

Predicting Suicidal Ideation and Attempts Using Biomarkers: Hope for Death Prevention in a Depressed Society

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Abstract

Suicide is a global health crisis with complex psychological, social, and biochemical dimensions. Despite numerous prevention efforts, a focus on the biochemistry of suicide offers new avenues for identifying those at risk and understanding the molecular mechanisms and interventions. This article reviews the biochemical mechanisms underlying suicide and the possible use of biomarkers to predict suicide ideation and attempts in humans. Information used for this review was obtained from several search engines such as Pubmed, Google Scholar, EMBASE, and AJOL. Evidence indicates that neurotransmitter imbalances, hormonal dysregulation, neuroinflammation, genetic predispositions, serotonin, dopamine, and noradrenaline imbalances, and stress hormones like cortisol contribute to suicidal behavior. Immune system dysregulation, inflammatory markers, and genetic or epigenetic modifications also play key roles in suicidal ideation and attempts. Findings suggest that understanding these biochemical factors can guide the development of early detection and targeted interventions, including pharmacotherapy and dietary adjustments. Such biochemically informed approaches could complement traditional psychological treatments, potentially reducing suicide ideation and attempts in humans.

Keywords

Suicidal Ideation, Biomarkers, Humans, Suicide, Risk Factors

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1. Introduction

With suicide rates rising across a range of populations, it has become a major global public health problem. It is a serious worldwide health concern that impacts people, families, and communities everywhere. According to the World Health Organization, nearly 700,000 people die by suicide every year, with many more attempting it [1] (World Health Organization, 2024). Suicide is a highly complex and heterogeneous phenotype with numerous underlying psychological, environmental, neurological, and genetic mechanisms [2] (Cheung *et al.*, 2020). The alarming statistics of suicide globally necessitate the urgency required to address this issue from multiple perspectives, including mental health, societal influence, and biological processes.

From a social perspective, factors like poverty, unemployment, discrimination, abuse, and a lack of access to mental health care services play a significant role in the prevalence of suicide. Psychological factors, including mental health disorders such as depression, anxiety, and substance use disorders, have a strong association with suicidal behavior [3] (Akkus *et al.*, 2022). This review explains one of the lesser discussed dimensions, the biochemistry of suicide, and explores how understanding this aspect can provide insights into identifying those at risk and prevention strategies.

Understanding the biochemistry behind suicidal behavior is crucial for addressing the complex issue of suicide from its roots. Suicide is often seen as the result of emotional, psychological, and social pressures, but emerging research emphasizes that biological factors, particularly biochemical processes in the brain, play a significant role. Investigating these biochemical processes offers a deeper understanding of how certain mental health disorders can exacerbate suicidal ideation and actions [4] (Mueller *et al.*, 2021).

Biochemical processes in the brain, including neurotransmitter activity, hormonal regulation, and genetic predispositions, are closely interrelated with mental health. Imbalance in neurotransmitters like serotonin and dopamine have been linked to depression, anxiety, and impulsive behavior, all of which are risk factors for suicide. Additionally, stress hormones such as cortisol, when dysregulated, can amplify feelings of despair and hopelessness. These biochemical irregularities create a vulnerable state where individuals may be more prone to suicidal thoughts and behaviors. A better understanding of these biochemical interactions is crucial for improving mental health support and identifying at-risk individuals [5] (Tasfi and Mostofa, 2024).

Addressing the global health crisis surrounding suicide is crucial. Biomarkers offer valuable insights by serving as predictive indicators, aiding in diagnostic differentiation, providing evidence of treatment response, and highlighting potential targets for new therapies [6] (Johnston *et al.*, 2021). Generally defined as objective indicators of a biological state or condition, biomarkers can be detected in various forms, such as changes in protein expression, epigenetic markers, and metabolomics shifts. These changes can be measured in both the central nervous system

(CNS) and the periphery.

This review explores how biochemical processes are interlinked with mental health and how actionable interventions can be implemented based on this understanding. By exploring the biochemical basis of suicide, it is possible to develop more effective prevention strategies that go beyond traditional psychological treatments. A biochemical understanding can inform the creation of targeted interventions such as pharmacological treatments, early diagnosis through the use of biomarkers, and personalized mental health care. This approach will enable healthcare providers to identify at-risk individuals early and offer treatment that directly addresses the biological factors contributing to their suicidal tendencies. Ultimately, understanding how biochemical processes influence suicidal behavior is not only a matter of scientific curiosity but also a vital step to saving lives [7] [8] (Macintyre *et al.*, 2021; Cremone *et al.*, 2023). The goal of this review was to highlight the biochemical factors associated with suicide and the use of biomarkers in identifying those at risk.

2. Method

A thorough search of the literature was carried out utilizing electronic databases, including Google Scholar, PubMed, EMBASE, and AJOL. The following terms and combinations were used: “predictive models,” “genetic factors,” “biomarkers,” “suicidal ideation,” “suicide attempt,” “hormones,” “inflammatory markers,” “neurotransmitters,” and “genetic factors.” The inclusion criteria were original research publications, review articles, and meta-analyses that examined the relationship between biological indicators and suicide ideation or attempts. Studies that did not report on biological markers or that did not use human participants were excluded.

From each included study, pertinent information was taken out, such as study participant characteristics, statistical analysis, biomarker evaluation techniques, and conclusions. Common themes, contradictions, and gaps in the literature were found by synthesizing and analyzing the retrieved material. To evaluate the methodological rigor, limits, and potential biases of the included studies, a critical appraisal was conducted. The results of the included research were analyzed with regard to their clinical relevance and the body of existing literature. It explored how biomarkers may be used to predict suicide thoughts and attempts, as well as the difficulties and constraints of existing studies.

3. Causes of Suicide

A combination of several factors, which could be individual and social, contribute to the risk of suicide. Specific risk factors for suicide in most societies include mental health disorders, substance misuse and abuse, relationship challenges, physical pains, financial or job challenges, cultural or religious beliefs, previous suicide attempts, family history of suicide, and possession of firearms [9] (Kaliszewski, 2022).

3.1. Mental Health and Substance Abuse

Some authors have reported that substance use disorder (SUD) is a recurrent risk factor for suicide in America [10] (Lynch *et al.*, 2020). When other substantial risk variables are taken into account, substance use disorders are still linked to a high risk of suicide mortality, particularly for women. It is very dangerous to have several substance use problems. The authors concluded that there is a need for more screening for suicide risk and preventative initiatives for people with drug use disorders [10] (Lynch *et al.*, 2020). Additionally, it was proposed that individuals with SUDs would benefit from more frequent screening for suicide risk. This might involve continuing suicide risk monitoring while receiving treatment or screening for suicide risk upon enrolling in drug abuse treatment programs. Literature has shown that women may be reluctant to seek care for substance use conditions compared to men; therefore, women are diagnosed with more severe conditions than men. Women who use drugs should have access to proper treatment, and treatment of substance use disorders must have a gender perspective [11] (Fonseca *et al.*, 2021). A study by Wilkins *et al.* (2022) [12] highlights the increasing rates of suicide among individuals with comorbid mental health disorders and substance use. Their research emphasizes that individuals struggling with addiction are at a significantly higher risk for suicidal thoughts and behaviors. The majority of persons who experience the symptoms of a mental health disease do not end their lives by suicide, and mental illness by itself does not cause suicide. On the other hand, mental illness is one of the risk factors that might increase a person's chance of having suicidal thoughts, making an attempt at suicide, or passing away. People who are being treated or assessed primarily for a mental health problem or suicidal thoughts are often screened for suicide risk by the majority of U.S. hospitals or health care systems. But, since there isn't a single cause or sign of suicide, some medical facilities have begun to check all patients for this risk in a procedure known as universal screening. Available data indicate that universal screening for suicide risk helps medical professionals better identify individuals who are at risk so they can be connected to appropriate care and services (Akkas and Corr, 2022) [13].

Disclosure of suicidal ideation, an early stage of the suicidal process, is frequently essential to suicide prevention initiatives. Data from the Health Monitor 2016 Dutch cross-sectional survey showed that five percent of the adult participants reported having suicide ideation, while over half of them had not. Non-disclosure was, therefore, a significant issue that may impede attempts to prevent suicide. In addition to being less likely to report frequent suicide ideation and poor mental health, adults who did not reveal suicide ideation were more likely to have few social interactions [14] (Bradvik *et al.*, 2018). This underscores the need for laboratory evaluations of these subjects. During the COVID-19 epidemic, unexpected behavioral changes could have had a role in the rising trend of reported suicide attempts.

3.2. Impact of COVID-19

A systematic review by Thakur and Jain (2021) [15] explored the psychological effects of the COVID-19 pandemic, indicating a rise in suicidal ideation linked to social isolation, fear of infection, and economic uncertainty. The authors found that the pandemic exacerbated pre-existing mental health conditions, contributing to increased suicide rates. According to the current study, a rising trend in suicide attempts during the COVID-19 pandemic compared with pre-pandemic rates has been reported. Before the COVID-19 pandemic, a review conducted in 2020 to identify suicidal behaviors and ideation during developing viral illness outbreaks discovered evidence of a large increase in suicide fatalities and suicidal attempts during emerging viral disease outbreaks [16] (Leaune *et al.*, 2020). During the COVID-19 epidemic, unexpected behavioral changes could have had a role in the rising trend of reported suicide attempts. Given the significance of averting suicide attempts and fatalities brought on by the COVID-19 pandemic, it is imperative that those exhibiting suicidal tendencies be identified early and treated promptly (Pathirathna *et al.*, 2022) [17].

3.3. Socioeconomic Factors

Qiu *et al.* (2023) [18] examined the relationship between socioeconomic status and suicide risk. The study found that individuals facing economic hardships, such as unemployment and low income, are more likely to experience suicidal thoughts and actions. The authors suggest that social support systems are critical in mitigating these risks (Qiu *et al.*, 2023) [18]. Suicidal thoughts were linked to a higher risk of working in precarious situations (job insecurity, part-time work), long workdays, job status changes, shift and night work, and occupational stress. The studies demonstrate that age and gender have an impact on the degree of correlation between a specific risk factor and suicidal behavior. Thus, it was shown that poor educational attainment was a risk factor for suicide attempts and completed suicides, particularly for women and younger individuals, and that wealth had a particularly high impact on males. There were differences in occupational pressures across the sexes as well; suicidal ideation was linked to interpersonal conflict for women and inadequate job control for males. Low socioeconomic status also seems to raise the likelihood of suicidal thoughts and actions. The included studies were unable to determine whether or not residence had an impact on the three suicidal behaviors under investigation (Naher *et al.*, 2020; Raschke *et al.*, 2022) [19] [20].

3.4. Cultural Influences

Pompili *et al.* (2022) [21] investigated the role of cultural attitudes toward mental health and suicide. Their findings indicate that cultural stigma can prevent individuals from seeking help, which increases their risk of suicide. The authors advocated for culturally sensitive interventions to improve mental health outcomes in diverse populations. Suicide and mental illness rates are influenced by social

variables. Suicide patterns and kinds vary with culture, as seen in India and Japan. Suicidal thoughts and intentional self-harm can be influenced by cultural norms and beliefs. Understanding cultural influences and how they may contribute to suicide is essential for clinical evaluations and treatment (Watson *et al.*, 2024) [22]. The cultural context a person is exposed to has an impact on their suicidal thoughts and attempts. Culture gives people coping skills, but as civilization develops, many of these coping mechanisms are eroded, exposing susceptible individuals to suicidal ideation. A systematic approach to education and re-orientation is required to stem the tide of the public health challenge. Deliberate attempts to focus on important culture-based therapies were recommended (Maharajh and Abdool, 2005) [23].

3.5. Digital Influence

According to research conducted in 24 countries, the incidence of mobile phone addiction is rising globally between 2014 and 2020, with significant regional variations. According to earlier research, the incidence of mobile phone addiction among college students varies by country, ranging from 14% to 48% [24] (Zhong *et al.*, 2022). Numerous research conducted in China has revealed a very high rate of juvenile mobile phone addiction (Tao *et al.*, 2018) [25]. The available data on the relationship between mobile phone addiction and the increased likelihood of suicide without gender bias was extended by a large population study that found that students with mobile phone addiction had a significantly greater prevalence of suicide [26] (Wang *et al.*, 2024). A study on the impact of social media on suicide risk reported how exposure to online content related to suicide and self-harm can lead to an increase in suicidal ideation among adolescents. The authors call for increased monitoring and intervention strategies in digital spaces to reduce this risk (Mendes *et al.*, 2023) [27].

4. Biochemistry of Suicide

Suicide is defined as the deliberate act of taking one's own life (Motillon-Toudic *et al.*, 2022) [28]. It does not only affect the individual but also leaves devastating impacts on families, friends, and communities. The implications of suicide stretch far beyond the immediate loss, as it often signals deeper struggles within an individual's mental state, ranging from depression and anxiety to hopelessness and emotional pain. The multifaceted nature of suicide demands a deeper exploration of the underlying causes, among which the biochemical processes in the brain play a crucial role (Yagci *et al.*, 2021) [29]. In particular, suicidal ideation is described as contemplating or planning to commit suicide, while suicide attempts are non-lethal, self-directed, injurious behavior with an intent to die [6] (Johnston *et al.*, 2021).

Research has identified several neurobiological factors involved in suicidality across various mental disorders. These include neurotransmitter imbalances, structural brain abnormalities, HPA axis dysfunction, genetic predispositions,

and neuroinflammation [30] (Sessa *et al.*, 2024). For example, imbalances in serotonin, norepinephrine (NE), and dopamine (DA) levels are strongly associated with mood disturbances and impulsivity, which are common precursors to suicidal acts. Furthermore, structural alterations in brain regions that are responsible for emotion regulation and decision-making, such as the prefrontal cortex, amygdala, and hippocampus, have been found in individuals with a history of suicide attempts [30] (Sessa *et al.*, 2024).

4.1. Serotonin

Serotonin is a monoamine synthesized by the rate-limiting enzyme tryptophan hydroxylase (TPH1 and TPH2) from the amino acid tryptophan [31] (Vargas-Medrano *et al.*, 2020). It is associated with a variety of functions in the nervous system, such as mood and anxiety, sleep, aggressiveness, appetite, feeding, and social behavior, among many others. Dysregulation in serotonin expression, its receptors, and transporters has been linked to various neuropsychiatric disorders, such as major depressive disorder (MDD), bipolar disorder, and schizophrenia (Pourhamzeh *et al.*, 2021) [32]. Serotonin, or 5-hydroxytryptamine (5-HT), is particularly important in determining an individual's threshold for suicidal impulses because of its association with impulsive/aggressive personality traits (Tatayeva *et al.*, 2024) [33]. As a neurotransmitter, serotonin transmits chemical messages to neurons in the central and peripheral nervous systems [34] (Kanova *et al.*, 2021). Notably, dysregulation of the serotonergic system was one of the first major findings that differentiated biomarkers of suicide from other neuropsychiatric disorders (Azmitia, 2020) [35]. In a CSF study, decreased expression of the serotonin metabolite 5-HIAA was observed in suicide attempters compared with non-attempters [36] (Hoertel *et al.*, 2021).

The serotonergic decrease is directly implicated in depression, obsessive, and impulsive tendencies, leading to increased vulnerability to suicidal behavior in adolescents and adults [31] (Vargas-Medrano *et al.*, 2020). There is compelling clinical and genetic evidence that the serotonin transporter (SERT) plays a critical role in suicide. An imaging study in individuals with depression and those who attempted suicide showed a low abundance of SERT in the midbrain and higher serotonin_{1A} receptors in the raphe nuclei [31] (Vargas-Medrano *et al.*, 2020).

4.2. Dopamine

Dopamine (DA), a catecholamine, is synthesized through a two-step process where tyrosine is converted into L-DOPA, a reaction catalyzed by tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis [31] (Vargas-Medrano *et al.*, 2020). Dopamine plays a critical role in movement control by influencing specific types of neurons within the brain's motor circuits. This discovery originally explored in relation to Parkinson's disease, suggests that dopamine's regulation of movement is just as integral as its role in reward signaling [37] (Northwestern University, 2023).

Dopamine, alongside serotonin, has a distinctive impact on social interactions [38] (Mount Sinai, 2024). Dopamine influences the speed and accuracy of decisions by modulating activity in brain regions associated with choice evaluation [39] (University of Cologne, 2023). Recent studies have shown a strong correlation between dysfunctions in dopaminergic systems and suicide [40] (Pizzagalli *et al.*, 2019). Inside the brain, dopamine functions as a neurotransmitter and neuro-modulator and is controlled by a set of mechanisms common to all monoamine neurotransmitters (Seeman, 2009) [41].

Analysis of key dopaminergic markers, including the dopamine transporter (DAT) and dopamine receptors D1 and D2, revealed an imbalance in D1 and D2 receptor levels in the dorsal striatum of individuals who died by suicide compared to controls. A significant reduction in DAT and D1 receptor levels correlated with age. However, mean receptor binding in the striatum did not differ between suicide victims and controls [42] (Fitzgerald *et al.*, 2017). Additionally, a reduction in dorsal striatal gray matter was observed in adolescents with suicidal behavior, highlighting the importance of the dorsal dopaminergic system in suicide vulnerability [43] (Ho *et al.*, 2018).

Dysregulation in the dopaminergic system can result in anhedonia (loss of pleasure), reduced motivation, and depressive symptoms—key risk factors for suicide. Disrupted dopamine transmission affects the brain's reward circuits, contributing to feelings of hopelessness and diminished life satisfaction [30] (Sessa *et al.*, 2024). Peripheral measures of dopamine activity, such as plasma levels of homovanillic acid (HVA), a major dopamine metabolite, offer indirect insights into central dopaminergic function. Reduced plasma HVA levels have been linked to suicidal behavior in depressed patients. Similarly, cerebrospinal fluid (CSF) studies have shown decreased CSF HVA levels in individuals with suicidal tendencies, especially those with major depressive disorder and schizophrenia. These findings suggest a deficiency in central dopaminergic activity [44] (Vismara *et al.*, 2020).

4.3. Nonadrenaline

Noradrenaline, also called norepinephrine (NE), is another catecholamine synthesized from tyrosine [45] (Gonzalez-Lopez and Vrana, 2020). Noradrenaline functions as a neurotransmitter in both the central and peripheral nervous systems, where it regulates cognitive functions, motivation, and impulsivity, among other roles [31] (Vargas-Medrano *et al.*, 2020). Similar to serotonin, dysfunction in noradrenergic neurotransmission is well-documented as a contributing factor to depression and suicide, supporting the monoamine hypothesis [46] (Sasamori *et al.*, 2019).

Elevated or dysregulated norepinephrine levels can exacerbate anxiety and stress. Imbalances in norepinephrine can lead to hyperarousal, irritability, and heightened stress responses, increasing suicidal ideation [30] (Sessa *et al.*, 2024). Several polymorphisms have been identified in key components of the noradrenergic system,

such as dopamine β -hydroxylase (D β H), the norepinephrine transporter, and norepinephrine receptors. These genetic variations, including insertions, deletions, or amino acid changes, have been strongly associated with depression, addiction, and suicide [45] (Gonzalez-Lopez and Vrana, 2020).

4.4. Inflammatory Cytokines

Cytokines are a group of proteins secreted by different cells that operate as signals between the cells in order to regulate the immune system. Dysregulations of cytokines have been observed in different psychiatric disorders, including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ) [47] (Dubois *et al.*, 2018). A study reported altered levels of some peripheral cytokines in patients with MDD compared to healthy controls, highlighting that cell-mediated immune activation may be a relevant aspect of MDD [48] (Kohler *et al.* 2017). Moreover, a meta-analysis by Capuzzi and colleagues in 2017 described the potential role of some cytokines as a state (decreasing after antipsychotic treatment) and trait markers (remaining stable independently from antipsychotic treatment) of illness in first-episode psychotic patients [49] (Capuzzi *et al.*, 2017). In addition, studies have reported that even individuals experiencing suicidal behaviors may present alteration in inflammatory cytokines such as interleukin (IL)-2, IL-4, and transforming growth factor (TGF)- β in suicidal subjects than both non-suicidal patients and healthy controls, thus supporting the hypothesis of altered inflammatory markers in patients with suicidal behavior independently form a mental disorder [50] [51] (Gonda *et al.*, 2023; Liu *et al.*, 2024). Moreover, some clinical studies found a positive association between plasma IL-6 levels and suicidal behaviors with violent methods, albeit others reported the opposite [52] (Eidan *et al.*, 2019). Furthermore, Cytokine dysregulation plays an important role in neuroinflammation establishment [53] (Sørensen *et al.*, 2023). Dysregulation of the immune system led to the hypothesis that cytokines are risk markers for suicide in adolescence, as early evidence suggested. Following this thought, data has shown that certain pro-inflammatory cytokines are risk markers for suicide. A study conducted by Amitai *et al.* (2019) [35] measured cytokines in adolescent suicide victims and found elevated levels of cytokines in comparison to the control group [35] (Amitai *et al.*, 2019).

Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), and interleukin-1 beta (IL1b) are commonly observed in individuals with major depressive disorders and suicidal behavior [54] (Kang *et al.*, 2024; Harsanyi *et al.*, 2023) [55]. These cytokines can cross the blood-brain barrier and affect brain regions involved in mood regulation, such as the prefrontal cortex and hippocampus, leading to altered neurotransmission and neuronal function [56] (AbdElmageed and Hussein, 2022).

4.5. Microglial Cells

Microglia are the brain's resident immune cells. Microglial cells, the immune cells

of the central nervous system, have been shown to play a role in regulating inflammation in the brain. In response to chronic stress or systemic inflammation, microglia can become overactivated, releasing pro-inflammatory cytokines and neurotoxic substances [57] [58] (Cai *et al.*, 2022; Wang *et al.*, 2023). Persistent microglial activation can result in neuroinflammation, synaptic dysfunction, and neuronal damage, contributing to mood disturbances and cognitive impairments associated with suicidal behavior [56] (AbdElmageed and Hussein, 2022). Specifically, chemokines were frequently found to be downregulated in the brains of individuals who died by suicide [59] (Shinko *et al.*, 2020), a pattern that was not observed in other neuropsychiatric disorders [60] (Leighton *et al.*, 2018).

4.6. Cortisol

The HPA axis involves neuroendocrine feedback interactions among the hypothalamus, anterior pituitary, and adrenal cortex. The hypothalamus releases corticotropin-releasing hormone (CRH) to the anterior pituitary, stimulating the release of adrenocorticotrophic hormone (ACTH). This, in turn, triggers the adrenal cortex to secrete cortisol, the main stress hormone [2] (Cheung *et al.*, 2020). Cortisol, in turn, induces several biochemical changes, such as increasing protein and fat mobilization, gluconeogenesis, increasing access to energy stores, and controlling the inflammatory response [61] (Peeters *et al.*, 2017).

It is worthy of note that baseline cortisol levels, total cortisol output, and cortisol reactivity during the Trier Social Stress Test (TSST) did not differentiate between suicide attempters and non-attempters. However, a heightened cortisol response was noted in a subgroup of suicide attempters with high impulsive aggression [62] (Stanley *et al.*, 2019). The TSST also revealed that individuals with brief episodes of suicidal ideation had a greater cortisol response compared to those with longer-lasting suicidal thoughts [63] (Rizk *et al.*, 2018). This suggests that HPA axis dysfunction may serve as both a biomarker and a potential target for therapeutic interventions in preventing suicide.

4.7. Gene Expression Markers

In research that used RNA-Seq to precisely assess gene expression in dorsolateral prefrontal cortex (DLPFC) from major depression disorder suicides (MDD-S, N = 21), depressed non-suicides (MDD-NS, N = 9), and controls (N = 29), it was discovered that both MDD groups had notable changes in the spermidine/spermine N1-Acetyltransferase1 (SAT1) gene [64] (Pantazatos *et al.*, 2015). SAT1 dysregulation and notable glial cell changes in MDD-S were documented in a related investigation [65] (Pantazatos *et al.*, 2016). According to translational studies, blood SAT1 expression may be a peripheral suicide biomarker for men [66] (Niculescu *et al.*, 2015), but not for females [67] (Levey *et al.*, 2016). This suggests a sex-specific impact that is not frequently considered in suicide research.

Mamdani *et al.* (2022) [68] used a targeted gene expression approach to assess

relevant suicide-specific biomarkers in victims, and four genes were shown to have highly significant differential expression in blood and brain. Between the blood and the brain, two of these genes: Period circadian regulator 3 and SRY Box Transcription factor 9 (PER3 and SOX9), exhibited comparable directionality, whereas two telomeric repeat binding factor 1 and beta lymphocyte antigen 19 (TERF1 and CD19) had opposite directions. Because the brain and blood may not be subjected to the same metabolic environment or stress-related stimuli, which might affect the expression levels for particular genes, the two organs' differences in direction are comprehensible. It has previously been demonstrated that MDD-S patients had lower levels of SOX9, an astrocytic marker in the brain and a B cell marker in the blood, in the prefrontal cortex when compared to controls. The findings demonstrated that, in comparison to MDD-NS, SOX9 expression is markedly lower in the brain and blood of MDD-S patients [68] (Mamdani *et al.*, 2022). Genetic variations in specific genes, such as those involved in serotonin and dopamine pathways, may increase susceptibility to suicidal behavior. Gene expressions associated with suicide, such as PER3, mitochondrial poly (A) polymerase (MTPAP), solute carrier Family 25 Member 26 (SLC25A26), and SOX9, have been identified to provide useful information for understanding molecular changes in suicide. These are essential biomarker signatures in blood to aid identification of subjects at high risk for suicide [68] (Mamdani *et al.*, 2022).

Epigenetic research has revealed that environmental stressors can lead to modifications in gene expression without altering the underlying DNA sequence. Methylation of the serotonin transporter gene (SLC6A4), for example, has been associated with increased suicide risk [69] (Hidalgo *et al.*, 2020). This study found that early life stress can lead to long-lasting epigenetic changes, which may influence vulnerability to suicidal thoughts and actions later in life (Rodríguez-Hidalgo *et al.*, 2020) [69]. These findings emphasize the importance of both genetic predisposition and environmental factors in understanding suicide risk.

5. Biomarkers of Suicidal Ideation and Suicide Attempt

Suicidal behavior prediction has historically proven difficult, especially as it depends on subjective metrics such as patient accounts of conduct, ideation, and family history. The predictive validity of suicidal ideation for suicide attempts overlaps with other neuropsychiatric disorders, and cultural differences in attitudes toward suicidal ideation or behavior that can affect reported suicide rates across nations are additional challenges [70] [71] (Miranda *et al.*, 2008; King *et al.*, 2014). The biggest obstacles in suicide research, according to a poll of academics and clinicians, include low baseline rates of suicidal behavior, small sample sizes in intervention studies, and issues transferring findings across disciplines [72] (O'Connor and Portzky, 2018).

Finding useful biomarkers to measure suicidal thoughts and suicide attempts is essential in this situation. The following are some of the markers evaluated in an attempt to find reliable markers for the prevention of suicide (Table 1).

Table 1. Biomarkers of suicidal ideation and attempt.

Biomarkers	Type of Specimen	Subjects Evaluated	Suicide Ideation	Suicide Attempt	Reference
BNDF	Blood	Psychiatric		No association was found between BDNF levels and SA	Eisen <i>et al.</i> , 2016 [73]
BNDF	Blood	MDD non-suicidal		No differences were found between MDD non-SA and SA groups	Pedrotti Moreira <i>et al.</i> , 2018 [74]
BNDF	Blood	MDD non-suicidal, HCs, SI	Serum BDNF levels differentiated non-suicidal MDD from MDD with SI, as well as mild-to-moderate SI. Lower BDNF levels were associated with increased SI		Khan <i>et al.</i> , 2019 [75]
Dopaminergic (HVA)	CSF	Psychiatric controls, HCs, SA		HVA levels were significantly lower in SA	Hoertel <i>et al.</i> , 2021 [36]
Glucocorticoid (Cortisol)	Saliva	SA impulsivity/aggression subtypes, non-SA		Higher cortisol response differentiated an SA subgroup with high impulsive aggression	Stanley <i>et al.</i> , 2019 [62]
Inflammatory marker (CRP)	Blood	SI, SA, HCs	Reduced CRP levels in SI compared to SA	Increased CRP levels in SA compared to SI	Melhem <i>et al.</i> , 2017 [76]
Inflammatory marker (CRP)	Blood	MDD, non-suicidal, HCs	Increased CRP levels in suicidal MDD compared to non-suicidal MDD and HCs	Increased CRP levels in suicidal MDD compared to non-suicidal MDD and HCs	Chen <i>et al.</i> , 2020 [77]
Inflammatory markers: Cytokine profile (IL-6, IL-10, IFN- γ , TNF- α , and CRP)	Blood	MDD, HCs	TNF- α at baseline significantly predicted SI over a 12-wk period		Choi <i>et al.</i> , 2021 [78]
Inflammatory marker (IL-6)	Blood	Depression and anxiety disorders treated with fluoxetine	IL-6 levels were higher in youth who developed treatment-associated SI		Amitai <i>et al.</i> , 2020 [35]
Inflammatory marker (NLR, PLR, and MLR)	Blood	MDD non-suicidal, SA		Higher ratios of NLR and PLR were found in those with a history of SA. NLR was significantly associated with suicidal behavior	Velasco <i>et al.</i> , 2020 [79]

Continued

Lipid profile (TC, LDL-c, TG)	Blood	Psychiatric controls, SA	No association between lipid profile and SA	Capuzzi <i>et al.</i> , 2018 [49]
Serotonergic (Serotonin)	Blood	BD type I non-attempters	Reduced levels in attempters compared with non-attempters, and lower levels in those who used a high-lethality method compared with low-lethality	Giurgiuca <i>et al.</i> , 2016 [80]
Circadian genes: period circadian regulator 3 (PER3) and PER2 MTPAP (Mitochondrial Poly(A) Polymerase), SLC25A26 (Solute Carrier Family 25 Member 26), CD19 (B-Lymphocyte Antigen CD19), and GAR1 (GAR1 Ribonucleoprotein) while SOX9 (SRY- Box Transcription Factor 9)	Blood	MDD-S and MDD-NS	Upregulated in MDD-S than MDD-NS Decreased in suicide than non-suicide MDD	Mamdani <i>et al.</i> , 2022 [68]

BA: Brodmann's area; BDNF: brain derived neurotrophic factor; BD: bipolar disorder; CRP: C-reactive protein; CSF: cerebrospinal fluid; HDL-c: high-density lipoprotein cholesterol; HVA: homovanillic acid; IFN- γ : interferon gamma; IL-6: interleukin 6; IL-8: interleukin 8; IL-10: interleukin 10; LDL: low-density lipoprotein; LDL-c: low-density lipoprotein cholesterol; MDD: major depressive disorder; MLR: mixed lymphocyte reaction; NLR: neutrophil-lymphocyte ratio; SA: suicide attempt; SERT: serotonin transporter; SI: suicidal ideation; SRB: suicide risk behavior; SSI: Scale for Suicide Ideation; TC: total cholesterol; TGC: triglycerides; TNF- α : tumor necrosis factor alpha.

6. Current Methods for Preventing Suicide

People in distress or at risk of suicide conduct can benefit from a number of efficient strategies. Safety planning, crisis response planning, and counseling to restrict access to fatal methods are short-term therapies that provide skills to handle suicidal crises and minimize suicidal tendencies. Evidence-based treatments have also been demonstrated to reduce suicidal thoughts and behaviors. These include cooperative assessment and management of suicidality, attachment-based family therapy [81] (Diamond *et al.*, 2021), cognitive behavioral therapy for suicide prevention, dialectical behavior therapy [82] (De Cou *et al.*, 2019), and prolonged grief disorder therapy for individuals who have lost a loved one to suicide. Good mental health prevention and intervention techniques may greatly lessen the

negative effects that mental health issues have on people's general well-being.

6.1. Psychotherapy Interventions

The main goal of the medical techniques now used to treat suicidal behavior is to lower risk factors, with a special emphasis on mental diseases, which are significant causes of suicide. The neurobiological causes of mental illnesses are thus the main focus of psychopharmacological therapy for suicide [50] (Gonda *et al.*, 2023). Clinical studies are also being conducted on a variety of psychotherapeutic approaches that aim to treat suicidal thoughts, desires, or recurrences by improving emotion regulation, encouraging adaptive coping strategies, and reducing cognitive processes associated with suicide risk while developing efficacious safety responses.

6.2. Cognitive Behaviour Therapy

One of the most researched and successful psychotherapy approaches for managing suicide is cognitive behavioral therapy [83] (Vesco *et al.*, 2022). Managing a patient's emotions, daily activities, and general cognitive abilities is the aim of cognitive behavioral therapy. To describe a person's suicidal belief system, cognitive behavioral therapy (CBT) involves jointly analyzing negative automatic thoughts and core beliefs. According to Serafini *et al.* (2023) [84], it entails determining triggers during case conceptualization, acquiring skills to handle and avoid suicidal crises in the future, and creating plans for safety and relapse prevention. According to several studies, learned helplessness may be used to predict an individual's level of depression and emotional disorders, and cognitive behavioral therapy can help lessen these problems [85] (Das, 2024).

6.3. Dialectical Behaviour Therapy (DBT)

DBT is based on the biosocial theory, which states that the goal of the therapy is to improve the skills that support better emotion regulation because suicidal and self-harming behaviors are often seen as attempts to cope with intense or painful emotions [86] (Asarnow *et al.*, 2021).

In order to improve relationships and develop adaptive emotion regulation and interpersonal skills, as well as distress tolerance and mindful awareness, DBT focuses on emotional dysregulation brought on by early invalidating environmental experiences, a lack of learned adaptive self-regulatory strategies, and the impulsive and maladaptive behaviors that result from these experiences [84] (Serafini *et al.*, 2023). According to Asarnow *et al.* (2021) [86], this multi-component treatment consists of therapist consultation teams, multifamily group skills training, individual psychotherapy, and telephone coaching available around the clock. Others include problem-solving therapy which is aimed 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 (Serafini *et al.*, 2023) [84]. The psychoanalytic and Psychodynamic therapies approach to suicide prevention emphasizes

understanding the intense emotional pain within an individual's internal experience, including feelings of humiliation, self-hatred, shame, or rage, alongside an urgent need for relief. These approaches also consider factors contributing to suicide vulnerability, such as personality traits, early attachment issues, and dissociation. Through creating a therapeutic space, individuals can explore their thoughts, fears, and fantasies in a supportive environment (Schechter *et al.*, 2022) [87].

6.4. Pharmacotherapy Intervention

Despite recent innovative pharmacological options now available for the management and treatment of suicidal behavior, traditional psychotropic drugs have been documented to exert anti-suicidal properties in the long-term treatment of psychiatric disorders linked to suicide risk. Some authors have reported that lower rates of suicide with greater use of antidepressants in Nordic countries and the USA have been recorded, but these findings have not been replicated elsewhere. Similarly, most meta-analyses reported only minor differences in suicide rates between depressed patients treated with antidepressants or placebo while usually identifying increased suicide risk in children and young adolescents who were treated with antidepressants [88] (Jollant *et al.*, 2023). 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 drugs.

6.5. Antipsychotic Drugs

Based on a large randomized trial (InterSePT) that compared clozapine with olanzapine among suicidal schizophrenia patients and reported lower rates of suicide attempts, the Food and Drug Administration (FDA) approved clozapine as the first antipsychotic medication for the management of suicide risk in schizophrenia patients (Serafini *et al.*, 2023) [84]. Atypical antipsychotics' safety and effectiveness have also been shown in the treatment of bipolar depression, where they have been shown to be beneficial for both depressive symptoms and agitated dysphoric mixed states, which are often linked to an increased risk of suicide.

6.6. The Use of Biomarkers in the Prevention of Suicide

Biomarkers are measurable biological indicators that offer a promising avenue for early identification and intervention in individuals at risk of suicide. Several studies have explored the association between specific biomarkers and suicidal behavior [67] [68] (Levey *et al.*, 2016; Mamdani *et al.*, 2022). Neurotransmitters, such as serotonin, dopamine, and norepinephrine, play a crucial role in mood regulation and impulse control. Dysregulation of these neurotransmitters has been implicated in suicidal behavior [89] (Sanusi *et al.*, 2024). Hormones, such as cortisol and oxytocin, are involved in the stress response and social bonding, respectively. Imbalances in these hormones can contribute to an increased risk of suicidal ideation and attempts [89] (Sanusi *et al.*, 2024). Elevated levels of inflammatory markers,

such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been associated with depression and suicidal behavior [90] (Fernandez-Sevillano *et al.*, 2022).

Evidence has shown that the assessment of the contribution of neuroendocrine parameters, neurotransmitters, inflammatory biomarkers, and gene expression profiles will identify individuals at risk of suicide. Studies have shown significant relationship in the alterations in the serum levels of cortisol, serotonin, hs-CRP, IL-6, and gene expression profile such as PER3, MTPAP, SLC25A26, and SOX9 between suicidal attempters and controls [32] [43] [45] [49] [51] [68] (Capuzzi *et al.*, 2017; Ho *et al.*, 2018; Gonzalez-Lopez and Vrana, 2020; Pourhamzeh *et al.*, 2021; Mamdani *et al.*, 2022; Liu *et al.*, 2023).

Evaluation of these parameters will provide insights into the underlying biological mechanisms of complex traits, such as suicidal behavior. By analyzing the expression of genes involved in neurotransmitter systems, stress response, and inflammation, the identification of subjects at risk will prevent loss of life.

Cortisol can be determined in saliva or blood, while cytokines such as IL-6 and C-reactive protein, serotonin, dopamine, and norepinephrine could be assayed in blood. The suitable methods of the assays include Enzyme-Linked Immunosorbent Assay (ELISA), Radioimmunoassay (RIA), High-Performance Liquid Chromatography (HPLC), Mass Spectrometry (MS), and Polymerase Chain Reaction (PCR) for Gene Expression Biomarkers.

7. Conclusion

This study highlights the critical role of biochemistry in understanding suicide, moving beyond traditional psychological and social explanations by targeting biochemical pathways associated with suicidal behavior. Collaboration among biochemists, healthcare providers, and mental health professionals is essential to translate these findings into effective clinical applications. Expanding research in biomarkers and targeted therapies will further refine preventative approaches, offering hope for reducing suicide rates globally. Enhanced public awareness and investment in biochemical research will be vital for creating a comprehensive, multidimensional approach to suicide prevention.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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