Suicide and suicide risk

*Gustavo Turecki[1] *, David A. Brent[2], David Gunnell[3,4], Rory C. O'Connor[5], Maria A. Oquendo[6], Jane Pirkis[7] and Barbara H. Stanley[8]*

Abstract | Although recent years have seen large decreases in the overall global rate of suicide fatalities, this trend is not reflected everywhere. Suicide and suicidal behaviour continue to present key challenges for public policy and health services, with increasing suicide deaths in some countries such as the USA. The development of suicide risk is complex, involving contributions from biological (including genetics), psychological (such as certain personality traits), clinical (such as comorbid psychiatric illness), social and environmental factors. The involvement of multiple risk factors in conveying risk of suicide means that determining an individual's risk of suicide is challenging. Improving risk assessment, for example, by using computer testing and genetic screening, is an area of ongoing research. Prevention is key to reduce the number of suicide deaths and prevention efforts include universal, selective and indicated interventions, although these interventions are often delivered in combination. These interventions, combined with psychological (such as cognitive behavioural therapy, caring contacts and safety planning) and pharmacological treatments (for example, clozapine and ketamine) along with coordinated social and public health initiatives, should continue to improve the management of individuals who are suicidal and decrease suicide-associated morbidity.

Although suicide is not a disease, suicidal behaviour, which includes suicide and suicide attempts, is an important public health problem. Thus, it has been the focus of increasing attention in research and public awareness campaigns over the past decade, as well as a major focus of the international public health community[1]. Despite a one-third reduction in the global suicide rate, suicide deaths remain frequent worldwide[1,2]. Each suicide death represents an individual tragedy and is estimated to indirectly affect many individuals, including family, friends and communities[3].

Advances in our understanding of the factors involved in suicide risk have enabled us to paint a more comprehensive picture of suicidal behaviour. Although the literature on suicidal behaviour has been growing, its interpretation and integration is at times complicated by the multiple phenotypes that may be considered across the suicide spectrum. These phenotypes include suicidal ideation, which is defined as thoughts about ending one's own life (whether active (with a plan) or passive (with only a wish to die but no plan)), suicide attempt and death by suicide (BOX 1). The risk of acting on suicidal thoughts increases with the frequency, intent and content (such as presence of a plan, levels of ambivalence or hopelessness, among other factors) of suicidal ideation. A suicide attempt is defined as self-injurious behaviour with inferred or actual intent to die. Although detailed nomenclature has been proposed for the terminology related to suicide[4,5], it has not been widely adopted and diverse terms are still frequently used to describe similar phenomena. As a consequence, this Primer uses the terms that are most consistent with the accepted nomenclature (BOX 1).

Although suicidal ideation occurs in depressive states across different psychopathologies, the transition from suicidal ideation to a suicide attempt is facilitated by co-occurring psychiatric conditions that increase distress (such as panic disorder or post-traumatic stress disorder) or decrease restraint (such as substance abuse or cluster B personality disorders)[6]. Additional factors involved in this transition, such as capability for suicide, exposure to suicide, mental imagery and access to the means of suicide[7–10], have been identified. In contrast to suicide attempts, non-suicidal self-injury most commonly involves self-cutting to relieve negative affect without suicidal intent and is classified separately from suicidal behaviour by North American clinicians. In Europe, non-suicidal self-injury is sometimes classified along with suicide attempts under the term self-harm because the risk factors for the two types of behaviour overlap and commonly co-occur[11].

Strategies for preventing suicide have been implemented in most countries, with varying degrees of success. Prevention strategies are typically grouped under universal (population-wide) strategies, selective strategies (targeting subpopulations or environments

*e-mail: gustavo.turecki@mcgill.ca

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Author addresses

[1]McGill Group for Suicide Studies, Department of Psychiatry, McGill University, Douglas Mental Health University Institute, Montreal, Quebec, Canada.
[2]Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA.
[3]National Institute of Health Research Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust, Bristol, UK.
[4]Department of Population Health Sciences, University of Bristol, Bristol, UK.
[5]Suicidal Behaviour Research Laboratory, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK.
[6]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.
[7]Centre for Mental Health, University of Melbourne, Melbourne, Victoria, Australia.
[8]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA.

within the larger population that could be at increased risk) or indicated strategies (in at-risk individuals who have already exhibited some form of suicidal behaviour or ideation). For these individuals, treatment strategies relying on psychotherapy or pharmacotherapy may also be indicated alone or in combination, depending on the characteristics of the individual.

This Primer discusses the epidemiology and global burden of suicide and suicidal behaviours, in addition to providing an overview of our current understanding of the mechanisms of suicide, including risk factors for suicidal ideation and the transition from ideation to suicide attempt. In addition, this Primer describes the prevention and treatment of suicide and quality of life issues faced by people with suicidal behaviours.

Epidemiology

Based on self-report survey data, the WHO has estimated that, for every death by suicide, ~20 people make suicide attempts[1]. This ratio varies from country to country depending on the lethality of commonly used suicide methods (FIG. 1). In many countries, the incidence of suicide attempts is highest in individuals 18–34 years of age[12], though reliable, global comparative data on suicide attempts is not available for individuals <18 years of age. By comparison, the lowest rates of suicide deaths are observed amongst young people <15 years of age, with the highest generally observed in people >70 years of age[1]. However, the age groups with the highest incidence at other ages vary from region to region; for example, in a number of high-income countries (such as the USA and UK) a second peak occurs amongst middle-aged men and women (45–60 years of age)[1]. Rates of suicide attempt are generally higher in females than in males[12], as is the prevalence of anxiety and depression[13]. However, in most countries, the rates of suicide are 2–3 times higher in males than in females[1], which could possibly be due to a male preference for higher lethality methods and the reluctance of males to seek help[1] (FIG. 2).

Suicidal ideations are considerably more frequent than suicidal behaviour, but incidence estimates vary depending on the definitions and wording used in the study — these definitions can range from thoughts that life is not worth living to making concrete plans to end one's life. For example, in an analysis of World Mental Health Survey data from 17 countries, the reported lifetime prevalence of suicidal ideation was 9.2%, with a lifetime prevalence of suicidal plans of 3.1%[12]. A person's willingness to report suicidal ideation and attempts may also depend on their religious beliefs, stigma and the methods used for collecting data (such as self-report questionnaire, interview administered survey or hospital admission data).

Geographic variations in incidence

The incidence of suicide varies more than ten-fold between countries (FIG. 3); incidence is relatively low in the Middle East and some South and Central American countries, and high in Eastern Europe, Russia, India and South Korea. Of note, the vast majority of suicides and suicide attempts worldwide occur in low-income and middle-income countries, where treatment options are limited[1]. Several factors are believed to account for these differences in suicide rates, including variations in the accuracy of suicide statistics. Indeed, several factors, such as inconsistent recording of suicides by coroners and cultural or religious acceptability of suicide, can affect the reporting of suicide. To this end, cultural factors (as well as possible genetic factors) might have a role, as a number of studies have shown that the between-country ranking of national suicide rates is maintained amongst first-generation migrants to a single country operating a consistent suicide recording process[14]. In addition, the availability and cultural preferences for high-lethality suicide methods can influence between-country suicide rates. For example, poisons commonly ingested in high-income countries, such as analgesics and psychotropic medications, are generally considerably less toxic than pesticides, which are commonly used in suicide attempts in many low-income countries[15]. Indeed, pesticides such as paraquat, which have a case fatality rate of >50%, are readily available in low-income countries in which many people are involved in subsistence farming — pesticide ingestion accounts for approximately one-fifth of global suicides[16]. Moreover, variations in the acceptability of suicide because of religious sanctions against suicidal behaviour (such as in predominantly Catholic or Muslim countries) as well as variations in levels of alcohol and drug misuse could contribute to the global differences in suicide rates. In terms of the latter point, high levels of alcohol misuse may account for the high incidence of suicide in Eastern Europe[17]. The effects of these various risk factors likely overlap and may be confounded by relative levels of prosperity and ethnic and religious diversity within individual countries.

Box 1 | **Definitions of terms commonly used in suicide research**

Suicide: Intentionally ending one's own life.

Suicidal behaviour: Behaviours that may result in ending one's life, whether fatal or not. This term excludes suicidal ideation.

Suicide attempt: Self-injurious, non-fatal behaviour with inferred or actual intent to die.

Suicidal ideation: Any thoughts about ending one's own life. May be active, with a clear plan for suicide, or passive, with thoughts about wishing to die.

Self-harm: Self-injurious behaviours with or without intent to die. Does not distinguish between suicide attempt and non-suicidal self-injury.

Non-suicidal self-injury: Self-injurious behaviours without any intent to die.

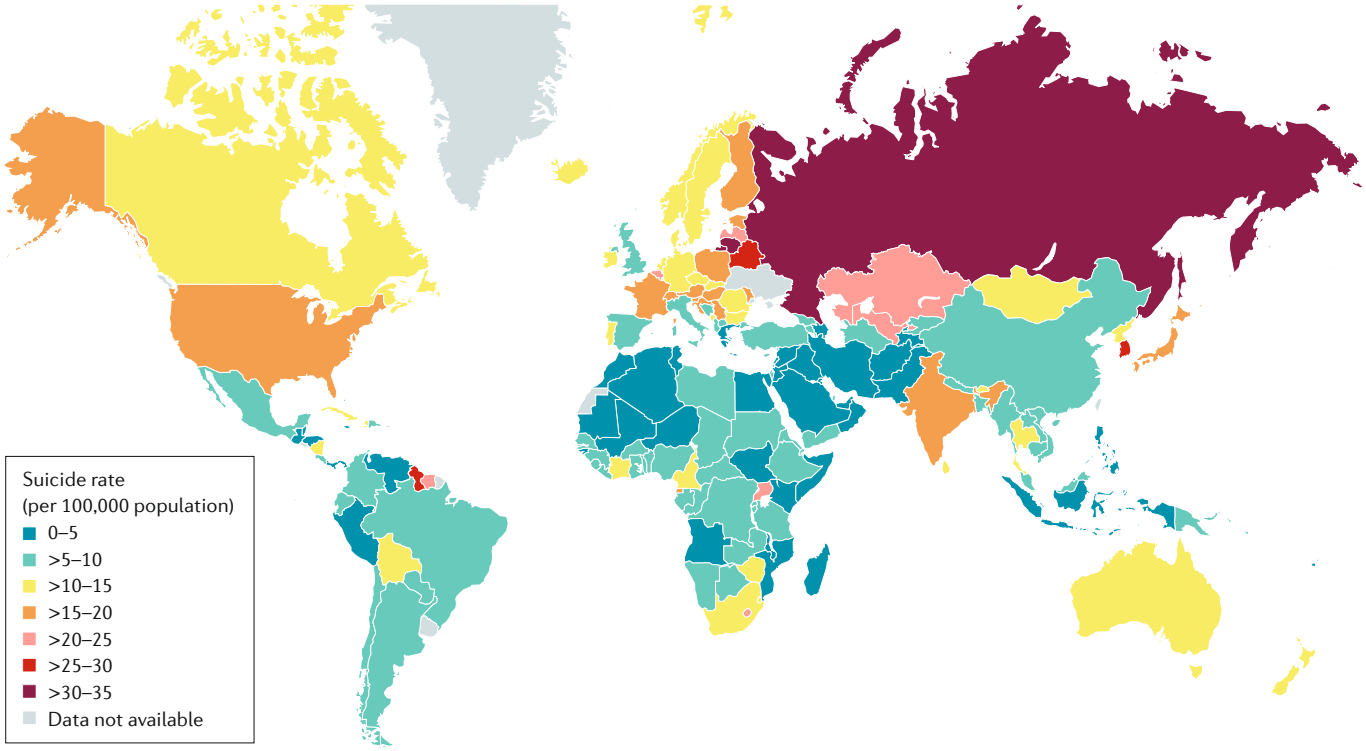

Fig. 1 | **Global variations in suicide rates.** World Map showing suicide rates in all countries for which data is available. Data from World Health Statistics, WHO 2016 (REF.[19]).

As well as global differences in suicide rates, several studies have reported marked (that is, two-fold to five-fold) variations in suicide rates within countries. For instance, one analysis of suicide in Taipei (Taiwan) documented five-fold variations in the incidence of suicide between areas[18]; the factor most strongly associated with area differences was average levels of household income.

Temporal trends

As mentioned above, the WHO estimates that there are ~785,000 suicides annually around the world, with an incidence of 10.6 per 100,000 population in 2016 (REF.[19]). Global suicide rates have fallen by ~30% in the 21st century[2], largely driven by marked falls in China and, to a lesser extent, India[2]. This overall trend has masked increases in other countries, such as the USA and Brazil, where rates rose by 35% between 2000 and 2016 (REF.[19]) (FIG. 2). Explanations for these differing trends are unclear. Economic growth in China has been accompanied with reductions in suicide rates, whereas the opposite has been observed in South Korea, which experienced a 130% rise in suicide between 2000 and 2010, although its rate has declined somewhat in recent years[19].

In addition to geographical differences, time trends in suicide rates vary within different age groups. For example, in recent years in the UK, suicide rates have fallen in elderly men but risen in middle-aged men and women[20,21]. In China, suicide rates are falling in almost all age groups[22], whereas in India they are falling in young people but rising in elderly individuals[23].

In general, key influences on secular trends in suicide include periods of economic recession (which are generally associated with increases)[24,25], changes in access to commonly used, high-lethality suicide methods[26,27], periods of war (which are generally associated with falls in suicide) and media reporting of celebrity suicides (which may lead to transient increases in suicide rates)[28].

Mechanisms/pathophysiology

Risk of suicide is influenced by the interaction of a variety of biological, clinical, psychological, social, cultural and environmental factors. General models to understand suicide risk have been proposed[9,10], and most models recognize that suicide risk is a result of the interplay between predisposing (also known as distal or diathesis) and precipitating (also known as proximal, triggering or stress) factors, with some models also specifying a role for developmental factors. One such example is the biopsychosocial model for suicide[6,29,30] (FIG. 4), which describes the interactions of genetic, experiential, psychological, clinical, sociological and environmental factors in the development of suicide risk. Although any number of these factors might be involved, their relative association with suicide risk varies greatly between individuals and can be mediated by a variety of factors, such as anxious or impulsive personality traits[31,32], and having social support and stable relationships, which lead to the aetiological heterogeneity of suicide and suicidal behaviour. The relative importance of these diverse factors also varies by age and sex[33]. This model is compatible with the multiple phenotypes along the suicide spectrum that are observed in practice, as described above. In the following sections, risk factors are classified as distal, developmental and proximal according to their temporal

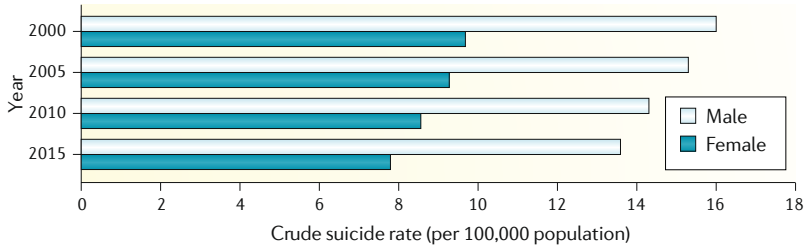

Fig. 2 | **Suicide rates by sex from 2000 to 2015.** Global suicide rates stratified by sex. In general, suicide rates in males are substantially higher than in females. Data from REF.[19].

relationship to suicide. Although this classification is helpful to understand relationships between risk factors and to build a model of suicide risk, it is imperfect as some risk factors, such a socioeconomic status or genetic and epigenetic factors, can act simultaneously in different categories.

Distal or predisposing factors

Familial and genetic predisposition. Suicidal behaviour has been known to cluster in families for >30 years, but convincing evidence for the heritability of suicidal behaviour has been provided only in the past decade from large cohort studies, including evidence that suicide and suicide attempts are transmitted independently of psychopathologies[31,32,34,35]. National registry-based studies as well as twin and adoption studies all suggest a heritability of 30–50%[36,37], although a more accurate estimate may be 17–36% once the heritability of comorbid psychiatric disorders is controlled for[37]. In addition, the offspring of individuals who have attempted suicide have a five-fold greater risk of attempting suicide than the general population[38], and suicide risk is doubled among individuals who lost a parent to suicide compared with those who lost a parent suddenly due to other causes, although <5% of people who take their own life have a history of parental suicide[39]. These data showing the familial clustering of suicidal behaviour further support the concept of genetic transmission. However, despite intensive investigations over the past 20 years, no single gene or group of genes has been identified as responsible for suicidal ideation, suicide attempt or suicide across multiple studies[30].

Suicide deaths are a rare event and, therefore, genome-wide studies (GWAS) generally investigate non-fatal suicidal behaviour; the findings of GWAS have been compiled and published elsewhere[30,40]. Of note, only a handful of GWAS have included suicide as a primary phenotype[40–42]. These studies identified a total of 32 single nucleotide polymorphisms (SNPs) of interest, of which multiple SNPs were associated with the *TBX20* locus[41,42]. The gene product of *TBX20* has been implicated in the central nervous system, although its specific roles are unknown[41]. Although these findings need replication, one study that used exome sequencing of brain tissue from individuals who died by suicide has identified a number of candidate gene variants associated with suicide, including variants of *COL6A6* (encoding the alpha-6 chain of collagen type VI, which is involved in axon guidance), *GNAL* (associated with schizophrenia), *BACE1* (potentially associated with Alzheimer disease), *NREP* (associated with neural regeneration) and *CDC34* (a ubiquitin-conjugating enzyme involved in cell cycle control)[43]. Other studies using suicide attempt and suicidal ideation as primary phenotypes identified multiple SNPs of interest that were associated with genes involved in nervous system development and function, immunological disease, infectious disease and the inflammatory response, among other biological processes[41].

Despite a few reports confirming associations between genes identified in GWAS and suicide phenotypes, overall, candidate gene-based studies[44,45] and GWAS[30,40,46–49] have not produced consistent results, with genes of interest frequently failing to pass rigorous reproducibility and significance testing. Similar to other behavioural phenotypes, individual genetic variants contribute only a small portion of the total variation in the suicidal behaviour phenotype, and despite the relatively large samples used in GWAS, they often lack appropriate power to detect significant loci and replicate previous findings[50]. Efforts to describe the association between genetic variance and suicidal behaviour using polygenic approaches have yielded promising results[50,51].

Early-life adversity. The past decade has seen great advances in our understanding of the ways that experiences can be translated into altered gene expression through epigenetic mechanisms[52,53]. Although changes to gene expression in response to environmental cues are essential in neurodevelopment, negative social experiences during critical periods of development can also lead to altered gene expression, believed to contribute to psychopathology. Indeed, early life adversity (ELA), defined as neglect or physical or sexual abuse during childhood, is strongly associated with suicidal behaviour later in life[29,54,55]. Evidence for this association comes from several observational studies[55–57], and has since been investigated by studying the biological imprinting of these negative early-life traumatic experiences through epigenetic changes, including DNA methylation and histone modifications[58–60] (see Stress response and the hypothalamic–pituitary–adrenal (HPA) axis, below).

Developmental factors

Although distal factors are important contributors to suicide risk, their link with suicidal behaviour is at least partially mediated by other factors. Such developmental or mediating factors, which may result in part from predisposing factors, increase vulnerability to maladaptive responses to proximal factors, thereby increasing the risk of suicidal ideation or suicidal behaviour. Of note, behavioural changes are regulated by biological processes[61], although these processes are often poorly understood.

Personality traits associated with suicidal ideation and suicidal behaviour. Key mediating factors between distal factors and proximal (also known as precipitating) factors include personality traits[62]. Among these, those most robustly associated with suicidal behaviour are anxiety and impulsive–aggressive traits (for example, the latter are traits that are associated with externalizing disorders like attention-deficit/hyperactivity disorder,

borderline personality disorder, oppositional defiant disorder and conduct disorder)[32,57,63].

Longitudinal trajectory studies have provided convincing evidence linking behavioural traits with long-term suicidal behaviour[57,64]. Although multiple studies have found an association between both childhood anxiety and stable anxiety in adulthood with suicidal behaviour[65,66], some studies have reported only a weak or non-significant link with suicidal behaviour when anxiety is considered as an independent variable for statistical analyses[66,67]. Anxiety is likely to contribute to suicidal behaviour by interacting with other characteristics of individuals who already have an increased vulnerability to suicide. For example, in trajectory studies accounting for ELA, anxiety convincingly explained the link between ELA and suicidal behaviour later in life[68], and some evidence suggests a stronger link between anxiety and suicidal behaviour in girls than in boys[63].

In studies examining the familial transmission of suicidal behaviour, the transmission of impulsive–aggressive traits has at least partially explained familial aggregation of suicidal behaviour[31,34,38]. Indeed, relatives of individuals who died by suicide are more likely to have increased impulsivity and aggression, and have an increased risk of suicidal behaviour compared with individuals without first-degree relatives who died by suicide[32,35].

The familial transmission of behavioural traits is likely explained by both genetics[69] and by lived experiences, as growing evidence has implicated epigenetic mechanisms in the regulation of aggression in adults[70,71]. The socially prescribed aspects of perfectionism (real or perceived social expectations of performance) are also associated with suicidal ideation and suicide attempts in clinical and population samples[72], and likely increase individual sensitivity to social rejection, defeat and entrapment[9]. The analysis of population samples might provide a relevant clinical perspective on the contributions of personality traits associated with suicide risk[73], including negative affect, which is a tendency to have negative emotions such as low self-esteem.

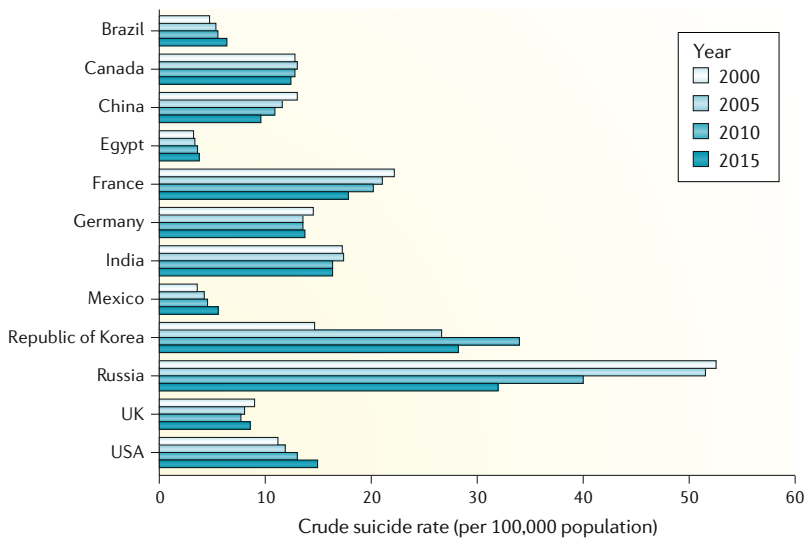

Fig. 3 | **Suicide rates in selected countries from 2000 to 2015.** Suicide rates over the 21st century have increased in some countries (such as Brazil, Mexico and the USA) but have decreased in others (such as China, Russia and France). Data here include both sexes combined. Data from World Health Statistics, WHO 2016 (REF.[19]).

Link between ELA and personality traits. As discussed above, ELA is strongly associated with suicidal behaviour and is associated with stable epigenetic changes. In animal models of ELA, negative experiences during postnatal development lead to behavioural changes in adulthood such as fearfulness[74] or aggression[75]. Subsequent work also linked altered behaviour in ELA models to lasting epigenetic changes in stress regulation pathways (see Stress response and the HPA axis, below)[76]. In addition, individuals who have experienced ELA have a greater risk of developing pathological traits and emotional dysregulation, including both internalizing and externalizing behaviours, altered brain structure and impaired executive function[77], all of which are traits that overlap with the suicidal phenotype[57,78].

Cognitive deficits. Diminished problem-solving ability, impaired memory and decreased positive future thinking have been associated with suicidal behaviour[79]. Additionally, hyperactive cortisol response to stress (see Stress response and the HPA axis, below), suicidal behaviour or having a first-degree relative with suicidal behaviour have all been associated with decreased cognitive function in stressful situations, suggesting that cognitive impairments are associated with risk factors for suicide[80,81], and individuals with poor problem-solving skills are more likely to experience suicidal ideation in response to stress[82]. In addition, a five-fold increased risk of suicide attempts has been reported between high-achieving and low-achieving students in cohort studies, highlighting the importance of IQ and school performance in influencing suicide risk[83].

Cognitive deficits are also more frequent among individuals with experiences of ELA[84]. This association is likely due to the interaction between ELA and the still-developing brain throughout childhood and young adulthood[85], which can lead to neuroanatomical and functional changes[30]. Together, these lines of evidence support a role for cognitive deficits as mediating risk factors for suicidal behaviour.

Proximal or precipitating factors

Beyond the factors that confer risk of suicidal behaviour, either distally to the suicidal episode or through development of traits associated with suicidal ideation and suicidal behaviour, there are identifiable factors that proximally associate with suicidal behaviour and that are commonly regarded as precipitating or facilitating it. Nonfatal suicidal behaviour is among the most robust predictors of future suicidal behaviour and suicide death. Indeed, ~40% of people dying by suicide have previously attempted suicide, and long-term follow-up studies have indicated that the risk of suicide amongst people who survived a suicide attempt is 1.6% within 12 months[86] and ~4% at 5 years[87]. Despite these data, it is important to note that the vast majority of individuals who experience suicidal ideation or attempt suicide do not ultimately die by suicide, and certain risk factors might

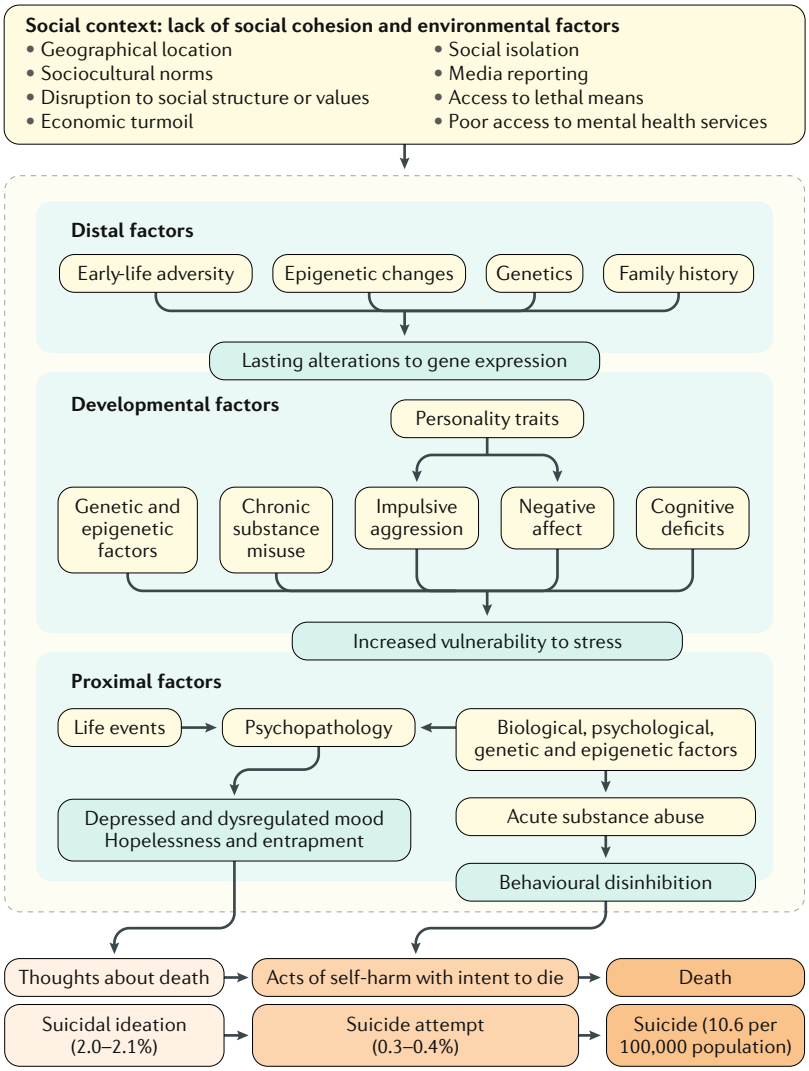

Fig. 4 | **The biopsychosocial model of suicide risk.** The biopsychosocial model for suicide risk presents a comprehensive view of the different types of factors that may contribute to suicide risk. Sociological, demographic, economic and environmental factors may influence any or all of the distal, developmental and proximal factors. The external, population or society-level factors, in addition to individual factors such as genetics, family history, personal history of abuse, behavioural dysregulation, substance abuse and psychopathology, may all interact to heighten the vulnerability to suicide through behavioural disinhibition and dysregulated mood, hopelessness and entrapment, which are in turn associated with suicidal ideation, suicide attempt and suicide. Data from REF.[337] (global suicidal ideation and suicide attempt statistics) and REF.[19] (global suicide statistic).

help to distinguish the likelihood of suicide attempt. In addition, some clinical factors that may influence the transition from suicidal ideation to suicide attempt include anxiety disorders, impulse-control disorders, post-traumatic stress disorder, eating disorders, previous self-harm, exposure to suicidal behaviour in others, and alcohol and drug abuse or dependence[6,7,88]. Additionally, epidemiological evidence supports a role for disorders that decrease restraint (such as substance abuse, oppositional defiant disorder and obsessive–compulsive disorder) or increase distress (panic disorder and post-traumatic stress disorder) in increasing the likelihood of a transition from suicidal ideation to suicide attempt, particularly in the context of mood disorders[86]. However, currently, it is not yet clear how to distinguish between individuals who may experience suicidal ideation but never progress to suicidal behaviour and those who may have one or multiple suicide attempts or who ultimately die by suicide.

Psychiatric disorders associated with suicide. Mental illness is a key antecedent to suicide. Indeed, estimates of the proportion of people experiencing a mental illness at the time of their suicide range from ~90% in North America to 30–70% in East Asia[89–92], with individual reports citing rates as low as 7% in some countries[93]. These disorders can be detected through retrospective interviews with family and friends of the deceased using psychological autopsy methods; however, they are not always diagnosed or treated before death, and likely represent one of the key modifiable aspects of an individual's suicide risk. Surprisingly, even in countries with accessible, free-at-the-point-of-use, mental health services such as the UK, only ~25% of people dying by suicide are in current or recent contact with mental health services[94].

The most common psychiatric diagnoses in people who die by suicide are major depressive disorder (MDD), bipolar disorder, substance use disorders and schizophrenia[89]. Although suicide is not an inevitable outcome of any psychiatric disease, specific features of individual diseases are associated with suicide, such as certain demographics and the individual's insight into their illness in schizophrenia[95], early-stage illness, mixed-state episodes and irritable dysphoric states for bipolar disorder[96], or number, duration and intensity of episodes for MDD[97,98]. It is likely that the co-occurrence of depressive symptoms and other factors that inhibit behavioural control may contribute to suicidal behaviour. In addition, one cross-national study has demonstrated that disorders characterized by anxiety and poor impulse control are strongly associated with the transition from suicidal ideation to a suicide attempt[88]. Furthermore, a birth cohort study identified substance use and personality traits as strong correlates of suicide attempt in both those who did or did not have previous suicidal ideation, with higher intellect/openness as a factor in those with suicidal ideation and lower extraversion as a factor in those without[7].

Substance use or misuse is found in a large proportion of people who die by suicide[89], with alcohol misuse observed in up to 40% and use of illicit substances in up to 25%[99]. In individuals who die by suicide, those with multiple predisposing factors (considered to have high-risk histories) tend to show higher rates of substance disorders at the time of death[100,101]. Although the association of suicidal behaviour with alcohol use has been more extensively studied than with other substances, there are indications that, in addition to the use of alcohol, recent (within 6 months) use of sedative-hypnotic drugs and cannabis is more frequently associated with suicide attempt than other substances[102,103]. Impulsivity is likely to be a key mediator of substance use associated with suicidal ideation and suicidal behaviour[99]. Indeed, individuals with high impulsivity are more

likely to use substances, and individuals with alcohol use disorder at the time of their suicide are more likely to also have high levels of impulsive–aggressive behaviour than those without alcohol use disorder at the time of suicide[104]. However, identifying causality is complex; animal studies have indicated that chronic substance use may drive increased impulsivity[105] and human studies have suggested that the pattern of consumption may be equally important, with binge use of both legal and illegal substances being more closely associated with suicide attempt than non-bingeing substance use[103,106].

In addition, ample evidence supports the contributions of concurrent physical and mental illness (such as central nervous system and psychiatric disorders, inflammatory diseases, chronic obstructive pulmonary disorder and pain) to suicide risk[107,108]. Although impulsive–aggressive traits, substance abuse and conduct disorder make proportionally larger contributions to suicide risk in younger people[7,97,109], depression, physical comorbidity, sleep and pain issues, and cognitive impairment are substantial contributors to suicidal behaviour in older people[110,111]. In terms of sleep problems, decreased sleep time, insomnia and nightmares have been related to risk for suicidal behaviour[112]. Chronic pain is also a predictor of suicide and suicidal behaviour, both independently as well as via the co-occurring difficulties of disability, sleep problems, reduced well-being and depression[113].

Psychological factors that contribute to suicide. From a psychological point of view, one of the key drivers of suicidal ideation and suicidal behaviour is the concept of unbearable psychological pain. Initial attempts to understand the components of psychological pain and their relationship with suicide attempts focused on a perceived lack of belonging, being an increased burden on others and acquired capability (that is, the ability to engage in suicidal behaviours)[10,114]. More recent efforts have identified a wider range of components, such as hopelessness and knowledge of or comfort with lethal means, and this approach has evolved to more specifically distinguish between factors that are associated with suicidal ideation and those that are associated with subsequent suicide attempt[8,9,115,116]. Indeed, the importance of other mediating factors, that, together with psychological pain, associate with subsequent suicidal ideation and suicidal behaviour, is increasingly acknowledged; these factors include psychological and cognitive traits (such as impaired problem-solving and memory biases and rumination) as well as proximally acting factors (such as feelings of defeat and entrapment, impulsivity, intentions/planning, implementation of a plan, access to means and imitation/exposure to suicidal behaviour of others). Of particular interest is work using population cohorts, in which volitional phase factors[9] (such as acquired capability, mental imagery about death, impulsivity and exposure) distinguished suicide attempt from suicidal ideation, whereas motivational factors did not[117]. Such ways of understanding suicidal ideation and suicidal behaviour may be particularly informative in terms of selecting psychotherapeutic approaches that will be most suited to the individual's needs.

Socioeconomic, environmental and other contextual factors associated with suicide risk. Important social and economic factors associated with suicide include proximal factors such as relationship breakdown, job loss, economic turmoil, being bullied and recent changes in socioeconomic position (having poor family connectedness, being single, having a low income and/or being in debt), as well as factors that may persist over time, such as poor social stability, stringent sociocultural norms, or being in a lesbian, gay, bisexual, transgender plus (LGBT+) group[107,118–121]. Some socioeconomic risk factors for suicide may operate differently in different social contexts; for example, the risk of suicide amongst individuals from minority ethnic groups is higher when they live in areas that have a low proportion of people from the same minority ethnic groups, compared with those living in areas that have a higher proportion of people from the same minority ethnic groups[122]. Social isolation, for example resulting from anxiety, bereavement or social exclusion[107,118], is also a strong contributor to suicide risk, whether isolation is measured objectively (such as living alone) or through perceived loneliness[123]. Conversely, clusters of suicide deaths may occur, particularly in young people, through social contagion, accounting for up to 1–2% of suicides in children and young people[124].

Among the environmental-based risk factors for suicide, one of the most important is access to means. To this end, there is a large volume of work showing the effect of access to more-lethal means as an important predictor of suicide[125]. Of interest, these are modifiable risk factors and an important aspect of preventive efforts is based on decreasing access to lethal means (see Prevention strategies, below).

Neurobiology of suicidal behaviour

Suicidal behaviour is associated with widespread neurobiological changes throughout the brain that affect a number of different functional pathways (FIG. 5). However, the extent to which these changes are specific for suicide and suicidal behaviour or are shared with depression and other psychopathologies is not always possible to determine given the intricate relationships between these phenotypes.

Monoamine dysregulation in suicidal behaviour. The serotonin pathway is by far the best described pathway in depression and several alterations in this pathway have been associated with suicidal behaviour. Serotonin function[126–128], and particularly serotonergic neurons[129], have been implicated in depression and suicide. For example, studies using post-mortem brain tissues of individuals who died by suicide have demonstrated decreased levels of 5-hydroxyindoleacetic acid[126], which is a serotonin metabolite, as well as a compensatory increase in the raphe nuclei of serotonergic neurons[130,131] and expression of tryptophan hydroxylase, a key enzyme in serotonin biogenesis[132,133]. In addition, dysregulated serotonin transmission has been demonstrated in both brain tissue[134,135] and cerebrospinal fluid of individuals

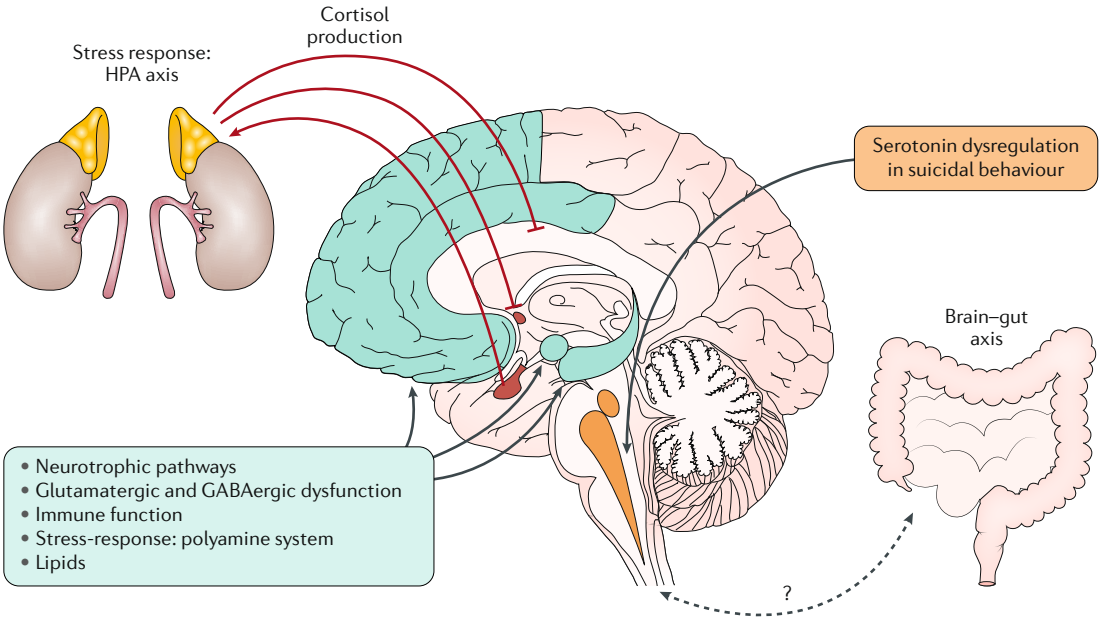

Fig. 5 | **Neurobiological changes in suicidal behaviour.** Suicidal behaviour is associated with widespread neurobiological alterations. Of these, alterations in the stress response pathways are among the best described in suicidal ideation, suicidal behaviour and suicide. Disruption of the hypothalamic–pituitary–adrenal (HPA) axis affects the coordination and signalling feedback mechanisms that control cortisol production, which is a key mediator of stress reactivity. Long-lasting changes to HPA axis function have been documented in individuals with histories of early-life adversity and epigenetic processes have been identified as key mediators of those changes. The polyamine system has been implicated in cellular responses to stress and may directly regulate mood through the antidepressant properties of some of its constituent proteins. In addition, multiple neurotrophic and neurotransmission pathways, primarily in the prefrontal cortex and the hippocampus as well as in the raphe nuclei of the brainstem, have been shown to be dysregulated in suicidal behaviour and constitute promising targets for therapy. More recent evidence has suggested coordination between signalling in the brain and in the gut, potentially through immune activation. GABA, γ-aminobutyric acid.

with suicidal behaviour[136]. An outstanding complication in the study of factors associated with suicidal behaviour is the high degree of comorbidity between depression and suicidal behaviour, yet some work has successfully shown discrete changes in expressions of both the serotonin transporter and serotonin receptor 1A in the midbrain in people with suicidal behaviour, compared with depressed individuals without suicidal behaviour[134,137]. Further investigation of alternative serotonin receptors[138], including those resulting from mRNA editing of serotonin receptor transcripts[139–142], may lead to new avenues of investigation of the role of serotonin in suicidal behaviour.

Stress response and the HPA axis. In normal situations, cortisol release is triggered by stress; its release is controlled by a feedback loop in which glucocorticoid receptors in the hypothalamus and other brain regions, including the hippocampus, are negatively regulated by cortisol binding and lead to the inhibition of cortisol release[29]. Altered cortisol reactivity may increase the risk of suicidal behaviour[29,80], although studies have provided contradictory results regarding the direction of association, which seems to be moderated by several factors such as age[143], family history of suicidal behaviour[80,144] and history of ELA[145], among other variables. Indeed, the epigenetic regulation of genes associated with ELA is exemplified by alterations in the HPA axis[29,60,146]. Individuals who experienced severe abuse during childhood have increased methylation of a regulatory region of *NR3C1* (encoding the glucocorticoid receptor) in the hippocampus[58], compared with either people who were not abused or to psychiatrically healthy controls. Furthermore, some evidence suggests that various forms of severe adversity affect the methylation status of *NR3C1* exons in central and peripheral tissues[29,145]. In addition, specific sequence variants of *FKBP5*, which encodes a protein that downregulates glucocorticoid receptor signalling, are associated with increased depressive symptoms and suicidal behaviour in people with ELA[147,148], presumably due to increased cortisol secretion and the development of anxiety traits. Another candidate target of epigenetic regulation that might explain the link between ELA and altered cortisol control is *SKA2*, which encodes the spindle and kinetochore associated protein 2 (REFS[149,150]).

In addition to alterations of the HPA axis, the polyamine stress response system seems to be differentially regulated in individuals with suicidal behaviour, although this pathway has been less thoroughly investigated than the HPA axis[29]. To this end, evidence that some polyamines exhibit antidepressant-like effects[151,152] suggests that alterations to the polyamine pathway may be important contributors to suicidal behaviour.

Neurotrophic pathways. Expression of neurotrophic genes, such as *BDNF* (encoding brain-derived neurotrophic factor (BDNF)) and *NTRK2* (encoding the BDNF

receptor tyrosine kinase B (TrkB)), are decreased in the brains of individuals who died by suicide compared with controls[153,154]. The link between BDNF and suicide has been studied intensively, and several studies have demonstrated altered BDNF expression in the sera of people who attempted suicide and in the brains of people who died by suicide[155,156], although to what extent these results are accounted for by underlying psychopathology is unclear. This altered expression is at least partially due to the epigenetic control of BDNF expression through methylation of its promoter; indeed, altered methylation of the promoter or exon 4 has been demonstrated in the brains of people who died by suicide[157] and in peripheral tissues of individuals who attempted suicide[158]. Additional evidence for the alteration of neurotrophic pathways in suicide is evidence of epigenetic regulation of TrkB-T1 (an astrocyte-specific variant of the BDNF receptor) in the brains of individuals who died by suicide, both through methylation of its promoter and through control by miRNA miR-185 (REFS[159,160]).

Glutamatergic and GABAergic dysfunction. Evidence from neuroanatomical studies of individuals with depression and suicidal behaviour have demonstrated changes in the density of glutamatergic neurons and glial cells[161,162] and in the volume[163] of the hippocampus, which relies on excitatory neurotransmission via glutamatergic signalling and is involved in learning and memory[164]. In brain tissue from individuals with depression (most of whom died by suicide), glutamate transporter expression is decreased[165], whereas *N*-methyl-D-aspartate (NMDA) receptor (a glutamate receptor) expression is increased[166] in the locus coeruleus, suggesting dysregulation of glutamatergic signalling. Importantly, specific proteins in the glutamate pathway that have been associated with suicidal behaviour (such as glutamate-ammonia ligase, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), NMDA and kainite glutamate receptors) have also been implicated in cognitive deficits[167]. *GRIN2B*, *GRIK3* and *GRM2* are among the glutamatergic genes that appear to be specifically upregulated in people with MDD who die by suicide, as opposed to those with MDD who die from other causes[168], with a concomitant downregulation of the GLUL protein in astrocytes[169]. The glutamatergic pathway has become a particular point of interest in recent years owing to its probable involvement in mediating the potent antidepressant and antisuicidal activity of the NMDA receptor antagonist ketamine[170–172], which not only leads to sustained effects in animals[173] and humans[172,174], but also appears to act through multiple mechanisms, including the inhibition of BDNF secretion by astrocytes[175], upregulation of insulin-like growth factor 2 in the hippocampus[176], and through regulation of AMPA and NMDA receptor expression levels[177]. In addition to the glutamate pathway, γ-aminobutyric acid (GABA)-associated genes, including those encoding the GABA-A and GABA-B receptors, are disrupted in the brains of individuals who died by suicide[178], particularly in regions linked to executive function[179,180] and stress responses[181], as well as in the integration of cognitive activity with affective experience.

Immune function and inflammation. Inflammatory responses have drawn a great deal of attention in recent years, with several lines of evidence suggesting a link between inflammation and depression[182,183]. Indeed, in individuals with somatic disease, disorders with a strong inflammatory component, such as autoimmune disease[184], and patients receiving cytokine therapy[185] are more likely to develop depression than those who do not experience inflammation. The role of inflammation in suicidal behaviour has been explored through a number of studies that identified increased proinflammatory cytokines such as tumour necrosis factor, IL-6 (REF.[186]), IL-8 (REF.[187]) and IL-1β[188] in individuals who attempted suicide or who died by suicide. In particular, increased plasma IL-6 levels have been associated with impulsivity and violent suicide attempts[189], thereby linking proinflammatory responses to the impulsive endophenotype for suicidal behaviour. High levels of inflammation may also be a tool to differentiate suicidal ideation from depression in adults[190], and several studies have indicated that systemic inflammation in depression could be linked to a leaky gut (that is, abnormal permeability of the intestinal walls), which could expose bacterial molecular motifs to the immune system[191]. Other molecules that have been associated with suicidal behaviour include IL-2 (REF.[186]) and vascular endothelial growth factor[192], which are decreased in individuals with suicidal behaviour. Altered levels of quinolinic acid (an agonist of NMDA glutamate receptors) and kynurenic acid (an antagonist of NMDA, AMPA and kainate glutamate receptors) have also been reported in individuals with suicidal behaviour[184,193]. Of particular interest are the studies with *Toxoplasma gondii*, a brain-tropic nematode that may increase the risks of self-directed violence and of suicide attempt[194,195]. To this end, *T. gondii* infection is thought to trigger an immune response in the brain that could lead to decreased tryptophan availability, decreased serotonin biosynthesis and increased levels of kynurenic acid[196,197]. Of note, *T. gondii* infection may also amplify specific behavioural traits that are linked with suicidal behaviour such as aggression in women and impulsivity in men[198,199].

Brain–gut axis. A new avenue that has garnered much enthusiasm in psychiatry and beyond is the potential contribution of the gut microbiome to psychopathology[200]. Evidence that intestinal flora may influence mood states has been mounting[201], with some studies demonstrating that certain bacterial strains can produce molecules to mimic dopamine signalling and to counter inflammation[202]. Although no findings have suggested a direct influence of the gut microbiome on suicidal behaviour, evidence of its effect on mood has been growing. As this nascent field begins to produce more results, concrete treatment targets might emerge for depression, suicidal ideation and suicidal behaviour.

Diagnosis, screening and prevention

Suicide prevention draws on a wealth of complementary approaches that span individual and populational approaches, and include diverse strategies for the assessment of suicide risk and prevention of suicide and suicidal behaviour (FIG. 6).

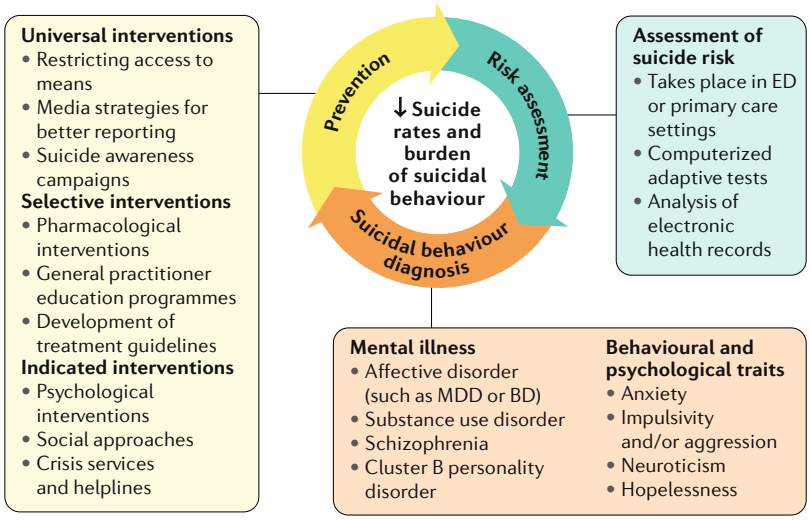

Fig. 6 | **Approaches for preventing suicide.** Prevention, risk assessment and diagnosis of suicidal behaviour are key to decreasing suicide rates. Prevention strategies range from universal interventions that target the general public, selective interventions that target subpopulations with a greater potential risk and indicated interventions that respond to individuals exhibiting suicidal ideation or suicidal behaviour. Risk assessment approaches can occur in a variety of settings and through a variety of methods, all aiming to detect individuals who may be at increased risk of suicidal behaviour to direct them to the most appropriate services. Diagnosis involves the diagnosis of psychiatric and psychological features associated with suicidal ideation and suicidal behaviour and includes psychopathologies and psychological traits that may contribute to suicide risk. BD, bipolar disorder; ED, emergency department; MDD, major depressive disorder.

Assessment and determination of risk

As previously mentioned, no single risk factor, whether previous suicidal ideation or behaviour, mental health disorder, or other psychological traits, is a strong predictor of suicidal behaviour[203,204]. Consequently, there is a nearly universal acknowledgement that prediction of suicide and suicidal behaviour can only improve substantially over chance by the examination of multiple risk factors simultaneously, with a specific focus on imminent suicide risk[203,205]. To this end, it is important to note that the factors that contribute to risk of suicidal ideation are different from those that contribute to the transition from suicidal ideation to suicidal behaviour. Broadly speaking, among psychiatric disorders that can contribute to suicidal behaviour, mood disorders are most closely associated with suicidal ideation, whereas disorders of distress (such as panic disorder or post-traumatic stress disorder) or of disrupted impulse control (such as substance abuse or behavioural disorders) can contribute to the transition from suicidal ideation to suicidal behaviour[88]. In addition, two important transdiagnostic risk factors for suicide and suicidal behaviour are sleep problems (including reduced sleep, insomnia and nightmares) and chronic pain.

Several approaches have attempted to examine individuals at high risk of suicide by assessing multiple risk factors simultaneously using standard suicide risk scales, computerized adaptive tests (CATs) and machine learning of electronic health records. For example, one systematic review of screening instruments for predicting future episodes of deliberate self-harm (including suicide attempts), primarily in psychiatric populations, demonstrated that the SAD PERSONS scale had low sensitivity but high specificity, with the opposite for the Manchester Self-Harm Rule (MSHR)[206]. In addition, the MSHR had a fair accuracy at predicting deliberate self-harm in individuals who had engaged in previous self-harming behaviour (with an area under the curve of 0.72) in one prospective study, but none of the six rating scales examined performed better than a global clinical rating of risk (area under the curve of 0.74)[207]. Other studies, including a systematic review, confirmed that there is no evidence to support the use of risk assessment instruments as predictors of suicidal behaviour among patients with a psychiatric disorder[208,209].

The last clinical contact for the majority of people who die by suicide is either in an emergency department (ED) or in primary care[210]. Screening for suicide risk in EDs is justified because as many as one in five individuals who die by suicide have visited the ED within 4 weeks of their death[210]; similarly, a visit to the ED for a mental health reason is a predictor of suicidal behaviour[87]. In addition, other reasons for visiting the ED can increase the risk for suicide (such as trauma or alcohol intoxication), and nearly half of individuals who screen positive for suicide risk in the ED do not spontaneously communicate suicidal ideation[211,212].

Although suicide risk screening, which aims to detect any signs of suicidal ideation or behaviour, in EDs is not routine, it is a recommended aspirational goal that is variably, albeit increasingly, being implemented in EDs in the USA (The Joint Commission: National Patient Safety Goals Effective 2019). The four-item Ask Suicide-Screening Questions (ASQ) tool[213] for children and adolescents shows a high sensitivity (93%) but lower specificity (43%) for predicting future suicide-related visits to the ED in the subsequent 6 months. The Emergency Department Safety Assessment and Follow-up Evaluation (ED-SAFE)/Substance Abuse and Mental Health Services Administration (SAMSHA) decision support tool was prospectively evaluated in adult attendees in an ED. Two items — having thought of a suicidal plan and having a history of a past attempt — both showed very high sensitivity (86.2–94.5%) for predicting a suicide attempt within the subsequent 6 weeks, but with low sensitivity (15.0–29.7%). Taken together, these two items predicted 83% of all suicide attempts within 6 weeks[214]. However, screening in EDs without an associated follow-up intervention to bolster treatment adherence and adherence to a safety plan is no better than usual care, whereas screening coupled with follow-up calls can reduce suicide attempts relative to usual care in the ED[215]. In addition, screening in primary care settings is also important, as the last clinical contact of people who die by suicide is most often in primary care[210]. In addition, one study demonstrated that those who reported frequent or daily suicidal thoughts in item 9 of the Patient Health Questionnaire (PHQ-9; a screening tool for depression that is typically delivered in primary care settings) were at markedly increased risk for suicide and suicide attempts[216]. However, this item has a relatively low sensitivity and, indeed, 39% of those who made suicide attempts and 36% of those who died by

suicide within 30 days of completing a PHQ-9 reported no suicidal ideation at the time[216].

Computerized adaptive tests. One challenge to screening for suicidal risk is that it is multidimensional and not easily or accurately captured in a scale that focuses on a single disorder such as depression. Moreover, as described above, approaches to screening for suicide risk have a high sensitivity but a lower specificity, which is problematic, for example, in ED settings[213]. To address this problem, CATs for suicidal risk have been developed, wherein the presentation of items or questions are personalized to an individual based on their responses to previous items or questions[217]. This technique allows for the assessment of a wide range of potentially relevant risk factors in a brief questionnaire of 6–10 items. A CAT for the detection of suicidal ideation and behaviour has been developed using a sample of adult outpatients with a pre-existing mental health condition, demonstrating strong discriminative validity, with both high sensitivity and specificity in the identification of individuals at moderate and high risk for suicidal behaviour in the ED[218]. Similarly, a CAT for assessing suicidal ideation or behaviour has been developed for children and adolescents, showing a high convergent and discriminative validity. However, predictive validity of both the adult and paediatric CATs for assessment of suicidal risk have yet to be reported[218,219].

Electronic health records. Machine learning is now being used to try and identify precursors of suicidal behaviour and suicide that can be detected from patients' medical records. The advantages of this approach are that it provides a sample size large enough to detect effects on suicide and suicide attempts, it bypasses patient self-report, and it allows the testing of the effect of a combination of risk factors, each of which might only make a small individual contribution to suicidal risk. In addition to a review of diagnoses, medication and service use, some studies have included natural language processing of the clinician's notes to try and identify phrases associated with risk or protective factors for suicide (such as social support or clinician optimism)[220,221]. Collectively, these approaches could alert clinicians that their patients are at increased risk of suicide, thereby facilitating referral to appropriate services.

One study of machine learning of health records for the prediction of suicide and suicide attempts examined the medical and psychiatric records of ~3 million patients with at least one mental health diagnosis across seven different health care systems[222]. In this study, an algorithm was developed that could identify 5% of the population, accounting for 43–48% of the suicides and suicide attempts, and was able to predict suicide and suicide attempts in the next 90 days with a specificity of ~70% and a sensitivity of ~80% in both specialty mental health and primary care settings[222]. The listed predictor variables were primarily those that have a well-established association with suicide risk (such as depression, alcohol abuse, drug abuse or a history of a suicide attempt), but the power of this approach was in the ability to test the predictive power of the combination of many variables simultaneously. Although these results are promising, it will be important to prospectively test whether algorithms generated from the use of artificial intelligence improve clinical knowledge for assessing suicide risk and to carry out randomized controlled trials (RCTs) to assess the effect of algorithm use on clinical outcomes[223].

Prevention strategies

One framework for suicide prevention that was proposed in the mid-1990s[224,225] and that is still widely used today was built on other frameworks for the prevention of mental[226] and physical[227] disorders. The framework takes a risk factor-based approach to suicide prevention, classifying suicide prevention efforts as universal, selective or indicated on the basis of their target groups (FIG. 6). Each type of intervention is discussed below, along with examples. The examples are by no means exhaustive but are intended to give an overview of the types of preventive interventions that have been trialled.

Universal interventions. Universal interventions aim to favourably shift risk and protective factors across the entire population, rather than in specific groups of individuals. In general, universal interventions usually either affect the social environment or promote resiliency within individuals[226] and target risk factors without necessarily identifying individuals with those risk factors. For example, a number of universal interventions have targeted 'access to means' as a risk factor for suicide, without specifically identifying those whose access might place them at risk. Examples of these efforts include banning pesticides[228], withdrawing medications associated with suicide (such as co-proxamol) from the market[229], removing charcoal from retail outlets[230], equipping vehicles with catalytic converters[231] and installing barriers on bridges and cliffs[232,233].

Other examples of universal interventions acknowledge the influential role of the media; to this end, many countries and organizations have produced guidelines for journalists to encourage the responsible reporting of suicide in the media in recognition of the fact that media presentations of suicide, for example, those glamorizing the decedent, can lead to 'copycat' acts[234]. More recently, efforts have shifted to adapting these guidelines for use in social media[235], for example, with resources being developed to assist young people to have safe discussions about suicide online[236] and reducing the availability of online information concerning lethal means[237]. In addition, suicide prevention media campaigns have also gained traction following the recognition of the potential of the media as a force for good in suicide prevention. These campaigns are delivered to the population as a whole, usually across multiple media platforms; additionally, most have brief community service announcements at their core and contain messages about offering or seeking help[238,239].

Other examples of universal interventions are delivered in specific settings and are usually designed to raise awareness about suicide and its prevention; often, these interventions target young people and take place in schools, universities and workplaces[240].

Selective interventions. Selective interventions target subgroups who exhibit risk factors that predispose them to suicidal thoughts or behaviours but who do not currently exhibit those behaviours[226]. Many selective interventions directly or indirectly target people with psychiatric disorders; for example, specific pharmacological treatments for mood disorders have been trialled (see below, Pharmacological interventions for suicidal behaviour). Similarly, interventions that aim to better equip general practitioners to detect, diagnose and manage depression (typically involving the provision of education and guidelines) have also been introduced, with the rationale that many people with depression will not see a specialist mental health care provider but will receive care from a general practitioner[241]. Other selective interventions target people with socioeconomic, environmental or contextual risk factors for suicide (see Mechanisms/pathophysiology, above), such as those experiencing bullying or social isolation. Selective interventions designed to reduce bullying and social isolation are often school based and tailored towards particular subgroups such as LGBT+ young people. For example, some schools have Gay–Straight Alliances that provide a safe and supportive environment to LGBT+ students, and there is emerging evidence that these interventions may have positive effects in reducing both suicidal ideation and suicide[242].

Indicated interventions. Indicated interventions are designed for people who are already starting to exhibit suicidal thoughts or behaviours, identified through screening programmes or by clinical presentation. As these interventions target people who already have suicidal ideation or suicidal behaviours, some individuals have argued that, unlike universal and selective intervention strategies that constitute true prevention, indicated intervention strategies fall into the realms of early intervention[224]. A key example of indicated intervention is the provision of psychosocial interventions to those who present to an ED or other health care setting following an episode of self-harm[243]. Such interventions include psychological therapies (see, Psychological interventions for suicidal behaviour, below) and social approaches designed to provide ongoing support (such as case management[244] and regular communication through channels like postcards or text messages[245]). Telephone crisis services (sometimes called 'hotlines') constitute a further example of an indicated intervention[246]. These services have existed since the 1950s[247], and many have now embraced newer technology like online chat and text-messaging services[248].

Multicomponent interventions. Universal, selective and indicated interventions are often delivered in combination through what is often termed a 'systems-based' approach[249], sometimes delivered in local regions or communities. For example, the Alliance Against Depression model, initially implemented in Nuremberg (Germany), included a suicide prevention media campaign (universal intervention), education for general practitioners, gatekeeper training for frontline workers and other professionals (selective interventions), and an 'emergency card', which gives people who have attempted suicide ready access to professional help, as well as additional 'self-help' activities (indicated intervention). Following its demonstrated 24% reduction in suicidal behaviour[250], the Alliance Against Depression model has since been adopted in a number of other regions in Europe, with the inclusion of an additional universal intervention (restricting access to means)[250]. Beyond regions and communities, multicomponent interventions have also been delivered in specific settings (such as health services[251] and schools[252]) and to particular population groups (for example, armed forces personnel)[253].

Evaluation of suicide prevention interventions. One systematic review has synthesized the evidence around specific suicide prevention interventions[254] and identified only a few interventions with unequivocal evidence of effectiveness in reducing suicide-related outcomes (suicides, suicide attempts and suicidal ideation) or which showed substantial promise. This review concluded that restricting access to means can prevent suicide and that school-based awareness programmes can reduce suicide attempts. Certain psychological treatments, particularly cognitive behavioural therapy (CBT), are also important in the suite of strategies to prevent suicide. Other interventions, such as pharmacological treatments (for example, lithium or antidepressants) also demonstrated benefits, although their effects might be specific for particular population groups.

Although this review highlights the effectiveness of several interventions, it is striking that there are many interventions for which the evidence base is rudimentary. There are a number of reasons for this poor evidence base, not least is that RCTs are often difficult to mount in the area of suicide prevention. This difficulty is partly because of the low base rate of suicide (which has implications for the sample size needed to demonstrate the effect of an intervention) and partly because it is unethical to withhold a potentially life-saving intervention from the control group. These problems are compounded in the case of universal interventions, which typically target whole communities. Increasingly, suicide prevention researchers are looking to alternative or augmented evaluation designs to strengthen the evidence base[255]. In the field, there is a recognition that RCTs are not always possible and that well-designed ecological studies (observational studies in which groups or populations, rather than individuals, are studied to provide evidence of change associated with a particular intervention) will sometimes provide the best available evidence[255]. Indeed, the systematic review included ecological designs, and the authors of this review observed that these designs were particularly common in assessing the effect of population-level restriction of access to means[254]. In addition, suicide prevention researchers are borrowing methodological approaches from disciplines like programme evaluation to evaluate complex interventions (such as designing programme logic models and triangulating data from a range of sources)[255]. They are also using increasingly sophisticated analysis strategies to analyse evaluation data (for example, interrupted time series analyses across multiple sites)[255].

In addition, some researchers are also beginning to go beyond effectiveness to consider the cost-effectiveness of interventions[256].

Management

In the past two decades, most efforts to develop suicide-specific psychosocial interventions have moved away from the view that treating the underlying psychiatric disorder would resolve suicidal urges and thoughts, to a perspective that suicide-specific treatments are necessary in addition to interventions for primary psychiatric disorders. Furthermore, in recognition that many people who become suicidal have limited access to behavioural treatments or do not wish to receive these treatments, brief suicide prevention approaches with limited or no health professional intervention have been developed (BOX 2).

Longer-term psychosocial interventions

Overall, psychosocial interventions, irrespective of type, have been shown to reduce suicide attempts. One meta-analysis demonstrated that, in adult and adolescent patients (hospitalized or not, and presenting with a variety of features such as borderline personality disorder, depression and schizophrenia-spectrum disorders) as well as in patients with or without a history of suicidal ideation or behaviour, psychosocial interventions were associated with significantly fewer suicide attempts during follow-up compared with those who received treatment as usual[257]. In addition, sensitivity analyses showed that psychosocial interventions are effective in outpatient settings among those with borderline personality disorder, irrespective of suicidal history[257]. The beneficial effect of psychosocial interventions demonstrated in this meta-analysis is consistent with a large-scale, register-based propensity score matching study which found that those who received a psychosocial intervention after self-harm were less likely to die by suicide at long-term follow-up[258].

Of all the longer-term psychosocial interventions, cognitive therapy (CT) and CBT have received the most research focus[243,257,259]. CT and CBT are types of psychological therapies that encourage an individual to manage their problems by changing the way in which they think and behave. Recent reviews confirm that CT and CBT that targets suicidal thoughts and behaviours in high-risk adults can reduce the incidence of self-harm at 6 months (OR 0.54, 95% CI: 0.34–0.85) and 12 months (OR 0.80, 95% CI: 0.65–0.98)[243]. In addition, in one RCT of active duty soldiers, brief CBT (12.5 h per patient) reduced the odds of suicide attempts in the 24-month follow-up compared with treatment as usual (HR 0.38, 95% CI: 0.16–0.87, NNT 3.88)[260]. However, it is important to note that there is considerable study heterogeneity in the CT and CBT field[243,259] and one analysis of studies demonstrated that the favourable effect for CBT was strongest when treatment as usual was not clearly described[261].

Dialectical behaviour therapy (DBT) is a cognitive behavioural treatment (including individual psychotherapy and weekly skills groups) that combines the change-focused aspects of CT with acceptance-based work[262]. Many studies of DBT have focused on patients with borderline personality disorder[243,263,264]. Although individual studies have provided evidence that DBT reduces suicidal ideation and suicide attempts, one systematic review examining treatment of patients (regardless of diagnosis) who have self-harmed within 6 months prior to treatment initiation concluded that, although DBT was associated with a decreased frequency of self-harm, it did not reduce the number of patients who repeated self-harm during follow-up[243].

Other approaches include the collaborative assessment and management of suicidality[265], a therapeutic framework to guide and manage suicide risk and inform treatment planning, mindfulness-based interventions, and acceptance and commitment therapy, a cognitive behavioural treatment that aims to promote psychological flexibility using six core processes, including acceptance and commitment to action[266]. Although collaborative assessment and management of suicidality has been shown to reduce suicidal ideation at 3 months[267], whether this treatment is effective for reducing suicide attempts has not yet been established[267,268]. Although interest in mindfulness-based interventions has grown in recent years, it is not yet clear whether these interventions reduce suicidal ideation or suicidal behaviour[269]. There is also some preliminary evidence for acceptance and commitment therapy in reducing suicidal ideation, although further studies are required[270].

Evidence on the use of psychosocial treatments in children and adolescents, irrespective of type, remains weak[257,271,272]. An evidence update concluded that DBT was the only intervention to meet the threshold for 'well established treatments' for reducing suicidal ideation and suicidal behaviour in children and adolescents[273]. Where there was probable or possible evidence for efficacy, these interventions tended to come from single studies[272,273]. However, an updated systematic review found that, if DBT is treated as a type of CBT, then there is evidence for the positive effects of CBT on self-harm in adolescents[274]. The authors of this study also noted that CBT with a family systems component are promising[274]. In addition, mentalization may also be effective in adolescents who self-harm[275].

Box 2 | **Interventions for suicidal ideation and suicidal behaviour**

Psychosocial

Longer-term psychosocial interventions

- Cognitive behavioural therapy
- Dialectic behavioural therapy
- Collaborative assessment and management of suicidality
- Acceptance and commitment therapy
- Mentalization
- Interpersonal psychotherapy

Brief interventions

- Caring contacts
- No suicide contacts
- Safety planning intervention
- Crisis response planning
- Attempted suicide short intervention programme
- Volitional help sheet

Pharmacological

Pharmacological agents with potential effect on suicidal behaviour

- Lithium
- Clozapine[a]
- Ketamine
- Selective serotonin reuptake inhibitors
- Buprenorphine

[a]Clozapine is indicated in treatment of patients with schizophrenia who present with suicidal ideation.

Very few studies have focused on preventing suicidal ideation or behaviour in older adults[276]. However, one study demonstrated that problem-solving therapy was associated with a reduction in suicidal ideation at 12 and 36 weeks, compared with supportive therapy[277]. In addition, findings from a pilot study of a 16-session course of interpersonal psychotherapy adapted for older adults found reduced suicidal ideation post-treatment[278].

There is no evidence from RCTs to support that any of these psychosocial interventions reduce the risk of suicide[279]. However, it is important to note that absence of evidence does not mean that these interventions are not effective but rather, for the most part, that studies have been insufficiently powered to detect a reduction in suicide given the relatively low frequency of deaths by suicide. Three other challenges to the management of suicide risk are important to highlight, namely that men are less likely to seek help than women[280], that men who die by suicide are less likely to be in contact with clinical services than women prior to death[210], and that it is not clear whether psychosocial interventions are as effective for men than for women[243].

Brief psychosocial interventions

Brief interventions to prevent suicidal behaviour are of great interest because they are easy to implement, inexpensive and require limited staff resources. These interventions are typically delivered in one session or via several brief contacts in person, by phone or mail. Typically, these interventions are often implemented with patients who had attended the ED for a suicidal crisis, most often a suicide attempt. Overall, the interventions target behaviour rather than symptoms associated with suicidal crises. The interventions, to varying degrees, focus on informing people about suicidal behaviour, helping people to become aware of problems, vulnerabilities and events linked to the behaviour, motivating people to engage in safety planning and help-seeking, problem solving, and developing practical strategies to manage future suicidal crises along with connecting to social and professional support.

Caring contacts. This approach, which was first tested more than four decades ago[281], refers to the routine sending of brief non-demanding messages (via, for example, postal mail, postcards, e-mail, texting and telephone) that express caring concern to suicidal patients following discharge from inpatient treatment. This intervention was shown to decrease suicide risk in one meta-analysis (OR 0.20, 95% CI: 0.09–0.42)[279], although this finding needs replication. One caring contacts (delivered via text message) trial for military personnel yielded inconsistent findings on the effectiveness of messages between primary (current suicidal ideation and hospitalization or medical evacuation due to suicide risk) and secondary outcomes (worst-point suicidal ideation, ED visits and suicide attempts)[282].

No-suicide contracts. Another form of brief intervention usually takes the form of asking patients to promise not to engage in suicidal behaviour and to contact professionals during times of crisis. These interventions have been used in various contexts, including emergency helplines and inpatient units. The contracts usually include a statement of assent, details of the duration of the agreement and a contingency plan if the person feels unable to uphold the agreement. However, there is a lack of data supporting their effectiveness[283] and they have fallen out of favour.

Safety Planning Intervention or Crisis Response Planning. The Safety Planning Intervention (SPI)[284] is a brief intervention that involves patients engaging in a suicide narrative aimed at identifying warning signs and provides individuals with a prioritized and specific set of coping strategies and sources of support that they can use if suicidal thoughts re-emerge. The intent of the SPI is to help individuals lower their imminent risk for suicidal behaviour by consulting a predetermined set of potential coping strategies and social supports. SPI has six steps: identify the warning signs; apply internal coping strategies; use people or social settings that could serve as a distraction; reach out to friends and family members who can provide support; contact professionals and agencies; and limit access to lethal means.

SPI, in combination with follow-up calls (known as SPI+), is effective in reducing the incidence of suicidal behaviour and increasing treatment engagement in the 6 months after discharge from the ED[285]. Crisis response planning is an abbreviated form of safety planning that uses four of six elements of the SPI (without social interaction as a means of distracting from suicidal thoughts and counselling to limit access to lethal means). Compared with a contract for safety, crisis response planning is more effective in preventing suicide attempts, resolving suicidal ideation and reducing inpatient hospitalization among high-risk active duty military personnel[286]. In addition, the ED-SAFE intervention includes a safety planning aspect (self-administered), along with a secondary suicide risk screening designed for ED physicians to evaluate suicide risk following an initial positive screen, and a series of telephone calls with the optional involvement of a friend or relative of the individual for 52 weeks following an ED visit. The ED-SAFE intervention resulted in fewer suicide attempts over a year compared to treatment as usual[215].

Additional brief interventions. Several other types of brief interventions have been described. The Attempted Suicide Short Intervention Program (ASSIP)[287] is a multi-session brief intervention that utilizes several elements of SPI and the crisis response plan in that it combines psychoeducation, a recorded patient-centred narrative description of a recent suicide crisis, safety planning and review of the recording to help continued long-term outreach contact. The ASSIP differs from other brief interventions in that it uses review of the recorded suicide narrative with the patient. ASSIP is administered in three weekly face-to-face therapy sessions supplemented by regular, personalized letters to the participants for 24 months. One recent study has demonstrated an 80% reduced risk of participants making at least one repeat suicide attempt when ASSIP was administered in addition to usual clinical treatment

compared with usual treatment with a single assessment interview[287]. In addition, ASSIP led to fewer suicide attempts but had no effect on suicidal ideation[287].

Another type of brief intervention — the Volitional Help Sheet — consists of a table with two columns and is designed to enhance self-determination with respect to self-harm. One column lists theoretically derived critical situations (in which the individual might engage in self-harm) and the other lists alternative responses to self-harm. Although this intervention had no overall effect on the recurrence of self-harm, it has been shown to be effective in reducing the number of self-harm repetitions following a suicide attempt in those previously hospitalized for self-harm, compared to a control group receiving treatment as usual[288].

Similarly, in teens, two brief interventions — Teens Options for Change (TOC)[289] and As Safe As Possible (ASAP)[290] — yielded encouraging, yet non-significant results. These studies offered different interventions to increase emotional regulation and coping skills in patients at risk of suicide from ED and inpatient settings, respectively.

Pharmacological interventions for suicidal behaviour

Lithium. From the potentially antisuicidal pharmacological agents available (BOX 2), lithium has been used the longest, with its antisuicidal effects having been reported for decades. However, most of the data supporting its utility in preventing suicide-related outcomes derives from observational studies of patients followed clinically with lithium[291,292] and some studies have reported conflicting data[293]. More recently, several methodologically rigorous pharmacoepidemiological studies, including >10,000 patients each[294,295], have strongly suggested that patients treated with lithium are relatively protected from suicide attempts, death by suicide, hospitalization for suicide attempts and other suicide-related outcomes, compared with patients treated with valproate or other mood stabilizers. However, several RCTs that compared lithium to either placebo or other mood stabilizers have been unable to demonstrate this effect[296,297], although some had very modest sample sizes[298]. Of interest, two of these studies identified antisuicidal effects based on secondary, post hoc analyses[296,299]. Although some meta-analyses that compared lithium to antiepileptic drugs and placebo found little effect[279,300], another recent meta-analysis with >6,500 participants demonstrated that, despite little effect on suicidal behaviour, lithium treatment was effective at reducing suicide deaths compared to placebo in people with MDD[300]. Importantly, the risk of suicidal behaviour was much greater before starting treatment with antiepileptic drugs compared with after treatment initiation in one study[301], whereas another study demonstrated no difference[302]; these findings are important, given the warning about possible increases in suicidal ideation in patients exposed to antiepileptic drugs by the US FDA.

Proper interpretation of these contradictory results about the antisuicidal properties of lithium is essential given the toxicity of lithium in overdose and its relatively narrow therapeutic window. Observational studies, no matter how well controlled, may spuriously demonstrate the protective effects of lithium. For example, these studies cannot control for important variables that affect a clinician's medication choice. Lithium toxicity and overdose risk may influence the likelihood of its prescription, particularly among individuals who have a greater risk of suicidal behaviour. Additionally, increased monitoring of patients who receive lithium may improve treatment efficiency and decrease suicide risk through repeated contact with clinical services.

Clozapine. Clozapine was the first medication approved by the US FDA to prevent suicidal behaviour. It is indicated in schizophrenia, in which the lifetime rate of suicide deaths of patients is ~10%, with ~50% of individuals attempting suicide[303]. Evidence supporting the use of clozapine for suicide came from the InterSePT study, a multicentre RCT that demonstrated the superiority of clozapine in reducing the risk of suicide attempts and the other primary outcome variables in people with schizophrenia or schizoaffective disorder, compared with olanzapine[303]. Of note, this study reported no difference in the rates of suicide in the two treatment arms, although the total number of deaths was relatively small (five with clozapine and three with olanzapine). More recently, a meta-analysis of observational and trial data demonstrated that clozapine, when taken consistently, decreased not only suicides but other causes of mortality as well[304], although this effect may be partially explained by closer monitoring of patients receiving clozapine treatment. Nonetheless, clozapine remains relatively underutilized for the prevention of suicidal behaviour in patients with psychosis, probably because of the required laboratory monitoring given the risk of neutropenia and agranulocytosis in patients treated with this drug[305].

Ketamine. The past decade has seen intense interest in the use of ketamine as a potential antisuicidal medication[306] and its relatively novel mechanism of action has spurred a search for other drugs with similar mechanisms that might also be of use[307]. Several studies have examined the effect of ketamine on suicidal ideation, mostly in people with mood disorders[308–310] and have demonstrated that ketamine decreases suicidal ideation independent of improvement in other mood symptoms[174,308–310], although one small study did not find this to be the case[311]. Of interest, the effects of ketamine on suicidal ideation may be linked to improvements in insomnia[312], a clinical variable that has been linked to suicidal behaviour[313]. Several additional studies are underway to examine the effects of intranasal ketamine (esketamine, the *S*-enantiomer of ketamine) on suicidal ideation in various populations, with some encouraging results[314]. Clearly, the intranasal administration route would facilitate the use of ketamine, if its therapeutic effects are verified. Some of the questions remaining include the duration of its effects and whether repeated administration would be a practical and efficient approach.

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are thought to have a more-pronounced effect on suicidal ideation than other

antidepressants, based on >50 years of studies showing the importance of serotonergic dysfunction in suicidal behaviour[61,128]. Earlier studies were mostly secondary analyses of depression trials; in fact, of 10 such studies that compared the effects of serotonergic and noradrenergic antidepressants on suicidal ideation, five favoured serotonergic drugs[315–319], one favoured a noradrenergic drug[320] and four found no difference[321–324]. However, these studies used one item from a depression scale to measure suicidal ideation and did not specifically recruit individuals with suicidal behaviour. However, one small pilot study using a double-blind, randomized, controlled methodology demonstrated that paroxetine was more effective in reducing suicidal ideation, even after adjusting for depression symptoms, compared with bupropion in patients with depression who had past suicide attempts or active suicidal ideation[325]. Of note, benefit increased as baseline severity of suicidal ideation was higher. Clearly, more evidence is required to determine whether SSRIs are superior than other therapies for the treatment of people with depression who are suicidal, and trials would do well to specifically recruit those at risk for suicidal behaviour. There also appears to be an age-related effect of SSRIs on suicidal events — in one meta-analysis of clinical trials, SSRIs appeared to increase the risk of suicidal events in those <24 years of age, and protected against suicidal events in those >65 years of age[326].

Buprenorphine. The effects of buprenorphine have recently been studied for the treatment of suicidal ideation. A small RCT delivered promising results suggesting that patients with depression who received low-dose buprenorphine were more likely to show decreases in suicidal ideation after 2 weeks and 4 weeks of treatment[327]. Buprenorphine was well tolerated. Similarly, a 3-day study of men with depression and opioid use disorder also demonstrated decreases in suicidal ideation after a large dose of sub-lingual buprenorphine, although this trial was not placebo controlled[328]. Larger studies are needed to replicate the finding that opioids may improve suicidal ideation; this is an observation that comports with the hypothesis that psychic pain is an important determinant of suicide risk[329].

Quality of life

Quality of life is a multidimensional concept that includes physical, mental and social aspects of subjective satisfaction with one's own life. Studies investigating health-related quality of life typically focus on the physical and mental components in the context of either past suicidal ideation or past suicide attempt. For mental health outcomes, suicidal ideation and suicide attempt are associated with trajectories of decreasing mental health over time[330]. In addition, several factors are associated with reduced mental health components of quality of life assessments such as being female, having borderline personality disorder, or having high impulsivity, hopelessness or hostility[331]. Similarly, suicidal behaviour is associated with reduced physical health over time[330,332], and depending on the method and severity of the suicide attempt, individuals might have physical disabilities that directly affect their quality of life[333]. Moreover, reduced quality of life can also affect those who are close to the individual attempting suicide. Indeed, scores for depression and anxiety are higher whereas scores for mental components of quality of life are lower in people who are related to an individual who died by suicide[334].

A continuing obstacle to suicide prevention and contributor to decreased quality of life in people who survive suicide attempts is the pervasive taboo surrounding suicidal ideation and suicidal behaviour. Although most countries have public health initiatives directed at breaking the stigma surrounding mental health issues, the perceived stigma associated with suicide is still an obstacle to help-seeking[1,335] and, therefore, constitutes an important target for public health initiatives aiming to decrease suicide rates. Additionally, the stigma or perceived stigma associated with suicide and suicide attempts is associated with reduced disclosure of personal or familial histories of suicidal behaviour and are associated with decreased self-esteem[335].

As noted above, the prevalence of suicidal ideation and suicide attempt are many times that of suicide and, therefore, the potential effect of suicidal ideation and suicidal behaviour goes beyond the direct loss of the individual. Studies investigating the economic burden of suicide and suicide attempt placed the cost of suicide at US$58.4 billion in the USA in 2013 when considering only reported suicides and suicide attempts, and up to US$93.5 billion when numbers are adjusted for underreporting[336]. Of note, the costs were mainly due to lost productivity[336]. In addition, suicidal ideation and suicide attempt are associated with increased health care costs, with up to one-third of patient admissions in psychiatric hospitals attributed to suicidal ideation or suicide attempt[331]. These costs may be related to the direct treatment of injuries or to the psychological and social aspects of suicidal behaviour and their effect on others[1]. With an estimated per capita cost of suicide nearing US$300 in the USA[336], investments in suicide prevention efforts are paramount.

Outlook

Suicide and suicidal behaviour continue to present a challenge both clinically and socially, and our theoretical understanding of the process involved in development of suicide risk continues to evolve as we obtain more evidence on the epidemiological, biological, clinical and psychological fronts.

Several factors regarding the detection and treatment of suicide continue to be explored, including developing and validating clear assessment algorithms to assist clinicians in determining which of their patients are at greatest risk of suicide attempts or suicide, and assessing the practicality of their implementation in clinical practices. In addition, understanding which psychological or pharmacological treatments are the most effective, and for whom, requires further study. On this point, > 100 registered clinical trials for suicide are currently underway (Supplementary Table 1). These trials are investigating various interventions, including those based on psychological and behavioural approaches, pharmacological approaches, mixed approaches, use of medical devices,

use of new media, screening, primary prevention and reducing access to lethal means.

Similarly, what biological mechanisms underlie the cognitive and behavioural changes associated with suicide risk, and how public policies can be tailored to better prevent, detect and treat at-risk groups to continue to decrease suicide rates across the globe, are important questions to address. In addition, efforts should also be made into better understanding sex differences as they apply to pathology and interventions for suicidal behaviour. Given the important contribution of the easy access to pesticides and firearms to global suicide rates as well as the clear evidence that selective measures to reduce access to these means have an effect on suicide rates, single measures such as legislation for stricter regulation of firearm access in the USA or further regulation on access to pesticides in China and other countries in Asia may have a tremendous effect on global suicide rates[125]. With suicide rates continuing to rise at an alarming rate in some countries[1], it is evident that suicide will remain an important public health concern, and one that can only be addressed through concerted, multidisciplinary and multifaceted efforts.

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1. World Health Organization. Preventing suicide: a global imperative (WHO, 2014).
A systematic overview of the global epidemiology of suicide and suicide attempts, including country-specific data and an assessment of key prevention strategies.
2. Naghavi, M. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the global burden of disease study 2016. *BMJ* **364**, l94 (2019).
This review, based on the Global Burden of Disease Study, provides the global and country-specific incidence (and trends in incidence) of suicide.
3. Cerel, J. et al. How many people are exposed to suicide? Not six. *Suicide Life Threat. Behav.* **49**, 529–534 (2019).
4. Crosby, A. E., Ortega, L. & Melanson, C. Self-directed violence surveillance: uniform definitions and recommended data elements (CDC, 2011).
5. Brenner, L. A. et al. Implementation of a suicide nomenclature within two VA healthcare settings. *J. Clin. Psychol. Med. Settings* **18**, 116–128 (2011).
6. Turecki, G. & Brent, D. A. Suicide and suicidal behaviour. *Lancet* **387**, 1227–1239 (2016).
7. Mars, B. et al. Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: a population-based birth cohort study. *Lancet Psychiatry* **6**, 327–337 (2019).
8. Klonsky, E. D., May, A. M. & Saffer, B. Y. Suicide, suicide attempts, and suicidal ideation. *Annu. Rev. Clin. Psychol.* **12**, 307–330 (2016).
9. O'Connor, R. C. & Kirtley, O. J. The integrated motivational-volitional model of suicidal behaviour. *Phil. Trans. R. Soc. B Biol. Sci.* **373**, 20170268 (2018).
10. Van Orden, K. A. et al. The interpersonal theory of suicide. *Psychol. Rev.* **117**, 575–600 (2010).
11. Kapur, N., Cooper, J., O'Connor, R. C. & Hawton, K. Non-suicidal self-injury v. attempted suicide: new diagnosis or false dichotomy? *Br. J. Psychiatry* **202**, 326–328 (2013).
12. Nock, M. K. et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br. J. Psychiatry* **192**, 98–105 (2008).
This epidemiological study is one of few to compare suicidal ideation and suicidal behaviour across low-income, middle-income and high-income countries (17 countries in total).
13. Seedat, S. et al. Cross-national associations between gender and mental disorders in the world health organization world mental health surveys. *Arch. Gen. Psychiatry* **66**, 785–795 (2009).
14. Spallek, J. et al. Suicide among immigrants in Europe — a systematic literature review. *Eur. J. Public Health* **25**, 63–71 (2015).
15. Gunnell, D. & Eddleston, M. Suicide by intentional ingestion of pesticides: a continuing tragedy in developing countries. *Int. J. Epidemiol.* **32**, 902–909 (2003).
16. Mew, E. J. et al. The global burden of fatal self-poisoning with pesticides 2006-15: Systematic review. *J Affect. Disord.* **219**, 93–104 (2017).
17. Pridemore, W. A., Chamlin, M. B. & Andreev, E. Reduction in male suicide mortality following the 2006 Russian alcohol policy: an interrupted time series analysis. *Am. J. Public Health* **103**, 2021–2026 (2013).
18. Lin, C. Y., Hsu, C. Y., Gunnell, D., Chen, Y. Y. & Chang, S. S. Spatial patterning, correlates, and inequality in suicide across 432 neighborhoods in Taipei City, Taiwan. *Soc. Sci. Med.* **222**, 20–34 (2018).
19. World Health Organization.World Health Statistics data visualizations dashboard. Noncommunicable diseases and mental health. Data tables (WHO, 2018).
20. Thomas, K. & Gunnell, D. Suicide in England and Wales 1861-2007: a time-trends analysis. *Int. J. Epidemiol.* **39**, 1464–1475 (2010).
21. Caine, E. D. Suicide and attempted suicide in the united states during the 21st century. *JAMA Psychiatry* **74**, 1087–1088 (2017).
22. Wang, C. W., Chan, C. L. & Yip, P. S. Suicide rates in China from 2002 to 2011: an update. *Soc. Psychiatry Psychiatr. Epidemiol.* **49**, 929–941 (2014).
23. India State-Level Disease Burden Initiative Suicide Collaborators. Gender differentials and state variations in suicide deaths in India: the Global Burden of Disease Study 1990-2016. *Lancet Public Health* **3**, e478–e489 (2018).
24. Chang, S. S., Stuckler, D., Yip, P. & Gunnell, D. Impact of 2008 global economic crisis on suicide: time trend study in 54 countries. *BMJ* **347**, f5239 (2013).
25. Stuckler, D., Basu, S., Suhrcke, M., Coutts, A. & McKee, M. The public health effect of economic crises and alternative policy responses in Europe: an empirical analysis. *Lancet* **374**, 315–323 (2009).
A comprehensive assessment of the impact of economic crises and increases in unemployment on all-cause and suicide mortality in Europe, showing that rises in unemployment are associated with increases in suicide, but the extent of the rise may be offset by appropriate social policy measures, particularly active labour market programmes.
26. Gunnell, D. et al. The impact of pesticide regulations on suicide in Sri Lanka. *Int. J. Epidemiol.* **36**, 1235–1242 (2007).
27. Kreitman, N. The coal gas story. United Kingdom suicide rates, 1960-71. *Br. J. Prev. Soc. Med.* **30**, 86–93 (1976).
28. Niederkrotenthaler, T. et al. Changes in suicide rates following media reports on celebrity suicide: a meta-analysis. *J. Epidemiol. Community Health* **66**, 1037–1042 (2012).
29. Turecki, G. The molecular bases of the suicidal brain. *Nat. Rev. Neurosci.* **15**, 802–816 (2014).
30. Lutz, P. E., Mechawar, N. & Turecki, G. Neuropathology of suicide: recent findings and future directions. *Mol. Psychiatry* **22**, 1395–1412 (2017).
31. Brent, D. A., Bridge, J., Johnson, B. A. & Connolly, J. Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. *Arch. Gen. Psychiatry* **53**, 1145–1152 (1996).
32. McGirr, A. et al. Familial aggregation of suicide explained by cluster B traits: a three-group family study of suicide controlling for major depressive disorder. *Am. J. Psychiatry* **166**, 1124–1134 (2009).
This paper is a key contributor to our understanding of how impulsive–aggressive behaviours contribute to the familial aggregation of suicidal behaviours.
33. O'Neill, S., Ennis, E., Corry, C. & Bunting, B. Factors associated with suicide in four age groups: a population based study. *Arch. Suicide Res.* **22**, 128–138 (2018).
34. Brent, D. A. et al. Familial transmission of mood disorders: convergence and divergence with transmission of suicidal behavior. *J. Am. Acad. Child Adolesc. Psychiatry* **43**, 1259–1266 (2004).
35. Kim, C. D. et al. Familial aggregation of suicidal behavior: a family study of male suicide completers from the general population. *Am. J. Psychiatry* **162**, 1017–1019 (2005).
36. Tidemalm, D. et al. Familial clustering of suicide risk: a total population study of 11.4 million individuals. *Psychol. Med.* **41**, 2527–2534 (2011).
37. Fu, Q. et al. A twin study of genetic and environmental influences on suicidality in men. *Psychol. Med.* **32**, 11–24 (2002).
38. Brent, D. A. et al. Familial pathways to early-onset suicide attempt: a 5.6-year prospective study. *JAMA Psychiatry* **72**, 160–168 (2015).
39. Burrell, L. V., Mehlum, L. & Qin, P. Sudden parental death from external causes and risk of suicide in the bereaved offspring: a national study. *J. Psychiatr. Res.* **96**, 49–56 (2018).
40. Coon, H. et al. Genome-wide significant regions in 43 Utah high-risk families implicate multiple genes involved in risk for completed suicide. *Mol. Psychiatry* https://doi.org/10.1038/s41380-018-0282-3 (2018).
41. Galfalvy, H. et al. A genome-wide association study of suicidal behavior. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **168**, 557–563 (2015).
42. Galfalvy, H. et al. A pilot genome wide association and gene expression array study of suicide with and without major depression. *World J. Biol. Psychiatry* **14**, 574–582 (2013).
43. Tombácz, D. et al. High-coverage whole-exome sequencing identifies candidate genes for suicide in victims with major depressive disorder. *Sci. Rep.* **7**, 7106 (2017).
44. Anguelova, M., Benkelfat, C. & Turecki, G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behaviour. *Mol. Psychiatry* **8**, 646–653 (2003).
45. Brezo, J., Klempan, T. & Turecki, G. The genetics of suicide: a critical review of molecular studies. *Psychiatr. Clin. North Am.* **31**, 179–203 (2008).
46. Erlangsen, A. et al. Genetics of suicide attempts in individuals with and without mental disorders: a population-based genome-wide association study. *Mol. Psychiatry* https://doi.org/10.1038/s41380-018-0218-y (2018).
47. Strawbridge, R. J. et al. Identification of novel genome-wide associations for suicidality in UK Biobank, genetic correlation with psychiatric disorders and polygenic association with completed suicide. *EBioMedicine* **41**, 517–525 (2019).
48. Levey, D. F. et al. Genetic associations with suicide attempt severity and genetic overlap with major depression. *Transl. Psychiatry* **9**, 22 (2019).
49. Kimbrel, N. A. et al. A genome-wide association study of suicide attempts and suicidal ideation in U.S. military veterans. *Psychiatry Res.* **269**, 64–69 (2018).
50. Sokolowski, M., Wasserman, J. & Wasserman, D. Polygenic associations of neurodevelopmental genes in suicide attempt. *Mol. Psychiatry* **21**, 1381–1390 (2016).
51. Ruderfer, D. M. et al. Significant shared heritability underlies suicide attempt and clinically predicted probability of attempting suicide. *Mol. Psychiatry* https://doi.org/10.1038/s41380-018-0326-8 (2019).
52. Consortium, E. P. An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57–74 (2012).

53. PsychENCODE Consortium. Revealing the brain's molecular architecture. *Science* **362**, 1262–1263 (2018).
54. Brezo, J. et al. Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. *Mol. Psychiatry* **15**, 831–843 (2010).
55. Caspi, A. et al. Influence of life stress on depression: moderation by a polymorphism in the *5-HTT* gene. *Science* **301**, 386–389 (2003).
56. Brezo, J. et al. Predicting suicide attempts in young adults with histories of childhood abuse. *Br. J. Psychiatry* **193**, 134–139 (2008).
57. Fergusson, D. M., Woodward, L. J. & Horwood, L. J. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychol. Med.* **30**, 23–39 (2000).
58. McGowan, P. O. et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat. Neurosci.* **12**, 342–348 (2009).
This work was the first to show biological mechanisms for the lasting impact of social trauma in humans and has been the basis for reconciling the effects of genetics and environment on behaviour.
59. Labonte, B. et al. Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. *Biol. Psychiatry* **72**, 41–48 (2012).
60. Turecki, G., Ota, V. K., Belangero, S. I., Jackowski, A. & Kaufman, J. Early life adversity, genomic plasticity, and psychopathology. *Lancet Psychiatry* **1**, 461–466 (2014).
61. van Heeringen, K. & Mann, J. J. The neurobiology of suicide. *Lancet Psychiatry* **1**, 63–72 (2014).
62. Mann, J. J. et al. Candidate endophenotypes for genetic studies of suicidal behavior. *Biol. Psychiatry* **65**, 556–563 (2009).
63. Brezo, J. et al. Childhood trajectories of anxiousness and disruptiveness as predictors of suicide attempts. *Arch. Pediatr. Adolesc. Med.* **162**, 1015–1021 (2008).
64. Brezo, J. et al. Broad and narrow personality traits as markers of one-time and repeated suicide attempts: a population-based study. *BMC Psychiatry* **8**, 15 (2008).
65. Sareen, J. et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. *Arch. Gen. Psychiatry* **62**, 1249–1257 (2005).
66. Orri, M. et al. Association of childhood irritability and depressive/anxious mood profiles with adolescent suicidal ideation and attempts. *JAMA Psychiatry* **75**, 465–473 (2018).
67. Bentley, K. H. et al. Anxiety and its disorders as risk factors for suicidal thoughts and behaviors: a meta-analytic review. *Clin. Psychol. Rev.* **43**, 30–46 (2016).
68. Wanner, B., Vitaro, F., Tremblay, R. E. & Turecki, G. Childhood trajectories of anxiousness and disruptiveness explain the association between early-life adversity and attempted suicide. *Psychol. Med.* **42**, 2373–2382 (2012).
69. Waltes, R., Chiocchetti, A. G. & Freitag, C. M. The neurobiological basis of human aggression: a review on genetic and epigenetic mechanisms. *Am. J. Med. Genet. Part B Neuropsychiatric Genet.* **171**, 650–675 (2016).
70. Palumbo, S., Mariotti, V., Iofrida, C. & Pellegrini, S. Genes and aggressive behavior: epigenetic mechanisms underlying individual susceptibility to aversive environments. *Front. Behav. Neurosci.* **12**, 117 (2018).
71. Provencal, N., Booij, L. & Tremblay, R. E. The developmental origins of chronic physical aggression: biological pathways triggered by early life adversity. *J. Exp. Biol.* **218**, 123–133 (2015).
72. Smith, M. M. et al. The perniciousness of perfectionism: a meta-analytic review of the perfectionism–suicide relationship. *J. Pers.* **86**, 522–542 (2018).
73. Batty, G. D. et al. Personality traits and risk of suicide mortality: findings from a multi-cohort study in the general population. *World Psychiatry* **17**, 371–372 (2018).
74. Caldji, C. et al. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc. Natl Acad. Sci. USA* **95**, 5335–5340 (1998).
75. Suomi, S. J. Early stress and adult emotional reactivity in rhesus monkeys. *Ciba Found. Symp.* **156**, 171–183; discussion 183–178 (1991).
76. Weaver, I. C. et al. Epigenetic programming by maternal behavior. *Nat. Neurosci.* **7**, 847–854 (2004).
77. van der Vegt, E. J., van der Ende, J., Ferdinand, R. F., Verhulst, F. C. & Tiemeier, H. Early childhood adversities and trajectories of psychiatric problems in adoptees: evidence for long lasting effects. *J. Abnorm. Child Psychol.* **37**, 239–249 (2009).
78. Johnson, J. G. et al. Childhood adversities, interpersonal difficulties, and risk for suicide attempts during late adolescence and early adulthood. *Arch. Gen. Psychiatry* **59**, 741–749 (2002).
79. Richard-Devantoy, S., Berlim, M. T. & Jollant, F. Suicidal behaviour and memory: a systematic review and meta-analysis. *World J. Biol. Psychiatry* **16**, 544–566 (2015).
80. McGirr, A. et al. Dysregulation of the sympathetic nervous system, hypothalamic–pituitary–adrenal axis and executive function in individuals at risk for suicide. *J. Psychiatry Neurosci.* **35**, 399–408 (2010).
81. Ding, Y. et al. Altered brain processing of decision-making in healthy first-degree biological relatives of suicide completers. *Mol. Psychiatry* **22**, 1149–1154 (2017).
82. Grover, K. E. et al. Problem solving moderates the effects of life event stress and chronic stress on suicidal behaviors in adolescence. *J. Clin. Psychol.* **65**, 1281–1290 (2009).
83. Sorberg Wallin, A. et al. Suicide attempt predicted by academic performance and childhood IQ: a cohort study of 26 000 children. *Acta Psychiatr. Scand.* **137**, 277–286 (2018).
84. Gould, F. et al. The effects of child abuse and neglect on cognitive functioning in adulthood. *J. Psychiatr. Res.* **46**, 500–506 (2012).
85. Lee, F. S. et al. Mental health. Adolescent mental health-opportunity and obligation. *Science* **346**, 547–549 (2014).
86. Nock, M. K. et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the national comorbidity survey replication adolescent supplement. *JAMA Psychiatry* **70**, 300–310 (2013).
87. 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* **9**, e89944 (2014).
88. Nock, M. K. et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. *PLOS Med.* **6**, e1000123 (2009).
89. Arsenault-Lapierre, G., Kim, C. & Turecki, G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry* **4**, 37 (2004).
90. Lin, L. & Zhang, J. Impulsivity, mental disorder, and suicide in rural China. *Arch. Suicide Res.* **21**, 73–82 (2017).
91. Phillips, M. R., Li, X. & Zhang, Y. Suicide rates in China, 1995-99. *Lancet* **359**, 835–840 (2002).
92. Zhang, J., Xiao, S. & Zhou, L. Mental disorders and suicide among young rural Chinese: a case-control psychological autopsy study. *Am. J. Psychiatry* **167**, 773–781 (2010).
93. Ahmed, H. U. et al. Suicide and depression in the World Health Organization South-East Asia Region: a systematic review. *WHO South East Asia J. Public Health* **6**, 60–66 (2017).
94. Kapur, N. et al. Mental health service changes, organisational factors, and patient suicide in England in 1997-2012: a before-and-after study. *Lancet Psychiatry* **3**, 526–534 (2016).
95. Hor, K. & Taylor, M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J. Psychopharmacol.* **24**, 81–90 (2010).
96. Holma, K. M. et al. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. *Bipolar Disord.* **16**, 652–661 (2014).
97. McGirr, A., Renaud, J., Seguin, M., Alda, M. & Turecki, G. Course of major depressive disorder and suicide outcome: a psychological autopsy study. *J. Clin. Psychiatry* **69**, 966–970 (2008).
98. Holma, K. M. et al. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. *Am. J. Psychiatry* **167**, 801–808 (2010).
99. Dumais, A. et al. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. *Am. J. Psychiatry* **162**, 2116–2124 (2005).
100. Kim, C. et al. Patterns of co-morbidity in male suicide completers. *Psychol. Med.* **33**, 1299–1309 (2003).
101. Seguin, M. et al. Life trajectories and burden of adversity: mapping the developmental profiles of suicide mortality. *Psychol. Med.* **37**, 1575–1583 (2007).
102. Artenie, A. A. et al. Licit and illicit substance use among people who inject drugs and the association with subsequent suicidal attempt. *Addiction* **110**, 1636–1643 (2015).
103. Artenie, A. A. et al. Associations of substance use patterns with attempted suicide among persons who inject drugs: can distinct use patterns play a role? *Drug Alcohol Depend.* **147**, 208–214 (2015).
104. Chachamovich, E., Ding, Y. & Turecki, G. Levels of aggressiveness are higher among alcohol-related suicides: results from a psychological autopsy study. *Alcohol* **46**, 529–536 (2012).
105. Schosser, A. et al. Genomewide association scan of suicidal thoughts and behaviour in major depression. *PLOS ONE* **6**, e20690 (2011).
106. Fournier, C. et al. Association between binge drug use and suicide attempt among people who inject drugs. *Substance Abuse* **39**, 315–321 (2018).
107. Qin, P., Agerbo, E. & Mortensen, P. B. Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: a national register-based study of all suicides in Denmark, 1981-1997. *Am. J. Psychiatry* **160**, 765–772 (2003).
108. Webb, R. T. et al. Suicide risk in primary care patients with major physical diseases: a case–control study. *Arch. Gen. Psychiatry* **69**, 256–264 (2012).
109. Seguin, M., Beauchamp, G., Robert, M., DiMambro, M. & Turecki, G. Developmental model of suicide trajectories. *Br. J. Psychiatry* **205**, 120–126 (2014).
110. Bernert, R. A., Turvey, C. L., Conwell, Y. & Joiner, T. E. Jr. Association of poor subjective sleep quality with risk for death by suicide during a 10-year period: a longitudinal, population-based study of late life. *JAMA Psychiatry* **71**, 1129–1137 (2014).
111. Morgan, C. et al. Self-harm in a primary care cohort of older people: incidence, clinical management, and risk of suicide and other causes of death. *Lancet Psychiatry* **5**, 905–912 (2018).
112. Bernert, R. A., Kim, J. S., Iwata, N. G. & Perlis, M. L. Sleep disturbances as an evidence-based suicide risk factor. *Curr. Psychiatry Rep.* **17**, 554 (2015).
113. Racine, M. Chronic pain and suicide risk: a comprehensive review. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **87**, 269–280 (2018).
114. Joiner, T. E. Jr., Brown, J. S. & Wingate, L. R. The psychology and neurobiology of suicidal behavior. *Annu. Rev. Psychol.* **56**, 287–314 (2005).
115. O'Connor, R. C. & Nock, M. K. The psychology of suicidal behaviour. *Lancet Psychiatry* **1**, 73–85 (2014).
116. Klonsky, E. D. & May, A. M. The three-step theory (3ST): a new theory of suicide rooted in the "ideation-to-action" framework. *Int. J. Cognit. Ther.* **8**, 114–129 (2015).
117. Wetherall, K. et al. From ideation to action: differentiating between those who think about suicide and those who attempt suicide in a national study of young adults. *J. Affect. Disord.* **241**, 475–483 (2018).
118. Batty, G. D. et al. Psychosocial characteristics as potential predictors of suicide in adults: an overview of the evidence with new results from prospective cohort studies. *Transl. Psychiatry* **8**, 22 (2018).
119. Bjorkenstam, C., Andersson, G., Dalman, C., Cochran, S. & Kosidou, K. Suicide in married couples in Sweden: is the risk greater in same-sex couples? *Eur. J. Epidemiol.* **31**, 685–690 (2016).
120. Brunstein Klomek, A., Sourander, A. & Gould, M. The association of suicide and bullying in childhood to young adulthood: a review of cross-sectional and longitudinal research findings. *Can. J. Psychiatry* **55**, 282–288 (2010).
121. King, M. et al. A systematic review of mental disorder, suicide, and deliberate self harm in lesbian, gay and bisexual people. *BMC Psychiatry* **8**, 70 (2008).
122. Neeleman, J. & Wessely, S. Ethnic minority suicide: a small area geographical study in south London. *Psychol. Med.* **29**, 429–436 (1999).
123. Calati, R. et al. Suicidal thoughts and behaviors and social isolation: a narrative review of the literature. *J Affect. Disord.* **245**, 653–667 (2019).
124. Niedzwiedz, C., Haw, C., Hawton, K. & Platt, S. The definition and epidemiology of clusters of suicidal behavior: a systematic review. *Suicide Life Threat. Behav.* **44**, 569–581 (2014).
125. Yip, P. S. et al. Means restriction for suicide prevention. *Lancet* **379**, 2393–2399 (2012).
126. Mann, J. J. The serotonergic system in mood disorders and suicidal behaviour. *Phil. Trans. R. Soc. B Biol. Sci.* **368**, 20120537 (2013).

127. Antypa, N., Serretti, A. & Rujescu, D. Serotonergic genes and suicide: a systematic review. *Eur. Neuropsychopharmacol.* **23**, 1125–1142 (2013).
128. Oquendo, M. A. et al. Toward a biosignature for suicide. *Am. J. Psychiatry* **171**, 1259–1277 (2014).
129. Asberg, M., Thoren, P., Traskman, L., Bertilsson, L. & Ringberger, V. "Serotonin depression" – a biochemical subgroup within the affective disorders? *Science* **191**, 478–480 (1976).
130. Arango, V. et al. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. *Neuropsychopharmacology* **25**, 892–903 (2001).
131. Mann, J. J. Neurobiology of suicidal behaviour. *Nat. Rev. Neurosci.* **4**, 819–828 (2003).
132. Boldrini, M., Underwood, M. D., Mann, J. J. & Arango, V. More tryptophan hydroxylase in the brainstem dorsal raphe nucleus in depressed suicides. *Brain Res.* **1041**, 19–28 (2005).
133. Bach-Mizrachi, H. et al. Elevated expression of tryptophan hydroxylase-2 mRNA at the neuronal level in the dorsal and median raphe nuclei of depressed suicides. *Mol. Psychiatry* **13**, 507–513 (2008).
134. Sullivan, G. M. et al. Positron emission tomography quantification of serotonin$_{1A}$ receptor binding in suicide attempters with major depressive disorder. *JAMA Psychiatry* **72**, 169–178 (2015).
135. Wang, L. et al. Serotonin-1A receptor alterations in depression: a meta-analysis of molecular imaging studies. *BMC Psychiatry* **16**, 319 (2016).
136. Jokinen, J., Nordstrom, A. L. & Nordstrom, P. CSF 5-HIAA and DST non-suppression — orthogonal biologic risk factors for suicide in male mood disorder inpatients. *Psychiatry Res.* **165**, 96–102 (2009).
137. Miller, J. M. et al. Positron emission tomography quantification of serotonin transporter in suicide attempters with major depressive disorder. *Biol. Psychiatry* **74**, 287–295 (2013).
138. Lutz, P. E. Multiple serotonergic paths to antidepressant efficacy. *J. Neurophysiol.* **109**, 2245–2249 (2013).
139. Dracheva, S. et al. Increased serotonin 2C receptor mRNA editing: a possible risk factor for suicide. *Mol. Psychiatry* **13**, 1001–1010 (2008).
140. Schmauss, C. Serotonin 2C receptors: suicide, serotonin, and runaway RNA editing. *Neuroscientist* **9**, 237–242 (2003).
141. Di Narzo, A. F. et al. A unique gene expression signature associated with serotonin 2C receptor RNA editing in the prefrontal cortex and altered in suicide. *Hum. Mol. Genet.* **23**, 4801–4813 (2014).
142. Weissmann, D. et al. Region-specific alterations of A-to-I RNA editing of serotonin 2C receptor in the cortex of suicides with major depression. *Transl. Psychiatry* **6**, e878 (2016).
143. O'Connor, D. B., Ferguson, E., Green, J. A., O'Carroll, R. E. & O'Connor, R. C. Cortisol levels and suicidal behavior: a meta-analysis. *Psychoneuroendocrinology* **63**, 370–379 (2016).
144. Melhem, N. M. et al. Blunted HPA axis activity in suicide attempters compared to those at high risk for suicidal behavior. *Neuropsychopharmacology* **41**, 1447–1456 (2016).
145. Turecki, G. & Meaney, M. J. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. *Biol. Psychiatry* **79**, 87–96 (2016).
146. Raison, C. L. & Miller, A. H. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am. J. Psychiatry* **160**, 1554–1565 (2003).
147. Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D. & Enoch, M. A. Interaction of *FKBP5*, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology* **35**, 1674–1683 (2010).
148. Lahti, J. et al. Associations between self-reported and objectively recorded early life stress, FKBP5 polymorphisms, and depressive symptoms in midlife. *Biol. Psychiatry* **80**, 869–877 (2016).
149. Kaminsky, Z. et al. Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. *Transl. Psychiatry* **5**, e627 (2015).
150. Guintivano, J. et al. Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. *Am. J. Psychiatry* **171**, 1287–1296 (2014).
151. Shopsin, B. The clinical antidepressant effect of exogenous agmatine is not reversed by parachlorophenylalanine: a pilot study. *Acta Neuropsychiatr* **25**, 113–118 (2013).
152. Gawali, N. B. et al. Agmatine ameliorates lipopolysaccharide induced depressive-like behaviour in mice by targeting the underlying inflammatory and oxido-nitrosative mediators. *Pharmacol. Biochem. Behav.* **149**, 1–8 (2016).
153. Dwivedi, Y. et al. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch. Gen. Psychiatry* **60**, 804–815 (2003).
154. Banerjee, R., Ghosh, A. K., Ghosh, B., Bhattacharyya, S. & Mondal, A. C. Decreased mRNA and protein expression of BDNF, NGF, and their receptors in the hippocampus from suicide: an analysis in human postmortem brain. *Clin. Med. Insights Pathol.* **6**, 1–11 (2013).
155. Eisen, R. B. et al. Association between BDNF levels and suicidal behaviour: a systematic review and meta-analysis. *Syst. Rev.* **4**, 187 (2015).
156. Grah, M. et al. Brain-derived neurotrophic factor as a suicide factor in mental disorders. *Acta Neuropsychiatr.* **26**, 356–363 (2014).
157. Keller, S. et al. Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Arch. Gen. Psychiatry* **67**, 258–267 (2010).
158. Kang, H. J. et al. BDNF promoter methylation and suicidal behavior in depressive patients. *J. Affect. Disord.* **151**, 679–685 (2013).
159. Ernst, C., Chen, E. S. & Turecki, G. Histone methylation and decreased expression of TrkB.T1 in orbital frontal cortex of suicide completers. *Mol. Psychiatry* **14**, 830–832 (2009).
160. Maussion, G. et al. Regulation of a truncated form of tropomyosin-related kinase B (TrkB) by Hsa-miR-185* in frontal cortex of suicide completers. *PLOS ONE* **7**, e39301 (2012).
161. Stockmeier, C. A. et al. Cellular changes in the postmortem hippocampus in major depression. *Biol. Psychiatry* **56**, 640–650 (2004).
162. Rajkowska, G. et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol. Psychiatry* **45**, 1085–1098 (1999).
163. Videbech, P. & Ravnkilde, B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am. J. Psychiatry* **161**, 1957–1966 (2004).
164. Amaral, D. G. & Witter, M. P. The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience* **31**, 571–591 (1989).
165. Chandley, M. J. et al. Gene expression deficits in pontine locus coeruleus astrocytes in men with major depressive disorder. *J. Psychiatry Neurosci.* **38**, 276–284 (2013).
166. Chandley, M. J. et al. Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. *Int. J. Neuropsychopharmacol.* **17**, 1569–1578 (2014).
167. Sokolowski, M., Wasserman, J. & Wasserman, D. An overview of the neurobiology of suicidal behaviors as one meta-system. *Mol. Psychiatry* **20**, 56–71 (2015).
168. Gray, A. L., Hyde, T. M., Deep-Soboslay, A., Kleinman, J. E. & Sodhi, M. S. Sex differences in glutamate receptor gene expression in major depression and suicide. *Mol. Psychiatry* **20**, 1057–1068 (2015).
169. Zhao, J. et al. Prefrontal changes in the glutamate-glutamine cycle and neuronal/glial glutamate transporters in depression with and without suicide. *J. Psychiatr. Res.* **82**, 8–15 (2016).
170. Price, R. B., Nock, M. K., Charney, D. S. & Mathew, S. J. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol. Psychiatry* **66**, 522–526 (2009).
171. McGirr, A. et al. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol. Med.* **45**, 693–704 (2015).
172. Ionescu, D. F. et al. Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. *J. Clin. Psychiatry* **77**, e719–e725 (2016).
173. Ramaker, M. J. & Dulawa, S. C. Identifying fast-onset antidepressants using rodent models. *Mol. Psychiatry* **22**, 656–665 (2017).
174. Wilkinson, S. T. et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am. J. Psychiatry* **175**, 150–158 (2018).
175. Stenovec, M. et al. Ketamine inhibits ATP-evoked exocytotic release of brain-derived neurotrophic factor from vesicles in cultured rat astrocytes. *Mol. Neurobiol.* **53**, 6882–6896 (2016).
176. Grieco, S. F., Cheng, Y., Eldar-Finkelman, H., Jope, R. S. & Beurel, E. Up-regulation of insulin-like growth factor 2 by ketamine requires glycogen synthase kinase-3 inhibition. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **72**, 49–54 (2017).
177. Ren, Z. et al. Bidirectional homeostatic regulation of a depression-related brain state by gamma-aminobutyric acidergic deficits and ketamine treatment. *Biol. Psychiatry* **80**, 457–468 (2016).
178. Klempan, T. A. et al. Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. *Mol. Psychiatry* **14**, 175–189 (2009).
179. Bunge, S. A., Klingberg, T., Jacobsen, R. B. & Gabrieli, J. D. A resource model of the neural basis of executive working memory. *Proc. Natl Acad. Sci. USA* **97**, 3573–3578 (2000).
180. Zhang, J. X., Leung, H. C. & Johnson, M. K. Frontal activations associated with accessing and evaluating information in working memory: an fMRI study. *Neuroimage* **20**, 1531–1539 (2003).
181. Herman, J. P., Ostrander, M. M., Mueller, N. K. & Figueiredo, H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **29**, 1201–1213 (2005).
182. Raison, C. L., Capuron, L. & Miller, A. H. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* **27**, 24–31 (2006).
183. Brundin, L., Bryleva, E. Y. & Thirtamara Rajamani, K. Role of inflammation in suicide: from mechanisms to treatment. *Neuropsychopharmacology* **42**, 271–283 (2017).
184. Kayser, M. S. & Dalmau, J. The emerging link between autoimmune disorders and neuropsychiatric disease. *J. Neuropsychiatry Clin. Neurosci.* **23**, 90–97 (2011).
185. Courtet, P. et al. Neuroinflammation in suicide: toward a comprehensive model. *World J. Biol. Psychiatry* **17**, 564–586 (2016).
186. Serafini, G. et al. The role of inflammatory cytokines in suicidal behavior: a systematic review. *Eur. Neuropsychopharmacol.* **23**, 1672–1686 (2013).
187. Janelidze, S. et al. Low IL-8 is associated with anxiety in suicidal patients: genetic variation and decreased protein levels. *Acta Psychiatr. Scand.* **131**, 269–278 (2015).
188. Black, C. & Miller, B. J. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. *Biol. Psychiatry* **78**, 28–37 (2015).
189. Isung, J. et al. High interleukin-6 and impulsivity: determining the role of endophenotypes in attempted suicide. *Transl. Psychiatry* **4**, e470 (2014).
190. Bergmans, R. S., Kelly, K. M. & Mezuk, B. Inflammation as a unique marker of suicide ideation distinct from depression syndrome among U.S. adults. *J. Affect. Disord.* **245**, 1052–1060 (2019).
191. Ohlsson, L. et al. Leaky gut biomarkers in depression and suicidal behavior. *Acta Psychiatr. Scand.* **139**, 185–193 (2019).
192. Isung, J., Mobarrez, F., Nordstrom, P., Asberg, M. & Jokinen, J. Low plasma vascular endothelial growth factor (VEGF) associated with completed suicide. *World J. Biol. Psychiatry* **13**, 468–473 (2012).
193. Erhardt, S. et al. Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology* **38**, 743–752 (2013).
194. Pedersen, M. G., Mortensen, P. B., Norgaard-Pedersen, B. & Postolache, T. T. *Toxoplasma gondii* infection and self-directed violence in mothers. *Arch. Gen. Psychiatry* **69**, 1123–1130 (2012).
195. Arling, T. A. et al. *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. *J. Nerv. Ment. Dis.* **197**, 905–908 (2009).
196. Flegr, J. How and why *Toxoplasma* makes us crazy. *Trends Parasitol.* **29**, 156–163 (2013).
197. Okusaga, O. et al. Combined *Toxoplasma gondii* seropositivity and high blood kynurenine — linked with nonfatal suicidal self-directed violence in patients with schizophrenia. *J. Psychiatr. Res.* **72**, 74–81 (2016).
198. Cook, T. B. et al. "Latent" infection with *Toxoplasma gondii*: association with trait aggression and impulsivity in healthy adults. *J. Psychiatr. Res.* **60**, 87–94 (2015).
199. Peng, X. et al. Moderation of the relationship between *Toxoplasma gondii* seropositivity and trait impulsivity in younger men by the phenylalanine-tyrosine ratio. *Psychiatry Res.* **270**, 992–1000 (2018).

200. Hall, A. B., Tolonen, A. C. & Xavier, R. J. Human genetic variation and the gut microbiome in disease. *Nat. Rev. Genet.* **18**, 690–699 (2017).
201. Foster, J. A. & McVey Neufeld, K.-A. Gut–brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci.* **36**, 305–312 (2013).
202. Valles-Colomer, M. et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat. Microbiol.* **4**, 623–632 (2019).
203. Franklin, J. C. et al. Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. *Psychol. Bull.* **143**, 187–232 (2017).
204. Ribeiro, J. D. et al. Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. *Psychol. Med.* **46**, 225–236 (2016).
205. Glenn, C. R. & Nock, M. K. Improving the short-term prediction of suicidal behavior. *Am. J. Prev. Med.* **47**, S176–S180 (2014).
206. Runeson, B. et al. Instruments for the assessment of suicide risk: a systematic review evaluating the certainty of the evidence. *PLOS ONE* **12**, e0180292 (2017).
207. Quinlivan, L. et al. Predictive accuracy of risk scales following self-harm: multicentre, prospective cohort study. *Br. J. Psychiatry* **210**, 429–436 (2017).
208. Chan, M. K. et al. Predicting suicide following self-harm: systematic review of risk factors and risk scales. *Br. J. Psychiatry* **209**, 277–283 (2016).
209. Steeg, S. et al. Accuracy of risk scales for predicting repeat self-harm and suicide: a multicentre, population-level cohort study using routine clinical data. *BMC Psychiatry* **18**, 113 (2018).
210. Ahmedani, B. K. et al. Health care contacts in the year before suicide death. *J. Gen. Intern. Med.* **29**, 870–877 (2014).
211. Betz, M. E. et al. Reducing suicide risk: challenges and opportunities in the emergency department. *Ann. Emerg. Med.* **68**, 758–765 (2016).
212. Boudreaux, E. D. et al. Improving suicide risk screening and detection in the emergency department. *Am. J. Prev. Med.* **50**, 445–453 (2016).
213. Ballard, E. D. et al. Identification of at-risk youth by suicide screening in a pediatric emergency department. *Prev. Sci.* **18**, 174–182 (2017).
214. Boudreaux, E. D. et al. Predictive utility of an emergency department decision support tool in patients with active suicidal ideation. *Psychol. Serv.* **15**, 270–278 (2018).
215. Miller, I. W. et al. Suicide prevention in an emergency department population: the ED-SAFE study. *JAMA Psychiatry* **74**, 563–570 (2017).
In this multicentre study conducted in 8 EDs, 1,376 patients were assigned to either usual care, univeral screen or universal screening plus a brief intervention, with only the latter resulting in a 5% risk reduction in suicide attempts in the subsequent year (OR=0.72).
216. Simon, G. E. et al. Risk of suicide attempt and suicide death following completion of the Patient Health Questionnaire depression module in community practice. *J. Clin. Psychiatry* **77**, 221–227 (2016).
217. King, C. A., Horwitz, A., Czyz, E. & Lindsay, R. Suicide risk screening in healthcare settings: identifying males and females at risk. *J. Clin. Psychol. Med. Settings* **24**, 8–20 (2017).
218. Gibbons, R. D. et al. Development of a computerized adaptive test suicide scale — the CAT-SS. *J. Clin. Psychiatry* **78**, 1376–1382 (2017).
219. Gibbons, R. D. et al. Computerized adaptive tests for rapid and accurate assessment of psychopathology dimensions in youth. *J. Am. Acad. Child Adolesc. Psychiatry* https://doi.org/10.1016/j.jaac.2019.08.009 (2019).
220. McCoy, T. H. Jr., Castro, V. M., Roberson, A. M., Snapper, L. A. & Perlis, R. H. Improving prediction of suicide and accidental death after discharge from general hospitals with natural language processing. *JAMA Psychiatry* **73**, 1064–1071 (2016).
221. Anderson, H. D. et al. Monitoring suicidal patients in primary care using electronic health records. *J. Am. Board Fam. Med.* **28**, 65–71 (2015).
222. Simon, G. E. et al. Predicting suicide attempts and suicide deaths following outpatient visits using electronic health records. *Am. J. Psychiatry* **175**, 951–960 (2018).
In this study of ~3 million patients, machine learning was used to predict suicide attempts and suicide deaths within 90 days of the last outpatient appointment in patients with a mental health diagnosis, with accuracy ranging between 0.83–0.85.
223. Belsher, B. E. et al. Prediction models for suicide attempts and deaths: a systematic review and simulation. *JAMA Psychiatry* **76**, 642–651 (2019).
224. Silverman, M. M. & Felner, R. D. Suicide prevention programs: issues of design, implementation, feasibility, and developmental appropriateness. *Suicide Life Threat. Behav.* **25**, 92–104 (1995).
225. Silverman, M. M. & Maris, R. W. The prevention of suicidal behaviors: an overview. *Suicide Life Threat. Behav.* **25**, 10–21 (1995).
226. Mrazek, P. & Haggerty, R. *Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research* (National Academy Press, 1994).
227. Gordon, R. S. Jr. An operational classification of disease prevention. *Public Health Rep* **98**, 107–109 (1983).
228. Gunnell, D. et al. Prevention of suicide with regulations aimed at restricting access to highly hazardous pesticides: a systematic review of the international evidence. *Lancet Glob. Health* **5**, e1026–e1037 (2017).
229. Hawton, K. et al. Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: time-series study. *PLOS Med.* **9**, e1001213 (2012).
230. Yip, P. S. et al. Restricting the means of suicide by charcoal burning. *Br. J. Psychiatry* **196**, 241–242 (2010).
231. Studdert, D. M., Gurrin, L. C., Jatkar, U. & Pirkis, J. Relationship between vehicle emissions laws and incidence of suicide by motor vehicle exhaust gas in Australia, 2001-06: an ecological analysis. *PLOS Med.* **7**, e1000210 (2010).
232. Pirkis, J. et al. The effectiveness of structural interventions at suicide hotspots: a meta-analysis. *Int. J. Epidemiol.* **42**, 541–548 (2013).
233. Pirkis, J. et al. Interventions to reduce suicides at suicide hotspots: a systematic review and meta-analysis. *Lancet Psychiatry* **2**, 994–1001 (2015).
234. Pirkis, J., Blood, R. W., Beautrais, A., Burgess, P. & Skehans, J. Media guidelines on the reporting of suicide. *Crisis* **27**, 82–87 (2006).
235. Maloney, J. et al. How to adjust media recommentations on reporting suicidal behaviour to new media developments. *Arch. Suicide Res.* **18**, 156–169 (2014).
236. Robinson, J. et al. The #chatsafe project. Developing guidelines to help young people communicate safely about suicide on social media: a Delphi study. *PLOS ONE* **13**, e0206584 (2018).
237. Gunnell, D., Derges, J., Chang, S. S. & Biddle, L. Searching for suicide methods: accessibility of information about helium as a method of suicide on the internet. *Crisis* **36**, 325–331 (2015).
238. Pirkis, J. et al. Suicide prevention media campaigns: a systematic literature review. *Health Commun.* **34**, 402–414 (2019).
239. Nicholas, A., Rossetto, A., Jorm, A., Pirkis, J. & Reavley, N. Importance of messages for a suicide prevention media campaign. *Crisis* **39**, 438–450 (2018).
240. Wasserman, D. et al. School-based suicide prevention programmes: the SEYLE cluster-randomised, controlled trial. *Lancet* **385**, 1536–1544 (2015).
241. Roskar, S. et al. Effects of training program on recognition and management of depression and suicide risk evaluation for Slovenian primary-care physicians: follow-up study. *Croat. Med. J.* **51**, 237–242 (2010).
242. Saewyc, E. M., Konishi, C., Rose, H. A. & Homma, Y. School-based strategies to reduce suicidal ideation, suicide attempts, and discrimination among sexual minority and heterosexual adolescents in western Canada. *Int. J. Child Youth Family Stud.* **5**, 89–112 (2014).
243. Hawton, K. et al. Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis. *Lancet Psychiatry* **3**, 740–750 (2016).
244. Kawanishi, C. et al. Assertive case management versus enhanced usual care for people with mental health problems who had attempted suicide and were admitted to hospital emergency departments in Japan (ACTION-J): a multicentre, randomised controlled trial. *Lancet Psychiatry* **1**, 193–201 (2014).
245. Kapur, N. et al. Messages from Manchester: pilot randomised controlled trial following self-harm. *Br. J. Psychiatry* **203**, 73–74 (2013).
246. Ramchand, R. et al. Characteristics and proximal outcomes of calls made to suicide crisis hotlines in California. *Crisis* **38**, 26–35 (2017).
247. Middleton, A., Gunn, J., Bassilios, B. & Pirkis, J. Systematic review of research into frequent callers to crisis helplines. *J. Telemed. Telecare* **20**, 89–98 (2014).
248. Predmore, Z. et al. Expanding suicide crisis services to text and chat responders' perspectives of the differences between communication modalities. *Crisis* **38**, 255–260 (2017).
249. Baker, S. T., Nicholas, J., Shand, F., Green, R. & Christensen, H. A comparison of multi-component systems approaches to suicide prevention. *Australas Psychiatry* **26**, 128–131 (2018).
This paper introduces the systems-based approach to suicide prevention and provides some key examples of where this is being used around the world.
250. Hegerl, U., Rummel-Kluge, C., Varnik, A., Arensman, E. & Koburger, N. Alliances against depression – a community based approach to target depression and to prevent suicidal behaviour. *Neurosci. Biobehav. Rev.* **37**, 2404–2409 (2013).
251. Labouliere, C. D. et al. "Zero Suicide" – A model for reducing suicide in United States behavioral healthcare. *Suicidologi* **23**, 22–30 (2018).
252. Wyman, P. A. et al. An outcome evaluation of the Sources of Strength suicide prevention program delivered by adolescent peer leaders in high schools. *Am. J. Public Health* **100**, 1653–1661 (2010).
253. Knox, K. L., Litts, D. A., Talcott, G. W., Feig, J. C. & Caine, E. D. Risk of suicide and related adverse outcomes after exposure to a suicide prevention programme in the US Air Force: cohort study. *BMJ* **327**, 1376 (2003).
254. Zalsman, G. et al. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry* **3**, 646–659 (2016).
The most up-to-date, comprehensive systematic review of the evidence for specific suicide prevention approaches.
255. Hawton, K. & Pirkis, J. Suicide is a complex problem that requires a range of prevention initiatives and methods of evaluation. *Br. J. Psychiatry* **210**, 381–383 (2017).
This paper discusses the need for rigorous and innovative evaluation methods in suicide prevention.
256. Bustamante Madsen, L., Eddleston, M., Schultz Hansen, K. & Konradsen, F. Quality assessment of economic evaluations of suicide and self-harm interventions: a systematic review. *Crisis* **39**, 82–95 (2018).
257. Calati, R. & Courtet, P. Is psychotherapy effective for reducing suicide attempt and non-suicidal self-injury rates? Meta-analysis and meta-regression of literature data. *J. Psychiatr. Res.* **79**, 8–20 (2016).
258. Erlangsen, A. et al. Short-term and long-term effects of psychosocial therapy for people after deliberate self-harm: a register-based, nationwide multicentre study using propensity score matching. *Lancet Psychiatry* **2**, 49–58 (2015).
An important study that demonstrates that psychosocial therapy after self-harm is linked to lower risks of repeated self-harm and suicide.
259. Tarrier, N., Taylor, K. & Gooding, P. Cognitive-behavioral interventions to reduce suicide behavior a systematic review and meta-analysis. *Behav. Modif.* **32**, 77–108 (2008).
260. Rudd, M. D. 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* **172**, 441–449 (2015).
261. Witt, K. et al. Treatment as usual (TAU) as a control condition in trials of cognitive behavioural-based psychotherapy for self-harm: impact of content and quality on outcomes in a systematic review. *J. Affect. Disord.* **235**, 434–447 (2018).
262. Chang, N. A., Jager-Hyman, S., Brown, G. K., Cunningham, A. & Stanley, B. in *The International Handbook of Suicide Prevention* (eds O'Connor, R. & Pirkis, J.) 416–430 (Wiley, Blackwell, 2016).
263. Oud, M., Arntz, A., Hermens, M. L. M., Verhoef, R. & Kendall, T. Specialized psychotherapies for adults with borderline personality disorder: a systematic review and meta-analysis. *Aust. NZ J. Psych.* **52**, 949–961 (2018).
264. Linehan, M. M. et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs. therapy by experts for suicidal behaviors and borderline personality disorder. *Arch. Gen. Psychiatry* **63**, 757–766 (2006).
265. Jobes, D. A. *Managing Suicide Risk: A Collaborative Approach* 2nd edn (Guilford Press, 2016).

266. Hayes, S. C., Strosahl, K. & Wilson, K. G. *Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change* (Guilford Press, 1999).
267. Jobes, D. A. et al. A randomized controlled trial of the collaborative assessment and management of suicidality versus enhanced care as usual with suicidal soldiers. *Psychiatry* **80**, 339–356 (2017).
268. Andreasson, K. et al. Effectiveness of dialectical behavior therapy versus collaborative assessment and management of suicidality treatment for reduction of self-harm in adults with borderline personality traits and disorder: a randomized observer-blinded clinical trial. *Depress. Anxiety* **33**, 520–530 (2016).
269. Chesin, M. et al. Reviewing mindfulness-based interventions for suicidal behavior. *Arch. Suicide Res.* **20**, 507–527 (2016).
270. Tighe, J., Nicholas, J., Shand, F. & Christensen, H. Efficacy of acceptance and commitment therapy in reducing suicidal ideation and deliberate self-harm: systematic review. *JMIR Ment. Health* **5**, 11 (2018).
271. Ougrin, D., Tranah, T., Stahl, D., Moran, P. & Asarnow, J. R. Therapeutic interventions for suicide attempts and self-harm in adolescents: systematic review and meta-analysis. *J. Am. Acad. Child Adolesc. Psychiatry* **54**, 97–107 (2015).
272. Hawton, K. et al. Interventions for self-harm in children and adolescents. *Cochrane Database Syst. Rev.* **12**, CD012013 (2015).
273. Glenn, C. R., Esposito, E. C., Porter, A. C. & Robinson, D. J. Evidence base update of psychosocial treatments for self-injurious thoughts and behaviors in youth. *J. Clin. Child Adolesc. Psychol.* **48**, 357–392 (2019).
274. Iyengar, U. et al. A further look at therapeutic interventions for suicide attempts and self-harm in adolescents: an updated systematic review of randomized controlled trials. *Front. Psychiatry* **9**, 583 (2018).
275. Malda-Castillo, J., Browne, C. & Perez-Algorta, G. Mentalization-based treatment and its evidence-base status: a systematic literature review. *Psychol. Psychother*. https://doi.org/10.1111/papt.12195 (2018).
276. Okolie, C., Dennis, M., Thomas, E. S. & John, A. A systematic review of interventions to prevent suicidal behaviors and reduce suicidal ideation in older people. *Int. Psychogeriatr.* **29**, 1801–1824 (2017).
277. Gustavson, K. A. et al. Problem-solving therapy reduces suicidal ideation in depressed older adults with executive dysfunction. *Am. J. Geriatr. Psychiatr.* **24**, 11–17 (2016).
278. Heisel, M. J., Talbot, N. L., King, D. A., Tu, X. M. & Duberstein, P. R. Adapting interpersonal psychotherapy for older adults at risk for suicide. *Am. J. Geriatr. Psychiatr.* **23**, 87–98 (2015).
279. Riblet, N. B. V., Shiner, B., Young-Xu, Y. & Watts, B. V. Strategies to prevent death by suicide: meta-analysis of randomised controlled trials. *Br. J. Psychiatry* **210**, 396-402 (2017).
280. Henderson, C., Evans-Lacko, S. & Thornicroft, G. Mental illness stigma, help seeking, and public health programs. *Am. J. Public Health* **103**, 777–780 (2013).
281. Motto, J. A. Suicide prevention for high-risk persons who refuse treatment. *Suicide Life Threat. Behav* **6**, 223–230 (1976).
282. Comtois, K. A. et al. Effect of augmenting standard care for military personnel with brief caring text messages for suicide prevention: a randomized clinical trial. *JAMA Psychiatry* **76**, 474–483 (2019).
283. Stanford, E. J., Goetz, R. R. & Bloom, J. D. The no harm contract in the emergency assessment of suicidal risk. *J. Clin. Psychiat.* **55**, 344–348 (1994).
284. Stanley, B. & Brown, G. K. Safety planning intervention: a brief intervention to mitigate suicide risk. *Cognit. Behav. Pract.* **19**, 256–264 (2012).
285. Stanley, B. et al. Comparison of the safety planning intervention with follow-up vs usual care of suicidal patients treated in the emergency department. *JAMA Psychiatry* **75**, 894–900 (2018).
A landmark study that highlights the use of safety planning with telephone support.
286. Bryan, C. J. et al. Effect of crisis response planning vs. contracts for safety on suicide risk in U.S. Army soldiers: a randomized clinical trial. *J. Affect. Disord.* **212**, 64–72 (2017).
287. Gysin-Maillart, A., Schwab, S., Soravia, L., Megert, M. & Michel, K. A novel brief therapy for patients who attempt suicide: a 24-months follow-up randomized controlled study of the attempted suicide short intervention program (ASSIP). *PLOS Med.* **13**, e1001968 (2016).
288. O'Connor, R. C. et al. A brief psychological intervention to reduce repetition of self-harm in patients admitted to hospital following a suicide attempt: a randomised controlled trial. *Lancet Psychiatry* **4**, 451–460 (2017).
289. King, C. A., Gipson, P. Y., Horwitz, A. G. & Opperman, K. J. Teen options for change: an intervention for young emergency patients who screen positive for suicide risk. *Psychiatr. Serv.* **66**, 97–100 (2015).
290. Kennard, B. D. et al. As Safe as Possible (ASAP): a brief app-supported inpatient intervention to prevent postdischarge suicidal behavior in hospitalized, suicidal adolescents. *Am. J. Psychiatry* **175**, 864–872 (2018).
291. Coppen, A. et al. Does lithium reduce the mortality of recurrent mood disorders? *J. Affect. Disord* **23**, 1–7 (1991).
292. Felber, W., Bauer, M., Lewitzka, U. & Muller-Oerlinghausen, B. Lithium clinics in Berlin and Dresden: a 50-year experience. *Pharmacopsychiatry* **51**, 166–171 (2018).
293. Ahearn, E. P. et al. Suicide attempts in veterans with bipolar disorder during treatment with lithium, divalproex, and atypical antipsychotics. *J. Affect. Disord* **145**, 77–82 (2013).
294. Hayes, J. F. et al. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. *JAMA Psychiatry* **73**, 630–637 (2016).
295. Song, J. et al. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. *Am. J. Psychiatry* **174**, 795–802 (2017).
296. Lauterbach, E. et al. Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. *Acta Psychiatr. Scand.* **118**, 469–479 (2008).
297. Oquendo, M. A. et al. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. *Am. J. Psychiatry* **168**, 1050–1056 (2011).
298. Girlanda, F. et al. Effectiveness of lithium in subjects with treatment-resistant depression and suicide risk: results and lessons of an underpowered randomised clinical trial. *BMC Res. Notes* **7**, 731 (2014).
299. Khan, A. et al. Differential pattern of response in mood symptoms and suicide risk measures in severely ill depressed patients assigned to citalopram with placebo or citalopram combined with lithium: role of lithium levels. *J. Psychiatr. Res.* **45**, 1489–1496 (2011).
300. Cipriani, A., Hawton, K., Stockton, S. & Geddes, J. R. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* **346**, f3646 (2013).
301. Gibbons, R. D., Hur, K., Brown, C. H. & Mann, J. J. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Arch. Gen. Psychiatry* **66**, 1354–1360 (2009).
302. Chen, T. Y. et al. Divalproex and its effect on suicide risk in bipolar disorder: a systematic review and meta-analysis of multinational observational studies. *J. Affect. Disord* **245**, 812–818 (2019).
303. Meltzer, H. Y. et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch. Gen. Psychiatry* **60**, 82–91 (2003).
304. Vermeulen, J. M. et al. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1-12.5 years. *Schizophr. Bull.* **45**, 315–329 (2018).
305. Warnez, S. & Alessi-Severini, S. Clozapine: a review of clinical practice guidelines and prescribing trends. *BMC Psychiatry* **14**, 102 (2014).
306. Reinstatler, L. & Youssef, N. A. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. *Drugs R D* **15**, 37–43 (2015).
307. Duman, R. S. Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide. *F1000Res* **7**, https://doi.org/10.12688/f1000research.14344.1 (2018).
308. Murrough, J. W. et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol. Med.* **45**, 3571–3580 (2015).
309. Grunebaum, M. F. et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *Am. J. Psychiatry* **175**, 327–335 (2018).
310. Grunebaum, M. F. et al. Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. *Bipolar Disord.* **19**, 176–183 (2017).
311. Price, R. B. et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress. Anxiety* **31**, 335–343 (2014).
312. Vande Voort, J. L. et al. Antisuicidal response following ketamine infusion is associated with decreased nighttime wakefulness in major depressive disorder and bipolar disorder. *J. Clin. Psychiatry* **78**, 1068–1074 (2017).
313. Kearns, J. C. et al. Sleep problems and suicide risk in youth: a systematic review, developmental framework, and implications for hospital treatment. *Gen. Hosp. Psychiatry* https://doi.org/10.1016/j.genhosppsych.2018.09.011 (2018).
314. Canuso, C. M. et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am. J. Psychiatry* **175**, 620–630 (2018).
315. Gonella, G., Baignoli, G. & Ecari, U. Fluvoxamine and imipramine in the treatment of depressive patients: a double-blind controlled study. *Curr. Med. Res. Opin.* **12**, 177–184 (1990).
316. Kasper, S., Moller, H. J., Montgomery, S. A. & Zondag, E. Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. *Int. Clin. Psychopharmacol.* **9** (Suppl. 4), 3–12 (1995).
317. Montgomery, S., Cronholm, B., Asberg, M. & Montgomery, D. B. Differential effects on suicidal ideation of mianserin, maprotiline and amitriptyline. *Br. J. Clin. Pharmacol.* **5** (Suppl. 1), 77S–80S (1978).
318. Mahapatra, S. N. & Hackett, D. A randomised, double-blind, parallel-group comparison of venlafaxine and dothiepin in geriatric patients with major depression. *Int. J. Clin. Pract.* **51**, 209–213 (1997).
319. Sacchetti, E., Vita, A., Guarneri, L. & Cornacchia, M. in *Serotonin-related Psychiatric Syndromes: Clinical and Therapeutic Links* (eds G. B. Cassano et al.) 47–53 (R. Soc. Med. Services, 1991).
320. Marchesi, C., Ceccherininelli, A., Rossi, A. & Maggini, C. Is anxious-agitated major depression responsive to fluoxetine? A double-blind comparison with amitriptyline. *Pharmacopsychiatry* **31**, 216–221 (1998).
321. Judd, F. K. et al. A multicentre double blind trial of fluoxetine versus amitriptyline in the treatment of depressive illness. *Aust. NZ J. Psychiatry* **27**, 49–55 (1993).
322. Lapierre, Y. D. Controlling acute episodes of depression. *Int. Clin. Psychopharmacol.* **6** (Suppl. 2), 23–35 (1991).
323. Moller, H. J. & Steinmeyer, E. M. Are serotonergic reuptake inhibitors more potent in reducing suicidality? An empirical study on paroxetine. *Eur. Neuropsychopharmacol.* **4**, 55–59 (1994).
324. Tollefson, G. D. et al. Is baseline agitation a relative contraindication for a selective serotonin reuptake inhibitor: a comparative trial of fluoxetine versus imipramine. *J. Clin. Psychopharmacol.* **14**, 385–391 (1994).
325. Grunebaum, M. F. et al. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. *Neuropsychopharmacology* **37**, 697–706 (2012).
326. Stone, M. et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* **339**, b2880 (2009).
327. Yovell, Y. et al. Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. *Am. J. Psychiatry* **173**, 491–498 (2016).
328. Ahmadi, J., Jahromi, M. S. & Ehsaei, Z. The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: a randomized, double-blind, clinical trial. *Trials* **19**, 462 (2018).
329. Lutz, P. E., Courtet, P. & Calati, R. The opioid system and the social brain: implications for depression and suicide. *J. Neurosci. Res*. https://doi.org/10.1002/jnr.24269 (2018).
330. Fairweather-Schmidt, A. K., Batterham, P. J., Butterworth, P. & Nada-Raja, S. The impact of

suicidality on health-related quality of life: a latent growth curve analysis of community-based data. *J. Affect. Disord.* **203**, 14–21 (2016).
331. Grendas, L. et al. Determinants of mental and physical health-related quality of life among patients hospitalized for suicidal behavior. *Psychiatry Res.* **257**, 56–60 (2017).
332. Goldman-Mellor, S. J. et al. Suicide attempt in young people: a signal for long-term health care and social needs. *JAMA Psychiatry* **71**, 119–127 (2014).
333. Stoddard, F. J. & Saxe, G. Ten-year research review of physical injuries. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 1128–1145 (2001).
334. Mitchell, A. M., Sakraida, T. J., Kim, Y., Bullian, L. & Chiappetta, L. Depression, anxiety and quality of life in suicide survivors: a comparison of close and distant relationships. *Arch. Psychiatr. Nurs.* **23**, 2–10 (2009).
335. Carpiniello, B. & Pinna, F. The reciprocal relationship between suicidality and stigma. *Front. Psychiatry* **8**, 35 (2017).
336. Shepard, D. S., Gurewich, D., Lwin, A. K., Reed, G. A. Jr & Silverman, M. M. Suicide and suicidal attempts in the United States: costs and policy implications. *Suicide Life Threat. Behav.* **46**, 352–362 (2016).
337. Borges, G. et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health surveys. *J. Clin. Psychiatry* **71**, 1617–1628 (2010).

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