# Clozapine Diminishes Suicidal Behavior: A Retrospective Evaluation of Clinical Records

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***Objective:*** To test the antisuicidal effect of clozapine, taking into consideration some potentially confounding variables.

***Method:*** A retrospective evaluation was conducted of the clinical charts of 94 inpatients treated continuously with clozapine for at least 6 weeks between 1962 and 1994. In a mirror design, a period of continuous clozapine treatment (mean duration of 15 months) was compared with a pre-clozapine period of equal length, and in 17 patients also with a post-clozapine period, with regard to suicidal behavior. The role of variables such as staying in a protective hospital milieu and receiving treatment with typical neuroleptics and antidepressants was considered.

***Results:*** The rate of suicidal behavior was 28% (26/94) in the pre-clozapine period, 3% (3/94) in the clozapine period, and 18% (3/17) in the post-clozapine period, the corresponding figures for serious suicidal behavior requiring medical attention being 12% (11/94), 1% (1/94), and 12% (2/17), respectively. The odds ratios were 11.6 (95% CI = 3.4 to 39.9) and 12.3 (95% CI = 1.6 to 97.5) for suicidal and serious suicidal behavior, respectively, in favor of the clozapine period in comparison with the pre-clozapine period. Staying in the hospital was associated with reduction in suicidal behavior. The antisuicidal effect of clozapine possibly disappears at doses that are too low.

***Conclusion:*** Clozapine diminishes the frequency of suicidal behavior including serious suicidal acts, regardless of comedication with antidepressants. In the protective hospital milieu, this effect is less pronounced, and it disappears after clozapine discontinuation.

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Suicide is the single largest cause of premature death among individuals diagnosed with schizophrenia,[1] and the lifetime suicide risk of these individuals remains high, even though the most recent estimates were lower (4%)[2] than the previous estimates (10%–13%).[3] Suicidal behavior in patients with schizophrenic disorders represents a challenge for clinicians and requires appropriate therapy, including psychopharmacotherapy.

In a series of 88 neuroleptic-resistant patients who had received a high dose of clozapine (mean dose of approximately 500 mg/day) for at least 6 months, a reduction of suicide attempts by 86% was noted.[4] Correspondingly, a significant reduction in the scores of suicidality and impulsive aggression was observed in a smaller sample of clozapine-treated but not haloperidol-treated chronic schizophrenia patients.[5] In studies of mortality rates in patients treated with clozapine, mortality from suicide was found to be significantly reduced in patients currently receiving clozapine compared with those who had discontinued the agent[6] and those treated with typical neuroleptics.[7]

It has been proposed that other atypical neuroleptics such as olanzapine could also exert an antisuicidal effect.[8] Nevertheless, the 2-year International Suicide Prevention Trial demonstrated that there was a significant decrease in the risk of suicidal behavior in patients taking clozapine compared with those taking olanzapine,[9] even in spite of the more frequent psychotropic comedication in the olanzapine group.[10]

However, the antisuicidal effect of clozapine has been questioned; when a larger group of patients in whom clozapine treatment was initiated while they were inpatients was compared with a group who had never been exposed to clozapine, no significant differences in the rate of completed suicides were found.[11] In addition, the influence of possible confounders has so far been paid little attention, a problem pointed to recently by Glick et al.[10] In the present study, we tested the antisuicidal effect of clozapine, considering some potentially confounding variables such as a stay in the hospital and concomitant medication.

## METHOD

A series of 141 patients was identified, all of them treated with clozapine continuously during a period of at least 6 weeks while hospitalized in the Psychiatric Uni-

Table 1. Basic Characteristics of the Sample (N = 94)

| Characteristic | Value |
|---|---|
| Male sex, N (%) | 49 (52) |
| Age, mean ± SD, y | 44 ± 16 |
| Marital status, single, N (%) | 70 (74) |
| Diagnosis, N (%)[a] | |
| Schizophrenia | 75 (80) |
| Schizoaffective disorder | 14 (15) |
| Affective disorder | 5 (5) |
| Illness duration, mean ± SD, y | 28 ± 13 |
| No. of hospital stays, mean ± SD | 8.8 ± 7.0 |
| Total duration of hospital stays, mean ± SD, y | 8.2 ± 10.8 |

[a]Diagnoses were made using ICD-10 criteria.

versity Hospital Zurich, Zurich, Switzerland, between 1962 and 1994. In the 1960s, clozapine was frequently prescribed as a first-choice neuroleptic; later, the indication for its prescription was restricted mainly to neuroleptic-resistant patients. In 94 of the patients, the following criteria were fulfilled: (1) Before their index hospitalization, they were in psychiatric treatment for a period of at least the same duration. (2) During that previous treatment, no clozapine was prescribed. (3) A complete history of psychopharmacologic interventions and of suicidal behavior was documented. (4) In none of the patients were there any doubts regarding medication compliance. The main characteristics of these patients are given in Table l.

Clinical charts of all of these patients were thoroughly scrutinized with regard to basic sociodemographic and clinical data and an exhaustive account of their psychopharmacotherapy. Special attention was paid to suicidal behavior, which was classified into 4 grades according to the clinically sound classification system by Motto.[12] The data were extracted, organized, and evaluated. Pre-clozapine and clozapine periods of exactly the same duration were compared with each other (mirror design) with regard to suicidal behavior (all suicidal acts including serious suicidal ideas and suicidal threats) and serious suicidal behavior (all actual suicide attempts leading to damage requiring medical attention, corresponding to Motto's grades 2–4). Also considered were potential confounding variables: psychiatric hospitalization (several patients were not hospitalized during the pre-clozapine period) and its length (which sometimes differed intraindividually in both periods), whether the suicidal behavior occurred during the hospital stay in the narrow sense of the words (and not during a hospital leave, both permitted and not permitted), and medication with typical neuroleptics and antidepressants.

## RESULTS

The required duration of both the pre-clozapine and the clozapine periods was at least 6 weeks, and the mean duration of each period was 15 months (SD = 22). During the clozapine period, all patients were continuously hospitalized. During the pre-clozapine period, 5 patients were not hospitalized, and the hospitalization time of the remaining 89 patients was shorter, lasting a mean of 12 months (SD = 23). A reason for hospital referral in both periods was, among others, suicidal behavior; it was indicated as the reason for referral in the same proportion of 30% of patients in both periods.

During the pre-clozapine period, the majority of patients, 72 (77%), received typical neuroleptics in a mean daily dose of 333 mg chlorpromazine (CPZ) equivalents (SD = 274). During the clozapine period, all patients were treated with clozapine at a mean daily dose of 231 mg (SD = 125). Nevertheless, 35 patients (37%) additionally—some of them only temporarily—received typical neuroleptics in a mean daily dose of 208 mg CPZ equivalents (SD = 252) along with clozapine. Antidepressants were prescribed to 24 patients (26%) and 25 patients (27%) in the pre-clozapine and clozapine periods, respectively, not always to the same patients in both periods. Altogether, 17 patients received no neuroleptics or antidepressants during the pre-clozapine period; in only 3 of them was suicidal behavior registered.

The comparison of both periods with regard to suicidal and serious suicidal behavior is presented in Table 2. Considering all 94 patients, the frequency of suicidal behavior decreased significantly in the clozapine period with an odds ratio of about 12. The odds ratio did not change substantially when only those 89 patients who were hospitalized in the course of both periods were considered or when only those 71 patients who were hospitalized in the course of both periods and were treated with typical neuroleptics during the pre-clozapine period were considered. When those patients who were treated with antidepressants were excluded, there was still a significant difference between both periods in favor of the clozapine period for the remaining 60 patients. In contrast, the odds ratio diminished when suicidal acts during hospital leaves were omitted and when only those 46 patients in whom the duration of hospital stay was equal in both periods (deviations of up to 10% accepted) were considered. The significance level was just missed for suicidal behavior in the first case and for serious suicidal behavior in the second case.

As Table 2 shows, suicidal behavior was registered in 3 patients (2 men, 1 woman) during the clozapine period. It is worthy of note that compared with all other patients these 3 patients received a lower mean clozapine dose: 109 mg/day (SD = 75) versus 235 mg/day (SD = 124). One of these patients received an additional typical neuroleptic (as compared with 37% [34/91] of all other patients), and 2 received an additional antidepressant (as compared with 25% [23/91] of all other patients).

In 20 (21%) of 94 study patients, clozapine therapy was discontinued at the end of the clozapine period; this

**Table 2. Intragroup Comparisons of Suicidal Behavior (SB) and Serious Suicidal Behavior (SSB) During Clozapine and Pre-Clozapine Periods Considering Some Potential Confounders**

| Patient Group | Pre-Clozapine Period, N (%) | Clozapine Period, N (%) | OR | 95% CI |
|---|---|---|---|---|
| All patients (N = 94) | | | | |
| SB | 26 (28) | 3 (3) | 11.6 | 3.4 to 39.9 |
| SSB | 11 (12) | 1 (1) | 12.3 | 1.6 to 97.5 |
| Patients hospitalized in both the clozapine and pre-clozapine periods (N = 89) | | | | |
| SB | 25 (28) | 3 (3) | 11.2 | 3.2 to 38.7 |
| SSB | 10 (11) | 1 (1) | 11.1 | 1.4 to 89.0 |
| Patients hospitalized in both periods and treated with typical neuroleptics in the pre-clozapine period (N = 71) | | | | |
| SB | 20 (28) | 2 (3) | 13.5 | 3.0 to 60.5 |
| SSB | 10 (14) | 1 (1) | 11.5 | 1.4 to 92.2 |
| Patients with suicidal behavior during hospital stay (N = 89) | | | | |
| SB | 10 (11) | 3 (3) | 3.6 | 0.96 to 13.7 |
| SSB | 8 (9) | 1 (1) | 8.7 | 1.1 to 71.0 |
| Patients with hospital stays of equal duration in clozapine and pre-clozapine periods (N = 46) | | | | |
| SB | 10 (22) | 2 (4) | 6.1 | 1.3 to 29.7 |
| SSB | 7 (15) | 1 (2) | 8.1 | 0.95 to 68.6 |
| Patients who received no antidepressants (N = 60)[a] | | | | |
| SB | 15 (25) | 0 (0) | | |
| SSB | 6 (10) | 0 (0) | | |

[a]Two-tailed Fisher exact test was performed: for suicidal behavior, $p < .0001$; for serious suicidal behavior, $p = .027$.
Abbreviations: CI = confidence interval, OR = odds ratio.

was due to side effects in 15 patients (16%), nonresponse in 3 patients (3%), and refusal to continue clozapine in 2 patients (2%). In 17 of the patients, all remaining in therapy for at least as long a period as the clozapine period lasted, a complete history of psychopharmacologic interventions and of suicidal behavior was documented. Clozapine and post-clozapine periods of the same duration (mean 11 months, SD = 8) were compared in these 17 patients. In 3 (18%) of these patients suicidal and in 2 (12%) serious suicidal behavior was registered during the post-clozapine period; incidentally, none of them exhibited suicidal behavior in the pre-clozapine or clozapine periods. Therefore, the overall rate of suicidal behavior was 28% (N = 26) in the pre-clozapine period (94 patients assessed), 3% (N = 3) in the clozapine period (94 patients assessed), and 18% (N = 3) in the post-clozapine period (17 patients assessed), the corresponding figures for serious suicidal behavior requiring medical attention being 12% (N = 11), 1% (N = 1), and 12% (N = 2), respectively.

## DISCUSSION

A sample of 94 inpatients was treated continuously with clozapine for an average period of 15 months. In a mirror design, the frequency of their suicidal behavior was studied by comparing this clozapine treatment period with the preceding pre-clozapine period of exactly the same duration. In 17 of these patients who discontinued clozapine, the post-clozapine period of an average duration of 11 months could be surveyed as well. In the course of the pre-clozapine period, 89 patients were hospitalized, and during the clozapine period, all patients were hospitalized. At the beginning of their hospitalizations, in both periods, an equal proportion of 30% of patients exhibited suicidal behavior. The occurrence of suicidal behavior can be influenced by environmental factors; for example, the hospitalization as such, i.e., staying in a protective milieu, can play a preventive role, even in the short term. Accordingly, a proportion of patients exhibited suicidal behavior—and especially suicidal behavior of a minor degree—only when they were on leave. The suicide rate of the discharged patients was shown to be higher than that of inpatients.[13]

A total of 77% of the patients were treated with typical neuroleptics in the pre-clozapine period, and 37% of the patients received additional typical neuroleptics in the clozapine period. There is no unequivocal relationship between typical neuroleptics and suicide.[14] On the one hand, typical neuroleptics have been accused of promoting the occurrence of depression,[15] and there is a well-known relationship between depression and suicide even in patients with schizophrenia.[16] Cases of suicidal behavior following akathisia were also reported.[17] On the other hand, many suicides in schizophrenia occur during the active illness phase, and a substantial number of suicide victims with schizophrenia have received inadequate neuroleptic

medication or are noncompliant.[18] Antidepressants can obviously reduce suicidality; for example, suicide risk was shown to be lower among depressed patients treated with antidepressants than among untreated persons.[19] Therefore, in studying antisuicidal effects of clozapine, these potential confounders should be considered.

Our results indicate that suicidality decreased by the factor of 12 regarding both suicidal behavior in general and serious suicidal behavior requiring medical intervention in particular. Comparing pre-clozapine and clozapine periods showed that the number of patients with suicidal acts decreased from 26 to 3 and from 11 to 1, which indicates an 88% and a 91% reduction, respectively—figures that are well comparable to the 80% to 85% quoted in the literature.[20] These results are all the more important, as they were reached with clozapine doses usually given in Europe, which are substantially lower (but not less effective) than those often given in the United States,[21] as also exemplified in the study by Meltzer and Okayli.[4] In some patients, the doses may have been too low; however, in none of the 3 patients who exhibited suicidal behavior during the clozapine period did the average clozapine dose exceed 245 mg/day.

As shown in Table 2, whether the patient was hospitalized and whether he or she was treated with typical neuroleptics in the pre-clozapine period had only a marginal bearing on the reduction of suicidality with clozapine; similarly, the prescription of antidepressants during both periods had little effect. In contrast, if only those patients who did not commit their suicidal acts when they were on leave are considered, and if only those patients in whom the hospitalization was of the same duration are considered, the odds ratio in favor of the clozapine period diminishes, and it does not reach the level of statistical significance for all suicidal acts in the former case or for serious suicidal acts in the latter case. It follows that other environmental factors can play a role and modify the antisuicidal effect of clozapine, possibly the more so, the lower the clozapine dose.

In a small subgroup of 17 patients in whom clozapine was discontinued, an increase in the suicidality rate was observed after discontinuation of clozapine; altogether, the rate of suicidal behavior was 28% in the pre-clozapine period, 3% in the clozapine period, and 18% in the post-clozapine period, the corresponding figures for serious suicidal behavior being 12%, 1%, and 12%, respectively. The latter finding is in disagreement with the observation that after clozapine discontinuation, during an average period of 6 to 7 months, no reappearance of suicidal behavior was observed.[4] Our results indicate that after clozapine discontinuation the rate of suicidal behavior probably returns to the level it was before clozapine prescription. Incidentally, the reappearance of suicidal behavior after clozapine discontinuation is in agreement with the finding of a similar suicide rate in patients who have discontinued clozapine recently and who did so in the past.[6] It could also explain the negative findings by Sernyak et al.[11]; continuous clozapine treatment was not guaranteed in their study.

Our study was based on a retrospective evaluation of clinical charts; nevertheless, full data sets were available for both periods, and suicidal behavior was paid due attention and was adequately registered. All data were registered at a time when a potential effect of clozapine on suicidal behavior was not yet known; therefore, the corresponding potential bias was primarily eliminated.

Altogether, our results confirm that clozapine has antisuicidal properties. It is indicated in potentially suicidal patients diagnosed with schizophrenia spectrum disorders. Its prescription can reduce the frequency of suicidal behavior in these patients and thus save lives. It has been estimated that if all patients with treatment-resistant schizophrenia received clozapine therapy, approximately 53 suicides could be avoided in the United Kingdom alone each year.[22] Accordingly, it has been argued that clozapine's antisuicidal effect outweighs its potential dangers, including agranulocytosis.[23]

*Drug names:* chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

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