Suicide and Schizophrenia: Clozapine and the InterSePT Study

Herbert Y. Meltzer, M.D.

Suicide is one of the most serious of schizophrenic symptoms and claims the life of 9% to 13% of patients. The annual rate of suicide in schizophrenic patients is reported to be in the range of 0.4% to 0.8%, a rate that has remained constant despite the introduction of antipsychotic therapy and attendant case-management systems. The risk of suicide is not significantly different in neuroleptic-resistant or -responsive schizophrenic patients. A study of 421 schizophrenic patients reported no significant difference in the incidence of lifetime and current episodes of suicidality in treatment-resistant and -responsive patients. A number of studies with clozapine, an atypical antipsychotic, have demonstrated an 80% to 85% reduction in suicide in neuroleptic-resistant patients. This is accompanied by a decrease in depression and psychopathology and improved cognition. Clozapine's modulation of serotonergic, noradrenergic, cholinergic, and dopamine function may be the biological basis for the reduction in suicide. Weekly contact with patients, for white blood cell monitoring, has also been put forward as one explanation. To further confirm suicide risk reduction as a benefit of clozapine therapy, the International Clozaril/Leponex Suicide Prevention Trial (InterSePT) is currently being conducted. This large, prospective treatment study will compare the rate of suicide attempts and completions in schizophrenic patients at high risk of suicide randomly assigned to receive clozapine or olanzapine. The bias of weekly visits will be excluded. Results should be available in 2001.

(J Clin Psychiatry 1999;60[suppl 12]:47–50)

Suicidality, a collective term for attempted and completed suicide, suicidal ideation, and suicide plans, occurs frequently in patients with schizophrenia. In 1911, Bleuler referred to the suicidal drive as "the most serious of schizophrenic symptoms."[1(p488)] Suicide claims the life of 9% to 13% of schizophrenic patients.[2] The suicide rate is more than 20 times greater than that in the general population, and over the course of their lifetime, at least 40% to 60% of schizophrenic patients will make a suicide attempt.[2] The annual rate of suicide in schizophrenic patients is reported to be between 0.4% and 0.8% in developed countries.[3–5] Despite the introduction of conventional antipsychotic therapy, there is no evidence that the rate of suicide has decreased. Approximately the same rate was observed in the long-term follow-up studies of Ciompi[6] and Winokur and Tsuang[7] in the preneuroleptic era. However, treatment with clozapine, an atypical antipsychotic, has been associated with a marked reduction in suicidality.[2] Clozapine is mainly indicated for treatment-resistant and neuroleptic-intolerant schizophrenia, since its use is associated with the development of agranulocytosis in approximately 1% of patients. However, with appropriate monitoring, the risk of death is about 1 in 10,000 patients. This morbidity and mortality must be weighed against the reduction in risk of suicide. The risk of agranulocytosis is greatest during the first 4 to 18 weeks of treatment with clozapine, while the risk of suicide persists throughout patients' lifetimes.

Suicide in schizophrenic patients represents the culmination of many factors, including depression, feelings of hopelessness, cognitive impairment, substance abuse, command hallucinations, family conflict, akathisia, and tardive dyskinesia. Men are considered to be more likely than women to commit suicide. Suicidal behavior in schizophrenic patients is responsible for the majority of hospitalizations.[8,9]

The most robust predictor of a future suicide attempt is having made a previous suicide attempt. Data from a review of 1000 schizophrenic patients indicated that a prior suicide attempt within the past 24 months was associated with approximately a 30% probability of making another attempt (H.Y.M. and G. McCleery, Ph.D., unpublished data, March 1997). These statistics are consistent with a recent long-term study that included 2 follow-up periods.[10] Data from 61 adolescent schizophrenic patients followed

From the Department of Psychiatry, Vanderbilt University, Nashville, Tenn.

Presented at the meeting "Treatment-Resistant Schizophrenia and Beyond: Current Concepts and Future Prospects," July 8–9, 1998, London, U.K. This meeting was supported by an educational grant from Novartis Pharma AG.

Reprint requests to: Herbert Y. Meltzer, M.D., Department of Psychiatry, Vanderbilt University, 1601 23rd Ave. S., Suite 306, Nashville, TN 37212.

up for at least 5 years and again after at least 11 years indicated that 36% had made a total of 55 suicide attempts, and 13.1% committed suicide. Most of the suicides occurred within the first decade of diagnosis, and all but 1 of the patients had made previous attempts.

SUICIDALITY IN RELATION TO TREATMENT RESPONSE

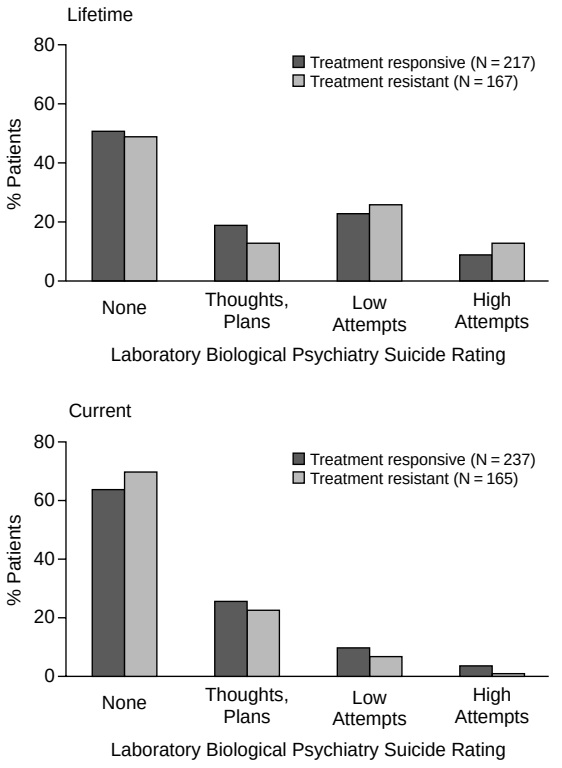
It has been suggested that neuroleptic-resistant patients are at greater risk of suicide than neuroleptic-responsive patients. To determine whether neuroleptic-resistant patients are at a greater risk, we prospectively assessed suicidality in a total of 237 neuroleptic-resistant and 184 neuroleptic-responsive patients.[2] Patients were diagnosed using the Schedule for Affective Disorders and Schizophrenia (SADS) rating scale. Suicidality was assessed at weekly intervals while patients were hospitalized and at intervals of 6 weeks and 6, 12, 18, and 24 months during outpatient visits. At the final visit, each patient was reinterviewed to review the previously collected information. The results demonstrated that there was no significant difference in the incidence of lifetime and current episodes of suicidality in treatment-resistant and treatment-responsive schizophrenic patients (Figure 1).

SUICIDE RATE AND CURRENT TREATMENT OF SCHIZOPHRENIA

The suicide rate among schizophrenic patients before the introduction of conventional antipsychotics and the attendant case-management systems has been reported to be in the range of 9% to 13%.[2] This high rate of suicide has persisted despite the introduction of conventional antipsychotics. These drugs are associated with frequent extrapyramidal side effects which may lead to noncompliance and relapse. In particular, they are often associated with tardive dyskinesia, one of the risk factors for suicide.

As patients increasingly receive care in the community, case managers are becoming overburdened. Furthermore, patients living in the community are often inadequately supervised. The increase in deinstitutionalization has led to more stress for the patients and less frequent assessment in many countries. For example, in Denmark, Mortensen and Juel examined mortality and causes of death in 9156 first-admitted schizophrenic patients.[11] Over the past decade, there has been a 50% reduction in the number of psychiatric inpatient beds available in Denmark. The authors evaluated whether this decrease in services had resulted in any changes in mortality or causes of death in schizophrenic patients. They confirmed that mortality in schizophrenic patients was significantly increased and that their results may indicate some adverse effects of deinstitutionalization.

Figure 1. Lifetime and Current Incidences of Suicidality in Treatment-Resistant and Treatment-Responsive Schizophrenic Patients[a]



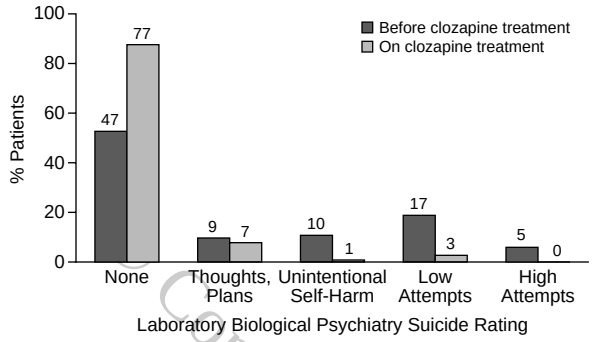
[a]Data from reference 2.

EFFECT OF CLOZAPINE ON SUICIDALITY IN SCHIZOPHRENIA

Clozapine is an effective antidepressant in patients with major depression.[12,13] It is also an effective mood stabilizer in bipolar as well as schizophrenic patients.[14,15] Several controlled studies have demonstrated that clozapine may be as effective as tricyclic antidepressants in major depression.[16,17] Unlike conventional antipsychotics, clozapine reduces hopelessness associated with tardive dyskinesia as well as aggressiveness and substance abuse, which are also risk factors for suicide.[18–20] The remarkable improvements in psychopathology and tolerability seen with clozapine have an impact on the suicide rate in schizophrenic patients.

Clozapine was first shown to reduce the suicide rate in 1995 in a cohort of 88 patients (73 with treatment-resistant schizophrenia and 15 schizoaffective patients), who were prospectively evaluated for periods of 6 months to 7 years.[2] Clozapine treatment resulted in markedly less suicide. Of the 88 patients, 22 had made a suicide attempt in the 2 years before clozapine therapy. Five had a high probability of success (method was of high inherent lethality and had little chance of detection), and 17 had a low probability of success (high likelihood of nonfatal outcome due to

Figure 2. Frequency of Suicidality Before and After 2 Years of Clozapine Treatment in 88 Treatment-Resistant Patients[a]



[a]Data from reference 2.

low inherent lethality of the method and the likelihood of detection). In the first 2 years on clozapine treatment, there were only 3 suicide attempts of low probability of success. This indicates an 85% decrease in suicide attempts in the first 2 years (Figure 2). The decrease in attempts was associated with a decrease in depression and feelings of hopelessness, decreased psychopathology, and improved cognition. The attempts occurred during the first few months of clozapine treatment.

It has been thought that this decrease in suicide may be due to a clozapine-specific effect. Naber and Hippius reported that 55% to 70% of patients with endogenous depression responded to clozapine treatment.[16] Clozapine is also associated with minimal extrapyramidal side effects, which are identified as risk factors for suicide.[21] The decrease in suicide may also be attributable to the weekly contact that is necessary for blood monitoring for white blood cell counts during the first 18 weeks of treatment. This contact with patients is undoubtedly important in improving compliance and possibly early detection of suicide risk. However, programs with close monitoring of patients have not reported lower suicide rates than other treatment modalities such as the Assertive Community Treatment Program, which provides intensive case management and community support.[22] There is anecdotal evidence that despite reduced monitoring in some European communities and China, the suicide rate is still decreased in clozapine-treated patients.

To determine whether the reduction in suicide that we obtained in our study in Cleveland[2] could be applied to the whole of the United States, we examined data from the U.S. Clozaril National Registry (CNR) over the period from 1990 to 1995 (data on file, Novartis). There were 102,000 patients listed in the registry, of whom 21,000 had been treated for at least 1 year with clozapine. A total of 39 suicides were reported during that period, providing a suicide rate of 0.18% per year, which is roughly 20% of the expected rate based on epidemiologic data. Therefore,

Table 1. Standardized Mortality Ratio (SMR) in Schizophrenic Patients

Reference	Patients (N)	Suicide (SMR)
Walker et al[23]	> 65,000	2.2
Allebeck[24]	1190	12.3
Anderson et al[25]	532	16.1
Berren et al[26]	1980	5.8
Black and Winokur[27]	636	2.6
Newman and Bland[28]	3623	19.6

there was an approximate 80% reduction in suicide in those patients who received clozapine.

To describe the effects of clozapine on mortality, Walker and colleagues compared the causes of death in 67,072 current and former clozapine users.[23] Data from the CNR were cross-linked with death records from medical examiners. Standardized mortality rates adjusted for age, sex, and race were calculated for the underlying cause of death. Mortality from suicide was decreased in current clozapine users compared with former users (rate ratio [RR] = 0.17; 95% confidence interval [CI] = 0.10 to 0.30). An 83% decrease in the suicide rate was found. The suicide rates for those patients on clozapine treatment compared with former users of clozapine were 39 and 222 per 100,000 person-years, respectively. These results strongly suggest that clozapine may reduce the suicide rate.

A review of the literature reveals that the standardized mortality ratio in schizophrenic patients ranges from 2.2 to 19.6 (Table 1).[23–28] There are several explanations for the decreased rate observed in the study by Walker and colleagues.[23] It could reflect underreporting; however, this is unlikely because all patients who did not complete the study were followed up. Patients taking clozapine might a priori have a lower risk of suicide. Results from a controlled clinical trial are needed in order to confirm that the reduction in suicide is attributable to clozapine.

BIOLOGICAL BASIS FOR REDUCTION IN SUICIDE

Diminished levels of dopamine and norepinephrine are thought to contribute to depression and, potentially, suicide. Clozapine increases the release of dopamine and norepinephrine in the prefrontal cortex. Clozapine is also associated with a normalization of dopamine and serotonergic function, due to a relative lack of blockade of dopamine receptors in the mesolimbic system, and down-regulation of serotonin-2A (5-HT_{2A}) receptors. This modulation may be the biological basis for the reduction in suicide.

INTERNATIONAL CLOZARIL/LEPONEX SUICIDE PREVENTION TRIAL

To further confirm suicide risk reduction as a benefit of clozapine, the International Clozaril/Leponex Suicide Pre-

vention Trial (InterSePT) is currently being conducted. This large, prospective treatment study will take place in 11 countries and will involve 69 centers in the United States, Europe, and the Southern Hemisphere. It is envisaged that 20 to 40 patients will be enrolled at each of the centers in Europe and the Southern Hemisphere and ≥ 40 at each center in the United States. The primary objectives of the study are to compare the rates of hospitalization for imminent risk of suicide and significant suicide attempts in schizophrenic patients at high risk of suicide randomly assigned to receive clozapine (300–900 mg/day) or olanzapine (10–20 mg/day). The effect of treatment on the severity of suicide attempt will also be assessed using the Clinical Global Impressions-Severity of Suicide scale (CGI-SS). Secondary objectives include the assessment of suicide-, psychotic-, and mood-related events and pharmacoeconomic aspects. The study will not be restricted to treatment-resistant patients and will exclude biases such as weekly visits. The comparator, olanzapine, is pharmacologically similar to clozapine. There is evidence from early clinical trials that olanzapine may be more effective than haloperidol in decreasing depression in schizophrenia.[29] Results from this study will be available in 2001.

CONCLUSIONS

The suicide rate in schizophrenic patients is more than 20 times that in the general population. Despite the introduction of conventional antipsychotic therapy, this rate remained unchanged. Clozapine, however, has been shown to reduce the rate of suicide by 80% to 85%. This reduction, when weighed against the mortality due to clozapine-induced agranulocytosis (1 in 10,000 patients), dramatically alters the risk/benefit profile for clozapine. The results from the InterSePT study are eagerly awaited in order to confirm this advantage of clozapine.

Drug names: clozapine (Clozaril, Leponex), haloperidol (Haldol and others), olanzapine (Zyprexa).

REFERENCES

1. Bleuler E. Dementia praecox of the group of schizophrenias (1911). Zinkin J, trans. New York, NY: International Universities Press; 1950
2. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190
3. Axelsson R, Lagerkvist-Briggs M. Factors predicting suicide in psychotic patients. Eur Arch Psychiatry Clin Neurosci 1992;241:259–266
4. Cohen LJ, Test MA, Brown RL. Suicide and schizophrenia: data from a prospective community treatment study. Am J Psychiatry 1990;147: 602–607
5. Newman SC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239–245
6. Ciompi L. Late suicide in former mental patients. Psychiatr Clin (Basel) 1976;9:59–63
7. Winokur G, Tsuang M. The Iowa 500: suicide in mania, depression and schizophrenia. Am J Psychiatry 1975;132:650–651
8. Solomon P. The admissions process in two state psychiatric hospitals. Hosp Community Psychiatry 1981;32:405–408
9. Hawton K, Fagg J. Suicide and other causes of death, following attempted suicide. Br J Psychiatry 1988;152:359–366
10. Krausz M, Müller-Thomsen T, Haasen C. Suicide among schizophrenic adolescents in the long-term course of illness. Psychopathology 1995;28: 95–103
11. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. Br J Psychiatry 1993;163:183–189
12. Nàhunek K, Rodovà A, Svestka J, et al. Clinical experience with clozapine in endogenous depression [letter]. Activ Nerv Super (Praha) 1973;15:102
13. Ranjan R, Meltzer HY. Acute and long term effectiveness of clozapine in treatment-resistant psychotic depression. Biol Psychiatry 1996;40: 253–258
14. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. Am J Psychiatry 1996;153:759–764
15. Suppes T, McElroy SL, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. Biol Psychiatry 1992;32:270–280
16. Naber D, Hippius H. The European experience with use of clozapine. Hosp Community Psychiatry 1990;41:886–890
17. Nahunek K, Svestka J, Misurec J, et al. Experiences with clozapine. Cesk Psychiatr 1975;41:886–890
18. Kane JM, Woerner MG, Pollack S, et al. Does clozapine cause tardive dyskinesia? J Clin Psychiatry 1993;54:327–330
19. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia. J Clin Psychopharmacol 1993;13:287–289
20. Buckley P, Thompson PA, Way L, et al. Substance abuse and clozapine treatment. J Clin Psychiatry 1994;55(9, suppl B):114–116
21. Hogan TP, Awad AG. Pharmacotherapy and suicide risk in schizophrenia. Can J Psychiatry 1983;28:277–281
22. Cohen LJ, Test MA, Brown RL. Suicide and schizophrenia: data from a prospective community treatment study. Am J Psychiatry 1990;147: 602–607
23. Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. Epidemiology 1997;8:671–677
24. Allebeck P. Schizophrenia: a life-shortening disease. Schizophr Bull 1989; 15:81–89
25. Anderson C, Connelly J, Johnstone EC, et al. Disabilities and circumstances of schizophrenic patients: a follow-up study: cause of death. Br J Psychiatry 1991;159:30–33
26. Berren MR, Hill KR, Merikle E, et al. Serious mental illness and mortality rates. Hosp Community Psychiatry 1994;45:604–605
27. Black DW, Winokur G. Age, mortality and chronic schizophrenia. Schizophr Res 1988;1:267–272
28. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239–245
29. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia. Arch Gen Psychiatry 1998;55:250–258