**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).

**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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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 patientsCLOZ=30FGAs=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  |
| 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-BPDpatients | 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%) | - |
| 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 |
| Ferrerri 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= 479Olanzapine= 477 | - | Concomitant drugs did not 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 onesCLOZ cessation is associated with suicidality increaseCLOZ anti-suicidal effect: unrelated to antidepressants’ co-administration |
| 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±156Duration 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 | - |
| 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 hours- 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 | - |
| 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 psychosisIncidence 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 |