

Suicidal behavior: Risk and protective factors.

Conducta suicida: factores de riesgo y protección.

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RESUMEN

Aproximadamente un millón de personas mueren cada año debido a suicidio. Poblaciones de alto riesgo de suicidio incluyen militares, adolescentes, ancianos, y pacientes con enfermedades crónicas mentales o médicas. Más de 90% de suicidios ocurren en personas que sufren de alguna enfermedad psiquiátrica. Prácticamente todas las enfermedades psiquiátricas aumentan el riesgo de suicidio, sin embargo la depresión está asociada a más de la mitad de los casos de suicidio. Hallazgos clínicos, epidemiológicos, autopsias psicológicas, en genética, neuroquímica, y neuroimágenes han incrementado significativamente nuestro conocimiento sobre el suicidio. El factor biológico más consistentemente asociado a suicidio es la disminución en la neurotransmisión serotoninérgica, particularmente en la zona ventral de la corteza prefrontal. Déficits en la función de la zona ventral de la corteza prefrontal están asociadas a impulsividad y a subóptima toma de decisiones. Las otras aminas biogénicas y el eje hipotalámico-pituitaria-adrenal (HPA) también parecen estar involucrados en la proclividad al suicidio. Los factores cognitivos y psicológicos involucrados en suicidio incluyen desesperanza, dolor psicológico o mental, impulsividad, pobre habilidad para solucionar problemas, perfeccionismo y pobre autoestima. Los factores de protección contra el suicidio más estudiados son: acceso y utilización de servicios de salud, conexión significativa con familia y la comunidad, y creencias religiosas y culturales que se oponen al suicidio. A pesar de la abundancia de estudios realizados, aun carecemos de factores fidedignos de predicción de riesgo de suicidio y debemos basarnos en el reporte del individuo y emplear el juicio clínico. Por eso continúa siendo tremendamente difícil predecir quién morirá por suicidio. Dada esta dramática carencia, continúa siendo una alta prioridad el desarrollo de estrategias de detección y prevención de suicidio, especialmente en poblaciones de alto riesgo.

PALABRAS CLAVE: Suicidio, depresión, neuroimágenes, genética, neurotransmisores.

SUMMARY

Approximately one million people worldwide die from suicide every year. High risk populations include active military, adolescents, the elderly and the chronically mentally and physically ill. More than 90% of suicides are in individuals with a diagnosable psychiatric disorder. Practically all of the major psychiatric disorders are associated with an increased risk for suicide, but depression accounts for more than half of the cases. Clinical observation, epidemiological studies, psychological autopsies, genetics, neurochemistry and brain imaging have yielded important findings that have contributed to our increased understanding of suicide. The strongest biological factor associated with suicide is decreased serotonergic neurotransmission, particularly in the ventral prefrontal cortex. Deficits in ventromedial prefrontal cortex function are associated with impulsivity and impaired decision making. Additionally, a burgeoning body of evidence supports a central role of other biogenic amines and the hypothalamic-pituitary-adrenal (HPA) axis in suicide diathesis. Cognitive and psychological factors for high suicide risk include hopelessness, psychological or mental pain, impulsivity, poor problem solving skills, perfectionism, and self-dislike. Strong protective factors against suicide include access and utilization of healthcare resources, connectedness to family and community, and culture and religious beliefs that discourage suicide. Despite this plethora of research,

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we still lack reliable predictors of suicide risk and must rely heavily upon self-report and clinical judgment. Thus, it remains singularly difficult to predict who is going to commit suicide. Therefore, there is an urgent unmet need to develop effective early detection methods and treatments, particularly for high-risk populations.

KEYWORDS: Suicide, depression, decision making, brain imaging, genetics, neurotransmitters.

INTRODUCTION

Each year approximately one million people worldwide die by suicide (1). In the US, suicide ranked the tenth highest among causes of death in 2010, claiming more than 38,000 lives (2). Estimates of the ratio of suicide attempts to completion range from 10:1 to 20:1. Moreover, more than 13% of the general US population experience suicidal ideation at some point in their lives. Approximately, 4% elaborate suicidal plans and a slightly higher number attempts suicide at some point (3,4). These statistics are believed to be underestimates, because a considerable number of suicides are likely underreported or misclassified as single person car accidents, accidental poisonings, etc. Of paramount importance to preventive efforts is the ability to predict who is at immediate risk for suicide, an assessment that currently is mostly done empirically. A critical element in this process of determining the likelihood of suicide is the evaluation of risk and protective factors, including behaviors. Identified risk factors for suicide can be classified as demographic, clinical, biological, psychological, cognitive, and family/social variables. Here, we discuss the suicide-associated risk and protective factors considered during the clinical decision-making processes of determining suicide risk and choosing therapeutic interventions.

Risk behaviors

Certain risk behaviors are the product of multiple factors and are known to precede suicide. The behaviors most associated with suicide are substance abuse (primarily alcohol), violence, impulsivity, self-harm, and irregular sleep.

Substance Abuse

Most studies that attempt to determine the correlation between chronic substance abuse and suicide risk have focused on alcohol. Current evidence points to a causal role of chronic alcohol use disorders in suicide, with odds ratios for ideation ranging from 2.0–2.5, and for attempts at 2.6–3.7 (5). Prior acute intoxication is not uncommon in completed suicides (6), and up to one-third of suicide completers had elevated blood alcohol levels (7,8). Powell et al.

(9) estimated an odds ratio of 6.2 (CI 3.2–11.8) for suicidal attempts associated with alcohol use three hours prior; and Borges and Rosovsky (10) reported a positive correlation between the amount of alcohol consumed and suicide attempts. Increased acute risk for suicide is also associated with cannabis-, inhalant-, and cocaine-intoxication (11). Use of multiple substances may escalate up to threefold the likelihood of suicide. Individuals with opioid use disorders and mixed intravenous drug use have an even higher risk for suicide than those with alcohol use disorders (12).

Violence

Violence directed toward self and/or others—even just witnessing violence—significantly increase the risk for suicide. Exposure to violence as a suicide risk factor can be represented on a continuum from predisposing (e.g., childhood trauma) to proximate (e.g., rape or self-injury) (13). Both suicidal and non-suicidal self-injury have been shown to increase the risk of suicide in different populations. History of suicidal attempts is considered one of the strongest predictors for suicide completion, although suicide risk declines over time. Prospective studies have shown that 4–13% of suicide attempters eventually complete suicide (14–18). On the other hand, non-suicidal self-injury, such as cutting and burning, also increases the risk of suicide at least twofold, particularly in populations suffering from psychiatric disorders (19).

History of childhood trauma increases two- to fivefold the risk of suicidal behavior (20). Childhood abuse can greatly disturb the development of the victim's self and of his/her interpersonal relationships, predisposing the individual to psychopathology and dysfunctional personality traits, which in turn increase the risk of suicide (21,22). Additionally, adolescent victims of dating violence are at higher risk for planning and attempting suicide (23). Frequent fighting among high school students is associated with a sixfold increase in risk of suicide (24).

The association between violence and suicide is also described in adults. Assaultive behavior and impulsivity are associated with suicidal ideation in

veterans (25). The Institute of Medicine reported in 2006, overwhelming evidence of an association between deployment to a war zone and elevation of suicide risk subsequent to that deployment (26). Exposure to combat can cause psychological and physical consequences such as post-traumatic stress disorder (PTSD), traumatic brain injury, chronic pain or physical impairments, which may explain the significantly higher suicide rates reported in veterans compared with the general population (27-29). For instance, 20% of the US veterans of the Iraq war require treatment for mental illness (30).

Risk factors (Table 1)

Demographic risk factors

Suicide is unevenly distributed among the population. For instance, despite suicidal ideation occurring more frequently among females, males commit suicide four times more frequently than females. The most common method for men in the US is use of firearms and for women is by poison, although gender-specificity of lethal method may vary across countries. Suicide is the third leading cause of death in people younger than 25 years worldwide (31). In several countries, ethnic or cultural minorities are at much greater risk for suicide. Young American Indians and Alaska natives commit suicide 2.5 times more frequently than the general population. The suicide rate among Hispanic female adolescents in the US is almost twice that of adolescent females in other ethnic groups. Such disparities in suicide risk among minorities may be associated with less access to healthcare services.

Interestingly, suicide rates by season have been reported to peak in the spring in several countries, regardless of geographic location. This seasonal association seems to be stronger for suicide by violent methods and greater in rural areas (for review see (32)). This phenomenon might be related to intensity of seasonal activities such as agricultural work in the rural areas, or ambient pollen concentration (33). Although the adolescent suicide rate is lower than the rate in the general population, it receives strong attention from the public and the media. Approximately 3% of adolescents worldwide make medically serious suicide attempts. After puberty, suicide rates increase until they stabilize in young adulthood. The 2003 Youth Risk Behavior Surveillance System (YBRSS) reported that 17% of US high school students seriously considered suicide, 16.9% had a plan, and 8.5%

had attempted suicide previously (34). Risk factors associated with suicide in adolescents are very similar to those in the general population and include: prior attempts, depressed mood, anger, impulsive aggressive behavior, substance abuse, hopelessness, problem-solving deficits, low family cohesion, high conflict, unsatisfactory parent-adolescent relationships, and physical or sexual abuse (35). Interpersonal factors associated with adolescent suicide include poor family and friends support, social isolation, peer victimization, and emotional neglect (36).

Worldwide, suicide is more common in the elderly than in any other age group (37). The highest suicide rate in the US is among men over 75; 36 per 100,000, about three times higher than in the general population (2). Non-Hispanic white men, age 85 and older, are the most likely demographic group in the US to die by suicide, with a rate more than fourfold higher than the general population (38). Suicide attempts in late life are more lethal than in mid-life (39), with up to one-half ending in death (40). In developed countries, elderly suicide is strongly linked to psychiatric illness, mainly depression and alcohol use disorders (41). Cognitive rigidity and obsessional traits increase suicide risk (42, 43), probably because they undermine the ability to make substantial adaptations often needed to cope with the challenges of aging. Physical illness, bereavement, and loss of independence are also important factors (44, 45).

Biological risk factors

There is a clear transmission of suicide within families (46). Much of the family history of suicidal behavior may be explained by the presence of mental illness (47). However, family, twin, and adoption studies have provided evidence for familial transmission of suicidal behavior even after controlling for mood and psychotic disorders (48). The strongest biological finding in suicide research is the association with reduced serotonergic neurotransmission. However, other monoamines and neuropeptides have also been intensely studied. For instance, the strongest predictors for completion of suicide in patients with mood disorders are biological (low levels of serotonin metabolites in cerebrospinal fluid [CSF], blunted serotonergic response to fenfluramine challenge, hyperactivity of the HPA axis, and low cholesterol) (49,50). Supporting evidence has been accrued from examination of CSF, postmortem brain tissue, genetics, and brain imaging (Table 1).

Table 1. Risk factors for suicide***Predisposing factors****Biological factors*

Serotonergic dysfunction
 Noradrenergic dysfunction
 Dopaminergic dysfunction
 Hypothalamic-pituitary-adrenal axis hyperactivity
 Chronic hypoxia
 Infections (i.e., HIV, *Toxoplasma gondii*)

Psychological factors

Aggression, hostility, or impulsivity tendencies
 Suicidal thoughts
 Presence of hopelessness
 Low self-esteem, feelings of failure
 Lack of religious or moral constraints against suicide

Clinical factors

Severe depressive symptoms
 Being in the first 3 months after the onset of the depressive episode
 Early onset of depression, being younger at first hospitalization, more previous hospitalizations
 Axis I comorbidities (e.g., mood, anxiety, psychotic, and substance use disorders)
 Comorbid personality disorders or traits (e.g., borderline, antisocial)
 Chronic medical illness
 Past personal history of suicide attempt
 Past history of taking precautions against being discovered after an attempt
 Presence of a family history of suicide

Demographic/social factors

Demographic factors (gender, race, age)
 Social isolation
 Not living with a child younger than 18
 Childhood history of physical or sexual abuse
 Parental loss through death before the age of 11
 Corporal punishment in adolescence
 Family history of child maltreatment

Triggering factors

Recent bereavement
 Social, financial, or family crisis or loss (negative life events)
 Unemployment or financial problems
 Access to means with greater lethality
 Contagion or recent exposure to suicide
 Acute substance intoxication
 Being recently widowed/separated/divorced

Serotonin (5-HT)

Numerous studies over the past three decades have linked functional abnormalities in the central serotonergic system with the pathogenesis of suicidal behavior (51). Several lines of evidence have revealed reduced serotonergic activity in individuals who have history of suicidal behavior, including reduced CSF concentrations of the major serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in suicide attempters with diagnoses of depression, schizophrenia, and/or personality disorders (52-54). Decreased CSF 5-HIAA concentrations also predict future suicide attempts and completions (55,56). Suicidal patients also exhibit a blunted prolactin

response to fenfluramine challenge (used as a tool to assess serotonin neurotransmission in vivo by inducing release of serotonin from synaptic vesicles) (57,58). The lethality of suicidal behavior is also associated with lower plasma serotonin concentrations (59) and reduction in serotonin binding density (60, 61). Postmortem studies of suicide attempters have shown decreased presynaptic 5-HT₂ receptor binding in ventromedial prefrontal cortex (VMPFC) (60). Polymorphisms in different genes of the serotonin system have been associated with suicide including serotonin, serotonin transporter (5-HTTLPR), serotonin receptors, and tryptophan hydroxylase (TPH2) (62,63). Many of these findings led to the view that serotonergic input to the VMPFC may modulate

vulnerability to suicide behavior, independent of psychiatric diagnosis (61). Lastly, low serotonergic tone has also been associated with cognitive factors predisposing to suicide (64,65).

Noradrenergic and dopaminergic systems

Striatal dopamine (DA) activity is directly associated with impulsivity (66). Norepinephrine (NE) and DA systems are much less explored in suicide than serotonin. Overall, decreased NE neurotransmission is associated with completed suicide and suicide attempts across different psychiatric conditions (67, 68). Decreased DA metabolites are found in the CSF of suicide attempters suffering from depression (54). Reduced DA transporter and increased DA_{2/3} receptor binding in the amygdala are described in depressed patients who committed suicide (69). Corresponding up-regulation in the density of the α_{2A} adrenergic receptor binding sites was found in the brains of depressed suicide victims. Moreover, patients with a history of suicidal behavior exhibited lower growth hormone response to apomorphine (70).

Also, abnormalities in the enzymes regulating the synthesis and catabolism of biogenic amines have been implicated in suicide. Monoamine oxidase A (MAOA) is a mitochondrial membrane enzyme that plays a key role in the metabolism of biogenic amines, including NE, DA and serotonin. High MAOA activity, resulting in reduced levels of these neurotransmitters, is found in mood disorders and aggressive behavior. Low platelet MAOA activity has been connected with personality traits such as impulsivity, sensation seeking, and aggression. A functional polymorphism of the MAOA gene has been linked to violent suicide methods (71). Catechol-O-methyltransferase (COMT), the major DA-degrading enzyme in the PFC, is of potential interest as a candidate gene for suicidal behavior. Modestly significant associations between the COMT and tyrosine hydroxylase polymorphisms and suicide have been reported (62,72). The DA receptor variant DRD2 has been similarly linked to suicide attempts (62). A single nucleotide polymorphism (SNP) within a coding region of the α_{2A} -adrenergic receptor gene (ADRA2A) may confer susceptibility to suicide, but this finding has not been replicated (63).

Other neurotransmitter systems

A vast body of literature supports increased HPA axis activity as a major risk factor for suicide (73). Increases in CSF concentrations of corticotropin-

releasing factor (CRF), reductions in CRF₁ receptor prefrontal binding sites, and reductions in CRF₁ receptor mRNA expression (74) are found in suicide victims. Further, a positive dexamethasone suppression test (defined as nonsuppression of cortisol) has consistently been associated with an increased risk for suicide (75). Variation of the CRF₂ receptor gene has been correlated with the severity of suicide attempts in schizophrenia (76).

Brain-derived neurotrophic factor (BDNF), the most prevalent neurotrophin in the brain, is reduced in plasma of schizophrenic and depressed suicidal patients. Conflicting findings regarding the implications of functional BDNF polymorphisms (i.e., BDNF Val66Met) and suicide remain.

Brain imaging studies

Both structural and functional studies have explored the underlying neural mechanisms of suicidal behavior. Deep white matter lesions particularly in the frontal cortex, reported in patients with mood disorders, have been associated with suicidal ideation (77). Depressed individuals who attempt suicide using a highly lethal method show decreased metabolic activity in the ventral PFC (78). Individuals who had a recent suicide attempt exhibited bilateral prefrontal hypoperfusion and increased left-sided thalamic neural activity (79). Amen, et al. (80) showed that patients who subsequently committed suicide displayed hypoperfusion of the ventrolateral prefrontal cortex (VLPFC) and nucleus accumbens.

Most cognitive assessments and brain imaging reports in individuals with suicidal behavior reflect prefrontal function abnormalities. Decreased orbitofrontal response to fenfluramine challenge has been associated with suicide. Asymptomatic subjects with a history of depression and suicide attempts show abnormal PFC processing of facial emotions (81), and decreased bilateral dorsolateral prefrontal cortex (DLPFC) activity during recall of suicide episodes (82). Poor performance during executive function tests is associated with decreased orbitofrontal activation in euthymic individuals with history of suicide attempts (83). Thus, abnormal PFC function seems to be a trait associated with suicidal behavior, which could represent the neurobiological correlate of impulsivity and faulty decision making.

Other recently identified biological risk factors for suicide (although mechanisms are unclear) include

infection with *Toxoplasma gondii* (84,85), human immunodeficiency virus infection (86), chronic sleep deprivation, and nocturnal sleep disturbances (87, 88). Chronic exposure to high altitudes has also been linked to suicide (89), likely mediated by depression severity (90). Another environmental factor, transient increase in particulate matter, was recently described to increase suicide risk, especially for individuals with preexisting cardiovascular disease (91).

Cognitive and psychological risk factors

In addition to a biological predisposition, suicide has been linked to personality characteristics, reactivity to stressful events, psychological states (i.e., hopelessness, anhedonia, impulsiveness, psychological pain, low self-esteem, poor anger management, or dysmorphic body image), impaired cognition, and flawed decision making. Many studies have consistently described three cognitive characteristics that distinguish depressed suicidal from depressed non-suicidal individuals: 1) attentional bias to particular life events reflecting signals of defeat (“loser” status), 2) sense of insufficient capacity to solve problems, and 3) absence of anticipation of problems, leading to hopelessness (77). It has been proposed that decreased serotonergic input to the PFC may mediate the cognitive propensity to suicidal behavior (61,92).

Cognitively, suicide is associated with impulsivity and executive function impairments. In a seminal study, Keilp, et al. (93) demonstrated substantial cognitive and executive function impairments in individuals who attempted suicide with highly lethal means. Euthymic patients with history of suicide attempts showed significant deficits in executive function suggestive of generalized PFC dysfunction (impaired visuospatial conceptualization, inhibition, and visual attention or reading fluency) (94). Impairments in executive function are reported in high-lethality suicide attempts independent of deficits associated with depression alone (93). Moreover, executive function deficits are more specific to suicidal behavior than to any given psychiatric diagnosis because this observation holds true for suicidal patients with depression, bipolar disorder, and even temporal lobe epilepsy (93-98).

Not surprisingly, poorer problem-solving abilities are also found in suicide attempters with different psychiatric disorders (99). This performance is worse in carriers of the short allele of the serotonin transporter gene (100). There is evidence that at least a subgroup of suicide attempters have poor

decision-making skills as evidenced by inability to delay gratification (101,102), and poor risk-sensitive decision making (103,104). A considerable subgroup of suicide attempters experience severe suicidal ideation in a very acute and transient fashion. For instance, 40% of suicide attempts were preceded by five minutes or less of planning (105). Impulsive suicide is traditionally associated with younger, female subjects, alcohol ingestion and availability of lethal means. Both impulsivity and inability to delay gratification are associated with hyposerotonergic states, underscoring the integration of biological and cognitive deficits in suicide. Impairments in decision making and executive function may lead susceptible individuals to get involved in dire interpersonal situations and to manage them poorly. In individuals with other risks factors, this could lead to suicidal ideation and behavior. We have previously reported transient impulsive choice abnormalities in a subset of suicide attempters, as well as in depressed patients with severe suicidal ideation (101).

Hopelessness is thought to reflect a cognitive style consisting of negative attributions about the future and about one’s helplessness to improve prospects for the future. Hopelessness is considered to be the strongest risk factor for suicide, increasing the risk more than sevenfold, and it is considered to mediate the relationship between depression and suicidal intent (106). Hopelessness and anhedonia have been described as predictors for suicide in prospective studies in patients with a variety of psychiatric diagnoses (107-111). Furthermore, hopelessness mediates the association between childhood sexual abuse and suicide attempts (112). Hopelessness is also found to predict development of suicidal ideation (113).

Psychological pain, in the form of psychic, mental, or emotional pain, depressive turmoil, or “psychache,” has been posited to be central for the completion of suicide. It is defined as “the introspective experience of negative emotions such as dread, despair, grief, shame, guilt, frustrated love, loneliness and loss” (114). It is thought that unbearable psychological pain triggers a transitory fragmentation of the self, overwhelming a susceptible individual who chooses an impulsive escapist strategy to terminate his/her own life while disregarding all future consequences (115). Intense psychological pain has previously been reported in recent suicide attempters and in depressed patients with severe suicidal ideation (101,116).

Social risk factors

The causative role of social factors in suicidal behavior is long established, and there is compelling evidence that they may contribute at least as much as genetic factors. Limited or lack of social support is recognized as a pervasive predisposing risk factor for suicide. Low socioeconomic status has been linked to suicidal behavior (117). Low levels of parental education are associated with higher adolescent suicidal risk. Additionally, low quality of life, unemployment, social deprivation, and social fragmentation independently increase the risk for suicide behavior (118). Children whose families move around frequently are more likely to make suicide attempts during adolescence, in a frequency-dependent fashion (119).

Family environment has been found consistently to be a predictor of suicidal behavior among adolescents, but can also represent stressful stimuli, chronic or episodic, that contributes to suicide risk in adulthood. The relevant family-related risk factors are parental psychopathology, family history of suicidal behavior, adoption, family discord, loss of a parent to death or divorce, poor quality of the parent-child relationship, and maltreatment (13,120,121). Additionally, same-sex sexual orientation is an independent risk factor for attempted suicide. In particular, family rejection after “coming out” increases the likelihood of attempting suicide eightfold (122).

Adverse experiences during adult life, including financial, legal, romantic or labor issues are associated with suicide. Interpersonal difficulties within family and marital contexts have also been clearly linked with suicidal behavior (123,124).

There is strong and convergent evidence that suicidal behavior in families is related to both genetic and environmental components. Social learning may be an important factor in both familial and non-familial transmission of suicidal behaviors. The concept of “suicide contagion” is based on the infectious disease model and assumes that suicidal behavior by one person may facilitate the occurrence of subsequent, similar behaviors by others (125). Clustering of suicide behavior is explained by imitation. Studies conducted primarily in adolescents revealed that up to 5% of all suicides may be the result of suicide clustering and that exposure to suicide behaviors in family and friends was predictive of suicide behavior and ideation (125). A large body of research in the last 10 years clearly

demonstrates that extensive newspaper and television coverage of suicide is associated with a significant increase in the rate of suicide (126). The magnitude of the increase is proportional to the amount, duration, and prominence of the media coverage. For instance, intense media coverage of the suicide of either an entertainment or political celebrity can increase 14 times the likelihood of a copycat than those suicides that are not covered (127). Today, the increasing popularity of the Internet and social media as a source of information and facilitation of suicide behavior is drawing increasing attention. Further research and regulation is warranted.

Regarding relationships with peers as a risk factor in suicide, bullying stands out as a robust predictor. Both bullying of others and being a victim of bullying during childhood increase the odds of suicide attempt (128). There is some evidence that conduct disorder might mediate this relationship (129). There seems to be gender specificity, with boys’ risk increased by bullying and girls’ risk elevated by victimization (128, 129).

Most theoretical models of suicidal behavior propose a diathesis-stress model in which the psychiatric, psychological, and biologic factors as described above predispose a person to suicidal ideation, while stressful life events interact with those factors to further increase risk of suicidal behavior. Consistent with such a model, suicidal behaviors often are preceded by stressful events, mostly of interpersonal nature, i.e., family or romantic conflicts, or school, work, or legal difficulties (123,124,130). The experience of persistent stress also may explain higher rates of suicidal behavior by people in certain occupations, such as physicians, military personnel, and police officers. Other highly stressful experiences such as intractable pain, pruritus, chronic or terminal illness have also been associated with suicide (41).

Access to lethal means such as firearms and high doses of medication (131) is an important risk factor for suicide, a condition that is susceptible to intervention. After some initial controversy related to confounding factors, the Behavioral Risk Factor Surveillance System (BRFSS) provided conclusive evidence about firearms and suicide. After controlling for psychological distress, rates of poverty, urbanization, unemployment, and drug and alcohol dependence and abuse, the analysis showed that household gun ownership increases the risk of firearm suicide more than threefold, but did not modify the rates of suicide

by other means (132). In particular, the presence of firearms in a home, regardless of how the weapons are stored, increases the risk of suicide not only to the gun owner but also to other household members. This increased risk is greater for young people, and greatest for those without known psychopathology (133). Possible explanations for this increased risk may lay in the abrupt and transient nature of suicidal ideation, as evidenced by the short period of time between onset of severe suicidal ideation and the actual attempt, and the relatively short duration of severe ideation with lethal intent (105,134,135).

Clinical risk factors

Psychiatric disorders

In suicide cases in which psychological postmortems are conducted, more than 90% are associated with a diagnosable psychiatric disorder. Nearly all psychiatric disorders increase the risk for suicide (136). Data related to the most significant factors are described below.

Depression

Affective disorders are the most common psychiatric disorders associated with suicide, followed by substance abuse (especially alcohol) and schizophrenia. The mortality risk for suicide associated with depression is approximately 20 times the general population risk, especially in the first weeks after inpatient discharge (137). More than half of all people who die by suicide fulfill criteria for a current depressive disorder (138). On the other hand, about 4% of depressed individuals die by suicide, and the risk is greatest in males and in those who have needed psychiatric hospitalization, especially for suicidality (108). Clinical predictors of suicide in patients with major depressive disorder (MDD) include a history of attempted suicide, high levels of hopelessness, presence of comorbidity, and high ratings of suicidal tendencies (108).

One of the most effective treatments for depression is antidepressant pharmacotherapy. However, a raging controversy exists about a small but significant increased risk of suicide after initiation of antidepressant treatment, particularly in young individuals (139). This issue has led to a FDA black box warning on antidepressants about an increased risk of suicidal thinking and behaviors in children, adolescents, and young adults (18–24 years old) during the first few weeks of treatment. A dramatic

reduction in youth antidepressant prescribing occurred after the launch of this warning. On the other hand, large observational studies show that risk of suicide declines after treatment is started (140) and that geographic areas with higher rates of antidepressant use tend to have lower rates of suicide death (141, 142).

Anxiety disorders

Clinical and epidemiologic studies have demonstrated a positive association between individual anxiety disorders and suicidal ideation and attempts (143-147). However, some controversy still remains whether this high risk for suicide is mainly because of the frequent comorbidity with other psychiatric (e.g., bipolar disorder, schizophrenia, substance abuse, or major depression) or medical conditions (e.g., multiple sclerosis or coronary artery disease) (148-150). Twelve-month prevalence rates of suicide ideation have been found to be greatest in obsessive compulsive disorder (OCD) (27.3%), with attempts being most common among patients with panic disorder (3.6%), OCD (3.3%) (151) and post-traumatic stress disorder (PTSD) (2.7%) (152). Severe anxiety or intense psychological pain is found to be the strongest predictor of inpatient suicide (153). A large scale study using data from the National Comorbidity Survey, which included assessment of all anxiety disorders except OCD, found that PTSD was the only anxiety disorder significantly associated with suicidal ideation and suicide attempts, after accounting for a wide range of other sociodemographic and psychiatric comorbid disorders (152).

Because of its close association with ongoing military conflicts, PTSD has captured much media attention. However, its prevalence as a result of civilian trauma, including child abuse, is often overlooked. In the military, PTSD, along with major depression and substance use disorders, is strongly associated with elevated risk for suicide. Suicidal ideation is found in 12–21% of veterans and is associated with combat exposure, depression, PTSD, substance use disorders, particularly alcohol, poor social support, poor social satisfaction, and poor resilience (26,154-159). PTSD is an independent risk factor for suicide (154) and increases the risk for suicidal ideation even in the presence of protective factors such as positive social support (154-158). In a cohort of young adults exposed to civilian trauma, PTSD was found to be an independent predictor of suicide, even adjusting for major depression or alcohol or substance dependence

Table 2. Protective Factors for Suicide

Effective clinical care for mental, physical, and substance abuse disorders
Easy access to healthcare
Family and community support (connectedness)
Support from ongoing medical and mental health care relationships
Skills in problem solving, conflict resolution, and nonviolent ways of handling disputes
Cultural and religious beliefs that discourage suicide and support instincts for self-preservation

Schizophrenia

The lifetime prevalence of suicide in schizophrenia is approximately 10%. Risk factors for suicide in schizophrenia are similar to those in the general population, including previous attempts, comorbid mood disorder, recent loss, and high risk-to-rescue ratio (referring to an increased probability of inflicting irreversible damage). Schizophrenia disease-specific factors associated with high suicide risk include the first year of illness, high level of premorbid functioning and IQ, fear of mental disintegration, agitation or restlessness, poor adherence to treatment, long duration of index hospitalization, and frequent rehospitalization (160).

Bipolar disorder

Up to 56% of suicide victims with bipolar disorder have had at least one previous suicide attempt. Established risk factors for suicide among those with bipolar disorder are severity of depression, agitation, hopelessness, self-blame and guilt, marital isolation and loss, long duration of illness, hopelessness, family history of suicide, adversity, early age at onset, psychiatric or medical comorbidity (161). The suicide risk in bipolar II disorder may be very high in part because of the high prevalence of comorbid anxiety disorders and substance use disorders. The most robust short-term predictors of suicide in bipolar disorder are few reasons for living, the wish to die, suicidal intent or plan, and communication of suicide intent. In contrast to classical euphoric mania, suicidal thoughts and attempts are common in dysphoric mania or the so-called mixed state (162). Recent life events, as well as psychosocial stressors (e.g., unemployment or financial problems) are risk factors for attempted suicide, particularly for individuals in a depressive or dysphoric manic episode (163).

Personality disorders

Personality disorders independently increase risk of suicide attempts as a function of the severity

of the illness, particularly in women. Borderline personality disorder occupies a preeminent role as risk factor for suicide. One of the core features of borderline personality disorder is frequent suicidal ideation and suicidal behavior, as well as non-suicidal self-harmful behaviors. For instance, between 60–70% of patients with borderline personality disorder attempt suicide and up to 5–10% are successful (164). Personality traits associated with suicidal behavior are impulsivity and impulsive aggression, neuroticism, perfectionism, and sensitivity to life events (64,65).

Protective factors (Table 2)

Protective factors are those that decrease the probability of an outcome in the presence of elevated risk. Although formal tests of protective factors are rare in suicide research, several studies of factors associated with lower risk of suicidal behavior consistently point to increased sense of belonging, purpose, transcendence, and connection to others, family, friends, community or religion. Religious beliefs, religious practice, and spirituality have been associated with a decreased risk of suicide attempts (165-167). Potential mediators seem to be moral objections to suicide (168) and social support (169). Perceptions of social and family support and connectedness also have been studied outside the context of religious affiliation and have been shown to be significantly associated with lower rates of suicidal behavior (170,171). Marriage, being pregnant, and having young children in the home are also protective against suicide (172,173), even though, the presence of young children is associated with a significantly increased risk of first onset of suicidal ideation. Also, having adult roles, like parent and provider, reduces the likelihood of suicide, possibly by reducing risk-taking behaviors (174). Lastly, factors that favor social connectedness correlate negatively with suicidal behavior, including coping skills, problem solving, conflict resolution, nonviolent ways of handling disputes, resilience, and reasons for living (175,176).

CONCLUSIONS

Suicide is one of the major causes of death worldwide. In the US, it ranks tenth among causes of death, above hypertension or homicide. Certain subpopulations are at greater risk for suicide, including teenagers, the elderly, and the psychiatrically ill. More than 90% of suicides are linked to psychiatric disorders. Depression accounts for more than half of suicide cases, though suicide is also a frequent outcome in substance abuse, bipolar disorder, and schizophrenia. A strong biological component in the diathesis for suicide is shown by its heritability and deficits in serotonergic neurotransmission, particularly to the VMPFC. Deficits in VMPFC function are associated with impulsivity and impaired decision making. Growing amounts of data suggest that other biogenic amines and the HPA axis also have a central role in suicide diathesis. Cognitive and psychological factors for high suicide risk include hopelessness, psychological pain, impulsivity and poor problem solving skills. Environmental factors related to suicide include history of childhood trauma, poor social support, recent discharge from the hospital and availability of lethal means. Despite this array of knowledge about suicide risk, predicting who is going to commit suicide continues to be a rather subjective decision in clinical practice. Further research exploring accurate objective predictive factors that could accurately inform clinicians in selecting effective preventive measures is warranted.

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REFERENCES

1. WHO. World report on violence and health. Geneva: World Health Organization, 2002.
2. McIntosh JL. USA Suicide: 2008. Official final data. American Academy of Suicidology, 2011.
3. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA*. 2005;293:2487-95.
4. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1999;56:617-26.
5. Borges G, Loera CR. Alcohol and drug use in suicidal behaviour. *Curr Opin Psychiatry*. 2010;23:195-204.
6. Zhang Y, Conner KR, Phillips MR. Alcohol use disorders and acute alcohol use preceding suicide in China. *Addict Behav*. 2010;35:152-6.
7. Holmgren A, Jones AW. Demographics of suicide victims in Sweden in relation to their blood-alcohol concentration and the circumstances and manner of death. *Forensic Sci Int*. 2010;198:17-22.
8. Sher L, Oquendo MA, Richardson-Vejlgaard R, Makhija NM, Posner K, Mann JJ, Stanley BH. Effect of acute alcohol use on the lethality of suicide attempts in patients with mood disorders. *J Psychiatr Res*. 2009;43:901-5.
9. Powell KE, Kresnow MJ, Mercy JA, Potter LB, Swann AC, Frankowski RF, Lee RK, Bayer TL. Alcohol consumption and nearly lethal suicide attempts. *Suicide Life Threat Behav*. 2001;32:30-41.
10. Borges G, Rosovsky H. Suicide attempts and alcohol consumption in an emergency room sample. *J Stud Alcohol*. 1996;57:543-8.
11. Vijayakumar L, Kumar MS, Vijayakumar V. Substance use and suicide. *Curr Opin Psychiatry*. 2011;24:197-202.
12. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. *Drug Alcohol Depend*. 2004;76 Suppl:S11-9.
13. Rajalin M, Hirvikoski T, Jokinen J. Family history of suicide and exposure to interpersonal violence in childhood predict suicide in male suicide attempters. *J Affect Disord*. 2012.
14. Suominen K, Isometsa E, Suokas J, Haukka J, Achte K, Lonnqvist J. Completed suicide after a suicide attempt: a 37-year follow-up study. *Am J Psychiatry*. 2004;161:562-3.
15. Suokas J, Suominen K, Isometsa E, Ostamo A, Lonnqvist J. Long-term risk factors for suicide mortality after attempted suicide--findings of a 14-year follow-up study. *Acta Psychiatr Scand*. 2001;104:117-21.
16. Owens D, Horrocks J, House A. Fatal and non-fatal repetition of self-harm. Systematic review. *Br J Psychiatry*. 2002;181:193-9.
17. Jenkins GR, Hale R, Papanastassiou M, Crawford MJ, Tyrer P. Suicide rate 22 years after parasuicide: cohort study. *BMJ*. 2002;325:1155.
18. De Moore GM, Robertson AR. Suicide in the 18 years after deliberate self-harm a prospective study. *Br J Psychiatry*. 1996;169:489-94.
19. Whitlock J, Muehlenkamp J, Eckenrode J, Purington A, Baral Abrams G, Barreira P, Kress V. Nonsuicidal

- Self-injury as a Gateway to Suicide in Young Adults. *J Adolesc Health*. 2012.
20. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. *JAMA*. 2001;286:3089-96.
 21. Fergusson DM, Woodward LJ, Horwood LJ. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychol Med*. 2000;30:23-39.
 22. Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, Williamson DF, Giovino GA. Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA*. . 1999;282:1652-8.
 23. Belshaw SH, Siddique JA, Tanner J, Osho GS. The relationship between dating violence and suicidal behaviors in a national sample of adolescents. *Violence Vict*. 2012;27:580-91.
 24. Swahn MH, Bossarte RM, Palmier JB, Yao H, Van Dulmen MH. Psychosocial characteristics associated with frequent physical fighting: findings from the 2009 National Youth Risk Behavior Survey. *Inj Prev*. 2013;19:143-6.
 25. Gradus JL, Shipherd JC, Suvak MK, Giasson HL, Miller M. Suicide attempts and suicide among Marines: a decade of follow-up. *Suicide Life Threat Behav*. 2013;43:39-49.
 26. Institute of Medicine (U.S.). Committee on Gulf War and Health: Physiologic Psychologic and Psychosocial Effects of Deployment-Related Stress., United States. Dept. of Veterans Affairs. Posttraumatic stress disorder : diagnosis and assesment. Washington, DC: National Academies Press; 2006.
 27. Kaplan MS, Huguet N, McFarland BH, Newsom JT. Suicide among male veterans: a prospective population-based study. *J Epidemiol Community Health*. 2007;61:619-24.
 28. Maynard C, Boyko EJ. Datapoints: suicide rates in the Washington State veteran population. *Psychiatr Serv*. 2008;59:1245.
 29. Kapur N, While D, Blatchley N, Bray I, Harrison K. Suicide after leaving the UK armed forces--a cohort study. *PLoS Med*. 2009;6:e26.
 30. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. *JAMA*. 2007;298:2141-8.
 31. Wasserman D, Cheng Q, Jiang GX. Global suicide rates among young people aged 15-19. *World Psychiatry*. 2005;4:114-20.
 32. Woo JM, Okusaga O, Postolache TT. Seasonality of suicidal behavior. *Int J Environ Res Public Health*. 2012;9:531-47.
 33. Postolache TT, Stiller JW, Herrell R, Goldstein MA, Shreeram SS, Zebrak R, Thrower CM, Volkov J, No MJ, Volkov I, Rohan KJ, Redditt J, Parmar M, Mohyuddin F, Olsen C, Moca M, Tonelli LH, Merikangas K, Komarow HD. Tree pollen peaks are associated with increased nonviolent suicide in women. *Mol Psychiatry*. 2005;10:232-5.
 34. Eaton DK, Kann L, Kinchen S, Ross J, Hawkins J, Harris WA, Lowry R, McManus T, Chyen D, Shanklin S, Lim C, Grunbaum JA, Wechsler H. Youth risk behavior surveillance--United States, 2005. *MMWR Surveillance summaries : Morbidity and mortality weekly report Surveillance summaries / CDC*. 2006;55:1-108.
 35. Spirito A, Esposito-Smythers C. Attempted and completed suicide in adolescence. *Annu Rev Clin Psychol*. 2006;2:237-66.
 36. King CA, Merchant CR. Social and interpersonal factors relating to adolescent suicidality: a review of the literature. *Arch Suicide Res*. 2008;12:181-96.
 37. World Health Organization. Regional Office for the Western Pacific. Towards evidence-based suicide prevention programmes. Manila, Philippines: World Health Organization, Western Pacific Region; 2010.
 38. CDC. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS). 2005.
 39. Dombrovski AY, Szanto K, Duberstein P, Conner KR, Houck PR, Conwell Y. Sex differences in correlates of suicide attempt lethality in late life. *Am J Geriatr Psychiatry*. 2008;16:905-13.
 40. Friedmann H, Kohn R. Mortality, or probability of death, from a suicidal act in the United States. *Suicide Life Threat Behav*. 2008;38:287-301.
 41. Conwell Y, Van Orden K, Caine ED. Suicide in Older Adults. *Psychiatric Clinics of North America*. 2011;34:451-+.
 42. Duberstein PR. Openness to experience and completed suicide across the second half of life. *International Psychogeriatrics*. 1995;7:183-98.
 43. Harwood D, Hawton K, Hope T, Jacoby R. Psychiatric disorder and personality factors associated with suicide in older people: a descriptive and case-control study. *Int J Geriatr Psychiatry*. 2001;16:155-65.
 44. Waern M, Rubenowitz E, Runeson B, Skoog I, Wilhelmson K, Allebeck P. Burden of illness and suicide in elderly people: case-control study. *BMJ*. 2002;324:1355.
 45. Harwood DMJ, Hawton K, Hope T, Harriss L, Jacoby R. Life problems and physical illness as risk factors for suicide in older people: a descriptive and case-control study. *Psychol Med*. 2006;36:1265-74.
 46. Baldessarini RJ, Hennen J. Genetics of suicide: an overview. *Harv Rev Psychiatry*. 2004;12:1-13.
 47. Kendler KS, Prescott CA. Genes, environment,

- and psychopathology : understanding the causes of psychiatric and substance use disorders. New York: Guilford Press; 2006.
48. Brent DA, Mann JJ. Family genetic studies, suicide, and suicidal behavior. *Am J Med Genet C Semin Med Genet.* 2005;133C:13-24.
 49. Mann JJ, Currier D. A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. *Arch Suicide Res.* 2007;11:3-16.
 50. Keilp JG, Oquendo MA, Stanley BH, Burke AK, Cooper TB, Malone KM, Mann JJ. Future suicide attempt and responses to serotonergic challenge. *Neuropsychopharmacology.* 2010;35:1063-72.
 51. Ryding E, Lindstrom M, Traskman-Bendz L. The role of dopamine and serotonin in suicidal behaviour and aggression. *Prog Brain Res.* 2008;172:307-15.
 52. Asberg M, Nordstrom P, Traskman-Bendz L. Cerebrospinal fluid studies in suicide. An overview. *Ann N Y Acad Sci.* 1986;487:243-55.
 53. Mann JJ, Malone KM, Psych MR, Sweeney JA, Brown RP, Linnoila M, Stanley B, Stanley M. Attempted suicide characteristics and cerebrospinal fluid amine metabolites in depressed inpatients. *Neuropsychopharmacology.* 1996;15:576-86.
 54. Traskman L, Asberg M, Bertilsson L, Sjostrand L. Monoamine metabolites in CSF and suicidal behavior. *Arch Gen Psychiatry.* 1981;38:631-6.
 55. Cooper SJ, Kelly CB, King DJ. 5-Hydroxyindoleacetic acid in cerebrospinal fluid and prediction of suicidal behaviour in schizophrenia. *Lancet.* 1992;340:940-1.
 56. Nordstrom P, Samuelsson M, Asberg M, Traskman-Bendz L, Aberg-Wistedt A, Nordin C, Bertilsson L. CSF 5-HIAA predicts suicide risk after attempted suicide. *Suicide Life Threat Behav.* 1994;24:1-9.
 57. Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL. Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry.* 1989;46:587-99.
 58. Etkin A. Functional Neuroanatomy of Anxiety: A Neural Circuit Perspective. In: Stein MB, Steckler T, editors. *Behavioral Neurobiology of Anxiety and Its treatment Current Topics in Behavioral Neurosciences 2010.* p. 251-77.
 59. Pandey GN. Altered serotonin function in suicide. Evidence from platelet and neuroendocrine studies. *Ann N Y Acad Sci.* 1997;836:182-200.
 60. Arango V, Underwood MD, Gubbi AV, Mann JJ. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Res.* 1995;688:121-33.
 61. Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM, Dwork AJ, Arango V. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry.* 2000;57:729-38.
 62. Brezo J, Bureau A, Merette C, Jomphe V, Barker ED, Vitaro F, Hebert M, Carbonneau R, Tremblay RE, Turecki G. Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. *Mol Psychiatry.* 2010;15:831-43.
 63. Tsai SJ, Hong CJ, Liou YJ. Recent molecular genetic studies and methodological issues in suicide research. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35:809-17.
 64. Baud P. Personality traits as intermediary phenotypes in suicidal behavior: genetic issues. *Am J Med Genet C Semin Med Genet.* 2005;133C:34-42.
 65. Courtet P, Jollant F, Castelnaud D, Buresi C, Malafosse A. Suicidal behavior: relationship between phenotype and serotonergic genotype. *Am J Med Genet C Semin Med Genet.* 2005;133C:25-33.
 66. Oswald LM, Wong DF, Zhou Y, Kumar A, Brasic J, Alexander M, Ye W, Kuwabara H, Hilton J, Wand GS. Impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. *Neuroimage.* 2007;36:153-66.
 67. Arango V, Underwood MD, Mann JJ. Fewer pigmented locus coeruleus neurons in suicide victims: preliminary results. *Biol Psychiatry.* 1996;39:112-20.
 68. Ordway GA, Widdowson PS, Smith KS, Halaris A. Agonist binding to alpha 2-adrenoceptors is elevated in the locus coeruleus from victims of suicide. *J Neurochem.* 1994;63:617-24.
 69. Klimek V, Schenck JE, Han H, Stockmeier CA, Ordway GA. Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. *Biol Psychiatry.* 2002;52:740-8.
 70. Pitchot W, Reggers J, Pinto E, Hansenne M, Fuchs S, Pirard S, Ansseau M. Reduced dopaminergic activity in depressed suicides. *Psychoneuroendocrinology.* 2001;26:331-5.
 71. Courtet P, Jollant F, Buresi C, Castelnaud D, Mouthon D, Malafosse A. The monoamine oxidase A gene may influence the means used in suicide attempts. *Psychiatric Genetics.* 2005;15:189-94.
 72. Kia-Keating BM, Glatt SJ, Tsuang MT. Meta-analyses suggest association between COMT, but not HTR1B, alleles, and suicidal behavior. *Am J Medical Genetics Part B-Neuropsychiatric Genetics.* 2007;144B:1048-53.
 73. Nemeroff CB, Compton MT, Berger J. The depressed suicidal patient. Assessment and treatment. *Ann N Y Acad Sci.* 2001;932:1-23.
 74. Merali Z, Du L, Hrdina P, Palkovits M, Faludi G, Poulter MO, Anisman H. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits

- in frontal cortical brain region. *J Neurosci*. 2004;24:1478-85.
75. Coryell W, Schlessner M. Combined biological tests for suicide prediction. *Psychiatry Res*. 2007;150:187-91.
 76. De Luca V, Tharmalingam S, Zai C, Potapova N, Strauss J, Vincent J, Kennedy JL. Association of HPA axis genes with suicidal behaviour in schizophrenia. *J Psychopharmacol*. 2010;24:677-82.
 77. Desmyter S, van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:796-808.
 78. Oquendo MA, Placidi GP, Malone KM, Campbell C, Keilp J, Brodsky B, Kegeles LS, Cooper TB, Parsey RV, van Heertum RL, Mann JJ. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. *Arch Gen Psychiatry*. 2003;60:14-22.
 79. Audenaert K, Peremans K, Goethals I, van Heeringen C. Functional imaging, serotonin and the suicidal brain. *Acta Neurol Belg*. 2006;106:125-31.
 80. Amen DG, Prunella JR, Fallon JH, Amen B, Hanks C. A comparative analysis of completed suicide using high resolution brain SPECT imaging. *J Neuropsychiatry Clin Neurosci*. 2009;21:430-9.
 81. Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, Courtet P, Phillips ML. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. *Am J Psychiatry*. 2008;165:740-8.
 82. Reisch T, Seifritz E, Esposito F, Wiest R, Valach L, Michel K. An fMRI study on mental pain and suicidal behavior. *J Affect Disord*. 2010.
 83. Jollant F, Lawrence NS, Olie E, O'Daly O, Malafosse A, Courtet P, Phillips ML. Decreased activation of lateral orbitofrontal cortex during risky choices under uncertainty is associated with disadvantageous decision-making and suicidal behavior. *Neuroimage*. 2010;51:1275-81.
 84. Pedersen MG, Mortensen PB, Norgaard-Pedersen B, Postolache TT. *Toxoplasma gondii* infection and self-directed violence in mothers. *Arch Gen Psychiatry*. 2012;69:1123-30.
 85. Carmen JC, Sinai AP. Suicide prevention: disruption of apoptotic pathways by protozoan parasites. *Mol Microbiol*. 2007;64:904-16.
 86. Keiser O, Spoerri A, Brinkhof MW, Hasse B, Gayet-Ageron A, Tissot F, Christen A, Battegay M, Schmid P, Bernasconi E, Egger M, Swiss HIVCS, Swiss National C. Suicide in HIV-infected individuals and the general population in Switzerland, 1988-2008. *Am J Psychiatry*. 2010;167:143-50.
 87. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry*. 2012;73:e1160-7.
 88. Li SX, Lam SP, Yu MW, Zhang J, Wing YK. Nocturnal sleep disturbances as a predictor of suicide attempts among psychiatric outpatients: a clinical, epidemiologic, prospective study. *J Clin Psychiatry*. 2010;71:1440-6.
 89. Brenner B, Cheng D, Clark S, Camargo CA, Jr. Positive association between altitude and suicide in 2584 U.S. counties. *High Alt Med Biol*. 2011;12:31-5.
 90. Gamboa JL, Caceda R, Arregui A. Is depression the link between suicide and high altitude? *High Alt Med Biol*. 2011;12:403-4.
 91. Kim C, Jung SH, Kang DR, Kim HC, Moon KT, Hur NW, Shin DC, Suh I. Ambient particulate matter as a risk factor for suicide. *Am J Psychiatry*. 2010;167:1100-7.
 92. Cáceda R, Strassnig M, Nemeroff CB. Advances in the Neuropsychobiology of Suicide. *Minerva Psichiatrica*. 2012;53:61-78.
 93. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological dysfunction in depressed suicide attempters. *Am J Psychiatry*. 2001;158:735-41.
 94. Raust A, Slama F, Mathieu F, Roy I, Chenu A, Koncke D, Fouques D, Jollant F, Jouvent E, Courtet P, Leboyer M, Bellivier F. Prefrontal cortex dysfunction in patients with suicidal behavior. *Psychol Med*. 2007;37:411-9.
 95. Garcia Espinosa A, Andrade Machado R, Borges Gonzalez S, Garcia Gonzalez ME, Perez Montoto A, Toledo Sotomayor G. Wisconsin Card Sorting Test performance and impulsivity in patients with temporal lobe epilepsy: suicidal risk and suicide attempts. *Epilepsy Behav*. 2010;17:39-45.
 96. Malloy-Diniz LF, Neves FS, Abrantes SS, Fuentes D, Correa H. Suicide behavior and neuropsychological assessment of type I bipolar patients. *J Affect Disord*. 2009;112:231-6.
 97. Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry*. 2004;161:262-70.
 98. Martino DJ, Strojilevich SA, Torralva T, Manes F. Decision making in euthymic bipolar I and bipolar II disorders. *Psychol Med*. 2010:1-9.
 99. Pollock LR, Williams JM. Problem-solving in suicide attempters. *Psychol Med*. 2004;34:163-7.
 100. Jollant F, Buresi C, Guillaume S, Jaussent I, Bellivier F, Leboyer M, Castelnau D, Malafosse A, Courtet P. The influence of four serotonin-related genes on decision-making in suicide attempters. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B:615-24.
 101. Cáceda R, Harvey PD, Durand D, Cortes E,

- Prendes S, Wojas J, Nemeroff CB. Decision making and psychological pain in acutely suicidal depressed patients. *Neuropsychopharmacology* 2012;38:S362-3.
102. Dombrovski AY, Szanto K, Siegle GJ, Wallace ML, Forman SD, Sahakian B, Reynolds CF, 3rd, Clark L. Lethal forethought: delayed reward discounting differentiates high- and low-lethality suicide attempts in old age. *Biol Psychiatry*. 2011;70:138-44.
103. Clark L, Dombrovski AY, Siegle GJ, Butters MA, Shollenberger CL, Sahakian BJ, Szanto K. Impairment in risk-sensitive decision-making in older suicide attempters with depression. *Psychol Aging*. 2011;26:321-30.
104. Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R, Castelnau D, Malafosse A, Courtet P. Impaired decision making in suicide attempters. *Am J Psychiatry*. 2005;162:304-10.
105. Williams CL, Davidson JA, Montgomery I. Impulsive suicidal behavior. *J Clin Psychol*. 1980;36:90-4.
106. Salter D, Platt S. Suicidal intent, hopelessness and depression in a parasuicide population: the influence of social desirability and elapsed time. *Br J Clin Psychol*. 1990;29 (Pt 4):361-71.
107. Beck AT, Brown G, Berchick RJ, Stewart BL, Steer RA. Relationship between hopelessness and ultimate suicide: a replication with psychiatric outpatients. *Am J Psychiatry*. 1990;147:190-5.
108. Coryell W, Young EA. Clinical predictors of suicide in primary major depressive disorder. *Journal of Clinical Psychiatry*. 2005;66:412-7.
109. Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P, Isometsa ET. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry*. 2005;66:1456-62.
110. Drake RE, Cotton PG. Depression, hopelessness and suicide in chronic schizophrenia. *Br J Psychiatry*. 1986;148:554-9.
111. Suominen K, Isometsa E, Henriksson M, Ostamo A, Lonnqvist J. Hopelessness, impulsiveness and intent among suicide attempters with major depression, alcohol dependence, or both. *Acta Psychiatr Scand*. 1997;96:142-9.
112. Spokas M, Wenzel A, Stirman SW, Brown GK, Beck AT. Suicide risk factors and mediators between childhood sexual abuse and suicide ideation among male and female suicide attempters. *J Trauma Stress*. 2009;22:467-70.
113. Sokero TP, Melartin TK, Rytala HJ, Leskela US, Lestela-Mielonen PS, Isometsa ET. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J Clin Psychiatry*. 2003;64:1094-100.
114. Shneidman ES. Suicide as psychache. *J Nerv Ment Dis*. 1993;181:145-7.
115. Vohs KD, Baumeister R. Escaping the self consumes regulatory resources: a self-regulatory model of suicide. *Suicide Science*. 2002:33-41.
116. Orbach I, Mikulincer M, Sirota P, Gilboa-Schechtman E. Mental pain: a multidimensional operationalization and definition. *Suicide Life Threat Behav*. 2003;33:219-30.
117. Kokkevi A, Rotsika V, Arapaki A, Richardson C. Adolescents' self-reported suicide attempts, self-harm thoughts and their correlates across 17 European countries. *J Child Psychol Psychiatry*. 2012;53:381-9.
118. Amitai M, Apter A. Social aspects of suicidal behavior and prevention in early life: a review. *Int J Environ Res Public Health*. 2012;9:985-94.
119. Qin P, Mortensen PB, Pedersen CB. Frequent change of residence and risk of attempted and completed suicide among children and adolescents. *Arch Gen Psychiatry*. 2009;66:628-32.
120. Furlanetto LM, Stefanello B. Suicidal ideation in medical inpatients: psychosocial and clinical correlates. *Gen Hosp Psychiatry*. 2011;33:572-8.
121. Slap G, Goodman E, Huang B. Adoption as a risk factor for attempted suicide during adolescence. *Pediatrics*. 2001;108:E30.
122. Ryan C, Huebner D, Diaz RM, Sanchez J. Family rejection as a predictor of negative health outcomes in white and Latino lesbian, gay, and bisexual young adults. *Pediatrics*. 2009;123:346-52.
123. Jollant F, Guillaume S, Jaussent I, Castelnau D, Malafosse A, Courtet P. Impaired decision-making in suicide attempters may increase the risk of problems in affective relationships. *J Affect Disord*. 2007;99:59-62.
124. Yen S, Pagano ME, Shea MT, Grilo CM, Gunderson JG, Skodol AE, McGlashan TH, Sanislow CA, Bender DS, Zanarini MC. Recent life events preceding suicide attempts in a personality disorder sample: findings from the collaborative longitudinal personality disorders study. *J Consult Clin Psychol*. 2005;73:99-105.
125. de Leo D, Heller T. Social modeling in the transmission of suicidality. *Crisis*. 2008;29:11-9.
126. Gould MS. Suicide and the media. *Ann N Y Acad Sci*. 2001;932:200-21; discussion 21-4.
127. Stack S. Media coverage as a risk factor in suicide. *J Epidemiol Community Health*. 2003;57:238-40.
128. Klomek AB, Sourander A, Niemela S, Kumpulainen K, Piha J, Tamminen T, Almqvist F, Gould MS. Childhood bullying behaviors as a risk for suicide attempts and completed suicides: a population-based birth cohort study. *J Am Acad Child Adolesc Psychiatry*. 2009;48:254-61.
129. Eaton DK, Kann L, Kinchen S, Shanklin S, Ross J, Hawkins J, Harris WA, Lowry R, McManus T, Chyen

- D, Lim C, Brenner ND, Wechsler H. Youth risk behavior surveillance--United States, 2007. *MMWR Surveill Summ.* 2008;57:1-131.
130. Rowe CA, Walker KL, Britton PC, Hirsch JK. The Relationship Between Negative Life Events and Suicidal Behavior. *Crisis.* 2012;1-9.
131. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lonnqvist J, Malone K, Marusic A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H. Suicide prevention strategies: a systematic review. *JAMA.* 2005;294:2064-74.
132. Miller M, Lippmann SJ, Azrael D, Hemenway D. Household firearm ownership and rates of suicide across the 50 United States. *J Trauma.* 2007;62:1029-34; discussion 34-5.
133. Miller M, Azrael D, Barber C. Suicide mortality in the United States: the importance of attending to method in understanding population-level disparities in the burden of suicide. *Annu Rev Public Health.* 2012;33:393-408.
134. Deisenhammer EA, Ing CM, Strauss R, Kemmler G, Hinterhuber H, Weiss EM. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? *J Clin Psychiatry.* 2009;70:19-24.
135. Simon OR, Swann AC, Powell KE, Potter LB, Kresnow MJ, O'Carroll PW. Characteristics of impulsive suicide attempts and attempters. *Suicide Life Threat Behav.* 2001;32:49-59.
136. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry.* 1997;170:205-28.
137. Harris EC, Barraclough B. Excess mortality of mental disorder. *British Journal of Psychiatry.* 1998;173:11-53.
138. Cavanagh JTO, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. *Psychol Med.* 2003;33:395-405.
139. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry.* 2006;63:332-9.
140. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry.* 2006;163:41-7.
141. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry.* 2005;62:165-72.
142. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. *Am J Psychiatry.* 2006;163:1898-904.
143. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* 1995;52:1048-60.
144. Cox BJ, Dorenfeld DM, Swinson RP, Norton GR. Suicidal Ideation and Suicide Attempts in Panic Disorder and Social Phobia. *American Journal of Psychiatry.* 1994;151:882-7.
145. Ferrada-Noli M, Asberg M, Ormstad K, Lundin T, Sundbom E. Suicidal behavior after severe trauma. Part 1: PTSD diagnoses, psychiatric comorbidity, and assessments of suicidal behavior. *J Trauma Stress.* 1998;11:103-12.
146. Kotler M, Iancu I, Efroni R, Amir M. Anger, impulsivity, social support, and suicide risk in patients with posttraumatic stress disorder. *J Nerv Ment Dis.* 2001;189:162-7.
147. Weissman MM, Klerman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in panic disorder and attacks. *N Engl J Med.* 1989;321:1209-14.
148. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Mult Scler.* 2007;13:67-72.
149. Artero S, Astruc B, Courtet P, Ritchie K. Life-time history of suicide attempts and coronary artery disease in a community-dwelling elderly population. *Int J Geriatr Psychiatry.* 2006;21:108-12.
150. Hawgood J, De Leo D. Anxiety disorders and suicidal behaviour: an update. *Curr Opin Psychiatry.* 2008;21:51-64.
151. Beautrais AL, Wells JE, McGee MA, Oakley Browne MA. Suicidal behaviour in Te Rau Hinengaro: the New Zealand Mental Health Survey. *Aust N Z J Psychiatry.* 2006;40:896-904.
152. Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJG, ten Have M, Stein MB. Anxiety disorders and risk for suicidal ideation and suicide attempts - A population-based longitudinal study of adults. *Archives of General Psychiatry.* 2005;62:1249-57.
153. Busch KA, Fawcett J, Jacobs DG. Clinical correlates of inpatient suicide. *J Clin Psychiatry.* 2003;64:14-9.
154. Guerra VS, Calhoun PS. Examining the relation between posttraumatic stress disorder and suicidal ideation in an OEF/OIF veteran sample. *J Anxiety Disord.* 2011;25:12-8.
155. Jakupcak M, Vannoy S, Imel Z, Cook JW, Fontana A, Rosenheck R, McFall M. Does PTSD moderate the relationship between social support and suicide risk in Iraq and Afghanistan War Veterans seeking mental health treatment? *Depress Anxiety.* 2010;27:1001-5.
156. Jakupcak M, Cook J, Imel Z, Fontana A, Rosenheck R, McFall M. Posttraumatic stress disorder as a risk factor for suicidal ideation in Iraq and Afghanistan War veterans. *J Trauma Stress.* 2009;22:303-6.
157. Pietrzak RH, Russo AR, Ling Q, Southwick SM. Suicidal ideation in treatment-seeking Veterans of

- Operations Enduring Freedom and Iraqi Freedom: the role of coping strategies, resilience, and social support. *J Psychiatr Res.* 2011;45:720-6.
158. Pietrzak RH, Goldstein MB, Malley JC, Rivers AJ, Johnson DC, Southwick SM. Risk and protective factors associated with suicidal ideation in veterans of Operations Enduring Freedom and Iraqi Freedom. *J Affect Disord.* 2010;123:102-7.
159. Mills KL, Teesson M, Ross J, Peters L. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being. *Am J Psychiatry.* 2006;163:652-8.
160. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol.* 2010;24:81-90.
161. Rihmer Z, Kiss K. Bipolar disorders and suicidal behaviour. *Bipolar Disord.* 2002;4 Suppl 1:21-5.
162. Vieta E, Benabarre A, Colom F, Gasto C, Nieto E, Otero A, Vallejo J. Suicidal behavior in bipolar I and bipolar II disorder. *Journal of Nervous and Mental Disease.* 1997;185:407-9.
163. Rihmer A, Gonda X, Balazs J, Faludi G. The importance of depressive mixed states in suicidal behaviour. *Neuropsychopharmacol Hung.* 2008;10:45-9.
164. American Psychiatric Association Practice G. Practice guideline for the treatment of patients with borderline personality disorder. American Psychiatric Association. *Am J Psychiatry.* 2001;158:1-52.
165. Colucci E, Martin G. Religion and spirituality along the suicidal path. *Suicide Life Threat Behav.* 2008;38:229-44.
166. Garroutte EM, Goldberg J, Beals J, Herrell R, Manson SM, Team A-S. Spirituality and attempted suicide among American Indians. *Soc Sci Med.* 2003;56:1571-9.
167. Dervic K, Oquendo MA, Grunebaum MF, Ellis S, Burke AK, Mann JJ. Religious affiliation and suicide attempt. *Am J Psychiatry.* 2004;161:2303-8.
168. Oquendo MA, Dragatsi D, Harkavy-Friedman J, Dervic K, Currier D, Burke AK, Grunebaum MF, Mann JJ. Protective factors against suicidal behavior in Latinos. *J Nerv Ment Dis.* 2005;193:438-43.
169. Meadows LA, Kaslow NJ, Thompson MP, Jurkovic GJ. Protective factors against suicide attempt risk among African American women experiencing intimate partner violence. *Am J Community Psychol.* 2005;36:109-21.
170. Resnick MD, Bearman PS, Blum RW, Bauman KE, Harris KM, Jones J, Tabor J, Beuhring T, Sieving RE, Shew M, Ireland M, Bearinger LH, Udry JR. Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. *JAMA.* 1997;278:823-32.
171. Marion MS, Range LM. African American college women's suicide buffers. *Suicide Life Threat Behav.* 2003;33:33-43.
172. Marzuk PM, Tardiff K, Leon AC, Hirsch CS, Portera L, Hartwell N, Iqbal MI. Lower risk of suicide during pregnancy. *Am J Psychiatry.* 1997;154:122-3.
173. Qin P, Mortensen PB. The impact of parental status on the risk of completed suicide. *Arch Gen Psychiatry.* 2003;60:797-802.
174. Rendall MS, Weden MM, Favreault MM, Waldron H. The protective effect of marriage for survival: a review and update. *Demography.* 2011;48:481-506.
175. Hirsch JK, Chang EC, Jeglic EL. Social problem solving and suicidal behavior: ethnic differences in the moderating effects of loneliness and life stress. *Arch Suicide Res.* 2012;16:303-15.
176. Li Z, Zhang J. Coping skills, mental disorders, and suicide among rural youths in China. *J Nerv Ment Dis.* 2012;200:885-90.

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