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Psychological and Neurobiological Mechanisms of Suicidal Behaviour: An Integrative Review

OJO Foluso Olamide[1,4], FOLUSO Janet Ifeoluwa[2], HASSAN Luqman Adepoju[1], ADEKUNLE Phebian Funmilayo[3], AWORENI Esther Opeyemi[4], ABIODUN Moses Folorunso[5], OGUNDIRAN Reuben Jesulayomi[4]

[1]Department of Anatomy, Faculty of Basic Medical Sciences, University of Ilesa, Ilesa Nigeria
[2]Department of Health Promotion and Education, Faculty of Public Health, University of Ibadan, Ibadan, Nigeria
[3]Department of Health Education, Faculty of Education, University of Ilesa, Ilesa, Nigeria
[4]Department of Anatomy, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomoso, Nigeria
[5]Department of Medicine and Surgery, Faculty of Clinical Sciences, Ladoke Akintola University of Technology.

Correspondence:
Department of Health Promotion and Education,
Faculty of Public Health,
University of Ibadan, Ibadan, Nigeria
Email ifeoluwaayanlade@gmail.com. Tel: +2347066024929

Abstract

Suicide is a complex, multifactorial phenomenon influenced by an interplay of psychological, neurobiological, and socio-environmental factors. Despite its global prevalence and significant public health impact, the underlying mechanisms of suicidal behaviour remain incompletely understood. This review combines established insights into psychological theories and neurobiological factors involved in suicidal behaviours; and highlights potential therapeutic targets. The major psychological models considered include the interpersonal-psychological theory, attachment theory, and cognitive-behavioural theory. Also, their relevance to suicidal ideation and actions were examined. Moreover, neurobiological factors, particularly the roles of serotonin, norepinephrine, dopamine, and neuro-inflammation, were explored. Psychological models elucidate how factors such as perceived burdensomeness, thwarted belongingness, insecure attachment, and maladaptive cognitive patterns contribute to suicide risk. Neurobiological evidence indicates dysregulation in serotonergic, noradrenergic, and dopaminergic systems, as well as neuro-inflammatory processes associated with increased vulnerability. The integrated motivational-volitional (IMV) model further demonstrates how genetic, neurochemical, and psychological factors interact across the trajectory from suicidal ideation to attempts. Due to the significance of certain brain regions in facilitating emotion regulation, decision-making, and stress responses, understanding the dynamic interplay between psychological constructs and neurobiological pathways is essential for developing effective prevention and intervention strategies. Targeting both cognitive-emotional processes and neurochemical imbalances holds promise for reducing suicide risk. Future research should focus on multidimensional approaches to suicide prevention, especially in high-risk populations.

KEYWORDS: Suicidal Behaviours, Psychological Theories, Depression, Psychological Models

1. Introduction

Suicide, an intentional act of an individual to end their own life is a complex and multifaceted issue that can be influenced by a variety of factors such as neurobiological [1], social-environmental [2], psychological [3], demographic [4], and mental health factors [5] among others. The World Health Organisation (WHO) reported more than seven hundred and three thousand (703,000) suicide cases worldwide annually, making it the fourth leading cause of death among young adults [6], with more female victims [7]. The increasing prevalence of suicide as reported by WHO is becoming a global threat and this necessitates a serious discussion, and finding a possible long-term solution.

Among the factors associated with suicide attempt, psychological and neurobiological factors have significant impacts [8]. This review examines the neurobiological and psychological factors associated with suicide, while also highlighting the potential therapeutic targets.

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2. Theories and models of suicidal behaviours

2.1 Psychological theory

Thomas Joiner in his book titled 'Why People Die by Suicide' [9], narrates the interpersonal-psychological theory of suicide (IPTS) as one major scheme that narrates the psychosocial theories of suicidal ideation which shows the interplay between the psychological factors in an individual and social context that aid suicidal actions. A key element of IPTS is subjective burden [10], a feeling that one is a liability to loved ones and does not add any value. In response to this hopelessness, death could be considered as an option. Another factor is the unfulfilled belonging (11), a feeling of disparity and isolation in an individual, which enhances the thought of ending one's life. Cognitive impairment [12], mood disorders [13], neuropsychiatric conditions [14], inflammation, and stress responses [15] are associated factors with this feeling. Isometsä, (in 2014) explained that the lifetime risk of suicide among individuals with mood disorders is estimated to be between 5% and 6%. This risk can be elevated in certain populations, particularly those with bipolar disorder, where the likelihood of attempting suicide over a lifetime may vary from 25% to 50% [13].

Acquired capability for suicide is not just a willingness to die, as the individual must also have the ability to do so. Such ability results from repeated exposure to chronic stress, pain, and experiences that induce fear, which is known to have a great impact on brain regions such as the amygdala, prefrontal cortex, orbitofrontal cortex, basal ganglia [16], anterior cingulate cortex [17], hippocampus, and insula [18], which control emotions. Dysregulation in these regions may result in suicidal ideation.

2.2 Attachment Theory

Attachment theory is an established model through which psychological and relational contributions to suicidal behaviours may be explored [19]. The theory highlights the fact that an individual's interactions with caregivers during childhood form their beliefs about the self and other people, thereby affecting their affect regulation and social relationships in the future [20]. Secure attachment and insecure attachment [21] are two contrasting factors associated with the attachment theory. Individuals with secure attachment possess a positive view of themselves, resulting in healthy emotions. On the other hand, people with insecure attachments often have the thought of being unworthy, and the fear of abandonment leading to maladaptive coping mechanisms that often increase the risk of suicidal thoughts.

2.3 Cognitive-Behavioural Theory

Cognitive-behavioural theory (CBT) [22] is a psychotherapeutic strategy that illustrates the interplay between thoughts, emotions, and behaviours. The theory affirms that dysfunctional thought patterns play a major role in causing emotional distress and unhealthy behaviours [23]. Depression, a hallmark of suicidal thought has been a matter of discuss as far back as the 1960s [24] when depressed patients were observed to often express distorted and unrealistic negative thoughts.

The cognitive-behavioural theory emphasises cognition and emotion; as it was revealed that thoughts, beliefs, and attitudes have a great influence on emotional responses; with negative or distorted thoughts such as making broad assumptions, exaggerating negative outcomes [25], and viewing situations in extremes often resulting in emotional distress, and maladaptive behaviours.

2.4 Integrated Models of Suicide

A cross-sectional study done by O'Connor and Kirtley 2018 [26] describes which theoretical pathways within the integrated motivational-volitional (IMV) model of suicidal behaviour have been empirically tested, and the phases involved in the suicide ideation, to the execution of suicide were elucidated. The pre-motivational phase [26] involves several biological, neuroendocrine, and genetic factors where individuals may have inherent vulnerabilities due to genetic predispositions that affect their mental health and emotional regulation. These biological and neuroendocrine factors include neurochemical imbalances such as dysfunction of serotonin, norepinephrine [27], dopamine [28], and the hypothalamic-pituitary-adrenal axis [29]; or inherited traits as seen in variations of genes CACNA1C and CACNB2 [30]. Genetic pleiotropy affects calcium channels in neurons, increasing the susceptibility to mood disorders. The motivational phase [31] focuses on the psychological processes that lead to the emergence of suicidal ideation and intent where an individual has feelings of defeat and humiliation, which often result in a sense of entrapment by one's thoughts and emotions or life circumstances where an individual sees self-harm or suicide as a potential solution. The volitional phase [32] is controlled by volitional moderators that are influenced by the likelihood of an individual moving from suicidal thoughts to suicidal attempts, it involves the act of having access to suicidal methods, reduced fear of death [33], increased pain tolerance, impulsivity and planning [34]. The volitional phase also involves cognitive and emotional factors such as mental imagery of suicide, and history of self-harm can play a significant role in the transition from ideation to behaviour.

3. The interplay between neurobiological factors and psychological factors in suicide

Consequent to the recognition of suicide as a threat to public health, researchers have continued to establish a connection point between the neurobiological and psychological factors in suicide. Lee *et al* [35] showed the link between the levels of neurochemicals (dopamine, glutamate, norepinephrine, and gamma-aminobutyric acid) in the brain, particularly serotonin,

and its association with psychological factors [35]. The brain's chemical messengers are often altered by psychological factors in many instances [36]. As earlier stated, the serotonergic system is often influenced by the stress response system, a complex physiological and biochemical process that is activated by the body in response to perceived threats or stressors. It primarily entails the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and various brain regions and neurotransmitters. A study by Murnane [37]I n 2019 found that stress can elevate the serotonin turnover in the brain, causing alterations in serotonin levels and function [37]. Also, there is a relationship between increased risk of suicide, childhood adversity, and trauma that can also result in lasting changes in stress response systems [38]. Beyond its association with serotonin dysregulation, it also involves long-lasting changes in brain function and structures, specifically those associated regions with control of impulse and regulation of emotion (prefrontal cortex, hippocampus, and amygdala). Other important and reoccurring psychological conditions relating to neurobiological alteration in suicidal behaviours are impulsivity and aggression, by their way of affecting the serotonin transporter gene [5-HTTLPR], [39]. A study done by Genis-Mendoza *et al.* [40] shows an increased cortisol level in the hypothalamic-pituitary-adrenal [HPA] axis which is responsible for the regulation of body responses to stress results in impulsivity and aggression, a vital reported behaviour responsible for suicide attempts [40].

Also, there are several reports regarding psychiatric disorders like depression, which is usually associated with a high impact on neurobiological systems such as neurotransmitter circuits [41] neuroendocrine pathways [42], neuroinflammation, and the gut-brain axis [43].

4. Neurotransmitter circuits and suicide

As earlier mentioned, the significance of serotonin; a feel-good neurochemical, norepinephrine; a neurotransmitter responsible for alertness and arousal, and dopamine; a pleasure and reward neurotransmitter which are associated with anhedonia, a key symptom of depression. The identified neurotransmitters in suicide do not solely influence suicidal behaviour, as suicidal attempts only result from the interplay of these neurotransmitters (44). The activities of the dopaminergic neurons in the ventral tegmental area and norepinephrine neurons in the locus coeruleus are widely regulated by the projections of serotonergic neurons from the dorsal raphe nucleus. The firing of the dopaminergic neurons in the ventral tegmental area are generally inhibited by serotonin (by activating 5-HT receptors), which further reduces dopamine release, affecting reward and motivation pathways.

4.1 Serotonin [5-HT] System

There is evidence that the serotonergic [5-HT] system plays a key role in suicidal behaviours. Post-mortem examination of suicidal cases using autoradiography [45], revealed a significant decrease in serotonin transporter binding and an increase in the content of 5-HT1A receptors.

This is probably because these changes are constrained to the anterior cingulate zone and the ventral part of the prefrontal cortex where the serotonin nerve terminals and target neurons of the serotonin system are located. Other aspects include the fact that there is reduced serotonin concentrations and its major metabolite 5-HIAA in the brainstem neurons compared to psychiatric controls. The decreased level of serotonin is not limited to the stated areas. Moreover, serotonin metabolite in the cerebrospinal fluid (CSF) is diminished in individuals who make more lethal suicide attempts and can forecast future suicide risk [27]. This deficiency seems to be evident in both fatal and non-fatal suicide attempts. The lack of sufficient serotonin transmission to brain regions responsible for behavioural control, decision-making, and impulsive aggression (the prefrontal cortex and anterior cingulate) contributes to the risk of suicide; also, a sleep-suicide relationship has been linked with serotonin dysregulation [46].

4.2 Norepinephrine (NE) System

Norepinephrine is one of the neurotransmitters that has previously been identified to be involved in the development of depression, the hallmark of suicide ideation. Norepinephrine α2 receptors are primarily located in the cerebral cortex and locus coeruleus, whereas β receptors, which are crucial for memory consolidation, are located in the basal ganglia, subthalamic nuclei, and deep nuclei of the cerebellum. It was found that dysfunction of the noradrenergic system plays a part in mood disorders, and these are common in those who attempt or commit suicide [47]. For instance, an increased density of norepinephrine has been documented in the prefrontal cortex of subjects who committed suicide, and a reduced density of alpha-2 adrenergic receptors also correlates with cortical over activity of norepinephrine [48]. Inhibition of norepinephrine release was shown to have an association with an increased level of alpha-2 adrenergic receptors in the brains of suicide victims. However, some controversies arise from studies as regards the levels of beta-adrenergic receptors in certain regions of the brain, a study discovered an increase in binding levels [49] while other studies discovered a decreased binding [50]. However, more consistent is the fact that dysregulation of the norepinephrine receptors is generally known and accepted to have an association with suicidal ideation, and such agreement is enough to pay close attention to it in suicide prevention.

4.3 Dopamine [DA] System

Dysfunctions of the dopaminergic system have been discovered in depressed individuals who have severally made suicide attempts [28]. Several pieces of research established the fact that a decreased level of dopamine is associated with suicidal attempts, on the other hand, aggressive behaviour which is an

established risk factor for suicidal behaviours have been kinked with increased dopamine levels.

Studies on the genetic variants of dopamine receptors and their relation with the patients having suicidal tendencies have produced conflicting conclusions. For instance, studies [28, 51] have failed to reveal the changes in dopamine D_1 and D_2 receptor mRNA in the brains of patients with suicidal attempts. However, other studies [52, 53] have in some way pointed at the D_2 receptor function as having an involvement in the manifestation of suicidal behaviour, thus pointing to the possibility of a more complex relationship.

5. Neuro-inflammation

Inflammatory responses within the central nervous system (brain and spinal cord) involves the activation of glial cells, and the release of inflammatory cytokines that are triggered by stress, infection, and injury [54]. The presence of cytokines in the plasma and cerebrospinal fluid confirms their systemic involvement in suicidal ideation. Studies [55, 56] have shown an increased level of the pro-inflammatory cytokine (probably through microglia activation) in an individual who had died by suicide. Moreover, a study done by Harris *et al.*, [57] shows that inflammation also disrupts the tryptophan-kynurenine pathway leading to increased production of neurotoxic compounds such as quinolinic acid. Dysregulation of this pathway impairs glutamate neurotransmission, which is crucial for mood regulation and cognition. Consequently, pro-inflammatory cytokines such as interferon-gamma (IFN-γ), catalyze the first step of the kynurenine pathway resulting in a shift in tryptophan metabolism towards kynurenine production, thereby reducing serotonin synthesis and increasing the levels of neurotoxic metabolites [58].

In addition to the association of inflammation with depression, lower expression of brain derived neurotropic factor (BDNF) has also been linked to suicidal behaviour independent of depression [59], postmortem studies have found a significantly reduced BDNF level in the hippocampus and prefrontal cortex of individuals who died by suicide compared to those who died of other causes [60, 61].

6. Gut-Brain Axis

Clinical trials [62- 65] have established that gut microbiota has been implicated in various psychiatric disorders, including depression, which is often associated with suicidal thoughts. It is believed that dysbiosis, or an imbalance in gut microbiota can lead to neuroinflammation and alterations in neurotransmitter levels, which may exacerbate mood disorders and increase suicide risk. However, Zerekidze *et al.* [66] presented a contrasting opinion, stating no significant relationship between gut microbiome composition and suicidal ideation severity in hospitalised patients [66]. The study acknowledged the possible theoretical relationship; however, the final evidence is not an affirmation of gut microbiota being a predictor of suicidal behaviour. Interestingly, a more consistent report by Zhu *et al*[64]. established the relationship between microbiota and depression [64]. Similarly, Onaolapo *et al* [59] highlighted the association between gut dysbiosis and the pathophysiology of depression, a hallmark of suicidal ideation [59]. Specific changes in microbial populations are known to influence neuroinflammatory processes and neurotransmitter levels, a critical predictor of mood regulation, and production of metabolites; a main factor that affects brain chemistry and behaviour [67].

7. Probable Therapeutic Targets

Despite the wide range of conditions associated with suicidal ideation, our understanding of both the established contributing factors and the continuing search for a solution could probably show us the way forward. Direct pharmacotherapeutic intervention still faces obstacles such as incomplete understanding of underlying neurochemistry. However, interventions that target behaviours are more likely to be successful. Enhancing awareness of the consequences of suicidal actions on valued life goals, as well as strategies to regain a sense of control during crises could serve as great interventions for suicidal ideation that arises from a long-standing conflict between personal goals, and a loss of control [68]. Moreover, cognitive-behavioural therapy (CBT) [22], interpersonal therapy (IPT) [69], motivational interviewing (MI) [70], mindfulness-based interventions [71], psychoeducation [72], group therapy [73], family therapy [74], trauma-informed care, attachment-based therapy [75] and community-based interventions [76] are other probable remedies for suicidal thought.

8. Integrated Models of Suicide

Regulation of catecholamine neurotransmitters such as dopamine, serotonin, and norepinephrine is a vital area of concern in finding a lasting solution to suicidal ideation. Dopamine agonists, such as apomorphine, have been studied for their effect in enhancing dopaminergic activity [48]. A study reveals that reduced growth hormone in response to apomorphine in depressed patients with a history of suicide attempts established the relationship between impaired dopaminergic function and suicide risk [77]. Interventions that modulate the activity of dopamine receptors, either through agonists that stimulate receptor activity or antagonists that block excessive stimulation, may help in managing mood disorders and reducing suicide risk [28].

Findings have continued to show the Potential therapeutic targets in modulating neuro-inflammation, particularly in the context of depression and neurodegenerative diseases, the studies suggest that pro-inflammatory cytokines, such as

Tumour Necrosis Factor Alfa (TNF-α), interleukin- 1beta (IL-1), and interleukin-6 (IL-6), play significant roles in neuro-inflammatory activities through their ability to facilitate the

migration of peripheral immune cells into the central nervous system and ultimately intensify the inflammatory responses, activations of glial cells, particularly, the microglia and astrocytes facilitate the production of the pro-inflammatory cytokines. Studies done by Fields *et al*. [78], Ballerini *et al*. [*79*], Liu *et al.* [80], and Craft [81] show that the use of antibodies or receptor antagonists to neutralize or inhibit these cytokines inhibits neuro-inflammation and its associated neurodegeneration and mood disorders [78-81]. Onaolapo and Onaolapo further suggest that lifestyle modifications, such as dietary changes and physical activity, can positively influence neuro-inflammation by reducing the overall inflammatory burden. Not limited to that, the study also stated some pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and some natural products, including Curcumin and Triterpenoids, and Biflavonoid quercetin, as probable interventions [82].

Moreover, Zhu et al [64]. suggested that modulating gut microbiota through dietary changes, probiotics, or other interventions could represent a novel approach to treating depression [64]. Also, the association between ketamine and the gut microbiome is an emerging area of research, particularly in understanding how ketamine's antidepressant effects may be mediated through interactions with gut bacteria, and its rapid antidepressant effects, particularly in treatment-resistant depression. While it primarily acts as an NMDA receptor antagonist, its broader effects on neuroplasticity and inflammation are also significant. Findings indicate that ketamine administration in animal models significantly changes gut microbiota composition [83]. These changes are associated with improved mood and reduced depressive-like behaviours. This approach may involve combining ketamine therapy with probiotics or dietary interventions aimed at improving gut health. However, the use of ketamine must be properly monitored, as cases have been reported in which repeated administration of ketamine in animal studies is associated with neurotoxicity [84, 85]. Moreover, treatments targeting inflammation have also shown promise in alleviating depressive symptoms [86]. Non-steroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors have been found to reduce depressive symptoms in clinical trials [87]. Cognitive-behavioural therapy (CBT)-based interventions targeting psychological distress correspond with pharmacological treatments modulating dopamine, serotonin, and norepinephrine, creating a complementary therapeutic approach. Furthermore, the psychological theories provide essential frameworks for understanding the cognitive and emotional processes underlying suicidal behaviour alongside neurobiological factors. The psychological theory, central to suicide risk and closely interacts with neurochemical imbalances, including serotonin, dopamine, and norepinephrine dysfunctions, and HPA axis dysregulation. Dysfunction of these neurobiological pathways compromises cognitive control, decreasing the individual's ability to avoid negative thoughts. This supports combining CBT interventions with pharmacotherapy targeting neurotransmitter systems for a better treatment. Also, insecure attachment styles associated with feelings of isolation are influenced by neurochemical disruptions and neuroinflammatory pathways identified in this review. It is important to address both psychological and biological components in prevention and intervention strategies.

Conclusion

This review points out the crucial role of integrating insights from psychological theories and neurobiological research to better understand and address the risk of suicide. Targeting both cognitive-emotional processes and neurochemical imbalances offers a promising path for prevention and intervention. Continued findings into personalized, multidimensional strategies are important to effectively reduce suicide rates, particularly among high-risk populations.

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