# Suicidality and Substance Abuse in Affective Disorders

Joseph F. Goldberg, M.D.; Tara M. Singer, M.A.;
and Jessica L. Garno, M.A.

The relationship between suicidality and substance abuse has long been recognized, although studies have only fairly recently begun to identify factors that may help clarify how alcohol or other drug abuse increases the susceptibility to suicidal behavior in vulnerable populations. In particular, alcohol and other psychoactive substance misuse has been linked with mood destabilization and the induction of manic or depressive episodes in affectively ill individuals, while also demarcating groups with heightened tendencies toward impulsivity, aggression, and sensitivity to interpersonal loss. Serotonergic mechanisms have been implicated in each of these clinical settings, along with possible dysregulation of other neurotransmitter systems. Psychosocial aspects of alcohol or drug abuse relevant to suicide may involve a heightened sensitivity to interpersonal loss, poor coping skills in response to adverse life events, and affective dysregulation induced by circadian and psychosocial stresses. Consequently, self-destructive behaviors with relatively little premeditation may arise during periods of increased stress, intoxication, depression, or other psychopathology. Early detection of substance abuse followed by appropriate pharmacologic and/or psychotherapeutic interventions may greatly help to minimize the formation of complex comorbid psychiatric conditions and reduce the potential for suicidal acts among high-risk populations.

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While numerous factors have historically been associated with suicidal behavior, alcohol abuse and drug abuse have repeatedly been identified as among the most robust predictors of both attempted and completed suicide. Alcohol and/or drug abuse is associated with more than half of reported suicides in the United States and abroad.[1,2] Current data suggest a 5- to 10-fold increase in risk for attempting suicide among alcohol abusers as compared to nonabusers, above and beyond the effects of psychiatric comorbidity.[3,4] Research efforts have extensively sought to clarify links between alcohol/substance abuse and suicidality, leading to the recognition of factors such as depression, impulsivity, serotonergic dysfunction, and genetic components as potent contributors. Yet, despite such clinical profiling, the actual positive predictive value of any individual risk factor or even constellations of risk factors appears relatively low.[5] Suicide prediction remains a tremendously elusive endeavor. Nevertheless, it is clear that a greater awareness and understanding about the role of alcohol and other drug abuse in suicidality may help clinicians to better recognize vulnerabilities and anticipate likely outcomes. It may also help clinicians to identify and directly treat those factors that pose the greatest risk for suicide.

This article will summarize and integrate current research findings regarding alcohol or other substance abuse and suicidality from several perspectives, including clinical phenomenology and comorbidity, hereditary diatheses, and neurotransmitter dysfunction. A distillation of these corollaries to suicidality and substance misuse is presented in Table 1. Finally, we will consider ways in which these findings may help to inform treatment decisions relative to suicide risk among affectively ill patients with comorbid substance use disorders.

*From the Bipolar Disorders Research Clinic, Payne Whitney Clinic-New York Presbyterian Hospital, New York (all authors); the Department of Psychiatry, Weill Medical College of Cornell University, New York (Dr. Goldberg); Lenox Hill Hospital and the Department of Psychology, New York University, New York (Ms. Singer); and the Department of Psychology, Long Island University and Montefiore Medical Center, Bronx, N.Y. (Dr. Garno).*

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*Reprint requests to: Joseph F. Goldberg, M.D., Payne Whitney Clinic, 525 E. 68th St., New York, NY 10021 (e-mail: JFGoldbe@mail.med.cornell.edu).*

**Table 1. Corollaries of Suicidality and Substance Use Disorders in Affectively Ill Patients**

| Dimension | Comment |
|---|---|
| Depression | Extent and severity of depression may be associated with suicide[6]; superimposed alcohol/drug abuse further increases suicide risk[9,20] |
| Bipolarity | High risk for comorbid alcohol or drug abuse in bipolar patients[11]; substance abuse linked with mixed states[12,19,21]; substance misuse and mixed states both may confer heightened risk for suicide attempts[19] and completions,[16] potentially via demoralization and hopelessness[26] |
| Impulsivity | High impulsivity/low premeditation and intent often characterize suicide attempts among individuals with alcohol dependence,[34,35] although high-lethality methods may be common[10] |
| Aggression | High aggression differentiates bipolar suicide attempters from nonattempters[22]; violence may be associated with suicidality among male alcoholics[39] |
| Family history | Familial suicide risk may be higher in mood disorder patients when substance misuse coexists[66]; family history of alcoholism may be associated with suicidal behavior in probands[62,63] |
| Interpersonal/ psychosocial | Interpersonal loss and negative reactions to life stresses may trigger drinking behavior and impulsive self-harm, especially during intoxication[103–105] |

## ALCOHOLISM, DEPRESSION, AND SUICIDALITY

It is by now widely recognized that alcohol abuse and/or other drug abuse is highly prevalent among individuals with severe forms of major affective illness. Tondo and colleagues[6] identified a significant association between substance abuse and suicidality among those with predominantly depressive or dysphoric (rather than predominantly manic) affective disorders, highlighting the importance of depression as a driving force behind suicide attempts, particularly with coexistent substance abuse. This is consistent with studies reporting that depressed alcoholics are more often suicidal than depressed nonalcoholics.[7,8] However, alcohol or drug abuse among depressed patients has also been associated with suicidal ideation above and beyond the contribution of depressed mood.[9] In addition, suicide attempts of high medical lethality may also be more common in mood disorders that involve substance misuse.[10] These findings suggest that the presence of substance abuse may increase suicide risk independent of the severity of depression and may result in more medically dangerous attempts.

These concerns are particularly salient for individuals suffering from bipolar disorder since epidemiologic studies suggest that the likelihood of a lifetime comorbid diagnosis of substance abuse or dependence is higher in bipolar illness than any other Axis I disorder.[11] Hence, the majority of patients with bipolar disorder are likely to manifest signs of alcohol or other drug abuse at some point in their lives. In addition, alcohol abuse and other drug abuse have been frequently associated with the propensity to develop mixed states in bipolar disorder.[12–15] Mixed states, in turn, have been shown to increase the likelihood of suicidality among bipolar patients.[16–19]

Research by our group found that a history of alcohol or other drug abuse was associated with an increased risk for suicidality and mixed states, both cross-sectionally and longitudinally.[19] Furthermore, we observed that the presence of alcohol abuse or dependence led to an approximate 4-fold increased risk for suicidality above and beyond the effects of mixed states or dysphoric manias.[20] In a related study, Keller and colleagues[21] found that drug abuse comorbidity accounted for a greater proportion of poor outcome among mixed manic patients than the presence of mixed states per se. This is consistent with the findings discussed above for unipolar depressive disorders and suggests that alcohol and substance abuse may have a strong, independent effect on suicidality above and beyond the contribution of mood state. Nonetheless, it should be noted that one recent study reported no increased association between substance abuse/dependence and a history of suicide attempts in a cohort of bipolar patients with or without lifetime suicide attempts.[22] However, these authors noted that because comorbid substance abuse/dependence was evident in the majority of their study sample, the high baseline comorbidity rate may have precluded detection of statistical differences in suicide risk as compared to bipolar patients without comorbid substance abuse.

Other authors have also observed an important connection between substance abuse and poor psychosocial outcome or illness course.[23–25] It may be that alcohol or substance abuse leads to a greater decline in functioning and an increase in the severity of the illness. These consequences, in turn, may lead to a greater sense of hopelessness and an increased vulnerability to suicide. Similarly, the passage of multiple affective episodes may worsen prognosis and diminish the likelihood of treatment responsivity in general, potentially heightening the risk for demoralization and hopelessness as further contributors to suicide risk.[26]

The onset of substance abuse relative to initial manifestations of affective disorder bears on theories about longitudinal suicide risk. Some authors have observed that substance abuse may often precede the development of a first episode of mania by several years or longer.[27] Other investigators have noted that among both adult and adolescent suicide victims, alcohol abuse and other drug abuse often arise years before death,[28,29] suggesting that substance misuse may exert a chronic influence on the longitudinal development of suicide risk.

There is some evidence that the complex relationship between suicidality, alcohol or substance abuse, and mood

disorders may be different for men and women. In a study of suicide completion in bipolar disorder over a 12-month period, alcohol dependence was identified in 56% of 18 male victims but none of 13 female victims.[16] This suggests the possibility of a strong gender difference in the role of alcoholism as a proximal risk for suicide completion. Frye and colleagues[30] also observed more extensive depressive morbidity among alcoholic than nonalcoholic bipolar women,[30] but more suicidality in alcoholic bipolar men than alcoholic bipolar women (Mark Frye, M.D., written communication, March 12, 2001). Gender differences in suicide attempts versus completions among bipolar patients may also reflect previous observations that, historically, women attempt suicide more often than men, but men appear more likely to complete suicide, perhaps in part due to their use of more lethal and/or violent methods.[2]

## IMPULSIVITY AND AGGRESSION

Impulsivity has also been thought to play an important role in the relationship between alcohol or substance abuse and suicidality. Several studies have found higher trait impulsivity in patients with affective disorders who have attempted suicide as compared with those who have not attempted suicide,[31–33] although one recent study did not find support for this relationship.[22] Other investigations have found that among affectively ill patients, violent suicide attempts are associated with greater impulsivity and lower intent than nonviolent attempts.[34,35] High impulsivity and low intent have been noted in depressed alcoholic suicide attempters as compared to depressed nonalcoholic suicide attempters.[34] In addition, neurobiological studies have observed lower levels of central serotonin function among impulsive than nonimpulsive attempters, independent of aggression.[36]

Distinct impulse-control disorders have been found in nearly 40% of individuals with alcohol dependence,[37] although it has been suggested that impulsivity among alcoholics may more often reflect sensation-seeking traits rather than aggressive or self-destructive tendencies.[38] However, at least among males with alcohol dependence, impulsivity and violent behavior have been shown to cooccur frequently.[39] This relationship may not be as strong in women who misuse alcohol.[40] High impulsivity levels have also been associated with greater relapse among polysubstance abusers who attend self-help groups.[41]

Although impulsivity has been separately linked to both suicidality and substance abuse, there have been few studies examining the relationship between these 3 factors. One such study found that substance abuse comorbidity and suicidality were both highly prevalent among individuals with borderline personality disorder.[42] Interestingly, another study found that high impulsivity was the sole factor associated with number of lifetime suicide attempts after controlling for depression and substance abuse in borderline personality disorder.[43] This finding suggests that impulsivity may have an independent relationship with suicidality, yet still represent a corollary to other forms of psychopathology.

Beck and colleagues[3] found that hospitalized suicide attempters with coexistent alcoholism were 5 times more likely to eventually commit suicide as compared to those without alcoholism. The only other predictor of eventual suicide completions in that cohort was the number of precautions taken to prevent intervention at the index attempt. This suggests that those individuals who were less impulsive and more premeditated in their planning were more likely to eventually complete suicide. A possible implication of these findings is that high impulsivity may be a more robust predictor of suicide attempts than completions. However, to the extent that pathways to suicide completion may differ from pathways to attempts only, impulsivity may hold greater significance for attempts involving low intent. In fact, Rossow and colleagues[4] observed that alcohol abuse conferred a higher risk for suicide attempts than completions, potentially reflecting a greater degree of impulsivity, intoxication, and low intent in suicide attempters versus completers.

Collectively, the current literature suggests that impulsivity plays a role in both suicidality and substance abuse. High levels of impulsivity and substance abuse may render individuals particularly vulnerable to suicide attempts or spontaneous or impulsive self-destructive behaviors. In contrast, a greater degree of premeditation associated with suicidality may be a stronger predictor of suicide completion. However, further longitudinal research is needed to clarify these dimensions in groups at high suicide risk.

Hostility and aggression are often linked conceptually with impulsivity based on observations involving forensic populations[44] as well as in clinical populations of individuals with affective and/or psychotic disorders, personality disorders, and other psychiatric conditions.[45,46] Convergent data from both preclinical and clinical studies demonstrate abnormalities of central serotonin function across a range of conditions that involve features of depression, alcohol dependence, aggression, impulsivity, and suicidality.[47] Impulsivity and aggression may also be synergistic factors for some suicide attempters.[48]

It is noteworthy that the distinct connection between impulsivity and aggression relative to suicidality has itself received surprisingly little study. In bipolar disorder, Oquendo et al.[22] found that aggression-hostility scale scores were significantly higher among ever- versus never-suicidal bipolar patients, but measures of trait impulsivity failed to differentiate suicide attempters from nonattempters. In addition, Stanley and colleagues[49] reported that among never-suicidal patients, aggressive behavior was related to low central serotonin function independent of features related to impulsivity.

It is possible that the link between impulsivity and aggression differs among alcohol-dependent versus nondependent individuals. For example, some authors have suggested that an association between serotonergic abnormalities and alcoholism may be strongest in type II/antisocial alcoholism,[50–53] perhaps more so than in alcoholism without antisocial features. Neuropharmacologic aspects of suicidality and alcoholism (including serotonin and other neurotransmitter systems) are discussed further below.

## NONAFFECTIVE MANIFESTATIONS OF PSYCHOPATHOLOGY

Anxiety—particularly panic attacks—has been described by some authors as markedly elevating the risk for suicide attempts, independent of the impact of coexistent depression or drug abuse.[54,55] Primarily alcohol-dependent patients who attempt suicide have been shown to have greater levels of panic disorder, phobic disorders, and generalized anxiety disorder as compared to alcohol-dependent nonattempters.[56]

Psychosis has also been identified in some investigations as an independent risk factor for suicide, and psychological autopsy studies have suggested that nearly 20% of suicide victims may be psychotic at the time of suicide.[57] Lifetime comorbid substance abuse has been reported to occur in as many as 40% of individuals with schizophrenia and may show a significant association with suicidal ideation independent of positive, negative, or depressive symptoms.[58,59] Multifactorial models of suicide completions have observed that psychosis in itself may not differentiate suicide attempters from nonattempters,[60] suggesting that psychosis—like depression—may contribute to the diathesis upon which additional stressors and clinical factors may precipitate suicidal behavior.

Further insights regarding the relationship between suicidality and alcoholism across psychiatric diagnoses may derive from considering in greater detail the family-genetic and neuropharmacologic mechanisms that appear common to both clinical situations.

## HEREDITARY LINKS

A number of contemporary studies indicate that suicidal behavior may cluster within certain families.[61] The potential role of drug abuse (particularly alcohol) in mediating this risk is suggested by several reports. Family histories of alcohol[62,63] or other drug dependence[64] have been associated with an increased likelihood of suicidal behavior among adults and adolescents who present for psychiatric treatment. Alcohol-dependent patients who have ever made a suicide attempt appear significantly more likely than those without prior suicide attempts to have a family history of completed suicide.[65] Among bipolar patients, attempted suicide in both probands and relatives may be especially likely when alcohol dependence is also present.[66] These findings suggest that genetics may provide a diathesis for suicidality both directly and indirectly through correlated vulnerabilities.

As a complex behavioral phenomenon, it would seem highly unlikely that suicide arises as the result of variation at any individual genetic locus. However, the collective impact of multiple genes, each of small effect, may together confer a heightened susceptibility to suicide-related behaviors. For example, concordance between monozygotic twin pairs has been demonstrated in temperamental or behavioral features such as irritability or aggression,[67] suggesting the possibility that psychological as well as affective and other biological factors might constitute the essence of a genetic predisposition toward behaviors linked to suicidality.[61]

Some authors have noted that, at least in the case of bipolar disorder, clinical phenomena such as suicidal behavior and alcoholism may each contribute to the designation of illness subtypes[26]; as such, alcohol comorbidity and suicidality may together represent distinct subgroupings of bipolar illness that constitute bona fide phenotypes.[68] Much the same way some clinicians regard lithium responsivity as an external marker for refining more genetically homogeneous subgroups,[69] bipolar disorder with comorbid alcoholism might also represent an illness subclassification for which genetic contributors may be especially salient. To the extent that alcohol dependence and suicide risk share a heightened co-occurrence across generations of bipolar pedigrees,[66] the exploration of other possible phenotypes linked to alcoholism may shed further light both on the nosology of bipolar subtypes and on the definition of bipolar groups at highest suicide risk.

## NEUROTRANSMITTER SYSTEMS IN ALCOHOLISM AND SUICIDE

### Serotonin Dysfunction

As noted earlier, serotonergic dysfunction has been thought to play a role in the pathophysiologies of impulsivity, aggression, alcohol dependence, suicide, and affective disorders and may suggest a common neurochemical connection among these factors.[70] In alcohol-abuse patients, functional neuroimaging studies of brain stem serotonin function indicate low levels of serotonin transporter (5-HTT) activity or brain stem serotonin blood flow and glucose metabolism.[53,71] Decreased 5-HTT binding has also been associated with alcohol intoxication and aggression.[72] In addition, impulsive, violent alcoholics have been observed to show low cerebrospinal fluid levels of the serotonin metabolite 5-HIAA.[73–75] Similarly, there is some evidence that suicide completers have locally reduced 5-HTT binding in the ventral prefrontal cortex as compared to nonsuicides.[76]

Molecular genetic studies have begun to identify the impact of specific aspects of the serotonin system on suicidality, impulsivity, and substance abuse. For example, the presence of a low activity polymorphic variant of the promoter region for the serotonin transporter has been linked with alcoholics as compared with controls.[77] Individuals who are polymorphic for this short variant of the 5-HTT promoter may also have a heightened risk for suicide attempts, particularly attempts that were repetitive and severe[78] or violent.[79] Low turnover of tryptophan hydroxylase (TPH), the rate-limiting enzyme in the synthesis of serotonin, has been associated with poor impulse control, and a polymorphic variant of the TPH gene has been associated with suicidality.[80] These findings suggest that the serotonin system may play an important role in the modulation of many factors related to suicidality. Lower levels of serotonin may be associated with alcoholism, impulsivity, and suicidality. However, possible causal links between these phenomena have not, as yet, been determined, nor have the implications of such a complex interconnection of factors been fully described.

### Other Neurotransmitter Dysfunction

Possible noradrenergic dysfunction among alcoholics and among suicidal patients has been preliminarily reported. Abnormal, age-inappropriate loss of locus ceruleus neurons has been described in both suicide victims and alcoholics as compared to nonpsychiatric controls,[81] although cell loss appears especially marked in alcoholic suicide victims.[81] Impulsivity and sensation-seeking both appear associated with increased noradrenergic function, but links to aggression and suicide are less clear.[82,83]

A direct contribution of dopamine dysfunction to suicidality and/or alcoholism has not been demonstrated, although dysregulation of the dopamine reward pathway could play a role in the genesis of high-risk behaviors that ultimately may lead to increased risk for dangerousness or self-harm. Diminished dopaminergic function, as evidenced by blunted growth hormone response to apomorphine, may also be a residual marker of alcohol dependence.[84]

Excitatory neurotransmitters (e.g., glutamate and aspartate) and inhibitory neurotransmitters (e.g., γ-amino-butyric acid [GABA]) are thought to play a central role in mood stabilization and impulsivity. Studies in alcoholism have provisionally reported increased frequencies of some GABA-system polymorphic variants among alcohol-dependent subjects versus controls.[85]

While these initial observations suggest that several neurotransmitter systems may contribute to the modulation of affect, impulsivity, and substance misuse, direct associations with suicidal behavior or alcoholism remain subject to speculation. Their clinical relevance bears on issues related to neuropharmacologic treatment decisions, particularly with respect to nonserotonergic drugs that may help to diminish the risk for impulsivity, aggression, and suicide.

### Implications for Pharmacotherapy

From the foregoing, decisions about differential pharmacotherapy for clinical conditions involving alcohol or drug dependence and suicide risk may follow particular pathways. The role of serotonergic antidepressants has been shown to dramatically reduce suicidal behavior among depressed patients.[86] At the same time, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine may help to diminish alcohol symptoms as well as depressive features in depressed alcoholics with suicidality.[87] The anti-impulsivity and antiaggression properties attributed to SSRIs[88,89] may suggest a role for their use in some depressed patients for whom both suicidality and alcoholism may be high risks.

For individuals with bipolar spectrum disorders, the use of antidepressants unopposed by mood stabilizers diverges from current best-practice recommendations in light of their risk for destabilization of mood.[90,91] While the anti-suicide property of lithium has been well demonstrated,[92] it is unknown whether this effect becomes attenuated in the presence of significant alcohol or other drug abuse in bipolar disorder. Preliminary studies have suggested that divalproex may also confer protection against suicidality that may be at least comparable to that of lithium.[93] Because anticonvulsant mood stabilizers such as divalproex may show better antimanic efficacy than lithium in the presence of comorbid alcohol or other drug abuse/dependence in bipolar illness,[94] anticonvulsant mood stabilizers may hold a clinical advantage for instances in which suicide risk may be deemed higher by virtue of dysphoric manias[95,96] and/or substance misuse. Further controlled treatment studies are needed to affirm these provisional observations.

The role of atypical antipsychotic agents as mood stabilizers has begun to receive growing attention.[97,98] Possible anti-suicide effects have been associated with clozapine,[99] and initial open studies support the use of atypical neuroleptics for the treatment of schizophrenic or bipolar patients with comorbid substance abuse.[100–102]

## PSYCHOSOCIAL DIMENSIONS: LIFE EVENTS AND INTERPERSONAL LOSS

Several studies have reported that adverse life events or interpersonal losses may be particularly likely to trigger suicidal behaviors among individuals with alcohol abuse or dependence,[103–107] especially among younger alcoholics who attempt suicide.[108,109] Adolescent suicide victims with alcohol abuse/dependence also may be more vulnerable to interpersonal separations and other psychosocial stresses as compared to nonalcoholic depressed adolescent suicide victims.[110,111] Social isolation and alcohol misuse have

also been linked with suicide among middle-aged men.[105] These findings suggest that the stabilization of support networks and stress reduction interventions may be an important consideration to reduce suicide risk for affectively ill substance-abusing patients.

### Implications for Psychotherapy

Findings noted above regarding the impact of interpersonal loss, as well as issues related to impulse control and sensation-seeking, bear on the psychotherapeutic approach to substance-abuse patients with particular attention to suicide risk. Targeted psychotherapy approaches that address the emotional, interpersonal, cognitive, and behavioral aspects most relevant to alcoholism and suicide risk have not been fully developed. Nevertheless, components of several current distinct psychotherapy approaches bear on clinical issues in this area, particularly in regard to the regulation of affect, impulsivity, aggression, and behavioral responses to interpersonal loss.

Cognitive-behavioral therapy has often been used to treat depressive disorders and suicidality.[112] The focus of the treatment involves helping the patient understand how feelings of depression and hopelessness are related to urges for self-destructive behavior and how stressors and other life difficulties impact these feelings and behaviors. Patients are also taught specific stress reduction and problem-solving skills and are helped to strengthen their support networks.

Dialectical behavior therapy, a modification of cognitive-behavioral treatment,[113] was developed for the specific treatment of borderline personality disorder. Dialectical behavior therapy focuses on reducing suicidal behavior, substance abuse, and treatment dropout while enhancing interpersonal functioning and overall adjustment. Standard dialectical behavior therapy consists of 4 basic modes of treatment aimed to enhance motivation, foster treatment compliance, decrease life-threatening behavior, provide validation of emotional responses, and enhance the acquisition and strengthening of skills through a variety of techniques. Patients are asked to keep a diary card in which they record relevant behaviors of the preceding week (including suicidal thoughts, behaviors, and significant interpersonal interactions and mood). Therapy focuses on understanding repeated dysfunctional chains of behavior and cognitions that lead to self-destructive actions. Skills training is then used to identify and implement alternative adaptive coping strategies. A key aspect of this approach is the development of "mindfulness," or awareness in the moment.

The acquisition of self-monitoring skills in dialectical behavior therapy bears similarity to the Social Rhythm Metric technique developed by Frank and colleagues[114] for the treatment of bipolar disorder. By recording daily the interpersonal and environmental factors that affect mood states, patients develop an enhanced capacity to recognize causal links in their behavior and ultimately generate alternative coping strategies and behaviors. It is likely that such daily charting techniques, with subsequent review and exploration in the context of a skills-training psychotherapy, may be of value in a broader range of psychiatric conditions involving high potential impulsivity, aggression, and/or self-harm.

A modification of dialectical behavior therapy has been developed for the treatment of substance abuse in individuals with borderline personality disorder.[115] In this model, the core dialectical behavior therapy approach was maintained with expanded use of a diary card to incorporate substance use, along with cognitive-behavioral strategies for substance abuse relapse prevention. There is an emphasis on abstinence coupled with the therapist's acceptance and nonjudgmental response to relapse.

Other authors have emphasized the role of family factors in treating and maintaining positive long-term outcomes in a variety of chronic psychiatric disorders. A number of lines of evidence suggest that problematic family relationships and communication styles may contribute importantly to relapse and diminished psychosocial functioning in schizophrenia and bipolar disorder.[116] In all likelihood, impulsive, self-destructive behaviors that heighten suicide risk may generate similar types of negative family attitudes, behaviors, and communication styles in a range of conditions (e.g., chronic alcoholism, bipolar disorder, schizophrenia). Family-focused psychotherapies designed to reduce negative expressed emotion may be of value in a broader range of psychiatric conditions to alleviate interpersonal discord and enhance the support network of patients at risk for suicide.

## CONCLUSION

In summary, substance use disorders frequently complicate the course of bipolar and unipolar affective disorders and may confer an increased susceptibility to treatment resistance, psychosocial impairment, extended morbidity, and poor functional outcome. The coalescence of substance abuse with depression, combined with impaired regulation of impulsivity and hostility-aggression, may contribute to an elevated risk for suicide attempts and completions in vulnerable populations. A range of pharmacotherapy options and specific psychotherapies has begun to emerge targeting these features, offering new opportunities for integrative treatment. Efforts to identify coexistent substance misuse and initiate early interventions may substantially help to reduce the risk of excess morbidity, complex psychopathology, and consequent suicide risk that might otherwise arise.

*Drug names:* clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, clozapine and divalproex sodium are not approved by the U.S. Food and Drug Administration for the

treatment of suicide prevention, and fluoxetine is not approved for symptoms related to alcoholism.

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