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How to save a life: From neurobiological underpinnings to psychopharmacotherapies in the prevention of suicide

Xenia Gonda [a,b,*], Peter Dome [a,c], Gianluca Serafini [d,e], Maurizio Pompili [f]

[a] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary
[b] NAP3.0-SE Neuropsychopharmacology Research Group, Hungarian Brain Research Program, Semmelweis University, Budapest, Hungary
[c] National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary
[d] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa, Genoa, Italy
[e] IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[f] Department of Neurosciences, Mental Health and Sensory Organs, Suicide Prevention Centre, Sant'Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy

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ABSTRACT

The impact of suicide on our societies, mental healthcare, and public health is beyond questionable. Every year approximately 700 000 lives are lost due to suicide around the world (WHO, 2021); more people die by suicide than by homicide and war. Although suicide is a key issue and reducing suicide mortality is a global imperative, suicide is a highly complex biopsychosocial phenomenon, and in spite of several suicidal models developed in recent years and a high number of suicide risk factors identified, we still have neither a sufficient understanding of underpinnings of suicide nor adequate management strategies to reduce its prevalence. The present paper first overviews the background of suicidal behavior including its epidemiology, age and gender correlations, and its association with neuropsychiatric disorders as well as its clinical assessment. Then we give an overview of the etiological background, including its biopsychosocial contexts, genetics and neurobiology. Based on the above, we then provide a critical overview of the currently available intervention options to manage and reduce risk of suicide, including psychotherapeutic modalities, traditional medication classes also providing an up-to-date overview on the antisuicidal effects of lithium, as well as novel molecules such as esketamine and emerging medications and further molecules in development. Finally we give a critical overview on our current knowledge on using neuromodulatory and biological therapies, such as ECT, rTMS, tDCS, and other options.

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Contents

Abbreviations: AEA, Anandamide; ASSIP, Attempted Suicide Short Intervention Program; BCBT, Brief Cognitive Behavior Therapy for Suicide Prevention; BDNF, Brain-derived neurotrophic factor; CAMS, Collaborative Assessment and Management of Suicidality; CBT, Cognitive-behavior therapy; CBT-SP, Cognitive-behavior Therapy for Suicide Prevention; CGI-SS-R, Clinical Global Impression of Severity of Suicidality-Revised; CSF, Cerebrospinal fluid; DBT, Dialectical Behavior Therapy; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECT, Electroconvulsive Therapy; EWAS, Epigenome-wide Association Studies; GABA, Gamma-aminobutyric acid; GR, Glucocorticoid receptor; GWAS, Genome-wide Association Study; HPA, hypothalamic-pituitary-adrenal axis; ISGC, International Suicide Genetics Consortium; MA, metaanalysis; MADRS, Montgomery-Asberg Depression Rating Scale; MBT, Mentalisation-based Treatment; MDD, Major Depressive Disorder; mGluR2/3, Metabotropic Glutamate Receptor 2/3; MVP, Million Veterans Program; NMDA, N-methyl-D-aspartate; NMS, Neuroleptic malignant syndrome; PEA, N-palmitoylethanolamide; PFC, Prefrontal cortex; PRS, Polygenic Risk Score; PST, Problem solving therapy; RCT, Randomised controlled trial; rTMS, Repetitive transcranial magnetic stimulation; SIBAT, Suicide Ideation and Behavior Assessment Tool; SAT1, Spermidine/spermine N1-acetyl transferase; SOC, Standard of care; TAU, Treatment as usual; tDCS, Transcranial Direct Current Stimulation; TFP, Transference Focused Therapy; TMBI, Teachable Moment Brief Intervention; VNS, Vagus Nerve Stimulation; WHO, World Health Organization.

* Corresponding author at: Gyulai Pál utca 2., Budapest 1085, Hungary.
E-mail address: gonda.xenia@semmelweis.hu (X. Gonda).

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1. Introduction

The impact of suicide on our societies, mental healthcare, and public health is beyond questionable. Every year approximately 700 000 lives are lost due to suicide around the world (WHO, 2021); more people die by suicide than by homicide and war (UN, 2009). Suicide is the second most common cause of death in young adults aged 18-25 years, and is most frequent in older adults (Briggs et al., 2019). Being a highly complex phenomenon, in spite of several suicidal models developed in recent years and a high number of suicide risk factor identified, we still have neither a sufficient understanding of underpinnings of suicide, nor adequate management strategies to reduce its prevalence. Suicide prevention is a key issue, as families and loved ones of those inflicted by suicide are left with not only grief and suffering, but also higher risk of mental illness and higher risk of subsequent suicide (Khangura, Kanga, Seal, & Spry, 2018). Therefore, reducing suicide mortality is a global imperative (WHO, 2014).

The importance and relevance of suicide, as well as it being an independent mental health condition rather than just being a complication of psychiatric disorders, has also been acknowledged by the inclusion of suicidal behavior as a separate category in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) (APA, 2013), which highlights the burden and clinical relevance of suicidal behavior as well as the need for better understanding and more effective therapeutic and preventive approaches. This attitude may improve the integration of screening for suicide into clinical routine tests, and may guide the development of more effective pharmacotherapeutic and psychotherapeutic interventions (Sobanski, Josfeld, Peikert, & Wagner, 2021). The present review details the currently available clinical methods for preventing suicidal behavior (but does not discuss some other kinds of preventive measures, such as restricting access to lethal means, with strong evidence for efficacy) (Mann, Michel, & Auerbach, 2021).

2. Prevalence, epidemiology, and risk factors of suicidal behavior

2.1. Prevalence and epidemiology of suicidal behavior

Essentially two phenomena, suicidal behavior and suicidal ideation belong to the suicide spectrum. Suicidal behavior is an umbrella term consisting of several forms of self-harm, mostly involving suicide attempts (a potentially self-injurious behavior associated with at least some intent to die) and completed suicide (a fatal self-injurious act with some evidence of intent to die). Suicidal ideation has two forms, active (thinking about taking action to end one's life, including a clear plan) and passive (thoughts about wishing to die) (Turecki & Brent, 2016; Turecki et al., 2019).

According to the WHO, suicide had a global death toll of 703,000 in 2019 and the global age-standardized suicide rate was 9.0/100 000/year. These figures place suicide (self-harm) 17th on the list of leading death causes. In 2019, suicide accounted for about 1.3% of deaths. In the period from 2000 to 2019, global suicide rate decreased by 36% (WHO, 2021). Marked falls in suicide cases in China, and to a lesser extent India, chiefly accounted for the decrease in global suicides in the 21st century (Turecki et al., 2019). The detailed discussion of the possible reasons for decreasing suicide numbers in these two countries is beyond the scope of this paper, however, it is likely that in the case of China improvements in socio-economic factors and regulatory changes for the safe use of highly toxic pesticides might have contributed to the decrease (Page et al., 2017). Before the recent decrease, the global rate was estimated to have increased by 49% and 33% from 1950 to 1995 in males and females, respectively (Bertolote & Fleischmann, 2002). Suicide rates vary tremendously between regions and countries. Rates are higher for the African Region (11.2/100,000/year), European Region (10.5/100,000/year) and South-East Asia Region (10.2/100,000/year) than the global average. The lowest rate is found in the Eastern Mediterranean Region (6.4/100,000/year) (WHO, 2021).

Suicide attempts are about 10-40 times more prevalent than completed suicides, while the prevalence of lifetime suicidal ideation is 1.6-22.3 times higher than that of lifetime suicide attempts (Bertolote et al., 2005; WHO, 2014). Attempting suicide is a moderate/strong predictor of future suicide death (the risk of suicide death is 30-40 times higher in those who have previously attempted suicide compared with the general population) (Fazel & Runeson, 2020; Tidemalm, Långström, Lichtenstein, & Runeson, 2008). About 50-80% of suicide victims die on their first attempt, which means that suicide countermeasure strategies applied after the first attempt are too late for the roughly two-thirds who die on the first suicide attempt (Bostwick, Pabbati, Geske, & McKean, 2016a; Fazel & Runeson, 2020; Jordan & McNiel, 2020). About 3.2% of first attempters die on their first suicide attempt (Bostwick et al., 2016a). According to various sources, 1.6%-2.8% of suicide attempters die by suicide within 1 year after their attempt, while the corresponding rates for 5 and 10 years are 3.9%-5.6% and 7.4%, respectively (Demesmaeker, Chazard, Hoang, Vaiva, & Amad, 2021; Fazel & Runeson, 2020). These and other data suggest that the risk of suicide death (or re-attempt) is the highest right after an attempt and gradually decreases over time (Bostwick, Pabbati, Geske, & McKean, 2016b; Demesmaeker et al., 2021; Fehling & Selby, 2021).

2.2. Gender differences in suicidal behaviors

Suicidal behaviors have specific gender-related characteristics. Concerning completed suicides, there is a male preponderance almost everywhere in the world. Globally, the age-standardized suicide rates were 12.6 and 5.4/100,000/year for males and females, respectively (WHO, 2021). This gender inequality of suicide rates is unevenly distributed across the globe. The male to female suicide rate ratio is the highest in the European Region (3.98 to 1) and the lowest (1.51 to 1) in South-East Asia (WHO, 2021), with only a few countries where suicide rates are estimated to be higher for females (China, Myanmar, Bangladesh, Morocco, Lesotho) (WHO, 2019, 2021). Another gender-dependent feature of suicidal behavior is that suicide attempts are more prevalent among females especially in adolescents and young adults (Miranda-Mendizabal et al., 2019). The phenomenon that females are overrepresented in non-fatal suicidal behavior, while males are overrepresented in completed suicide has been dubbed the "*gender paradox of suicidal behavior*" (Schrijvers, Bollen, & Sabbe, 2012).

2.3. Age differences in suicidal behaviors

The risk of suicide is not equal in all age groups. A general finding from different countries/regions indicates that suicide rates in both genders are the highest among elderly individuals (i.e. those aged≥65-70 years) and the lowest among those aged under 15 (WHO, 2014). Despite the global decrease in suicide rates in the past decades, especially among the elderly, the suicide rates of the elderly have remained the highest virtually everywhere in the world (De Leo & Giannotti, 2021). The ratio of completed and attempted suicides is the highest in aged individuals (1:2-10 in older people vs. 1:200 in adolescents), and the male-to-female proportion of completed suicides is higher than the

corresponding proportions in younger age bands (De Leo & Giannotti, 2021; Dome, Gonda, & Rihmer, 2015). Another specific feature of suicidal behavior in elderly people is that the difference between genders (female>male) in the incidences of suicide attempts tends to be similar in old age (De Leo et al., 2001; De Leo & Arnautovska, 2019; Dome et al., 2015). Finally, it seems that suicidal ideations are less frequent in old age compared with adolescence and young adulthood (De Leo & Arnautovska, 2019). While global suicide rates are lower for adolescents and young/middle-aged adults than for older people, it does not mean that the suicide toll is negligible among young people. At the global level, the raw number of suicide deaths has a right-skewed distribution with a maximum value at 25-year-olds (WHO, 2021). The contradiction that elderly age bands have higher suicide rates but the number of suicide deaths is lower among them can be explained by the fact that there are many more young people than elderly people. In 2012, suicide accounted for 8.5% of all death cases among young people (15-29 years old), a figure that highly exceeds the corresponding one (1.3%) from 2019 with regard to the total population (WHO, 2021). In contrast to completed suicide, the rate/incidence of attempts is higher in people under 30-35 years of age than the rate/incidence among older subjects (however, the lethality of attempts is lower in young subjects than in older subjects) (Fazel & Runeson, 2020).

2.4. Association between suicide and neuropsychiatric disorders

Presence of neuropsychiatric disorders increases risks of suicidal behavior (Fazel & Runeson, 2020). A recent systematic review found that the relative risks (RR) for suicide for subjects with various mental disorders were significantly elevated (for example, the RRs for suicide in major depressive disorder [MDD], bipolar disorder, schizophrenia and anxiety disorders were 7.64, 6.05, 5.98 and 4.89, respectively) (Moitra et al., 2021). In high-income countries up to 80-90%, and in low-income countries 60-70% of suicide victims suffered from a psychiatric disorder (Knipe et al., 2019; Moitra et al., 2021). Moreover, suicidal ideations and attempts are more prevalent in subjects with mental illnesses than in the general population (Bai et al., 2021; Cai et al., 2021). Among patients with psychiatric disorders, some epidemiologic features of suicide differ from those of the general population. One such interesting epidemiological feature of suicide in patients with severe psychiatric disorders (i.e. mood disorders and schizophrenia) is that the differences between genders concerning the risks of both attempted and completed suicides are smaller than in the general population, where completed suicide is more frequent among males, while attempted suicide is unambiguously more frequent among females (Dome, Rihmer, & Gonda, 2019; Hettige, Bani-Fatemi, Sakinofsky, & De Luca, 2018). Another intriguing feature of suicidal behavior among patients with a psychiatric disorder is that the ratio of attempted to completed suicides is much lower in patient populations (mood disorders: 3-10:1; schizophrenia: 2-3:1) than in the general population (10-40:1) (Desîlets, Labossière, McGirr, & Turecki, 2016; Dome et al., 2019; Ventriglio et al., 2016).

2.5. Risk factors for suicidal behaviour

There are numerous risk factors for suicide that can be classified in several ways (Turecki & Brent, 2016). According to one of these classifications, risk factors are grouped into two categories: population-level (or environmental) and individual risk factors. For instance, poor access to health care, media reports of suicide, economic turmoil, and access to lethal means belong to the group of population-level (environmental) risk factors. Individual risk factors are further divided into three subgroups, including distal/predisposing factors, developmental/mediating factors, and proximal/precipitating factors (these three groups of risk factors are discussed in details in Chapter 4.1.) (Fazel & Runeson, 2020; Turecki et al., 2019; Turecki & Brent, 2016). Other classifications of the risk factors are also known (e.g. Rihmer, 2007). High-quality evidence suggests that neuropsychiatric disorders, family history of suicidal behavior, and substance misuse are *strong* risk factors for suicide. Evidence of high or moderate quality suggests that access to lethal means, life events, recent diagnosis of a terminal or chronic somatic illness, previous suicide attempt(s), and negative childhood events are suicide risk factors of *moderate strength* (Fazel & Runeson, 2020).

3. Clinical assessment of suicidal risk

A relatively high proportion of suicide victims visit their primary care physician or a mental health specialist within the month before their suicidal act (about 40-45% and 10-20%, respectively) (Saab et al., 2021), which would provide the possibility for using screening tests with good psychometric properties to identify subjects with high levels of suicidality. Unfortunately, there is increasing evidence that suicide risk assessment tools are unsuitable for accurately predicting suicidal behavior (Blasco-Fontecilla & de Leon, 2021; Chan et al., 2016; Fazel & Runeson, 2020; Saab et al., 2021). Two reasons stand behind this disappointing fact. Firstly, due to the rarity of suicide, some of these reasons are of statistical nature. Secondly, suicidal individuals frequently do not reveal their suicidal thoughts/intentions during clinical assessment (Blasco-Fontecilla & de Leon, 2021).

Furthermore, several risk factors of suicidal behavior are so common in clinical populations that their predictive value with regard to suicidal behavior is limited. Accordingly, the utility of clinical assessment based on risk factors and unstructured clinical interview is also not properly justified (Airey & Iqbal, 2022; Chan et al., 2016; Saab et al., 2021). However, the limited capacity of various scales and risk factors to predict suicidal behavior does not mean that clinicians should ignore the risk assessment process. Combining two or more risk assessment tools with clinical judgement/interview may be more effective than using single approaches (APA, 2003; Blasco-Fontecilla & de Leon, 2021; Fazel & Runeson, 2020; Saab et al., 2021). If the risk factors of a given patient are identified, priority should be given to mitigation of the modifiable factors (e.g. through treatment of psychiatric disorders and symptoms, limiting access to lethal means, and augmenting social support networks). Healthcare providers should be especially vigilant towards the threat of suicidal behavior in risk periods (e.g. during the first few months after hospital discharge, break-up of a relationship, melancholic circumstances).

4. Etiological background of suicidal behavior

4.1. The biopsychosocial context of suicidal behavior

Suicide develops as a result of interactions between genetic, biological, psychological, environmental, and social factors. Most models explaining the emergence of suicide risk emphasize an interplay between predisposing/distal and precipitating/proximal factors (Turecki et al., 2019). Predisposing/distal factors, also referred to as diathesis-like factors, include familial and genetic predisposition, as well as early life adversity such as trauma, neglect, sexual and physical abuse, which contribute to lasting neurobiological changes triggered by epigenetic alterations in stress regulation pathways (Weaver et al., 2004), emotional dysregulation, impaired executive function and other cognitive deficits (Van der Vegt, van der Ende, Ferdinand, Verhulst, & Tiemeier, 2009). The effect of early adverse experiences and other distal factors are at least in part mediated by developmental factors such as impulsive-aggressive traits, anxiety, neuroticism or hopelessness, increasing the likelihood of maladaptive responses to precipitating or proximal factors and therefore increasing the risk of emergence of suicidal thoughts and behaviors (Turecki et al., 2019).

Several precipitating factors also play a role in suicidal behaviors. Besides a previous suicide attempt being most strongly associated with suicide risk, other clinical factors impacting the transition from ideation to attempt include psychiatric disorders decreasing restraint or

increasing distress such as anxiety disorders, major depressive disorder (MDD), post-traumatic stress disorders (PTSD), impulse control disorders, and substance abuse or dependence (Turecki et al., 2019). Furthermore, somatic illnesses, especially pain, sleep problems, as well as cognitive impairment are also important contributors to suicide especially in elderly populations (Morgan et al., 2018), whereas in younger populations conduct disorder, impulsive-aggressive traits and substance abuse have more influence (Séguin, Beauchamp, Robert, DiMambro, & Turecki, 2014). Several psychological factors are also important contributors to suicidal ideation and attempts such as unbearable psychological pain, thwarted belongingness, increased burdensomeness, and acquired capability to commit suicide (Joiner Jr, Brown, & Wingate, 2005). Finally, environmental, contextual or socioeconomic risk factors are also associated with suicidal risk which can be proximal, such as economic problems and recent socioeconomic changes, loss of job, relationship problems, or lack of social support, as well as persistent factors such as belonging to a sexual or ethnic minority (King et al., 2008; Neeleman & Wessely, 1999; Qin, Agerbo, & Mortensen, 2003). The combination of multiple risk factors multiply the risk of manifestation of suicidal behavior thus such risk factors should always be considered in constellation.

4.2. Genetic background of suicidal behavior

The genetic architecture of suicide is less understood, hindering establishment of biomarkers or genetic predictors. Familial transmission of suicide is in part independent from transmission of psychiatric disorders (Brent & Mann, 2005; Tidemalm et al., 2011), pointing to suicide-specific genetic contributors leading to a genetically based trait-like suicide risk. Epidemiological, family, and twin studies estimate the heritability of suicidal phenotypes between 17-55% (Lee et al., 2022), specifically at 43% for ideation, 55% for attempt, and 47% for completed suicide (Edwards et al., 2021). However, it must also be noted that heritability of suicidal behavior strongly depends on the age of the individual (Edwards et al., 2021). The likelihood of attempting or committing suicidal behavior is at least 10 times higher in relatives of suicide completers, regardless of psychiatric disorders (Kim et al., 2005). On the other hand, the SNP-based heritability of suicidal behavior is much smaller than the heritability estimated in epidemiological studies (Mirza et al., 2022), and was estimated recently in large GWAS-es at 3% in case of suicide attempts (Mullins et al., 2019), 5-7% for suicide attempt/death (Docherty et al., 2022; Mullins et al., 2022), and at 7.6% for suicidal thoughts and behaviors (Strawbridge et al., 2019). These low values suggest that environmental influences play a key role in the expression of the suicidal phenotype.

The most comprehensive systematic review on the genetic background of suicidal phenotypes identified 438 candidate gene studies, the large majority of which focused on serotonergic genes, especially *TPH* and *SLC6A4*. A much smaller number of them investigated dopaminergic genes (*TH*, *DRD2*, *DAT1*), neurotrophic factor or neuroplasticity-related genes (*BDNF*, *NTRK2*, *HOMER1*, *NRXN1*), HPA axis genes (*CRH*, *FKBP5*, *NR3C1*, *SKA2*), or genes involved in inflammation and immune response (*TNFα*, *IL1*). While none of these studies showed reliable association, with a general failure of replication, 27 meta-analyses supported the role of variants in *FKBP5*, *NOS1*, *SLC6A4*, *TPH1*, *HTR1B* and *BDNF* (Mirza et al., 2022). None of these genes were confirmed in subsequent GWAS studies on suicidal phenotypes.

To date there has been 31 GWAS studies on suicidal phenotypes (Mirza et al., 2022). The largest GWAS on suicide attempt merging International Suicide Genetics Consortium (ISGC) and Million Veterans Program (MVP) studies (Docherty et al., 2022) identified 12 genome-wide significant loci. In GWAS studies, gene-based tests implicated *RETREG1*, *GSN*, *GNAS*, *CACNA1D* for suicide attempt (Sokolowski, Wasserman, & Wasserman, 2018), *HGF* for suicide ideation (Polimanti et al., 2021), *HEPACAM*, *CNTN5*, *PSMD14*, *HEPN1* for ordinal suicidality (Strawbridge et al., 2019) (a suicidal phenotype where suicidal behaviors are investigated using several mutually exclusive severity or risk categories spanning from no suicidal behaviour, through types of ideation and self-harm, to suicide attempt) (Wendt et al., 2021), *BTN2A1* for suicidal attempts/suicidal death (Mullins et al., 2022) and for suicidal ideations/behaviors (Mirza et al., 2022), while pathway analyses similarly implicated multiple relevant biological processes for different suicidal phenotypes including neurocircuitry (Strawbridge et al., 2019), synaptic function and brain development (Lybech, Calabró, Briuglia, Drago, & Crisafulli, 2021; Sokolowski et al., 2018), nervous system development, cell proliferation regulation, cell death and survival, inflammatory response, nerve impulse transmission (Galfalvy et al., 2013; Galfalvy et al., 2015), immune processes (González-Castro et al., 2019), oxytocin signaling, glutamatergic synapse, dopaminergic synapse, axon guidance, circadian entrainment, cortisol synthesis and secretion, and circadian rhythm (Kimbrel et al., 2022). A recent analysis (Sokolowski & Wasserman, 2021) pooling data from GWAS and whole exome studies implicated a set of 54 core genes involved in synaptic and nervous system development associated with completed suicide (Mirza et al., 2022). 39 polygenic risk score (PRS) studies were identified which reported an association between PRSs built for various psychiatric disorders and suicidal phenotypes with schizophrenia PRS explaining 11.8% of variability in childhood suicide attempts (Joo et al., 2022), and a multigenic score built from 750 neurodevelopment-related genes explaining 4.9% of variance in suicide attempt (Sokolowski, Wasserman, & Wasserman, 2016). Polygenic risk scores created for ordinal suicidality predicted longitudinal suicidal ideation trajectories (Na et al., 2022), while PRS built for suicidal death identified suicidal death cases from high risk families (Coon et al., 2022). While PRS studies explain only a small portion of variability in suicidal outcomes, studies focusing on rare variants explain more variability (Mirza et al., 2022).

Suicidal behavior has previously been linked to DNA methylation-based epigenetic factors directly related to environmental stimuli (Moore, Le, & Fan, 2013). Epigenetically modified candidate genes with relevance for suicide include those encoding the γ-aminobutyric acid (GABA) neurotransmission, hypothalamic-pituitary-adrenal (HPA) axis-related stress response system, and the polyamine system (Turecki, 2014). Studies in astrocytes of suicide subjects (Maussion et al., 2014; Nagy et al., 2015) also documented DNA-based methylation in dysregulating gene function. Overall, DNA methylation-based epigenetic factors seem to determine dysfunctional implications of multiple cellular pathways in critical brain regions involved in neurocognitive and neurovegetative functions resulting in impaired information processing (Turecki, 2014). Moreover, some genes seem to be abnormally regulated by specific epigenetic modifiers, known as non-coding miRNAs (Smalheiser et al., 2012). Epigenome-wide association studies (EWAS) focusing on epigenetic alterations influenced by environmental events and experiences also yielded significant results (Mirza et al., 2022).

4.3. Neurobiology of suicidal behavior

Altered function in several pathways have been hypothesized to contribute to the neurobiological underpinnings of suicidal behavior. Overall, the serotonergic system emerged as one of the most promising diagnostic, predictive, and therapeutic indicators of suicidal behavior (Johnson, McKernan, & Bruehl, 2022). Abnormalities in the serotonergic system have also been later linked with altered inflammatory pathways, kynurenine system, and other monoaminergic and neurotrophic signaling pathways (Oxenkrug, 2013). The results of initial studies implicating candidate genes encoding the serotonergic and dopaminergic systems, as well as brain-derived neurotrophic factor (BDNF) (Dwivedi, 2010; Zai et al., 2012) or TPH1 (Turecki et al., 2001), were in line with previous studies (Asberg, Träskman, & Thorén, 1976; Linnoila & Virkkunen, 1992; Perroud et al., 2009) reporting lower cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA) linked to aggression,

impulsiveness, and higher risk of suicide attempts; or lower central BDNF and BDNF mRNA levels (Dwivedi et al., 2003) and decreased BDNF TrkB receptor and mRNA expression levels of the full length or truncated isoforms in specific brain regions (prefrontal cortex (PFC) and hippocampus) (Dwivedi et al., 2003; Ernst et al., 2009) in postmortem brains of suicide victims. Furthermore, a correlation between higher methylation status and lower BDNF mRNA expression was found, pointing towards a repressive effect of methylation on transcription and suggesting that epigenetic regulations affecting neuroplasticity may have a potential role in suicide (Kim & Lee, 2017).

Maladaptive neuroendocrine system function predominantly related to blunted HPA-axis functioning and explained by the association between early-life adverse experiences and dysregulated hippocampal glucocorticoid receptor (GR) activity was suggested as a major risk factor for suicidal behavior (Carballo, Akamnonu, & Oquendo, 2008). Nutritional deprivation, maternal separation, and childhood abuse may be considered as early risk factors able to enhance the likelihood of suicidal behavior through altered stress responsiveness due to dysregulated HPA axis functioning (Roy & Dwivedi, 2021). During childhood adverse experiences DNA methylation-based epigenetic factors on multiple promoters of the GR gene may contribute to abnormally reduced GR expression and HPA dysregulation which are directly related to enhanced suicide risk.

The prominent role of neuroinflammation with existing evidence showing abnormal proinflammatory cytokine levels in the pathophysiology of suicidal behavior is increasingly implicated (Serafini et al., 2020). Specific studies demonstrated a distinct neuroinflammatory profile underlying suicidal behavior (Brundin, Erhardt, Bryleva, Achtyes, & Postolache, 2015; Enache, Pariante, & Mondelli, 2019; Wiener et al., 2019). In addition, an imbalance among pro-inflammatory and anti-inflammatory cytokines has been found in untreated depressed patients (Maes, 1999, 2011). Overall, in patients at an increased risk of suicide, specific inflammatory changes in the central nervous system, cerebrospinal fluid (CSF), and periphery can be identified.

The polyamine stress response appears to be a key contributor in the appropriate response mechanisms, with polyamines also regulating GR activity; pointing to a complex interaction between stress levels, polyamines, glucocorticoids, and suicidal behavior (Gross & Turecki, 2013). Currently, the most consistent findings implicating polyamines in suicide are related to the downregulation of spermidine/spermine N1-acetyl transferase (*SAT1*) gene expression, which is the rate-limiting enzyme of polyamine catabolism. In particular, SAT1 downregulation in depressed suicide victims across several brain areas in gene expression studies (Fiori, Mechawar, & Turecki, 2009; Sequeira et al., 2006) has been shown to be partly associated with genetic variation in the promoter.

In addition, the relation between cholesterol and violent suicidal behavior has been investigated with the first evidence demonstrating an association between lower serum total cholesterol concentration and violent but not non-violent suicide (Tanskanen et al., 2000). Human and animal studies both showed associations between cholesterol levels and serotonergic activity (Kim & Lee, 2017), the dysfunctions of which are implicated in suicidal behavior. Moreover, abnormal levels of omega-3 polyunsaturated fatty acids which can induce changes in the epigenome may be associated with suicidal behavior (Pompili et al., 2017).

The potential role of endocannabinoids has been explored in recent years as possible biomarkers for suicidal behavior (Johnson et al., 2022). Recently, abnormally higher serum levels of endogenous cannabinoids such as anandamide (AEA) and N-palmitoylethanolamide (PEA) have been found in suicide attempters relative to psychiatric controls (Herranz-Herrer et al., 2020) suggesting that endocannabinoid hyperactivity may contribute to suicidal behavior. Overall, endogenous cannabinoids might distinguish between suicide attempters and non-attempters.

Finally, other potential candidate biomarkers for suicidal behavior such as metabolites of dopamine and noradrenaline (e.g., homovanillic acid and 3-methoxy-4-hydroxyphenylglycol) (Hoertel et al., 2021), as well as uric acid levels (Peng, Dai, & Li, 2018) have been recently explored. Although these results seem promising, the predictive nature of these neurobiological findings warrants further investigation.

5. Treatment of suicidal behavior

5.1. Psychotherapy

The current medial approach to managing suicidal behavior tends to reduce risk factors contributing to suicide, with mental illnesses being the most prominent. Psychopharmacological agents applied in treatment of suicide therefore focus on the neurobiological contributors of psychiatric illnesses. However, in case of suicidal behaviors, the etiological processes behind the evolution of suicidal thoughts and actions are often highly complex and involve environmental influences and the reactions they trigger. Several different psychotherapeutic methods are being tested in clinical trials to reduce emergence of suicidal ideation or suicidal urge or repetition of attempts, focusing on impairments of emotion regulation and lack of adaptive coping mechanisms, and reducing cognitive behaviors associated with suicide risk while creating safety response patterns.

5.1.1. Cognitive-behavior therapies in managing suicide risk and behavior

Cognitive-behavior therapy (CBT) is one of the most studied and most effective psychotherapeutic interventions for suicide management. In case of suicidal behavior, the cognitive theory underlying CBT postulates that biopsychosocial vulnerability leads to automatic negative thoughts and a state of hopelessness triggering the suicidal mode, which encompasses cognitions, emotions, behavioral patterns, and physiological symptoms emerging in an on-and-off pattern (Rudd, 2000). CBT involves the collaborative exploration of negative automatic thoughts and core beliefs to map the suicide belief system; the detection and understanding of the triggering conditions during case conceptualization; the building of skills to prevent and manage future suicidal crises; and the development of strategies such as safety planning and relapse prevention (Brown et al., 2005; Rudd et al., 2015). Versions of CBT specifically targeting suicide have been developed, including Cognitive-Behavior Therapy for Suicide Prevention (CBT-SP) (Bryan, 2019) or Brief Cognitive Behavior Therapy for Suicide Prevention (BCBT) (Bryan & Rudd, 2018). Cognitive therapy was found to reduce suicide risk, but not ideation, by approximately 50% after 18 months compared to treatment as usual (TAU) (Brown et al., 2005). BCBT also significantly reduced suicide attempts compared to TAU after 24 months (Rudd et al., 2015). The effects of CBT are most pronounced in high-risk cases and may last beyond five years (Sobanski et al., 2021) and according to studies three 90-minute sessions may lead to long-term suicide risk reduction (Calati et al., 2022; Gysin-Maillart, Schwab, Soravia, Megert, & Michel, 2016).

Dialectical Behavior Therapy (DBT) is a third-generation CBT developed for borderline patients as a combination of cognitive and behavioral strategies from CBT, acceptance strategies, and supportive therapies involving individual and group sessions and phone coaching. DBT focuses on emotional dysregulation resulting from genetic vulnerability, early invalidating environmental experiences, lack of acquired adaptive self-regulatory strategies and the resulting maladaptive and impulsive behaviors, and is aimed at building adaptive emotion-regulation and interpersonal skills, distress tolerance, and mindful awareness as well as improving relationships (Linehan, Armstrong, Suarez, Allmon, & Heard, 1991). Effectiveness of DBT in the management of suicide risk has been better investigated, and a meta-analysis of 18 RCTs found that DBT was effective in reducing self-directed violence although not suicidal ideation (DeCou, Comtois, & Landes, 2019).

Problem-solving therapy (PST), also developed in the CBT framework, aims at developing and strengthening cognitive and behavioral skills to deal with life events and stressors more effectively and adaptively, by targeting stress resilience, emotion regulation, problem orientation, and problem solving style (Bell & D'Zurilla, 2009). Its efficacy compared to TAU in reducing self-harm, suicidal ideation, and hopelessness after 6 and 12 months has also been supported by metaanalyses (Hawton et al., 2016).

5.1.2. Psychoanalytic and psychodynamic therapies for the management of suicide risk

The psychoanalytic and psychodynamic approach to suicide prevention focuses on understanding the unbearable emotional pain in the internal subjective experience, including humiliation, self-hatred, shame or rage; coupled with an immediate need for relief, and other factors leading to suicide vulnerability such as personality and character traits, early attunement problems or dissociation, via the establishment of a therapeutic space for exploring thoughts, fears, and fantasies (Schechter, Goldblatt, Ronningstam, & Herbstman, 2022). Recent studies and two meta-analyses on the efficacy and effectiveness of psychodynamic therapies (Calati et al., 2022) showed some effect compared with controls in reducing self-harm and suicide in borderline patients (Cristea et al., 2017) as well as reduced number of attempters at 12-month follow-up and reduced self-harm after 6 but not 12 months compared to TAU (Briggs et al., 2019).

Transference Focused Therapy (TFP), developed for the treatment of borderline patients, focuses on the integration of aggressive internalized object relations with idealized ones through analysis of relational experience with the therapist and linking positive and negative transferences to integrate split-off idealized and persecutory fragments of experience (Calati et al., 2022; Kernberg, 2016), and appears to be promising in reducing suicidal behavior in a few studies (Doering et al., 2010; Giesen-Bloo et al., 2006).

Mentalization-based Treatment (MBT), also developed for personality disorders, focuses on problems of mentalization, a process involved in gaining a sense of identity and making sense of others' mental processes and subjective states (Fonagy, 1989). MBT was found to reduce self-harm compared to TAU even 5 years after completion of therapy (Bateman & Fonagy, 2008) and to be more effective in suicide attempts compared to control therapies in personality disorder patients (Bateman & Fonagy, 2009, 2016; Calati et al., 2022; Jørgensen et al., 2013).

Interpersonal therapy (IPT), which focuses on current interpersonal problems, conflicts, deficits and role transitions and their connection to depression also reduces suicidal ideation (Kumpula et al., 2019).

5.1.3. Brief interventions for managing suicide risk and behavior

Since suicide risk often presents as an emergency, warranting immediate, easily administered, and fastly delivered interventions, several brief intervention methods to target suicidal behavior in various healthcare settings such as the ER, have also been developed.

The Attempted Suicide Short Intervention Program (ASSIP), consisting of 3 sessions and developed for suicide attempters to prevent reattempt (Michel, Valach, & Gysin-Maillart, 2017), reconstructs the path leading to suicide based on a video-recorded interview, yielding a case conceptualization including vulnerabilities, triggers, and safety strategies handed out to the patient, followed by letters from the therapist during the following two years to remind of long-term suicidal crisis risk and safety strategies. ASSIP robustly reduces suicide reattempt risk compared to TAU (Gysin-Maillart et al., 2016) even at 24-month follow (Michel et al., 2017). The Collaborative Assessment and Management of Suicidality (CAMS) (Jobes & Drozd, 2004) involves five steps of collaborative risk assessment, treatment planning, clinical suicide status monitoring and resolution, and rapidly reduces suicidal ideation compared to TAU (Jobes, Wong, Conrad, Drozd, & Neal-Walden, 2005), however, RCTs are lacking (Calati et al., 2022).

5.1.4. Studies assessing the efficacy and effectiveness of psychotherapeutic interventions in the management of suicide

In recent years several meta-analyses supported that psychotherapeutic interventions in suicide are promising, and found that CBT-based interventions are highly effective.

A meta-analysis of 32 studies involving 4114 patients with different diagnoses randomized to psychotherapeutic treatment or TAU to evaluate the efficacy of various short- and long-term psychotherapies concluded that patients receiving psychotherapy were significantly less likely to attempt suicide, although in this study psychoanalytically oriented partial hospitalization or MBT was the only effective method, and psychotherapies reduced suicide risk in borderline patients, but not in depression or schizophrenia spectrum disorders in post hoc analyses (Calati & Courtet, 2016).

A systematic review of 41 observational studies including mostly DBT and CBT in mostly borderline and MDD patients found a significant reduction in both suicidal ideation and attempt (Méndez-Bustos et al., 2019). A systematic review on prevention of future reattempts and suicide including 18 RCTs found psychotherapeutic interventions to be significantly more effective than TAU or other control conditions in reducing reattempt risk by one-third. Altogether modest differences between different types of therapeutic interventions were found, but separate investigations show that while CBT and psychodynamic interventions did have a significant effect in reducing reattempts compared to controls no such effect was found for DBT or problem solving therapy (Sobanski et al., 2021).

A very recent Cochrane review (Witt et al., 2021), including 76 RCTs with 21414 participants found that, although with low quality evidence, individual CBT may reduce repetition of self-harm compared to TAU or other psychotherapies at the end of the intervention, and at 6- and 12-month follow up. In case of DBT compared to TAU, slightly lower repetition rates were found. In case of MBT, evidence was of high quality of reduction of repetition and frequency of self-harm at post-intervention assessment. No evidence was found for psychodynamic therapy, case management, GP management, remote contact interventions, and other multimodal interventions or brief emergency department-based interventions (Witt et al., 2021).

A systematic review and metaanalysis including 15 studies and 29071 participants focusing on comparing the effect size of psychotherapeutic interventions found a significant large effect on completed suicides and a significant moderate effect on suicide attempts emphasising that the preferred intervention strategy differs between the two outcomes, and highlighting the need for careful risk appraisal. Furthermore, this study also found that there was a significantly higher effect of interventions for suicide prevention related to number of intervention levels, pointing out that multilevel interventions may have greater effects and a synergistic potential (Hofstra et al., 2020)

Concerning the long-term effect of psychotherapeutic interventions, a study followed up 5678 patients receiving different interventions including CBT, problem-solving crisis management, DBT, integrative, psychoanalytic, psychodynamic, systemic and support therapies compared to no psychosocial treatment for 1, 5, 10 and 20 years, and found significantly lower self-harm risk within 1 year and reduced repeated self-harm and suicidal death after 10 and 20 years with the highest benefit in women, young people, and those with a first episode of self-harm (Calati, Courtet, & Lopez-Castroman, 2018; Erlangsen et al., 2015).

In spite of the effectiveness of several psychotherapeutic methods in reducing suicide risk, there is still a great need to better understand their role and improve their therapeutic benefits. More psychotherapeutic concepts would need to be integrated in suicide prevention, with several, otherwise effective psychotherapies now only having a marginal role in suicide management (Michel, 2021). Currently, the decision concerning treatment of suicidal patients, especially in case of psychotherapeutic interventions, is based on clinical experience rather than guidelines. Methodological consensus, treatment algorithms, and evidence-based guidelines are urgently needed to ensure a structured

approach and standard delivery to improve suicide-related outcomes (Méndez-Bustos et al., 2019). Structured therapies with well-adaptable manuals would need to be developed. Furthermore, a deeper understanding of the mechanisms of action of different therapies is needed to match them to processes underlying suicide risk in different psychopathologies and patient populations, as well as direct comparisons of psychotherapies are still needed (Calati et al., 2018). Both RCTs and observational studies reflecting real-world circumstances are warranted as well (Méndez-Bustos et al., 2019). Finally, besides the limited possibility of the healthcare system to provide psychotherapeutic interventions (Michel, 2021), it also needs to be acknowledged that psychotherapy with suicidal patients is extremely challenging for therapists who often lack the appropriate tools for intervention (Schechter, Ronningstam, Herbstman, & Goldblatt, 2019).

5.2. Pharmacotherapy for the management of suicide risk and behavior

5.2.1. Traditional pharmacotherapy for suicidal behavior

Despite recent innovative pharmacological options now available for the management and treatment of suicidal behavior (e.g., esketamine), traditional psychotropic drugs have been documented to exert antisuicidal properties in the long-term treatment of psychiatric disorders linked to suicide risk.

5.2.1.1. Antidepressant medications. Although there are studies suggesting that both short- and long-term treatment with antidepressant medications may attenuate suicidal risk in general, several studies have also found inconclusive results. While in MDD patients evidence concerning short- and long-term efficacy of antidepressant treatment is consistent, the use of these drugs in bipolar depression is a matter of debate given their possible destabilizing properties (Pacchiarotti et al., 2013). Increased risk for suicidal behavior has been reported in subjects with agitation, anger and dysphoria, irritability, insomnia, and behavioral disinhibition, particularly in the case of comorbidity with substance abuse/dependence and in younger individuals (Tondo & Baldessarini, 2016).

While ecological studies reported lower rates of suicide with greater use of antidepressants in Nordic countries and USA, these findings have not been replicated elsewhere (Søndergård, Kvist, Lopez, Andersen, & Kessing, 2006). In addition, specific concerns have been suggested according to retrospective and case-control studies including large samples of depressed patients which found inconsistent results (Möller, 2009). Unfortunately, randomized controlled studies are limited concerning numbers and exposure times while outcome events are relatively rare. Similarly, most meta-analyses reported only minor differences in suicide rates between depressed patients treated with antidepressants or placebo, while usually identifying an increased suicide risk in children and young adolescents who were treated with antidepressants (Barbui, Esposito, & Cipriani, 2009; Wise, 2016). The use of antidepressant medications in specific clinical conditions including mixed symptoms should be avoided given the risks related to cycle acceleration and destabilizing properties of these compounds (Ghaemi, 2012; Vieta, 2014).

5.2.1.2. Anxiolytic and sedative agents. The efficacy of anxiolytic drugs on suicidal risk in the short- and long-term period is not supported by clinical evidence (Yerevanian & Choi, 2013). The use of benzodiazepines or other sedatives may be associated with behavioral disinhibition, enhanced impulsivity, and aggressive behaviors, particularly when combined with alcohol abuse/dependence or personality disorders (Gaertner, Gilot, Heidrich, & Gaertner, 2002). Furthermore, the use of specific sedative agents (Shih et al., 2013) or hypnotics such as zolpidem (Sun, Lin, Lu, Hsu, & Kao, 2016) has been associated with increased self-poisoning rates whereas rapid benzodiazepine discontinuation may significantly strengthen suicidal risk (Gaertner et al., 2002). Although it may be hypothesized that anxiolytic medications attenuate suicidal risk, existing evidence does not support this assumption, perhaps because these drugs are usually not used as primary treatments for this condition.

5.2.1.3. Antipsychotic medications. The atypical antipsychotic clozapine was the first antipsychotic drug to be approved by Food and Drug Administration (FDA) for the management of suicide risk in schizophrenia patients based on a large randomized trial (InterSePT) which compared clozapine with olanzapine among suicidal schizophrenia patients and reported reduced rates of suicide attempts (Meltzer et al., 2003). A subsequent trial (Haukka, Tiihonen, Härkänen, & Lönnqvist, 2008) replicated the beneficial effect of clozapine relative to risperidone, quetiapine, or olanzapine in schizophrenia patients. The efficacy and safety of atypical antipsychotics have also been demonstrated in the treatment of bipolar depression in which these agents provided therapeutic benefits not only for depressive symptoms but also for agitated dysphoric mixed states which are frequently associated with higher suicide risk (Pacchiarotti et al., 2013; Swann et al., 2013). Clozapine also demonstrated its effectiveness in bipolar disorder patients who have not responded appropriately to other treatments (Ifteni et al., 2014; Li, Tang, Wang, & de Leon, 2015) or in those with psychotic features (Ciapparelli et al., 2000). Concerning aripiprazole, cariprazine, asenapine, lurasidone, olanzapine, and ziprasidone, evidence suggests their potential benefits as monotherapy or in combination with lithium or mood-stabilizing agents, given their positive effects on depressive/manic conditions (Poo & Agius, 2014) as well as their effect on attenuating suicidal risk in schizophrenia (Earley et al., 2020; Ulcickas Yood et al., 2010). In addition, olanzapine and risperidone attenuated suicidal ideation/behavior in schizophrenia (Barak, Mirecki, Knobler, Natan, & Aizenberg, 2004; Kerwin & Bolonna, 2004; Reeves et al., 2008). Evidence also showed the effectiveness of olanzapine, compared with placebo, when added to lithium or divalproex to reduce suicidal ideation in bipolar disorder patients with mixed symptoms (Houston et al., 2006). The rapid discontinuation of atypical antipsychotic medications in schizophrenia patients may increase suicide attempts and suicide rates (Herings & Erkens, 2003) as well as specific adverse effects (e.g., akathisia and agitation) related to the use of these medications and potentially linked to higher suicidal risk (Seemüller et al., 2012; Seemüller et al., 2012), which has been reported for aripiprazole, ziprasidone, and clozapine. Overall, with the exception of clozapine, the use of atypical antipsychotics to attenuate suicide risk or exert direct antisuicidal properties in patients with mood disorders requires further longitudinal investigation in large cohorts.

5.2.1.4. Anticonvulsants. Limited evidence is available regarding the possible effects of mood stabilizers other than lithium in reducing suicidal risk (Oquendo et al., 2011; Søndergård, Lopez, Andersen, & Kessing, 2008). Evidence suggested that some anticonvulsants may exert a beneficial effect on suicidal behavior (Yerevanian & Choi, 2013; Yerevanian, Koek, & Mintz, 2007). Notably, adding valproate or lithium was associated with similarly lower suicidal risk than treatment with only antipsychotics based on a 6-year Danish study including more than 16,000 subjects (Smith, Søndergård, Lopez, Andersen, & Kessing, 2009) with lithium and valproate having similar associations with suicidal behavior (Oquendo et al., 2011; Smith et al., 2014). However, the observed rate of suicidal acts accounted for 0.3% per year during lithium treatment *vs.* 0.9% per year when using anticonvulsants favoring lithium relative to valproate, carbamazepine and lamotrigine (Baldessarini & Tondo, 2009) in terms of antisuicidal properties. Finally, although some evidence exists in this specific regard, research on anticonvulsants and suicidal risk remains largely inconsistent and needs further testing.

5.2.2. Lithium in the treatment and prevention of suicidal behavior

The first hypotheses on the suicide prevention action of lithium were reported by Barraclough (Barraclough, 1972), who pointed out the role of lithium in preventing "recurrent affective illness" and

ultimately preventing suicide. In the mid-eighties, it was speculated that lithium could have a major role in suicide prevention, but possibly an answer would come in the next ten years (Jamison, 1986). Several subsequent contributions by German scholars reported convincing evidence of antisuicidal properties of lithium salts, pointing to possible anti-aggressive effects and reduced suicide risk even in patients not responding satisfactorily in terms of reduced number of mood episodes (Müller-Oerlinghausen, Müser-Causemann, & Volk, 1992). Further studies consistently reported lithium's long-term role in reducing mortality in patients with manic-depressive and schizoaffective illnesses by prophylactic protection (Ahrens, Berghöfer, Wolf, & Müller-Oerlinghausen, 1995; Müller-Oerlinghausen et al., 1992; Thies-Flechtner, Müller-Oerlinghausen, Seibert, Walther, & Greil, 1996).

In some seminal contributions, Tondo, Baldessarini and colleagues (Baldessarini, Tondo, & Hennen, 1999; Tondo et al., 1998) reported strong evidence of the role of lithium in suicide risk protection among patients suffering from mood disorders. In a sample of bipolar disorder patients, lithium maintenance was associated with a robust reduction of severely life-threatening suicidal behavior, which markedly increased after the discontinuation of lithium. Suicidal acts were more frequent during the early illness course before treatment with lithium, and also showed an association with younger age, a greater proportion of time depressed, as well as prior suicide attempts. This study showed that in the first year after stopping lithium for various clinical reasons, the crude rate of suicidal acts was almost three times higher than in the subsequent or pre-treatment times. Moreover, the fatality rate was 8.7-times lower during versus after discontinuing lithium. These authors found that gradual vs. rapid discontinuation of lithium could limit the risk of suicidal behavior (Tondo et al., 1998).

Further evidence revealed that the antisuicidal action of lithium was robust both in completed suicides and suicide attempts among major affective disorder patients without versus with long-term lithium maintenance treatment compared to reported suicide rate estimates in the general population. According to these data, suicide attempt rates in patients treated with lithium versus population base rates do not differ significantly. Still, treated rates for suicide were ten times above the international suicide rate in the general population (Baldessarini, Tondo, & Hennen, 2001). Moreover, robustly decreased suicidal risk (attempts > suicides) was demonstrated with lithium maintenance therapy in unipolar ≥ bipolar II ≥ bipolar I patients, to overall levels close to general population rates. On the other hand, patients who did not receive lithium had alarming rates of both suicides and suicide attempts in all instances of the mood disorders mentioned above (Baldessarini, Tondo, & Hennen, 2003).

A study (Goodwin et al., 2003) in a large sample of bipolar disorder patients demonstrated that suicide attempt and suicide death rates were substantially larger during periods of exposure to divalproex than during lithium treatment. In case of carbamazepine results were qualitatively similar to those observed for divalproex, however much less precise (reflecting the smaller sample size). Nevertheless, findings reported in this big sample are consistent with substantial previous data indicating that lithium reduces both suicide attempts and suicide mortality. A meta-analysis (Baldessarini et al., 2006) reported that during treatment with lithium for an average of 18 months, risk of both attempted and completed suicide were consistently lower, by approximately 80%, in major affective disorder patients. These benefits were sustained in randomized and open clinical trials, and antisuicidal action of lithium emerged in all sub-analyses for the various subgroups of patients included in the study. In these studies a strong association between lithium treatment and the ratio of attempted to completed suicides (A/S) was observed, which latter was proposed as a novel index of the lethality of suicidal acts. The attempted to completed suicide ratio was 2.5 times greater in lithium-treated subjects compared to those not receiving lithium, and it was almost three times higher in bipolar disorder patients, suggesting a robust reduction in lethality of suicidal behavior, attributable to lithium treatment. In this high-risk group of patients a significantly decreased rate of suicide attempts compared to pre-lithium figures was also found, and not only in patients with excellent treatment outcomes but also in those with moderate or poor response to lithium prophylaxis (Ahrens & Müller-Oerlinghausen, 2001), suggesting an independent antisuicidal effect. Cipriani et al. (Cipriani, Pretty, Hawton, & Geddes, 2005) also found that lithium effectively prevented deliberate self-harm, suicide, and all-cause death in mood disorder patients. More recent studies also confirmed the antisuicidal properties of lithium in mood disorders (Cipriani, Hawton, Stockton, & Geddes, 2013; Smith & Cipriani, 2017).

However, some studies did not find consistent antisuicidal action of lithium salts. For example, a randomized controlled trial (Oquendo et al., 2011) did not find differences between lithium and valproate in preventing suicide attempts and suicide events among bipolar disorder patients. Another randomized placebo-controlled clinical trial reported that adding lithium to treatment did not lead to a decrease in the incidence of suicidal events in veterans with major depression or bipolar disorder who experienced a recent suicide event. In addition, they observed that adding lithium to existing medication regimens was ineffective in preventing a broad range of suicide-related events in patients who were being treated for mood disorders and previously engaged in suicidal behavior (Katz et al., 2022).

Overall, in spite of some mixed evidence, lithium seems to be unique in protecting mood disorder patients from suicide risk (Tondo & Baldessarini, 2018). It has the potential to act transdiagnostically, given evidence emerging from studies of lithium in drinking water and the rates of suicide risk in selective areas where concentrations are higher (Del Matto et al., 2020).

5.2.3. Novel and emerging pharmacological treatments for suicidal behavior

5.2.3.1. Esketamine for the treatment of suicidal behavior. By the early 2000s, evidence pointed to impaired glutamate signaling as relevant to the pathophysiology of MDD. Ketamine first emerged as an important option targeting the glutamatergic system and rapidly reducing symptoms of MDD.

Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine. Esketamine is the S-enantiomer of ketamine, which is more potent at the NMDA glutamate receptor than its mirror image, R-ketamine. Esketamine is a non-competitive NMDA receptor antagonist that modulates glutamatergic transmission (Covvey, Crawford, & Lowe, 2012) which may play a central role in restoring physiological glutamate signaling, and by targeting the glutamatergic system, a substantial portion of patients would experience dramatic improvement of symptoms in few hours after dosing.

In patients with treatment-resistant depression (TRD), administration of a single dose of intranasal esketamine resulted in a rapid reduction in depressive symptoms. This led to considering intranasal esketamine as a valid treatment option for TRD and use of this device to rapidly reduce depressive symptoms of MDD with suicidal ideation and intent (Daly et al., 2018).

Canuso and colleagues (Canuso et al., 2018) investigated the effects of intranasal esketamine in a sample of 68 patients (treated with esketamine or placebo in addition to comprehensive standard-of-care treatment) and found a significantly greater improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score in the esketamine group compared to placebo-treated patients at 4 hours and 24 hours. However, such an effect was not observed on Day 25. In the group treated with esketamine there was a greater improvement on the MADRS 'suicidal thoughts' score at 4 hours (but not at 24 hours or Day 25). Notably, patients were also evaluated with the Suicide Ideation and Behavior Assessment Tool (SIBAT). Results of this trial showed that risk of suicide decreased overall, in both groups, throughout the study, as assessed by the 'suicidal thoughts' item of MADRS as 'enjoying life or take it as it comes' or 'weary of life, reporting fleeting suicidal

thoughts'. Patients at risk of suicide were moved into a comfort zone with only mild suicidal wishes. These results are highly promising for a selected population receiving a valuable standard of care (SOC) to reduce suicide risk, regardless of the type of treatment. Notably, a consistent improvement of suicidal ideation was also observed in those receiving placebo plus SOC during the study period. This was probably because patients on the placebo arm received the same accurate assistance as those on the esketamine arm. It is necessary to consider that particular medical assistance includes clinical supervision and evaluation of various clinical and physical parameters. In this context, it must be remembered that the studies on esketamine are among the only ones to have enrolled patients at imminent risk of suicide. This feature must have predisposed clinicians to extra support for the suicidal crisis regardless of the treatment arm; a specific modality of the study could explain the reduction of the risk of suicide in both groups, causing loss of statistical significance.

The ASPIRE trials (Fu et al., 2020; Ionescu et al., 2021), which were the first to investigate efficacy of treatment in patients at an acute risk of suicide who have previously been mostly excluded from such studies, demonstrated that esketamine plus a comprehensive SOC rapidly reduced depressive symptoms in MDD patients with acute suicidal ideation or behavior, and particularly in patients with a history of prior suicide attempts, establishing a novel treatment option for this particularly ill and vulnerable population. The ASPIRE studies had a primary endpoint investigating the change from baseline (Day 1, pre-dose) to 24 hours post-first dose in depressive symptoms (measured by MADRS total score). There was also a key secondary endpoint investigating the change from baseline (Day 1, pre-dose) to 24 hours post-first-dose in severity of suicidality (measured by CGI-SS-R). These two recent large-scale studies reported that 24 hours following the first dose of study medication, esketamine plus SOC lead to a both clinically meaningful and statistically significant reduction of depressive symptoms compared to placebo. However, both the esketamine and the placebo groups demonstrated an improvement in the severity of suicidality from baseline to 24 hours following the first dose, with no statistically significant difference between the two treatment groups, possibly due to various variables and interventions such as hospitalization and implemented medical attention with an empathic understanding of the suicidal crisis (Pompili, 2019).

Recently, Canuso et al. (Canuso et al., 2021) summarized the results of the ASPIRE studies and concluded that esketamine plus a comprehensive SOC rapidly reduced depressive symptoms in MDD patients with acute suicidal ideation or behavior compared to placebo, especially in those with a history of suicide attempts. According to the MADRS, early benefit with esketamine was greatest on reported sadness, apparent sadness, inner tension, suicidal thoughts, inability to feel, and pessimistic thoughts at 4 hours following the first dose, and on concentration difficulties, inner tension, apparent sadness, reported sadness, inability to feel, reduced sleep, and pessimistic thoughts at 24 hours. Especially the rapid alleviation of depressive symptoms in patients at an imminent risk of suicide is a very important result. Furthermore, CGI-SS-R (a module of SIBAT) score decreased from baseline to 24 hours following the first dose both in the esketamine group plus SOC and in the placebo plus SOC group, showing that patients in both treatment groups experienced a rapid reduction in the severity of suicidality and the difference between the groups was not statistically significant. Already at 4 hours following the first dose, the mean change from baseline showed a significant improvement in both groups. At the end of double-blind treatment there was an improvement in the severity of suicide risk in both groups, with no statistically significant difference between them. The lack of statistically significant difference between the groups may be due to the substantial beneficial effects of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis in patients in both treatment groups, extraordinary care in both groups when monitoring the suicide risk scenario with empathic and medical approach which is likewise of help in ameliorating the will to die. However, it is noteworthy that beneficial effects were observed among patients with acute suicidal ideation or behavior, and particularly among those with a history of prior suicide attempts, providing a novel treatment option for a particularly sick and vulnerable population (Canuso et al., 2021). As the ASPIRE trials were designed to observe patients over four weeks, the reduction of acute suicidal ideation or behavior was limited to such observation time, without information for longer-term effects. New evidence based on case presentations in major depressive disorder with esketamine treatment in the real world, including a psychiatric emergency such as suicide, are now also available suggesting successful outcomes with esketamine in treatment resistant patients with suicide risk (Pompili, Sarli, Erbuto, Manfredi, & Comparelli, 2023).

5.2.3.2. Emerging pharmacotherapeutic possibilities for the treatment of suicidal behavior beyond esketamine. Only a few evidence-based pharmacological treatments exist that specifically target on active suicide risk, and most of the available pharmacological options are limited by the delayed onset of action of these compounds. The introduction of esketamine and related rapid-acting compounds is currently promising in order to provide rapid efficacious treatments of depression and suicidal behaviors. New antidepressant and potentially antisuicidal glutamatergic or GABAergic agents such as AV-101, brexanolone, and zuranolone have been recognized as breakthrough therapies or fast-track active compounds by the FDA and novel medications acting as NMDA allosteric modulators or blocking mGluR2/3 autoreceptors might allow clinicians to effectively approach suicide risk in MDD patients (Duman, 2018).

Psychedelic drugs such as psilocybin have also been suggested as innovative treatment strategies for treatment-resistant mood disorders and suicidal behavior given their ability to modify the default mode network connectivity, and consequently strengthen cognitive flexibility (Reiff et al., 2020). The remodeling of cognitive flexibility mediated by psychedelic agents may play a crucial role in suicidal patients due to the importance of altered decision-making, impaired cognitive flexibility, and poor problem-solving ability as well as dysfunctional maladaptive avoidance in the emergence of suicidal behaviour (Obegi, 2019). Increased cognitive flexibility supported in the long-term period by psilocybin treatment may allow patients to switch from avoidance to acceptance of dysfunctional thoughts and behavioral patterns (Wolff et al., 2020), the importance of which process in decreasing suicidal risk and treatment of suicidal behavior has also been demonstrated by the effectiveness of acceptance and commitment therapy in subjects with suicidal ideation (Ducasse et al., 2018). However, we are only at the beginning of an initial fascinating journey with many interesting options now available in the pharmacological treatment armamentarium.

5.3. Biological therapy and neuromodulation in the treatment of suicidal behavior

5.3.1. Electroconvulsive therapy

For decades, electroconvulsive therapy (ECT) has been an essential non-pharmacological treatment modality primarily for severe depression, mania, and catatonic states, and neuroleptic malignant syndrome (NMS) (Espinoza & Kellner, 2022). ECT is an inpatient procedure performed under general anesthesia and muscle relaxation. Despite its historically bad reputation, nowadays ECT is generally considered a very safe intervention (Osler, Rozing, Jorgensen, & Jorgensen, 2021; Rhee et al., 2021; Tørring, Sanghani, Petrides, Kellner, & Østergaard, 2017; Watts, Peltzman, & Shiner, 2021). Because of its rapid onset of action, ECT is particularly indicated when a prompt recovery is essential (e.g. in cases with marked suicidality). This message appears in several MDD treatment guidelines authored by professional organizations (APA, 2010; Malhi et al., 2021; Milev et al., 2016).

Historically, the first indications of ECT's suicide protective effects date back to the 1940s. ECT became the primary approach in the treatment of psychiatric disorders at that time and studies found that suicide

rates of patients with psychiatric disorders in the ECT era were lower than in the pre-ECT era (O'Leary, Paykel, Todd, & Vardulaki, 2001). Unfortunately, the implementation of high-quality studies for the assessment of the suicide preventive properties of ECT is not feasible for various reasons. Above all, due to the nature of ECT administration and ethical reasons, it is almost impossible to ensure the blinding that would be essential to carry out a RCT. Since suicide is a rare event even among psychiatric patients and, furthermore, ECT is an infrequently indicated treatment modality, carrying out a prospective study with an appropriate number of suicide cases for statistical calculations would require a very large clinical cohort. Finally, since ECT is frequently reserved for the treatment of the most severely ill subjects, confounding by indication/severity may be a source of bias in observational studies (Kaster et al., 2021; Peltzman, Shiner, & Watts, 2020; Wilkinson et al., 2022). Furthermore, methodological shortcomings (e.g. with regard to 1) frequently lacking data on the potential add-on treatments (e.g. pharmacotherapy) to ECT; 2) heterogeneity of study design [cohort or case-control or RCT]; 3) heterogeneity of the psychiatric disorders of the included subjects) of the studies often hinder the comparability of results (Chen et al., 2021; Salagre, Rohde, & Østergaard, 2022; Wilkinson et al., 2022).

Bearing in mind methodological limitations and sometimes inconclusive results, studies tend to support the suicide preventive effects of ECT. A recent systematic review that estimated the anti-suicide effects of various brain stimulation techniques (including ECT, repetitive transcranial magnetic stimulation [rTMS], or transcranial direct current stimulation [tDCS]) concluded that out of these modalities only ECT may be supported for the treatment of acute suicidal ideation (based on a review of 14 ECT studies conducted between 1978-2018 mainly in subjects with major depressive, bipolar or schizoaffective disorders) (Chen et al., 2021). At the same time, a meta-analysis of 11 studies published between 1948-2018, conducted in subjects with mood and/or psychotic disorders found that ECT was not associated with decreased suicidality. It is of note, however, that the association between ECT use and decreased risks of suicidality was significant at the level of $p \leq 0.1$ (OR[95% CI]: 0.77 [0.59-1.00]; $p = 0.053$) in that study (Wilkinson et al., 2022). Results of the most recent studies are not entirely consistent. On one hand, the majority of them identified the protective effects of ECT against suicidal behavior or ideation (Kaster et al., 2022; Rhee et al., 2021; Rönnqvist, Nilsson, & Nordenskjöld, 2021; Salagre et al., 2022; Sienaert et al., 2022). On the other hand, two studies found that ECT was not associated with a greater decrease in suicide risk than SOC (Peltzman et al., 2020; Watts, Peltzman, & Shiner, 2022). Furthermore, authors of another study reported that ECT was associated with an increased risk of suicide in mild/moderate/severe (without psychotic symptoms) depression and was not associated with any increase in suicide risk in the "severe with psychotic features" category only. However, the authors acknowledged that register-based data on depression severity at baseline used in the study might not had fully captured the symptom severity of patients, which might have had an impact on the decision to choose ECT as a treatment modality and, later, the risk of suicidality (Jørgensen, Rozing, Kellner, & Osler, 2020). Finally, an investigation in homeless veterans found notable reductions in suicidality among subjects receiving ECT, but these reductions were smaller compared with those subjects who did not receive ECT. However, since the authors did not control the study for symptom severity, those who received ECT might have had more severe MDD (Tsai, Peltzman, Watts, & Shiner, 2021).

5.3.2. Repetitive transcranial magnetic stimulation for the prevention and treatment of suicidal behavior

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method that has received FDA approval for the treatment of some psychiatric and addictive disorders (MDD, obsessive-compulsive disorder and nicotine addiction) (Lefaucheur et al., 2020). In addition, rTMS is endorsed by various guidelines for the treatment of MDD (typically for those patients who have failed to respond to at least one antidepressant) (e.g. Malhi et al., 2021; Milev et al., 2016). rTMS has some advantages over ECT. For instance, rTMS does not require general anesthesia and muscle relaxation, it has no cognitive side effects, and is free from negative social/media perceptions (Abdelnaim et al., 2019). Since depressive episode is the most frequent underlying psychopathology in suicide victims and rTMS has antidepressant effects, the question arises whether rTMS treatment also has suicide protective effects (Abdelnaim et al., 2019). Several trials have been conducted and systematic reviews are also available. Unfortunately, almost all studies have methodological shortcomings (such as using rTMS as an add-on treatment to antidepressants; small sample size; retrospective design; exclusion of subjects with high levels of suicidality; lack of sham control). Furthermore, the application of heterogeneous rTMS parameters (e.g. site/frequency/intensity of the stimulation) in different studies makes it difficult to compare and contrast different results (Abdelnaim et al., 2019; Chen et al., 2021; Godi, Spoorthy, Purushotham, & Tikka, 2021; Serafini et al., 2021).

A recently published meta-analysis of 9 sham-controlled studies in MDD patients found that the reduction in the severity of suicidal ideations was more pronounced among those who received active treatment (Cui et al., 2021). By contrast, another meta-analysis of 6 other sham-controlled studies was unable to confirm that the efficacy of active rTMS is superior in treating suicidal ideation in subjects with mainly MDD (Mehta et al., 2022). A third meta-analysis of five controlled studies on the safety of rTMS in MDD found no difference in suicide attempts between active and sham TMS treatment groups (Wang et al., 2022). Finally, authors of a recent systematic review also concluded that they cannot recommend rTMS in the treatment of acute suicidal ideations (Chen et al., 2021). Accordingly, current evidence does not support the efficacy of rTMS in the treatment of suicidality in MDD subjects.

5.3.3. Transcranial direct current stimulation for the prevention and treatment of suicidal behavior

Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation method with some advantages (e.g. ease of use and low costs) over similar treatment modalities (Lefaucheur et al., 2017). It was investigated in the treatment of MDD but solid evidence supporting its efficacy (especially administered as a monotherapy) in this indication is still lacking. Accordingly, treatment guidelines either do not support the clinical use of tDCS in MDD or recommend it only as a third-line treatment (Malhi et al., 2021; Milev et al., 2016; Wang et al., 2021). Almost no data exist on the impact of tDCS on suicidality. Systematic reviews identified only one RCT which found that active tDCS was more effective against suicide ideations than sham (Brunoni et al., 2014; Chen et al., 2021). Another systematic review could not identify any tDCS study in completed suicide (Wilkinson et al., 2022). Due to the scarcity of data, the role of tDCS in the treatment of suicidality cannot be established.

5.3.4. Other biological therapies for suicide prevention

A few other types of biological and neuromodulatory interventions have been tested in suicide. It is not possible to conduct a meta-analysis on the effects of Vagus Nerve Stimulation (VNS) on suicide-related outcomes (Aaronson et al., 2017), while studies assessing the effect of Magnetic Seizure Therapy showed only limited efficacy and need to be adequately replicated. Finally, the results of a small pilot trial demonstrated that adjunctive Triple Chronotherapy was feasible and tolerable in acutely suicidal and depressed inpatients (Sahlem et al., 2014). Still, the small number of participants, open label design, and lack of a comparison group do not allow for generalization of the findings.

6. Conclusion

Prevention of suicidal behavior has come a long way following the first large decline in suicide rates in the 1990s, largely thanks to the

better recognition and treatment of depression with the introduction of widely available and well-tolerated antidepressants. However, in spite of evidence concerning the antisuicidal properties of some traditional drugs like lithium, recent advances in the field of pharmacotherapy leading to drugs acting on novel targets such as esketamine, increasing investigation of neuromodulatory and biological therapies in suicidal behavior, and the development and randomized controlled trials of suicide-specific psychotherapies, suicide and suicide attempt rates remain high in certain groups such as young adolescents, the elderly, and in psychiatric patients. This is in part due to our lack of reliable and specific suicide risk factors as well as precision predictive tools to identify those at risk. We thus need further research to foster an in-depth understanding of the complex pathophysiological mechanisms, including biological and psychosocial processes driving suicide risk, to develop effective and accurate markers for screening and developing novel treatments targeting these etiological processes, and to aid currently available and future treatments to reduce the risk of suicide and to save the lives of our patients.

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Declaration of Competing Interest

MP took part in advisory boards and educational activities on intranasal esketamine, receiving occasional fees for consultations or lectures by Janssen, which are unrelated to this article. In the last two years, he has received lectures or advisory board honoraria or engaged in clinical trial activities with Angelini, Lundbeck, Janssen, Pfizer, MSD, and Recordati. The other authors declare no conflicts of interest.

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