

Suicide in Schizophrenia: Risk Factors and Clozapine Treatment

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Suicide is the major cause of premature death in patients with schizophrenia. Among these patients, 40% report suicidal thoughts, 20% to 40% make unsuccessful suicide attempts, and 9% to 13% end their lives by suicide. Traditional antipsychotic drugs undertreat many schizophrenic patients and can produce serious side effects, such as tardive dyskinesia. Clozapine is the only antipsychotic drug that has been shown in controlled clinical trials to be effective in reducing both positive and negative symptoms in schizophrenic patients who fail to respond to typical neuroleptic drugs. The potential decrease in suicide among schizophrenic patients treated with clozapine is estimated to be as high as 85%. Treatment with clozapine is cost-effective, and the significant decrease in the risk of suicide far outweighs the very low risk of mortality from agranulocytosis. Clozapine should be considered for treatment of both neuroleptic-resistant and neuroleptic-responsive schizophrenic patients who have persistent suicidal thoughts or behavior.
(J Clin Psychiatry 1998;59[suppl 3]:15-20)

Suicide is currently the ninth leading cause of death in the United States, and there has been relatively little variation in the overall national rate in the past 15 years.¹ More than 90% of completed suicides in any age group are associated with mental or addictive disorders.¹ Suicide is a major cause of excess mortality in schizophrenia^{2,3}; between 20% and 40% of patients with schizophrenia attempt suicide at some point during their lifetimes.^{4,5} There are numerous reports of the clinical and demographic characteristics of schizophrenics who attempt and/or complete suicide. Identifying the distinguishing characteristics of the suicidal patient is useful in determining who is at most risk and requires intensive monitoring and treatment to minimize the possibility of suicide.⁶⁻¹¹

EPIDEMIOLOGY OF SUICIDE IN SCHIZOPHRENIA

Suicide is the chief cause of premature death among schizophrenic persons.⁷ The risk of suicide in patients with schizophrenia is 20 to 50 times greater than that in the general population,⁵ and it is quite close to the risk in patients with major affective disorder.⁸ Schizophrenia is the most common diagnosis among inpatient suicides.¹² The life expectancy of schizophrenics as a group is shorter by 9 to 10

years than that of the general population, and the additional deaths are primarily suicides and accidents.⁸

Studies from different areas report that the increased risk of suicide in schizophrenia is worldwide.⁸ The lifetime risk of suicide in schizophrenia is between 9% and 13%,⁸ and it may be rising.¹³ Among schizophrenic patients, 40% report suicidal ideation, 20% to 40% attempt suicide unsuccessfully, and 9% to 13% successfully commit suicide.¹⁰ Approximately 3800 schizophrenics die by suicide each year in the United States.¹⁴ Among persons with schizophrenia, annual suicide rates consistently range between 350 and 600 per 100,000 compared with 11.4 per 100,000 in the general population.⁸ Approximately 1% to 2% of patients with chronic schizophrenia complete suicide within 1 year after their initial attempt, and 0.4% to 0.8% complete suicide each subsequent year.⁵

RISK FACTORS FOR SUICIDE IN SCHIZOPHRENIA

Schizophrenic patients share some risk factors for suicide with the general population. Males and whites are overrepresented among suicides in both populations.^{8,15} Depression, the self-reported symptom of hopelessness, suicidal ideation and behavior, and previous suicide attempts are all signs of increased risk.^{8,16-19} Poor psychosocial functioning, inadequate social support, social isolation, deteriorating health after a high level of premorbid functioning, and significant losses are common among people who turn to suicide among both schizophrenics and the general population.^{7,8}

Additional risk factors, which appear to be a function of the schizophrenic disorder itself, also have been re-

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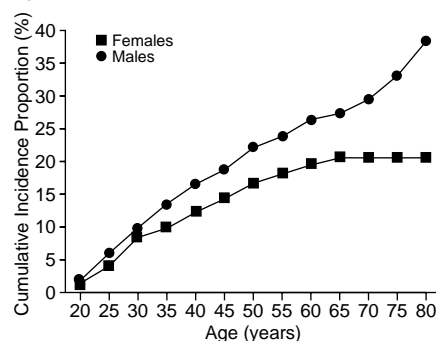
Supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

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Table 1. Risk Factors for Suicide in Individuals With Schizophrenia

Gender	Male
Race	White
Marital status	Never married, divorced, or widowed
Suicide history	Family history of suicide History of suicide attempts
Intelligence	Relatively high IQ
Vocational history	Unemployed Early vocational difficulties Poor work functioning
Social support	Social isolation Limited external support
Substance-abuse history	Current or past substance abuse, especially alcohol
Depressive symptoms	Significant depressive symptoms or mood Depressive episode at last psychiatric visit Sense of hopelessness, hostility, depression, paranoid ideation, obsessive-compulsiveness Hospitalization for which a depressive episode was part of diagnosis
Nondepressive symptoms	Diagnosed via structured clinical interview (DSM-III-R) Command hallucinations Negative association with positive symptoms
Awareness of illness	Fear of further mental deterioration Awareness of deteriorative effects of schizophrenia
Course of illness	Realistic assessment of future Frequent hospitalizations Recent discharge Acute exacerbations Worsening disease trend Frequent relapses and hospitalizations High postdischarge levels of psychopathology and functional impairment
Length of illness	Shorter duration of illness
Medication	Not receiving neuroleptics Relatively low neuroleptic dose

ported.⁷ The most well-documented disease-specific risk factors are long-term schizophrenia with numerous acute exacerbations and remissions; a postdischarge course characterized by high levels of psychopathology and impaired functioning; awareness, during a nonpsychotic phase, of the deteriorative effects of schizophrenia and of what the future might hold⁷⁻²⁰; fear of further mental deterioration; and excessive dependence on or loss of faith in treatment.^{6,7} Young men are particularly at risk.^{9,21} However, Rossau and Mortensen¹¹ recently reported that when other factors were controlled, the effect of age, i.e., the greater risk in young patients, disappeared. Similarly, Heilä et al.²² reported the results of a study of all suicides in Finland during a 1-year period and found that suicides occurred at all stages of illness. Rossau and Mortensen¹¹ noted that the risk of suicide was greatest during the 6 months following the first admission for schizophrenia. Of particular interest is their finding that multiple admissions during the year just before suicide increased the relative risk of suicide greatly. This effect was noted even when

Figure 1. Estimated Lifetime Suicide Risk in Schizophrenic Patients (age specific rates)*

*Reprinted with permission from Mortensen.²⁴

there were as few as 2 admissions within a year. Such patients had a risk of 3.5 times greater than those with no admissions, even after adjusting for other risk factors. This risk, however, rose to almost 11 in patients with 9 or more admissions. They also found that the first weeks and months after discharge from the hospital were associated with high rates of suicide. The risk factors for suicide in patients with schizophrenia are summarized in Table 1.

Hopelessness, loneliness, depression, irritability, and paranoid ideation are characteristic of patients with schizophrenia who attempt suicide. Depressive symptoms may be the strongest of these indicators.¹⁰ Postpsychotic depression has been reported in up to 25% of schizophrenic patients after acute exacerbation; this form of depression often predicts an unfavorable prognosis and an increased suicide risk.¹⁰ Neuroleptic treatment itself may contribute to postpsychotic depression associated with neuroleptic dysphoria or side effects relating to movement (e.g., akathisia).^{10,23}

The relative risk for suicide is highest at the time when schizophrenia is first diagnosed.²⁴ Although the first 10 years of the illness are a period of significantly heightened suicide risk, schizophrenics remain at risk for suicide throughout their lives. Figure 1 shows the estimated lifetime risk of suicide in patients with schizophrenia based on results of a Danish study in more than 9000 first-admission patients with schizophrenia.²⁴ Among schizophrenic outpatients, the period immediately following discharge is a high-risk time.⁹ Rossau and Mortensen¹¹ concluded that the course of hospitalization and duration of illness were key factors that emerged during multivariate analysis of risk factors. Patients who require frequent admissions are more vulnerable, especially right after discharge.¹¹ This may be related to problems in making connections between inpatient and outpatient treatment programs that are often unrelated.

It has been suggested that patients with schizophrenia who are resistant to or intolerant of neuroleptics are at higher risk for suicide than neuroleptic-responsive patients.⁵

However, studies yield no evidence to support this hypothesis. In one study, the long-term incidence and current-episode incidence of suicidal thoughts, plans, threats, and attempts are comparable between neuroleptic-responsive and neuroleptic-resistant schizophrenic groups.⁵

Two additional presumed risk factors have not been borne out by mortality studies. Some clinicians believe that neuroleptic treatment contributes to suicidality, but there is no definitive evidence to support this contention. In fact, data from one study suggest that individuals who committed suicide had lower doses of neuroleptics.²⁵ The role of positive symptoms in suicidality is another controversial issue; some researchers describe a negative association, while others claim a positive association,²⁵ wherein as many as 81% of first-admission psychotic patients who attempted suicide had histories of hallucinations.¹⁸ Results of a recent study by Fenton et al.²⁶ support an association between positive symptoms and suicidality. Data from this study suggest that the paranoid subtype of schizophrenia, typified by prominent suspiciousness, is associated with a high risk of suicide, whereas prominent negative symptoms present a low risk.

EFFICACY OF CLOZAPINE IN PREVENTING SUICIDE

Reduction of Suicidality

Clozapine is the only antipsychotic drug that has been shown in clinical trials to be effective in reducing both positive and negative symptoms in patients with schizophrenia who fail to respond to typical neuroleptics. Recent findings indicate that clozapine decreases suicidality in this treatment-resistant population.⁵ With clozapine treatment, the potential decrease in the mortality rate from suicide is estimated to be as high as 85%.¹⁰

A prospective study of 88 evaluable neuroleptic-resistant schizophrenic patients demonstrated that clozapine was very effective in decreasing suicidality.⁵ Suicidality was totally eliminated in 10 of 13 patients who had made more than 1 prior attempt; 4 of these had each made more than 4 prior attempts. There was an 86% reduction in suicide attempts with clozapine treatment, and there were reductions in suicidality and lethality of attempts,⁵ which may be attributed to an overall improvement in psychopathology.

Walker et al.³ recently reported the results of a retrospective analysis of mortality (due to specific medical conditions) of 67,072 schizophrenic patients receiving clozapine in the interval between April 1, 1991, and December 31, 1993. The data were acquired from the Clozaril National Registry (CNR), and patients were classified as current, recent, or past clozapine users. The most striking finding was that of a dramatic reduction in the incidence of suicide among current users of clozapine. While the incidence of suicide in this cohort was 19% of overall

mortality, the patients who completed suicide were primarily those who had stopped using clozapine, indicating that clozapine reduces mortality in schizophrenia, mostly by decreasing the suicide rate.³ Although there was a slightly elevated risk of mortality due to pulmonary embolism/respiratory causes among current clozapine users, this risk was small when viewed alongside the dramatic reduction in the risk of suicide among current users of clozapine.³

Novartis Pharmaceuticals Corporation reported an annual rate of 34 suicides among 51,333 patients treated with clozapine.¹⁰ This is a much lower annual rate than the 0.4% to 0.8% usually reported in follow-up studies of patients with schizophrenia.

Mechanisms of Action of Clozapine

There is extensive evidence relating diminished serotonergic activity to suicide. A reduction in central serotonin function appears to be associated with a tendency toward suicidal, parasuicidal, and impulsive-aggressive behavior in both animal and clinical studies.

The reduction by clozapine of suicide risk in schizophrenic patients is consistent with its reported antidepressant effects, which are achieved, in part, by normalizing serotonergic function.¹⁰ Long-term clozapine administration increases the release of serotonin and dopamine in rat prefrontal cortex.¹⁰ In patients with schizophrenia, increased availability of serotonin and dopamine may lessen suicidality.²⁷

Effects on Other Mental Health Factors That Predispose to Suicide

The onset of schizophrenia in late adolescence is associated with a decline in social and occupational performance in almost all patients. Awareness of this loss of function, together with persistent associated symptomatology, predisposes individuals to feelings of despair and hopelessness, which put them at high risk for suicide.²⁰ Clozapine is effective in improving positive, negative, and disorganization symptoms as well as cognitive function. It may also reduce suicidality by improving work function and the quality of life of patients with schizophrenia.

EXPANDED CLINICAL APPLICATIONS

Extrapyramidal Symptoms/Tardive Dyskinesia

Clozapine is especially indicated for treatment-resistant schizophrenia, but it also has expanded clinical applications.²⁸ As the prototype atypical antipsychotic agent, clozapine is not associated with extrapyramidal symptoms or tardive dyskinesia, unlike typical antipsychotics. For these reasons, adherence to clozapine treatment is usually high despite the need for periodic white blood cell monitoring. Especially for patients who have been taking neuroleptics and are able to compare preclozapine and postclozapine

states, the better tolerability and dramatic improvement in overall symptomatology result in a psychiatric state that is less compatible with suicide.

Mood Disorders

Clozapine has demonstrated efficacy in treating mood disorders,²⁹ including depression.³⁰ Presumably, this is due in part to the increase in the serotonin availability in the synaptic cleft, which has an antidepressant effect.³¹ The efficacy of clozapine in reducing symptomatology in schizophrenia and affective disorders suggests an overlapping neurobiological mechanism in these mental illnesses.

Depressed mood is a common risk factor among suicides in the general population and in persons with schizophrenia. Depression typically precedes suicide in schizophrenic patients.^{16,17} Approximately 57% of schizophrenic patients who committed suicide and 33% of first-admission psychotic patients who attempted suicide had been diagnosed with depression.^{18,19} Other common symptoms among suicide victims included hopelessness, hostility, paranoid ideation, anxiety, and obsessive-compulsive ideation.³²

Violence and Persistent Aggression

Clozapine is useful in reducing violence and persistent aggression among individuals with treatment-resistant schizophrenia.^{33,34} Studies have shown a significant correlation between suicidal and violent behavior, particularly in individuals with conduct disorders.³⁵ Typically, schizophrenics show signs of increased agitation, such as irritability and assaultiveness, prior to committing suicide.³⁶ The antiaggressive properties of clozapine may be related to the reduction in suicidality.³³

Substance Abuse

Substance abuse, especially of alcohol, has been associated with an increased risk of suicide.^{15,16,37} Westermeyer and colleagues¹⁵ reported that 54% of schizophrenic/psychotic suicides are related to histories of drug abuse. However, in a recent case-control study of suicide in an epidemiologic sample in Denmark, Rossau and Mortensen¹¹ found that the increased risk of suicide in patients with schizophrenia who were comorbid for substance abuse (1.3 times those without substance abuse) was reversed when other risk factors were taken into account. Moreover, a recent study based on interviews of suicide attempters³⁷ indicates a prevalence of heavy smoking in this cohort. It is unclear whether the increased risk for suicide attempts is directly attributable to cigarette smoking or if other factors predispose individuals to suicidal behavior.³⁷

Schizophrenic substance abusers are notorious for medication noncompliance. The increased suicidality of substance abusers may well be associated with the compromised therapeutic regimen and the ensuing persistence of psychotic symptoms. Clozapine is efficacious in reducing

substance abuse in schizophrenic patients.^{38,39} In one study, chronic alcohol users reportedly abstained from substance use while on clozapine treatment.³⁹

RISK-BENEFIT ASSESSMENT OF CLOZAPINE

Although clozapine has been found to be the most effective antipsychotic drug for treatment-resistant schizophrenia, its use has been greatly limited because of the risk of agranulocytosis, which has, in fact, been shown to be less than 1%.⁴⁰ The suicide mortality rate in patients with schizophrenia not treated with clozapine is much higher than the mortality from agranulocytosis in patients being treated with clozapine.^{3,10} A risk-benefit evaluation of clozapine therapy requires that the risk of death due to agranulocytosis during treatment be weighed against the reduced risk of suicide in patients treated with this drug.

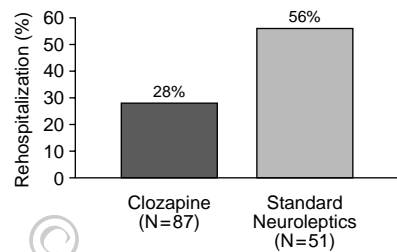
With periodic blood monitoring, the agranulocytosis risk is 0.38%.⁴⁰ Of patients with chronic schizophrenia not treated with clozapine, however, 9% to 13% commit suicide.⁵ The potential decrease in suicide mortality with clozapine treatment is estimated to be as high as 85%.⁵ In terms of benefit versus risk, while 1.5 of every 10,000 patients with schizophrenia who were treated with clozapine would be expected to die from agranulocytosis, 1000 to 1300 would be expected to complete suicide with standard treatment.¹⁰ The decreased mortality due to decreased suicidality indicates a definite benefit for clozapine relative to its risk.

In the first 3 years of clozapine use in the United States, 43,000 patients were treated with the drug, amounting to at least 50,000 patient-years of treatment.⁴¹ Among these patients, only 15 definite suicides and 3 questionable cases were reported. Because a typical treatment-resistant schizophrenic population has an annual suicide rate conservatively estimated at 200 per 100,000, 100 deaths due to suicide would have been predicted.⁴¹

The frequent visits for blood monitoring required of clozapine patients are often cited as a disadvantage, in light of the availability of other atypical agents that do not have such a requirement. However, these periodic visits can have therapeutic utility beyond monitoring white blood cell counts, particularly for the suicidal patient. Social isolation and feelings of hopelessness and despair are buffered by the therapeutic alliance formed between patient and clinician. Furthermore, such visits are useful for detection of emerging depression and suicidality as well as for monitoring medication compliance.

The unique pharmacologic properties and therapeutic regimen associated with clozapine provide benefits that far outweigh its risks. Clozapine can save lives while improving quality of life for patients with schizophrenia. As stated by Fuchs, clinicians who refuse to use clozapine "because of its risks of agranulocytosis are in fact causing

Figure 2. Rates of Rehospitalization Within 2 Years of Initial Hospital Discharge for Schizophrenic Patients Who Received Clozapine vs. Standard Neuroleptics*



*Adapted from Revicki et al.⁴³

more deaths among their patient population than they are saving lives.”⁴¹

COST-EFFECTIVENESS OF CLOZAPINE TREATMENT

Attempted and completed suicides result in significant medical, economic, and societal costs. Wyatt et al.⁴² estimate that the cost of completed and attempted suicide in patients with schizophrenia in the United States was approximately \$65 billion in 1991, based on medical expenses, investigational costs of completed suicide, and lost productivity. The implications of completed suicide at an early age for lifetime costs of treating schizophrenia, leaving aside lost productivity, are a sensitive issue and have not been adequately addressed. Suicidal behavior causes considerable distress to relatives and friends as well as to careers. There is increasing concern regarding litigation involving health care providers following suicide. Among schizophrenic patients, suicidal behavior results in a large number of hospital admissions and readmissions.^{4,5} Any treatment that proves effective in reducing suicide in schizophrenic patients can lower these costs.

The decrease in suicide attempts associated with clozapine treatment contributes to its cost-effectiveness. Several studies have found that the cost of clozapine is more than offset by a decreased need for hospitalization (Figure 2).^{43,44} Clozapine has also been shown to improve quality of life,⁴⁵ meaning, intrapsychic functions; interpersonal relations; instrumental role functioning; and common objects and activities.

A retrospective cost-benefit analysis determined that the average total cost of treatment per treatment-resistant schizophrenic patient in the year before clozapine therapy was begun was more than \$73,000. After 2 years of clozapine treatment, the total cost had declined to \$55,867. A comparison group treated with standard drugs also showed decreased costs over time, but the average decrease over 2 years was only approximately \$10,500.⁴⁶

In an assessment of the cost of treatment of 38 schizophrenic patients in the 2 years before and 2 years after

clozapine treatment was begun, the savings during clozapine therapy averaged \$25,000 per patient. This included the cost of weekly monitoring of white blood cell counts and costs associated with case management.⁴⁵

SUMMARY

Risk factors for suicide have been identified to assist clinicians in predicting and preempting an event. Detailed preadmission evaluation is advisable, especially questions pertaining to feelings of hopelessness, suicidal ideas, history of hospitalization, and previous suicide attempts. Prophylactic pharmacotherapy with an agent that has proven efficacy in reducing suicide should be considered.

The comprehensive care of patients with schizophrenia who are suicidal has been addressed by Harkavy-Friedman and Nelson.⁴⁷ They note that treatment plans must address symptoms; social problems, including recent stressors; adequacy of social support; substance abuse; and medication.

Like clozapine, however, the new atypical antipsychotics produce fewer extrapyramidal side effects than typical antipsychotic agents, and this should lead to better compliance. They also appear to have greater efficacy for negative symptoms and may be more effective for positive symptoms in some patients. There is some evidence that they may be useful in decreasing depressive symptoms in some schizophrenic patients; however, the new atypical antipsychotics have not been shown to be effective in neuroleptic-resistant patients. Future studies are needed comparing these agents with clozapine with regard to their abilities to decrease suicidality. Clinicians will frequently add antidepressant medications when patients are depressed or suicidal, but there is no evidence to indicate that antidepressant drugs have a significant effect on the rate of attempted or completed suicide in schizophrenia.

The 2 large Scandinavian studies of completed suicide indicate that the risk of suicide is high among schizophrenic patients throughout the course of illness.^{11,22} They also suggest that patients with unstable courses resulting in multiple hospitalizations should be considered in need of particular attention to reduce the risk of suicide. The use of newer antipsychotics in such patients, if they have not previously received them, should be considered. Clozapine is particularly indicated if patients have had poor response, in terms of positive and negative symptoms, to typical neuroleptic drugs or to one or more of the newer antipsychotic drugs such as risperidone, olanzapine, sertindole, or quetiapine.

Clozapine is currently unsurpassed in efficacy in the reduction of the symptoms of treatment-resistant schizophrenia; evidence is accumulating that this agent is efficacious, as well, in reducing suicidality in schizophrenia. Moreover, expanded indications of its clinical utility are emerging: Clozapine is useful in controlling affective

states and reducing extrapyramidal symptoms/tardive dyskinesia, violence, and substance abuse—conditions that have been individually associated with increased suicide risk. These findings suggest a common underlying pathophysiology that is improved with clozapine treatment.

More widespread use of clozapine has been hindered by fear of the associated risk of agranulocytosis. However, analysis of the prevalence of agranulocytosis versus suicide and other morbidity/mortality caused by violence and substance abuse clearly indicates overwhelming benefits relative to risks. The benefits include improved quality of life due to efficacy in symptom reduction, reduced hospitalization and use of emergency facilities, and increased productivity, all translating into cost savings.

Drug names: clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect).

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