Pharmacologic Approaches to Suicide Prevention

Sidney Zisook, M.D., Isabel Domingues, M.D., Jason Compton, M.D.

Suicide is a leading cause of death that is often preventable. This article reviews the role of medications in treating suicidal behavior and in preventing suicide. For an acute suicidal crisis, ketamine, and perhaps esketamine, are emerging as important tools. For patients with chronic suicidality, clozapine remains the only U.S. Food and Drug Administration (FDA) approved antisuicidal medication, and its use is predominantly for patients with schizophrenia and schizoaffective disorder. An abundance of literature supports the use of lithium among patients with mood disorders, including those with major depressive disorder. Despite the black box warning regarding antidepressants and suicide risk among children, adolescents, and young adults, antidepressants are widely used and remain helpful in reducing suicidal thoughts and behaviors, primarily among patients with mood disorders. Treatment guidelines focus on the importance of optimizing treatment of the psychiatric conditions known to be associated with suicide risk. For patients with these conditions, the authors recommend focusing on suicide as an independent treatment target and using an enhanced medication management strategy that includes maintaining a supportive, nonjudgmental therapeutic relationship; flexibility; collaboration; measurement-based care; consideration of combining medications with nonpharmacologic, evidence-based strategies; and ongoing safety planning.

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Suicide is a public health problem. The 12th leading cause of death in the United States, suicide led to the loss of almost 46,000 U.S. lives in 2020. In the same year, another 1.2 million people in the United States attempted suicide, and about 10% of U.S. adults had suicidal thoughts (1). Despite these sobering statistics, we know that many suicides can be prevented. Several helpful approaches for individuals who are in distress or at risk for suicidal behavior are available. Brief interventions that provide tools for managing suicidal crises and for reducing suicidal behaviors include safety planning interventions, lethal means counseling, and crisis response planning. In addition, several evidence-based therapies have been found to reduce suicidal ideation and behavior: cognitive-behavioral therapy–suicide prevention (2), dialectical behavior therapy (3), collaborative management and assessment of suicidality (4), attachment-based family therapy (5), and prolonged grief disorder therapy for survivors of suicide loss (6). This article focuses on the role of medications in suicide prevention.

DEFINITIONS AND MEASURES

For purposes of this review, the terms "suicidal thoughts" and "suicidal ideation" are used interchangeably and are divided into "passive" thoughts (wish to be dead, to disappear, or to not wake up) and "active" thoughts (method, plan, or intent to die by suicide). The term "suicide attempt" refers to nonfatal, self-directed, potentially injurious behavior with intent to die as a result of the behavior. The term "suicide" is defined as death caused by self-directed injurious behavior with the intent to die. The term "suicidal behaviors" encompasses attempts and completed suicide.

Measuring actual rates of suicidal behaviors is challenging. Many ecological studies on pharmacological approaches to reduce suicide use suicide as the primary outcome. One problem with interpreting such studies is inconsistency in the methods of determining when a death is the result of suicide. In the United States, decisions about whether deaths are listed as suicides on death certificates are made by a coroner or medical examiner. These decisions frequently lack consistency and clarity, and laws and procedures for guiding these decisions vary from state to state and even from county to county. Another problem is that ecological studies do not identify the presence or absence of important measures of interest (e.g., antidepressant treatment) at the level of individual persons, and they rely on indirect indices of drug usage (sales or prescription rates). Therefore, unidentified intervening variables can lead to apparent, but misleading, correlation with suicide rates (7, 8).

By contrast, most clinical trials do not measure actual suicides, but rather suicidal ideation or attempts. Because suicide is uncommon in experimental treatment trials and in clinical practice, these studies rely on these suicide proxies, which may not be highly correlated with actual suicides (8, 9). Of note, most individuals with suicidal ideation never make an attempt, and at least 85%–90% of attempters do not go on to suicide (10, 11). Moreover, most therapeutic trials involving patients with acute depression exclude those

considered at high risk of suicidal behavior, and in most such studies, suicidal thoughts or behaviors are not explicit outcome measures but, instead, incidental adverse events, reported with uncertain reliability and accuracy.

When explicit suicide outcome measures are used, they often are limited to single items on depression rating scales, such as item 10 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (12), item 3 on the Hamilton Depression Rating Scale (13), item 12 on the Quick Inventory of Depressive Symptomatology (14), or item 9 on the Physician Health Questionnaire (15). Validated scales that give more comprehensive and nuanced assessments of suicidal thoughts and behaviors include the Sheehan–Suicidality Tracking Scale (16), the Concise Health Risk Tracking scale (17), and the Scale for Suicide Ideation (18). In 2012, the U.S. Food and Drug Administration (FDA) made the Columbia–Suicide Severity Rating Scale (C-SSRS) the preferred instrument—the gold standard—for measuring suicidal ideation and behavior in clinical trials (19). Three versions of the C-SSRS are available for use in clinical practice. The lifetime/recent version allows practitioners to gather lifetime history of suicidality as well as any recent suicidal ideation or behavior. The since-last-visit version of the scale assesses suicidality since the patient's last visit. The screen version of the C-SSRS is a truncated form of the full version. When used in conjunction with other suicide prevention measures, any of these relatively brief and validated suicide scales can be used to help prevent suicidal behaviors.

Because few medication trials have focused on prevention of suicidal behaviors, the role of medications in suicide prevention remains elusive. Yet, in clinical practice, medications play a prominent role in helping to prevent suicide. This review addresses medications and classes of medications that have data to support their use in suicide prevention: clozapine, lithium, ketamine or esketamine, and antidepressants. The review ends with clinical guidelines for an integrative, multipronged approach for reducing suicide risk in clinical settings.

MEDICATIONS

Clozapine

Clozapine is an atypical antipsychotic medication used to treat individuals who have schizophrenia or schizoaffective disorder and have not responded to other antipsychotics. It is the only medication with a specific FDA indication for reducing risk of recurrent suicidal behavior among at-risk patients with schizophrenia or schizoaffective disorder.

The regulatory approval was largely based on results from the multicenter, randomized, double-blinded, 2-year International Suicide Prevention Trial (20). The trial compared clozapine with olanzapine among patients with schizophrenia and schizoaffective disorder who were at high risk for suicide as determined by previous suicide attempts or current suicidal ideation. Patients were seen weekly for 6 months and then biweekly for 18 months. Suicidal behavior was significantly reduced among patients treated with clozapine versus olanzapine. Fewer clozapine-treated patients attempted suicide; required hospitalizations or rescue interventions to prevent suicide; or required concomitant treatment with antidepressants, anxiolytics, or soporifics. Overall, five clozapine-treated patients versus three olanzapine-treated patients died by suicide during the study. In addition to its strong evidence-base for reducing suicidal behavior of patients with schizophrenia or schizoaffective disorder, some reports (21) have suggested clozapine may reduce intentional self-harm and overdoses among patients with borderline personality disorder.

Despite clozapine's unique antisuicidal profile, it tends to be underutilized (22). This is in large part because of its serious and burdensome side effect profile. Clozapine has five black box warnings: severe neutropenia; orthostatic hypotension, bradycardia and syncope; seizures; myocarditis and cardiomyopathy; and increased mortality among elderly patients with dementia-related psychosis. Compared with other antipsychotics, clozapine has an increased risk of blood dyscrasias, in particular agranulocytosis during the first 18 weeks of treatment. After 1 year, this risk reduces to that associated with most antipsychotics. Clozapine's use is therefore reserved for people who have not responded to two other antipsychotics, and it requires stringent blood monitoring. This monitoring includes obtaining a complete blood count prior to initiating treatment, to ensure the presence of a normal baseline absolute neutrophil count (ANC) ($\geq$1500/μL) and to permit later comparisons. Weekly ANC monitoring is required during the first 6 months of treatment. If a patient's ANC remains normal for the first 6 months, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains normal for the second 6 months, ANC monitoring frequency may be reduced to once every 4 weeks thereafter. Other, more common adverse effects include neutropenia, constipation, dizziness, drowsiness, hypersalivation, hypotension, tachycardia, and weight gain.

In 2015, the individual manufacturer patient registries were consolidated by request of the FDA into a single shared patient registry (the Clozapine Risk Evaluation and Mitigation Strategy [REMS] Registry). This program requires health care professionals and pharmacies prescribing or dispensing clozapine to be certified and trained in the program; patients also must be enrolled and must adhere to the ANC monitoring requirements.

Clozapine's niche in suicide prevention is in reducing risk of recurrent suicidal behavior among patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk, as determined by their history and recent clinical state, for experiencing suicidal behavior. Whether clozapine reduces death by suicide among these patients has not been established.

Lithium

An abundance of observational data and randomized controlled trials (RCTs) attest to lithium's antisuicidal effects

among patients with mood disorders. Observational studies have the advantage of being able to capture large cohorts over long periods. Baldessarini et al. (23) reviewed 33 studies published between 1970 and 2000. Results yielded threefold lower rates of suicide and reported attempts during long-term lithium treatment than without it or after it was discontinued. Although greatly reduced, these rates remained above those estimated for the general population. The authors concluded that evidence for substantial, if incomplete, protection against suicide with lithium was supported by more compelling evidence than that for any other treatment for patients with mood disorders.

Subsequently, Goodwin et al. (24), in a study of a large, population-based sample of 20,638 individuals (ages 14 years or older with at least one outpatient diagnosis of bipolar disorder and at least one filled prescription for lithium, divalproex, or carbamazepine) found a risk of suicide attempt or suicide that was 1.5 to 3 times higher among those treated with divalproex compared with those treated with lithium. The investigators concluded:

> This evidence of lower suicide risk during lithium treatment should be viewed in light of the declining use of lithium by psychiatrists in the United States, particularly among recently trained psychiatrists. Many psychiatric residents have no or limited experience prescribing lithium, largely a reflection of the enormous focus on the newer drugs in educational programs supported by the pharmaceutical industry. If lithium does have an antisuicidal effect not matched by currently available alternatives, then current prescribing patterns should be reevaluated. At the least, use of lithium to treat mood disorders should be an essential component of training in psychiatry (24).

Another large, longitudinal cohort study, in a nationally representative U.K. sample of almost 7,000 patients diagnosed as having bipolar disorder and prescribed lithium, valproate, olanzapine, or quetiapine as a maintenance mood stabilizer treatment (25), showed that those taking lithium had reduced self-harm and unintentional injury rates compared with those prescribed any of the other drugs. Self-harm rates were lower among patients taking lithium compared with those taking valproate, olanzapine, or quetiapine; unintentional injury was lower with lithium compared with valproate and quetiapine but not with olanzapine. Although the suicide rate was lower among the lithium group, there were too few events to allow accurate estimates.

Several RTCs also have attested to lithium's antisuicidal effects. In a review of 48 RTCs of patients with mood disorders (26), those who received lithium were less likely to die by suicide (and had fewer deaths overall) than patients treated with placebo for both bipolar and unipolar depression. One study that stands in sharp contrast to most others was a large Veterans Affairs Cooperative Study RTC (27) that enrolled veterans with bipolar disorder or depression who had survived a recent suicide-related event. Participants received lithium augmentation of usual care. The main outcome was time to the first repeated suicide-related event (suicide attempt, interrupted attempt, hospitalization to prevent suicide, and death from suicide). The trial was stopped for futility after 519 veterans were randomly assigned, because no overall difference was found in repeated suicide-related events between treatments. The authors concluded that adding lithium to existing medication regimens was unlikely to effectively prevent suicide-related events among patients undergoing active treatment for mood disorders. Baldessarini and Tondo (28), however, noted several limitations of the Veterans Affairs study (low concentrations of lithium, brief treatment exposure and high drop-out rate, poor adherence to prescribed lithium or placebo, and the three suicides among participants receiving placebo compared with one suicide among those receiving lithium—an important, albeit nonsignificant difference), leading them to conclude that this study did not provide evidence that lithium lacks antisuicidal effects.

Despite the considerable evidence that lithium helps prevent suicidal behaviors among patients with mood disorders, as with clozapine, the use of lithium remains underrepresented in clinical practice (29). This underuse may be related to insufficient training of psychiatrists in the use of lithium, fear of toxicity, aggressive marketing of alternative medications that are patentable and therefore more profitable, and the need to monitor blood levels and thyroid and kidney function (30). Of particular concern is lithium's potential for nephrotoxicity, affecting tubular or glomerular function. In tubular dysfunction, which is more common, the kidney's ability to concentrate urine is reduced, and the intraluminal lithium concentration can increase to toxic levels. Monitoring for diabetes insipidus, the most common renal complication of lithium therapy, is vital because it is initially reversible with lithium withdrawal but may become irreversible because of structural damage. Annual assessment of urine production, which should not exceed 4 liters per day, is recommended. Clinical decision making will need to take a balanced view of the likely benefits and harms of lithium for the individual patient.

Lithium's niche in suicide prevention is most likely for treatment of patients who have chronic or recurrent mood disorders and are considered at risk for persistent or intermittent suicidal behaviors.

Ketamine

Ketamine, a glutamatergic modulator and N-methyl-D-aspartate receptor antagonist, is a versatile drug used in anesthesiology, pain management, and most recently, as either monotherapy or adjunctive treatment for major depressive disorder and treatment-resistant depression. Multiple double-blind, placebo-controlled, randomized trials have established the rapid antidepressant efficacy of subanesthetic-dose (0.5 mg/kg) ketamine administered intravenously for treatment-resistant depression (31) and bipolar depression (32). The rapidity of ketamine's antidepressant effects, together with its efficacy among patients not responding to conventional antidepressant treatment, has

sparked interest in its potential as an antisuicide treatment (33). An RCT (34) comparing ketamine with midazolam, among 57 patients with treatment-resistant depression, found a rapid (within 24 hours postinfusion) reduction in suicidal ideation with ketamine but not with midazolam. A systematic review of RTCs on the effect of ketamine on suicidal ideation (35) reported on four RCTs and confirmed a rapid antisuicidal ideation effect of ketamine (within 24–48 hours postadministration), and that effect was at least partially independent of effects on depressive symptoms. In a preliminary study of longer-term effects (36), repeated doses of open-label ketamine rapidly and robustly decreased suicidal ideation among 14 pharmacologically treated outpatients with treatment-resistant depression and stable suicidal thoughts; in two patients, this decrease was maintained for at least 3 months following the final ketamine infusion. Whether any of these findings can be translated into a reduction in actual suicidal behavior has yet to be established.

Despite the excitement surrounding ketamine's rapid and robust antidepressant and antisuicidal effects, several precautions and limitations remain. For one, medical insurance companies usually cover ketamine's FDA-approved use as an anesthetic but do not cover its use for other purposes, such as in the treatment of psychiatric disorders; therefore, patients must independently pay hundreds of dollars a dose for repeated ketamine infusions. The ideal frequency of treatment with intravenous ketamine has not been established. With repeated intravenous dosing, ketamine has been demonstrated to reduce suicidality for≤6 weeks but has not been shown to reduce risk for completed suicide.

Side effects of ketamine tend to be mild and short-lived. Intravenous ketamine promotes dissociation in nearly three-quarters of patients treated for treatment-resistant depression. Dissociation peaks within 40 minutes after ketamine administration and resolves within 1–2 hours. Ketamine is associated with increases in blood pressure and pulse rate among 10%–50% of patients treated. These effects usually resolve within 2–4 hours after drug administration. Patients should be monitored for at least 2 hours after treatment. The reported incidence of serious adverse events or persistent medical sequelae in clinical trials is low; however, there is a paucity of data concerning long-term safety. Moreover, ketamine is a known drug of abuse, which raises concern that repeated administration of the drug could entail liability for drug abuse (37).

Ketamine's niche in suicide prevention may be for treatment of patients who are acutely suicidal in emergency rooms or inpatient settings. Although ketamine may not be the ideal medication for suicide prevention, its rapid and robust action has spurred great interest among clinicians and researchers alike and has triggered a long overdue search for rapidly acting, well-tolerated, safe, and sustainable antisuicidal interventions.

Esketamine

Along with an oral antidepressant, intranasal esketamine, the S-enantiomer of ketamine racemate, is approved by the FDA to treat adults who have treatment-resistant depression and depressive symptoms in adults diagnosed as having major depressive disorder who experience suicidal thoughts or behaviors. Note that the second indication does not mean esketamine is an approved treatment for suicide prevention. It is not known whether esketamine is safe and effective for use in preventing suicide or in reducing suicidal thoughts or behaviors. It carries the same black box warning as other antidepressants regarding an increased risk of suicidal thoughts and behaviors among pediatric and young adult patients. A meta-analysis (38) of randomized, double-blind RCTs examining the effectiveness, tolerability, and safety of intranasal esketamine in treating major depressive disorder (three of the studies included only patients with treatment-resistant depression) found intranasal esketamine to have an ultra-rapid antidepressant effect (within hours), which peaked at 24 hours and lasted for up to 28 days. Another systematic review (39) found racemic ketamine to be more efficacious than esketamine. One RCT (40) found significantly greater improvement with intranasal esketamine than with placebo on the MADRS item of suicidal thoughts at 4 hours postadministration, but not at 24 hours or at day 25. Another RCT (41) found no group differences in reducing the percentage of patients reporting suicidal ideation.

After several preliminary studies suggested adjunctive intranasal esketamine might be an effective antidepressant for adults with major depressive disorder and active suicidal ideation or behavior (42), two phase-3 RCTs, ASPIRE I and II, were conducted to further assess the efficacy and safety of esketamine in treating patients who had depression and were at imminent risk of suicide. These trials of esketamine among patients with major depressive disorder and active suicidal ideation or behavior were the first large-scale RCTs of patients considered at imminent risk of suicide. ASPIRE I showed a significant reduction in depression severity among the esketamine plus oral antidepressant treatment group compared with the placebo plus oral antidepressant group 24 hours after the first treatment, with a notable increase in the antidepressant effect among patients with prior suicide attempts or more severe depressive symptoms. Severity of suicidal ideation showed improvement in both groups, but no significant difference was found between treatment groups (43). ASPIRE II also showed significant reduction in depression severity from baseline to 24 hours after the first treatment, which was greater for the esketamine plus oral antidepressant group than for the placebo plus oral antidepressant group. Differences were significant as soon as 4 hours after the first treatment and also 25 days later. Again, although both groups showed rapid reduction in suicidal ideation and scores on behavior assessments, the difference between the treatment groups was not significant (44).

Common side effects of intranasal esketamine include sedation, fainting, dizziness, spinning sensation, and anxiety. Dissociation also occurs. There also is a risk for abuse and for physical and psychological dependence. As with clozapine, because of the risks for abuse and misuse, esketamine is only

available through a restricted REMS program. Patients treated in outpatient health care settings (e.g., medical offices and clinics) must be enrolled in the REMS program, and esketamine can only be administered at health care settings certified in the program. Patients are required to wait in the facility for at least 2 hours after inhalation, which may provide an opportunity for psychotherapy focused on suicide prevention.

Intranasal esketamine's niche in suicide prevention may be as an adjunctive treatment for acutely suicidal patients, but this role remains unproven. Esketamine does not appear to have as robust an antisuicidal ideation effect as intravenous ketamine. The long-term therapeutic effect and safety of intranasal esketamine require further examination in large-scale RCTs.

Antidepressants

Although none of the standard antidepressants have been demonstrated in methodologically rigorous RCTs to decrease suicidal behaviors, antidepressants remain a key tool in suicide prevention. Antidepressants not only have beneficial effects for depression, but also for a host of other conditions often associated with increased suicide risk, such as panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and binge eating disorders. Several studies, including cohort studies (45) and large multisite open (46) and controlled (47, 48) trials have reported reductions in suicidal ideation with antidepressants, and, on a population level, large ecological studies (49–51) have shown associations with antidepressant use and decreased suicidal behaviors. Perhaps the most compelling data on the risk of suicide attempts after initiation of antidepressants have come from a study by Simon and Savarino (52) that compared the time patterns of suicide attempts among outpatients starting depression treatment with medication or psychotherapy. Outpatient claims data from a prepaid health plan were gathered to identify new episodes of depression treatment beginning with an antidepressant prescription in primary care (N=70,368), an antidepressant prescription from a psychiatrist (N=7,297), or an initial psychotherapy visit (N=54,123). In that study, the overall risk of suicide attempts was highest in the months before starting treatment and declined after depression treatment was started with either medication or psychotherapy. Yet, since 2004, all antidepressants have a black box warning indicating that they are associated with an increased risk of suicidal thinking, feeling, and behavior among young people.

The initial 2004 black box warning was based on data from 23 trials conducted in pharmaceutical company–supported programs evaluating antidepressant efficacy among pediatric patients and on one large multicenter trial (the Treatment for Adolescents with Depression Study) (53). Although there were no completed suicides in any of the clinical trials evaluated, this meta-analysis (54) revealed a modestly increased risk of suicidal thoughts and behaviors associated with antidepressant treatment (4%), compared with placebo (2%), among children and adolescents. The FDA therefore directed antidepressant manufacturers to revise the labeling and to alert health care providers and patients about an increased risk of suicidality among children and adolescents who take antidepressants. In 2006, on the basis of a second, expanded meta-analysis of 372 RCTs of antidepressants involving nearly 100,000 participants (54), the FDA extended the warning to include young adults up to age 24. The analysis showed that the increased risk was significant only among children and adolescents under age 18; there was no evidence of increased risk among adults older than age 24, and among adults age 65 or older, antidepressants had a protective effect against development of suicidal ideation and behavior (54). The FDA recommended prescribers advise patients about this risk and maintain close contact after patients began the medication.

Although the warning was meant to increase safety, several studies have suggested unintended consequences (55, 56), including decreased diagnosis of depression (57) and reduced antidepressant usage (58). At the same time, suicide rates have continued to climb. There remains a lively debate on whether the black box warning has had an untoward effect on suicide rates (59). In any case, it is important to balance this modest risk of increased suicidal thoughts and attempts among children, adolescents, and young adults treated with antidepressants versus the risk of untreated or inadequately treated depression and to incorporate suicide prevention–informed management strategies as described in the next section.

TREATING UNDERLYING PSYCHIATRIC CONDITIONS RELATED TO SUICIDE RISK

At the individual clinician's level, treating underlying psychiatric conditions related to suicide risk has long been recognized as the cornerstone treatment for suicidal behaviors and suicide prevention. The list of such conditions is long, and many of these conditions benefit from evidence-based or evidence-informed pharmacologic strategies. These conditions include mood disorders (46, 47, 54), psychotic disorders (48), neurocognitive disorders (60), anxiety and sleep disorders (61, 62), and substance use disorders (63). We caution that although some studies have found a reduction in the likelihood of suicide among patients with anxiety and sleep disorders who were treated with benzodiazepines in concordance with treatment guidelines, for limited durations and with concomitant psychotherapy or antidepressants (61), other studies have suggested a positive association between benzodiazepine use and suicide risk. Of these high-risk conditions, mood disorders, particularly major depressive disorder, have been the most widely studied and play the most prominent role in suicide prevention efforts.

At least 10% of the time, however, no accompanying mental health condition can be ascertained at the time of the

Box 1. General principles for optimizing clinical treatment for suicidal behavior and for preventing suicide

Acute Care for Patients in or Near a Suicidal Crisis (e.g., Patient With Mood Disorder Feeling Overwhelmed, Hopeless, Expressing Plans and Intent, and Having Means)

Consider hospitalization or increased surveillance.
Consider intravenous ketamine or possibly intranasal esketamine as an adjunctive to antidepressants for short-term reduction in suicidal ideation among patients with major depressive disorder and suicidal ideation.
Keep in mind that although practice standards suggest electroconvulsive therapy (ECT) is a good choice for at-risk patients with severe mood disorders, the evidence for the effects of ECT on suicide death has been inconsistent (63).

Chronic Care for Patients With a Psychiatric Condition That Increases Suicide Risk or Who Have Suicidal Thoughts or Past Attempts

Consider clozapine to decrease risk of suicide among patients with schizophrenia or schizoaffective disorder and suicidal ideation or past suicide attempt(s).
Consider lithium alone (for patients with bipolar disorder) or in combination with another psychotropic agent (for patients with unipolar depression or bipolar disorder) to decrease the risk of suicide among patients with mood disorders.

Treat Co-Occurring Psychiatric Disorders (Depression, Posttraumatic Stress Disorder, Addictive Disorders) With Enhanced Clinical Management

Develop and maintain an open, honest, nonthreatening, nonjudgmental, patient-centered, therapeutic relationship.
Maintain a collaborative approach:
With the patient.
With other treating clinicians.
With your team—"Never worry alone."

Stay Flexible

Increase contact and provide safety nets during transitions or gaps in care as necessary.
Consider increasing modes of contact, such as telephone calls or email between sessions as needed.

Incorporate other evidence-informed nonpharmacologic treatments for enhanced coping strategies, preventing future suicide attempts, and managing associated conditions.

Involve the patient's family wherever possible.
Have a safety plan. The safety plan intervention is a prioritized set of coping skills and support, developed in collaboration with the patient, and, ideally, a family member or other support person (67). The plan includes individualized warning signs, internal coping strategies, social contacts to distract from suicidal thoughts, and social and professional support to assist with resolving suicidal crises.
Include means restriction and firearms safety.
Include reasons for living.
Continue monitoring the patient and updating the treatment.

Special Considerations for Treating Depression

Recognize that major depressive disorder is a chronic and recurrent (sometimes lifelong) illness, and that suicide risk waxes and wanes in intensity over time among many individuals with the disorder.
Closely monitor patients for changes in thoughts of suicide or suicidal behaviors after antidepressant treatment has been initiated or when the medication dosage is changed.
Pay attention to the risk of overdose when prescribing antidepressants for patients at risk for suicide, and limit the amount of medication dispensed and refilled.
Consider lithium augmentation of antidepressant treatment for patients with a major or persistent depressive disorder in an effort to reduce suicide risk.
Update safety plans regularly and provide long-term monitoring even after remission, because suicidal thoughts and behaviors may wax and wane over time, independent of other symptoms.

suicide. Furthermore, even with the psychiatric conditions associated with high risk for suicidal behavior, most patients do not engage in it (64). Thus, many clinical investigators have argued that suicidal behaviors should be defined as a separate diagnosis so they can be more readily identified and treated in clinical practice (64, 65). A corollary of suicidal behavior being defined as a separate disorder is to consider suicide risk as its own treatment target. Indeed, a common feature of all the evidence-based psychotherapies is the focus on suicidal thoughts and behaviors over and above co-occurring psychiatric conditions (66). Another common feature is the incorporation of a safety plan (67). These common features may be equally applicable to optimizing pharmacological care to treat suicidal behaviors or to prevent suicide. Box 1 enumerates general principles of optimizing clinical care for suicidal behavior and for preventing suicide. Box 1 is organized into treatment interventions (setting, ketamine or esketamine, electroconvulsive treatment) (68) for acute risk and for chronic risk. The section on chronic risk includes comments on the use of clozapine, lithium, and the treatment of coexisting disorders. The key components of what we call enhanced clinical management, are outlined, and the importance of including a collaborative, live, safety plan (66, 67) is emphasized. Box 1 ends with special considerations for treating depression.

CONCLUSIONS

Medications are not stand-alone treatments for suicidal behaviors. There is no single cause of suicide. Rather, suicidal thoughts and behaviors have multiple determinants. Similarly, there is no single approach to reducing suicidal ideation or behaviors that is suitable for all individuals and situations. Fortunately, we have a growing list of evidence-based brief interventions, therapies, and medications in our

toolkit. As part of a multipronged approach to suicide prevention, medications can, and often do, play a prominent role. Determining whether and which medication makes sense for an individual patient at risk for suicide requires careful weighing of the risks and benefits of the medication as well as the risks and benefits of not using the medication. When rapid reduction in suicidal thoughts and behaviors is needed, off-label ketamine and possibly esketamine may be considered, but the roles of these drugs in long-term management of suicidal behaviors remain to be determined. For longer-term management, both clozapine for schizophrenia and schizoaffective disorder and lithium for mood disorders remain underutilized. Care management for patients with psychiatric disorders associated with suicide risk, or for individuals with suicidal thoughts and behaviors but no underlying psychiatric diagnosis, should always include a thorough assessment of lifetime and current suicidal thoughts and behaviors and individualized risk and protective factors and a nonjudgmental, empathic, and collaborative therapeutic relationship (69). When medications are part of the treatment, we recommend the enhanced clinical management approach outlined in Box 1.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, University of California, San Diego, San Diego. Send correspondence to Dr. Zisook (szisook@health.ucsd.edu).

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