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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]

1McGill 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
4Department of Population Health Sciences, University of Bristol, Bristol, UK
5Suicidal Behaviour Research Laboratory, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK
6 Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, 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

e-mail: gustavo.turecki@mcgill.ca

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 (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 using computer testing and genetic screening, is an area of ongoing research. Prevention is key to reduce the number of suicide deaths, and current 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) and coordinated social and public health initiatives, should continue to improve the management of suicidal patients and decrease suicide-associated morbidity.

[H1] Introduction

Although suicide is not a disease, suicidal behaviour, which includes suicide and suicide attempts, is an important public health problem and 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 across the globe[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 various factors involved in suicide risk have enabled us to paint a more comprehensive picture of suicidal behaviour. Although the literature base 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 others) of suicidal ideation. A suicide attempt is defined as self-injurious behaviour with inferred or actual intent to die. Although detailed nomenclatures have been proposed for the terminology related to suicide[4,5], they have not been widely adopted and diverse terms are still frequently used to describe similar phenomena. As a consequence, this Primer uses 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 that are involved in this transition have been identified, such as capability for suicide, exposure to suicide, mental imagery and access to the means of suicide[7-10]. 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 with suicide attempts under the term self-harm because the risk factors for the two types of behaviour overlap and they 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 sub-populations or environments 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.

[H1] 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. In all countries, the incidence of suicide attempts is highest in individuals 15–24 years of age. By comparison, the lowest rates of suicide is observed amongst young people <15 years of age, with the highest generally observed in people >75 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] (Figure 1). 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).

[H2] Geographic variations in incidence

The incidence of suicide varies more than ten-fold between countries (Figure 2); 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 global suicides and suicide attempts 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, such as variations in the accuracy of suicide statistics. Indeed, several factors can affect the reporting of suicide, such as inconsistent recording of suicides by coroners and cultural or religious acceptability 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 that 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), and 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.

As well as global differences in suicide rates, several studies have reported marked (that is, 2–5 fold) variations in suicide rates within countries. For instance, one analysis of suicide in Taipei (Taiwan) documented 5-fold variations in the incidence of suicide between areas[18]. In this study, the factor most strongly associated with area differences was average levels of household income[18].

[H2] 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], which has largely been 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[19] (Figure 3). 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 in different age groups. In addition to geographic differences, time trends in suicide rates vary in different age groups. For example, in recent years suicide rates have fallen in elderly men but risen in middle-aged men and women in the UK[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 the elderly[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]).

[H1] 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 (Figure 4)[6,29,30], 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 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.

[H2] Distal or predisposing factors

[H3] 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, 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 5-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, such as 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's 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 several biological processes including, among others, nervous system development and function, immunological disease, infectious disease and the inflammatory response[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].

[H3] 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 that is 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[54,55,29]. 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).

[H2] 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.

[H3] 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 those 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], when anxiety is considered as an independent variable for statistical analyses, some studies have reported only a weak or non-significant link with suicidal behaviour[66,67]. Anxiety is likely to contribute to suicidal behaviour by interacting with other characteristics of individuals who already have 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 to 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 to have low self-esteem.

[H3] 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 post-natal 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].

[H3] 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 associate with

risk factors for suicide[80,81], and individuals with poor problem-solving skills are more likely to exp4erience 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 youth 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.

[H2] Proximal or precipitating factors

Beyond the factors that confer risk to 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 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, from those who may have one or multiple suicide attempts or who ultimately die by suicide.

[H3] 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]; 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], and one birth cohort study has 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 suicidal ideation[7].

Substance use or misuse is found in a large proportion of people who died by suicide[89], with alcohol misuse 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 are 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 as animal studies have indicated that chronic substance use may drive increased impulsivity[105], and human studies have suggested that the pattern of consumption may equally be 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 co-occurring difficulties of disability, sleep problems, reduced well-being and depression[113].

[H3] 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 attempt initially 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 selecting psychotherapeutic approaches that will be most suited to the individual's needs.

[H3] Socioeconomic, environmental and other contextual factors associated with suicide risk. Important social and economic factors that are associated with suicide include relationship breakdown, low socioeconomic position, job loss, low income and debt. In addition, other social factors that are associated with suicide include poor social stability, stringent sociocultural norms, economic turmoil, socioeconomic position (having poor family connectedness, being single, having a low income and/or being in debt), being in a LGBT+ group or being bullied[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 individuals live in areas that have a low proportion of people from the same minority ethnic groups, compared with individuals living in areas that have a higher proportion of people from minority ethnic groups [122]. In addition, some of these factors may act more immediately to precipitate suicidal behaviour, such as job loss and relationship breakdown[107]. 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, and these may account for up 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).

[H2] Neurobiology of suicidal behaviour

Suicidal behaviour is associated with widespread neurobiological changes throughout the brain that affect a number of different functional pathways. 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 (Figure 5).

[H3] 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. Indeed, serotonergic neurons[126], specifically, and altered serotonin function have been implicated in depression and suicide[127-129]. For example, studies using postmortem brain tissues of individuals who died by suicide have demonstrated decreased levels of 5-hydroxyindoleacetic acid (5-HIAA)[127], which is a serotonin metabolite, and a compensatory increase in the raphe nuclei of serotonergic neurons[130,131] and expression of tryptophan hydroxylase (TPH), 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 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 (SERT) and

serotonin receptor 1A ($5HT_{1A}$) in the midbrain in people with suicidal behaviour, compared to 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.

[H3] 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 to 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, and 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. Other candidate targets of epigenetic regulation that might explain the link between ELA and altered cortisol control, include *SKA2,* which encodes the spindle and kinetochore associated protein 2[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 anti-depressant-like effects[151,152] suggests that alterations to the polyamine pathway may be an important contributor to suicidal behaviour.

[H3] 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 suicide 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[159,160].

[H3] Glutamatergic and GABA-ergic dysfunction. Evidence from neuroanatomical studies of individuals with depression and suicidal behaviour have demonstrated changes in density of glutamatergic neurons and glial cells[161,162], and 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, some of the specific proteins 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 who died by suicide, as opposed to MDD[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 anti-suicidal 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 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 the stress responses[181], as well as in the integration of cognitive activity with affective experience.

[H3] 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 tumor 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 pro-inflammatory 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 authors 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[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, which may increase the risk of self-directed violence, and risk 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].

[H3] 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.

[H1] 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 (Figure 6).

[H2] 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 than 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 individual at high risk of suicide by assessing multiple risk factors simultaneously, such as have included the use of 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 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 (AUC) of 0.72) in one prospective study, but none of the 6 rating scales examined performed better than a global clinical rating of risk (AUC 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 or in primary care.[210] Screening for suicide risk in emergency departments (EDs) is justified because as many as 1 in 5 individuals who die by suicide have visited the ED within 4 weeks of their death[210] and, conversely, 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, but increasingly being implemented in EDs in the United States

(https://www.jointcommission.org/assets/1/6/NPSG_Chapter_HAP_Jan2019.pdf). The 4-item ASQ[213] for children and adolescents shows high sensitivity (93%) but lower specificity (43%) for predicting future suicide-related visits to the ED in the subsequent 6 months. The EDSAFE/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 died 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 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 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].

[H3] Computerized adaptive tests. One challenge to screening for suicidal risk is that it is multi-dimensional and not easily or accurately captured in a scale that focuses on a single disorder such as depression. Moreover, as described above, current 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 have been developed for suicidal risk that personalize the presentation of items or questions 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, and has demonstrated strong discriminative validity, with both high sensitivity and sensitivity 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 behavior has been developed for children and adolescents that shows 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].

[H3] 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 that accounted 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 list

of predictor variables was 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 if 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].

[H2] 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 disorders[226] and physical disorders[227]. The framework takes a risk factor-based approach to suicide prevention, classifying suicide prevention activities as universal, selective or indicated on the basis of their target groups (Figure 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.

[H3] 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 who have 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], with, for example, 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, as the potential of the media as a force for good in suicide prevention has been recognized. These campaigns are delivered to the population as a whole, usually across multiple media platforms, and 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].

[H3] 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 are tailored towards particular subgroups, such as LGBT+ young people. For example, some schools have Gay-Straight Alliances (GSAs) that provide a safe and supportive environment to LGBT+ students, and there is emerging evidence that these may have positive effects in reducing suicidal ideation and suicide[242].

[H3] 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 healthcare setting following an episode of self-harm[243] . Such interventions include psychological therapies (see, Psychological interventions for suicidal behaviour, below) and social approaches that are 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].

[H3] Multi-component interventions. Universal, selective and indicated interventions are often delivered in combination through what is often termed a 'systems-based' approach[249]. This approach is sometimes delivered in local regions or communities, such as with the Alliance Against Depression model. This model was initially implemented in Nuremberg (Germany), and included a suicide prevention media campaign (universal intervention), education for general practitioners and gatekeeper training for frontline workers and other professionals (selective interventions) and an 'emergency card' which gives people who have made a suicide attempt 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, multi-component 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]).

[H3] Evaluation of suicide prevention interventions. One systematic review has synthesised 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 the least of which 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].

[H1] 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).

[H2] 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, schizophrenia-spectrum disorders), and in patients with or without 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 cognitive behaviour therapy (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 hours 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, NTT 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 favorable 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 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 (CAMS)[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 6 core processes including acceptance and commitment to action[266]. Although CAMS 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].

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].

No evidence from RCTs supports 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[281], and that it is not clear whether psychosocial interventions are as effective for men than for women[243].

[H2] 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.

[H3] Caring Contacts. This approach, which was first tested more than four decades ago[282], refers to the routine sending of brief non-demanding messages (via, for example, postal mail, postcards, email, 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. A recent 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, emergency department visits, and suicide attempts)[283].

[H3] 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[284] and they have fallen out of favour.

[H3] Safety Planning Intervention or Crisis Response Planning. The Safety Planning Intervention (SPI[285]) is a brief intervention that involves patients engaging in a suicide narrative that is 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 6 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; limit access to lethal means.

SPI, in combination with follow-up calls (known as SPI+), is effective in reducing incidence of suicidal behaviour and increasing treatment engagement in the 6 months after discharge from the ED[286]. Crisis response planning is an abbreviated form of safety planning that uses 4 of 6 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[287]. 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].

[H3] Additional brief interventions. Several other types of brief interventions have been described. The Attempted Suicide Short Intervention Program (ASSIP)[288] 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-centered 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 utilizes review of the recorded suicide narrative with the patient. ASSIP is administered in three weekly face-to-face therapy sessions that are 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[288]. In addition, ASSIP led to fewer suicide attempts but had no effect on suicidal ideation[288].

Another type of brief intervention — the Volitional Helpsheet — 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 hospitalised for self-harm, compared to a control group receiving treatment as usual[289].

Similarly, in teens, two brief interventions — Teens Options for Change (TOC)[290] and As Safe As Possible (ASAP)[291] — 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.

[H2] Pharmacological interventions for suicidal behaviour

[H3] Lithium. Among potentially anti-suicidal pharmacological agents (Box 2), lithium has been used the longest. The anti-suicidal effects of lithium have 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[292,293] and some studies have reported conflicting data[294]. More recently, several methodologically rigorous pharmacoepidemiological studies have been conducted, with >10,000 patients in each study[295,296] and 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 to other mood stabilizers have been unable to demonstrate this effect[297,298], although some had very modest sample sizes[299]. Of interest, two of these studies identified anti-suicidal effects based on secondary, post-hoc analyses[297,300]. Although some meta-analyses that compared lithium to antiepileptic drugs and placebo found little effect[279,301], 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[301]. Importantly, the risk of suicidal behaviour was much greater before starting treatment with antiepileptic drugs compared with after treatment initiation in one study[302], whereas another study demonstrated no difference[303]; 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 anti-suicidal 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 effect a clinician's medication choice. Lithium toxicity and overdose risk may influence the likelihood of its prescription, particularly among individuals who are 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.

[H3] 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[304]. Evidence supporting the use of clozapine for suicide came from the InterSePT study, a multicentre RCT that demonstrated the superiority of clozapine in decreasing the risk of suicide attempts and the other primary outcome variables in people with schizophrenia or schizoaffective disorder, compared with olanzapine[304]. 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 (5 with clozapine and 3 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[305], 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[306].

[H3] Ketamine. The past decade has seen intense interest in the utility of ketamine as a potential anti-suicidal medication[307] and its relatively novel mechanism of action has spurred a search for other drugs with similar mechanisms that might also be of use[308]. Several studies have examined the effect of ketamine on suicidal ideation, mostly in people with mood disorders[309-311] and have demonstrated that ketamine decreases suicidal ideation independent of improvement in other mood symptoms,[174,309-311] although one small study did not find this to be the case[312]. Of interest, the effects of ketamine on suicidal ideation may be linked to improvements in insomnia[313], a clinical variable that has been linked to suicidal behaviour[314]. 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[315]. Clearly, intranasal administration route would facilitate the use of ketamine, were its therapeutic effects verified. Some of the questions remaining include the duration of its effects and whether repeated administration would be a practical and efficient approach.

[H3] SSRIs. 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[61,129]. Earlier studies were mostly secondary analyses of depression trials. In fact, of 10 such studies that compared the effects of serotonergic antidepressants to noradrenergic antidepressants on suicidal ideation, five

studies favored serotonergic drugs[316-320], one study favored a noradrenergic drug[321], and four studies found no difference[322-325]. 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 a past suicide attempts or active suicidal ideation[326]. 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. Indeed, 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[327].

[H3] 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[328]. 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[329]. Larger studies are needed to replicate the finding that opioids may improve suicidal ideation, and this is an observation that comports with the hypothesis that psychic pain is an important determinant of suicide risk[330].

[H1] 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 components and mental components in the context of either past suicidal ideation or past suicide attempt. For mental health outcomes, suicidal ideation and suicide attempt associate with trajectories of decreasing mental health over time.[331] 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[332]. Similarly, suicidal behaviour is associated with reduced physical health over time[331,333], and depending on the method and severity of the suicide attempt, individuals might have with physical disabilities that directly affect their quality of life[334]. 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[335].

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 that are directed at breaking the stigma surrounding mental health issues, the perceived stigma associated with suicide is still an obstacle to help-seeking[1,336] 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[336].

As noted above, the prevalence of suicidal ideation and suicide attempt are many times that of suicide, 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 $58.4 billion in the USA in 2013, when considering only reported suicides and suicide attempts, and up to $93.5 billion when numbers are adjusted for under-reporting[337]. Of note, the costs were mainly due to lost productivity[337]. 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[332]. 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 $300 in the USA[337], investments in suicide prevention efforts are paramount.

[H1] 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, such as developing and validating clear assessment algorithms to assist clinicians in determining which of their patients are at greatest risk of suicide attempt 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 go into better understanding sex differences as they apply to pathology and interventions for suicidal behaviour. Given the important contribution to global suicide rates of easy access to pesticides and firearms, and the clear evidence that selective measures to reduce access to these means may have 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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Figure 1. Global variations in suicide rates. World Map showing suicide rates in all countries for which data is available. Data from World Health Statistics, World Health Organization 2016 (Ref[19]).

Figure 2. Suicide rates in selected countries from 2000–2015.

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, World Health Organization 2016 (Ref [19]).

Figure 3. Suicide rates by sex from 2000-2015.

Global suicide rates stratified by sex. In general, suicide rates in males are substantially higher than in females. Data from World Health Statistics, World Health Organization 2016 (Ref[19]).

Figure 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. The sociological, demographic and economic factors, as well as 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 vulnerability to suicide through behavioural disinhibition and dysregulated mood, hopelessness and entrapment, which are in turn associated with suicidal ideation, suicide attempt and suicide. Based data from Global suicidal ideation and suicide attempt statistics, Borges et al.[338]; global suicide statistic, World Health Statistics[19].

Figure 5. Neurobiological changes in suicidal behaviour. Suicidal behaviour is associated with widespread neurobiological alterations. Of these, the 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. In addition, more-recent evidence has suggested coordination between signalling in the brain and in the gut, potentially through immune activation.

Figure 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 heightened 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. MDD: Major depressive disorder; BD: Bipolar disorder; ED, emergency department.

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.

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.

Suicide attempt: self-injurious non-fatal behaviour with inferred or actual intent 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.

Box 2. Interventions for suicidal ideation and suicidal behaviour.

[H1] 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 helpsheet

[H1] Pharmacological

Pharmacological agents with potential effect on suicidal behaviour

- Lithium
- Clozapine[a]
- Ketamine
- Selective Serotonin Reuptake Inhibitors
- Buprenorphin

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

Suicide and suicidal behaviour continue to present key challenges for public policy and health services. This Primer discusses the global burden of suicide and suicidal behaviours, and provides 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.