Suicide in Schizophrenia, Clozapine, and Adoption of Evidence-Based Medicine

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Evidence-Based Medicine

Real progress in medicine is based upon obtaining new knowledge that provides clear guidance as to how to prevent or treat serious clinical problems. However, obtaining that knowledge, in itself, is insufficient. Unless patients, clinicians, and those who fund, authorize, and oversee the delivery of services utilize the knowledge, its acquisition may have little significance, except, perhaps, as a base for further research. Experts in the health care field, including psychiatry, urge the adoption of evidence-based medicine as a way to improve care and reduce costs.[1] Yet, a recent review of 12 leading mental health journals concluded that data needed to inform and advance evidence-based practice do not have a prominent place in these journals and that there was minimal evidence of studies evaluating treatment effectiveness in routine practice settings.[2] The story of clozapine and its ability to reduce the risk of suicide in schizophrenia and schizoaffective disorder is an interesting case history in that regard. Clozapine's ability in this respect may demonstrate that the prescription of antipsychotic drugs is not based upon evidence-based guidance that takes into account the individuation of treatment choices based upon patient characteristics,[3,4] e.g., risk of suicide, or it may demonstrate that scientific evidence can change prescribing behavior; this outcome remains to be determined.

The Risk of Suicide in Schizophrenia

Between 4% and 13% of patients with schizophrenia commit suicide, and between 25% and 50% make at least 1 suicide attempt during their lifetime.[5–7] The rate of suicide among patients with schizophrenia, which is especially high in young people during the first episode, has increased, although there has been an overall decline in the suicide rate in the general population (reviewed by Nordentoft et al.[8]). Suicide in schizophrenia is most common during the first decade of illness, making suicide the leading cause of early mortality in schizophrenia and, thus, a cause of enormous sorrow and loss to the families of those who die or have permanent disability beyond that caused by the psychosis and cognitive impairment associated with schizophrenia.[6] The risk of suicide, or the aftermath of a suicide attempt, may be the most common reason for hospitalization of patients with schizophrenia and among the most likely reasons for an emergency evaluation by a mobile crisis team or an emergency room visit.[9] Kallert et al.[9] noted the need for care related to suicidality in a cohort of patients living in the Dresden region (Germany). They noted that 30% to 40% of the cohort had a constant high level of need for care because of suicidal behavior. In the United States, under managed care that often restricts access to hospital and length of hospitalization except when persistent suicidality or violence toward others is present, suicidal behaviors account for billions of dollars of the direct costs associated with schizophrenia and a large portion of the indirect costs as well, due to such things as family burden, funeral expenses, and autopsies.

Evidence That Clozapine Reduces the Risk of Suicide

The first evidence that clozapine reduced the risk of suicide was provided by Meltzer and Okayli[5] in a mirror-image study of 88 patients with schizophrenia who were treated with clozapine. Twenty-two of the 88 patients had made a suicide attempt in the 2 years before clozapine treatment, but only 3 did in the 2 years on clozapine treatment, an 85% decrease in the rate. This study was followed by a number of cohort studies from the United States and England, reviewed elsewhere, that demonstrated similar reductions in completed suicides.[6] These studies could not rule out the additional benefit of the weekly clinical contact associated with monitoring white blood cell counts in patients treated with clozapine. To do that, the International Suicide Prevention Trial (InterSePT), a randomized clinical trial comparing the effect of clozapine and olanzapine in 990 patients at risk for suicide, was carried out.[10] This study clearly demon-

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strated that clozapine reduced the risk of suicide attempts by 25% compared with olanzapine. This finding led the U.S. Food and Drug Administration (FDA) to approve an indication for clozapine to reduce the risk of suicide in patients at high risk for suicide. The American Psychiatric Association guidelines for reducing the risk of suicide in schizophrenia support the use of clozapine for this indication.[11]

Novartis, the sponsor of InterSePT and the manufacturer of Clozaril, the branded form of clozapine, made an effort to educate clinicians about this indication, hiring a special sales force for this purpose and sponsoring continuing medical education programs and symposia at national meetings, but there was no evidence that the use of clozapine increased thereafter to the extent that would be expected if the new evidence-based indication changed clinical practice significantly. The market share of clozapine remained unchanged, as less than 5% of the total. Novartis stopped marketing Clozaril less than a year after obtaining the indication for suicide because of the perceived lack of return on the investment. At the current time, the only promotion of clozapine to prescribers is from Alamo Pharmaceutical, who recently introduced an oral disintegrating tablet formulation, FazaClo, and they are prohibited from discussing the suicide indication by FDA regulations, preserving that right for Novartis for at least another year.

New Evidence That Clozapine Reduces the Risk of Suicide

Using a mirror-image design, Modestin et al.[7] (this issue) have now provided strong additional evidence that clozapine reduces the risk of suicide. In a retrospective study of data from hospitalized patients with schizophrenia, Modestin et al. found an 88% decrease in the risk of suicide, nearly identical to the 85% decrease previously reported by Meltzer and Okayli.[5] They calculated a 12-fold decrease in the risk of suicidal behaviors. This study was done in hospitalized patients with schizophrenia. It is well known that the majority of patients with schizophrenia who commit suicide do so in the hospital or shortly after discharge.[11] Moreover, Modestin and colleagues found that the rate of suicidal behavior increased to the baseline rate in those patients who discontinued clozapine. This is a most important finding and concurs with this author's experience in this regard.[12] Their finding obviously has implications for the need for prolonged treatment with clozapine once it has been instituted for suicide risk reduction. The Modestin et al. study controlled for the issue of clinical contact, which was not possible with the Meltzer and Okayli study.[5] As naturalistic studies, with each patient as his or her own control, these 2 studies provide a reasonable estimate of the reduction in the risk of suicide that should be possible in clinical practice. The InterSePT study,[10] for all its methodological niceties, could not provide an indication of what would be expected in clinical practice. Similarly, the effect size noted in a recent meta-analysis of 6 studies that provided comparative data on the effect of clozapine versus other treatments on the risk for suicide was probably an underestimate.[13] This study reported that the risk ratio for suicidal behaviors was 3.3-fold in favor of clozapine (95% CI = 1.7 to 6.3; $p < .0001$). For completed suicides, the risk ratio was 2.9 (CI = 1.5 to 5.7; $p = .002$).[13] This estimate included the only published negative data, from the large study by Sernyak et al.,[14] which will be discussed subsequently. Both the Texas Medication Algorithm Project[15] and the International Psychopharmacology Algorithm Project[16] recommend the use of clozapine in the suicidal patient with schizophrenia, as do a number of reviews.[17,18] There is some evidence that clozapine reduces the risk for suicide in bipolar disorder and depression,[19] but whether it is as effective at reducing the risk of suicide as lithium carbonate is in bipolar disorder[20] or electroconvulsive therapy is in depression is completely unknown.

Neither the InterSePT study nor any other existing controlled evidence allows any conclusions as to whether olanzapine or other atypical antipsychotic drugs have any ability to reduce the risk for suicide in schizophrenia. Data from a secondary analysis of phase 3 controlled studies suggest not,[21] while another study, which did not control for possible drug assignment bias, indicated that risperidone and olanzapine may have been protective compared with other treatments that were not specified.[22]

Why Is the Evidence for Clozapine's Effect on Suicide Not Widely Utilized to Guide Treatment?

Why has this abundant evidence not led to a wide-scale adoption of clozapine in the majority of patients with schizophrenia who have made a recent suicide attempt? It may be due, in part, to the influence of the one negative study of the effect of clozapine on suicide.[14] This study, which employed an unusual methodology that attempted to compare rates during clozapine treatment with those of an ersatz control group, has been criticized on methodological grounds[23,24] but is often given equal weight in reviews with the other more reliable and consistent evidence.[25] However, it is more likely that other factors are responsible for the low rate of use of clozapine in the suicidal patient with schizophrenia or schizoaffective disorder, in particular, the side effects of clozapine, such as agranulocytosis, metabolic side effects, seizures, hypotension, and hypersalivation. The requirement of some type of indefinite blood monitoring, though slightly less rigorous now that it has been decreased in the United States to every other week after 6 months, places a real burden on patient and caregiver. This issue will be discussed subsequently. Together with the lack of marketing, these side effects and the requirement of monitoring have contributed

to profound reluctance to use clozapine both for suicide risk reduction and for its primary indication, failure to respond to 2 or more antipsychotic drugs.

What Can Be Done About Expanding the Utilization of Clozapine for Reducing the Risk of Suicide?

The evidence that clozapine reduces the risk for suicide in schizophrenia is now very strong. However, just as the use of clozapine for patients with persistent positive symptoms who have failed 2 or more trials of other antipsychotic drugs, though supported by a similar body of evidence, influences clinical practice much less than it should, the same fate may await the indication for suicide. However, given the importance of suicidal behaviors and the finality and horror of completed suicide, it seems rational to expect that the only drug shown to significantly diminish the risk and rate would be rapidly and widely adopted for that purpose. It is to be hoped that the additional data provided by the study by Modestin et al.[7] in this issue will persuade those who are doubtful that this is a real effect. It seems likely, though, that other fundamental issues with regard to using clozapine will need to be addressed if clinical practice is to change.

The fundamental barriers to the wider use of clozapine are most likely the fear of agranulocytosis and the policy, at least in the United States, of indefinite monitoring of the white blood cell count, which necessitates a weekly or biweekly blood analysis. The risk of fatal agranulocytosis associated with the use of clozapine needs reappraisal.[26,27] It has proven to be about two thirds lower than was thought when clozapine was first introduced.[28] With no monitoring requirement, agranulocytosis was known to occur in a small proportion of patients treated with typical antipsychotic drugs with subsequent mortality.[26]

Reducing the white blood cell monitoring schedule to less than every 2 weeks after 12 months or somewhat longer would encourage some of the patients who stand to obtain the greatest benefit from clozapine for any of its indications, suicide risk in particular. It can be estimated that with monitoring, 1 in 10,000 people treated with clozapine will die from agranulocytosis.[6] Clearly, among patients at high risk for suicide, where approximately 1 in 10 to 20 will die from suicide, the relative risk strongly favors clozapine. Data are available from registries throughout the world to calculate the risk of developing and dying from agranulocytosis if all monitoring were to be eliminated entirely after 12 months or later.[25] The rate should be approximately 1 in 5000 or less, because agranulocytosis rarely occurs after 12 months, and treatment for any infections that develop will be effective in most but not all individuals.[26–28] This rate is comparable to those of many other drugs for which there is no monitoring requirement and has led to the conclusion that it is not prudent to monitor after 6 months.[29] While this conclusion may be challenged, the available data can be the basis for a discussion among all stakeholders, including bioethicists who can consider the complex life-and-death issues involved, as to how long monitoring should be continued and at what intervals. Any infection that developed after the cessation of monitoring could be treated with antibiotics and colony-stimulating factors, as is the case now.[25,29,30] Any individual who prefers more frequent monitoring should have the right to be monitored, including those whose care is provided in the public sector, but it would be voluntary for the rest.

As the risk for suicide returns when clozapine treatment is stopped,[7,12] it is likely that individuals who benefit from clozapine would take it for very prolonged times, perhaps indefinitely. Thus, they must accept lifelong biweekly blood sampling in the United States under current regulations. This is a great challenge for many patients.

The metabolic side effects of clozapine are a real risk and another factor that causes some patients and physicians to be reluctant to use clozapine, but these side effects do not affect all patients and can be minimized by diet, exercise, and use of a statin or other anti-lipid medications. The newly introduced oral disintegrating form of clozapine, FazaClo, should be helpful for assuring medication ingestion in patients who have trouble with compliance or swallowing. As previously mentioned, this is the only form of clozapine that is now being promoted. Because so many clinicians receive their information about clinical practice from pharmaceutical company representatives, it is important that all companies that provide clozapine to the marketplace make a concerted effort to see that this agent is used for its special indications in schizophrenia, i.e., resistance to other antipsychotic drugs and high risk of suicidality.

In addition, there should be efforts by managed care and governmental agencies, including the National Institute of Mental Health and the Departments of Mental Health of the 50 states, to make clinicians aware of the evidence in support of this application of clozapine. Finally, it is essential that this information about suicide and clozapine be introduced during residency training, as there is evidence that treatment practices acquired during this time are enduring. Further education of all practicing clinicians about the benefits of clozapine to reduce suicide is essential. Evidence such as that provided by Modestin et al.[7] will no doubt help. When it becomes widely accepted that the standard of care for patients with schizophrenia or schizoaffective disorder who are at increased risk for suicide requires discussing the option of clozapine to reduce the risk of suicide, then many clinicians will feel compelled to do so. When that happens, lives will be saved, and the cost of treating schizophrenia, in both human and monetary terms, will be significantly reduced.

Drug names: clozapine (Clozaril, FazaClo, and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), risperidone (Risperdal).

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See also article beginning on page 534.