Managing Suicidality in Schizophrenia

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ABSTRACT

Objective: The primary objective of this review article is to provide a coherent, systematic synthesis of the literature on the management of suicidality in schizophrenia that is relevant to the front-line clinician.

Method: Literature searches were conducted on MEDLINE (1996 to 2007) and PubMed (1993 to 2007), using the key words "schizophrenia" and "suicide," as well as references from the resulting articles. I used my own clinical experience to create fictional case examples to illustrate the applicability of the literature discussed in this paper.

Results: Suicidality in schizophrenia is high, and early detection relies on the appreciation and evaluation of the clinical manifestations of depression, despair, and hopelessness, as well as on the nature and severity of the psychotic experience itself, particularly in recent-onset patients with higher cognitive function and educational background. Clinical management includes ensuring immediate safety, the use of psychosocial techniques to address depression and psychosocial stressors, targeted pharmacotherapy for depression and psychosis, and adequate discharge planning. Clozapine is the only antipsychotic with good evidence for efficacy in decreasing suicidal behaviour in schizophrenia.

Conclusions: The optimal management of suicidality in schizophrenia involves the incorporation of traditional bedside clinical skills, selection of psychosocial modalities based on individual needs, and selective pharmacotherapy directed primarily at psychotic and depressive symptoms.

RÉSUMÉ

Objectif : L'objectif principal de cet article de synthèse est de procurer une synthèse cohérente et systématique de la documentation sur la prise en charge de la suicidabilité dans la schizophrénie qui soit utile au clinicien de première ligne.

Méthode : Des recherches documentaires ont été menées dans MEDLINE (1996 à 2007) et PubMed (1993 à 2007) à l'aide des mots clés « schizophrénie » et « suicide », ainsi que dans les bibliographies des articles trouvés. Je me suis servi de ma propre expérience clinique pour créer des exemples de cas fictifs afin d'illustrer l'applicabilité de la documentation présentée dans cet article.

Résultats : La suicidabilité est élevée dans la schizophrénie, et la détection précoce repose sur l'appréciation et l'évaluation des manifestations cliniques de dépression, de désespoir et d'impuissance, ainsi que sur la nature et la gravité de l'expérience psychotique même, en particulier chez les patients où la maladie est apparue récemment et qui ont une fonction cognitive élevée et une bonne instruction. La prise

en charge clinique comporte d'assurer la sécurité immédiate, le recours à des techniques psychosociales pour aborder la dépression et les stresseurs psychosociaux, une pharmacothérapie axée sur la dépression et la psychose, et une planification adéquate du congé. La clozapine est le seul antipsychotique dont l'efficacité est prouvée pour diminuer le comportement suicidaire dans la schizophrénie.

Conclusions : La prise en charge optimale de la suicidabilité dans la schizophrénie comporte l'incorporation des compétences cliniques de soins classiques, la sélection de modes psychosociaux fondés sur les besoins individuels, et une pharmacothérapie sélective axée principalement sur les symptômes psychotiques et dépressifs.

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Key Words: *schizophrenia, suicide, suicidality, clinical management, prevention*

Schizophrenia is a devastating neuropsychiatric condition often striking in late adolescence to early adulthood, time periods that are critical for psychological, interpersonal, and vocational development. Indeed, managing patients in the early years of their illness often entails addressing these key areas through various forms of psychotherapeutic and vocational interventions. The illness manifests with various combinations of positive, negative, and cognitive symptoms. Even with successful treatment, full eradication of these symptoms is not possible in most patients. Mortality in schizophrenia patients is 2 to 3 times higher than that in the general population, the excess being accounted for by both suicide and premature natural death.[1] Not surprisingly, this devastating condition is associated with a very high risk of suicide attempts (4% to 30%)[2] and completed suicide (4% to 13%),[3,4] similar to that seen in affective disorders,[5] though a recent study suggested the rate of true suicide completion is closer to 5%.[6] Given the nature of losses experienced by patients with schizophrenia—be they real (for example, social isolation or vocational disruptions) or perceived (that is, related to delusional or referential thinking)—a sense of despair is not an unexpected finding,[7] reinforcing the observation that 50% of individuals with schizophrenia either consider or attempt ending their life.[8,9] Owing to their blunted or flattening of affective response and difficulty in engaging others in conversation, they are often perceived by others to be alienated from reality, including the reality of their isolation and losses. Such complex interplay between cultural norms and negative symptoms may distract the clinician from maintaining a high index of suspicion and completing a thorough assessment of suicidality.[10–12] In contrast to the rate found in affective dis- orders, the sex difference in suicide rate is less pronounced in patients with schizophrenia, and those who attempt suicide are more likely to be successful in the attempt and use more violent means.[13–17]

It is widely believed that suicide in schizophrenia is an impulsive act that cannot be predicted—a myth that is probably in part related to the affective blunting and disorganized behaviour associated with psychosis. Unfortunately, this view may lead to a nihilistic attitude and is not supported by epidemiologic studies, which suggest that communication of suicidal intent before suicide occurs at least as frequently in patients with schizophrenia (even during acute exacerbations) as in patients with other psychiatric conditions.[18] Since almost 90% of suicides occur in individuals with a DSM-IV diagnosis of a major mental health disorder, and 83% of these patients have at least one contact with a medical practitioner within 1 year of completed suicide (more than 60% have had contact within 1 month), physician education has been a valid target in suicide prevention strategies.[19] Physician education has been shown to increase the detection rate and prescription of antidepressant medication in the community, which in turn is inversely related to suicide rates.[19] While it is not known whether the results of these interventions generalize to patients with schizophrenia, completed suicide in schizophrenia has been associated with poor treatment adherence and untreated mood, substance abuse, and psychotic disorders. The highest risk for completed suicide occurs during or soon after hospitalization. Active measures in the prevention of suicide in schizophrenia should therefore be invested in preventative strategies through education and programs focusing on the early identification and management of depression and suicidality in schizophrenia. As for any other psychiatric condition, when significant suicidality is recognized, psychiatric

hospitalization is often an appropriate step in the patient's treatment plan. However, this disposition is not without its drawbacks since it can mislead the clinician to a false sense of security: the first and last weeks of hospitalization seem to be particularly vulnerable periods for risk of completed suicide, as are the first 6 months following discharge.[15]

The initial management of suicidality should therefore be guided by a heightened index of suspicion based on the aforementioned epidemiologic findings.[15] The following typical clinical case scenario of a high-risk situation serves to illustrate this principle.

Consider the following clinical scenario. You are clinically responsible for a young man with a 5-year history of schizophrenia and a documented history of multiple hospitalizations over the past 6 months ("revolving door syndrome"). You have read that this well-educated young man first experienced psychotic symptoms in university and that he has since dropped out of school; he has become alienated from his previously extensive social support network and lives in a local boarding home. He is difficult to engage, tends to keep to himself, but shows no behavioural problems. In your brief interactions with this patient you sense a deep sense of sadness and regret for lost opportunities masked behind a somewhat blunted affect. His paranoid delusions focus on his highly successful siblings, whom he believes have controlled his life and brought him to his ruin. He reassures you that he has figured out a plan to thwart their malicious schemes but will not share it with you for fear it will be intercepted by his family. He reassures you that he has no homicidal intent toward his family because he will not partake in their "demonic schemes." You also learn that he believes that he was rejected by his family "just like all prophets" are rejected, but he reminds you that his arrival on earth had long been predicted and that he will "purge the earth of its evil schemes." You note that he becomes unusually energized as he talks of his grandiose delusional thoughts, often laughing to himself and seeming to be responding to auditory hallucinations. Nursing staff, who have known this man during multiple recent admissions, reassure you that "he is no problem at all" and that this is his baseline behaviour. You adjust his antipsychotic medication and after a few weeks you note some decline in delusional preoccupation, although you continue to perceive dysphoric sentiments behind a mask of blunted affect. Members of your multidisciplinary team feel he is now ready for an overnight pass as part of the discharge planning process. You remain discomfited by your observations, though you cannot articulate a valid reason to defer the leave of absence. Nonetheless, you do not inquire about feelings of hopelessness and suicidal thoughts or plans—you realize this omission only as you write your progress note later in the day.

Such seemingly routine assessments potentially mask suicide risk and, unless the patient is formally evaluated for potential suicide risk, might contribute to the misperception of the "impulsive" nature of suicide in schizophrenia. This is not to suggest that one can accurately identify or predict a completed suicide on an individual basis,[20,21] but to highlight that clinicians may have a mistaken sense of security that has no basis in empirical evidence. This is supported by the results of a national survey in the United Kingdom of completed suicide with 12 months of contact with mental health services, which showed that mental health staff underestimated the suicide risk at the final visit in most of the completed suicides in this survey. The health teams involved in the index cases in this survey also identified that in their view 22% of the deaths could have been prevented and suicide risk could have been decreased in at least 6% of cases through measures aimed at improving adherence and supervision.[22]

> **Key Point:** The risk of suicide and suicidal behaviour in schizophrenia is significant and matches that of mood disorders. The clinician needs be alert to subtle hints of suicidality, particularly during high-risk periods. Suicide in schizophrenia is often not as impulsive as is commonly believed.

Since completed suicide cannot be reliably predicted in the individual patient, what then should constitute a "red alert" in terms of suicide risk in patients suffering from schizophrenia? Since most clinicians are trained to assess suicidality in the presence of a major mood disorder, such as a major depressive episode, a mixed manic state, or even a dysphoric state reactive to interpersonal conflict in persons with certain personality traits, it is critical to appreciate that in schizophrenia the presence of depression is only one of many factors contributing to the patient's suicidality and, if present, may be masked by a primary negative syndrome state. In a cross-sectional study of 290 patients suffering from a nonaffective psychosis, Fialko and colleagues[23] report a high prevalence of suicidal ideation (41%) that was associated not only with depression, anxiety, and alcohol consumption, as expected, but also with negative perception of the self (for example, "I am unloved"), others ("other people are harsh"), and their illness itself (loss of control, indefinite course, impact on their lives). Interestingly, the perception of their illness was not correlated with positive symptoms but rather with general psychopathology, suggesting that patients experiencing suicidal ideation may be more likely to suffer a wider range of mental problems in addition to positive symptoms. The authors consider this finding in light of one view that suicide may be a rational attempt to escape from feelings of entrapment.[24]

To illustrate this, consider a young woman struggling with an internal conflict concerning delusional religious beliefs, such as delusional guilt for which she sees only eternal damnation and her deserving of death. She can see no way out of this life-long curse and perceives no support in friends or family members, whom she perceives as equally critical. She is aware of, though cannot explain, her inability to "get up and go" or perform activities she was previously proficient in, and her inability to communicate meaningfully with others further contributes to her profound sense of isolation. This combination of what we call "symptoms" (but what our patients call "experience") is actually quite a typical scenario of a patient with schizophrenia. Indeed, we may become so desensitized to these *symptoms* that we hear, but fail to listen to, an intense sense of despair masked behind a blunted dysphoric affective tone in the narrative. In so doing, we fail to use the tool of empathy, which is to the psychiatrist what the stethoscope and palpating hand are to the internist. Our patients too often tell us how "the voices are so real to me, but nobody believes me," that we easily become desensitized to the pain and isolation being expressed—if we did allow ourselves to listen, we would immediately realize how easily such an individual can spiral down a state of suicidal despair, even in the absence of clinical depression.

A recent cross-sectional study including a relatively small number of patients with schizophrenia ($n = 62$), recently admitted to hospital following a suicide attempt, identified 2 subgroups of suicide attempters—a subgroup primarily motivated by depressive symptoms and another subgroup motivated by psychotic symptoms.[25] In contrast to the psychotic subgroup, the depressive subgroup was characterized by greater hopelessness and depression, higher educational attainment, longer duration of illness, and past suicide attempts. Both subgroups were characterized by the persistence of hopelessness at 1-year follow-up, while low mood persisted in the depressive subgroup. This study highlights the importance of understanding the nature and content of the psychotic experience, as well as the trait-like nature of low mood and hopelessness as risk factors in the identification of schizophrenia patients at high risk of suicidality.

The importance of the level of psychotic symptoms in suicidality in schizophrenia was highlighted in the results of a recent Canadian case–control study of suicide victims ($n = 45$) compared with control subjects with schizophrenia who had not completed suicide. In addition to a diagnosis of depressive disorder not otherwise specified (NOS) and a documented family history of suicidal behaviour, moderate-to-severe current positive (but not negative) psychotic symptoms emerged as an independent predictor of completed suicide.[26] The protective nature of negative symptoms is consistent with previous reports,[27] while the absence of correlation with impulsive-aggressive behaviours argues against the myth of impulsivity of the act of suicide in schizophrenia. Similarly, cluster A and C personality traits were protective, possibly owing to indirect effects of negative symptoms and avoidance of social stressors.

Risk factors for suicidality in schizophrenia are best grouped into those common to other psychiatric disorders and those specific to schizophrenia. General risk factors for suicide in general psychiatry include a history of impulsivity, violence, substance abuse, low mood, lifetime suicide attempts, suicidal plan or intent, hopelessness, perceived or real losses, poor social support, and a history of self-injurious behaviour.[28] Hawton and colleagues recently completed a systematic literature review of risk factors more specific to schizophrenia.[29] Affective symptoms along with history of depression, previous attempts, substance abuse, motor restlessness, poor adherence to treatment, fear of mental disintegration, and recent loss were identified as major risk factors for suicide in schizophrenia.[29] Other risk factors published in the literature include severity of hallucinations and delusional thinking,[30] the first 2 years of the illness[31] (though the risk persists throughout the course of the disorder),[30,32] high premorbid socioeconomic class and high IQ,[33,34] later age of onset,[35] better cognitive functioning,[36] revolving door syndrome,[15] recent hospitalization,[15] severity of parkinsonism,[37] and, albeit its role is more controversial, command auditory hallucinations.[30] Comorbid obsessive–compulsive disorder is found in close to 10% of patients with schizophrenia and has recently been associated with a higher rate of suicide attempts in 2 studies.[38,39]

While mood, symptom pattern, and higher education have been consistently shown to be risk factors in schizophrenia, a recent study comparing these variables in 2 samples of patients with schizophrenia or schizoaffective disorder in Pittsburgh, Pennsylvania, and New Delhi, India, found no relation with reported history of suicide attempts in the New Delhi sample.[40] While several social and cultural differences in the samples may have contributed to these results (including a greater societal taboo relating to suicide in India, which may lead to underreporting), this study highlights the potential for cross-cultural differences in the study of suicidality. An analysis of the transcultural differences in suicide attempters participating in the International Suicide Prevention Trial (InterSePT)[41] consisting of subjects recruited from North America, South America, South Africa, eastern Europe, and western Europe, however, found no differences in clinical variables across the 5 groups except for an earlier age at first suicide attempt and larger number of past attempts in the North American group.

The clinician should take all these aspects into account before proceeding to the next stage of the management: a clinical

judgment regarding the appropriate level of care for the individual patient. In so doing the clinician is encouraged to 1) direct his or her attention to the patient's level of despair, sadness, or hopelessness, 2) review risk factors applicable to the particular patient within the patient's biopsychosocial constraints, 3) develop a thorough understanding of primary and secondary diagnoses, and 4) make an informed judgment free from personal, sociocultural, or political bias (for example, hospital or emergency department capacity issues or other perceived or real pressures to discharge patients from an emergency department).

> **Key Point:** General risk factors for suicidality in schizophrenia are similar to those in other conditions. Risk factors specific to schizophrenia include recent onset, severe positive symptoms, high IQ and socioeconomic origins, frequent brief prior hospitalizations, and a recent hospitalization. Despair, sadness, or hopelessness are important warning signs and can occur in the absence of a depressive syndrome.

Treatment Modalities

Following a thorough assessment of the patient's suicidal ideation or behaviour, suicide risk, and contributing primary and secondary sources of the suicidality (for example, relapse of psychotic symptoms with auditory hallucinations and comorbid substance abuse), a clinical decision must be taken regarding the appropriate milieu and level of restriction (including inpatient or day hospital or outpatient, physical or pharmacologic restraints if necessary, level of observation required, and community or specialized services). While inpatient psychiatric admission may often be the safest course of action in the suicidal patient, suicide completion in patients with schizophrenia during and around inpatient hospitalization is very high.[42] Other safety strategies may be necessary, depending on the level of risk determined on assessment of the individual case. These may include closer observation by staff, planned accompanied therapeutic passes outside the hospital, and close follow-up on discharge from hospital. Within this framework, subsequent active treatment modalities can be safely instituted and with maximal efficacy.

The principal goals of active treatment are to 1) reduce psychotic and depressive symptoms, 2) alleviate demoralization and despair, 3) instil hope, and 4) address other contributory and comorbid psychopathology, including substance abuse and anxiety disorders. A full range of biopsychosocial modalities should be considered to reach these therapeutic goals; indeed, hopelessness, despair, and demoralization are fundamental human experiences that have their origin in the interpersonal and psychosocial domains and thus need to be addressed within the context of an empathic therapeutic relationship and understanding the psychosocial context. This notwithstanding, most literature has focused on pharmacologic interventions, specifically, the use of clozapine and other atypical antipsychotic drugs. In view of the relatively low incidence of suicide and the consequently very large numbers of patients required for systematic studies, the outcome of these interventions in preventing completed suicide has not been systematically addressed. Further, there are limited data on the value of combining psychosocial and pharmacologic approaches,[43] so it may often be necessary to generalize from the evidence derived from studies directed at the management of affective disorders. Such extrapolations may not necessarily apply to affective symptoms occurring in the context of a primary psychotic disorder. Sensitively addressing subjective distress and hopelessness may be particularly pertinent to the high-risk patient, since despair has been identified as a significant risk factor for completed suicide,[44] including in patients with schizophrenia.[43,45] This was highlighted in a prospective community treatment study of a high-risk group of 122 patients suffering from early-onset schizophrenia or schizoaffective disorder. The authors identified a baseline measure of subjective (but not objective or interviewer-rated) distress as predictive of completed suicide.[45]

The remainder of this section focuses on modalities backed by solid empirical evidence. The goal is to establish what has been empirically supported and what has been standard care even if not well-studied or supported by empirical evidence, not to diminish the importance of other important pharmacologic and psychosocial interventions. The reader is also referred to articles on managing suicidality in affective disorders for a discussion on the use of other specific psychosocial (for example, cognitive-behavioural therapy [CBT]) and pharmacologic (for example, antidepressants and lithium) modalities that may have specific value in the management of primary psychotic disorders with coexisting mood fluctuations (as in schizoaffective disorder and comorbid depressive disorder NOS) or distorted sense of self or others that is amenable to psychotherapeutic intervention (such as CBT). The field of psychiatry has acquired, and continues to acquire, a large breadth and depth of evidence on which to base clinical decisions. Nevertheless, much of clinical practice requires us to apply our therapeutic modalities to conditions or combinations of disorders for which specific evidence is lacking. In these situations we routinely "borrow" therapeutic strategies from other areas in the field to fill the gap in our armamentarium: physicians have been doing this for centuries, and there is no reason to stop, given our obligation to relieve our patients' suffering. The awareness of these gaps in our knowledge is critical. The consequence of not knowing where the specific empirical evidence stops and "borrowing"

begins is the misplaced belief that certain interventions "should work." This may lead, for example, to the use of indiscriminate polypharmacy in cases where a focus on adjunctive psychosocial interventions would be more sensible. Nowhere is this problem more pertinent than in a chronic illness like schizophrenia, where the passage of time brings with it a greater sensitivity to the adverse effects of our interventions. A good example illustrating the gap between empirical evidence and clinical practice is the use of mood stabilizers, including lithium, in schizophrenia and schizophrenia-like psychoses. Notwithstanding the strong evidence for lithium's efficacy in bipolar disorder as well as its effect of reducing suicidal behaviour and all-cause mortality in mood disorders,[46] evidence for its efficacy in psychotic disorders (alone or in combination with an antipsychotic) is either weak or altogether absent, even though it appears to have some benefit in schizoaffective disorder.

> **Key Point:** The goals of treatment are to reduce psychotic and depressive symptoms and alleviate demoralization and despair. Treatment of comorbid conditions including substance abuse and anxiety disorders may be critical in achieving these goals. Careful consideration should be given to the choice of treatment setting appropriate for the individual patient. Awareness of the extent of existing empirical knowledge allows the clinician to borrow other therapeutic interventions while maintaining an open mind and keen eye on potential adverse effects.

Psychosocial Modalities

While the greatest impact on the outcome of schizophrenia has been derived from the institution of and the adherence to antipsychotic drug treatment,[47] an integrated approach using several psychosocial modalities is generally regarded as standard practice in managing patients with severe psychiatric conditions such as schizophrenia.[48–50] This principle was supported by a recent 2-year randomized controlled trial (RCT) comparing integrated biomedical and psychosocial treatment with standard care (pharmacotherapy and case management) in patients with recent-onset schizophrenia.[51] Integrated care was shown to result in superior overall outcome measures, including positive and negative symptoms. One of the primary goals of psychosocial interventions in schizophrenia is to enhance adherence with psychiatric care, and poor adherence with treatment is itself associated with a risk of suicidality.[29] A recent study exploring the patterns of adherence with atypical antipsychotics in Quebec and Saskatchewan confirmed that good adherence with medication was associated with the expected reduction in hospitalization and also demonstrated a significant association of poor

adherence with risk of death (adjusted hazard ratio of 0.58) and suicide (adjusted hazard ratio of 0.68) in Quebec.[52]

Nonetheless, the independent impact of psychosocial interventions on suicidality has not been systematically measured. Interventions supported by some degree of consistent empirical evidence for schizophrenia include family intervention, assertive community treatment, psychoeducation, social skills training, and supportive employment.[50] When used in conjunction with standard care, CBT for schizophrenia is showing promise in decreasing positive and depressive symptoms, while increasing insight without increasing suicidal ideation,[53,54] though this has not yet been definitively shown to translate into improved long-term function.[55] A recent Cochrane review concluded that, while CBT is a promising treatment modality, the current trial-based evidence does not yet support its widespread adoption for use in clinical management of primary psychotic disorders.[56] Case management, while widely practised, is also surprisingly underevaluated and possibly overvalued, though this may partly be a result of the widely variant case management approaches for different subpopulations.[57] There is no indication for psychodynamic interventions,[58] and even though an understanding of the psychodynamic theories may successfully inform beneficial supportive therapy when combined with standard treatment, psychodynamic therapies in schizophrenia demonstrate no advantages over antipsychotic drug treatment alone.[59]

There is no literature addressing the value of these interventions in the specific management of suicidality in schizophrenia, so the value of these approaches in suicidal patients with schizophrenia can only be extrapolated from 1) the sparse literature and accepted expert opinion that integration of these modalities with pharmacotherapy decreases nonadherence and therefore improves clinical outcome[48] and 2) the emerging evidence for the value of cognitive-behavioural interventions for depression, hopelessness, and suicidality in the context of primary affective disorders described elsewhere in this compendium.

The absence of published literature on the efficacy of these psychosocial modalities on suicidality in schizophrenia does not exclude the possibility of an indirect effect through several important psychosocial factors that are known to be associated with demoralization and suicidality itself. Psychosocial interventions would be expected to result in increased hopefulness, adherence to treatment, and enhanced therapeutic alliance, which in turn may be protective (in terms of suicidality) for the individual patient. It has been suggested that the maintenance of family structure and enhanced adherence to psychiatric follow-up may account in part for the better outcome of schizophrenia in less-developed countries.[60] Similarly, poor staff–patient relationships, poor continuity of care, and inadequate management of depression are

key factors associated with lack of "preventability" of completed suicide.[11,22]

Several caveats pertain to the literature on psychosocial interventions in schizophrenia. First, these interventions are generally administered by highly trained therapists and often involve the use of standardized manuals, a situation that is unlikely to generalize to the community. However, a recent study comparing CBT (administered by trained psychiatric nurses) with standard therapy has challenged the necessity of intensive training for the effective delivery of these therapeutic modalities.[53] The real-world applicability of these techniques is critical if they are to have a palpable impact on the routine care of patients suffering from primary psychotic disorders. A second caveat pertains to the presence or attainment of insight—that is, the awareness of illness, its consequences, and need for treatment—often an explicit goal of psychoeducation strategies. Perhaps not surprisingly, insight may not necessarily lead to improved outcome. This was illustrated in one randomized controlled study that failed to find any beneficial effects on clinical outcome of brief psychoeducation following discharge from an inpatient setting.[34] Insight regarding the condition and need for treatment clearly has positive implications for adherence with treatment, but it has also been associated with depression and increased suicidal risk in some,[7,33,34,61,62] but not all,[53] studies, posing a potential therapeutic dilemma. It is not known whether the advantages of insight in improving adherence and outcome outweigh their potential risk for demoralization and suicidal behaviour. Data from InterSePT have shown that, while awareness of the illness at baseline was associated with increased suicidality, awareness that was derived in the course of treatment was associated with a decreased risk of suicidal behaviour.[63]

How can a practising clinician apply this to his or her daily practice? It's much like delivering bad news in general medicine—a patient is not to be overburdened with details on initial diagnosis, and the clinician provides as much information as the patient is willing and able to receive, a process in which the physician gently leads but takes his or her cues from the patient's state and willingness to know more. If the patient formulates the illness as a sleep disorder and has difficulty focusing his or her attention despite a physician's initial appraisal and discussion of psychosis, then it is unlikely that aggressive insistence on accepting a schizophrenia diagnosis at that time is going to be of any benefit to the patient. Rather, discussion of the medication and side effects, including emphasis on the sedative side effect of the medicine and its impact on reducing distractibility, may be both genuine as well as more likely to promote adherence and therapeutic alliance. This is indeed the core of the art of medicine and can only be learnt at the bedside.

Notwithstanding these caveats, the integration of psychosocial and pharmacotherapeutic modalities tailored to the patient's particular needs[64] remains an integral component in managing suicidality in schizophrenia.[48,50,57] This is supported by results from a 1-year follow-up of first-episode patients participating in a randomized controlled study comparing integrated treatment (consisting of antipsychotic treatment, assertive community treatment, social skills training, and psychoeducational family treatment) with standard treatment (antipsychotic medication and variable family psychoeducation).[43] These data not only showed superior effects of the integrated approach on positive and negative symptoms but also increased patient satisfaction and significantly decreased hopelessness in this group.[43]

> **Key Point:** The efficacy of individual psychosocial modalities on suicidality in schizophrenia has not yet been validated, but integrating psychosocial treatments with standard care is recommended when treating suicidality in schizophrenia to address despair and encourage adherence to treatment.

Pharmacologic Approaches

First-Generation Antipsychotic Drugs. The literature on the effects of first-generation antipsychotic drugs on suicidal behaviour has been inconsistent in determining whether these neuroleptics have had any impact on suicidality in schizophrenia.[65] These inconsistencies may be related to several methodological factors, including the (retrospective) design of most of these studies, failure to address confounding factors, comorbidity, multiple medications, and absence of randomization in treatment assignment in many of these studies.[66] No clear dose–effect relation with suicidality has been found for neuroleptics, with studies suggesting no differences in daily neuroleptic dose in completed suicides when compared with that in control cases,[67] higher suicidality with lower doses,[68–71] and even higher suicidality at higher doses.[72,73] It has been suggested that these inconsistencies reflect an interaction of selection bias (more severely ill patients receiving higher doses), adverse effects (extrapyramidal symptoms [EPS] at higher doses contributing to increased suicide risk), and diagnosis (patients with more mood symptoms than psychotic symptoms may have received or tolerated lower neuroleptic doses),[65] though they certainly do not definitively exclude a small effect of neuroleptics on suicide risk.[74] Wilkinson and Bacon found a lower likelihood of suicide attempts in patients receiving antipsychotic drugs, even though suicide completers did not differ in their use of antipsychotics.[75] Further, in a prospective case–control study, Johnson and colleagues found more self-injurious behaviours following discontinuation of depot neuroleptics at 18 months

when compared with patients who were maintained on the medication, arguing for a protective effect of neuroleptics on suicidal behaviour in schizophrenia.[76]

The early literature on suicide and schizophrenia suggests that the advent of neuroleptic medications has done little to decrease the suicide rate in schizophrenia (in the United States) from preneuroleptic times.[5,77] This (and the evidence discussed above does not fully support this conclusion) suggests that the etiology of suicidal behaviour in schizophrenia is by far more complex than that of a direct relation with illness severity as described by positive symptoms (the primary target of neuroleptics). Considering our earlier discussion of the devastating impact of the illness beyond positive symptoms alone, this should not come as a surprise. Indeed, one retrospective analysis of suicidality found no difference in suicidality in responders to neuroleptics, compared with those who were deemed treatment-resistant,[78] suggesting a mechanistic separation between the effects on (positive) symptoms and those on suicidality. Prospective studies of patients with borderline personality disorders[79,80] and multiple suicide attempts[81] have suggested a specific reduction in suicidal tendencies following neuroleptic treatment, implying that, if neuroleptics have any impact on suicidality in schizophrenia, this effect may be mediated through pathophysiologic mechanisms other than direct intervention in the psychotic process itself.

While the foregoing discussion should serve as a reminder that suicide in schizophrenia is not necessarily driven by positive symptoms alone, a note of caution is warranted on the interpretation of these data, since active illness, including command auditory hallucinations, has been associated with suicidality in schizophrenia in a Finnish psychological autopsy study of suicide victims suffering from schizophrenia.[30] Results from the same psychological autopsy study also suggested that most suicide victims either received inadequate doses of antipsychotic medication or were nonadherent to their prescribed medications.[82] These data, as well as the literature discussed earlier in this article, lead us to argue that suicidal ideation or behaviour in the context of active illness (that is, positive symptoms) ought to continue to be taken seriously, even when schizophrenia is being treated. Further, the increased rate of suicide with the advent of antipsychotic drugs has recently been attributed to neuroleptic-induced akathisia and dysphoria,[83] which in turn have been associated with increased suicidal behaviour and ideation.[72,84,85] This suggests that all patients should be carefully monitored for side effects from antipsychotic drugs, particularly in the early titration stage, and any emerging neurologic side effects ought to be managed aggressively.[86] The best-designed prospective study on the subject of suicide and antipsychotic management (InterSePT),[87] comparing the effects of olanzapine and clozapine on suicidal behaviour over 2 years, showed that the severity of parkinsonism was 1 of the 4 major factors accounting for most of the suicidal behaviour in this cohort.[37] The American Psychiatric Association's practice guidelines recommend that the use of first-generation antipsychotics in individuals with suicidal behaviours be reserved for those needing depot antipsychotic medications.[48] While we have reservations about some of the negative conclusions reached with regards to the first-generation antipsychotic drugs, and taking into consideration the data pertaining to the second-generation antipsychotics discussed below, we concur with the general spirit of these recommendations—that is, that avoidance of EPS ought to be an important consideration in the pharmacologic management of suicidal behaviour in schizophrenia.

Atypical Antipsychotics. The advent of second-generation antipsychotic drugs, heralded by the front-runner and still benchmark clozapine, brought a new sense of hope to the management of schizophrenia. While there remained some doubt as to the impact of the first-generation drugs on suicidality in schizophrenia, the second-generation drugs had the benefit of allowing direct comparison with the earlier drugs, and these data have so far been very promising.[66] In light of the foregoing discussion and the risk-factor analysis from the InterSePT study,[37] a drug intended to treat suicidality in schizophrenia should ideally fulfill the following criteria:

- Eliminate positive symptoms

- Enhance quality of life through improved cognitive and social functioning

- Target affective symptoms

- Be free of extrapyramidal side effects

- Decrease substance abuse

The second-generation antipsychotic drugs fulfill these criteria to varying degrees, with the best evidence available for clozapine.[66] Clozapine has emerged in both epidemiologic and clinical studies as the front-runner in the race for empirical evidence for an effect of atypical antipsychotics on suicidal behaviour. Clozapine has been shown to have a substantial effect on attempted suicide[78,88,89] and completed suicide,[78, 90–92] though clozapine's impact on completed suicide remains debatable mainly because of the large numbers of subjects that must be included in clinical studies to detect an effect.[93,94]

No prospective randomized controlled studies have been completed comparing the effect of first- and second-generation antipsychotic drugs on suicidality, although one small retrospective study shows that patients attempting suicide were more likely to receive first-generation antipsychotic medication, while nonattempters were more frequently

prescribed atypical antipsychotic drugs.[88] The limitations of such studies as retrospective design have been discussed earlier. Two large metaanalyses using data from randomized, double- blind, placebo-controlled studies of risperidone, quetiapine, and olanzapine reported no difference in suicide attempts or completed suicide.[95,96] These data need to be interpreted with caution since the duration of these trials was relatively brief and the subjects were carefully selected, with patients at high risk for suicide behaviour often excluded. There is some suggestion of a decrease in suicidal thoughts and behaviour with olanzapine treatment, compared with haloperidol and risperidone, though there are no systematic data for other atypical antipsychotics.[97, 98] Given the emerging literature on the effect of certain atypical antipsychotic drugs, including olanzapine, quetiapine, and ziprasidone, on mood symptoms, as well as their known relative freedom from EPS at therapeutic dosages, one might predict some degree of decreased suicidality in patients treated with these medications, though this awaits empirical validation.[65]

The InterSePT study[91] is the only prospective, randomized, large-scale study that sought to explore the effect of antipsychotic drugs on suicidal behaviour, and the methodology addresses many of the limitations inherent to retrospective and metaanalyses of smaller-scale RCTs. Using an open-label design, this 2-year multicentre international study (industry-funded, primarily by Novartis Pharmaceuticals) recruited patients with schizophrenia or schizoaffective disorder who were deemed at high risk for suicidal behaviour (previous suicide attempts or current suicidal ideation) and who were then randomized to treatment with either clozapine 300 to 900 mg ($n = 479$) or olanzapine 10 to 20 mg ($n = 477$). Subjects were followed at the same regular intervals in both treatment groups, and clinical ratings were performed by blinded raters. The outcome of interest was any suicidal behaviour that included suicide attempts or completions, hospitalization to prevent suicide (type 1 event), and worsening of suicidality from baseline according to the suicide severity subscale of the Clinical Global Impression (CGI) scale (type 2 event). The endpoints were determined by an independent suicide monitoring board consisting of an international team of experts in the management of suicide behaviour who were blinded to treatment group assignment.[99] The results of the study showed that clozapine was associated with significantly fewer type 1 and type 2 events, even though the olanzapine group received significantly more concurrent antidepressant and anxiolytic medication; they suggested that, compared with olanzapine, treatment with clozapine reduced serious suicide attempts and hospitalizations to prevent suicide by 25% (with a remarkably low number "needed to treat," only

12 subjects). The results of this study were accepted by the US Food and Drug Administration (FDA) as sufficient to include suicidal behaviour in schizophrenia as an indication for clozapine treatment and have been used to advocate for the inclusion of this indication in other countries.[83] The Canadian health and safety authorities have not gone as far as the FDA to license suicide prevention in schizophrenia as an indication, but the pharmaceutical company has been given permission to include the study data in their briefings to the medical profession.

While it has been suggested that the use of clozapine in patients at high risk for suicide may be both life-saving as well as cost-effective,[65,100] this may not generalize to patients with schizophrenia at lower risk for suicide, owing to clozapine's additional side effect burden, when compared with the effects of other first- and second-generation antipsychotic drugs. Indeed, one study has suggested that any beneficial effects of clozapine on decreased mortality from suicide may be offset by an increased mortality from cardiovascular consequences of metabolic side effects such as obesity and diabetes.[101]

Treatment of Depressive Symptoms. Given the importance of depressive symptoms, including low mood and hopelessness, as risk factors for suicidality in schizophrenia, managing depression needs to be at the forefront of any treatment plan for these patients. The literature on managing depression in schizophrenia is somewhat inconsistent and does not allow for clear, evidence-based guidelines for the practicing clinician. Two randomized, placebo-controlled studies using imipramine augmentation of neuroleptics suggested that adjunctive treatment with imipramine might be useful in the acute and maintenance treatment of postpsychotic depression.[102,103] However, subsequent studies with selective serotonin reuptake inhibitors have yielded inconsistent results,[104] with the only double-blind controlled study (using sertraline) showing a large placebo effect.[105] Given the paucity of consistent literature in this area, as well as the very high prevalence of depression in schizophrenia, the clinician should use clinical judgment in managing individual patients. The initial approach needs to be directed to reversible factors, such as abuse of and withdrawal from illicit drugs, as well as dysphoria and akathisia secondary to antipsychotic drugs. In the presence of significant syndromal depressive symptoms, a trial of antidepressant at the generally recommended doses is warranted, though there are no data to conclusively guide the clinician in determining whether a failure of an antidepressant trial is an indication for a switch in the antidepressant or antipsychotic drug being used.[48] In general, it has been recommended that depressive symptoms in schizophrenia be targeted with antidepressants only if symptoms do not subside

after treating the psychotic symptoms with an atypical antipsychotic.[106]

The clinician should also be alert to the possibility of pharmacokinetic interactions (for example, fluvoxamine and clozapine) as well as other potential interactions on the basis of the known side effect profile of the drug being used (for example, combined bupropion and clozapine increase the risk of seizures). Further, there is no empirical evidence to guide the duration and safety of maintaining antidepressant treatment following remission of symptoms.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) remains a useful therapeutic option in schizophrenia and schizoaffective disorder and may have a place in managing the severe depressive symptoms that accompany these disorders.[107] An acute therapeutic benefit in suicidal ideation occurring in the context of a concurrent mood disorder would be clinically expected, at least in the short term, though there are no data at this time to support this claim. Similarly the literature does not provide supportive evidence that schizoaffective disorder or mood symptoms accompanying schizophrenia predict a response to ECT, a belief commonly held by practising psychiatrists.[48] In practice, we recommend that attention be given to a thorough differential diagnosis and diagnostic formulation before proceeding to ECT, especially given that depressive symptoms in the context of an acute psychotic relapse in schizophrenia often resolve with the use of antipsychotic drugs and that the persistence of psychotic symptoms and significant suicidality ought to alert the clinician to the possible indication of clozapine in such patients. Similarly, secondary negative symptoms from neuroleptic treatment should be considered, although this is less frequently an issue with the widespread use of atypical antipsychotic drugs.

Notwithstanding the limited evidence base for ECT in schizophrenia, ECT remains a therapeutic option that one should continue to consider carefully in acutely suicidal patients with schizophrenia in the context of comorbid mood or psychotic symptoms that have not responded to standard pharmacologic treatment.

Conclusion

Schizophrenia carries a very high risk of suicidality (Category A evidence), and a heightened awareness of this risk is key to its early detection and management (Category C). Communities with early detection programs have already been shown to be associated with lower rates of severe suicidality, compared with other communities offering standard care,[108] even though it may be too early to estimate the precise benefit of these programs on suicide completion.[109] Individualized

treatment plans should focus on the integration of pharmacologic and psychosocial therapies (Category B). Depressive symptoms, positive psychotic symptoms, and hopelessness are important predictors of suicidality and should be managed aggressively (Category B), and comorbid psychiatric conditions should also be addressed (Category C). Clozapine should be considered in patients showing significant suicidal behaviour (Category A), though other atypical antipsychotic drugs may be useful in patients for whom clozapine is either contraindicated or otherwise undesirable (Category B). Extrapyramidal side effects should be avoided in all patients, but especially so in patients at high risk for suicide (Category B), and the use of first-generation antipsychotic drugs in patients with suicidal behaviour should generally be limited to patients needing depot formulations where depot formulations of second-generation antipsychotic drugs are unavailable (Category C).

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