SUICIDALITY IN SCHIZOPHRENIA: PHARMACOLOGIC TREATMENT

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Summary

The risk of suicide is a major factor in the morbidity and mortality of schizophrenia and schizoaffective disorder, accounting for at least 5% of deaths. The use of antipsychotic, antidepressant, anxiolytic, and mood stabilizing drugs to reduce the risk of suicide in schizophrenia is reviewed. Typical antipsychotic drugs, e.g. haloperidol, have not been reliably shown to reduce the risk of suicide. There is significant evidence from both mirror image, registry, and one controlled trial, the International Suicide Prevention Trial (InterSePT), which indicate that clozapine can greatly reduce the risk of a suicide attempt, and most likely completed suicide, in patients with schizophrenia or schizoaffective disorder. Evidence that other atypical antipsychotic drugs reduce the risk for suicide in schizophrenia and schizoaffective disorder is limited. As the major clinically evident risk factors for suicide in schizophrenia have been identified, e.g. prior serious suicide attempts, substance abuse, male sex, first decade of illness, social isolation, depression, and feelings of hopelessness, it is possible to use this information to guide pharmacologic treatment which may reduce the risk of suicide attempts and completed suicide.

Key Words: Schizophrenia – Suicide – Schizoaffective Disorder – Pharmacologic Treatment – Depression

Declaration of interest: The author has been a consultant and grantee of Novartis, manufacturer of clozapine.

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Introduction

Schizophrenia is a devastating disease that usually begins in late adolescence or early adulthood, and is associated with enduring cognitive impairment as well as intermittent or sometimes persistent psychotic, negative, and mood symptoms. Psychotic symptoms are the most prominent features of the illness but not the most prevalent or important from the point of view of functional outcome. Cognitive decline is believed to be the major reason for the poor outcome in terms of academic performance, ability to work, and interpersonal relationship (Green et al. 2000). Mood symptoms, especially depression, but sometimes disinhibited and elated mood states, are also clinically significant features of this illness which affects about 1% of the adult population world-wide (Siris 2000). Insight into illness as the basis for symptoms, cognitive decline, and functional impairment is highly variable in patients with schizophrenia and often does not emerge until many years after the onset of psychotic features (Kim et al. 2003). As individuals with this illness decline in performance, and experience frequent relapses and rehospitalizations, the support systems which sustain them during the early periods of the illness become less available in many cases. Taken together, the persistent cognitive impairment, the often poor work and social function, the ensuing depression, and reduced familial support often leads to a feeling of hopelessness (Siris 2001, Kim et al. 2003). This is the background for the high rate of suicide in schizophrenia, which will now be described. This article will briefly consider the epidemiology of suicide in schizophrenia, risk factors, and integrate this information into a pharmacologic strategy for the treatment of suicidality in schizophrenia and schizoaffective disorder.

Epidemiology of suicide in schizophrenia

Suicidal thoughts or plans, acts of unintentional self-harm, suicide attempts which may or may not be intended to be lethal, and completed suicide constitute the spectrum of suicidal behaviour, which will be referred to as suicidality. In this article, patients with schizoaffective disorder are included in the group of patients with schizophrenia, except when there is a need to distinguish between the two groups. It is recognized that this diagnostic distinction is difficult to make, that criteria are variable, and that some patients with bipolar disorder are likely to receive the diagnosis of schizoaffective disorder, at least at some stages of their illness.

Suicidality is much more frequent in patients with schizophrenia compared to the general population but lags behind that of major depression and bipolar disor-

der (Inskip et al. 1998). It is estimated that between 25-50% of patients with schizophrenia will attempt suicide at some point during their life (Niskanen et al. 1973, Planansky and Johnston 1971). The suicide rate in the United States general population is estimated as 11.1 per 100,000, making it the 9th leading cause of death in the United States (Anderson et al. 1997). The rate in patients with schizophrenia is approximately 90 per 100,000, about 8-13 times greater than that of the general population (Allebeck 1989, Mortensen and Juel 1993, Black 1988). Various cohort studies have suggested that between 4-9% of patients with schizophrenia or schizoaffective disorder will commit suicide during their lifetime. A recent comprehensive review of the literature suggests that the lower end of this range, e.g. 4.9%, is the more accurate figure (Palmer et al. 2005). This is likely to be an underestimate , but regardless, it is still an unacceptably high rate. However, it should be noted that there is evidence from Denmark of a recent decrease in the rate of suicide in patients with schizophrenia, which parallels the decrease in the rate in the general population (Nordentoft et al. 2004). In the United States, with an adult population of approximately 200,000,000, approximately 3600 people with schizophrenia complete suicide each year. This is most likely an underestimate because of the reluctance to attribute death to suicide in the absence of a note or other unequivocal evidence. Suicide is the leading cause of death in patients with schizophrenia under the age of 35 (Allebeck 1989). Mortality from suicide in previous suicide attempters has been estimated to be 1% per year of follow-up for up to five years following an attempt (Ettlinger 1975). The risk of suicide in schizophrenia continues throughout the patient's lifetime, although rates are highest during the first year and decade after onset of psychosis (Heila et al. 1997, Nordentoft et al. 2004).

Risk factors for suicide in schizophrenia

A number of risk factors have been reliably identified for patients with schizophrenia. These have been reviewed by Caldwell and Gottesman (1992). These include: 1) prior suicide attempts; 2) substance abuse; 3) depression or depressed mood; 4) hopelessness, including a fear of further intellectual, social, and physical decline; 5) male sex; 6)being unmarried, socially isolated or unemployed; 7) diminished external support from family, significant others, or public entities; 8) high levels of premorbid functioning, which make the decline in performance more difficult to accept; 9) poor response to treatment, including non-compliance; 10) recent loss or rejection; 11) command hallucinations or delusions, which urge self-harm; 12)presence of insight into the effects of illness; 13) Caucasian vs. Afro-American; and 14) family history of suicide. It has been suggested that decreasing length of hospitalization for patients in an acute episode has increased the risk for suicide, most likely because of inadequate time for assessment of risk, crisis resolution, and adequate discharge planning (Mortensen and Juel 1993). There does not appear to be a difference in suicidality between neuroleptic-resistant schizophrenic patients who have persistent psychotic symptoms and patients whose positive symptoms respond to treatment with typical or atypical antipsychotic drugs (Meltzer and Okayli 1995)

Effect of Psychotropic Drug treatment on suicide in Schizophrenia

Effect Of Typical Antipsychotic Drugs

The first effective treatment for schizophrenia was chlorpromazine, the prototypical first generation antipsychotic drug. Introduced in 1954 in France, its use spread rapidly throughout the rest of world, based upon its ability to diminish hallucinations and delusions in about 70% of patients with schizophrenia. As early as 1911, Bleuler (1950), who gave schizophrenia its name, recognized suicide as one of the chief problems in suicide. There was, at first, much hope that chlorpromazine and other neuroleptic drugs [called that because of their ability to produce catalepsy in rodents and extrapyramidal symptoms (EPS) in man] would reduce the risk of suicide. However, the initial impression of clinicians was that the rate of suicide in schizophrenia *increased* after their introduction because of neuroleptic-induced depression and side effects (Hussar 1962, Beisser and Blanchetter 1961). Subsequent studies did not bear out this conclusion, nor did they find any evidence for a decrease in the rate (Ciompi 1976, Winokur and Tsuang 1975). Akathisia due to EPS has been linked to suicide in schizophrenia (Planansky and Johnston 1971; Drake and Ehrlich 1985, Shear et al. 1983). The discovery, in 1959, that clozapine did not cause catalepsy or significant EPS, led to it being labelled an atypical antipsychotic and the neuroleptics, as typical antipsychotic drugs. This terminology will be used in this article. Typical neuroleptic drugs do not appear to have significant antidepressant action, aside from secondary improvement that might occur from their ability to treat positive symptoms (Siris 2000).

Effect of antidepressants and mood stabilizers

The use of antidepressants and mood stabilizers in patients with schizophrenia, including those who are suicidal, is very common, reaching 50% for either or both drugs in some series. However, the data to support this practice is very limited and it does not appear to affect the suicide rate. Some controlled studies report a beneficial effect of imipramine in post-psychotic depression, but this appears to be modest and least in those who need the most protection, those with more severe symptoms (Siris et al. 1994, 2000). Goff et al. (1995) found no effect of augmentation of antipsychotic drugs with fluoxetine in a placebo-controlled, randomized study but the patients entered this study lacked a high level of depression. As will be discussed, the greater use of antidepressant drugs in patients treated with olanzapine compared to clozapine in the InterSePT study, did not equalize the efficacy of the two drugs to prevent suicidality in patients at high risk for suicide. However, an effect within the two groups to reduce suicidality cannot be ruled out.

Suicide risk reduction with atypical antipsychotics

Suicide Risk Reduction with Quetiapine, Risperidone and Olanzapine

The effect of the newer atypical antipsychotic agents (aripiprazole, risperidone, olanzapine, quetiapine and ziprasidone) on suicide rates among patients with schizophrenia has had very limited study. A recent review of phase III data submitted to the US FDA for approval of risperidone, olanzapine, and quetiapine found no significant differences in the rate of suicide or suicide attempts compared to typical neuroleptic drugs of placebo. However, these data came from short-term studies and included subjects who were not considered to be at high risk for suicide at the time of entry (Khan et al. 2001). Tran et al. (1997) compared olanzapine and risperidone in a 28 week study involving 339 patients with schizophrenia, schizoaffective, or schiozophreniform disorder, and, in a secondary analysis, reported significantly lower suicide attempt rates with olanzapine than risperidone but did not report the actual percentages. No differences in suicidal ideation was reported in a six week, blinded, randomized, study of 62 patients with schizophrenia, schizoaffective disorder, or psychotic depression treated with risperidone or haloperidol and amitriptyline (Müller-Siecheneder et al. 1998). Neither of these studies provides sufficient evidence for conclusions about the ability of these drugs to reduce suicidality.

Suicide Risk Reduction and Clozapine

In contrast with the lack of evidence that typical neuroleptic drugs reduce the risk of suicide, considerable data indicate that the prototypical atypical antipsychotic drug, clozapine, may reduce the risk of suicide (Meltzer and Okayli 1995, Walker et al. 1997, Reid et al. 1998; Spivak et al. 1998, Munro et al. 1999, Meltzer et al. 2003, Duggan et al. 2003, Wagstaff and Perry 2003, Modestin et al. 2005). Clozapine was first reported to reduce the rate of suicidality by Meltzer and Okayli (1995) who examined suicidality in 88 neuroleptic-resistant patients diagnosed with chronic schizophrenia (N=73) or schizoaffective disorder (N=15) according to DSM-III-R criteria. These authors reported that the percentage of patients with no suicidality increased from 53% at baseline to 88% during treatment with clozapine. There were 22 suicide attempts in the two years in this cohort prior to the initiation of clozapine therapy and only 3 suicide attempts, with low probability for lethality, in patients treated with clozapine over the two years of follow-up, a decrease of 86% attempts. Before clozapine treatment, the lethality of reported attempts was assessed as minimal-to-mild in 11 instances and moderate-to-severe in 11 attempts. All three attempts after clozapine treatment were considered to have no substantial potential for lethality. The decrease in suicidality among this cohort of patients was also associated with an improvement in hopelessness and depression. The limitations of this study will be discussed subsequently. As will be discussed, nearly identical results were obtained in a study of hospitalized patients with schizophrenia using the same mirror image design (Modestin et al. 2005).

Following the report of Meltzer and Okayli (1998), an epidemiologic study of mortality and morbidity in current and former clozapine users based upon the US Clozaril® National Registry (white blood count monitoring system for patients treated with clozapine from April 1991 until the end of 1993) was conducted by an independent expert epidemiology group (Walker et al. 1997). The rate of various causes of death was compared in 67,072 current and former clozapine users. Data from the national registry of clozapine users was linked to the National Death Index and Social Security Administration Death Master Files and death certificates. The overall standardised mortality ratio (for age, sex, and race) for the cohort compared with the United States general population was 1.73. During 1991-1993, there were 396 deaths in 85,3999 person-years for patients ages 10-54. (Older patients were excluded because of the high rate of use of clozapine for treating L-DOPA-induced psychosis in that group). In patients aged 10 to 54 years, the overall standardised mortality ratio was reduced by 54% in current users of clozapine compared with former users. This was primarily due to an 83% reduction in death by suicide among current compared with past clozapine users. In addition, the overall mortality rate during current clozapine use was much lower than during periods of non-use (322 vs. 693 deaths per 100,000 person-years). The suicide rates among current and former users of clozapine were 39 and 222 per 100,000 person-years, respectively. Mortality from suicide was decreased in current clozapine users by comparison with past users [rate ratio (RR) = 0.17; 95% confidence interval = 0.10-0.30]. It was concluded that clozapine reduced mortality in schizophrenia, mostly by decreasing suicide rates.

Data from the US Clozaril® National Registry for the period April 1991 to the end of 1993 showed an incidence of suicide of 0.039% and 0.22% per year for current and former users of clozapine, respectively (Meltzer & Okayli 1995) Data from this same registry from the beginning of 1990 to June 1996 revealed that the incidence of suicide was 0.0157% per year (Reid et al. 1998, Reid 1999) compared with the rate of 0.4 to 0.8% per year reported in previous studies with classical antipsychotics (Cohen et al. 1990, Axelsson and Lagerkvist-Brigss 1992). The reduced risk of suicide among patients treated with clozapine was confirmed in a retrospective study of patients with schizophrenia or schizoaffective disorders in the Texas State Mental Health System (Reid 1999, Reid et al. 2000). These authors found that among patients with schizophrenia and schizoaffective disorder, the annual suicide rate in those treated with clozapine was 12.7 per 100,000 patients. The annual suicide rate for all psychiatric patients was 60.2 per 100,000 patients. Similar results were found in data from the United Kingdom (Munro et al. 1999).

Suicidality, impulsiveness and aggressiveness were evaluated in 30 neuroleptic-resistant, chronic schizophrenic patients who had been maintained on clozapine for at least one year and compared with these symptoms in 30 chronic schizophrenic patients who had been treated with neuroleptic drugs for the same period (Spivack et al. 1998). Clozapine was associated with

fewer suicidal attempts ($p < 0.05$), as well as less impulsiveness ($p < 0.05$) and aggressiveness ($p < 0.01$) compared with chlorpromazine.

Finally, Sernyak et al. (2001) used the method of propensity scaling to compare the effect of clozapine on suicide as well as all causes of mortality with standard treatment. However, the variables available for matching subjects did not include the four most important variables which are necessary for matching for suicide risk, i.e. the number, timing, and lethality of prior suicide attempts, and severity of depression at index admission. None of the variables used to create the comparison group, with the exception of substance abuse, are relevant to suicidality (Ertugrul 2002). This tracks confidence that the two groups were at equivalent risk for suicide. The major limitation in the study, however, was that it did not adjust the risk period for the clozapine-treated patients to the time they were actually taking clozapine. It seems likely that most of the clozapine patients were not taking clozapine for the majority of the possible 6-year follow up. Unfortunately, the authors chose not to restrict their analysis to the time clozapine was actually taken as prescribed (Meltzer 2002). Nevertheless, Sernyak et al. (2001) still found a trend for clozapine to reduce suicide. Using a one-tailed test ,which would have been the appropriate statistic, this would have been significant at the customary statistical level.

The InterSePT Study: A Controlled Randomized Clinical Trial of the Effect of Clozapine on Suicidality

Taken together, the results reported above strongly suggested that clozapine significantly reduced the rate suicide attempts or completed suicide in clinical practice. However, there are various limitations in these studies which bear upon the confidence that the findings reach the highest standards of evidence based medicine. These include:1) retrospective data; 2) possible differences in the risk of suicide between clozapine and comparison groups because subjects were not randomly assigned to treatment; 3) possible differences in dosages of clozapine and the comparison antipsychotic drug(s) relative to optimal dose for reduction of suiciality; 4) uncontrolled and possibly differential use of concomitant psychotropic medications such as antidepressants, mood stabilizers, anxiolytic drugs and drugs to reduce EPS; 5) weekly and biweekly clinical contact during treatment with clozapine to examine white cell count compared to less frequent visits for those not taking clozapine; 6) lack of examination of compliance with clozapine or prior treatment; 7) lack of control of possible differential access to psychosocial support programs; and 8) lack of comparison with other atypical antipsychotic drugs which may have greater benefit for treating suicidality than typical antipsychotics.

A prospective, randomized, masked (blinded) parallel-group study to compare the effects of treatment with clozapine versus another atypical antipsychotic drug in which patients were seen equally frequently and with equal access to other psychotropic drugs and psychosocial treatment was concluded by the author to be the best means to test the hypothesis that clozapine had a specific benefit to reduce suicidality in schizophrenia. This was the origin of the International Suicide Prevention Trial (InterSePT), which was principally designed by the author, and Drs. Larry Alphs and Ravi Anand, then of Novartis, the patent holder for branded clozapine, Clozaril® (Alphs et al. 2004). Members of the InterSePT research group also contributed greatly to the design and execution of the study (Meltzer et al. 2003). It was determined that clozapine would be compared to olanzapine in patients with schizophrenia or schizoaffective disorder, regardless of whether they had persistent psychotic symptoms on prior treatments, but who were at more than average risk for a subsequent suicide attempt, based primarily on having made at least one suicide attempt in the three years prior to study entry or to be currently suicidal. Olanzapine was selected as the comparator because it had been previously suggested that it, too, might be able to reduce the suicide attempt rate in patients with schizophrenia who had depressive symptoms or syndrome compared to haloperidol (Tran et al. 1997).

The primary outcome measures for the InterSePT Study was either time to a suicide attempt (including death by suicide), or a hospitalization to prevent suicide as determined by an independent blinded, suicide Monitory Board (SMB) or time to much worsening/very much worsening from baseline on a clinical global impression of suicidality scale as rated by a blinded rater.

The study was not designed to compare the effect of the two drugs solely on a difference in the time to completed suicide because this would have required over 20,000 patients at high risk for suicide to complete such a study with adequate power. No typical antipsychotic drug was included because of the additional expense and because it was felt the use of these drugs was otherwise not advantageous for patients with schizophrenia. With the chosen primary end point, it was determined that inclusion of approximately 1000 patients would be required to determine a significant difference between the two drugs with a probability of 0.8.

A two year study duration was chosen to provide time to obtain sufficient endpoints to differentiate between the two treatments. A randomized, open-label trial with blinded ratings by trained raters and a blinded psychiatrist, and determination of whether potential endpoints met criteria for a suicide attempt or a hospitalization to prevent suicide who had no direct contact with the participating sites or the sponsor of the study were major features of this study. Treatment was prescribed by a psychiatrist who had full knowledge of the drugs prescribed as well as control of ancillary therapies to reduce the risk of suicide.

The visit schedule for both groups was identical, except that the olanzapine-treated patients had vital sign measurement instead of blood drawing. To ensure the safety of patients during this trial, clinicians were allowed to make any interventions necessary to prevent the occurrence of suicide attempts, including dosage changes, addition of other medications, switching medications, and increased surveillance. Of the total sample, 609 patients (62.1%) were diagnosed with schizophrenia, and 371 (37.9%) with schizoaffective disorder. Eighty-three percent of patients had attempted suicide at least once during their lifetime and 84% were hospitalized to prevent a suicide attempt. Sixty-three percent

had attempted suicide in the previous 36 months. The mean prescribed dosages of study drugs were 16.8 ± 7.4 mg daily for olanzapine and 306 ± 166 mg daily for clozapine. No significant difference in dropout rate for patients treated with either drug was noted.

A significant difference was demonstrated between clozapine and olanzapine in reducing suicidality as measured by SMB-determined suicide attempts (including completed suicides) or hospitalizations to prevent suicide and much/very much worsening in rating scales compared to baseline as assessed by the blinded psychiatrist. Overall, there was a 24% difference in the hazard ratio for this endpoint in favor of clozapine. The number of patients needed to treat with clozapine to reduce the risk of one event was 13. It was concluded that clozapine was superior to olanzapine in patients with schizophrenia or schizoaffective disorder, regardless of whether they were neuroleptic-resistant and neuroleptic responsive, as well as males and females. There was minimal evidence for ethnic or country of origin differences in this regard. The two drugs did not differ in overall efficacy to reduce total psychopathology, positive or negative symptoms, or depression. Thus, the difference between the drugs on suicidality was not secondary to other efficacy differences, confirming the view of suicide as a separate dimension of the schizophrenia syndrome.

Key secondary measures such as the mean daily doses of concomitant antipsychotic drugs, antidepressants and convulsants to augment the efficacy of the primary treatment also favored clozapine (Glick et al. 2004). It is of interest that approximately 90% of patients in both treatment groups received at one least of these medications. For each type of medication, the mean daily dose and proportion of patients who received these medications was significantly lower for clozapine. There is no evidence to determine whether these concomitant medications actually reduced the risk of suicide. No cases of agranulocytosis developed in either group. The total number of deaths and completed suicides was not significantly different between groups. The number of suicide attempts prior to study entry and current substance abuse were the most important predictors of an event during the course of the study (Potkin et al. 2003). It was concluded that the InterSePT study provided compelling evidence for the ability of clozapine to substantially reduce the risk of suicide in patients with schizophrenia or schizoaffective disorder who are at high risk for schizophrenia. On the basis of this study, plus the Walker et al. (1997) data, the Food and Drug Administration of the United States approved an indication for clozapine to reduce the risk of suicide in schizophrenia. Some other regulatory authorities have acted similarly, but others, e.g., Australia, have not. In the case of Australia, it was concluded that the InterSePT study was not adequately blinded. Sakinofsky et al. (2004) have carefully described the work of the masked SMB in the InterSePT trial and concluded that the decisions made by the board were made without knowledge of which drug treatment was used for the cases they were called upon to evaluate as a potential suicide event.

Fontaine et al. (2001) have argued that the lives saved from suicide by the use of clozapine should be compared to the lives lost due to clozapine-induced metabolic complications such as weight gain, diabetes mellitus, hyperlipidemia, etc. They estimated that 492 suicide deaths per 100,000 schizophrenia patients would be prevented over 10 years with the use of clozapine, compared to 416 deaths due to antipsychotic-induced weight gain. However, they utilized data from Harris and Baraclough (1997) to estimate the lives saved due to the effect of clozapine on suicide. The estimate these data provides assumes that clozapine would be used for this purpose in the general population of patients with schizophrenia, not those selected for likelihood of a suicide attempt based on the risk factors discussed previously in this paper, e.g. one or more medically serious suicide attempts in the recent past, feelings of hopelessness, substance abuse, etc. It is difficult to provide a precise estimate of the number of lives that could be saved from suicide in this group but given the fact that in there at least 3600 patients with schizophrenia who suicide each year in the United States, 36,000 in ten years, that clozapine reduces the risk of an attempt in clinical practice by approximately 80%, and that one in every seven serious attempters dies due to completed suicide within a two year period, it would seems that the number of lives saved with clozapine in this high risk population could easily be many times as great as that proposed by Fontaine et al. (2001).

Additional Evidence Beyond InterSePT that Clozapine Reduces the Risk of Suicide in Schizophrenia

Following the completion of this study, Modestin et al. (2005) reported a mirror image study of inpatients, compaing suicidality of all types and medically serious suicide attempts in 94 Swiss inpatients with schizophrenia. The duration of treatment pre-post clozapine was 15 months in each case. The rate of suicidal behaviour was 28% in the pre-clozapine period, 4% in the clozapine period, and 18% in 17 patients who were followed after the discontinuation of clozapine. The rate of medically serious suicide attempt was 12, 1 and 12%, respectively. The odds ratios favoring clozapine in these two periods were 11.6 and 12.4, respectively. The consistency in the reduction of suicide attempts in the studies of Meltzer and Okayli (1995), Walker et al. (1997), Munro et al. (1999); and Modestin et al. (2005) is noteworthy and can be considered to provide a good estimate of the extent of reduction of suicide attempts in clinical practice.

Hennen and Baldessarini (2005) recently completed a meta-analysis of six studies which provide an overall assessment of the suicide risk during clozapine treatment. They included the studies of Meltzer and Okayli 1995, Walker et al. 1997, Reid et al. 1998, Munro et al. 1999, Sernyak et al. 2001, and Meltzer et al, 2003. They did not include the study of Modestin et al. (2005) which would have strengthened their conclusions. A random-effects analysis indicated a substantially lower overall risk of suicidal behaviors favoring clozapine (risk-ratio [RR] 3.3; 95% confidence interval [CI]1.7-6.3; $p<0.001$). For completed suicides, the RR was 2.9 ([CI 1.5-5.7]; $p = 0.002$).

A reasonable conclusion from the InterSePT study and the rest of the evidence that clozapine reduces the risk for suicide is that is now well established that

clozapine has a clinically relevant advantage over both typical and atypical antipsychotic drugs to reduce suicidality and that this is not due to the additional clinical contact associated with clozapine use. The pharmacologic basis for this advantage remains to be determined. This information about the efficacy of clozapine must be considered in determining its suitability for use in patients who are at high risk for suicide. The risk factors noted above should be fully utilized to determine risk, which can only be done with a comprehensive clinical interview. Of course, many factors go into the final choice of medication for any given patient. It remains to be determined if clinicians will utilize this evidence-based information in clinical practice.

Non-Pharmacologic Treatment of Suicide in Schizophrenia

Although it is clear that the benefit of clozapine to reduce the risk of suicide in schizophrenia is not entirely due to non-pharmacologic treatments that accompany it use, it is nevertheless likely that non-pharmacologic treatments can augment the effects of clozapine. This may be true for other antipsychotic drugs as well. Research is needed to determine which non-pharmacologic treatments would be most helpful and whether those treatments might be differentially effective with specific psychotropic drugs. Among the treatments to be considered would by rehabilitation programs to restore work function, individual, group or family therapy to identify area of vulnerability and conflict, cognitive enhancement treatment, social enrichment programs, etc. These modalities are discussed in detail elsewhere (Pompili et al. 2003, 2004; Power et al. 2003). Subsequent research in which psychotherapeutic approaches and clozapine are tested alone, and in combination, will be of great interest.

Clozapine, Suicide, and Mood Disorders

There is also some evidence that clozapine may reduce the risk for completed suicide in patients with mood disorders. This may be inferred from the finding of a significantly lower standardised mortality rate in 150 patients receiving antipsychotic drug treatment compared to 256 who did not. Of those receiving antipsychotic drugs, 104 (69.3%) received an atypical antipsychotic drug. Clozapine, at a mean dose of 119 mg/day, which is lower than that used to treat schizophrenia, was the most commonly prescribed antipsychotic drug (Angst et al. in press). There is substantial evidence that lithium treatment reduces the risk of suicide in bipolar disorder (Tondo et al. 2001, Müller-Oerlinghausen et al. 2003). Further study is need to determine whether clozapine might also reduce the risk for suicide in bipolar and other mood disorders, and whether the combination of the two drugs might be superior to either drug alone.

Conclusion

Suicide is the major cause of death in schizophrenia, accounting for the death of at least 5% of people with schizophrenia. Suicide attempts are made by 25-50% of all patients with schizophrenia and add greatly to the suffering and cost of this syndrome. Typical neuroleptics have not been shown to reduce the suicide rate in schizophrenia. However, there is now an overwhelming amount of evidence from a variety of studies, including InterSePT, a randomized controlled trial of 990 patients with schizophrenia or schizoaffective disorder at high risk for suicide, that clozapine reduces the risk of suicide compared to olanzapine and presumably other typical and atypical antipsychotic drugs as well. There is no evidence for or against the possibility that atypical antipsychotic drugs other than clozapine reduce the risk for suicide compared to typical antipsychotic drugs. Thus, the available evidence strongly suggest that reducing the risk of suicide in schizophrenia is increased by utilization of clozapine in patients deemed to be at current and prolonged risk for suicide. Awareness of the risk factors for suicide in schizophrenia is essential in determining when to use clozapine for this indication. In addition, availability and utilization of protective environments, e.g. emergency rooms, respite housing, and hospitalization, during a period of heightened suicidality, psychosocial support, including some forms of counselling, and integration of in-patient and out-patient care, will serve to complement the effects of clozapine.

Aknowledgments

Supported, in part, by grants from the Ritter Foundation, the William K Warren Foundation, and the Bixler Fund for Psychiatry

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