cycling BD), methodology (open-label trial or RCT) and outcome definition (response or remission). Although meta-analysis is a powerful tool for analyzing data (55), confounding inter-study variables that cannot be controlled may violate basic statistical assumptions, making these types of analyses error-prone (56, 57). Therefore, we only extracted data onto standard, simple forms on a case-by-case basis and reported the efficacy of clozapine for TRBD when available, as well as other descriptive statistics. Compared with efficacy, there was less heterogeneity in ADRs. Therefore, we conducted data synthesis using this term, and all trials with ADR details were included; the percentage of each ADR was computed in this review and presented in Table 6.

We were unable to locate the protocols for three RCTs; therefore, we assessed the reporting bias by means of comparing outcomes listed in the methods with the results, which indicated that the reported results were approximately consistent with outcomes listed in the methods.

Quality assessment of the included studies based on the GRADE approach showed many limitations of the study designs, no obvious indirectness, imprecision in result reporting and large treatment effect. Based on the above assessments, the quality of evidence presented for each outcome ranged from “very low” to “moderate” (Table 5).

### *Clozapine RCTs for TRBD*

Our literature search yielded two clozapine RCTs for TRBD (Table 1). Among them, adjunctive clozapine treatment was superior to treatment as usual for TRBD (45). In addition, clozapine with added lithium was better than clozapine augmented with valproate in rapid-cycling BD (43).

### *Clozapine retrospective trials for TRBD*

Three clozapine retrospective trials for TRBD were identified (Table 2). Two trials described the number and duration of hospitalizations, the number of psychotropic co-medications and hospital visits for medical reasons and for intentional self-harm/overdose as significantly reduced during clozapine treatment (12, 29, 51, 58). Another retrospective study comparing schizophrenia and psychotic BD patients indicated that the latter had significantly higher response rates to clozapine (12).

### *Clozapine open-label prospective trials for TRBD*

The 10 clozapine open-label prospective studies for TRBD (Table 3), included 5 long-term follow-up studies (11, 16, 59-61), 4 focused on mania (44, 62-64), and another 1 focused on adolescent patients (65). Studies found that patients on clozapine demonstrated a significant decrease in the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression Scale (CGI) scores (44, 66); the presence of suicidal ideation and aggressive behavior at intake predicted greater improvement at endpoint (59, 65) and improvement in social functioning (16). In addition, they also found that BD patients showed greater clinical improvement than those with schizophrenia in the long-term follow-up (11, 60).

### *Clozapine ADRs in TRBD*

ADRs were summarized in Table 6. The prevalences of the most serious ADRs were leukopenia (2%), agranulocytosis (0.3%), and seizure (0.5%). There were no cases of myocarditis. The most frequent clinically significant ADRs were sedation (12%), constipation (5%), sialorrhea

(5%), weight gain (4%), and any kind of pain (2%). Other ADRs with frequency of 0.5-1% were dizziness, diarrhea (1%), leucopenia, transient fever, urinary incontinence, abnormal EEG, tachycardia, orthostatic hypertension, and nausea. Other ADRs are described in Table 6.

## **Discussion**

This is the first systematic review of clozapine for TRBD summarizing its efficacy and safety. Our comprehensive systematic review includes 15 studies with a total of 1,044 patients and suggested that clozapine may be an effective therapy, safe and well tolerated. Although we excluded all of the case series and case reports in this comprehensive review, the literature search provided 13 case reports/series using clozapine for TRBD (Table 4). The 13 articles included 5 on mania (42, 70-73), 5 on rapid cycling BD (15, 74-77) and 3 on other TRBDs (29, 78, 79). Overall, almost all cases were treatment-resistant and had a remission after switching to clozapine monotherapy or adding clozapine to other drugs.

### *Strength of the study*

While many patients with BD respond well to conventional medications (including antidepressants, mood stabilizers and antipsychotics), a substantial proportion do not reach satisfactory response (67-69). This systematic review showed that clozapine may be an efficacious therapy for TRBD. First, RCTs showed that: (a) clozapine add-on treatment was superior to treatment as usual in mania, and (b) clozapine plus lithium was better than clozapine plus valproate in rapid cycling BD. Second, retrospective studies of clozapine for TRBD indicated that total number and duration of hospitalizations and the number of psychotropic co-medications were significantly reduced during clozapine treatment. Third, in open-label perspective studies, patients with clozapine demonstrated a significant decrease in the YMRS, HDRS, BPRS, and CGI scores, evidenced improvement in social functioning and suicidal ideation and aggressive behavior, and had fewer subsequent affective episodes; furthermore, TRBD patients showed greater clinical improvement than those with schizophrenia in the long-term follow-up in these trials. The current

review also suggests that clozapine may have antimanic properties in some children and adolescents with TRBD.

In general, this review found that clozapine for TRBD was safe and well-tolerated (Table 6). Sedation, constipation, sialorrhea, weight gain, and pain were the common ADRs, which is consistent with schizophrenia studies (80, 81), and they were rather mild and tolerable to most patients. Moderate ADRs included dizziness, diarrhea, transient fever, urinary incontinence, abnormal EEG, tachycardia, orthostatic hypertension, and nausea. Rare ADRs were sweating, hyperlipidemia, diabetes type 2, influenza-like syndrome, postprandial regurgitation, ileus, and bradykinesia, which is also comparable with schizophrenia studies (80, 82). These ADRs were not severe enough to result in drug discontinuation. The ADRs in the metabolic system were obviously low; there is the possibility of a major underreport in the included trials.

Among all the reports, 17 patients had leukopenia (2%), 2 had agranulocytosis (0.2%), and 5 had seizures (0.5%). These figures tend to be lower than averages reported in schizophrenia reviews (83-89). We are not sure whether the lower ADR frequency in BPD vs schizophrenia trials is real or an artefact. Greater underreport and different methodologies may contribute to artificially low ADR frequency. Some clozapine ADRs are dose-related; others are not. Doses in BPD trials appear lower than doses in Western schizophrenia studies, but it was not possible to control doses for confounders such as smoking (which induced clozapine metabolism probably by inducing CYP1A2) and racial differences (see the commentary in the limitation section) (64, 87, 89). The agranulocytosis risk is still a concern for clinicians, but mandatory blood monitoring has been shown to considerably reduce the incidence of fully developed cases of agranulocytosis (80). Thus, appropriate management of clozapine ADRs facilitates a maximization of the benefits of clozapine treatment, and physicians and patients alike should be aware that there is a range of benefits to clozapine use that outweighs its risk (80, 90, 91).

Clozapine treatment was associated with significant improvement in tardive dyskinesia in seven patients (92-94); clozapine may be useful for long-term treatment to lower tardive

dyskinesia risk (93, 95, 96). Furthermore, once tardive dyskinesia or dystonia is established, clozapine may be useful for both control of the movement disorder and BD (93, 96).

The major strength of this study is that we also searched Chinese databases in this systematic review, which included all TRBD clozapine trials conducted in China, where clozapine is widely used. Thus, it is the first review to include all trials available without applying any language restrictions. We found clozapine RCTs in monotherapy or combined with other medications versus other treatments in TRBD patients; the comparison treatments included mood stabilizer (97, 98), other antipsychotics (99-102), clozapine plus mood stabilizer versus mood stabilizer (97, 103, 104), clozapine plus mood stabilizer versus other antipsychotics plus mood stabilizer (103-109) in the treatment of BD in China. We also found 2 RCTs, 1 open-label perspective study and 2 case reports of clozapine for TRBD in the Chinese literature, including the only placebo-controlled clozapine RCT for TRMD (41).

#### *Limitations of the study*

A few limitations of the current review need to be acknowledged. First, it was not possible to conduct a meta-analysis because of the study's heterogeneity, including differences in illness phase (mania, depression or rapid cycling BD), methodology (open-label trials or RCTs) and outcome definition (response or remission). This great heterogeneity may violate basic statistical assumptions and make these analyses error-prone. Therefore, we only extracted data onto standard, simple forms on a case-by-case basis and reported the efficacy of clozapine for TRBD when available. Compared with data on efficacy, there was lower heterogeneity with ADR data, therefore data synthesis using ADRs was conducted and the percentage of each ADR was computed (Table 6).

Second, most of the clinical trials included here had major methodological problems: although this review included 15 clinical trials, most of them were open-label observational trials; only 2 RCTs were available. There were no obvious reporting biases in the RCTs, but reporting biases in other studies is possible. Furthermore, the GRADE approach showed the quality of the

evidence was “very low” in CGI score and psychosocial function; other outcomes were from “low” to “moderate” (Table 5). Therefore, the current review provided limited evidence for clozapine use. However, two strengths of this current review also need to be mentioned: (1) all available trials were included, without applying any language restrictions; and (2) we provided certain supporting evidence by means of reporting the efficacy case-by-case analysis and computing the percentage of each ADR (Table 6).

Third, some trials were “contaminated” by some patients with a diagnosis of SAD or schizophrenia; which does not correspond to the population described as the target population of interest (TRBD). In some trials, we could not separate TRBD patients from the others but the tables provide the details of these “contaminated” studies.

A fourth limitation of this review and all the studies reviewed in it is the lack of close attention to clozapine pharmacokinetic issues on dosing. Clozapine dosing is influenced by racial differences, drug-drug interactions and smoking. In 1997, it was already reported that Chinese patients tend to receive approximately half of the clozapine dosage used in Western countries (110, 111) but appear to have roughly similar clozapine levels, which is indicative of lower clozapine metabolism in Chinese patients. The literature has not stressed this difference nor provided an explanation. Sirot et al. (2009) completed a very important study that has not received enough attention in the literature (112). They described CYP2C19 poor metabolizers (PMs) as having 2.3-fold higher plasma clozapine concentrations than patients with other CYP2C19 genotypes. Approximately 25% of the Chinese population is CYP2C19 PMs.

Studies of adjunctive clozapine treatment in TRBD usually ignore the major differences in clozapine metabolism associated with co-medication. Carbamazepine is a major inducer of clozapine metabolism (113) and it is possible that valproate may be a mild inducer (114). Fluvoxamine is a major inhibitor of clozapine metabolism (115) and paroxetine and fluoxetine are mild inhibitors (114, 115).

In conclusion, future studies and meta-analysis of clozapine for TRBD will need to pay attention to important pharmacokinetic differences associated with racial differences, co-medication and smoking, which may have major influences on clozapine dosing but at present are ignored in most published articles.

#### *Comparison with other studies*

Poon et al. (2012) performed a literature review on TRBD research findings (17). It provided few promising leads other than the use of clozapine for TRBD mania, which is comparable to our analysis. Their review was limited by: 1) inclusion of only 2 clozapine trials (44, 45), 2) lack of report on clozapine ADRs, and 3) lack of inclusion of Chinese studies which include the larger numbers of patients.

Gitlin et al. (2003) conducted a review on this topic (116). Their review indicated that combining multiple agents was the commonly used clinical strategy for TRBD; an approach that may be effective for treatment-resistant patients included high-dose thyroid augmentation, clozapine, calcium channel blockers, and electroconvulsive therapy (ECT), which is consistent with our findings. However, only 3 studies of clozapine treatment were included (45, 60, 64), and none of the Chinese studies were included. Similarly, there was no safety analysis or data synthesis.

Frye et al. (1998) reviewed the use of atypical antipsychotics in the treatment of BD, focusing on clozapine as the prototypical agent (117). It indicated that the early clinical experience of clozapine as a potential mood stabilizer suggests greater antimanic than antidepressant properties. However, this review only included some trials conducted before 1998, which excluded most trials of clozapine for TRBD. Similarly, there was no safety analysis or data synthesis in this analysis.

#### **Conclusions**

TRBD is a complex, often severe and disabling psychiatric disorder and it often poses a therapeutic challenge (17, 118). This systematic review showed that clozapine monotherapy or its combination with other medications for TRBD may be both safe and effective. Long-term use of

clozapine appeared to be associated with improvement in clinical symptoms, measurable social and functional gains, and decreased hospitalization. Constipation, sedation, sialorrhea, weight gain, aches and pain were the common reported ADRs, though none were severe enough to result in drug discontinuation. The percentage of leukocytopenia, agranulocytosis and seizure were lower than in studies of clozapine for schizophrenia, but it cannot be ruled out that they may be contaminated by ADR underreport. Clozapine for TRBD may increase treatment compliance, which may offer additional therapeutic benefits. On the other hand, some patients may have poor adherence or may not be willing to start clozapine treatment due to the required blood collections to avoid agranulocytosis.

This comprehensive review focused on TRBD but future reviews need to focus on the role of clozapine for the treatment of BD in general. Though clozapine is rarely used for non-treatment-resistant BD elsewhere in the world, emerging evidence from China is encouraging (41, 97, 98). Since the early 1980s, few clozapine RCTs for BD in general have been published; once more clozapine RCTs are published, a meta-analysis on this important topic will provide clinicians with more choices when treating patients with all kinds of BD, including those with non-treatment-resistant forms.

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## References

1. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45: 789-796.
2. Marder SR, Van Putten T. Who should receive clozapine? *Arch Gen Psychiatry* 1988; 45: 865-687.
3. Meltzer HY. Dimensions of outcome with clozapine. *Br J Psychiatry* 1992; Supplement 17: 46-53.
4. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry* 1995; 152: 183-190.
5. Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Library* 2010; CD006633.
6. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382:951-962.
7. Attard A, Taylor DM. Comparative effectiveness of atypical antipsychotics in schizophrenia. *CNS drugs* 2012; 26: 491-508.
8. Owen Jr R, Beake B, Marby D, Dessain E, Cole J. Response to clozapine in chronic psychotic patients. *Psychopharmacol Bull* 1989; 25: 253.

9. Naber D, Hippus H. The European experience with use of clozapine. *Hosp Comm Psychiatry* 1990; 41: 886-890.
10. Leppig M, Bosch B, Naber D, Hippus H. Clozapine in the treatment of 121 out-patients. *Psychopharmacology* 1989; 99: S77-S79.
11. Banov MD, Zarate Jr CA, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. *J Clin Psychiatry* 1994; 55: 295-300.
12. McElroy SL, Dessain EC, Pope HG, Jr., et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 1991; 52: 411-414.
13. Lindström LH. The effect of long-term treatment with clozapine in schizophrenia: A retrospective study in 96 patients treated with clozapine for up to 13 years. *Acta Psychiatr Scand* 1988; 77: 524-529.
14. Frakenburg FR. Clozapine and bipolar disorder. *J Clin Psychopharmacology* 1993; 13: 289-290.
15. Suppes T, Phillips KA, Judd CR. Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: a report of three cases. *Biol Psychiatry* 1994; 36: 338-340.
16. Suppes T, McElroy SL, Gilbert J, Dessain EC, Cole JO. Clozapine in the treatment of dysphoric mania. *Biological Psychiatry* 1992; 32: 270-280.
17. Poon SH, Sim K, Sum MY, Kuswanto CN, Baldessarini RJ. Evidence-based options for treatment-resistant adult bipolar disorder patients. *Bipolar Disord* 2012; 14: 573-584.
18. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002; 159 (4 Suppl): 1-50.

19. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002; 59: 530-537.
20. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; 64: 543-552.
21. Hwu H-G, Joyce PR, Karam EG, Lee C-K, Lellouch J, Wickramaratne PJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 1996; 276: 293-299.
22. McElroy SL, Frye M, Denicoff K, Altshuler L, Nolen W, Kupka R, et al. Olanzapine in treatment-resistant bipolar disorder. *J Affect Disord* 1998; 49: 119-122.
23. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 2004; 161: 564-566.
24. Ghaemi SN, Katzow JJ. The use of quetiapine for treatment-resistant bipolar disorder: a case series. *Ann Clin Psychiatry* 1999; 11: 137-140.
25. Dell'Osso B, Mundo E, D'Urso N, Pozzoli S, Buoli M, Ciabatti M, et al. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disord* 2009; 11: 76-81.
26. Erfurth A, Michael N, Stadtland C, Arolt V. Bupropion as add-on strategy in difficult-to-treat bipolar depressive patients. *Neuropsychobiol* 2002; 45: 33-36.

27. Pacchiarotti I, Mazzarini L, Colom F, Sanchez-Moreno J, Girardi P, Kotzalidis G, et al. Treatment-resistant bipolar depression: towards a new definition. *Acta Psychiatrica Scand* 2009; 120: 429-440.
28. Gitlin MJ. Treatment-resistant bipolar disorder. *Bull Menninger Clin* 2001; 65: 26-40.
29. Benedetti A, Di Paolo A, Lastella M, Casamassima F, Candiracci C, Litta A, et al. Augmentation of clozapine with aripiprazole in severe psychotic bipolar and schizoaffective disorders: a pilot study. *Clin Pract Epidemiol Ment Health* 2010; 6: 30-35.
30. Sachs GS. Treatment-resistant bipolar depression. *Psychiatr Clin North Am* 1996; 19: 215-236.
31. Sharm V, Khan M, Corpse C. Role of lamotrigine in the management of treatment-resistant bipolar II depression: a chart review. *J Affect Disord* 2008; 111: 100-105.
32. Phillips MR, Zhang J, Shi Q, Song Z, Ding Z, Pang S, et al. Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey. *Lancet* 2009; 373: 2041-2053.
33. Tsai S-Y, Chen C-C, Yeh E-K. Alcohol problems and long-term psychosocial outcome in Chinese patients with bipolar disorder. *J Affect Disord* 1997; 46: 143-150.
34. Si TM, Shu L, Yu X, Ma C, Wang GH, Bai PS, et al. A cross-sectional study on treatment patterns of bipolar disorders in China in 2006. *Chin J Psychiatry* 2012; 45: 29-34.
35. Chen XL, Xing BP, Zhang YQ, Jin WD. Atypical antipsychotics in the treatment of elder patients with mania. *Herald Med* 2008; 27: 672-633.

36. Fan ZG, Chen JM, Lu GH. Comparison analysis of clozapine treatment for 54 cases with mania  
Chin J Neurol 1994; 39: 202.
37. Liu YQ, Zhun FY, Yang LZ, Wang RJ, Chen CM. Clinical treatment analysis of 528 cases of  
affective disorders patients. Chin J Pharmacoepidemiol 1997; 5: 158-161.
38. Wang GY, Dong YM. The investigation and analysis of outpatient drug use in psychiatry. Chin J  
Modern Drug Application 2007; 1: 44.
39. Liu TB, Gao H, Shen QJ. Clozapine combined with lithium carbonate in the treatment of acute  
mania. J Clin Psychiatry 2000; 10: 350-351.
40. Zhang L, Chen JD. A double-blind study of clozapine combined with lithium carbonate. J  
Psychiatry 2002; 15: 40-41.
41. Yan JX. A double-blind clinical trial of add-on clozapine in the treatment of  
treatment-resistant depression. Clin J Psychol Med 2001; 11: 170-1.
42. Xu XH. One case of treatment-resistant twin mania. J Clin Psychosom Dis 2003; 9: 26.
43. Tan J. The efficacy and safety of Lithium and low-dose clozapine treatment for refractory  
bipolar. Youjiang Med 2010; 38: 150-151.
44. Calabrese JR, Kimmel SE, Woysville MJ, Rapport DJ, Faust CJ, Thompson PA, et al. Clozapine  
for treatment-refractory mania. Am J Psychiatry 1996; 153: 759-764.
45. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized  
1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and  
a history of mania. Am J Psychiatry 1999; 156: 1164-1169.

46. Si TM, Shu L, Yu X, Ma C, Wang GH, Bai PS, et al. Antipsychotic drug patterns of schizophrenia in China: a cross-sectional study. *Chin J Psychiatry* 2004; 37: 152-155.
47. Zhang GP, Wang CY. The One-Day Survey On Psychotropic Drugs Use In 788 Psychotic Inpatients In Beijing Anding Hospital. *Chin J Clin Pharmacol* 2001; 17: 287-289.
48. Luo RL, Chen Q. Investigation and analysis of psychotropic in 296 inpatients in one day. *J Chin People Health* 2009; 21: 1755-1756.
49. Tang YL, Mao PX, Jiang F, Chen Q, Wang CY, Cai ZJ, et al. Clozapine in China. *Pharmacopsychiatry* 2008; 41: 1-9.
50. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264-269.
51. Nielsen J, Kane JM, Correll CU. Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. *Bipolar Disord* 2012; 14: 863-869.
52. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012; 344: e2156.
53. Higgins JP, Green S, Collaboration C. *Cochrane handbook for systematic reviews of interventions*. Hoboken: Wiley Online Library; 2008.
54. Higgins J, Altman DG. Assessing risk of bias in included studies. *Cochrane Handbook for Systematic Reviews of Interventions*. Hoboken: Cochrane Book Series, 2008:187-241.

55. Leandro G. Meta-analysis in medical research: the handbook for the understanding and practice of meta-analysis. Wiley. com; 2008: <http://www.books.google.com>.
56. Ried K. Interpreting and understanding meta-analysis graphs: A practical guide. Aust Fam Physician 2006; 35: 635-638.
57. Hoffer ZS, Roth RL, Mathews M. Evidence for the partial dopamine-receptor agonist aripiprazole as a first-line treatment of psychosis in patients with iatrogenic or tumorogenic hyperprolactinemia. Psychosomatics 2009; 50: 317-324.
58. Chang JS, Ha KS, Young Lee K, Sik Kim Y, Min Ahn Y. The effects of long-term clozapine add-on therapy on the rehospitalization rate and the mood polarity patterns in bipolar disorders. J Clin Psychiatry 2006; 67: 461-467.
59. Ciapparelli A, Dell'Osso L, Pini S, Chiavacci MC, Fenzi M, Cassano GB. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. J Clin Psychiatry 2000; 61: 329-334.
60. Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, Carmassi C, Cecconi D, Fenzi M, et al. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: a naturalistic 48-month follow-up study. J Clin Psychiatry 2003; 64: 451-458.
61. Zarate CA, Jr., Tohen M, Banov MD, Weiss MK, Cole JO. Is clozapine a mood stabilizer? J Clin Psychiatry 1995; 56: 108-112.
62. Kimmel SE, Calabrese JR, Woynshville MJ, Meltzer HY. Clozapine in treatment-refractory mood disorders. J Clin Psychiatry 1994; 55(Suppl B): 91-93.

63. Green AI, Tohen M, Patel JK, Banov M, DuRand C, Berman I, et al. Clozapine in the treatment of refractory psychotic mania. *Am J Psychiatry* 2000; 157: 982-986.
64. Fehr BS, Ozcan ME, Suppes T. Low doses of clozapine may stabilize treatment-resistant bipolar patients. *Eur Arch Psychiatry Clin Neurosci* 2005; 255: 10-14.
65. Kowatch RA, Suppes T, Gilfillan SK, Fuentes RM, Granneman BD, Emslie GJ. Clozapine treatment of children and adolescents with bipolar disorder and schizophrenia: a clinical case series. *J Child Adolesc Psychopharmacol* 1995; 5: 241-253.
66. Liu NH, Ying D. The clinical observation of clozapine add valproate and propranolol for treatment-resistant depression. *Med J Chin People Health* 2006; 18: 771.
67. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KR, Daniel DG, et al. Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry* 1999; 156: 702-709.
68. Ketter TA, Kimbrell TA, George MS, Dunn RT, Speer AM, Benson BE, et al. Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol Psychiatry* 2001; 49: 97-109.
69. Vieta E, Reinares M, Corbella B, Benabarre A, Gilaberte I, Colom F, et al. Olanzapine as long-term adjunctive therapy in treatment-resistant bipolar disorder. *J Clin Psychopharmacol* 2001; 21: 469-473.
70. Antonacci DJ, Swartz CM. Clozapine treatment of euphoric mania. *Annal Clin Psychiatry* 1995; 7: 203-206.

71. Poyurovsky M, Weizman A. Safety and effectiveness of combined ECT and clozapine in treatment-resistant mania. *Eur Psychiatry* 1996; 11: 319-321.
72. Mahmood T, Devlin M, Silverstone T. Clozapine in the management of bipolar and schizoaffective manic episodes resistant to standard treatment. *Aust N Z J Psychiatry* 1997; 31: 424-426.
73. Chanpattana W. Combined ECT and clozapine in treatment-resistant mania. *J ECT* 2000; 16: 204-207.
74. Calabrese JR, Meltzer HY, Markovitz PJ. Clozapine prophylaxis in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 1991; 11: 396-397.
75. Lancon C, Llorca PM. Clozapine in the treatment of refractory rapid cycling bipolar disorder. *Encephale* 1996; 22: 468-469.
76. Chen CK, Shiah IS, Yeh CB, Mao WC, Chang CC. Combination treatment of clozapine and topiramate in resistant rapid-cycling bipolar disorder. *Clin Neuropharmacol* 2005; 28: 136-138.
77. Bastiampillai TJ, Reid CE, Dhillon R. The long-term effectiveness of clozapine and lamotrigine in a patient with treatment-resistant rapid-cycling bipolar disorder. *J Psychopharmacol* 2010; 24: 1834-1836.
78. Gupta M. Clozapine monotherapy for 66 months in treatment resistant bipolar disorder: a case report. *J Clin Psychopharmacol* 2009; 29: 501-503.
79. Vijay Sagar KJ. Treatment-refractory, juvenile-onset bipolar affective disorder. *Ind J Psychiatry* 2005; 47: 124-125.

80. Lieberman JA. Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry* 1998; 59 (Suppl 3): 38-43.
81. Safferman A, Lieberman JA, Kane JM, Szymanski S, Kinon B. Update on the clinical efficacy and side effects of clozapine. *Schizophrenia Bull* 1991; 17: 247-261.
82. Daniel DG, Goldberg TE, Weinberger DR, Kleinman JE. Different side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder: A pilot study. *Am J Psychiatry* 1996; 153: 417-419.
83. Alvir JMJ, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis--incidence and risk factors in the United States. *N J Engl Med* 1993; 329: 162-167.
84. Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva I. Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; 11: 193-198.
85. Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; 169: 483-438.
86. Fan ZY, Cui HS, Shen AZ, Ju FY, Tang M, Bai SZ. 3113 cases of WBC count of psychiatric patients after clozapine treatment. *New Drug Clin* 1992; 10: 330-331.
87. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. *Neurology* 1991; 41: 369-371.
92. Pacia SV, Devinsky O. Clozapine-related seizures Experience with 5,629 patients. *Neurology* 1994; 44:2247-2249.
89. Haller E, Binder RL. Clozapine and seizures. *Am J Psychiatry* 1990;147:1069-1071.

90. Miller DD. Review and management of clozapine side effects. *J Clin Psychiatry* 2000; 61(Suppl 8): 14-17.
91. Naber D, Holzbach R, Perro C, Hippus H. Clinical management of clozapine patients in relation to efficacy and side-effects. *Br J Psychiatry* 1992 (Suppl 17): 54-59.
92. Lieberman JA, Saltz BL, Johns CA, Pollack S, Borenstein M, Kane J. The effects of clozapine on tardive dyskinesia. *Br J Psychiatry* 1991; 158: 503-510.
93. Casey DE. Clozapine: neuroleptic-induced EPS and tardive dyskinesia. *Psychopharmacology* 1989; 99: S47-S53.
94. Tamminga C, Thaker G, Moran M, Kakigi T. Clozapine in tardive dyskinesia: Observations from human and animal model studies. *J Clin Psychiatry* 1994; 55(Suppl B): 102-106.
95. Small JG, Milstein V, Marhenke JD, Hall DD. Treatment outcome with clozapine in tardive dyskinesia, neuroleptic sensitivity, and treatment-resistant psychosis. *J Clin Psychiatry* 1987; 48: 263-267.
96. Simpson GM, Lee JH, Shrivastava RK. Clozapine in tardive dyskinesia. *Psychopharmacology* 1978; 56: 75-80.
97. Liu TZ, Song SY. A comparative study of clozapine versus lithium in the treatment of mania. *Shandong Arch Psychiatry* 1990; 3: 21-23.
98. Liu HY, Gong CF, Ma ZL. A controlled study of clozapine, sodium valproate and carbamazepine in the treatment of 84 patients with mania. *Health Psychol J* 2002; 10: 228-230.

99. Wu YH. Comparative study of clozapine versus olanzapine in the treatment of mania. *Pract Chin Clin Med* 2004; 21: 34-35.
100. Wei XY, Wang QM, Yang YJ, Liu MY. The comparison of olanzapine and clozapine in the treatment of mania. *J Clin Psychol Med* 2002; 12: 347-348.
101. Xie WJ, Zhao YM, Li J, Zhou Y, Chen M. A study of aripiprazole versus clozapine in the treatment of mania. *Shandong Arch Psychiatry* 2006; 19: 2.
102. Liao GS. A comparative study of quetiapine and clozapine in the treatment of mania episode. *Med J Chin People Health* 2009; 21: 2993-2994.
103. Yan JX, Chu PH, Liu QH, Chu JF, Lv XS, Zhang YQ. Clozapine combined with lithium in the treatment of mania. *Chin J Nerv Ment Dis* 1997; 23: 104-106.
104. Tao Q, Yang XJ, Wang RQ. A comparative study of lithium and chlorpromazine versus lithium and clozapine in the treatment of mania. *Sichuan Arch Psychiatry* 1999; 12: 56-57.
105. Zhang GY, Xie QM, Wang YX, Liu CM. Antipsychotics combined with lithium in the treatment of mania. *J Clin Psychol Med* 2006; 16: 2.
106. Jing YL, Wang LT, Li J. A comparative study of olanzapine and clozapine combined with lithium in the treatment of mania. *Shandong Arch Psychiatry* 2005; 18: 256-257.
107. Tao H, Jin WD, Liu ZC, Qiu DS, Ma YC, Shen Y, et al. Controlled studies on olanzapine or clozapine and stabilizer in patients with mania. *J Clin Psychosom Dis* 2004; 10: 164-166.
108. Dong YY, Gan JG. Randomized controlled study of clozapine combined lithium versus ziprasidone combined lithium in the treatment of mania. *J Pract Med* 2010; 26: 1806-1807.

109. Tang XW, Wu H, Chen Q. Randomized controlled trial comparing quetiapine with lithium and clozapine with lithium in the treatment of female patients with mania. *Shanghai Arch Psychiatry* 2011; 23: 291-298.
110. Chang W, Lin S, Lane H, Hu W, Jann M, Lin H. Clozapine dosages and plasma drug concentrations. *J Form Med Assoc* 1997; 96: 599-605.
111. Chong S-A, Tan C-H, Khoo Y-M, Lee H-S, Wong K-E, Ngui F, et al. Clinical evaluation and plasma clozapine concentrations in Chinese patients with schizophrenia. *Ther Drug Monit* 1997; 19: 219-223.
112. Sirot EJ, Knezevic B, Morena GP, Harenberg S, Oneda B, Crettol S, et al. ABCB1 and cytochrome P450 polymorphisms: clinical pharmacogenetics of clozapine. *J Clin Psychopharmacology* 2009; 29: 319-326.
113. de Leon J, Santoro V, D'Arrigo C, Spina E. Interactions between antiepileptics and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol* 2012; 8: 311-334.
114. Diaz F, Santoro V, Spina E, Cogollo M, Rivera T, Botts S, et al. Estimating the size of the effects of co-medications on plasma clozapine concentrations using a model that controls for clozapine doses and confounding variables. *Pharmacopsychiatry* 2008; 41: 81-91.
115. Spina E, De Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. *Basic Clin Pharmacol Toxicol* 2007; 100: 4-22.
116. Gitlin M. Treatment-resistant bipolar disorder. *Mol Psychiatry*. 2006; 11: 227-240.

117. Frye MA, Ketter TA, Altshuler LL, Denicoff K, Dunn RT, Kimbrell TA, et al. Clozapine in bipolar disorder: treatment implications for other atypical antipsychotics. *J Affect Disord* 1998; 48: 91-104.
118. Ranjan R, Meltzer HY. Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. *Biol Psychiatry* 1996; 40: 253-258..

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Table 1. Clozapine RCTs for TRBD

**Suppes et al. 1999 (45)**

**Population:** Thirty-eight patients meeting the DSM-IV criteria for BD (n=26) or SAD (n=12) who were deemed treatment-resistant [failure of adequate treatment with two mood stabilizers (lithium, valproate, carbamazepine) at standard therapeutic levels]. Subjects were randomly assigned to clozapine add-on treatment (N = 19) or treatment as usual (no clozapine) (N = 19).

**Intervention:** Clozapine (355 mg/day) add-on therapy

**Comparison:** Treatment as usual

**Measures:** Patients received monthly ratings on the BPRS, CGI, BRMS, HDRS, SAPS, SANS, AIMS, and a 40-item side effect checklist.

**Study design:** Randomized, treatment as usual – controlled study followed up for 1 year.

**Results<sup>a</sup>:** Significant between-group differences were found in scores on all rating scales except the HDRS. Total medication use over 1 year significantly decreased in the clozapine group. No significant differences in physical complaints between groups were noted.

**Tan et al. 2010 (43)**

**Population:** 71 patients with DSM-IV BD who were classified as TRBD were randomly assigned to clozapine added to lithium treatment (N = 35) or clozapine added to valproate treatment (N = 36). Treatment resistance was defined as failure of adequate treatment with 2 different antidepressants.

**Intervention:** Clozapine (100-300 mg/day) added to lithium (500-1500 mg/day)

**Comparisons:** Clozapine (100-300 mg/day) added to valproate (600-1800 mg/day)

**Measures:** Patients received ratings on BPRS, HDRS, and TESS at weeks 0, 1, 2, 4 and 6.

**Study design:** Randomized, open-controlled study

**Results<sup>a</sup>:** In the study group, 89% of patients were responders (based on BPRS and HDRS) to clozapine added to lithium compared with 64% of patients receiving clozapine added to valproate (p<0.05). No significant differences in ADRs between groups.

AD = antidepressant; ADR = adverse drug reaction; AIMS = Abnormal Involuntary Movement Scale; BD = bipolar disorder; BPRS = Brief Psychiatric Rating Scale; BRMS = Bech-Rafaelsen Mania Scale; CGI= Clinical Global Impression; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4<sup>th</sup> edition; ECG = electrocardiogram; GAS = Global Assessment Scale; HDRS = Hamilton Depression Rating Scale; RTC= randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAD = schizoaffective disorder; SAPS = Scale for the Assessment of Positive Symptoms; TCA= tricyclic antidepressant; TESS = Treatment Emergent Symptom Scale; TRBD = treatment-resistant bipolar disorder.

<sup>a</sup>Clinical remission and response was defined differently in each study

Table 2. Clozapine retrospective studies for TRBD

**McElroy et al. 1991 (12)**

**Sample:** All patients were either inadequately responsive to or unable to tolerate standard biological therapies.

**Methods:** Survey of treating clinicians and chart data for all 85 consecutive patients, including 39 with schizophrenia, 25 with SAD, and 14 with psychotic BD, who received clozapine for at least 6 weeks at one center.

**Results:** Compared to patients with schizophrenia, patients with SAD and psychotic BD had significantly higher response rates to clozapine (10% for schizophrenia vs. 15-20% for SAD and 43% for psychotic BD, respectively).

**Chang et al. 2006 (58)**

**Sample:** TRBP to conventional treatment.

**Methods:** Analysis of clinical data from medical records of 51 patients with DSM-IV BD treated with add-on clozapine for > 6 months

**Results:** The number of hospital days per year was reduced in 90% of patients after clozapine add-on treatment. Total number and duration of hospitalizations per year also decreased. Significant reductions were found in the number and duration of hospitalizations associated with manic, depressive, and hypomanic episodes. Long-term efficacy of clozapine add-on was supported by continuous decreases in hospital days per year in the 27 selected patients.

**Nielsen et al. 2012 (51)**

**Sample:** A total of 21,473 patients with a lifetime diagnosis of ICD-10 BD, of which only 326 (1.5%) were treated with clozapine and were included in a mirror-image analysis.

**Methods:** A pharmacy-epidemiologic database study was carried out in Denmark, investigating the effectiveness of clozapine in BD patients (without a schizophrenia-spectrum disorder), between 1996 and 2007, using a two-year mirror-image design.

**Results:** Clozapine appears to be an appropriate choice for TRBD. Compared to the pre-clozapine period, during clozapine treatment, the mean number of bed-days decreased from 179 to 35. The mean number of admissions was reduced from 3.2 to 2.0. Overall, 240 patients (74%) had reduced bed-days and 130 (40%) were not admitted while treated with clozapine. Moreover, the number of psychotropic co-medications was reduced from 4.5 DDD (25-75 percentiles: 2.4-8.2) to 3.9 DDD (25-75 percentiles: 2.4-6.1). The percentage of patients with hospital visits for intentional self-harm/overdose was reduced significantly from 8% to 3%.

ADR = adverse drug reaction; BD = bipolar disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; DDD = defined daily doses; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4<sup>th</sup> edition; ICD-10 = International Classification of Diseases, 10<sup>th</sup> edition; TRBD = treatment-resistant bipolar disorder.

**Table 3.** Clozapine open-label trials for TRBD

Study	Subjects	Resistance definition (Failure of)	Treatments (mg/day)	Duration (months)	Main findings
Suppes et al. 1992 (16)	7 with dysphoric mania	Standard treatments including ACs	CLZ (50-500) + ACs	36-60	Symptomatic and functional improvement was assessed. Most of the patients sustained substantial gains in psychosocial function follow-up over 3 years. No further hospitalizations were needed in 6 of 7 patients.
Banov et al. 1994 (11)	52 BD, 81 SAD, 14 UD, 40 SCH	Undefined	CLZ	18.7	BD manic and SAD bipolar had significantly better outcomes than UD, BD, and SAD depressed patients. BD and SAD patients had significantly greater improvement in social functioning than SCH patients. One or more episodes of depression prior to CLZ predicted CLZ discontinuation.
Kimme et al. 1994 (62)	25 manic with BD or SAD	Li, ACs, and $\geq 2$ APs, or intolerant	CLZ	13	18 of 25 patients demonstrated a greater than 50% decrease in the YRMS
Kowatch et al. 1995 (66)	5 children or adolescents with BD	Multiple trials of APs and ACs, or intolerance	CLZ (75-225)+Li	2	There was a 42% decrease in the CGI. Treatment was for aggressive behavior and psychotic symptoms.
Zarate et al. 1995 (61)	17 mood disorders	Combinations of Li, ACs, APs, and ECT; or had tardive dyskinesia.	CLZ	16.1	65% (11/17) had no subsequent rehospitalization or mood episode. Significant improvement in CGI scores.
Calabrese et al. 1996 (44)	25 acutely manic	Li, ACs, and APs, intolerable ADRs, or both	CLZ (494)	4	72% (18/25) improved on the YMRS and 32% (8/25) improved on the BPRS. The BD patients as compared to SAD patients, and the non-rapid patients as compared to rapid cyclers, had significantly greater improvement in total BPRS score.
Green et al. 2000 (63)	22 active manic	500 mg/day of chlorpromazine or its equivalence and Li of at least 6 weeks	CLZ	3	57% (13/22) improved on BPRS; 57% (12/22) on YMRS; 39% (8/22) on CGI and 77% (17/22) experienced at least a 20% reduction on all three scales.
Ciapparelli et al. 2000 (59)	34 psychotic BD, 31 SCH, 26 SAD, bipolar type	Adequate treatment with 3 different classes of APs	CLZ flexible doses	24	All patients showed significant improvement 24 months from intake (based on BPRS and CGI). The presence of suicidal ideation at intake predicted greater improvement at endpoint.
Ciapparelli et al. 2003 (60)	37 psychotic BD, 34 SCH, 30 SAD, bipolar type	Adequate treatment with 3 different classes of APs	CLZ flexible doses	48	SAD and BD show greater clinical improvement than those with SCH. Patients with BD have the shortest time to response and the highest psychosocial and occupational functioning levels (based on BPRS, CGI and GAF).
Fehr et al. 2005 (64)	9 BD	2 ACs + APs	CLZ(156+/-77)	12	3 patients demonstrated striking mood stabilization and returned to previous levels of functioning (based on BPRS and HDRS); 5 patients had moderate improvement in mood

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stabilization and functioning (based on BPRS and HDRS); and  
1 patient showed a minimal response.

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AC = anticonvulsant; AD = antidepressant; ADRs = adverse drug reaction; AP = antipsychotic; BD = bipolar disorder; BPRS = Brief Psychiatric Rating Scale; CGI= Clinical Global Impression; CLZ = clozapine; ECT = electroconvulsive therapy; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; Li = lithium; SCH = schizophrenia; SAD = schizoaffective disorder; TRBD = treatment-resistant bipolar disorder; UD = unipolar depression; VPA = valproate; YMRS = Young Mania Rating Scale.

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Table 4. Clozapine case series and reports for TRBD

Subjects	Author, year	Age gender	Resistance definition (Failure of)	Treatments (mg/day)	Duration (months)	Main findings
2 RC BD	Calabrese et al. 1991 (74)	47 yo ♀ 48 yo ♀	AC+ AP	CLZ (250-350)	1.5-3.5	Remission
3 RC BD	Suppes et al. 1994	43 yo ♀ 25 yo ♀ 45 yo ♀	AP + AC	CLZ (150-400) + Li	12-20	2 remission, 1 response
4 euphoric mania	Antonacci et al. 1995 (70)	Unavailable	Standard treatments + AC	CLZ	–	Enhanced functioning and insight
2 mania	Poyurovsky et al. 1996 (71)	24 yo ♂ 41 yo ♀	AP + AC	CLZ (250-350) + ECT	–	Remission
1 RC BD	Lancon et al. 1996 (75)	42 yo ♀	Conventional therapy	CLZ	–	Successfully treated
3 mania	Mahmood et al. 1997 (72)	Unavailable	AP + AC	CLZ	–	Successfully treated
1 mania	Chanpattana et al. 2000 (73)	26 yo ♂	Conventional treatment	CLZ (200) +ECT	18	Complete remission
1 mania	Xu et al. 2003 (42)	40 yo ♀	AP + AC	CLZ (600) + Li (1500) + CBZ (600)	1	Remarkably effective
1 RC BD	Chen et al. 2005 (76)	38 yo ♀	Various biological therapies	CLZ (350) + TPR (300)	36	Complete remission
1 juvenile-onset BD	Vijay Sagar et al. 2005 (79)	18 yo ♀	AC combinations	CLZ (200)	24	Remission
3 BD, 2 UD	Quante et al. 2007 (74)	Not provided	Medications + ECT	CLZ (125 and 375)	12	4/5 patients showed steady improvement
1 BD	Gupta et al. 2009 (78)	28 yo ♂	Standard AC	CLZ (350)	66	No hospitalization and no more episodes
1 RC BD	Bastiampillai et al. 2010 (77)	52 yo ♀	Standard APs + ACs	CLZ (150) + LTG (100)	60	Sustained remission

7 SAD and psychotic BD	Benedetti et al. 2010 (29)	3 36yo ♂s 4 40 yo ♀s	Treatment resistant	Aripiprazole (6.8) +CLZ (293)	-	Remission
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AC = anticonvulsant; AD = antidepressant; AP = antipsychotic; BD = bipolar disorder; CBZ = carbamazepine; CLZ = clozapine; ECT = electroconvulsive therapy; Li = lithium; LTG = lamotrigine; RC = rapid cycling; SAD = schizoaffective disorder; TCA = tricyclic antidepressant; TPR= topiramate; TRBD = treatment-resistant bipolar disorder; UD = unipolar depression; yo = year old.

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**Table 5. GRADE Analysis: quality assessment of clozapine for TRBP.**

Critical outcome	Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Public bias	Large effect	Overall quality of evidence <sup>d</sup>
<b>Open studies</b>								
CGI score	236(5)	Serious <sup>a</sup>	No	No	No	Undetected	No	Very Low
BPRS score	248(5)	No	No	No	No	Undetected	No	Low
YMRS score	47(2)	No	No	No	No	Undetected	No	Low
Social functioning	304(4)	Serious <sup>b</sup>	No	No	No	Undetected	No	Very Low
Hospital days per year	377(2)	No	No	No	No	Undetected	No	Low
The mean number of admissions	377(2)	No	No	No	No	Undetected	No	Low
<b>RCTs</b>								
BPRS score	109(2)	No <sup>c</sup>	No	No	No	Undetected	No	Moderate
HDRS score	109(2)	No <sup>c</sup>	No	No	No	Undetected	No	Moderate

CGI= Clinical Global Impression; BPRS = Brief Psychiatric Rating Scale; HDRS = Hamilton Depression Rating Scale; RCT= Randomized clinical trial; TRBD = treatment-resistant bipolar disorder; YMRS = Young Mania Rating Scale.

<sup>a</sup>Incomplete accounting of patients and outcome events.

<sup>b</sup>Relatively few patients (n≤10).

<sup>c</sup>Lack of allocation concealment.

<sup>d</sup>The quality of evidence was rated using the GRADE Working Group system. High quality indicates that further research is very unlikely to change our confidence in the estimate of effect but none of the studies reached that level. Moderate quality indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality indicates that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality indicates that we are very uncertain about the estimate.

Table 6. Clozapine ADRs in TRBD

	<i>ADRs</i>	<i>N (% in 797 total)</i>
<b>Blood cells</b>	<i>Leukopenia</i>	14 (1.7)
	<i>Decreases in WBC</i>	6 (0.8)
	<i>Agranulocytosis</i>	2 (0.3)
<b>Metabolic system</b>	<i>Weight gain</i>	31 (4.0)
	<i>Weight loss</i>	1 (0.1)
	<i>Hyperlipidemia</i>	1 (0.1)
	<i>Increased appetite</i>	1 (0.1)
	<i>Diabetes type 2</i>	1 (0.1)
<b>Endocrine system</b>	<i>Sialorrhea</i>	42 (5.2)
	<i>Sweating</i>	4 (0.5)
	<i>Dry mouth</i>	1 (0.1)
	<i>Influenza-like syndrome</i>	1 (0.1)
<b>Cardiovascular system</b>	<i>Abnormal EEG</i>	6 (0.8)
	<i>Orthostatic hypertension</i>	6 (0.8)
	<i>Tachycardia</i>	6 (0.8)
	<i>Orthostatic hypotension</i>	2 (0.2)
<b>Digestive system</b>	<i>Constipation</i>	40 (5.0)
	<i>Diarrhea</i>	8 (1.1)
	<i>Nausea/vomiting</i>	5 (0.6)
	<i>Postprandial regurgitation</i>	1 (0.1)
	<i>Ileus</i>	1 (0.1)
<b>Nervous system</b>	<i>Sedation</i>	98 (12.2)
	<i>Body ache and pain</i>	15 (1.8)
	<i>Dizziness</i>	11 (1.4)
	<i>Sleep cycle inversion</i>	7 (1.1)
	<i>Transient fever</i>	8 (0.9)
	<i>Urinary incontinence</i>	6 (0.8)
	<i>Seizure</i>	4 (0.5)
	<i>Tremors</i>	2 (0.2)
	<i>Fatigue</i>	2 (0.2)
	<i>Neuroleptic malignant syndrome</i>	1 (0.1)
	<i>Bradykinesia</i>	1 (0.1)
	<i>Enuresis</i>	1 (0.1)
	<i>Mental confusion</i>	1 (0.1)

ADR = adverse drug reaction; EEG = electroencephalography; TRBD = treatment-resistant bipolar disorder; WBC = white blood cell count.

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Figure 1 PRISMA flow diagram

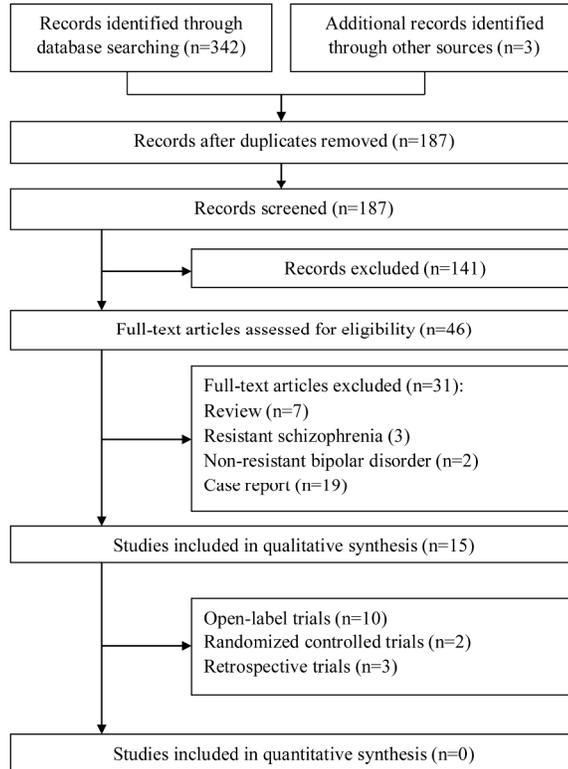


Figure 1 PRISMA flow diagram  
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