

Suicide and suicidal behaviour

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Suicide is a complex public health problem of global importance. Suicidal behaviour differs between sexes, age groups, geographic regions, and sociopolitical settings, and variably associates with different risk factors, suggesting aetiological heterogeneity. Although there is no effective algorithm to predict suicide in clinical practice, improved recognition and understanding of clinical, psychological, sociological, and biological factors might help the detection of high-risk individuals and assist in treatment selection. Psychotherapeutic, pharmacological, or neuromodulatory treatments of mental disorders can often prevent suicidal behaviour; additionally, regular follow-up of people who attempt suicide by mental health services is key to prevent future suicidal behaviour.

Introduction

Suicide takes a staggering toll on global public health, with almost 1 million people dying from suicide worldwide each year.¹ WHO has declared that reducing suicide-related mortality is a global imperative, a welcome contrast to the traditional taboo that has surrounded suicidal behaviours. Cultural and moral beliefs about suicide, and unnecessarily pessimistic views about treatment and prevention of suicide, are barriers to patient self-disclosure and clinicians' routine inquiries about suicidal thoughts. About 45% of people who die by suicide consult a primary care physician within 1 month of death, yet documentation of physician inquiry or patient disclosure is rare.² We review the epidemiology, risk factors, and effective interventions in primary care and specialty mental health facilities aimed at the prevention or treatment of suicidal behaviour.

Definitions and assessment

Clear discussion, accurate research, and efficient treatment require accepted definitions of suicidal behaviours. The difficulty of establishing intent of self-harming behaviours has hindered efforts to streamline the historically heterogeneous suicide nomenclature, but efforts, such as those resulting in the Columbia Classification Algorithm of Suicide Assessment,³ have contributed to standardising nomenclature (table). The severity of suicidal behaviour varies, on the basis of family studies showing the progression from less to more severe forms of suicidal ideation and behaviour, and from family and biological studies showing overlap between attempted and completed suicide.⁴

Epidemiology

Precise global estimates of suicide rates are difficult to obtain, as only 35% of WHO member states have comprehensive vital registration with at least 5 years of data.¹ Globally, an estimated 11.4 suicides per 100 000 people occur per year, resulting in 804 000 deaths.¹ Suicide rates vary within and between countries, with as much as a ten-times difference between regions; this variation is partly correlated with economic status and cultural differences.¹ Cultural influences might trump geographic location, because the suicide rates of immigrants are more closely correlated with their country

of origin than with their adoptive country.⁵ Indigenous peoples have high rates of suicide,⁶ which might be caused by disruption of traditional cultural and family supports, lower socioeconomic status, and increased prevalence of alcohol and substance use, which are also risk factors for suicide in the general population.⁶

Non-fatal suicidal behaviours are more common than suicides.^{7,8} Data from 108 705 people included in the WHO World Mental Health Survey⁸ suggest that the average 12-month prevalence of ideation is 2.0% in high-income countries versus 2.1% in low-income countries, and the prevalence of suicide attempts is 0.3% versus 0.4%. The worldwide lifetime prevalence of ideation is 9.2% and that of attempts is 2.7%,⁹ but rates of ideation and suicidal behaviour vary greatly between countries (figure 1).¹⁰⁻¹² Individuals who report suicide ideation within the previous 12 months have significantly higher 12-month prevalence rates of suicide attempts (15.1% in high-income countries and 20.2% in low-income countries), and suicidal planning further increases risk.^{7,8} Roughly a third of adolescents with suicide ideation will go on to attempt suicide within 1 year,⁷ and people who attempt suicide presenting to an emergency department have a 12-month risk of suicide of 1.6% and of repeated suicide attempt of 16.3%, with a 5-year risk of suicide of 3.9%.¹³

In high-income countries, suicide is most common among middle-aged and elderly men.¹ However, rates of suicide in young people are increasing, and suicide is

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Search strategy and selection criteria

The previous *Lancet* Seminar on suicide was published in 2009. We searched PubMed and the Cochrane Library from Jan 1, 2009, to May 30, 2015, with the terms suicide, suicidal behaviour, and self-harm along with category-specific terms, including epidemiology, genetics, intervention, prevention, and psychotherapy. Titles and abstracts of search results were read and sorted to assess inclusion of the article. We identified further articles by scanning the reference sections of selected publications. We primarily selected articles published in the past 6 years, but also included relevant and notable articles published before 2009. We selected only English language publications.

For the 2009 *Lancet* Seminar on suicide see *Lancet* 2009; 373: 1372-81

	Definition	Comments
Suicide	A fatal self-injurious act with some evidence of intent to die	..
Suicide attempt	A potentially self-injurious behaviour associated with at least some intent to die	Some younger people who attempt suicide report that their main motivation is other than to die, such as to escape an intolerable situation, to express hostility, or to get attention; however, many nonetheless acknowledge the possibility that their behaviour could have resulted in death; suicide attempt is characterised by greater functional impairment than non-suicidal self-injury
Active suicide ideation	Thoughts about taking action to end one's life, including identifying a method, having a plan, or having intent to act	Highly specific ideation, such as having made a plan or having intent, is associated with a much greater risk of a suicide attempt within 12 months
Passive suicide ideation	Thoughts about death or wanting to be dead without any plan or intent	..
Non-suicidal self-injury	Self-injurious behaviour with no intent to die	Differs from suicide attempt in terms of motivation, familial transmission (found only in suicidal behaviour), age of onset (younger in non-suicidal self-injury), psychopathology, and functional impairment (greater in suicide attempt); non-suicidal self-injury most commonly consists of repetitive cutting, rubbing, burning, or picking; the main motivations are either to relieve distress, to "feel something", to induce self-punishment, to get attention, or to escape a difficult situation
Suicidal events	The onset or worsening of suicide ideation or a suicide attempt, an emergency referral for ideation, or suicidal behaviour	Often used as an endpoint in pharmacological studies; rescue procedures are included in this category because a patient with ideation who then received emergency intervention might have made an attempt had he or she not been recognised and treated
Preparatory acts toward imminent suicidal behaviours
Deliberate self-harm	Any type of self-injurious behaviour, including suicide attempts and non-suicidal self-injury	The combination of suicide attempts and non-suicidal self-injury into one category reflects their high comorbidity, shared diathesis, and the fact that non-suicidal self-injury is a strong predictor of eventual suicide attempt; not all events classified as a suicide attempt are motivated by a true desire to die, but rather by desires to attract attention, to escape, and to communicate hostility; however, when only deliberate self-harm is reported, suicide attempts and non-suicidal self-injury cannot be subsequently disaggregated

Table: Nomenclature for suicidal and related behaviours and suicidal ideation

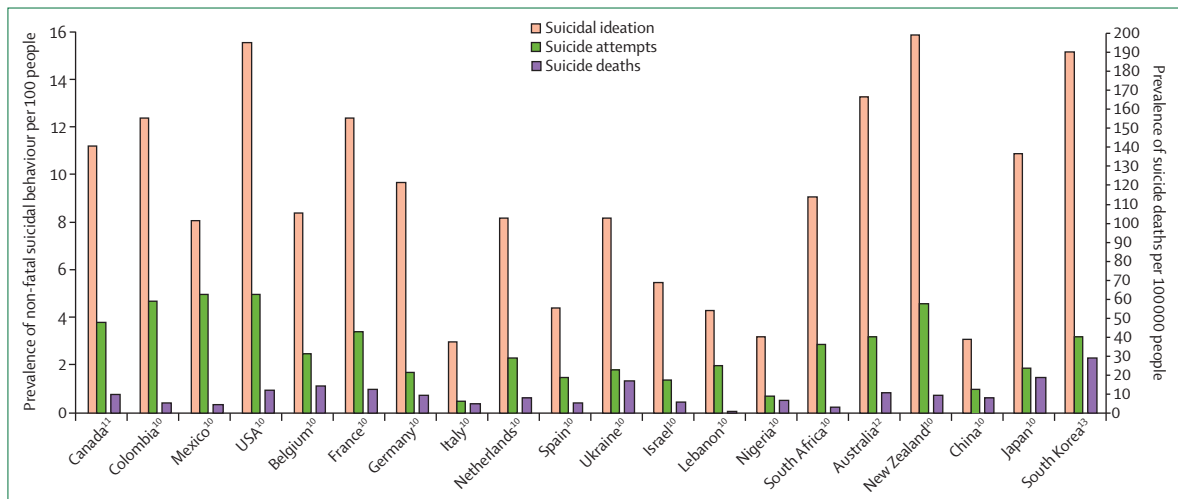


Figure 1: National prevalences of suicidal behaviours

Sources for data for non-fatal suicidal behaviours are cited in the figure; data for deaths from suicide are from the WHO 2014 report.¹

the second leading cause of death in individuals aged 15–29 years.¹ The incidence of suicide ideation and suicidal behaviour peaks in adolescents and young adults, with a lifetime prevalence of suicidal ideation of 12.1–33%, and of suicidal behaviour of 4.1–9.3%.^{7,14} In elderly people, rates of suicidality are also high,

particularly among those with physical disorders, depression, and anxiety.¹⁵ Sex is also a factor in suicidal behaviour, with higher rates of ideation and suicide attempts among women;^{8,9} however, rates of suicide deaths are generally higher in men (15 per 100 000 men vs eight per 100 000 women, worldwide).¹ The ratio of

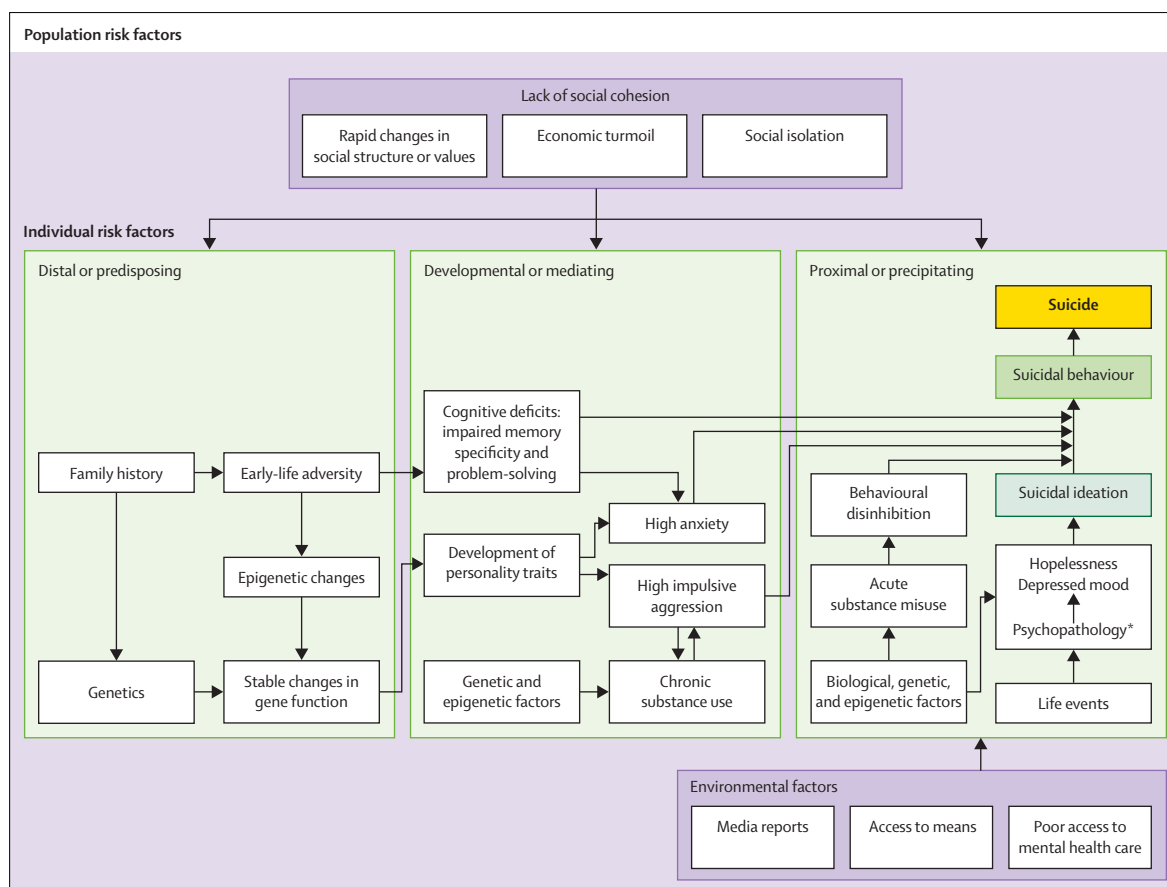


Figure 2: Model for suicide risk

Suicide risk is modulated by a range of factors both at the population and individual levels. Individual risk factors can be grouped into distal (or predisposing), developmental (or mediating), and proximal (or precipitating) factors, and many of these factors interact to contribute to the risk of developing suicidal behaviours.

*Any single mental illness associated with suicide risk, or a combination of mental illnesses, including major depressive disorder, bipolar disorder, schizophrenia, and personality disorders; the presence of a depressive episode is often a sign of increased risk of suicide.

male to female deaths by suicide is higher in high-income countries (3·5) than in low-to-middle-income countries (1·6), and in Europe and the Americas (3·6–4·1) than in Asian Pacific countries (0·9–1·6).¹ Seasonal variation in suicide rates has also been reported, with peak incidence in spring and summer, and suicide rates might correlate with latitude and exposure to sunshine.¹⁶

Contemporary models of suicide risk

In the past century, the contributions of both social and individual factors to understanding suicide risk have been recognised. Several models have been proposed, most emphasising the interaction between predisposing and precipitating factors.^{17–20} Figure 2 shows putative temporal relationships between different suicide risk factors. Suicide has many causes, with substantial variability in the strengths and patterns of association of risk factors across sex, age, culture, geographic location, and personal history. Thus, models have been proposed to explain risks of suicide in specific subgroups, such as in people exposed to early-life adversity.^{21,22}

Factors and associated mechanisms that increase risk of suicide

Population-level risk factors

More than a century ago, Durkheim recognised the effect of population-level social factors on suicide rates. Increases in suicide rates among indigenous peoples, such as Canadian Inuits, correlate with social changes such as forced settlement, assimilation, and disruption of traditional social structure.⁶ Conversely, suicide is rare in homogeneous societies with high social cohesion, common values, and moral objections to suicide.^{23,24} although the latter might also lead to under-reporting. Economic crises resulting in unemployment and decreased personal income have been correlated with increases in suicide, particularly in men, although a direct causal relationship has not yet been established.^{25,26}

Media reporting of suicide also affects suicide rates, particularly within the first 30 days of publicity, with increases in the rate of suicide proportional to the amount of publicity, when details of a method are provided, if the decedent was a celebrity, and if the

suicide was romanticised rather than reported in association with mental illness and the adverse consequences of the suicide on survivors.²⁷ Adolescents and young adults are particularly susceptible to the effects of media publicity.²⁸

Individual risk factors for suicide

Distal or predisposing risk factors

Suicidal behaviours run in families (odds ratio [OR] for first or second degree relatives is 1.7–10.62, when adjusting for degree of relation),^{4,29,30} indicating that distal factors can increase suicide risk. Family studies show that the risk of attempts is higher in relatives of people who died by suicide, and that the risk of dying by suicide is higher in relatives of people with a history of suicide attempts.³¹ These effects are unlikely to result from imitation because adoption studies show concordance between biological, but not adoptive relatives.³² Although psychopathological disorders also aggregate in families, the transmission of suicidal behaviour seems to be mediated through the transmission of impulsive aggression.^{4,33} Twin and adoption studies suggest that genetic factors account for part of the familial transmission of suicidal behaviour, with estimates of heritability of 30–50%.^{34,35} However, when the heritability of other psychiatric conditions is taken into account, the specific heritability of suicidality is estimated as 17.4% for suicide attempts and 36% for suicide ideation.³⁵ Ideation seems to be cotransmitted with mood disorders and shows a distinct pattern for transmission from suicidal behaviour.^{4,36} Despite consistent evidence for the heritability of suicidal behaviour, the identification of specific genes associated with suicide risk remains elusive, despite several candidate-gene and genome-wide association studies, which have mostly provided inconclusive results.²¹ Modelling the interactions between experience and genes would be useful.

In addition to heritable factors, other psychosocial, demographic, and biological factors increase vulnerability to suicide.¹⁷ Sexual orientation affects suicide risk, and although psychological autopsy-based studies of completed suicides have not consistently shown an over-representation of sexual minority status in people who die by suicide, analysis of registry-based data suggests that individuals with a history of same-sex relationships have a 3–4-times greater risk of dying by suicide, with a disproportionately greater risk for men than for women. Belonging to a sexual minority is universally linked with increased rates of suicide attempts irrespective of sex.³⁷

Another well characterised risk factor is exposure to early-life adversity, generally defined as parental neglect or childhood physical, sexual, or emotional abuse. The association between early-life adversity and lifetime suicide risk is supported by evidence from prospective^{38,39} and retrospective longitudinal studies,⁴⁰ as well as

multiple case-control studies,²² and is moderated by several factors, including the type of abuse (neglect, physical abuse, or sexual abuse), the frequency of the abuse, and the relationship between the victim and the abuser.³⁹ Early-life adversity might also be transmitted through families, partly explaining the familial aggregation of suicidal behaviour.⁴¹ Early-life adversity might induce long-term effects through epigenetic changes in gene pathways. The hypothalamic–pituitary–adrenal axis regulates physiological responses to stress to facilitate coping with changing environments or challenging events, mainly through cortisol regulation. Individuals who have experienced early-life adversity often have a hyperactive hypothalamic–pituitary–adrenal axis and an increased stress response,⁴² which is partly caused by decreased hippocampal expression of glucocorticoid receptors and is associated with increased DNA methylation of its promoter⁴³ in both central nervous tissues and peripheral tissues such as blood or saliva.⁴⁴ FKBP5 inhibits glucocorticoid receptor signal transduction and might contribute to the risk of suicidal behaviour; FKBP5 sequence variants are associated with an increased risk of suicidal behaviour, especially in people who have had early-life adversity.²¹

Early-life adversity is also associated with epigenetic modification of genes involved in neuronal plasticity, neuronal growth, and neuroprotection.^{45,46} Animal models of early-life adversity show hypermethylation and consequent downregulation of *BDNF*.⁴⁷ Studies of brain tissue from people who completed suicide show that mRNAs encoding BDNF and its receptor *TRKB* are downregulated in several brain regions including the prefrontal cortex and the hippocampus, and some studies report differential methylation of *BDNF* and *TRKB* in the brains of people who died by suicide compared with in people who died from other causes.^{48,49} Genome-wide association studies of people with depression or people who have died by suicide and who had early-life adversity have identified methylation changes in genes associated with stress, cognitive processes, and neural plasticity.^{45,46} This evidence supports the hypothesis that early-life adversity mediates suicide risk through long-term epigenetic regulation of gene expression.

Another potential risk factor for suicidal behaviour is infection with the brain-tropic parasite *Toxoplasma gondii*.^{50,51} In a large sample of women tested for *T gondii* infection at childbirth and followed up for more than a decade, seropositive women had increased risk of self-directed violence (OR 1.53, 95% CI 1.27–1.85), violent suicide attempt (1.81, 1.13–2.84), and suicide (2.05, 0.78–5.20), with risk of self-directed violence correlated with concentrations of anti-toxoplasma antibodies.⁵⁰ One proposed mechanism for this association involves immunological responses to infection, which might alter neurotransmitter activity.⁵²

Developmental or mediating risk factors

Distal factors probably act through personality traits and cognitive styles that mediate their association with suicidal behaviour. Although depression and anxiety make strong contributions to the risk of suicidal behaviour throughout life, results of both retrospective and prospective studies suggest that interpersonal conflict, impulsive aggression, conduct disorder, antisocial behaviour, and alcohol and substance misuse are more salient for suicidal behaviour in adolescents and young adults, whereas harm avoidance and mood disorders become more common with increasing age.^{53,54} Young people who die by suicide often have a high burden of adversity and a history of childhood abuse or neglect.⁵⁴ The highest risk for suicidal behaviour across the lifespan exists when a mood disorder that is associated with suicidal ideation co-occurs with other disorders that either increase distress (panic disorder, post-traumatic stress disorder) or decrease restraint (conduct and antisocial disorders, substance misuse).⁷ The development of high impulsive-aggressive behaviours and high anxiety traits might also partly explain the relation between early-life adversity and suicide risk,⁵⁵ and these traits explain part of the familial aggregation of suicidal behaviour.^{33,56}

Early-life adversity causes cognitive deficits, particularly in problem-solving and memory specificity, which are contributors to suicidality.^{57,58} It might have an especially important role in suicidal behaviour in adolescent and young adults because adversity is related to earlier age of onset of psychiatric disorder,⁵⁹ and because the cognitive effects of adversity interact with adolescents' and young adults' incompletely developed prefrontal cortical systems, which in turn increases the likelihood of risk-taking and impulsive behaviour.⁶⁰ Individuals with a higher than average cortisol response to stress,⁶¹ a history of suicide ideation,⁶² or a first-degree relative who has died by suicide⁶³ have impaired cognitive functions after social or emotional stressors, as measured by decision making, problem-solving, and executive function. Adolescents who are poor at problem-solving are more likely to experience suicide ideation after a stressful experience than other adolescents,⁶⁴ suggesting that altered cognitive patterns might mediate the effect of early-life adversity on suicidal behaviour.

Proximal or precipitating risk factors

Proximal risk factors are temporally associated with suicidal behaviours and act as their precipitants. Aside from past suicide attempts, psychopathology is the most important predictor of suicide and strongly associates with other forms of suicidal behaviour.^{65,66} Retrospective, proxy-based interviews with informants, commonly referred to as psychological autopsies, have often been used to investigate the association between psychopathology and suicide, and consistently show that roughly 90% of individuals who die by suicide had an identifiable

psychiatric disorder before death.⁶⁵ Most individuals with a psychiatric illness do not die by suicide, but some psychiatric illnesses are more strongly linked to suicidal behaviours than others. Major depressive episodes, associated with either major depressive disorder or bipolar disorder, account for at least half of suicide deaths.⁶⁷ Among patients with bipolar disorder, mixed state episodes most strongly associate with suicide attempts, with risk increasing according to the amount of time spent in mixed depressive episodes;⁶⁷ suicide risk is highest within the first year of illness⁶⁸ and associates with feelings of hopelessness.⁶⁷ Adults with schizophrenia and other psychotic disorders are also at heightened risk;⁶⁹ the main clinical predictors of suicide include presence of depressive symptoms, young age, male sex, education, positive symptoms, and illness insight.⁷⁰

Multiple other factors, such as alcohol and drug-related disorders, are common in people who die by suicide and might exacerbate underlying risk or interact with depression to increase risk of engaging in suicidal behaviours.^{66,71}

Other illnesses common in people who die by suicide include eating disorders and personality disorders, particularly cluster B personality disorders such as borderline and antisocial personality disorder, which are characterised by aggressive and impulsive traits.⁷² People who die by suicide often have a history of more than one disorder, and in individuals with psychiatric illnesses such as depression, which is associated with suicide ideation, comorbidity with disorders characterised by severe anxiety or agitation or poor impulse control predicts suicidal behaviour.^{71,72} Studies also suggest that people who die by suicide who did not meet criteria for a mental illness were probably affected by a psychiatric disorder, but the psychological autopsy protocol failed to detect it.⁷³ Although psychological autopsies have several limitations because they are retrospective and done by proxy, they are often the only way to identify and describe risk factors that contribute to suicide and generally show strong concordance between independent raters, personal and proxy-informants, and ante-mortem and post-mortem diagnoses.⁷⁴

In addition to methodological factors, age, geographic location, and sex largely explain the variability between studies. Younger age at suicide is associated with comorbidity, particularly with cluster B personality pathology and substance misuse disorders.^{53,75} In middle-aged people, alcohol and substance misuse, high anxiety, and comorbid major depression disorder are associated with suicide risk,^{76,77} whereas in older people there is a stronger association between suicide and psychopathology, particularly major depressive disorder.⁷⁸ Geographic origin is another source of variation, with more people who die by suicide in Europe and the Americas meeting criteria for psychiatric disorders than in those from Asia,¹ where other factors might also contribute to the risk of suicide. In China, rural areas have three-times higher rates of suicide

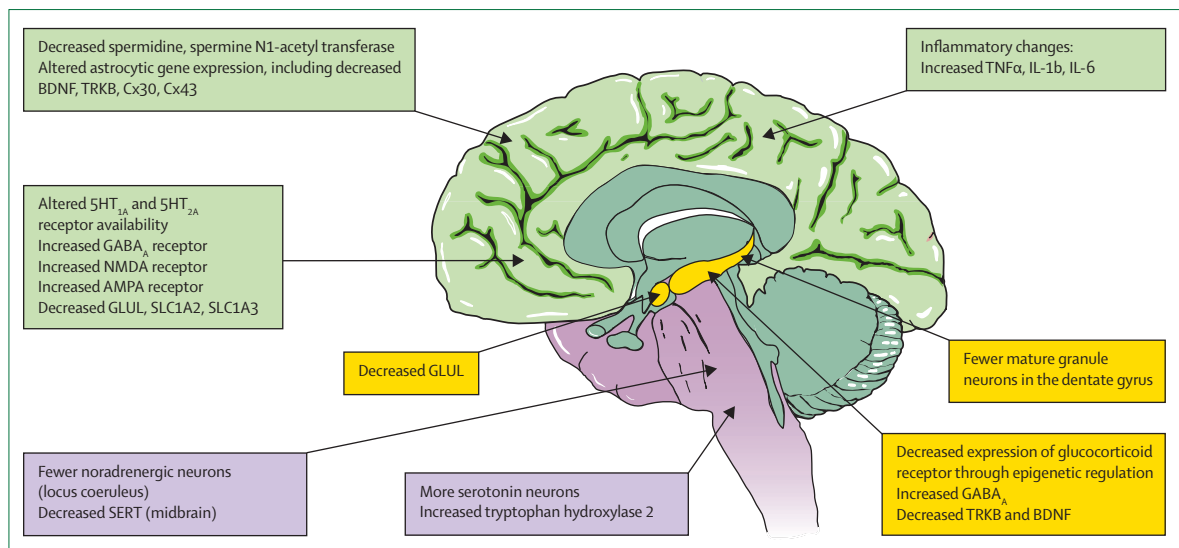


Figure 3: Biological changes in the brains of people with suicidal behaviours

SHT=5-hydroxytryptamine, or serotonin. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. BDNF=brain-derived neurotrophic factor. Cx=connexin. GABA=γ-aminobutyric acid. GLUL=glutamine synthetase. IL=interleukin. NMDA=N-methyl-D-aspartic acid. SERT=serotonin transporter. SLC=solute carrier family. TNF=tumour necrosis factor. TRKB=tropomyosin receptor kinase B.

than do urban areas.⁷⁹ The easy access to highly lethal pesticides, which are the most common method of suicide in China, might contribute to the high fatality rate of the largely impulsive low-intent suicide attempts that characterise suicide in rural China; increased lethality of suicide attempts might partly explain why, relative to men, women in China have higher rates of suicide death than in other parts of the world.⁷⁹ In sum, although several factors explain variation among studies in the strength and characteristics of the association between psychopathology and suicide, almost all individuals who intentionally end their lives, irrespective of whether or not they meet structured criteria for a psychiatric disorder, show evidence of hopelessness, depressed mood, and suicide ideation.

Suicidal states associate with various molecular changes that are detectable both in the periphery, such as blood and saliva, and in the brain (figure 3).²¹ Among the first to be described was the altered levels of serotonin and serotonin signalling in individuals exhibiting suicidal behaviours.⁸⁰ Several studies link disrupted serotonin expression to suicide attempt or suicide, and despite discrete differences in serotonin receptor and transporter expression between patients with depression and those who exhibit suicide ideation or suicidal behaviours,⁸¹ it is unclear to what extent altered serotonin signalling in people who die by suicide can be distinguished from changes associated with depression because these two phenotypes often occur together.⁸² There is evidence that individuals exhibiting suicidal behaviours have unique serotonin genotype and expression patterns,^{83,84} and low serotonin is associated with personality traits linked to suicidality, such as impulsive aggression.⁸⁵ Other neurotransmitters implicated in depression and suicide are glutamate and γ-aminobutyric acid,^{86,87} and treatments

targeting the glutamate pathway, such as ketamine, have yielded some promising initial results in the treatment of severe depression and suicide ideation.⁸⁸ Aside from neurotransmitters, inflammatory responses have been linked to suicidal behaviour, with some evidence suggesting that inflammation linked to suicidality might occur both in the central nervous system and in peripheral tissues, as detected in blood samples.⁸⁹

Consistent with the data from studies of early-life adversity, stress response systems might be altered during suicidal states. Substantial alterations of the polyamine system⁹⁰ and the hypothalamic–pituitary–adrenal axis^{93,91} have been described in the brains of people who attempt suicide and who die by suicide. Altered responses to stressful social situations might lead to psychopathological disorders and suicidal behaviour, with evidence that suicidality is associated with several changes in the brains of people with suicidal ideation or behaviours.⁹² Glial cell function might also be disrupted in people who show suicidal behaviours,⁹³ where astrocyte-specific genes linked to structural integrity are downregulated,^{94,95} and neurotrophic factors such as the BDNF receptor TRKB are expressed differently in people who die by suicide and controls.⁴⁸

Other proximal risk factors also have a role in risk of suicide, either independently or by interacting with psychopathological disorders (panel 1).^{96–99}

Interventions to prevent or treat suicidal behaviour

Prevention

Several reviews of the efficacy of different prevention practices have been published.^{100–103} School, workplace, and community-based interventions, and multicomponent

Panel 1: Social and physical factors that affect risk of suicide**Social factors associated with an increased risk of suicide**

- Living alone
- High introversion
- Extreme hopelessness, helplessness and worthlessness, or defeat and entrapment, which may result from depressive psychopathology
- Traumatic events in adulthood
- Interpersonal stressors
- Loss or bereavement: causes emotional distress, can lead to an enduring inability to cope with the loss; complicated grief and development of suicide ideation or behaviour is more likely in cases of bereavement caused by a violent death such as suicide
- Financial or legal difficulties
- Physical illnesses with concurrent depression: respiratory diseases such as chronic obstructive pulmonary disorder and asthma (for death by suicide vs other causes, odds ratio 1.5–2.1), cardiovascular diseases such as coronary heart disease and stroke (1.53–1.54), degenerative diseases such as osteoporosis and multiple sclerosis (2.33–2.54); differs by sex, with increased risk for women^{96,97}
- Chronic diseases acting independently of mental disorders: inflammatory bowel disease, migraine (hazard ratio 1.34),⁹⁸ and epilepsy (adjusted odds ratio 2.9, when controlling for

sociodemographic factors and using sibling controls);⁹⁹ in patients with epilepsy, suicidal behaviours can precede onset of seizures or be a sequela of treatment

- Sleep disturbances and insomnia: increased risk of suicide ideation or suicidal behaviours can be independent of depression; might be mediated by increased impulsivity, negative cognitive bias, and reward-seeking
- Traumatic brain injury: athletes and war veterans who have sustained chronic traumatic encephalopathy are especially vulnerable; possibly mediated by a decrease in impulse control following repeated injuries; lifetime occurrence of psychiatric disorder associated with a greater risk of suicide in patients with traumatic brain injury

Social factors associated with a decreased risk of suicide

- Well developed social support network
- Strong reasons for living
- Responsibility for young children
- Religiosity (frequent attendance of religious services or personal religiosity); might be related to religious views on suicide, or to social support derived from the religious community
- Extraversion and optimism
- Effective coping and problem-solving

primary care interventions, can reduce the incidence of suicide or suicidal behaviour, as can the organisation of and access to care, and reduced access to means of suicide.

School-based interventions reduce the incidence of suicide ideation or suicidal behaviour. The Good Behaviour Game, a teacher-led classroom intervention for children aged 6–7 years, reduced suicide ideation and suicidal behaviour in one of two randomised trials (the other trial was underpowered),¹⁰² and the Signs of Suicide (SOS) programme, which educates students about the relation between mental disorders and suicide, self-identification of depression and suicidal risk, and encourages appropriate help-seeking, also reduced the incidence of suicide attempts.¹⁰² An international cluster randomised trial that compared screening and referral, gatekeeper training (in which strategically positioned individuals are trained to recognise people at risk of suicide and refer them to appropriate services), and a mental health awareness programme similar to the SOS programme showed that only the mental health awareness programme was associated with a lower incidence of serious suicide ideation and suicide attempts.¹⁰⁴ Studies of post-high school suicide prevention similarly showed no effect for educational or gatekeeper interventions, but one quasi-experimental study showed that method restriction and mandatory professional assessment of students who exhibit suicidal behaviours reduced the suicide rate.¹⁰³

A multi-component preventive intervention programme in the US Air Force, including leadership and gatekeeper training, increased access to mental health services, coordination of care for high-risk individuals, and a higher level of confidentiality for those who disclosed suicidality reduced suicide rates by 35%.¹⁰⁵ Among elderly people, some evidence suggests that interventions to decrease isolation and augment social support through activity groups and telephone outreach might also reduce mortality caused by suicide.¹⁰¹

A substantial proportion of patients access primary care within 1 month of suicide, but are rarely diagnosed with a mental disorder.² Education programmes for primary care doctors targeting identification and treatment of depression can decrease regional suicide rates, particularly in women, but need continued education and additional physician support to improve patient outcomes.^{106–108} In particular, websites for physicians, increasing liaison between physicians and psychiatric facilities, public education campaigns to train key community facilitators in the recognition of depression and suicide risk, and a suicide hotline might all be important aspects of prevention strategies.¹⁰⁹ Collaborative care, in which care for psychiatric disorders is co-located with primary care, provides substantial benefits over usual care in outcomes for depression and anxiety,¹¹⁰ and improves suicide ideation in older patients with depression.¹¹¹

Patients recently discharged from psychiatric inpatient units are at very high risk for completed suicide.

Through decades of research, Appleby and colleagues have identified factors of mental health services that are associated with increased suicide risk (eg, lack of 24 h crisis care), made recommendations for systems change, and assessed the relation between regional changes in suicide rate and the level of regional implementation of the recommended systems modifications.¹¹² Declining regional suicide rates are related to the extent of care, clear policies for the management of dual diagnosis patients, and multidisciplinary reviews of suicide deaths.

The effect of means restriction is estimated on the basis of before-and-after or other types of quasi-experimental designs. Means restriction strategies are guided by the assumption that many suicides are impulsive, and restricting access to lethal methods might forestall a suicidal crisis; even if method substitution takes place, the person will have access to less lethal, potentially non-fatal means of suicide.¹¹³ The effect of means restriction on attempting or completing suicide have been assessed in case-control studies and regional comparisons of suicide rates and methods. The rate of suicide by a given method, whether firearms, natural gas, car exhaust, paracetamol, substitution of less toxic drugs (eg, selective serotonin reuptake inhibitors vs tricyclic antidepressants), pesticides, or jumping from bridges, is related to the ease of access.¹¹³ Laws that impede access to a method, whether stricter firearms control laws, detoxification of domestic gas or car exhaust, limitation of access and use of blister packs for paracetamol, lockboxes for pesticides, or bridge barriers (often combined with a telephone hotline for crisis intervention), reduce suicides by that method, although some method substitution might occur.¹¹³ Brief, individual-level interventions to encourage safe storage of hazardous items such as pesticides or firearms can work, although the effect of these interventions on morbidity or mortality has not been recorded.¹¹³

Case management and outreach

Panel 2 summarises the key aspects of detecting and treating suicidal behaviour.^{114,115} Maintaining follow-up with people who present to an emergency department after a suicide attempt can reduce repetition of suicide attempt in the following 12 months (overall relative risk 0.83, 95% CI 0.71–0.97; n=5319),¹¹⁶ as evidenced by two interventions that decreased the suicide rate compared with usual care:¹¹⁷ a large international study of an emergency department-based intervention that provided follow-up case management and encouragement of adherence resulted in a suicide rate of 0.2% versus 2.2% with usual care (n=1867); and supportive letters sent to patients who had exhibited suicidal behaviors, did not adhere to treatment, and had been discharged from an inpatient unit, decreased the suicide rate within the first 2 years of the intervention (1.8% vs 3.5% with usual care, n=843). Many studies trying to replicate the latter findings using postcards for patients who attempted self-poisoning showed a reduction in the risk of repeated overdose.¹¹⁷

Somatic treatment for suicidal behaviour

Meta-analyses of randomised controlled trials of drug treatment for depression show that antidepressant treatment decreases suicide ideation in individuals aged 25 years and older.¹¹⁸ Some evidence suggests that selective serotonin reuptake inhibitors result in greater reduction of suicide ideation than either venlafaxine or bupropion.^{119,120} In participants aged 24 years and younger, antidepressant treatment decreases depressive symptoms, but does not always diminish suicide ideation.¹¹⁸ Antidepressant treatment in people younger than 25 years is associated with a 1–2% risk difference in the incidence of suicidal events—ie, new-onset or worsening suicide ideation, or suicide attempts.¹²¹ The US Food and Drug Administration issued a warning in 2004 about the possibility of increased suicidality associated with antidepressants in young people, and several other countries followed. After this warning, rates of diagnosis of depression and prescriptions of antidepressants for young people have declined,¹²² and overdoses of psychotropic drugs and suicide in this group have increased.¹²³ Pharmacoepidemiological studies using data from 26 countries show that sales and prescriptions of selective serotonin reuptake inhibitors are inversely correlated with national and regional suicide rates, including in young people.¹²⁴ The larger size and unselected nature of samples used in pharmacoepidemiological studies, which include high-risk patients who typically would be excluded from randomised controlled trials, might explain the discrepancy between the apparent protective effect of antidepressants in pharmacoepidemiological studies and increased incidence of suicidal events reported in young people enrolled in clinical trials.

Other drugs used in mood disorders have shown some efficacy for suicidal behaviour. Observational studies show that lithium content in water is inversely correlated with regional suicide rates,¹²⁵ naturalistic treatment studies associate exposure to lithium with a low suicide and suicide attempt rate compared with antiepileptic drugs,^{126,127} and meta-analyses of randomised controlled trials support lithium's protective effect against suicide.¹²⁸ In 48 randomised controlled trials involving 6674 individuals with unipolar or bipolar depression, lithium was associated with a diminished rate of suicide relative to placebo (OR 0.13, 95% CI 0.03–0.66) and a decreased rate of deliberate self-harm for lithium compared with carbamazepine.¹²⁸ Although the exact mechanisms by which lithium decreases suicidal behaviours are unknown, it might act by reducing mood disorder episodes or by decreasing impulsive and aggressive behaviour.¹²⁹

There is growing enthusiasm for use of ketamine, a glutamatergic drug used as an anaesthetic, to treat suicidal behaviour. Trials using low doses have shown an antidepressant response within minutes of administration in patients with major depressive disorder or bipolar disorder.¹³⁰ Preliminary studies have

Panel 2: Interventions for detection and treatment of suicidal behaviours

Detection of patients at risk of suicide

Contact with health-care services:

- People who attempt and complete suicide often seek medical help within 12 months of their suicide or suicide attempt, most often consulting primary care services
- Primary health-care workers have an opportunity to reach individuals who are contemplating suicide before they act

Adolescents are less likely than are adults to seek help in the last year and month before suicide:

- Despite high prevalence of lifetime contact for emotional or substance-related difficulties, fewer than 20% use services within 1 year of onset of suicidal behaviours
- More effective outreach programmes for young people are needed

Assessing the degree of risk

Often primary care doctors do not adequately assess suicide risk at the last visit before a patient's death

Clinical indicators of suicide risk:

- The Columbia Suicide Severity Rating Scale¹¹⁴ is widely used to establish the risk of suicide
- Previous suicide attempt and method of suicide attempt predicts increased suicide risk
- Suicide completers are likely to have had repeated hospital admissions; recurrence of self-harming is most likely within 3–6 months of first presentation
- Ambivalence, worthlessness, helplessness, and hopelessness are key indicators of heightened suicide risk
- High-risk patients should be followed up closely after discharge

Diagnosis of patients:

- Less than one-third of patients with suicidal behaviours express their suicidal intent to their health-care professional

- The Self-Injury–Implicit Association Test¹¹⁵ detects implicit thoughts of deliberate self-harm, but its sensitivity is poor
- Previous history, presence of risk factors, and collateral information can inform physicians about suicide risk
- Particular states, such as mixed state bipolar disorder and psychotic episodes during depression, can significantly increase the risk of imminent suicidal acts and require particular attention

Defining the level of intervention

- Treatment can include drug treatment, behavioural therapy, or referral to specialised care, such as psychological, psychiatric, or social therapists or to an emergency department, in case of serious risk of imminent harm
- Any diagnosed psychiatric illness should guide treatment decisions, including selection of drug treatments
- Treatment should be selected on the basis of the patient's profile and manifestations of suicidal behaviours: multidisciplinary interventions strongly based on psychotherapy for chronic suicidal behaviours and more aggressive forms of intervention for acute suicidal behaviours
- Elderly patients manifesting acute suicidal behaviours typically require interventions that guarantee safety, such as hospital admission
- Internet-based applications to monitor patients after discharge and between appointments can improve patient outcomes, although further study is necessary to show their effectiveness
- Improved coordination between primary and secondary care and frequent follow-up after discharge probably improve outcomes

shown that single and repeated doses of ketamine can reduce suicide ideation, making it a promising treatment for patients with suicidal behaviours in emergency departments.⁸⁸ The main disadvantages of ketamine are its potential for misuse, the transient nature of the response, and cardiac and psychotomimetic side-effects.

Other classes of drugs also have antisuicidal effects. In the InterSePT trials, clozapine, an atypical antipsychotic used for treatment-refractory schizophrenia, decreased suicide attempts and emergency referrals for suicide ideation compared with olanzapine (hazard ratio 0.76, 95% CI 0.58–0.97) in patients with schizophrenia or schizoaffective disorder at high risk for suicidal behaviour.¹³¹ Naturalistic studies (observational studies in community or in clinical settings, typically with no control) show that patients treated with clozapine have one-third the incidence of completed and attempted suicide compared with patients treated with other antipsychotics.¹³²

In addition to drug interventions, electroconvulsive therapy might reduce suicidal behaviour. In an open-label study of patients with depression at high suicidal risk, more than three-quarters of patients treated with electroconvulsive therapy had no suicidal thoughts or intent after nine sessions, which is consistent with previous studies.^{133,134} Other neuromodulatory treatments might have similar effects on suicide ideation. Preliminary evidence suggests that high doses of repetitive transcranial magnetic stimulation applied to the left prefrontal cortex might rapidly decrease suicide ideation.¹³⁵

Psychotherapeutic interventions for recurrent suicidal behaviour

Most efficacious treatments for suicidal behaviour share several common elements: use of exploratory interventions to understand the behaviour and interventions to encourage positive, and discourage negative, behaviours; explicitly focusing on suicidal behaviour; having the

therapist adopt an active attitude to treatment including problem-solving; planning for coping with suicidal urges; and focusing on emotional and cognitive precursors of suicidal behaviour.¹³⁶

Dialectic behaviour therapy is probably the most commonly investigated psychotherapy for recurrent suicidal behaviour. It has mainly been studied in patients with borderline personality disorder; dialectic behaviour therapy promotes belief in one's own ability to succeed, interpersonal effectiveness, and emotional regulation, and has repeatedly been shown to reduce the recurrence of suicidal behaviour compared with usual treatment, with more modest differences compared with expert community care.¹³⁷ Dialectic behaviour therapy is derived from cognitive behaviour therapy, which can also reduce recurrence of suicidal behaviour, with larger effects in adults than in adolescents, with individual versus group treatment, and when suicidality is an explicit focus of treatment.^{138,139} The psychodynamically derived mentalisation-based therapy, in which patients are taught how to think about their and other people's actions as the result of underlying thoughts and emotions, thereby improving their ability to understand their own and others' perceptions, is also effective in reducing suicidal behaviours according to two trials in adults with borderline personality disorder.¹³⁷ For adolescents, a meta-analysis of studies addressing self-harm showed an overall effect of treatment compared with usual treatment, with some of the most promising interventions being cognitive behavioural therapy, dialectic behaviour therapy, mentalisation, and family therapy; successful interventions were more likely to have a family component and be offered as multiple sessions.¹⁴⁰

Perspectives

Suicidal behaviours are heterogeneous, both in terms of presentation and treatment, making it difficult to provide an all-encompassing model of suicide risk or to suggest a clear treatment formula. Because of the complexity and the breadth of the subject, we present an overview of the present state of knowledge in suicide research. Certain aspects, such as detailed discussions of the psychology of suicide and suicide prevention, have been well described elsewhere.^{17,141} Ongoing advances in suicide research are enriching the clinician's options to manage suicidal patients. Based on clinical trials and natural experiments of drug and psychotherapeutic interventions, improvements in patient identification and treatment, outreach, and method restriction, there is strong evidence that suicide is preventable. Greater sensitivity to the potential for suicidal behaviour, continued improvements in public health policy, and basic and translational research have the potential to contribute to reducing global rates of suicide in the future.

Contributors

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References

- 1 WHO. Mental health: suicide prevention. 2014. http://www.who.int/mental_health/suicide-prevention/en/ (accessed Nov 5, 2014).
- 2 Ahmedani BK, Simon GE, Stewart C, et al. Health care contacts in the year before suicide death. *J Gen Intern Med* 2014; **29**: 870–77.
- 3 Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007; **164**: 1035–43.
- 4 Brent DA, Bridge J, Johnson BA, Connolly J. Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. *Arch Gen Psychiatry* 1996; **53**: 1145–52.
- 5 Spallek J, Reeske A, Norredam M, Nielsen SS, Lehnhardt J, Razum O. Suicide among immigrants in Europe—a systematic literature review. *Eur J Public Health* 2015; **25**: 63–71.
- 6 King M, Smith A, Gracey M. Indigenous health part 2: the underlying causes of the health gap. *Lancet* 2009; **374**: 76–85.
- 7 Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry* 2013; **70**: 300–10.
- 8 Borges G, Nock MK, Haro Abad JM, et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *J Clin Psychiatry* 2010; **71**: 1617–28.
- 9 Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry* 2008; **192**: 98–105.
- 10 Weissman MM, Bland RC, Canino GJ, et al. Prevalence of suicide ideation and suicide attempts in nine countries. *Psychol Med* 1999; **29**: 9–17.
- 11 Johnston AK, Pirkis JE, Burgess PM. Suicidal thoughts and behaviours among Australian adults: findings from the 2007 National Survey of Mental Health and Wellbeing. *Aust N Z J Psychiatry* 2009; **43**: 635–43.
- 12 Jeon HJ, Lee JY, Lee YM, et al. Lifetime prevalence and correlates of suicidal ideation, plan, and single and multiple attempts in a Korean nationwide study. *J Nerv Ment Dis* 2010; **198**: 643–46.
- 13 Carroll R, Metcalfe C, Gunnell D. Hospital presenting self-harm and risk of fatal and non-fatal repetition: systematic review and meta-analysis. *PLoS One* 2014; **9**: e89944.
- 14 Brezo J, Paris J, Barker ED, et al. Natural history of suicidal behaviors in a population-based sample of young adults. *Psychol Med* 2007; **37**: 1563–74.
- 15 Conwell Y, Van Orden K, Caine ED. Suicide in older adults. *Psychiatr Clin North Am* 2011; **34**: 451–68.
- 16 Christodoulou C, Douzenis A, Papadopoulos FC, et al. Suicide and seasonality. *Acta Psychiatr Scand* 2012; **125**: 127–46.
- 17 O'Connor RC, Nock MK. The psychology of suicidal behaviour. *Lancet Psychiatry* 2014; **1**: 73–85.
- 18 Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci* 2003; **4**: 819–28.
- 19 Mościcki EK. Gender differences in completed and attempted suicides. *Ann Epidemiol* 1994; **4**: 152–58.
- 20 Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE Jr. The interpersonal theory of suicide. *Psychol Rev* 2010; **117**: 575–600.

- 21 Turecki G. The molecular bases of the suicidal brain. *Nat Rev Neurosci* 2014; **15**: 802–16.
- 22 Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci* 2012; **35**: 14–23.
- 23 Egeland JA, Sussex JN. Suicide and family loading for affective disorders. *JAMA* 1985; **254**: 915–18.
- 24 Jollant F, Malafosse A, Docto R, Macdonald C. A pocket of very high suicide rates in a non-violent, egalitarian and cooperative population of South-East Asia. *Psychol Med* 2014; **17**: 1–7.
- 25 Fountoulakis KN, Kawohl W, Theodorakis PN, et al. Relationship of suicide rates to economic variables in Europe: 2000–2011. *Br J Psychiatry* 2014; **205**: 486–96.
- 26 Reeves A, McKee M, Stuckler D. Economic suicides in the Great Recession in Europe and North America. *Br J Psychiatry* 2014; **205**: 246–47.
- 27 Pirkis J, Nordentoft M. Media influences on suicide and attempted suicide. In: O'Connor RC, Platt S, Gordon J, eds. *International handbook of suicide prevention: research, policy and practice*. Chichester, Malden, MA: John Wiley & Sons, 2011: 531–44.
- 28 Gould MS. Suicide and the media. *Ann N Y Acad Sci* 2001; **932**: 200–21.
- 29 Kim CD, Seguin M, Therrien N, et al. Familial aggregation of suicidal behavior: a family study of male suicide completers from the general population. *Am J Psychiatry* 2005; **162**: 1017–19.
- 30 Tidemalm D, Runeson B, Waern M, et al. Familial clustering of suicide risk: a total population study of 11.4 million individuals. *Psychol Med* 2011; **41**: 2527–34.
- 31 Brent DA, Melhem N. Familial transmission of suicidal behavior. *Psychiatr Clin North Am* 2008; **31**: 157–77.
- 32 Schulsinger F, Kety SS, Rosenthal D, Wender PH. A family study of suicide. In: Schou M, Strömgen E, eds. *Origin, Prevention and Treatment of Affective Disorders*. London: Academic Press, 1979: 277–87.
- 33 McGirr A, Alda M, Séguin M, Cabot S, Lesage A, Turecki G. Familial aggregation of suicide explained by cluster B traits: a three-group family study of suicide controlling for major depressive disorder. *Am J Psychiatry* 2009; **166**: 1124–34.
- 34 Statham DJ, Heath AC, Madden PA, et al. Suicidal behaviour: an epidemiological and genetic study. *Psychol Med* 1998; **28**: 839–55.
- 35 Fu Q, Heath AC, Bucholz KK, et al. A twin study of genetic and environmental influences on suicidality in men. *Psychol Med* 2002; **32**: 11–24.
- 36 Lieb R, Bronisch T, Höfler M, Schreier A, Wittchen HU. Maternal suicidality and risk of suicidality in offspring: findings from a community study. *Am J Psychiatry* 2005; **162**: 1665–71.
- 37 Haas AP, Eliason M, Mays VM, et al. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex* 2011; **58**: 10–51.
- 38 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.
- 39 Brezo J, Paris J, Vitaro F, Hébert M, Tremblay RE, Turecki G. Predicting suicide attempts in young adults with histories of childhood abuse. *Br J Psychiatry* 2008; **193**: 134–39.
- 40 Affi TO, Enns MW, Cox BJ, Asmundson GJ, Stein MB, Sareen J. Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *Am J Public Health* 2008; **98**: 946–52.
- 41 Melhem NM, Brent DA, Ziegler M, et al. Familial pathways to early-onset suicidal behavior: familial and individual antecedents of suicidal behavior. *Am J Psychiatry* 2007; **164**: 1364–70.
- 42 Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. *Dev Psychobiol* 2010; **52**: 671–90.
- 43 McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; **12**: 342–48.
- 44 Turecki G, Meaney MJ. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. *Biol Psychiatry* 2014; published online Dec 13. DOI:10.1016/j.biopsych.2014.11.022.
- 45 Weder N, Zhang H, Jensen K, et al. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 417–24.
- 46 Labonté B, Suderman M, Maussion G, et al. Genome-wide epigenetic regulation by early-life trauma. *Arch Gen Psychiatry* 2012; **69**: 722–31.
- 47 Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry* 2009; **65**: 760–69.
- 48 Ernst C, Deleva V, Deng X, et al. Alternative splicing, methylation state, and expression profile of tropomyosin-related kinase B in the frontal cortex of suicide completers. *Arch Gen Psychiatry* 2009; **66**: 22–32.
- 49 Keller S, Sarchiapone M, Zarrilli F, et al. Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Arch Gen Psychiatry* 2010; **67**: 258–67.
- 50 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.
- 51 Arling TA, Yolken RH, Lapidus M, et al. *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. *J Nerv Ment Dis* 2009; **197**: 905–08.
- 52 Flegr J. How and why *Toxoplasma* makes us crazy. *Trends Parasitol* 2013; **29**: 156–63.
- 53 McGirr A, Renaud J, Bureau A, Seguin M, Lesage A, Turecki G. Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. *Psychol Med* 2008; **38**: 407–17.
- 54 Séguin M, Beauchamp G, Robert M, DiMambro M, Turecki G. Developmental model of suicide trajectories. *Br J Psychiatry* 2014; **205**: 120–26.
- 55 Wanner B, Vitaro F, Tremblay RE, Turecki G. Childhood trajectories of anxiousness and disruptiveness explain the association between early-life adversity and attempted suicide. *Psychol Med* 2012; **42**: 2373–82.
- 56 Brent DA, Melhem NM, Oquendo M, et al. Familial pathways to early-onset suicide attempt: a 5.6-year prospective study. *JAMA Psychiatry* 2015; **72**: 160–68.
- 57 Yang B, Clum GA. Childhood stress leads to later suicidality via its effect on cognitive functioning. *Suicide Life Threat Behav* 2000; **30**: 183–98.
- 58 Sinclair JM, Crane C, Hawton K, Williams JM. The role of autobiographical memory specificity in deliberate self-harm: correlates and consequences. *J Affect Disord* 2007; **102**: 11–18.
- 59 Scott KM, McLaughlin KA, Smith DA, Ellis PM. Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. *Br J Psychiatry* 2012; **200**: 469–75.
- 60 Lee FS, Heimer H, Giedd JN, et al. Mental health. Adolescent mental health—opportunity and obligation. *Science* 2014; **346**: 547–49.
- 61 van den Bos R, Hartevelde M, Stoop H. Stress and decision-making in humans: performance is related to cortisol reactivity, albeit differently in men and women. *Psychoneuroendocrinology* 2009; **34**: 1449–58.
- 62 Williams JM, Barnhofer T, Crane C, Beck AT. Problem solving deteriorates following mood challenge in formerly depressed patients with a history of suicidal ideation. *J Abnorm Psychol* 2005; **114**: 421–31.
- 63 McGirr A, Diaconu G, Berlim MT, et al. Dysregulation of the sympathetic nervous system, hypothalamic-pituitary-adrenal axis and executive function in individuals at risk for suicide. *J Psychiatry Neurosci* 2010; **35**: 399–408.
- 64 Grover KE, Green KL, Pettit JW, Monteith LL, Garza MJ, Venta A. Problem solving moderates the effects of life event stress and chronic stress on suicidal behaviors in adolescence. *J Clin Psychol* 2009; **65**: 1281–90.
- 65 Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry* 2004; **4**: 37.
- 66 Hoertel N, Franco S, Wall MM, et al. Mental disorders and risk of suicide attempt: a national prospective study. *Mol Psychiatry* 2015; **20**: 718–26.
- 67 Holma KM, Haukka J, Suominen K, et al. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. *Bipolar Disord* 2014; **16**: 652–61.
- 68 Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord* 2002; **68**: 167–81.

- 69 Sharifi V, Eaton WW, Wu LT, Roth KB, Burchett BM, Mojtabai R. Psychotic experiences and risk of death in the general population: 24-27 year follow-up of the Epidemiologic Catchment Area study. *Br J Psychiatry* 2015; **207**: 30–36.
- 70 Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* 2010; **24** (suppl): 81–90.
- 71 Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 868–76.
- 72 Tyrer P, Reed GM, Crawford MJ. Classification, assessment, prevalence, and effect of personality disorder. *Lancet* 2015; **385**: 717–26.
- 73 Ernst C, Lalovic A, Lesage A, Seguin M, Tousignant M, Turecki G. Suicide and no axis I psychopathology. *BMC Psychiatry* 2004; **4**: 7.
- 74 Conner KR, Beautrais AL, Brent DA, Conwell Y, Phillips MR, Schneider B. The next generation of psychological autopsy studies. Part I. Interview content. *Suicide Life Threat Behav* 2011; **41**: 594–613.
- 75 Kim C, Lesage A, Seguin M, et al. Patterns of co-morbidity in male suicide completers. *Psychol Med* 2003; **33**: 1299–309.
- 76 Akechi T, Iwasaki M, Uchitomi Y, Tsugane S. Alcohol consumption and suicide among middle-aged men in Japan. *Br J Psychiatry* 2006; **188**: 231–36.
- 77 Park JE, Lee JY, Jeon HJ, et al. Age-related differences in the influence of major mental disorders on suicidality: a Korean nationwide community sample. *J Affect Disord* 2014; **162**: 96–101.
- 78 Conwell Y, Duberstein PR, Cox C, Herrmann JH, Forbes NT, Caine ED. Relationships of age and axis I diagnoses in victims of completed suicide: a psychological autopsy study. *Am J Psychiatry* 1996; **153**: 1001–08.
- 79 Phillips MR, Yang G, Zhang Y, Wang L, Ji H, Zhou M. Risk factors for suicide in China: a national case-control psychological autopsy study. *Lancet* 2002; **360**: 1728–36.
- 80 Asberg M, Thorén P, Träskman L, Bertilsson L, Ringberger V. “Serotonin depression”—a biochemical subgroup within the affective disorders? *Science* 1976; **191**: 478–80.
- 81 Arango V, Underwood MD, Mann JJ. Serotonin brain circuits involved in major depression and suicide. *Prog Brain Res* 2002; **136**: 443–53.
- 82 Mann JJ. The serotonergic system in mood disorders and suicidal behaviour. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20120537.
- 83 Sullivan GM, Oquendo MA, Milak M, et al. Positron emission tomography quantification of serotonin1A receptor binding in suicide attempters with major depressive disorder. *JAMA Psychiatry* 2015; **72**: 169–78.
- 84 Brezo J, Bureau A, Mérette C, et al. 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.
- 85 Yanowitch R, Coccaro EF. The neurochemistry of human aggression. *Adv Genet* 2011; **75**: 151–69.
- 86 Sequeira A, Mamdani F, Ernst C, et al. Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One* 2009; **4**: e6585.
- 87 Choudary PV, Molnar M, Evans SJ, et al. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. *Proc Natl Acad Sci USA* 2005; **102**: 15653–58.
- 88 Rajkumar R, Fam J, Yeo EY, Dawe GS. Ketamine and suicidal ideation in depression: jumping the gun? *Pharmacol Res* 2015; **99**: 23–35.
- 89 Black C, Miller BJ. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. *Biol Psychiatry* 2015; **78**: 28–37.
- 90 Turecki G. Polyamines and suicide risk. *Mol Psychiatry* 2013; **18**: 1242–43.
- 91 Nemeroff CB, Owens MJ, Bissette G, Andorn AC, Stanley M. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch Gen Psychiatry* 1988; **45**: 577–79.
- 92 van Heeringen K, Mann JJ. The neurobiology of suicide. *Lancet Psychiatry* 2014; **1**: 63–72.
- 93 Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry* 2000; **48**: 766–77.
- 94 Bernard R, Kerman IA, Thompson RC, et al. Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. *Mol Psychiatry* 2011; **16**: 634–46.
- 95 Ernst C, Nagy C, Kim S, et al. Dysfunction of astrocyte connexins 30 and 43 in dorsal lateral prefrontal cortex of suicide completers. *Biol Psychiatry* 2011; **70**: 312–19.
- 96 Bolton JM, Walld R, Chateau D, Finlayson G, Sareen J. Risk of suicide and suicide attempts associated with physical disorders: a population-based, balancing score-matched analysis. *Psychol Med* 2014; **17**: 1–10.
- 97 Webb RT, Kontopantelis E, Doran T, Qin P, Creed F, Kapur N. Suicide risk in primary care patients with major physical diseases: a case-control study. *Arch Gen Psychiatry* 2012; **69**: 256–64.
- 98 Ilgen MA, Kleinberg F, Ignacio RV, et al. Noncancer pain conditions and risk of suicide. *JAMA Psychiatry* 2013; **70**: 692–97.
- 99 Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet* 2013; **382**: 1646–54.
- 100 Nordentoft M. Crucial elements in suicide prevention strategies. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35**: 848–53.
- 101 Lapierre S, Erlangsen A, Waern M, et al, and the International Research Group for Suicide among the Elderly. A systematic review of elderly suicide prevention programs. *Crisis* 2011; **32**: 88–98.
- 102 Katz C, Bolton SL, Katz LY, Isaak C, Tilston-Jones T, Sareen J, and the Swampy Cree Suicide Prevention Team. A systematic review of school-based suicide prevention programs. *Depress Anxiety* 2013; **30**: 1030–45.
- 103 Harrod CS, Goss CW, Stallones L, DiGiuseppi C. Interventions for primary prevention of suicide in university and other post-secondary educational settings. *Cochrane Database Syst Rev* 2014; **10**: CD009439.
- 104 Wasserman D, Hoven CW, Wasserman C, et al. School-based suicide prevention programmes: the SEYLE cluster-randomised, controlled trial. *Lancet* 2015; **385**: 1536–44.
- 105 Knox KL, Pflanz S, Talcott GW, et al. The US Air Force suicide prevention program: implications for public health policy. *Am J Public Health* 2010; **100**: 2457–63.
- 106 Rutz W, von Knorring L, Wälinder J. Long-term effects of an educational program for general practitioners given by the Swedish Committee for the Prevention and Treatment of Depression. *Acta Psychiatr Scand* 1992; **85**: 83–88.
- 107 Szanto K, Kalmar S, Hendin H, Rihmer Z, Mann JJ. A suicide prevention program in a region with a very high suicide rate. *Arch Gen Psychiatry* 2007; **64**: 914–20.
- 108 Sikorski C, Luppá M, König HH, van den Bussche H, Riedel-Heller SG. Does GP training in depression care affect patient outcome? A systematic review and meta-analysis. *BMC Health Serv Res* 2012; **12**: 10.
- 109 Székely A, Konkoly Thege B, Mergl R, et al. How to decrease suicide rates in both genders? An effectiveness study of a community-based intervention (EAAD). *PLoS One* 2013; **8**: e75081.
- 110 Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. *Cochrane Database Syst Rev* 2012; **10**: CD006525.
- 111 Alexopoulos GS, Reynolds CF 3rd, Bruce ML, et al, and the PROSPECT Group. Reducing suicidal ideation and depression in older primary care patients: 24-month outcomes of the PROSPECT study. *Am J Psychiatry* 2009; **166**: 882–90.
- 112 While D, Bickley H, Roscoe A, et al. Implementation of mental health service recommendations in England and Wales and suicide rates, 1997–2006: a cross-sectional and before-and-after observational study. *Lancet* 2012; **379**: 1005–12.
- 113 Yip PS, Caine E, Yousuf S, Chang SS, Wu KC, Chen YY. Means restriction for suicide prevention. *Lancet* 2012; **379**: 2393–99.
- 114 Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011; **168**: 1266–77.
- 115 Nock MK, Banaji MR. Assessment of self-injurious thoughts using a behavioral test. *Am J Psychiatry* 2007; **164**: 820–23.
- 116 Inagaki M, Kawashima Y, Kawanishi C, et al. Interventions to prevent repeat suicidal behavior in patients admitted to an emergency department for a suicide attempt: a meta-analysis. *J Affect Disord* 2015; **175**: 66–78.

- 117 Luxton DD, June JD, Comtois KA. Can postdischarge follow-up contacts prevent suicide and suicidal behavior? A review of the evidence. *Crisis* 2013; **34**: 32–41.
- 118 Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Arch Gen Psychiatry* 2012; **69**: 580–87.
- 119 Vitiello B, Emslie G, Clarke G, et al. Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. *J Clin Psychiatry* 2011; **72**: 388–96.
- 120 Grunebaum MF, Ellis SP, Duan N, Burke AK, Oquendo MA, John Mann J. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. *Neuropsychopharmacology* 2012; **37**: 697–706.
- 121 Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009; **339**: b2880.
- 122 Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. *Arch Gen Psychiatry* 2009; **66**: 633–39.
- 123 Lu CY, Zhang F, Lakoma MD, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. *BMJ* 2014; **348**: g3596.
- 124 Ludwig J, Marcotte DE, Norberg K. Anti-depressants and suicide. *J Health Econ* 2009; **28**: 659–76.
- 125 Vita A, De Peri L, Sacchetti E. Lithium in drinking water and suicide prevention: a review of the evidence. *Int Clin Psychopharmacol* 2015; **30**: 1–5.
- 126 Søndergård L, Lopez AG, Andersen PK, Kessing LV. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. *Bipolar Disord* 2008; **10**: 87–94.
- 127 Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA* 2003; **290**: 1467–73.
- 128 Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 2013; **346**: f3646.
- 129 O'Donnell KC, Gould TD. The behavioral actions of lithium in rodent models: leads to develop novel therapeutics. *Neurosci Biobehav Rev* 2007; **31**: 932–62.
- 130 Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology (Berl)* 2014; **231**: 3663–76.
- 131 Meltzer HY, Alphas L, Green AI, et al, and the International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; **60**: 82–91.
- 132 Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr Res* 2005; **73**: 139–45.
- 133 Fink M, Kellner CH, McCall WV. The role of ECT in suicide prevention. *J ECT* 2014; **30**: 5–9.
- 134 Avery D, Winokur G. Suicide, attempted suicide, and relapse rates in depression. *Arch Gen Psychiatry* 1978; **35**: 749–53.
- 135 Hadley D, Anderson BS, Borckardt JJ, et al. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for treatment-resistant depression in a clinical setting. *J ECT* 2011; **27**: 18–25.
- 136 Weinberg I, Ronningstam E, Goldblatt MJ, Schechter M, Wheelis J, Maltsberger JT. Strategies in treatment of suicidality: identification of common and treatment-specific interventions in empirically supported treatment manuals. *J Clin Psychiatry* 2010; **71**: 699–706.
- 137 Stoffers JM, Völlm BA, Rucker G, Timmer A, Huband N, Lieb K. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst Rev* 2012; **8**: CD005652.
- 138 Tarrier N, Taylor K, Gooding P. Cognitive-behavioral interventions to reduce suicide behavior: a systematic review and meta-analysis. *Behav Modif* 2008; **32**: 77–108.
- 139 Rudd MD, Bryan CJ, Wertenberger EG, et al. Brief cognitive-behavioral therapy effects on post-treatment suicide attempts in a military sample: results of a randomized clinical trial with 2-year follow-up. *Am J Psychiatry* 2015; **172**: 441–49.
- 140 Ougrin D, Tranah T, Stahl D, Moran P, Asarnow JR. Therapeutic interventions for suicide attempts and self-harm in adolescents: systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 97–107.
- 141 van der Feltz-Cornelis CM, Sarchiapone M, Postuvan V, et al. Best practice elements of multilevel suicide prevention strategies: a review of systematic reviews. *Crisis* 2011; **32**: 319–33.