

BIOMARKERS FOR SUICIDAL BEHAVIOR: THE NARRATIVE LITERATURE REVIEW

Savižudiško elgesio biožymenys: naratyvinė literatūros apžvalga

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SUMMARY

Introduction. Suicidal behavior remains a complex and pressing public health concern worldwide, necessitating a deeper understanding of its underlying mechanisms to enhance prevention and intervention strategies. Biomarkers, measurable indicators of biological processes or states, offer promising avenues for elucidating the biological underpinnings of suicide risk.

Aim. To review the experience of clinical trials and the most relevant study data regarding the relationship between suicidal behavior and various biomarkers, aiming to emphasize the neurobiological basis of mental health conditions and monitor changes in biomarkers over the course of treatment to enhance patient treatment response.

Methods. Literature search was performed using research published in the PubMed, PsycINFO, and Google Scholar databases, that reviewed the suicidal behavior and relationship between genetic, neuroendocrine, neurobiological, neuroimaging, metabolic and inflammatory biomarkers.

Results. This literature review analyzed 54 articles which investigated the relationship between biomarkers and suicidal behavior. The results suggest that suicidal behavior is influenced by a complex interplay of genetic, neurobiological, neuroendocrine, neurotrophic, inflammatory, metabolic, and neuroimaging markers. Genetic predispositions, particularly involving serotonin-related genes, combined with dysregulations in neurotransmitter systems, hormone levels, and inflammatory processes, contribute to increased suicide risk. Structural brain changes associated with emotional regulation and decision-making further underscore the multifactorial nature of suicide.

Conclusion. The interplay between genetic, neurobiological, neuroendocrine, inflammatory, metabolic, and neuroimaging markers contributes to the understanding of suicidal behavior. Integrating these biomarkers enhances to understanding of suicide etiology and informs the development of more effective prevention and intervention strategies.

Keywords: Suicidal behavior, biomarkers, inflammation, neuroimaging, genes

SANTRAUKA

Įvadas. Savižudiškas elgesys visame pasaulyje išlieka sudėtinga ir opi visuomenės sveikatos problema, kuri reikalauja gilesnio supratimo apie savižudiško elgesio pagrindinius mechanizmus, siekiant gerinti prevencijos ir intervencijos strategijas. Biožymenys yra perspektyvūs rodikliai padedantys geriau suprasti savižudybės rizikos biologinius mechanizmus.

Tikslas. Apžvelgti klinikinių tyrimų patirtį ir aktualiausius tyrimų duomenis tarp savižudiško elgesio ir įvairių biožymenų, siekiant pabrėžti psichikos sutrikimų neurobiologinį pagrindą ir stebėti biožymenų pokyčius gydymo eigoje, siekiant pagerinti paciento atsaką į gydymą.

Metodai. Literatūros paieška buvo atlikta naudojant PubMed, PsycINFO ir Google Scholar duomenų bazėse paskelbtus tyrimus, kurie apžvelgė savižudišką elgesį ir ryšį tarp genetinių, neuroendokrininių, neurobiologinių, neurovaizdinių, metabolinių ir uždegiminių biožymenų.

Rezultatai. Šioje literatūros apžvalgoje buvo analizuojami 54 straipsniai, kuriuose buvo tiriamas ryšys tarp biožymenų ir savižudiško elgesio. Rezultatai rodo, kad savižudišką elgesį įtakoja sudėtinga genetinių, neurobiologinių, neuroendokrininių, neurotrofinių, uždegiminių, metabolinių ir neurovaizdinių žymenų sąveika. Genetinis polinkis, ypač susijęs su serotoninu susijusiais genais, kartu su neurotransmiterių sistemų, hormonų lygio ir uždegiminių procesų reguliavimo sutrikimais, padidina savižudybių riziką. Struktūriniai smegenų pokyčiai, susiję su emociniu reguliavimu ir sprendimų priėmimu, dar labiau pabrėžia daugiafaktorinį savižudybės pobūdį.

Išvada. Genetinių, neurobiologinių, neuroendokrinologinių, uždegiminių, metabolinių ir neurovaizdinių žymenų sąveika prisideda prie supratimo apie savižudišką elgesį. Šių biologinių žymenų integravimas pagerina supratimą apie savižudybių etiologiją ir padeda kurti veiksmingesnes prevencijos ir intervencijos strategijas.

Raktiniai žodžiai: Savižudiškas elgesys, biožymenys, uždegimas, neurovaizdiniai tyrimai, genai

INTRODUCTION

Suicide affects people of all ages, genders, and backgrounds. According to World Health Organization (WHO), more than 700 000 people die by suicide every year globally [1]. According to the data of the Lithuanian Institute of Hygiene, 562 suicides were registered in Lithuania in 2023 [2]. Suicide is a complex phenomenon influenced by a combination of genetic, environmental, and psychological factors. While there is evidence suggesting that biological factors may play a role in suicide risk, it's crucial to emphasize that suicide is a multifaceted issue with no single cause. Biological factors often interact with other dimensions to contribute to an individual's vulnerability. These factors undoubtedly contribute to the complex interplay of variables influencing suicide risk. Understanding the specific molecular, genetic, or neurobiological factors associated with suicidal thoughts and behaviors contributes to a more comprehensive understanding of the phenomenon. Understanding how suicide depends on biomarkers is instrumental in advancing suicide prevention strategies, providing more accurate risk assessments, and fostering the development of targeted interventions.

Research on suicide biomarkers involves exploring various biological, genetic, neurobiological, and psychosocial factors. Numerous biomarkers have been investigated, but it's important to note that the field is complex, and no single biomarker can definitively predict suicide risk. Instead, a combination of factors is typically considered for a more comprehensive assessment. The most important categories of biomarkers that have been examined in the context of suicide.

Methods

This literature review was performed using search criteria on keywords in research published at PubMed, PsycINFO, and Google Scholar. The keywords were "suicidal behavior", "biomarkers", "inflammation", "neuroimaging" and "genes". The search was carried out in December 2023 and included studies published up to 2023 to ensure the inclusion of the most recent research findings. Studies were included if they investigated the association between biomarkers (genetic, neurobiological, neuroendocrine, inflammatory, metabolic, or neuroimaging) and suicidal behavior. Only peer-reviewed articles written in English were considered for inclusion. Studies focusing on animal models, non-human subjects, or non-suicidal outcomes were excluded. In the end 54 articles were used for this review.

RESULTS

Genetic biomarkers

Numerous studies have suggested a genetic component in suicidal behavior, indicating that individuals with a family history of suicide or mental health disorders may be at a higher risk [3, 4]. The heritability of suicidal behavior is estimated to be around 30–50%, as reported by various twin, family, and adoption studies [5–7]. One of the key genetic factors associated with suicide risk is a family history of mental health disorders, particularly mood disorders like depression and bipolar disorder [8]. Mann, Brent and others researchers has identified specific genetic markers and variations associated

with an increased susceptibility to these disorders, which in turn may contribute to a higher risk of suicidal behavior [9, 10].

Genes also play a role in regulating the levels and functioning of neurotransmitters, which are chemicals that transmit signals in the brain. Serotonin, in particular, is a neurotransmitter associated with mood regulation, and variations in genes related to serotonin function may contribute to suicide risk. The serotonin transporter gene (5-HTT) and the tryptophan hydroxylase gene (TPH) are two key genetic components that have been studied in the context of suicide risk and mental health disorders. Understanding the genetic basis of suicide risk, including the role of genes like 5-HTT and TPH, is an ongoing area of research. Both genes are involved in the regulation of serotonin, a neurotransmitter that plays a crucial role in mood regulation, emotion, and behavior [11, 12].

The serotonin transporter gene, also known as SLC6A4, codes for the serotonin transporter protein responsible for reabsorbing serotonin from the synaptic cleft, terminating its action in the synaptic cleft and recycling it for future use. The 5-HTT gene has a common polymorphism known as the serotonin transporter-linked polymorphic region (5-HTTLPR), which has two main variants: the long (L) allele and the short (S) allele. Individuals with the short allele may have reduced serotonin reuptake efficiency. Caspi et al., has associated the short allele of 5-HTTLPR with an increased risk of developing mood disorders, including depression, and a higher susceptibility to suicidal behaviors [13, 14]. The interplay between the 5-HTT gene and environmental factors, such as stress and trauma, is crucial in understanding how genetic predispositions contribute to suicide risk. The interaction between the short allele and environmental stressors has been implicated in an elevated risk of suicidal ideation and attempts [13, 15].

Tryptophan hydroxylase (TPH) is an enzyme involved in the synthesis of serotonin. The TPH gene, particularly the TPH1 and TPH2 isoforms, codes for this enzyme. Variations in the TPH gene have been associated with altered serotonin levels and have been investigated in the context of mood disorders and suicidal behavior. Studies have explored the role of TPH polymorphisms in suicide risk, with some findings suggesting an association between certain genetic variants and an increased susceptibility to suicidal thoughts and behaviors [16, 17].

Neurobiological markers

Research on the link between suicide and neurobiological markers has been a growing area of interest, and several studies have explored various aspects of the neurobiology of suicide. The serotonin system is a key component of the neurobiological mechanisms implicated in suicide behavior. Serotonin, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter that plays a crucial role in regulating mood, emotion, impulsivity, and aggression. Dysregulation of the serotonin system has been consistently associated with an increased risk of suicidal behavior. Serotonin is involved in the modulation of mood, and alterations in serotonin levels have been linked to mood disorders such as depression.

Reduced serotonin availability in the synaptic cleft has been associated with dysregulated mood states and an increased vulnerability to suicidal ideation. [18]. Post-mortem studies of the brains of individuals who died by suicide have shown alterations in serotonin receptor density and distribution [19]. Changes in serotonin receptor subtypes, such as the 5-HT1A and 5-HT2A receptors, have been reported in specific brain regions associated with mood regulation and impulsivity [20, 21, 22].

Neuroendocrine biomarkers

The relationship between the neuroendocrine system and suicide is complex, involving intricate interactions between hormones, stress response pathways, and neurotransmitter systems. The neuroendocrine system, which includes the hypothalamus, pituitary gland, and adrenal glands (HPA axis), plays a crucial role in regulating various physiological processes and responding to stressors. It regulates the secretion of cortisol, the primary stress hormone. Chronic activation of the HPA axis, leading to elevated cortisol levels, has been observed in individuals with mood disorders and those at risk for suicide [23, 24]. Corticotropin-Releasing Hormone (CRH) and vasopressin, released by the hypothalamus, are also involved in the regulation of the stress response. Alterations in the release of these hormones have been implicated in mood disorders and suicidal behavior [25, 26]. Thyroid hormones, including triiodothyronine (T3) and thyroxine (T4), play a role in regulating metabolism and energy balance. Alterations in thyroid function have been associated with mood disorders and may contribute to suicidal ideation [27]. Oxytocin is a neuropeptide that plays a crucial role in social bonding, emotional regulation, and stress modulation. It is released during positive social interactions, such as hugging or bonding between individuals. While oxytocin is often associated with positive social behaviors, recent research has explored its potential involvement in the neurobiology of suicide [28]. Oxytocin has been shown to modulate the stress response and may have anxiolytic (anxiety-reducing) effects. Dysregulation of the stress response is implicated in mood disorders and suicidal behavior [29]. Variations in the oxytocin receptor gene (OXTR) have been studied in relation to psychiatric conditions, including mood disorders and suicidal behavior. Polymorphisms in OXTR may influence individual differences in oxytocin receptor sensitivity, potentially impacting social behavior and emotional regulation [30]. Oxytocin administration has been explored as a potential treatment for improving maternal mental health during the perinatal period [31].

It's very important to mention sex hormones, including testosterone and estrogen, which can influence mood and behavior. Testosterone is the primary male sex hormone, and its role in aggression and mood regulation has been studied in the context of suicide. Some studies have suggested a potential association between low testosterone levels and an increased risk of suicide in men [32]. Estrogen, the primary female sex hormone, has neuroprotective and mood-stabilizing effects. Some studies have suggested a potential protective role of estrogen against suicidal behavior, particularly in women. Estrogen has been implicated in regulating serotonin and other

neurotransmitter systems, which may contribute to its impact on mood and suicidal behavior [33]. Transitions involving hormonal fluctuations, such as puberty, postpartum, and menopause, may be associated with changes in mood and an increased vulnerability to mental health disorders, including suicidal behavior [34].

Neurotrophic Factor Biomarkers

Neurotrophic factors are proteins that play a crucial role in the development, survival, and function of neurons. Altered levels of neurotrophic factors have been implicated to suicidal behavior. Brain-derived neurotrophic factor (BDNF), a protein that supports the survival and growth of neurons, has been studied in relation to suicide. Reduced BDNF levels have been reported in post-mortem studies of the brains of individuals who died by suicide [35]. Nerve Growth Factor (NGF) is another important neurotrophic factor involved in the growth, differentiation, and survival of neurons. It is involved in various processes, including synaptic plasticity and neuronal maintenance. Changes in NGF levels have been implicated in mood disorders, and some studies suggest a potential link to suicidal behavior [36, 37]. Insulin-Like Growth Factor (IGF), which shares structural similarities with insulin, is involved in cell growth and differentiation, including in the central nervous system. IGF is involved in neuroplasticity, which refers to the brain's ability to reorganize itself and form new connections. Dysregulation in neuroplasticity is often observed in mood disorders and conditions linked to suicidal behavior [38, 39]. Transforming Growth Factor-Beta (TGF- β) is involved in various cellular processes, including cell growth and differentiation. Changes in TGF- β signaling have been implicated in mood disorders, and its role in suicidal behavior is an area of ongoing investigation [40]. It's essential to note that the relationship between neurotrophic factors and suicide is complex, and alterations in their levels may be influenced by various factors, including genetics, environmental stressors, and comorbid psychiatric conditions.

Inflammatory biomarkers

There was identified alterations in inflammatory markers in individuals who have attempted or died by suicide. Some studies suggest that elevated levels of certain cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), may be associated with an increased risk of suicidal behavior. Additionally, alterations in the levels of other immune system-related molecules, including C-reactive protein (CRP) and certain inflammatory signaling pathways, have been observed in individuals with suicidal tendencies. Elevated levels of inflammatory markers, such as CRP, have been observed in individuals at risk for suicide [41]. Interleukin-6 (IL-6), a key pro-inflammatory cytokine, has been associated with suicidal behavior [42]. Elevated levels of Tumor Necrosis Factor-Alpha (TNF- α) are often associated with inflammatory dysregulation, which has been observed in individuals with psychiatric conditions linked to suicide risk [43]. TNF- α is implicated in the activation of microglia, the immune cells in the brain, contributing to neuroinflammatory processes that may impact mood and behavior [44]. Dysregulation of TNF- α is associated with alterations in the

stress response, including the hypothalamic-pituitary-adrenal (HPA) axis, which is relevant to mood disorders and suicide risk [45]. Dysregulation of Interferon-Gamma (IFN- γ), an immune regulatory cytokine, has been associated with suicidal ideation [46].

Metabolic biomarkers

The association between dysregulation of lipid metabolism and suicide is an area of research that explores how disruptions in lipid balance may contribute to the risk of suicidal behavior. Lipid metabolism involves the synthesis, storage, and breakdown of lipids, which play crucial roles in various physiological processes, including the structure of cell membranes and signaling pathways. Lipid peroxidation can result in the production of reactive aldehydes, such as malondialdehyde (MDA), which serve as biomarkers of oxidative stress. Increased lipid peroxidation has been associated with suicidal behavior [47, 48].

Neuroimaging markers

Neuroimaging studies have provided valuable insights into the neural mechanisms underlying suicidal behavior. Various brain regions and functional connectivity patterns have been implicated in individuals with a history of suicidal thoughts or attempts. Some data suggests that structural alterations in specific brain regions, particularly those involved in emotion regulation, decision-making, and impulse control, may contribute to the neurobiological basis of suicide. Alterations in the prefrontal cortex, amygdala, and hippocampus have been reported in suicide-related neuroimaging studies [49, 50]. The prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC), is implicated in decision-making, impulse control, and emotional regulation. Structural abnormalities in the prefrontal cortex (PFC) have been associated with suicide risk [51]. A key region for emotional processing is amygdala. Changes in amygdala structure, such as alterations in volume or connectivity, have been linked to suicidal behaviors and emotional dysregulation [52]. The hippocampus, involved in memory and emotion regulation, may show structural changes in individuals with suicidal thoughts or behaviors. Reduced hippocampal volume has been reported in some studies [53]. The Anterior Cingulate Cortex (ACC) plays a role in emotional regulation and decision-making. Alterations in ACC structure have been associated with suicidal ideation and impulsive behavior [54]. The Orbitofrontal Cortex (OFC) is involved in reward processing and decision-making. Structural changes in the OFC have been linked to impaired decision-making and increased suicide risk [55].

DISCUSSION

Suicide risk involves intricate interactions among genetic, neurobiological, hormonal and environmental factors. Family history of suicide or mental health disorders indicates a higher risk of suicidal behavior. Also, specific genetic markers and variations, particularly those related to serotonin regulation, contribute to suicide risk. Polymorphisms in genes like 5-HTT and TPH are associated with altered serotonin function and increased susceptibility to mood disorders and suicidal behaviors. Dysregulation of the serotonin system, including altered serotonin levels and receptor distribution, is consistently linked to an increased risk of suicidal behavior. Post-mortem studies reveal alterations in serotonin receptor density in individuals who died by suicide. Neuroimaging studies show structural changes in brain regions involved in emotion regulation, decision-making, and impulse control in individuals with suicidal thoughts or attempts. These findings highlight the complex interplay between genetic predispositions, neurotransmitter dysregulation, and neurobiological abnormalities in the manifestation of suicidal behavior. Understanding these biomarkers is crucial for developing effective strategies for suicide risk assessment, prevention, and intervention.

CONCLUSION

Biomarkers may serve as early indicators of suicidal tendencies before overt symptoms manifest. Early identification through biomarkers allows for timely intervention, potentially preventing the escalation of suicidal thoughts into attempts. Biomarkers can aid in the development of personalized treatment approaches. Understanding an individual's unique biological profile may lead to targeted therapeutic interventions, enhancing the effectiveness of treatments for individuals at risk of suicide. Also biomarkers provide objective measures that complement traditional subjective assessments for mental health professionals. Monitoring changes in biomarkers over the course of treatment can provide insights into treatment response. Biological markers help emphasize the neurobiological basis of mental health conditions, potentially reducing the stigma associated with mental health issues. This shift in perception can contribute to more empathetic and informed societal attitudes toward suicide. Suicide prevention and understanding require a comprehensive approach that addresses the multifaceted nature of this public health concern.

REFERENCES

- World Health Organization. Suicide worldwide in 2019: Global Health Estimates. World Health Organization, Geneva. 2019.
- https://public.tableau.com/app/profile/aurelija5653/viz/Mirtiespriepasikospriemon_16183214023990/Pradia
- DiBlasi E, Kang J, Docherty AR. Genetic contributions to suicidal thoughts and behaviors. *Psychol Med*. 2021 Oct 25;51(13):2148–55.
- Lee PH, Doyle AE, Silberstein M, Jung JY, Liu RT, Perlis RH, et al. Associations Between Genetic Risk for Adult Suicide Attempt and Suicidal Behaviors in Young Children in the US. *JAMA Psychiatry*. 2022 Oct 1;79(10):971.
- Mann JJ, Arango VA, Avenevoli S, Brent DA, Champagne FA, Clayton P, et al. Candidate Endophenotypes for Genetic Studies of Suicidal Behavior. *Biol Psychiatry*. 2009 Apr;65(7):556–63.
- Brent DA, Melhem N. Familial Transmission of Suicidal Behavior. *Psychiatric Clinics of North America*. 2008 Jun;31(2):157–77.
- Brent DA, Melhem NM, Oquendo M, Burke A, Birmaher B, Stanley B, et al. Familial Pathways to Early-Onset Suicide Attempt. *JAMA Psychiatry*. 2015 Feb 1;72(2):160.
- McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. *The Lancet*. 2020 Dec;396(10265):1841–56.
- Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci*. 2003 Oct;4(10):819–28.
- Brent DA, Melhem N. Familial Transmission of Suicidal Behavior. *Psychiatric Clinics of North America*. 2008 Jun;31(2):157–77.
- Hernández-Díaz Y, Genis-Mendoza AD, González-Castro TB, Tovilla-Zárate CA, Juárez-Rojop IE, López-Narváez ML, et al. Association and Genetic Expression between Genes Involved in

- HPA Axis and Suicide Behavior: A Systematic Review. *Genes* (Basel). 2021 Oct 13;12(10):1608.
12. Popova NK, Tsybko AS, Naumenko VS. The Implication of 5-HT Receptor Family Members in Aggression, Depression and Suicide: Similarity and Difference. *Int J Mol Sci*. 2022 Aug 8;23(15):8814.
13. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science* (1979). 2003 Jul 18;301(5631):386–9.
14. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, et al. Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression. *JAMA*. 2009 Jun 17;301(23):2462.
15. Harika-Germaneau G, Lafay-Chebassier C, Langbour N, Thirioux B, Wassouf I, Noël X, et al. Preliminary Evidence That the Short Allele of 5-HTTLPR Moderates the Association of Psychiatric Symptom Severity on Suicide Attempt: The Example in Obsessive-Compulsive Disorder. *Front Psychiatry*. 2022 Apr 1;13.
16. Zalsman G, Frisch A, King RA, Pauls DL, Grice DE, Gelernter J, et al. Case control and family-based studies of tryptophan hydroxylase gene A218C polymorphism and suicidality in adolescents. *Am J Med Genet*. 2001 Jul 8;105(5):451–7.
17. Bellivier F, Chaste P, Malafosse A. Association between the TPH gene A218C polymorphism and suicidal behavior: A meta-analysis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2004 Jan 12;124B(1):87–91.
18. Mann JJ. The serotonergic system in mood disorders and suicidal behaviour. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2013 Apr 5;368(1615):20120537.
19. Baharikhoo P, Kolla NJ. Microglial Dysregulation and Suicidality: A Stress-Diathesis Perspective. *Front Psychiatry*. 2020 Aug 11;11.
20. Steinberg LJ, Underwood MD, Bakalian MJ, Kassir SA, Mann JJ, Arango V. 5-HT 1A receptor, 5-HT 2A receptor and serotonin transporter binding in the human auditory cortex in depression. *Journal of Psychiatry and Neuroscience*. 2019 Sep 1;44(5):294–302.
21. Boldrini M, Underwood MD, Mann JJ, Arango V. More tryptophan hydroxylase in the brainstem dorsal raphe nucleus in depressed suicides. *Brain Res*. 2005 Apr;1041(1):19–28.
22. Bach H, Huang Y, Underwood MD, Dwork AJ, Mann JJ, Arango V. Elevated serotonin and 5-HIAA in the brainstem and lower serotonin turnover in the prefrontal cortex of suicides. *Synapse*. 2014 Mar 23;68(3):127–30.
23. O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC. Effects of childhood trauma on cortisol levels in suicide attempters and ideators. *Psychoneuroendocrinology*. 2018 Feb;88:9–16.
24. Hernández-Díaz Y, Genis-Mendoza AD, González-Castro TB, Tovilla-Zárate CA, Juárez-Rojop IE, López-Narváez ML, et al. Association and Genetic Expression between Genes Involved in HPA Axis and Suicide Behavior: A Systematic Review. *Genes* (Basel). 2021 Oct 13;12(10):1608.
25. Pittenger C, Duman RS. Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms. *Neuropsychopharmacology*. 2008 Jan 12;33(1):88–109.
26. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide Prevention Strategies. *JAMA*. 2005 Oct 26;294(16):2064.
27. Peng P, Wang Q, Lang X, Liu T, Zhang XY. Clinical symptoms, thyroid dysfunction, and metabolic disturbances in first-episode drug-naïve major depressive disorder patients with suicide attempts: A network perspective. *Front Endocrinol (Lausanne)*. 2023 Feb 24;14.
28. Tabak BA, Teed AR, Castle E, Dutcher JM, Meyer ML, Bryan R, et al. Null results of oxytocin and vasopressin administration across a range of social cognitive and behavioral paradigms: Evidence from a randomized controlled trial. *Psychoneuroendocrinology*. 2019 Sep;107:124–32.
29. Neumann ID, Slattery DA. Oxytocin in General Anxiety and Social Fear: A Translational Approach. *Biol Psychiatry*. 2016 Feb;79(3):213–21.
30. Sippel LM, Han S, Watkins LE, Harpaz-Rotem I, Southwick SM, Krystal JH, et al. Oxytocin receptor gene polymorphisms, attachment, and PTSD: Results from the National Health and Resilience in Veterans Study. *J Psychiatr Res*. 2017 Nov;94:139–47.
31. Sippel LM, Allington CE, Pietrzak RH, Harpaz-Rotem I, Mayes LC, Olf M. Oxytocin and Stress-related Disorders: Neurobiological Mechanisms and Treatment Opportunities. *Chronic Stress*. 2017 Feb 17;1:247054701668799.
32. Sher L, Grunebaum MF, Sullivan GM, Burke AK, Cooper TB, Mann JJ, et al. Testosterone levels in suicide attempters with bipolar disorder. *J Psychiatr Res*. 2012 Oct;46(10):1267–71.
33. Sublette ME. Lipids and Suicide Risk. In 2020. p. 155–77.
34. Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Benefits From Antidepressants. *Arch Gen Psychiatry*. 2012 Jun 1;69(6).
35. Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN. Altered Gene Expression of Brain-Derived Neurotrophic Factor and Receptor Tyrosine Kinase B in Postmortem Brain of Suicide Subjects. *Arch Gen Psychiatry*. 2003 Aug 1;60(8):804.
36. Duman RS, Monteggia LM. A Neurotrophic Model for Stress-Related Mood Disorders. *Biol Psychiatry*. 2006 Jun;59(12):1116–27.
37. Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci*. 2012 Jan;35(1):14–23.
38. Torres-Aleman I. Toward a comprehensive neurobiology of IGF-I. *Dev Neurobiol*. 2010 Apr 22;70(5):384–96.
39. Tajiri M, Suzuki Y, Tsuneyama N, Arinami H, Someya T. Hormonal Dynamics Effect of Serum Insulin-Like Growth Factor I and Cortisol/Dehydroepiandrosterone Sulfate Ratio on Symptom Severity of Major Depressive Disorder. *J Clin Psychopharmacol*. 2019 Jul;39(4):367–71.
40. Thomas N, Armstrong CW, Hudaib AR, Kulkarni J, Gurvich C. A network meta-analysis of stress mediators in suicide behaviour. *Front Neuroendocrinol*. 2021 Oct;63:100946.
41. McCallum RT, Perreault ML. Glycogen Synthase Kinase-3: A Focal Point for Advancing Pathogenic Inflammation in Depression. *Cells*. 2021 Sep 1;10(9):2270.
42. González-Castro TB, Tovilla-Zárate CA, López-Narváez ML, Genis-Mendoza AD, Juárez-Rojop IE. Interleukin-6 Levels in Serum, Plasma, and Cerebral Spinal Fluid in Individuals with Suicide Behavior: Systematic Review and Meta-Analysis with Meta-Regression. *Journal of Interferon & Cytokine Research*. 2021 Jul 1;41(7):258–67.
43. Pandey GN, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC, et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res*. 2012 Jan;46(1):57–63.
44. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res*. 2008 Jan;42(2):151–7.
45. Menard C, Pfau ML, Hodes GE, Kana V, Wang VX, Bouchard S, et al. Social stress induces neurovascular pathology promoting depression. *Nat Neurosci*. 2017 Dec 13;20(12):1752–60.
46. Lindqvist D, Wolkowitz OM, Picard M, Ohlsson L, Bersani FS, Fernström J, et al. Circulating cell-free mitochondrial DNA, but not leukocyte mitochondrial DNA copy number, is elevated in major depressive disorder. *Neuropsychopharmacology*. 2018 Jun 30;43(7):1557–64.
47. Nam TG. Lipid Peroxidation and Its Toxicological Implications. *Toxicol Res*. 2011 Mar 1;27(1):1–6.
48. Sowa-Kućma M, Styczeń K, Siwek M, Misztak P, Nowak RJ, Dudek D, et al. Are there differences in lipid peroxidation and immune biomarkers between major depression and bipolar disorder: Effects of melancholia, atypical depression, severity of illness, episode number, suicidal ideation and prior suicide attempts. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018 Feb;81:372–83.
49. Kim DJ, Bartlett EA, DeLorenzo C, Parsey R V., Kilts C, Cáceda R. Examination of structural brain changes in recent suicidal behavior. *Psychiatry Res Neuroimaging*. 2021 Jan;307:111216.
50. Jollant F, Lawrence NL, Olié E, Guillaume S, Courtet P. The suicidal mind and brain: A review of neuropsychological and neuroimaging studies. *The World Journal of Biological Psychiatry*. 2011
51. Gifuni AJ, Perret LC, Lacourse E, Geoffroy MC, Mbekou V, Jollant F, et al. Decision-making and cognitive control in adolescent suicidal behaviors: a qualitative systematic review of the literature. *Eur Child Adolesc Psychiatry*. 2021 Dec 9;30(12):1839–55.
52. Nawaz H, Shah I, Ali S. The amygdala connectivity with depression and suicide ideation with suicide behavior: A meta-analysis of structural MRI, resting-state fMRI and task fMRI. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023 Jun;124:110736.
53. Kang W, Shin J, Han K, Kim A, Kang Y, Kang J, et al. Local shape volume alterations in subcortical structures of suicide attempters with major depressive disorder. *Hum Brain Mapp*. 2020 Dec 17;41(17):4925–34.
54. Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlösser RG. Structural brain alterations in patients with major depressive disorder and high risk for suicide: Evidence for a distinct neurobiological entity? *Neuroimage*. 2011 Jan;54(2):1607–14.
55. Huber RS, Subramaniam P, Kondo DG, Shi X, Renshaw PF, Yurgelun-Todd DA. Reduced lateral orbitofrontal cortex volume and suicide behavior in youth with bipolar disorder. *Bipolar Disord*. 2019 Jun 13;21(4):321–9.

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