



REVIEW

Prevention of suicide by clozapine in mental disorders: systematic review



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KEYWORDS

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Abstract

Background: Previous research has investigated the efficacy of clozapine in reducing suicidality in patients with schizophrenia and schizoaffective disorder. We aimed to systematically review published evidence, including studies concerning clozapine administration to treat: (a) refractory suicidality in other mental disorders, including bipolar disorder and borderline and other personality disorders; and (b) refractory cases of non-suicidal self-injury.

Method: We performed a PUBMED-search (last day: July 17, 2022) of English-language studies, combining the keywords “clozapine”, “suicidality”, and “suicide” with various psychopathological terms (e.g. “schizophrenia”). All duplications were eliminated.

Results: Fifty-one studies were eligible for inclusion in the review. Most studies suggest a superior anti-suicide effect of clozapine in schizophrenia/schizoaffective disorder, compared to other antipsychotics, or no antipsychotic therapy, which is not due to the close monitoring of patients for blood dyscrasias. No consensus exists as to whether other antipsychotic drugs share this effect. Discontinuation of clozapine is associated with increases in suicidality. Reductions in refractory suicidality/NSSI are observed in clozapine-treated patients with bipolar disorder or borderline personality disorder, but the evidence is limited. Potential biological underpinnings of the anti-suicide effect of clozapine include its unique profile of modulation of brain neurotransmitters; its non-selectivity for neurotransmitter receptors; specific genetic and hormonal factors; effects on neuroinflammation; and ability to elicit epileptiform activity.

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Conclusion: The superior anti-suicide effect of clozapine in schizophrenia/schizoaffective disorder patients is well established. It may have a role in severe and refractory cases of suicidality and non-suicidal self-injury in patients with bipolar disorder or borderline personality disorder, but the level and quality of supporting evidence is limited.

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1. Introduction

1.1. Background

The risk of suicide in patients with schizophrenia is 20-50 times higher than that for the general population: between 25-50% of patients attempt suicide, while 4-13% die by suicide (Meltzer, 2001; Hor and Taylor, 2010). A meta-analysis revealed that among all specific-cause mortality in patients with schizophrenia, death by suicide was the most elevated - up to 9.7-fold - compared to the general population, suggesting that suicide is the greatest relative risk factor for mortality in these patients (Correll et al., 2022).

Clozapine is an 'atypical' antipsychotic approved for the treatment of resistant schizophrenia. It has a distinct pharmacological profile and exerts its action on multiple receptors. It has a higher affinity for D1 and D4 than D2 receptors, and its rapid dissociation from D2 receptors ('fast off' phenomenon) probably accounts for the more robust antipsychotic effect and lower propensity to cause extrapyramidal symptoms and hyperprolactinemia. It also has affinity for the serotonergic 5-HT_{1A}, 5-HT_{1C}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, 5-HT₇ receptors, adrenergic α_1 and α_2 receptors, histaminergic H₁, H₃, H₄ receptors, and muscarinic M₁ and M₅ receptors (De Berardis et al., 2018).

Clozapine is not considered a first-line treatment because some patients have troublesome adverse effects (e.g. sedation, weight gain, constipation, nocturnal hypersalivation, etc.) and may decline to start or continue treatment with this medication. Other adverse effects of clozapine are potentially more dangerous and life-threatening (including myocarditis, seizures, agranulocytosis or granulocytopenia), and these may influence a clinician's decision to introduce this drug (Warnez and Alessi-Severini, 2014; De Berardis et al., 2018).

However, clozapine seems to have unique anti-suicidal effects. More precisely, a number of studies have investigated the potential effectiveness of clozapine in the reduction of suicidality, mainly in patients suffering from schizophrenia or schizoaffective disorder (SZA). Based on data from the International Suicide Prevention Trial (InterSePT) (Meltzer et al., 2003), the Food and Drug Administration (FDA) approved clozapine as the only medication to treat suicidality manifestations in patients with schizophrenia/schizoaffective disorder (U.S. Food and Drug Administration, 2002).

Another important issue in clinical practice is whether discontinuation of clozapine is associated with significantly greater risk of relapse not only of psychotic manifestations, but of suicidality symptoms in particular, when compared to continuing treatment. Notably, rates of discontinuation

of antipsychotic medications in general (Lieberman et al., 2005), and of clozapine in particular (Ciapparelli et al., 2003) are high, with the latter ranging between 20% and 60% (Krivoy et al., 2011).

Refractory suicidality is often seen in patients suffering from clinical conditions other than schizophrenia and related psychoses, including bipolar disorder (Ciapparelli et al., 2000) and borderline personality disorder (Vangala et al., 1999). Furthermore, patients with non-suicidal self-injury (NSSI) are often resistant to multiple pharmacological and psychological interventions (Frankenburg and Zanarini 1993; Yang et al., 2022). Consequently, it would be important to investigate the literature regarding the use of clozapine for the above-mentioned refractory clinical conditions.

Overall, there are many uncertainties about the effects of clozapine in reducing suicidality: including whether this results from its unique pharmacological profile, or arises indirectly from the close monitoring of patients and their treatment; whether clozapine is the only antipsychotic drug with this effect, or whether it is shared with at least some other antipsychotic medications; whether clozapine cessation is associated with a significant risk of re-emergence of suicidality manifestations; and whether the anti-suicidal effect of clozapine is specific to patients with schizophrenia or schizoaffective disorder, or whether it extends to patients with other conditions, including bipolar disorder, borderline personality disorder, or recurrent non-suicidal self-injury.

1.2. Aims of the review

(a) We aimed to systematically review all publications that report on the effect of clozapine - when compared to various other antipsychotics, or to no antipsychotic medication - on 'suicidality', including suicide ideation, intention, attempted and completed suicide, in patients with schizophrenia, schizoaffective disorder and related psychotic disorders. (b) Furthermore, we systematically searched for publications regarding the potential increase in suicidality when clozapine treatment is terminated. (c) We also systematically investigated the use of clozapine to treat refractory suicidality in other diagnostic categories, including bipolar disorder, personality disorders, and clinical states in which non-suicidal self-injury is a predominant clinical feature. (d) Moreover, we attempted to delineate potential confounders as to the specificity of clozapine's anti-suicidal effects. (e) Finally, we consider possible biological mechanisms underlying clozapine's potential anti-suicidal effects.

2. Method

2.1. Criteria for the appraisal of quality of reports

For an original research publication to be included within this review, it had to: 1. report an investigation of the potential associations between clozapine administration and any aspect of co-occurring suicidality for any clinical condition; 2. report baseline and post-treatment changes in suicidality, including suicide ideation, attempts and completed suicides; 3. record the diagnosis of the clozapine-treated patients based on broadly accepted international diagnostic systems (i.e. DSM, ICD); 4. be published in a peer-reviewed scientific journal. We also considered review papers, in which a systematic search of database(s) was conducted: narrative reviews with limited reference to related articles, or mini-reviews were excluded.

2.2. Search terms-search methodology

We performed a PUBMED search combining the keywords “clozapine”, “suicidality” and “suicide” with various psychopathological terms. More precisely we used the following keyword combinations: (1) “clozapine AND [suicide OR suicidality]” (367 results); (2) “clozapine AND schizophrenia AND [suicide OR suicidality] (269 results); (3) “clozapine AND bipolar AND [suicide OR suicidality] (52 results); (4) “clozapine AND self-injury” (218 results); and (5) “clozapine AND personality AND [suicide OR suicidality] (195 results). The last day of PUBMED search was the 17th July 2022. Only English-language studies were reviewed.

In total, 1101 publications were found at this first stage of the investigation. Through the screening process, all duplications were removed, and publications not meeting our criteria (sub-Section 2.1.) were excluded from the review.

3. Results

Through the method described above, a total of 51 studies were eligible to be included. More precisely:

- (a) Regarding comparison of clozapine to other antipsychotics or no antipsychotic in reducing suicidality in schizophrenia, schizoaffective disorder and related psychotic disorders we found a total of 32 studies, including 9 clinical studies (Meltzer and Okayli, 1995; Spivak et al., 1998; Ciapparelli et al., 2000; Altamura et al., 2003; Meltzer et al., 2003; Potkin et al., 2003; Spivak et al., 2003; Glick et al., 2004; Hassan et al., 2021), 12 epidemiological studies (Reid et al., 1998; Munro et al., 1999; Modai et al., 2000; Sernyak et al., 2001; Kuo et al., 2005; Tihonen et al., 2009; Kiviniemi et al., 2013; Reutfors et al., 2013; Ringbäck Weitoft et al., 2014; Taipale et al., 2020, 2021; van der Zalm et al., 2021), 5 meta-analyses (Hennen et al. 2005; Vermeulen et al., 2019; Forte et al., 2021); Correll et al., 2022; Wilkinson et al., 2022), and 6 review papers (Ernst and Goldberg, 2004; Aguilar and Siris 2007; Kasckow et al., 2011; Pompili et al., 2016; Zalsman et al., 2016; Hawkins et al., 2021).
- (b) Regarding the comparison of suicidality rates between patients remaining on clozapine and those who discontinued it, we found 3 epidemiological studies (Walker et al., 1997; Modestin et al.,

2005; Krivoy et al., 2011) and a single case-series (Patchan et al., 2015).

- (c) Regarding the use of clozapine to treat suicidality in clinical states other than schizophrenia/psychosis, we found one case-report (Poyurovsky et al., 2020) and one case-series (Wilkowska et al., 2019a) concerning anti-suicidal effects in treatment-resistant bipolar disorder and 3 case-reports regarding administration of clozapine in treatment-resistant borderline personality disorder (Vangala et al., 1999; Amamou et al., 2016; Garakani et al., 2020).
- (d) Regarding the use of clozapine to treat non-suicidal self-injury mostly in borderline personality disorders (but also in other clinical states) we found 6 case-series (Frankenburg and Zanarini, 1993; Chengappa et al., 1999; Hammock et al., 2001; Parker et al., 2002; Zarzar and McEvoy, 2013; Zarzar et al., 2019) and 4 case-reports (Ferrerri et al., 2004; Vohra, 2010; Jansen and L’Ecuyer, 2021; Yang et al., 2022).

3.1. Comparison of clozapine to other antipsychotics or no antipsychotic in reducing suicidality in schizophrenia and related psychotic disorders

3.1.1. Clinical studies

Meltzer and Okayli (1995) were the first to report potential anti-suicidal properties of clozapine. More precisely, among 184 neuroleptic-resistant patients, 88 (schizophrenia=73; schizoaffective disorder=15) received clozapine and were prospectively evaluated for suicidality for periods lasting from 6 months to 7 years. Twenty-two patients (25%) had attempted suicide during the 2-year period prior to clozapine therapy. A marked reduction of suicide attempts “with a high probability of success” (i.e., “the method used was of high inherent lethality and had little chance of detection”) from five to zero was observed. Suicidality was totally eliminated in 10 of the 13 patients who had made more than one prior attempt; four of these patients had made more than 4 prior attempts. Overall, there was an 86% reduction in suicide attempts with clozapine treatment which was associated with improvement in both depression and hopelessness. Consequently, the authors proposed a re-evaluation of the risk-benefit assessment of clozapine, due to its superiority regarding morbidity and mortality, compared to other antipsychotic drugs (Meltzer and Okayli., 1995).

Next, a study of chronic neuroleptic-resistant schizophrenic patients maintained on clozapine ($N = 30$) or other antipsychotic drugs ($N = 30$) for 1 year, showed that clozapine was superior regarding number of suicidal attempts ($p < 0.05$), and reductions in impulsiveness ($p < 0.05$) and aggressiveness ($p < 0.01$) (Spivak et al., 1998). Similarly, the “suicide”-item score of the Brief Psychiatric Rating Scale (BPRS) was significantly reduced ($p < 0.027$) in 91 patients with treatment-resistant (defined as inadequate response to three classes of antipsychotic drugs) schizophrenia, schizoaffective disorder or bipolar disorder with psychotic features after two years of clozapine treatment (160-237 mg/day) (Ciapparelli et al., 2000).

Altamura et al. (2003) investigated the possible association of “suicidal behaviors” (lifetime presence/absence of

suicidal attempts) with clinical and pharmacological variables in systematically followed-up patients with chronic schizophrenia/schizoaffective disorder. Patients with no history of suicide attempts had been prescribed 'atypical' antipsychotics (clozapine or risperidone) more frequently (chi-square=3.979, $df=1$, $p<0.05$). Only 4 (18.2%) of 22 suicide attempters had been prescribed atypical antipsychotics (clozapine $N=2$; risperidone $N=2$), while 36 (44.5%) out of the 81 non-attempters had been prescribed either clozapine ($N=12$) or risperidone ($N=24$).

The seminal InterSePT (International Suicide Prevention Trial) study (Meltzer et al., 2003) was a multicenter, international, randomized, 2-year trial, with masked outcome raters, comparing the effectiveness of clozapine versus olanzapine in suicide prevention in patients ($N=980$; 490 for each medication) with schizophrenia or schizoaffective disorder (refractory patients=26.8%). To control for the closer monitoring required for clozapine concerning agranulocytosis, all study patients had the same frequency of clinical follow-up. The main finding was that suicidal behavior was significantly less in clozapine-treated patients versus olanzapine-treated ones (hazard ratio [HR] = 0.76, 95% CI: 0.58-0.97, $p=0.03$). Furthermore, clozapine-treated patients had significantly reduced suicide attempts, fewer hospitalizations and less rescue interventions to prevent suicide, while they required less co-administration of antidepressants, anxiolytics and/or hypnotics. The identified hazard ratios indicate that serious suicide attempts and hospitalizations to prevent suicides can be reduced by approximately one-quarter in clozapine-treated compared to olanzapine treated-patients. The anti-suicidal superiority of clozapine was found to be independent of the presence of risk factors, including number of hospitalizations in the previous 36 months to prevent suicide, baseline score on the Calgary Depression Scale, severity of Parkinsonian manifestations, history of substance/alcohol/tobacco abuse, and lifetime suicide attempts (Potkin et al., 2003). Moreover, the concomitant medications (including antipsychotic, antidepressant, sedative/anxiolytic, and mood-stabilizing drugs) that patients received did not influence study outcomes (Glick et al., 2004). The results of the InterSePT study led the United States Food and Drug Administration FDA to specifically approve the use of clozapine for reducing the risk of recurrent suicidal behaviors in patients with schizophrenia/schizoaffective disorder at risk of re-experiencing suicidal behavior, not necessarily those having treatment-resistant schizophrenia (U.S. Food and Drug Administration, 2002). Interestingly, the FDA was persuaded by the study data even though clozapine was found to only reduce the risk of suicide attempts, and not completed suicide (Ernst and Goldberg, 2004): possibly because few of even high-risk patients died of suicide during the InterSePT (5 clozapine-treated versus 3 olanzapine-treated patients, $p=0.73$). The major finding of the InterSePT study is that clozapine therapy is superior to olanzapine therapy in reducing key measures of suicidality in patients with schizophrenia or schizoaffective disorder who are at high risk for suicide (Meltzer et al., 2003).

Hassan et al. (2021) followed-up patients with schizophrenia-spectrum disorders for at least six months to compare the reduction of suicidal ideation (assessed by Beck Scale for Suicidal Ideation [BSSI]) by various an-

tippsychotics. They found no significant differences between clozapine and other antipsychotics in reduction of suicidal ideation: however, the number of patients with actual suicidal ideation (i.e., BSSI>0) at baseline was small (clozapine=10; other antipsychotics=20), and all participants were clinically stable outpatients, and not experiencing acute psychotic episodes.

Data of the studies of this sub-section are summarized in Table 1.

3.1.2. Epidemiological studies

Reid et al. (1998) investigated annual suicide rates in patients with schizophrenia or schizoaffective disorder in general, and clozapine-treated patients in particular. For this purpose, all suicide 'cases' in the mental health system of Texas, USA, during a 2-year period were evaluated. Additionally, the records of all clozapine-treated deceased patients during a 6-year period were reviewed to identify cases of suicide. The annual suicide rate for all patients ($N=30,130$) was 63.1 per 100,000 patients, approximately five times that in the general population. By contrast, the annual suicide rate in all clozapine-treated patients who were of similar diagnosis, age and sex ($N=1310$) was significantly lower at 12.7 per 100,000 patients. (Reid et al., 1998). Likewise, in a sample of 12,760 clozapine-treated schizophrenic patients, the risk for suicide over a 7-year period was five-fold increased to that expected for the UK population, but far smaller than the 20-fold increase in death by suicide among schizophrenic patients in general (Munro et al., 1999).

In a subsequent study ("FIN11"), Tihonen et al. (2009) explored nation-wide registers in Finland to compare schizophrenic patients ($N=66,881$) with the total population (5.2 million) between 1996 and 2006, to evaluate all-cause mortality during current and cumulative exposure to any antipsychotic drug versus no use of antipsychotics, and during exposure to the six most frequently prescribed antipsychotics (haloperidol, olanzapine, perphenazine, quetiapine, risperidone, and thioridazine) versus exposure to perphenazine. Clozapine treatment was associated with the lowest risk of death from suicide (HR= 0.34, 95% CI 0.20-0.57) compared to other antipsychotics, including: [a] the first-generation drugs haloperidol (HR= 0.61, 95% CI 0.27-1.37), perphenazine (HR= 1.00; drug of comparison), and thioridazine (HR= 0.93 95% CI 0.56-1.55); [b] the second-generation drugs olanzapine (HR= 0.94 95% CI 0.61-1.45), quetiapine (HR= 1.58 95% CI 0.89-2.79), and risperidone (HR= 1.12 95% CI 0.72-1.76); and [c] drugs from the categories of "polypharmacy" (HR= 0.86 95% CI 0.59-1.24) and "other" (HR= 1.55 95% CI 1.07-2.25). This study suggests that long-term treatment with antipsychotics is associated with lower all-cause mortality, compared with no antipsychotic use. Clozapine was associated with the lowest rates both of all-cause mortality and of death from ischaemic heart disease, leading the authors to recommend reassessment of prevailing restrictions on use of clozapine (Tihonen et al., 2009). However, De Hert et al. (2010) considered this study to be compromised by numerous issues, e.g., exclusion of deaths occurring during hospitalization leading to an exclusion of 64% of deaths on current antipsychotics from the analysis and important unmeasured risk factors.

Table 1 Studies investigating the potential anti-suicide effect of clozapine versus other antipsychotics or no antipsychotic treatment in mental disorders (Articles in *chronological order*; for articles of the same year, alphabetical order is followed).

Authors, year of publication	Type of study-Aim	Number of patients-diagnosis	Clozapine's dosages-duration of treatment	Outcome	Comments
Frankenburg and Zanarini, 1993	Case series; explored CLOZ for BPD with NSSI and refractory atypical psychosis	15 BPD patients with refractory self-injurious behaviors, BPD and atypical psychosis	Mean dose= 253.3 ± 163.7 mg/day; mean duration of treatment= 4.2 ± 2.1 months	Significant reductions in self-injury and psychosis-like symptoms	-
Meltzer and Okayli, 1995	Prospective; evaluation of CLOZ efficacy to reduce suicide attempts in SZ/SZA	88 neuroleptic-resistant SZ (N = 73) or SZA (N = 15) patients received CLOZ	Prospective evaluation of suicidality for period of 6 months-7 years	86% reduction in suicide attempts with CLOZ therapy	CLOZ is superior to FGAs concerning overall morbidity and mortality in neuroleptic-resistant SZ patients
Walker et al., 1997	Retrospective; national registry; compared all-cause mortality in current vs. former CLOZ users	N = 67,072 current and former CLOZ-treated patients	-	Suicide rates per 100,000 person-years: current CLOZ users=39; former CLOZ users=222	Stopping clozapine therapy is associated with an increase in suicide rate
Reid et al., 1998	Retrospective; database; explored annual suicide rates of SZ/SZA patients in general vs. clozapine-treated ones	SZ/SZA All=30,130; Clozapine-treated=1310	-	Annual suicide rates of SZ/SZA patients: [a] all patients= 63.1/100,000; [b] clozapine-treated= 12.7/100,000	CLOZ therapy is associated with a reduced suicide risk among SZ/SZA patients
Spivak et al., 1998	Case-control; comparison of CLOZ vs neuroleptics	60 SZ patients CLOZ=30 FGAs=30	1-year maintenance treatment	CLOZ superior to FGAs in number of suicide attempts, impulsiveness, aggressiveness	CLOZ-induced elevations of norepinephrine may underlie its antisuicidal/anti-aggressive properties
Chengappa et al., 1999	Case series; CLOZ for refractory NSSI-BPD	7 female; refractory BPD and NSSI	-	Significant reductions of self-mutilations and aggression	-
Munro et al., 1999	Retrospective; national database; among other, explored suicide risk in SZ patients	N = 12.760 clozapine-treated SZ patients	7-year observation period	Increase of suicide risk compared to U.K. population: CLOZ-treated: 5-fold; SZ in general=20-fold	Clozapine-treated SZ patients have significantly reduced suicide risk compared to SZ patients in general

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Table 1 (continued)

Authors, year of publication	Type of study-Aim	Number of patients-diagnosis	Clozapine's dosages-duration of treatment	Outcome	Comments
Vangala et al., 1999	Case report: use of CLOZ in patient with bipolar disorder	34-year old female; BD; substances abuse; BPD	CLOZ up to 500 mg/day (maintenance: 325 mg/d)	Suicide attempts eliminated; suicide ideation reduced	Improvements remained in maintenance phase
Ciapparelli et al., 2000	Naturalistic; explored CLOZ effectiveness in treatment-resistant SZ/SZA/BD patients	91 patients: SZ=31; SZA=26; BD with psychotic features=34	2-year CLOZ therapy (160-237 mg/d)	Significant reductions of BPRS-suicide item score in all diagnostic groups	CLOZ possibly effective for bipolar disorder with psychotic features
Modai et al., 2000	Retrospective; database; review of sudden deaths that occurred during 6 years in a hospital	115 deaths among 5479 patients (clozapine=561; other antipsychotics=4918)	-	Clozapine group had a 3.6 times higher suicide rate compared to 'other antipsychotics' group	Limitation: no baseline randomization to antipsychotics
Hammock et al., 2001	Case series; CLOZ for refractory NSSI in mental retardation	2 patients with intellectual disability	200 mg/d	Marked reductions in NSSI and aggression	CLOZ possibly effective for refractory NSSI and aggression in intellectual disability
Sernyak et al., 2001	Retrospective; database; CLOZ vs. other antipsychotics as to mortality	SZ; clozapine-treated=1415; controls=2830	3-year post-discharge follow-up	Post-discharge mortality due to suicide: no differences between the groups	Clozapine therapy is not superior to other antipsychotics regarding mortality due to suicide
Parker et al., 2002	Retrospective chart review; CLOZ for refractory NSSI in BPD patients	8 (psychotic features=3); refractory NSSI-BPD patients	Mean dosage= 334 mg/d (range 175-550 mg/d)	7 of 8 patients markedly improved; discharged after long hospitalization	-
Altamura et al., 2003	Cross-sectional; comparison of SZ/SZA patients with presence vs. absence of lifetime suicidal attempts	SZ/SZA; 22 attempters (CLOZ=2, risperidone=2) 81 non-attempters (CLOZ=12, risperidone=24)	-	Atypical antipsychotics (CLOZ/risperidone) were more frequently prescribed to non-attempters (44.5%) than to attempters (18.2%)	-

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Table 1 (continued)

Authors, year of publication	Type of study-Aim	Number of patients-diagnosis	Clozapine's dosages-duration of treatment	Outcome	Comments
Meltzer et al., 2003	InterSePT: prospective, randomized trial; CLOZ vs. olanzapine in suicide prevention	N = 980 SZ/SZA patients: CLOZ=490; olanzapine=490	2 years	CLOZ-group had fewer suicide attempts/ hospitalizations/ rescue interventions to prevent suicide	CLOZ possess superior anti-suicide properties compared to olanzapine
Spivak et al., 2003	Open prospective 6-month trial comparing CLOZ to depot haloperidol	SZ; N = 44; clozapine=18; depot haloperidol=26	6 months	Only in the CLOZ group: Positive correlations between reduction in suicidality and reductions in impulsiveness/ aggressiveness	CLOZ may reduce suicidality, mainly through reductions in impulsiveness and aggressiveness
Ferreri et al., 2004	Case report; use of CLOZ in BPD with NSSI	19-year old patient with BPD and recurrent NSSI	300 mg/day	4-week CLOZ therapy: remission of self-mutilating behaviors	-
Glick et al., 2004	Investigated whether concomitant drugs influenced InterSePT results	SZ/SZA; CLOZ=479 Olanzapine=477	-	Concomitant drugs did <u>not</u> influence InterSePT results	CLOZ superior anti-suicidal effects derive from its pharmacological properties
Kuo et al., 2005	Case-control study comparing patients who died by suicide versus controls	N = 4237 SZ inpatients; suicide=78; controls=78	-	Clozapine therapy had no association with completed suicide	-
Modestin et al., 2005	Retrospective study with mirror design; investigated whether clozapine cessation increases suicidality	94 inpatients (17 patients for the post-CLOZ period)	Mean duration of each period of observation (pre-CLOZ, CLOZ treatment phase, post-CLOZ) =15 months	Rates of suicidal behavior: pre-CLOZ=28%; CLOZ=3%; post-CLOZ=18% Rates of "serious suicidal behavior requiring medical attention": pre-CLOZ=12%; CLOZ=1%; post-CLOZ=12%	CLOZ reduces suicidal behavior rates including serious ones CLOZ cessation is associated with suicidality increase CLOZ anti-suicidal effect: unrelated to antidepressants' co-administration

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Table 1 (continued)

Authors, year of publication	Type of study-Aim	Number of patients-diagnosis	Clozapine's dosages-duration of treatment	Outcome	Comments
Tihonen et al., 2009	Retrospective cohort study; national database; 10-year cause-specific mortality of SZ patients vs. general population, including death by suicide	66,881 SZ patients	-	CLOZ therapy had lowest risk of death from suicide compared to haloperidol, thioridazine, olanzapine, perphenazine, risperidone, quetiapine, "other", and poly-pharmacy	Authors' recommendation: reassessment of restrictions on use of clozapine
Vohra, 2010	Case report, use of CLOZ for NSSI in patient with BPD	1 female BPD patient with chronic NSSI	175 mg/day	10-week CLOZ therapy: dramatic improvement in NSSI/BPD symptoms	-
Krivoy et al., 2011	Retrospective analysis; effect of CLOZ discontinuation in suicidality	$N = 100$ SZ patients; continued CLOZ=58; discontinued CLOZ=42	CLOZ maximal dose (mg/d): continued= 440 ± 138 ; discontinued= 339 ± 156 Duration of CLOZ treatment (years): continued= 5.75 ± 2.17 ; discontinued= 0.9 ± 1.25	Significantly less suicide attempts in patients continuing CLOZ vs. those who discontinued ($p = 0.02$)	-
Kiviniemi et al., 2013	Retrospective; nationwide, register; explored mortality during antipsychotic therapy	First-onset SZ; At study's end: dead by suicide=122; alive=6630	5-year follow-up after first onset of SZ	Among SGAs, only clozapine reduced mortality due to suicide	-
Reutfors et al., 2013	Case-control study; investigated suicide risk in relation to psychotropic drugs	SZ/SZA; $N = 4000$; died by suicide within 5 y from diagnosis ("cases") =88; SGA-treated= 12 cases, 20 controls	-	SGA-therapy associated with 70% reduction of suicide risk compared to no therapy; no difference if CLOZ or other SGA was administered	No significant association between suicide and prescription of "any antipsychotic", depot injection-antipsychotics, antidepressants, or lithium
Zarzar and McEvoy, 2013	Case series of the use of CLOZ in BPD patients with NSSI	4 female BPD patients with persistent NSSI	150, 400, 200, and 200 mg/day, respectively	Remission of self-injurious behaviors and aggression	-

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Table 1 (continued)

Authors, year of publication	Type of study-Aim	Number of patients-diagnosis	Clozapine's dosages-duration of treatment	Outcome	Comments
Ringbäck Weitoft et al., 2014	Population-based cohort study; explored anti-suicide effect of antipsychotics	SZ/SZA; N = 26.046	-	CLOZ (vs. haloperidol): lower odds of death by suicide/ attempted suicide/ re-hospitalization	-
Patchan et al., 2015	Case series of death by suicide after abrupt CLOZ discontinuation	N = 3 male SZ patients	300-400 mg/d for 1-2y	After CLOZ discontinuation: death by suicide after 48 h- 8 months	-
Amamou et al., 2016	Case report of clozapine in patient with BPD suicidality	33-year-old male; BPD with refractory suicidal ideation	300 mg/day	Remission of suicidal ideation; functioning markedly improved	-
Wilkowska et al., 2019a	Case series; treatment of suicidality in bipolar disorder	Three female BD inpatients (age: 26-42 years) with refractory suicidality	100 mg/day as monotherapy (1 patient) or as add-on-therapy	In all cases: significant improvement of suicidality	-
Zarzar et al., 2019	Case series; clozapine administration in refractory NSSI	10 prisoners; median age=28 years; antisocial or BPD; refractory NSSI	Median dosage= 125 mg/day	70% reduction in emergency room visits due to NSSI	-
Garakani et al., 2020	Case report; clozapine plus oxytocin for refractory suicidality in comorbid BPD-SZA	Female patient, 29 years old	Clozapine= 150 mg/day; oxytocin=10 units sublingually twice daily	Remission of suicidality within 4 weeks of starting augmentation with oxytocin	Clozapine-oxytocin combination may reduce refractory suicidality in SZA-BPD comorbidity
Poyurovsky et al. 2020	Case report; clozapine for severe suicidality in comorbid BD-OCD	Female patient; 41 years old	250 mg/day	Complete remission of suicide ideation after 6-week clozapine therapy	Low-dose clozapine may reduce refractory suicidality in BD-OCD comorbidity
Taipale et al., 2020	Nationwide, register-based cohort study; compared efficacy of antipsychotics in suicidality	62,250 SZ patients	Up to 20 years follow-up (median 14.1)	CLOZ was superior to all other antipsychotics as to mortality from suicide and all-cause and cardiovascular mortality	-

(continued on next page)

Table 1 (continued)

Authors, year of publication	Type of study-Aim	Number of patients-diagnosis	Clozapine's dosages-duration of treatment	Outcome	Comments
Hassan et al., 2021	Follow-up study; comparison of anti-suicidal effect	SZ-spectrum; with suicidal ideation: CLOZ-treated=10; non-clozapine=20	6-month follow-up	No differences regarding reduction in suicidal ideation	Limitation: all patients were clinically stable at study entry
Jansen and L'Ecuyer, 2021	Case report; clozapine for NSSI	Female; NSSI, depression, 9 suicide attempts	350 mg/day; five weeks as inpatient	Drastic decrease in NSSI	-
Taipale et al., 2021	Nationwide register-based cohort studies (Finland, Sweden); compared antisuicide effect of antipsychotics (monotherapy)	$N = 91,712$ SZ patients; Finnish cohort=61,889; Swedish cohort=29,823	-	Compared to no use of antipsychotics, CLOZ was the only antipsychotic associated with decreased risk of attempted or completed suicide	Authors propose that CLOZ should be considered as first-line treatment for high-risk patients
van der Zalm et al., 2021	National data base. Comparison of suicide effect of CLOZ vs. other antipsychotics	Non-affective psychosis Incidence cohort=22,100 Prevalence cohort= 50,881	-	"Current use": CLOZ was superior in both the incidence and prevalence cohorts as to suicide risk "Cumulative use" for up to 1 year: "other antipsychotics" were superior to CLOZ as to suicide risk	The opposing trends of "current" and "cumulative use" suggest that clozapine cessation marks a period of high risk for suicide
Yang et al., 2022	Case series; use of clozapine in NSSI	2 female adolescents; refractory NSSI and depression	12.5 mg/d and 25 mg/d, respectively	Improvement in both NSSI and depression	Low dose CLOZ may be useful for refractory NSSI and depression

Abbreviations: BD= bipolar disorder; BPD= borderline personality disorder; BPRS= Brief Psychiatric Rating Scale; CI= confidence intervals; CLOZ= clozapine; d=day; FGAs= first generation antipsychotics; HR= hazard ratio; mg/d= mg/day; InterSePT= International Suicide Prevention Trial; NSSI= non-suicidal self-injury; OCD= obsessive-compulsive disorder; OR= odd ratio; SGAs= second generation antipsychotics; SZ= schizophrenia; SZA= schizoaffective disorder; y= years.

Kiviniemi et al. (2013) assessed the impact on mortality - including death by suicide - of the antipsychotics widely used in everyday practice, including first-generation drugs chlorprothixene, levomepromazine, perphenazine and thioridazine and the second-generation drugs clozapine, olanzapine, quetiapine and risperidone in a nationwide, register-based, 5-year (1998-2003) follow-up study of all patients with first-onset schizophrenia ($N = 6752$). After adjusting for age, gender, comorbid physical diseases and patient group, clozapine was the only atypical antipsychotic associated with lower likelihood of suicide (HR= 0.35 95% CI 0.21-0.58, $p < 0.001$; comparison group: no antipsy-

chotic administration during the six months prior to patients' death). When compared to treatment with second-generation drugs, pharmacotherapy with first-generation drugs was associated with increased all-cause mortality, but decreased mortality by suicide.

A subsequent case-control study explored suicide risk in schizophrenic patients treated with various antipsychotics, antidepressants, and lithium (Reutfors et al., 2013). Among 4000 patients with a first discharge diagnosis of schizophrenia or schizoaffective disorder during a 17-year period (1984-2000), a total of 88 ("cases"; 54% male) died within five years of diagnosis. The suicide risk was reduced by ap-

proximately 70% in patients (12 cases and 20 controls) who had ever been prescribed a second-generation antipsychotic (clozapine, olanzapine, risperidone, or ziprasidone) compared to those who had not (adjusted odds ratio [OR]=0.29, 95% CI 0.09-0.97). When the 6 cases and 8 controls who had been prescribed clozapine were excluded, the association did *not* change substantially (OR=0.23, 95% CI 0.06-0.89). Thus this study did not show superiority of clozapine versus other atypicals in antisuicide effects. There was no significant association between suicide and prescription of “any antipsychotic”, depot injection antipsychotics, all antidepressants, selective serotonin reuptake inhibitors, or lithium (Reutfors et al., 2013).

Ringbäck Weitoft et al. (2014) investigated the odds of death by suicide and of attempted suicide in 26,046 patients with schizophrenia or schizoaffective disorder receiving antipsychotics from 2006 to 2009 in Sweden. Clozapine-treated patients showed lower odds of death by suicide (odds ratio, OR=0.45, 95% CI 0.20-0.98) and attempted suicide (OR=0.44 [0.28-0.70]) than haloperidol-treated patients (OR=1.00, reference group) after adjustment for age, sex and year of discharge. Clozapine-treated patients were most likely to refill prescriptions and had lower rates of re-hospitalization (hazard ratio=0.73 [95% CI 0.59-0.90]). Only one death and 23 cases of agranulocytosis were reported, compared with 223 suicides and 831 suicide attempts. The authors calculated that use of clozapine instead of other antipsychotics could have prevented 95 suicide attempts during this period (olanzapine-treated patients demonstrated approximately the same favorable pattern).

In a nationwide, register-based cohort study, Taipale et al. (2020) investigated the comparative efficacy of antipsychotics in reducing suicide risk in patients with schizophrenia, compared to no therapy with antipsychotics. Data were drawn from a non-randomized, observational, nationwide sample of all inpatients ($N = 62,250$) treated for schizophrenia between 1972 and 2014 in Finland with up to 20 years of follow-up (median 14.1 years). Long-term antipsychotic use was associated with substantially decreased mortality compared to no therapy with antipsychotics. Among specific antipsychotics, clozapine was associated with the most beneficial outcome concerning mortality from suicide (adjusted hazard ratio [aHR]=0.21, 95% CI: 0.15-0.29). The respective aHR (95% CI) of the rest of the antipsychotics were [a] first-generation: chlorprothixene 0.79 (0.53-1.18); flupentixol 0.21 (0.03-1.48); flupentixol long-acting injectable (LAI) 0.54 (0.13-2.17); fluphenazine-LAI 0.52 (0.13-2.16); haloperidol 0.44 (0.22-0.87); haloperidol-LAI 0.9 (0.53-1.53); levomepromazine 0.81 (0.52-1.26); perphenazine 0.43 (0.28-0.66); perphenazine-LAI 0.69 (0.43-1.1); zuclopenthixol 0.53 (0.23-1.2); zuclopenthixol-LAI 0.46 (0.28-0.76); [b] second-generation: aripiprazole 0.74 (0.38-1.44); olanzapine 0.55 (0.43-0.71); olanzapine-LAI 0.35 (0.05-2.48); quetiapine 0.81 (0.56-1.17); risperidone 0.64 (0.47-0.86); risperidone-LAI 0.44 (0.24-0.83); [c] “polytherapy” 0.41 (0.33-0.51). Clozapine was superior to all other antipsychotics in terms of all-cause mortality (aHR=0.39, 95% CI 0.36-0.43) and mortality due to cardiovascular disease (aHR=0.55, 95% CI 0.47-0.64). The cumulative mortality rates during maximum follow-up of 20 years were 46.2% for no antipsychotic use, 25.7% for any antipsychotic use, and 15.6% for clozapine

use. In conclusion, this study revealed the superiority of clozapine compared to other antipsychotics with regard to mortality from suicide, and also both all-cause and cardiovascular mortality, in the long-term antipsychotic treatment of patients with schizophrenia (Taipale et al., 2020).

Subsequently, Taipale et al. (2021) reported findings of two nationwide register-based cohort studies, which included all schizophrenic patients ($N = 91,712$) in Finland and Sweden, and which investigated the comparative effectiveness of 10 most-commonly used monotherapies with antipsychotics in reducing the risk of attempted or completed suicide. The Finnish cohort included all inpatients ($N = 61,889$) treated for schizophrenia between 1972 and 2014, the Swedish cohort included all persons aged 16-64 ($N = 29,823$) registered as receiving treatment for schizophrenia between 2006 and 2013. They found that - compared to no antipsychotic treatment - clozapine therapy was consistently associated with significantly reduced risk of suicidal outcomes. Hazard ratios and 95% CI for attempted or completed suicide were 0.64 (0.49-0.84) in the Finnish cohort and 0.66 (0.43-0.99) in the Swedish cohort. No other antipsychotic drug was associated with a reduced risk of attempted and/or completed suicide, including: (a) the first-generation drugs haloperidol, levomepromazine, perphenazine and zuclopenthixol long-acting injectable (LAI); (b) the second-generation drugs aripiprazole, olanzapine, quetiapine, risperidone, and risperidone-LAI; (c) medications from the general categories “other oral”, “other LAI”, and “polytherapy”. Adjunctive pharmacotherapy with antidepressants, lithium, or mood stabilizers had no impact on suicidality (attempted/completed suicide), but add-on therapy with benzodiazepines or Z-drugs (non-benzodiazepine hypnotics such as zopiclon and zolpidem) increased suicidality (attempted/completed suicide). In conclusion, the major finding was that clozapine was the only antipsychotic drug associated with decreased risk of attempted or completed suicide among patients with schizophrenia (SZ); subsequently the authors suggest that it should be considered as first-line treatment for high-risk patients (Taipale et al., 2021).

A recent study compared mortality - including death by suicide - between clozapine-treated patients and patients treated with other antipsychotics, in an incidence cohort of 22,100 patients with a first diagnosis of “non-affective psychotic disorder” (1995-2013) and a prevalence cohort of 50,881 patients who had ever received this diagnosis (1969-2013) (van der Zalm et al., 2021). Hazard ratios (HR) - with adjustment for somatic comorbidity - were calculated for the antipsychotic drug used at the time of the death (“current use”: incidence and prevalence cohort) and for the drug used for the longest period at that time (“cumulative use”: incidence cohort), with clozapine as the reference drug. Regarding “current use”, the risk of suicide was higher among users of other antipsychotics in both the incidence (HR= 1.76 95% CI 0.72-4.32) and prevalence (HR= 2.20 95% CI 1.35-3.59) cohorts, compared to clozapine-treated patients. However, the “cumulative use” of other antipsychotics for up to one year was associated with a lower suicide risk than a similar period of clozapine use (HR= 0.65 95% CI 0.46-0.91). The authors contended that these opposing trends toward a lower risk of suicide during “current

use” of clozapine and a higher risk of suicide associated with “cumulative use” up to one year suggests that clozapine cessation marks a period of high risk for suicide (van der Zalm et al., 2021).

In contrast to the findings outline above, other studies do not support the superiority of anti-suicide effect for clozapine (Modai et al., 2000; Sernyak et al., 2001; Kuo et al., 2005). More precisely, Modai et al. (2000) found an inverse association between treatment with clozapine and death by suicide, having reviewed sudden deaths that occurred in a hospital during a 6-year period and finding that the suicide rate among clozapine-treated patients was 3.6 times higher than among patients treated with other antipsychotics: however, the patients had naturally not been randomized to differing antipsychotic drugs, and clozapine-treated patients may have had more severe suicidality at baseline (Aguilar and Siris 2007). Subsequently, a retrospective study which compared clozapine-treated schizophrenic inpatients ($N = 1,415$ veterans) versus those who did not receive clozapine ($N = 2,830$) during a 4-year period (Sernyak et al., 2001) found that over 3 years after discharge, the rates of mortality due to suicide were similar between the two groups. Although the clozapine group had a lower overall mortality, this was attributable to the lower rate of death due to respiratory disorders. Meltzer (2002) criticized the study of Sernyak et al. (2001) for not taking into account when in the course of psychosis was clozapine administered (one-third of the sample received clozapine for less than six months), even though the reported follow-up period was 5-6 years: moreover, the comparison group was not matched on previous suicide attempts and depressive symptoms, both parameters being closely linked to suicide risk. Furthermore, the study was not randomized and the groups may have differed in the severity of suicidality at baseline (Aguilar and Siris 2007; Kasckow et al., 2011). Finally, 4237 acutely-ill patients with schizophrenia who were admitted during a 16-year period (1985-2000) were followed until 2001, 78 patients who died from suicide during this period being matched with controls: among other variables, “clozapine use” was recorded and found not to be related to completed suicide (Kuo et al., 2005).

The data of the studies of this sub-section are summarized in Table 1.

3.1.3. Meta-analyses

The following meta-analyses explored - among other treatment modalities - the antisuicidal effects of clozapine:

Hennen et al. (2005) searched for publications with contrasting rates of suicides or attempts by chronically psychotic patients treated with clozapine versus other agents, and included six studies, involving 240,564 patients with schizophrenia or schizoaffective disorders, representing 104,796 person-years of exposure to clozapine and 447,281 person-years of exposure to other treatments. Random-effects meta-analysis indicated that clozapine was associated with a three-fold overall reduction of risk of suicidal behaviors ($RR = 3.3$, 95% CI 1.7 - 6.3, $p < 0.0001$) when compared with other agents: for completed suicides, the risk ratio was 2.9 (95% CI 1.5 - 5.7, $p < 0.002$).

Another meta-analysis explored the influence of clozapine on long-term mortality, including death by sui-

cide, in 22 samples of clozapine-treated patients with schizophrenia-spectrum disorders during a follow-up of 1.1-12.5 (median=5.4) years (Vermeulen et al., 2019). The findings did not support previous data reported by Fontaine et al. (2001), namely that the lives saved via reduction in suicide may be offset by clozapine-induced cardiovascular deaths. Moreover, continuous pharmacotherapy with clozapine was associated with a significantly lower long-term all-cause mortality rate compared to other antipsychotics. However, regarding specifically long-term mortality from suicide death, Vermeulen et al. (2019) - analyzing data from 13 relevant studies - did not find significant differences between clozapine-treated patients and those receiving other antipsychotics ($p = 0.455$).

A recent meta-analysis compared clozapine to other second-generation drugs - including aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone - concerning the reduction of attempted and completed suicide (Forte et al., 2021). A total of 18 reports with data regarding 35 paired comparisons of an atypical antipsychotic with another treatment was included in the random-effects meta-analysis. The ranking of non-clozapine drugs by possible anti-suicidal efficacy was (OR, [95% CI]): risperidone (0.733, [0.463-1.16]) \geq olanzapine (0.796 [0.573-1.11]) \geq aripiprazole (0.872 [0.700-1.09]), and the OR exceeded 1.0 (higher apparent suicidal risk) with quetiapine (1.31 [1.01-1.70]) and ziprasidone (1.26 [0.682-2.34]): however, none of these effects was statistically significant. In striking contrast, there was a large and consistent effect of clozapine in all seven trials (OR=0.229, 95% CI 0.111-1.12, $p < 0.0001$). Therefore, this meta-analysis indicates that clozapine is unique in providing strong protection against suicidal behavior, and that other antipsychotics evaluated (aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone) do not share this effect (Forte et al., 2021).

A recent meta-analysis found that suicide is the greatest relative risk factor for mortality in schizophrenia, when compared to the general population ($RR = 9.76$, 95% CI: 7.60-12.55) (Correll et al., 2022). Clozapine treatment significantly reduced mortality by suicide, compared to no antipsychotic treatment ($RR = 0.22$, 95% CI: 0.16-0.30). In incident (i.e. earlier-phase) schizophrenia, clozapine exerted the greatest protection concerning suicide-related mortality ($RR = 0.29$, 95% CI: 0.14-0.62); by contrast, oral first-generation antipsychotics were associated with increased suicide-related mortality ($RR = 2.17$, 95% CI: 1.36-3.48). In prevalent (i.e. more chronic) schizophrenia, clozapine-treated patients had the lowest risk of suicide-related mortality ($RR = 0.21$, 95% CI: 0.15-0.29), while the closest to null effect emerged for any antipsychotic ($RR = 0.73$, 95% CI: 0.36-1.49) (Correll et al., 2022).

A meta-analysis of the potential anti-suicide effectiveness of various biological therapies (including seven studies with clozapine), which involved 5424 clozapine-treated patients and 56,548 controls receiving either another antipsychotic or no antipsychotic (Wilkinson et al., 2022) found that clozapine significantly reduced the odds of suicide in patients with psychotic disorders (OR=0.46, 95% CI=0.27-0.81, $p = 0.007$). No significant antisuicide effect was found concerning electroconvulsive therapy (ECT) (OR=0.77, $p = 0.053$), antipsychotics (excluding clozapine) in patients with bipolar disorder (OR=0.73, $p = 0.069$), or

antipsychotics (excluding clozapine) in patients with psychotic disorders (OR=0.39, $p = 0.069$).

3.2. Suicidality rates in patients remaining or discontinuing clozapine

3.2.1. Epidemiological studies

Using data from a U.S. national registry, Walker et al. (1997) compared the causes of death in 67,072 current and former clozapine users during a 33-month period. Mortality from suicide was significantly decreased in current clozapine users compared to former ones: the suicide rates per 100,000 person-years were 39 and 222, respectively (rate ratio=0.17; 95% CI=0.10-030).

Subsequently, a retrospective study with a mirror-image design investigated the suicidal behavior of 94 inpatients with schizophrenia, comparing a period (mean=15 months) of continuous clozapine treatment with a pre-clozapine period of equal length, and - in a sub-group of 17 with a 15-month post-clozapine period - concerning suicidal behavior (Modestin et al., 2005). Clozapine treatment resulted in a decrease of suicidal behavior from 28% to 3%, which increased to 18% after discontinuing medication. Accordingly, the rates of "serious suicidal behavior requiring medical attention" dropped from 12% to 1% during clozapine treatment but increased to 12% after clozapine discontinuation.

A retrospective analysis of 100 patients with schizophrenia who had initiated clozapine pharmacotherapy during hospitalization between 2002 and 2008, found that individuals who remained on clozapine ($N = 58$) were significantly less likely to attempt suicide ($p = 0.02$) than those who had discontinued it ($N = 42$) (Krivoy et al., 2011). Predictors for drug discontinuation were old age at clozapine initiation, and comorbid substance use disorder (SUD).

3.2.2. Case-series

Patchan et al. (2015) described the cases of three patients with schizophrenia who committed suicide soon after (8 months, 2 weeks and 48 h respectively) abrupt discontinuation of clozapine (300-400 mg/day) (Table 1).

In conclusion, data from three epidemiological studies (Walker et al., 1997; Modestin et al., 2005; Krivoy et al., 2011) and a case-series (Patchan et al., 2015) suggest that discontinuation of clozapine therapy is associated with significant increase in risks of suicide attempts and death by suicide, when compared to continuation therapy with this medication. The data of the studies of this sub-section are summarized in Table 1.

3.3. Administration of clozapine to treat other clinical entities besides schizophrenia and related psychoses

3.3.1. Administration of clozapine to treat suicidality in patients with bipolar disorder

Some authors have speculated that the anti-suicidal properties of clozapine could extend beyond schizophrenia, to bipolar disorder (Wilkowska et al., 2019b); however, data are few and limited to one naturalistic study (Ciapparelli et al., 2000), one case-series (Wilkowska et al.,

2019a) and two case-reports (Vangala et al., 1999; Poyurovsky et al., 2020).

3.3.1.1. *Clinical trials.* In a naturalistic study in a mixed sample of 91 patients (with refractory bipolar disorder with psychotic features, schizophrenia, or schizoaffective disorder), suicidality was significantly reduced after a 2-year period of clozapine treatment (160-237 mg/day) (more details concerning this study: sub-section 3.1.1.) (Ciapparelli et al., 2000).

3.3.1.2. *Case-reports and case-series.* Wilkowska et al. (2019a) reported significant reduction in suicidality in three female inpatients (age: 26, 26 and 42 years, respectively) with refractory bipolar disorder after clozapine (100 mg/day) monotherapy (1 patient) or add-on-therapy. Poyurovsky et al. (2020) reported the case of a 41-year-old female patient with comorbid bipolar disorder and obsessive-compulsive disorder, with severe suicidality, who had not responded to several 'atypicals' and mood stabilizers: 6 weeks of clozapine therapy (250 mg/day) resulted in the "complete disappearance" of suicidal ideation and several other symptoms (mood instability, delusional thoughts, fears of harm). Another case-report concerning administration of clozapine in a patient with bipolar disorder and borderline personality disorder is described in sub-section 3.4.1 (Vangala et al., 1999). Overall, there is limited evidence of clozapine's effectiveness in treating suicidality in treatment-resistant bipolar disorder, so further systematic research with rigorous methodology is needed in larger patient samples. Data of the studies of this sub-section are summarized in Table 1.

3.3.2. Administration of clozapine to treat suicidality in patients with borderline personality disorder

Two case-reports have explored the potential efficacy of clozapine in treating refractory suicidality in borderline personality disorder, either as a stand-alone therapy (Vangala et al., 1999; Amamou et al., 2016) or combined with oxytocin (Garakani et al., 2020). More case-series/case-reports have investigated clozapine for non-suicidal self-injurious behaviors in this condition, and are described in Subsection 3.3.3.

3.3.2.1. *Case-reports.* Vangala et al. (1999) administered clozapine, up to 500 mg/d, to treat the severe suicidality and mood instability of a 34-year-old female with borderline personality disorder comorbid with bipolar I disorder, and alcohol and amphetamine abuse. Despite lack of significant changes in mood symptoms, a great reduction in suicide ideation and termination of suicide attempts were observed. These gains remained during the next 12 months (maintenance dose: 325 mg/d). Amamou et al. (2016) administered clozapine (300 mg/day) in a 33-year-old male patient with persistent suicidal ideation refractory to various antidepressants, antipsychotics and mood stabilizers: suicidal ideation remitted, and social and professional functioning improved to the point where there was no longer need for intensive observation or restrictive procedures. Garakani et al. (2020) augmented clozapine (150 mg/day) therapy with oxytocin (10 units sublingually twice daily) to treat refractory suicidality - including self-cuts with razor and suicide attempts with overdose of medications - in a 29-year-old female patient with borderline personality disorder comorbid with schizoaffective disorder: 4 weeks after

adding oxytocin, the patient neither self-injured, nor had urges to cut anymore, symptoms which had not remitted with clozapine alone.

The data of the studies of this sub-section are summarized in [Table 1](#).

3.3.3. Administration of clozapine to treat recurrent non-suicidal self-injury

The lifetime prevalence of non-suicidal self-injury in adolescents is approximately 18% and it strongly predicts suicide ([Karasouli et al., 2015](#); [Yang et al., 2022](#)). There is no consensus on pharmacotherapy and medications are administered empirically, mainly to treat psychiatric disorders that are linked to NSSI, including mood, psychotic and anxiety disorders. Only few case-reports/case-series have explored the effect of clozapine in refractory NSSI.

3.3.3.1. Case-reports/case-series. [Frankenburg and Zanarini \(1993\)](#) administered clozapine (mean dose= 253.3 ± 163.7 mg/day; mean duration of treatment= 4.2 ± 2.1 months) in 15 patients with borderline personality disorder, self-injurious behaviors and persistent atypical psychotic manifestations - all refractory to multiple pharmacotherapies. Significant reductions were seen in self-injurious and aggressive behaviors, as well psychosis-like symptoms and overall symptomatology (BPRS scores). [Chengappa et al. \(1999\)](#) administered clozapine in seven female patients (mean age=37 years) with protracted hospitalizations due to borderline personality disorder and NSSI, refractory to several pharmacotherapies: clozapine treatment significantly reduced self-mutilations and injuries against staff and peers; four patients finally terminated hospitalization, and the others no longer needed seclusion and restraint.

[Hammock et al. \(2001\)](#) reported that in two patients with intellectual disability clozapine therapy (200 mg/day) markedly reduced NSSI and aggression, which had been refractory to numerous psychopharmacological and behavioral interventions: side effects were mild and the drug was well tolerated. [Parker et al. \(2002\)](#), in a retrospective chart review, reported that among eight patients (females=6; with psychotic features=3) with refractory borderline personality disorder and NSSI who underwent clozapine therapy (mean dose=334 mg/day; range 175-550 mg), seven were able to be discharged after long hospitalization: the authors estimated that up to 36,000 US dollars per patient per year were saved.

[Ferreri et al. \(2004\)](#) described the case of a 19-year old patient with borderline personality disorder and recurrent severe NSSI, which had been refractory to numerous pharmacotherapies with antidepressants, mood stabilizers, benzodiazepines and/or antipsychotics: 4 weeks after adding clozapine (300 mg/day), self-mutilating behaviors completely stopped and the patient was discharged. [Vohra \(2010\)](#) described the case of a 24-year old female patient with severe and refractory borderline personality disorder, numerous hospitalizations, and severe NSSI: after 10 weeks of clozapine treatment, 175 mg/day, a dramatic decrease in NSSI behaviors and other BPD symptoms was observed.

[Zarzar and McEvoy \(2013\)](#) administered clozapine (150, 400, 200, and 200 mg/day respectively) to four female inpatients (27, 41, 32, and 27 years old respectively) with

persistent, treatment-refractory NSSI: soon after initiating clozapine, self-injurious behaviors and aggression fully remitted and all patients were successfully discharged from hospital. [Zarzar et al. \(2019\)](#) administered clozapine (median dose=125 mg/day) in 10 imprisoned offenders (median age= 28 years) with antisocial ($N = 7$) or borderline ($N = 3$) personality disorder and chronic, repetitive treatment-resistant NSSI: 6 patients remained on treatment and demonstrated a 70% reduction in emergency care visits due to NSSI, and a 67% reduction in disciplinary infractions.

[Jansen and L'Ecuyer \(2021\)](#) described the case of an 18-year female with chronic severe depression, complicated by NSSI which had proved refractory to antidepressants, lithium, anticonvulsants, antipsychotics, transcranial magnetic stimulation, ECT, ketamine and psychodynamic and cognitive-behavioral psychotherapies: 5 weeks after initiating clozapine (350 mg/day), a "drastic decrease" in both NSSI and urge to self-harm was observed and the patient could safely be discharged. [Yang et al. \(2022\)](#) administered low doses of clozapine (25 mg/day and 12.5 mg/day respectively) in two female adolescents (15- and 18-year-old respectively), with recurrent depression and NSSI, both resistant to multiple trials with antidepressants, antipsychotics and ECT: After clozapine administration, both the NSSI and depressed mood significantly improved and the clinical gains were sustained over four months after discharge.

Data of the studies of this sub-section are summarized in [Table 1](#).

3.4. Potential clinical, pharmacological and social confounders as to the specificity of clozapine's anti-suicidal effects

3.4.1. Clinical confounders

It is possible that the greater anti-suicidal effect of clozapine may be secondary to its overall superiority compared to other antipsychotics in the reduction of psychosis. In addition, due to the risk of clozapine-induced blood dyscrasias, patients have closer clinical follow-up compared to patients treated with other antipsychotics, so suicidality may be more easily detected and managed - a factor also considered to be contributing to lower suicide rates in lithium-treated patients ([Forte et al., 2021](#); [Hawkins et al., 2021](#)). However, reports from samples of clozapine-treated patients in countries with reduced monitoring suggest that the suicide rate is still significantly decreased ([Meltzer, 1999](#)). Moreover, therapy with long-acting injectable antipsychotic medications does not appear to reduce suicidality, despite close and regular follow-up. Therefore, most researchers attribute the superior anti-suicidal effects of clozapine not to the close clinical follow-up, but instead to its specific pharmacological properties ([Taipale et al., 2021](#)).

[Spivak et al. \(2003\)](#) explored whether clozapine-induced reductions in impulsiveness and aggressiveness are the main causes for its superior anti-suicidal properties, in 44 chronic schizophrenics who underwent a 6-month therapy with either clozapine ($N = 18$) or haloperidol decanoate ($N = 26$): significant and positive correlations between reduction in suicidality and reductions in impulsiveness and aggressiveness were observed only in the clozapine-treated patients. Notably, reductions in suicidality, impulsiveness and aggres-

siveness were not correlated with reductions in depressed mood or in positive and negative psychotic symptoms in either group (Spivak et al., 2003).

Vermeulen et al. (2019) have postulated that the lower mortality of clozapine-treated patients might be due to fewer prescriptions of clozapine to patients with comorbid severe somatic diseases (i.e., “confounding by contraindication”): however, clozapine is most often administered to the more severely-ill psychiatric patients, at higher risk of mortality compared to those receiving other antipsychotics (“confounding by indication”). The influence of these potential confounders could be diminished by “survival treatment bias”, since patients must survive at least two treatments - according to most official guidelines - before clozapine is indicated (Vermeulen et al., 2019).

3.4.2. Pharmacological confounders

Taipale et al. (2020) noted that although clozapine was the most effective antipsychotic regarding suicide mortality (hazard ratio=0.21, 95% CI: 0.15-0.29), other typical and atypical antipsychotics in oral form or in long-acting injectable form also reduced suicide risk (see sub-Section 3.1.2. for more details of this study). If this is the case, it possibly means that biological processes which are shared with other antipsychotics (and not specific to clozapine) must underlie its anti-suicidal properties. Other studies have not found antisuicidal properties with other antipsychotics (e.g. Forte et al., 2021). Overall, there is no clear consensus on whether other second generation antipsychotics possess anti-suicidal properties (Zalsman et al., 2016).

3.4.3. Social confounders

The close follow-up of clozapine-treated patients for monitoring the potential agranulocytosis side-effect, leads to interaction with people who may provide warmth and empathy, thus alleviating to some extent feelings of loneliness and inadequacy due to social isolation - factors associated with suicidality (Pompili et al., 2002).

3.5. Biological correlates of anti-suicidal effects

3.5.1. Modulation of neurotransmitters and clozapine’s anti-depressant and anti-suicidal effects

Clozapine possesses superior antidepressant effects compared to other antipsychotics (Meltzer and Okayli, 1995; Leucht et al., 2009). In the InterSePT study, fewer clozapine-treated SZ/SZA patients needed antidepressants, compared to olanzapine-treated ones (Meltzer et al., 2003). Clozapine uniquely modulates the relationship between brain serotonin, dopamine, norepinephrine and their metabolites. It increases the release of dopamine in the prefrontal cortex, and exerts greater serotonergic effects than other antipsychotics, through the relative lack of blockade of dopamine receptors in the mesolimbic system and down-regulation of 5-HT_{2A} receptors, respectively (Meltzer, 1999; Ernst and Goldberg, 2004; Taipale et al., 2021). Additionally, it dramatically and chronically increases peripheral norepinephrine levels (Green et al., 1993; Taipale et al., 2021). In patients with refractory schizophrenia treated for 1 year, those receiving clozapine demonstrated a 3-fold higher

norepinephrine plasma level compared to those on other antipsychotics (Spivak et al., 1998). Moreover, in clozapine-treated patients - but not in haloperidol-treated ones - reductions in impulsivity and aggression were associated with elevated noradrenaline plasma levels (Spivak et al., 2003). Clozapine - but not other antipsychotics - increases norepinephrine levels both through its α -2 receptor antagonism and by blocking norepinephrine reuptake following synaptic release (Khokhar et al., 2015). In sum, certain clozapine-induced neurotransmitter modulations may contribute to its superiority in reducing suicidality, impulsivity and aggression (Meltzer, 1999; Meltzer et al., 2003; Wagstaff and Perry, 2003; Ernst and Goldberg, 2004; Taipale et al., 2021).

3.5.2. Lower propensity to cause extrapyramidal side-effects, akathisia, or tardive dyskinesia

The superior anti-suicidal effect of clozapine may also be due to its lower propensity for extrapyramidal side effects, including akathisia or tardive dyskinesia, which may increase suicidal behavior (Meltzer 1999; Aguilar and Siris, 2007). This effect is due to its interaction with dopamine receptors in the mesolimbic (related to antipsychotic effects) rather than the neostriatal (related to extrapyramidal symptoms) areas of the brain (Wagstaff and Perry, 2003).

3.5.3. Dopamine receptors D4/D2 ratio and anti-aggression properties

Clozapine has superior anti-aggression properties when compared to other antipsychotics including haloperidol, risperidone and olanzapine. This effect occurs at therapeutic doses, independently of its antipsychotic and sedation effects and is possibly due to blockade of the D4 receptor, without concomitant significant blockade of D2 receptors. Medications that inhibit both receptors equally (e.g. haloperidol) demonstrate weaker anti-aggressive properties compared to clozapine (Citrome et al., 2001; Frogley et al., 2012; El-Mallakh and McKenzie, 2013).

3.5.4. Genetic factors

The rs1800532 polymorphism of the SLC6A4 gene, encoding for the serotonin transporter, is potentially correlated with both suicide vulnerability and a poor response to clozapine and lithium (De Berardis et al., 2021).

3.5.5. Neurosteroids

In schizophrenia and bipolar disorder, death by suicide - compared to death by other causes - was associated with decreased pregnenolone levels in the parietal cortex and, moreover, this decrease was associated with the severity of suicidality (Youssef et al., 2015). Youssef et al. (2015) consider the increase of pregnenolone levels induced by both clozapine and lithium to contribute to their anti-suicidal properties. Notably, in rats, clozapine markedly elevates pregnenolone in hippocampus, cerebral cortex, and serum (Marx et al., 2006).

3.5.6. Other biological mechanisms

Neuroinflammation may increase suicidality by activating the kynurenine pathway and the subsequent serotonin depletion, stimulation of glutamate neurotransmission, re-

duced brain-derived neurotrophic factor (BDNF), and hyperactive hypothalamo-pituitary-adrenal axis (Wisłowska-Stanek et al., 2021). The anti-suicidal effect of clozapine may be due to regulation of intracellular systems-dependent modulation of N-methyl-D-aspartate receptor expression, BDNF upregulation, and regulation of the arachidonic acid cascade (Leveque et al., 2000; Marx et al., 2006). These mechanisms may be independent from those underlying the antipsychotic effect (Griffiths et al., 2014). Clozapine acts on multiple dopaminergic, serotonergic, muscarinic, adrenergic, and histaminergic receptor subtypes, and this non-selectivity may contribute to clozapine's distinct efficacy (Gould et al., 2017).

3.5.7. ECT and clozapine: potentially common biological mechanisms

Clozapine and ECT may share common biological underpinnings regarding their antisuicidal properties, including the ability to alter EEG activity and elicit epileptiform activity, to increase neuroplasticity and elevate brain levels of neurotrophic factors, to correct imbalances in the relationship between glutamate and γ -aminobutyric acid, and to reduce inflammation through effects on neuron-glia interactions (Gammon et al., 2021).

3.5.8. Reduction of substance use disorder

In patients with schizophrenia, clozapine significantly reduced the comorbid substance use disorder - a condition closely linked to suicidality - and was superior to first-generation antipsychotics in poly-substance abusers, and superior to risperidone (but not to olanzapine or ziprasidone) in poly-substance or cannabis users (Arranz et al., 2018). Additionally, clozapine reduces the initiation of SUD in schizophrenia, possibly due to the decreased release of dopamine in the mesolimbic system as a result of clozapine-induced dopamine release in the prefrontal cortex (Khokhar et al., 2018; Krause et al., 2019).

4. Conclusion

Studies of various types have investigated the efficacy of clozapine in reducing suicidality, mainly in patients with schizophrenia, schizoaffective disorder and related disorders. The vast majority suggest that clozapine has a stronger anti-suicide effect when compared to other antipsychotics, or to no antipsychotic treatment. Moreover, current data suggest that discontinuation of clozapine therapy is associated with significant increases in suicide attempts and death by suicide, when compared to continuing this medication. There is no consensus as to whether an antisuicide effect is unique to clozapine, or whether other atypical antipsychotics might share this effect (even to a smaller extent).

The anti-suicidal properties might extend beyond schizophrenia, to patients with bipolar disorder. Some data suggest that clozapine could be used in refractory cases of suicidality in bipolar patients, but evidence is limited and further systematic research with rigorous methodology is needed in larger patient samples. The same is true regarding the use of clozapine to treat suicidality in patients with borderline personality disorder. Of interest are the findings

that clozapine may also improve refractory suicidality manifestations in patients with antisocial personality disorder and intellectual disability, but the data are drawn only from one case series for each of these conditions. Almost all data concern the administration of clozapine to treat severe and refractory cases of non-suicidal self-injury or suicide attempts in patients with borderline personality disorder, and suggest that it may produce significant therapeutic gains. However, all data come from case-reports/case-series, and randomized trials with large patient samples are needed.

It is probable that the superior anti-suicidal effect of clozapine is not due to the close monitoring of patients for blood dyscrasias, as treatment with long-acting injectable antipsychotics (in which patients are also closely monitored) has inferior (or no) effects on reduction of suicidality. Other potential confounders in the anti-suicidal effect of clozapine include its superiority in reducing psychotic symptoms, impulsiveness and aggressiveness; together with the regular interaction with health professionals and others during hematological monitoring, which may diminish the feelings of loneliness in socially isolated patients.

A number of hypotheses have been postulated concerning the biological underpinnings of anti-suicidal properties (see Table 2). The superior antidepressant and antisuicide effect of clozapine compared to other antipsychotics may reflect its unique modulation of the relationship between serotonin, dopamine, norepinephrine and their metabolites. The antisuicidal effect may also be due to its lower propensity to cause extrapyramidal side effects, which they increase suicidality. The superior anti-aggression properties when compared to other antipsychotics, may arise from blockade of the D4 receptor, without concomitant significant blockade of D2. Genetic and hormonal factors, the role of neuroinflammation, the ability to elicit epileptiform activity, and the reduction of substance abuse and of its initiation, are other parameters under investigation.

The main causes of clinicians' hesitation to administer clozapine are potentially lethal adverse drug reactions such as agranulocytosis, pneumonia, myocarditis, and metabolic side-effects, which may have a significant impact on life expectancy (Hirsch et al., 2017; De Berardis et al., 2018). However, most recent epidemiological data suggest that cardiovascular mortality and all-cause mortality are similar between clozapine-treated patients and those undergoing treatment with other antipsychotics (van der Zalm et al., 2021). Van der Zalm et al. (2021) reported that although cumulative use of clozapine for up to 1 year was associated with a higher all-cause mortality - unrelated to myocarditis - than cumulative use of most other antipsychotics, this difference in all-cause mortality was not present after longer use of these medications. A major finding from a recent epidemiological study was that clozapine was the only antipsychotic drug associated with decreased risk of attempted or completed suicide among patients with schizophrenia, which led the researchers to propose that clozapine be considered a first-line treatment for high-risk patients (Taipale et al., 2021). This recommendation is more important when also considering that the superior antisuicidal effect may be linked to a lower propensity for extrapyramidal side effects, including akathisia or tardive dyskinesia, which may increase suicidal behavior (Meltzer 1999; Aguilar and Siris, 2007). In sum, most recent research data

Table 2 Potential biological correlates of the anti-suicidal effects of clozapine.

Biological correlates		Studies
Modulation of neurotransmitters	<p>↑ dopamine release in the prefrontal cortex</p> <p>↑ serotonergic effects compared to other antipsychotics</p> <p>↑ peripheral norepinephrine levels</p>	<p>Green et al., 1993;</p> <p>Meltzer 1999; Ernst and Goldberg 2004; Taipale et al., 2021</p>
Lower propensity to cause extrapyramidal side-effects, akathisia, or tardive dyskinesia	<p>Interaction with D-receptors:</p> <p>↑ in the mesolimbic areas (antipsychotic effect)</p> <p>↓ in the neostriatal areas (extrapyramidal symptoms)</p>	<p>Meltzer 1999; Wagstaff and Perry 2003; Aguilar and Siris 2007</p>
Dopamine receptors D4/D2 ratio and anti-aggression properties	<p>CLOZ: ↑ anti-aggression properties</p> <p>Due to ↑ D4-receptor blockade/ ↓ D2-receptor blockade</p>	<p>Citrome et al., 2001;</p> <p>Frogley et al., 2012;</p> <p>El-Mallakh and McKenzie 2013</p>
Genetic factors	<p>rs1800532 polymorphism of the SLC6A4 gene (serotonin transporter) associated with: suicide vulnerability; response to CLOZ/ lithium</p>	<p>De Berardis et al. 2021</p>
Neurosteroids	<p>Completed suicide in SZ/BD: ↓ pregnenolone in parietal cortex (common path for the anti-suicidal properties of CLOZ/ lithium?)</p> <p>CLOZ markedly elevates brain pregnenolone (rats)</p>	<p>Youssef et al., 2015</p> <p>Marx et al., 2006</p>
Other biological mechanisms	<p>Neuroinflammation: ↑ suicidality through: activation of kynurenine pathway; serotonin depletion; ↑ glutamate; ↓ BDNF; ↑ HPA-axis activity</p> <p>CLOZ anti-suicidal effect resulting from: modulation of NMDA receptor expression; BDNF upregulation; regulation of the arachidonic acid cascade</p> <p>CLOZ efficacy due to its non-selectivity: it acts on dopaminergic, serotonergic, muscarinic, adrenergic, and histaminergic receptors</p>	<p>Wislowska-Stanek et al. 2021</p> <p>Leveque et al., 2000;</p> <p>Marx et al., 2006;</p> <p>Griffiths et al., 2014</p> <p>Gould et al., 2017</p>
ECT and clozapine: potentially common biological mechanisms	<p>Alteration of EEG activity; ↑ epileptiform activity; ↑ neuroplasticity; ↑ neurotrophic factors; corrects glutamate/GABA imbalances; reduces inflammation through effects on neuron-glia interactions</p>	<p>Gammon et al., 2021</p>
Reduction of substance use disorder	<p>In SZ, CLOZ reduces comorbid SUD</p> <p>CLOZ superior to FGAs or risperidone in poly-substance abusers</p> <p>CLOZ reduces the <i>initiation</i> of SUD in SZ: due to ↓ dopamine release in mesolimbic system</p>	<p>Khokhar et al., 2018;</p> <p>Krause et al., 2019</p> <p>Arranz et al., 2018</p>

Abbreviations: BD= bipolar disorder; BDNF= brain-derived neurotrophic factor; CLOZ= clozapine; d-receptors= dopamine receptors; FGAs= first generation antipsychotics; GABA= γ -aminobutyric acid; NMDA= N-methyl-D-aspartate; SZ= schizophrenia; SUD= substance use disorder.

support the notion that treatment with clozapine is associated with reduced all-cause mortality and death by suicide, while cardiovascular mortality is similar between clozapine and antipsychotics: in view of these new findings, clinicians must weigh the risk-benefit ratio concerning the administration of clozapine in suicidal patients, especially the high-risk ones.

Decades ago, researchers emphasized that the improved quality of life that clozapine can give to 40-60% of patients, could result in dramatic reductions in deaths due to suicide and that this benefit far overcame any loss of life due to agranulocytosis (Fuchs, 1994). Subsequent research findings have provided support for this notion, but many issues remain unresolved as to the exact biological underpinnings of this effect and the effect of clozapine in reducing suicidality in other psychiatric conditions, (Table 2).

Contributors

Conceptualisation: VM and DSB; Literature search: VM; Paper appraisal: VM and DSB; manuscript preparation and finalization: VM and DSB

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Conflict of Interest

Neither of the authors reports any conflict of interest.

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