Psychopharmacological Treatment to Reduce Suicide Risk

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Adequate treatment of the underlying psychiatric illness consistently appears to be the most effective use of medication in suicidal patients.

Suicide may be the culmination of a complex combination of psychological, biological, social, and cultural factors, and it is particularly likely to occur during periods of individual, family, and socioeconomic crises associated with loss and shame. Psychiatric disorders, especially depression, bipolar disorder, and substance abuse, are most often associated with suicide. In bipolar disorder, mixed manic-depressive states are often associated with increased suicide risk. Suicide rates are also surprisingly high among persons who have anxiety disorders, and severe anxiety may accompany suicidal behavior. However, evidence of the efficacy of antianxiety medications in lowering suicide risk is limited.

The effect of treatment on suicide risk has been a topic of growing research interest in recent years. There is limited evidence that psychiatric treatments reduce suicide risk, although a decrease in the long-term suicide rate for patients with mood disorders treated with lithium, neuroleptics, and antidepressants has been reported in more recent studies. Psychiatric treatments as diverse as psychotherapy, rapid hospitalization, and ECT can be lifesaving in acute emergencies, but there are limited data to suggest that any of them decrease suicide risk. In this article, we review psychopharmacological interventions that have been associated with suicide prevention in patients with major psychiatric illnesses.

**Clozapine and other novel antipsychotics**

The first FDA-approved medication with an antisuicide indication was clozapine for schizophrenia. The regulatory approval in 2003 was largely based on the International Suicide Prevention Trial (InterSePT), a remarkable randomized trial that compared clozapine with olanzapine in patients with schizophrenia and schizoaffective disorder who were at high risk for suicide. In that trial, suicidal behavior (measured by suicide attempts, hospitalizations, and rescue interventions) was significantly decreased in patients treated with clozapine.

The efficacy of other antipsychotic drugs in reducing suicide risk has not been adequately tested. However, some evidence suggests that olanzapine may reduce suicidal ideation when given in combination with a mood-stabilizing agent in patients with bipolar I disorder mixed-episode. Quetiapine (300 to 600 mg) may help prevent suicide in patients with bipolar depression.
diagnoses for which clozapine cannot or should not be used.

**Lithium**

In 1986, Jamison\(^2\) prophetically stated:

One of the most interesting questions in preventive medicine today is the impact of lithium on suicide rates. There are no systematic data available at this time [about its efficacy], although it can be hoped that a well-documented answer will be possible within the next 10 years. Until then, we must rely upon preliminary speculations and clinical observations.

Just a decade later, the first scientific evidence convincingly supported a suicide risk-reducing effect of long-term treatment of bipolar and other manic-depressive disorders with lithium.\(^13,14\)

A recent meta-analysis of data on long-term lithium treatment in bipolar disorder or a mix of major mood disorders supported a marked reduction (5-fold, or approximately 80%) in risk of suicide attempts and of completed suicides.\(^15\) Interestingly, the researchers also found that the proportion of suicide attempts relative to completed suicides during treatment with lithium was more than 2-fold higher, which suggests reduced lethality of suicidal behavior. The evident beneficial effects of lithium in reducing mortality from suicide are all the more remarkable in light of its potentially lethal toxicity in acute overdoses.

**What is already known about pharmacotherapy interventions for reducing suicidality?**

? Robust treatment of the underlying psychiatric illness has been the most effective antisuicide approach.

**What new information does this article provide?**

? Clozapine appears to be useful in decreasing suicide risk in persons with schizophrenia; lithium appears effective for suicidal bipolar patients.

**What are the implications for psychiatric practice?**

? SSRIs are useful in the treatment of suicidal depressed patients. However, patients should be carefully monitored, especially adolescents who receive these agents.

**Antidepressants**

Evidence that antidepressant treatment decreases suicide risk or suicide attempts is mixed. It is often based on data from correlative or “ecological,” pharmacoepidemiological studies that compare suicide rates by regions or years with concurrent rates of prescriptions for antidepressant drugs.\(^16\)

There have been moderate decreases in overall suicide rates, varying by sex and age-groups, in some Nordic countries and in the US since the 1990s; these decreases are possibly associated with the emergence of the modern, less toxic antidepressants that now dominate current clinical practice.\(^17,18\) Data from observational studies indicate that SSRIs may be associated with a reduced risk of suicide in adults with depression, while their use may increase suicidality in adolescents.\(^19\)

This remains a controversial topic. Findings from a meta-analysis of randomized placebo-controlled studies suggest a modestly increased risk of suicidality associated with the use of antidepressants in pediatric patients.\(^20\) However, a more recent review of suicides in adolescents found that only 1.6% of these young people had recently been exposed to SSRIs.\(^21\) Most adolescents who died by suicide were not taking antidepressants at the time of their death. Following the introduction of the FDA’s regulatory action on restriction of antidepressants in children and adolescents, there has been an increase in suicides. The decrease in antidepressant prescriptions for children and adolescents paralleled the increase in suicide rates; before the FDA’s warning, the suicide rates had been decreasing.\(^22,23\) These findings support the use of SSRIs as part of a comprehensive treatment plan for adolescents with significant depression.

Medication nonadherence occurs for various reasons and presents risk of relapse of depression with an increase in symptoms. Relational psychopharmacology emphasizes collaboration between patient
and pharmacologist toward a shared goal of symptom relief. Bostwick suggests that pharmacologists rely on “informed intuition and close follow-up” as part of an empathic therapeutic relationship that enables the patient to tolerate some amount of adverse effects and delay in achieving therapeutic response.

Patients who independently interrupt or discontinue treatment without consulting their prescribing physician are at greatly increased risk for recurrence or early relapse. The decision to discontinue medication may provide relief from unpleasant adverse effects; however, there are associated risks related to recurrence of symptoms. These risks appear to be higher if medications with shorter half-lives are abruptly discontinued. Furthermore, findings from some studies indicate that antidepressant discontinuation is associated with increased risk of suicide. The therapeutic alliance may minimize unilateral actions that lead to premature termination or discontinuation of pharmacological treatments. The therapeutic alliance enables the patient to tolerate unpleasant adverse effects.

**Antiepileptic drugs**

These agents are receiving increasing attention because of a possible association with suicidal thoughts or behaviors. Recent studies, however, have yielded inconsistent findings regarding suicide risk conferred by specific antiepileptic drugs (AEDs). In patients with epilepsy, heightened suicide risk has also been attributed to comorbid psychiatric conditions.

In 2008, the FDA reported an apparent suicide risk among epileptic patients treated with anticonvulsants. However, questions have been raised about the report; the anticonvulsants grouped together were pharmacodynamically highly heterogeneous. The report also included outcomes of questionable comparability, including suicidal ideation, suicidal acts, and 4 completed suicides. Moreover, the data were acquired as passive and incidental “adverse event reports” of uncertain reliability and completeness. Parenthetically, it is curious that epileptic patients would volunteer for potential exposure to placebo treatment.

It is unclear whether the action of AEDs in patients with affective disorders is similar to that in patients with seizure disorders. It is crucial to determine whether suicide risk with anticonvulsants and high-potency benzodiazepines with anticonvulsant activity carries over to psychiatric patients, because these drugs are widely used to treat serious psychiatric disorders. Two studies have examined this potential association between AEDs and suicide risk, with inconclusive results. Reported investigations that examined suicide risk and AEDs are strikingly inconsistent in their rankings of relative risks associated with particular drugs. Nevertheless, levetiracetam, lamotrigine, and topiramate were among the top 3 AEDs with the highest observed suicide risks in at least 2 of the 5 reported analyses. Levetiracetam was among the top 3 drugs in all 5 studies that found increased suicide risk. Lamotrigine and topiramate appeared in the top 3 in 3 of the 5 studies. Only topiramate has been associated with clinical depression. These 3 drugs differ in their pharmacodynamics. Thus, it is difficult to conclude which biological mechanisms lead to increased suicide risk.

Lamotrigine monotherapy is an effective and well-tolerated treatment for mania and bipolar depression, and it may be used as an augmentation strategy for unipolar depression. Other pharmacological issues

Some pharmacological challenges go beyond diagnostic categories. There are many clinical challenges in which medications play key roles in reducing generalized symptoms, such as anxiety and insomnia, that worsen during a psychosocial crises and are associated with increased suicide risk. Adequate treatment of insomnia and agitation is important anecdotally in suicidal patients. Although suicide rates are surprisingly high among persons with anxiety disorders and severe anxiety may accompany suicidal behavior, evidence that antianxiety medications may alter suicide risk is limited. Acute relief of agitation in suicidal depressed patients may play a significant role in suicide prevention.

**Conclusion**

Adequate treatment of the underlying psychiatric illness consistently appears to be the most effective use of medication in suicidal patients. Although studies are limited, there are indications that some medications will provide specific antisuicidal protection. The use of illness-specific medication provided through the therapeutic relationship is key to decreasing the risk of suicide. Clozapine has shown some efficacy at reducing suicide risk in schizophrenia, and olanzapine and quetiapine appear promising. Similarly, lithium has been shown to be effective for patients who have bipolar disorder. SSRIs are useful in the treatment of suicidal depressed adults. However, patients who are receiving SSRIs, especially adolescents, should be carefully monitored. Additional research
is urgently needed to determine the safety of antiepileptic drugs. A good therapeutic alliance is key to effective pharmacotherapy. By forging a therapeutic relationship, the prescribing psychiatrist encourages patient adherence and enables physician and patient to monitor suicide risk across the spectrum of diagnoses and possible adverse effects.

References:


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