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Review

REVIEW

Suicide Biomarkers to Predict Risk, Classify Diagnostic Subtypes, and Identify Novel Therapeutic Targets: 5 Years of Promising Research

Jenessa N. Johnston, BA, Darcy Campbell, BSc, Hector J. Caruncho, PhD, Ioline D. Henter, MA, Elizabeth D. Ballard, PhD, Carlos A. Zarate Jr, MD

Division of Medical Sciences, University of Victoria, Victoria, British Columbia, Canada (Ms Johnston, Dr Caruncho); Experimental Therapeutics and Pathophysiology Branch, Division of Intramural Research Programs, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA (Ms Johnston, Ms Campbell, Dr Caruncho, Ms Henter, Dr Ballard, and Dr Zarate).

Correspondence: Jenessa N. Johnston, BA, Division of Medical Sciences, University of Victoria, Medical Sciences Building, Room 250, Victoria, BC, Canada V8W 2Y2 (jenessaj@uvic.ca).

Abstract

Background: Suicide is a global health crisis. However, no objective biomarkers of suicide risk currently exist, and self-reported data can be unreliable, which limits prediction, diagnostic, and treatment efforts. Reliable biomarkers that can differentiate between diagnostic subgroups, predict worsening symptoms, or suggest novel therapeutic targets would be extremely valuable for patients, researchers, and clinicians.
Methods: MEDLINE was searched for reports published between 2016 and 2021 using search terms (suicid*) AND (biomarker*) OR (indicat*). Reports that compared biomarkers between suicidal ideation, suicide attempt, death from suicide, or any suicide subgroup against other neuropsychiatric disorders were included. Studies exclusively comparing suicidal behavior or death from suicide with healthy controls were not included to ensure that biomarkers were specific to suicide and not other psychopathology.
Results: This review summarizes the last 5 years of research into suicide-associated biomarkers and provides a comprehensive guide for promising and novel biomarkers that encompass varying presentations of suicidal ideation, suicide attempt, and death by suicide. The serotonergic system, inflammation, hypothalamic-pituitary-adrenal axis, lipids, and endocannabinoids emerged as the most promising diagnostic, predictive, and therapeutic indicators.
Conclusions: The utility of diagnostic and predictive biomarkers is evident, particularly for suicide prevention. While larger-scale studies and further in-depth research are required, the last 5 years of research has uncovered essential biomarkers that could ultimately improve predictive strategies, aid diagnostics, and help develop future therapeutic targets.

Introduction

Globally, the World Health Organization estimates that nearly 1 million people die from suicide each year (World Health Organization, 2019). Although it is imperative to address this global health crisis, the current scarcity of diagnostic and predictive biomarkers makes suicide prevention and treatment as well as the development of novel therapeutics considerably more difficult (Costanza et al., 2014; Sudol and Mann 2017; Capuzzi et al., 2020a).

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Biomarkers can provide a great deal of critical information by functioning as predictive indicators, guiding diagnostic distinctions, providing evidence of treatment response, and suggesting potential targets for novel treatments. Broadly defined as objective indicators of a biological state or condition, biomarkers can be measured in multiple ways, including changes in protein expression and epigenetic markers and metabolomic changes that can be detected in both the central nervous system (CNS) and periphery (Niciu et al., 2014). In a clinical sense, biomarkers for suicidal ideation and attempt would be valuable specifically because they provide a greater degree of certainty about diagnosis or treatment plans than psychological measures alone.

However, predicting suicidal behavior has historically been challenging, particularly because such prediction relies on subjective measures such as patient reports of ideation, behavior, and family history (Davis and Schrueder, 1990; Blasco-Fontecilla et al., 2013; Smith et al., 2013). Additional difficulties include overlap with other neuropsychiatric disorders, the predictive validity of suicidal ideation for suicide attempts (Miranda et al., 2008; King et al., 2014), and cultural inconsistencies in attitudes towards suicidal ideation or behavior that can influence reported suicide rates across countries (Vijayakumar 2005; Colucci 2013). A recent survey of researchers and clinicians listed the largest challenges in suicide research as small sample sizes in intervention studies, low baseline rates of suicidal behavior, and difficulties translating research among different fields (O'Connor and Portzky, 2018).

In this context, determining practical, usable biomarkers to quantify suicidal ideation, suicide attempt, or potential death from suicide is crucial. It should be noted from the outset that these terms have been defined in guidelines from the CDC (Crosby et al., 2011). Specifically, suicidal ideation is characterized as thinking, considering, and/or planning suicide; suicide attempt is designated as non-lethal, self-directed injurious behavior with an intent to die; and death by suicide is defined as intentional self-injurious behavior resulting in death. Self-injurious behavior without intent to die is not considered suicide attempt or ideation and will not be included in this review. The distinction between each of these facets is critical, as each exists across a similar spectrum without completely overlapping. For example, suicidal ideation varies considerably in severity and does not always predict resultant behavior. Suicide attempts can also vary in lethality; some individuals attempt suicide numerous times and never die by suicide whereas others can die on their first attempt. While attempt and death from suicide are distinct, it is important to note that previous psychiatric hospitalization and suicide attempt are the largest risk factors for death by suicide (Brown et al., 2000).

Synthesizing multiple sources of information provides the most fruitful path forward for understanding the neurobiology of suicide and of suicide biomarkers, as each source is associated with advantages and limitations. For instance, while post-mortem research provides valuable insight into biomarkers, it is often difficult to determine the mental state that led participants to act on their suicidal thoughts. Suicide method can also complicate certain analyses, as head wounds may damage brain tissue and overdoses may complicate measures of inflammation or toxicity. Cross-sectional research can help determine the mental state of participants and help differentiate subgroups, but it cannot conclusively determine predictive biomarkers. Lastly, longitudinal research can help determine valuable predictive biomarkers of suicidal ideation, suicide attempt, or death by suicide. However, such research is costly and time-intensive to conduct due to the need for large samples sizes to capture the rare event of suicide death as well as reliance on self-report measures that may not reflect the true mental state of each patient. Integrating these methodologies and samples can aggregate findings and bolster weaknesses in the data.

In the roughly 5 years since a major review of this topic was published (Oquendo et al., 2014; Sudol and Mann 2017), considerable research has been conducted to differentiate biomarkers of suicidal ideation, suicide attempt, and death by suicide from each other and from various other neuropsychiatric diagnoses. Although it focuses on the most recent research, it should be noted from the outset that the present review builds on considerable previous research that identified several promising predictive and differentiating biomarkers of suicidal ideation, attempt, and death related to the serotonergic system and hypothalamic-pituitary-adrenal (HPA) axis. Historically, the serotonergic system has been extensively studied for its role in suicide and suicidal behaviors. In particular, 5-hydroxyindoleacetic acid (5-HIAA)—the main metabolite of serotonin (5-HT)—was found to be downregulated in the cerebrospinal fluid (CSF) of those who died by suicide compared with those with other neuropsychiatric disorders (Asberg et al., 1976; Träskman et al., 1981). Low serotonin transporter binding in the prefrontal cortex and raphe nuclei was also reported to differentiate between non-suicidal and suicidal depression (Arango et al., 1995). Furthermore, 5-HT2A receptor density was identified as a key difference between suicidal and non-suicidal patients with depression (Alda and Hrdina 2000) as well as the chosen lethality of suicide attempts (Malone et al., 2007). Finally, in the HPA axis, the dexamethasone suppression test has been extensively studied as a suicide risk biomarker. Non-suppression on the dexamethasone suppression test (DST) predicted significantly higher suicide risk in those diagnosed with depression or who had made a previous suicide attempt, though this finding was not always consistent (reviewed in Currier and Mann 2008).

This paper reviews findings drawn from post-mortem studies, case-control studies, cross-sectional studies, and longitudinal studies. In addition, both CNS and peripheral biomarkers are discussed to highlight differences and similarities between the CNS and periphery. Comparisons with only healthy volunteers as controls are not included except as part of the study subtypes listed above due to concerns about the biomarkers being specific to suicide rather than general psychopathology. Structural and functional brain imaging studies were excluded because they have recently been investigated (we refer the interested reader to several recent reviews: Balcioglu and Kose, 2018; Bani-Fatemi et al., 2018; Schmaal et al., 2020). Broadly, this paper seeks to provide a comprehensive, up-to-date guide for clinicians on suicide biomarkers. These include biomarkers that hold promise as predictive indicators of suicidal ideation, suicide attempt, and death by suicide as well as those that may one day help identify novel therapeutic targets.

SEARCH STRATEGY

MEDLINE was searched between December 2020 and July 2021 for reports using search terms (suicid*) AND (biomarker*) OR (indicat*). Inclusion criteria were (1) reports published between 2016 and 2021; (2) studies comparing biomarkers between 2 of the following groups: suicidal ideation, suicide attempt, death from suicide; and (3) studies that compared suicide ideation, attempt, and death from suicide to individuals with various neuropsychiatric disorders. Exclusion criteria were (1) studies that examined neuroimaging data exclusively; (2) studies that

compared suicide ideation, attempt, and death from suicide to exclusively healthy controls; and (3) studies that had no comparison groups. Genetic and epigenetic markers will not be discussed; we refer the interested reader to several recent detailed reviews (Olié and Courtet, 2017; Roy and Dwivedi, 2017; Vaquero-Lorenzo and Vasquez, 2020; Zhou et al., 2020).

BIOMARKERS OF SUICIDAL IDEATION, SUICIDE ATTEMPT, AND DEATH BY SUICIDE

This section will discuss the major focal points of recent research into promising biomarkers for classification and diagnosis of suicidal ideation, suicide attempt, and death by suicide, beginning with biomarkers that have the strongest supporting evidence.

All biomarkers mentioned are compiled in Table 1 for ease of reference.

The Serotonergic System

Serotonin is a monoaminergic transmitter and a key regulator of mood, sleep, and appetite. Dysregulation of serotonergic expression, receptors, and transporters has previously been implicated in many neuropsychiatric disorders, including major depressive disorder (MDD), bipolar disorder, and schizophrenia (Pourhamzeh et al., 2021). While serotonin is primarily produced in the gastrointestinal tract, correcting serotonergic deficits in the CNS is the primary mechanism of action underlying most traditional antidepressants—though it should be noted that traditional selective serotonin reuptake inhibitors (SSRIs) are not efficacious for all patients with depression. The serotonergic system is also heavily intertwined with inflammatory pathways, the kynurenine system, and other monoaminergic and neurotrophic signaling pathways (Mössner and Lesch, 1998; Seo et al., 2008; Oxenkrug, 2013).

Notably, dysregulation of the serotonergic system was one of the first major findings that differentiated biomarkers of suicide from other neuropsychiatric disorders (Arango et al., 2002; Azmitia, 2020). 5-HT1A binding was found to be greater in individuals who died by suicide, independent of a diagnosis of depression (Underwood et al., 2018). In bipolar disorder, levels of platelet serotonin were significantly lower in suicide attempters compared with non-attempters and even lower in those who used a high-lethality method (Giurgiuca et al., 2016). In a CSF study, decreased expression of the serotonin metabolite 5-HIAA was observed in suicide attempters compared with non-attempters (Hoertel et al., 2021). Tryptophan, an amino acid involved in serotonergic production, was significantly lower in participants with MDD who had at least 1 suicide attempt than in non-suicidal patients (Messaoud et al., 2019). The same study found that the kynurenine to tryptophan ratio was higher in participants who had attempted suicide, suggesting that serotonergic interactions with other pathways could be important for differentiation.

While the serotonergic system clearly plays a complicated role in the pathogenesis of suicide, the strong evidence associated with predictive and genetic biomarkers—for instance, *SLC6A4* and *5-HTTLPR* (Rahikainen et al., 2017; Consoloni et al., 2018; Daray et al., 2018)—underscores the importance of this line of research. Future studies should further explore the aforementioned genetic findings as well as analyze ratios (e.g., kynurenine/tryptophan) to understand how serotonin interacts with and influences other systems. One area of particular interest is the complicated history between suicide and the efficacy of traditional antidepressants—particularly SSRIs—suggesting that manipulation of the serotonergic system does not work for everyone. Further work in this area could ultimately help predict suicidal ideation, suicide attempt, or death from suicide.

HPA Axis Dysregulation

The HPA axis is the neuroendocrine regulator of the stress response, primarily impacting the CNS through the release of glucocorticoids (GCs). Beginning in the paraventricular nucleus, the HPA axis eventually triggers the pituitary gland to synthesize adrenocorticotropin-releasing hormone and stimulates GC synthesis. This stress response is modulated through a negative feedback loop by the binding of GCs to their mineralocorticoid or glucocorticoid receptors, which shuts off the response of the paraventricular nucleus. In many neuropsychiatric disorders, including depression, this negative feedback loop is dysregulated, causing an overabundance of GCs and HPA axis hyperactivity (Pariante and Lightman 2008).

Cortisol resistance to the DST, which measures HPA axis activity, has consistently been linked to risk of suicide attempt or death by suicide (Coryell and Schlesser, 2001). The DST studies support the stress-diathesis model, which hypothesizes that a stressful life event can trigger suicidal behavior in those with a pre-existing vulnerability (Van Heeringen and Mann, 2014). HPA axis hyperactivity also appears to be a predictor of death by suicide (Jokinen and Nordström 2008, 2009; Ventriglio et al., 2015).

Interestingly, baseline cortisol level, total cortisol output, and cortisol reactivity during the Trier Social Stress Test (TSST) did not differentiate suicide attempters from non-attempters, though a high cortisol response distinguished a subgroup of suicide attempters with high levels of impulsive aggression (Stanley et al., 2019). The TSST also identified greater cortisol response in individuals with brief suicidal ideation vs those with longer periods of suicidal ideation (Rizk et al., 2018). Finally, additional studies found that blunted cortisol levels were higher in those hospitalized for a suicide attempt compared with those with severe suicidal ideation (Melhem et al., 2016; Melhem et al., 2017).

It should be noted that extensive genetic research also supports the role of the HPA axis in suicidal ideation, attempt, and death by suicide. Major findings include the decreased expression of spindle and kinetochore associated complex subunit 2 (*SKA2*) in suicidal compared with non-suicidal patients (Guintivano et al., 2014; Pandey et al., 2016; Clive, 2017) and *FKBP5* polymorphisms that dysregulate GC receptor signaling (Roy et al., 2010). For a more in-depth discussion of HPA axis genetic markers, we refer the interested reader to several recent reviews (Olié and Courtet, 2017; Roy and Dwivedi, 2017; Turecki et al., 2019; Vaquero-Lorenzo and Vasquez, 2020; Zhou et al., 2020).

The HPA axis also modulates levels of various neurotransmitters, including serotonin (Pompili et al., 2010). Nevertheless, gross measures such as HPA axis hyper- and hypo-activity are unlikely to provide enough detail to serve as biomarkers of diagnostic categorization. More specific measures, such as levels of GC receptors and their binding affinities, may be better indicators of suicide risk or help distinguish behavioral subgroups.

Inflammatory Markers

Central and peripheral chronic inflammation has consistently been observed in neuropsychiatric disorders (Bauer and Teixeira,

Table 1. Biomarkers of Suicidal Ideation, Attempt, and Death by Suicide

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
BDNF	BDNF	Blood (serum)	Psychiatric controls, HCs, SA	Case-control	(Eisen et al., 2016)		No association was found between BDNF levels and SA	
BDNF	BDNF	Blood (plasma)	SI (received ketamine)	Pilot	(Zheng et al., 2020)	No changes in BDNF found across patients throughout baseline, infusion, and follow up. No association between BDNF and reported SI		
BDNF	BDNF	Blood (serum)	MDD non-suicidal, HCs, SA	Cross-sectional	(Pedrotti Moreira et al., 2018)		No differences found between MDD non-SA and SA groups	
BDNF	BDNF	Blood (serum and plasma)	Psychiatric controls, SI, and SA	Meta-analysis	(Salas-Magaña et al., 2017) *used suicidal behavior—could be SI or SA	No difference in serum BDNF levels between psychiatric controls and those with suicidal behavior, but plasma levels were lower in patients with suicidal behavior	No difference in serum BDNF levels between psychiatric controls and those with suicidal behavior, but plasma levels were lower in patients with suicidal behavior	
BDNF	BDNF	Blood	General population, SA (all women)	Cross-sectional	(Kudinova et al., 2019)		Women with history of SA had lower peripheral levels of BDNF	
BDNF	BDNF	Blood (serum)	MDD non-suicidal, HCs, SI	Cross-sectional	(Khan et al., 2019)	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		
BDNF	BDNF	Blood (serum)	BD treated with ketamine or midazolam, SI	Pilot	(Grunebaum et al., 2017)	Decreased BDNF was associated with reduced SI after ketamine infusion but not midazolam treatment		
BDNF	BDNF, DST suppression	Blood	SA	Cross-sectional	(Ambrus et al., 2016)		Female non-suppressors had lower BDNF levels than suppressors	
BDNF	proBDNF, mBDNF	Blood (serum)	MDD, BD, SA, HCs	Cross-sectional	(Lin et al., 2021)		High serum mBDNF differentiated SA from psychiatric controls, but not from HCs	

Table 1. Continued

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
Biometals	Biometal profile (over 16 metals)	Cortical tissue	MDD, BD, HCs, death by suicide	Post-mortem	(Dean et al., 2019)			Significant changes of 16 metals in BA. Six of those died by suicide compared with psychiatric controls and HCs
Biometals	Iron transport (ceruloplasmin, APP, tau, transferrin, prion)	Cortical tissue	MDD, BD, HCs, death by suicide	Post-mortem	(Dean et al., 2020)			Copper containing cerulo-plasmin was lower in suicide, while APP, tau, and transferrin were higher
Dopa-minergic	HVA	CSF	Psychiatric controls, HCs, SA	Systematic review and meta-analysis	(Hoertel et al., 2021)		HVA levels were significantly lower in SA	
Endo-cannabinoids	AEA, 2-AG	Blood (whole)	Veteran population, SA	Cross-sectional	(Sher et al., 2020)	AEA levels correlated negatively with SSI scores in SA group, but not others	2-AG levels were significantly higher in SA group	
Endo-cannabinoids	AEA, 2-AG, PEA, OEA	Blood (serum)	Psychiatric controls, SA	Cross-sectional	(Herranz-Herrer et al., 2020)		AEA and PEA expression was higher in SA	
Endo-cannabinoids	CB1 Receptor Density	Cortical tissue	AUD controls	Post-mortem	(Colino et al., 2018)			Significant increases in CB1 receptor density in those who died by suicide
Gluco-corticoid	GR-α mRNA	Blood	SI, SA, HCs	Cross-sectional	(Melhem et al., 2017)	Higher GR-α mRNA in SI than SA	Lower GR-α mRNA in SA than SI	
Gluco-corticoid	Cortisol	Saliva	Suicide Risk Behavior (SRB) (preparation, interruption, ideation), non-suicidal, HCs	Cross-sectional, after SA—sample taken after the TSST	(Melhem et al., 2016)	Pre-task cortisol higher in SRB compared with all other groups	Pre- and post-task cortisol lower in SA compared with all other groups	
Gluco-corticoid	Cortisol	Hair	SI, SA, HCs	Cross-sectional	(Melhem et al., 2017)	Higher cortisol levels in SI than SA	Lower cortisol levels in SA than SI	
Gluco-corticoid	Cortisol Response	Saliva	SA impulsivity/ aggression subtypes, non-SA	Cross-sectional	(Stanley et al., 2019)		Higher cortisol response differentiated an SA subgroup with high impulsive aggression	
Gluco-corticoid	Cortisol Response	Saliva	SI—brief or long ideation, HCs	Cross-sectional	(Rizk et al., 2018)	After the TSST, higher cortisol response seen in those with brief SI than long SI		
Inflammatory marker	CRP	Blood	SI, SA, HCs	Cross-sectional	(Melhem et al., 2017)	Lower CRP levels in SI than SA	Higher CRP levels in SA than SI	

Table 1. Continued

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
Inflammatory marker	CRP	Blood	MDD, non-suicidal, HCs	Meta-analysis	(Chen et al., 2020) *note: no differentiation between SI, SA, or completed suicide	Higher CRP levels in suicidal MDD over non-suicidal MDD and HCs	Higher CRP levels in suicidal MDD over non-suicidal MDD and HCs	Higher CRP levels in suicidal MDD over non-suicidal MDD and HCs
Inflammatory marker	CRP	Blood	MDD	Cross-sectional	(Köhler-Forsberg et al., 2017)	CRP levels were positively associated with SI in women, but not men		
Inflammatory marker	hsCRP and ESR	Blood	SI, non-suicidal MDD	Cross-sectional	(Chang et al., 2017)	Those with SI had higher levels of hsCRP and ESR than those with non-suicidal MDD. hsCRP levels positively correlated with SI severity		
Inflammatory marker	CRP	Blood	General population	Longitudinal	(Russell et al., 2021)			No association found between CRP levels at baseline and death by suicide
Inflammatory marker	Cytokine profile (IL-6, IL-10, IFN-γ, TNF-α, and CRP)	Blood	MDD, HCs	Longitudinal	(Choi et al., 2021)	TNF-α at baseline significantly predicted SI over a 12-wk period		
Inflammatory marker	Cytokine profile (IL-6, IL-1β, TNF-α)	Blood	MDD non-suicidal, SI, SA, HCs	Cross-sectional	(Ganança et al., 2021)	SI was not differentiated from non-suicidal group	Compared with those with SI and non-suicidal groups, those with SA had the lowest IL-1β levels	
Inflammatory marker	hsCRP	Blood	Psychiatric controls, SA, SI	Retrospective analysis	(Gibbs et al., 2016)	hsCRP levels were higher in those with SI than in controls, but lower in those with SA	As hsCRP level increased, the probability of SA increased from SI and controls	
Inflammatory marker	hsCRP	Blood	SI, SA, psychiatric controls, HCs	Cross-sectional	(Park and Kim, 2017)	Higher levels of hsCRP were associated with SI	hsCRP levels were highest in SA, though there were no significant differences between SI and SA	
Inflammatory marker	IL-1β	Blood	Depression and anxiety disorders treated with fluoxetine	Longitudinal	(Amitai et al., 2020)	IL-1β levels were not associated with TWSI		
Inflammatory marker	IL-6	Blood	General population, SI, SA	Cross-sectional	(Knowles et al., 2019)	No genetic correlation between SI and IL-6	No genetic correlation between SA and IL-6, though BMI may have affected these results	

Table 1. Continued

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
Inflammatory marker	IL-6	Blood	Depression and anxiety disorders treated with fluoxetine	Longitudinal	(Amitai et al., 2020)	IL-6 levels were increased in youth who developed treatment-associated SI		
Inflammatory marker	IL-8	Blood	General population, SI, SA	Cross-sectional	(Knowles et al., 2019)	No genetic correlation between SI and IL-8	Significant genetic correlation observed between SA and IL-8, mainly in females	
Inflammatory marker	Inflammatory profile (23 biomarkers)	Blood	MDD non-suicidal, SI, SA	Cross-sectional	(Su et al., 2020) *note: used suicide risk as categorization factor, which can include SI and SA	Higher levels of inflammatory markers were associated with increased suicide risk, particularly CXCL-1	Higher levels of inflammatory markers were associated with increased suicide risk, particularly CXCL-1	
Inflammatory marker	Inflammatory profile (CRP, WBC, IgE, DII)	Blood	MDD non-suicidal, MDD SI, non-MDD SI	Cross-sectional	(Bergmans et al., 2019)	MDD SI was indistinguishable from MDD, but non-MDD SI was associated with DII		
Inflammatory marker	Inflammatory profile (IL-6, IL-1β, TNF-α, IL-1ra, CRP)	Blood	MDD non-suicidal, SA	Cross-sectional	(Coryell et al., 2018)		Low levels of IL-1β, but no other cytokines, were associated with SA	
Inflammatory marker	Inflammatory profile, including 45 immuno-biological factors	Blood	Neuro-psychiatric population	Cross-sectional	(Keaton et al., 2019) *note: used suicide risk, which includes SI and SA	IL-6, lymphocytes, WBC count, and polymorphonuclear leukocyte count were positively associated with significant suicide risk. IL-8 was negatively associated with suicide risk	IL-6, lymphocytes, WBC count, and polymorphonuclear leukocyte count were positively associated with significant suicide risk. IL-8 was negatively associated with suicide risk.	
Inflammatory marker	NLR and PLR, SIII	Blood	MDD non-suicidal, SA	Retrospective	(Meydaneri and Meydaneri, 2018)		No measures were significantly different in SA	
Inflammatory marker	NLR	Blood	Non-violent and violent SA	Cross-sectional, after SA	(Capuzzi et al., 2020b)		NLR was significantly lower in violent SA compared with non-violent SA	

Table 1. Continued

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
Inflammatory marker	NLR, PLR, and MLR	Blood	MDD non-suicidal, SA	Cross-sectional	(Velasco et al., 2020) *note: also included suicidal behavior, which can include SI and SA		Those with a history of SA had significantly higher NLR and PLR ratios. NLR was significantly associated with suicidal behavior	
Inflammatory marker	TNF-α	Blood	General population, SI, SA	Cross-sectional	(Knowles et al., 2018)	No genetic correlation between SI and TNF-α	No genetic correlation between SA and TNF-α	
Inflammatory marker	TNF-α	Blood	Depression and anxiety disorders treated with fluoxetine	Longitudinal	(Amitai et al., 2020)	TNF-α levels were not associated with TWSI		
Inflammatory marker	WBC count	Blood	General population	Longitudinal	(Russell et al., 2021)			Significant association between WBC count at baseline and death by suicide
Inflammatory marker, lipid	Inflammatory and lipid profile (CRP, TRSF, HCY, AAT, HDL-c, APOA1)	Blood	MDD non-suicidal, HCs, SI	Cross-sectional	(Bai et al., 2021)	A panel of AAT, TRSF, HDL-c, and APOA1 effectively differentiated SI from MDD and HCs. Lipids were more effective than inflammatory markers		
Lipid	AA%, DHA%, EPA%	Blood	MDD non-suicidal, SI, SA, HCs	Cross-sectional	(Ganança et al., 2021)	SI was not differentiated from the non-suicidal group	DHA% had the lowest IL-1β levels from SI and non-suicidal groups	
Lipid	Cholesterol	Blood	MDD, non-suicidal	Case-control, after SA	(Eidan et al., 2019)		Lower LDL levels in SA	
Lipid	Cholesterol	Blood	Non-violent SA	Case-control, after SA	(Capuzzi et al., 2020b)		Lower cholesterol levels in violent SA	
Lipid	Esterified cholesterol, unesterified cholesterol, cholesterol efflux capacity	Blood	Mexican-American population, SA	Retrospective/ longitudinal	(Knowles et al., 2018)		Esterified cholesterol shared genetic overlap with SA. The relationship between unesterified cholesterol and SA was mediated bycholesterol efflux capacity (ABCA-1 mediated)	
Lipid	LDL	Blood	MDD, non-suicidal	Case-control, after SA	(Eidan et al., 2019)		Lower LDL levels in SA	
Lipid	LDL	Blood	Non-violent SA	Cross-sectional, after SA	(Capuzzi et al., 2020b)		Lower LDL in violent SA	

Table 1. Continued

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
Lipid	Leptin	Blood (serum)	Psychiatric controls, HCs, SA	Meta-analysis	(González-Castro et al., 2021)		Lower leptin levels were associated with increased risk of SA	
Lipid	Lipid profile (TC, LDL-c, TGC)	Blood (serum)	BD non-suicidal, SA	Meta-analysis	(Bartoli et al., 2017)		No association between lipid profile and SA	
Lipid	Lipid profile (TC, LDL-c, TGC)	Blood (serum)	Psychiatric controls, SA	Cross-sectional	(Capuzzi et al., 2018)		No association between lipid profile and SA	
Lipid	Lipid profile (TC, TGC, HDL-c, LDL-c)	Blood	MDD non-suicidal, HCs, SA	Cross-sectional	(Messaoud et al., 2017)		TC in plasma was significantly decreased in SA compared with all other groups; no differences in other measures	
Lipid	TC	Blood	Veterans: non-suicidal, SI, SA	Retrospective/ longitudinal	(Reuter et al., 2017)	TC was significantly lower in SI or SA veterans. In the available data, TC was significantly decreased in these populations from an earlier visit	TC was significantly lower in SI or SA veterans. In the available data, TC was significantly decreased in these populations from an earlier visit	
Lipid	VLDL	Blood	Non-violent SA	Cross-sectional, after SA	(Capuzzi et al., 2020b)		Lower VLDL levels in violent SA	
Lipid	Androgens (testosterone, andro-stenedione, DHEAS)	Blood (plasma)	Psychiatric population, healthy population	Longitudinal	(de Wit et al., 2020)	No androgen levels at baseline were implicated in SI or SA after a nine-year follow up		
Nora-drenergic	MHPG	CSF	Psychiatric controls, HCs	Systematic review and meta-analysis	(Hoertel et al., 2021)		No differences in MHPG levels between groups	
Serotonergic	5-HIAA	CSF	Psychiatric and healthy controls	Systematic review and meta-analysis	(Hoertel et al., 2021)		5-HIAA levels were significantly lower in attempters	
Serotonergic	Kynurenine/ tryptophan ratio	Blood	Non-suicidal MDD, HCs	Cross-sectional, after SA	(Messaoud et al., 2019)	Kynurenine/ tryptophan ratio was higher in suicidal MDD than non-suicidal and HCs		
Serotonergic	Serotonin	Blood	BD type I non-attempters	Cross-sectional, after SA	(Giurgiuca et al., 2016)		Lower levels in attempters compared with non-attempters, and lower levels in those who used a high-lethality method compared with low-lethality	

Table 1. Continued

Category [a]	Marker	Source	Comparison group	Study design	Reference	Suicidal ideation	Suicide attempt	Death by suicide
Serotonergic	SERT, 5-HTR1A, and 5-HTR2A binding	Brain Tissue	MDD, non-suicide, AUD	Post-mortem	(Underwood et al., 2018)			SERT binding was lower, and 5-HT1A binding was greater in suicides independent of MDD diagnosis
Serotonergic	Tryptophan	Blood	Non-suicidal MDD, HCs	Cross-sectional, after SA	(Messaoud et al., 2019)	Tryptophan levels were lower in suicidal MDD than non-suicidal and HC		
MicroRNA	miR-3688 and miR-5695	Blood	TWSI	Longitudinal	(Belzeaux et al., 2019)	Both miRNA significantly predicted TWSI		
Uric Acid	Uric acid levels	Blood (serum)	SA, MDD non-suicidal	Cross-sectional	(Peng et al., 2018)		No differences in uric acid levels between MDD controls and those with a previous SA	

α2-AG, 2-Arachidonoylglycerol; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTR1A, 5-Hydroxytryptamine Receptor 1A; 5-HTR2A, 5-Hydroxytryptamine Receptor 2A; AA%, arachidonic acid %; AAT, alpha 1-antitrypsin; AEA, anandamide; APOA1, Apolipoprotein A1; APP, amyloid precursor protein; AUD, alcohol use disorder; BA, Brodmann's area; BDNF, brain derived neurotrophic factor; BD, bipolar disorder; BMI, body mass index; CB1, cannabinoid receptor type 1; CRP, C-reactive protein; CSF, cerebrospinal fluid; CXCL-1, CXC ligand-1; DHA%, docosahexaenoic acid %; DII, dietary inflammatory index; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; EPA%, eicosapentaenoic acid %; ESR, erythrocyte sedimentation rate; GR-α, glucocorticoid receptor alpha; HCs, healthy controls; HCY, homocysteine; HDL-c, high-density lipoprotein cholesterol; hsCRP, high-sensitivity CRP; HVA, homovanillic acid; IFN-γ, interferon gamma; IgE, immunoglobulin E; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IL-1β, interleukin 1 beta; IL-1ra, Interleukin 1 receptor antagonist; LDL, low-density lipoprotein; LDL-c, low-density lipoprotein cholesterol; mBDNF, mature brain derived neurotrophic factor; MDD, major depressive disorder; MHPG, 3-methoxy-4-hydroxyphenylglycol; MLR, mixed lymphocyte reaction; mRNA, messenger ribonucleic acid; NLR, neutrophil-lymphocyte ratio; OEA, oleoylethanolamide; PBMC, peripheral blood mononuclear cell; PEA, palmitoylethanolamide; PLR, platelet lymphocyte ratio; proBDNF, BDNF precursor; SA, suicide attempt; SERT, serotonin transporter; SI, suicidal ideation; SIII, systemic immune inflammatory index; SRB, suicide risk behavior; SSI, Scale for Suicide Ideation; TC, total cholesterol; TGC, triglycerides; TNF-α, tumor necrosis factor alpha; TNFAIP3, TNF alpha induced protein 3; TRSF, transferrin; TSST, Trier Social Stress Task; TWSI, treatment-worsening suicidal ideation; VLDL, very-low-density lipoprotein; WBC, white blood cell.

2019). Inflammatory response is typically induced by tissue damage or infection. Sensors (membrane or intracellular receptors) on both immune and non-immune cells then trigger a reaction to the induction stimulus. This reaction recruits multiple mediators (including cytokines and chemokines) to the damaged site, which in turn affects the target tissues. Most research into the links between chronic inflammation and neuropsychiatric disorders has focused on mediators, as these are easier to measure and could ultimately act as potential therapeutic targets. However, results regarding the role that different cytokines play in the inflammatory profile have been mixed (Hong et al., 2016; Wang and Miller 2018), lending additional urgency to efforts seeking to identify concise inflammatory biomarker profiles that may help differentiate those who are experiencing suicidal ideation from those who will attempt or die by suicide as well as from the larger population of those diagnosed with neuropsychiatric disorders.

Higher levels of C-reactive protein (CRP) have frequently been implicated in suicidal ideation, suicide attempt, and death by suicide. A recent meta-analysis found that concentrations of peripheral CRP were significantly elevated in those who exhibited suicidal behavior (defined as anything from ideation to death by suicide) compared with participants with depressive disorders as well as healthy volunteers (Chen et al., 2020). Other studies found increased suicidal ideation in participants with high CRP levels and erythrocyte sedimentation rate, a gross measure of peripheral inflammation (Chang et al., 2017). Some studies found that serum CRP levels were higher in suicide attempters than in those with suicidal ideation (Gibbs et al., 2016; Melhem et al., 2017), though at least 1 study found no significant differences between the 2 groups (Park and Kim, 2017). Interestingly, another study found that this association between suicidal ideation and CRP levels was significantly higher in females (Köhler-Forsberg et al., 2017). Finally, in a large study of Taiwanese adults, a high baseline white blood cell count was associated with risk of death by suicide, but CRP levels were not (Russell et al., 2021).

Another area of interest is peripheral cytokine measures. In women, a cluster of pro-inflammatory biomarkers, including interleukin-6 (IL-6), IL-8, white blood cell count, and polymorphonuclear leukocyte count, was significantly associated with increased risk of suicidal ideation and suicide attempt compared with those diagnosed with depression who were not experiencing suicidal ideation (Keaton et al., 2019; Knowles et al., 2019). Interestingly, IL-6 levels increased in children who worsened in response to treatment with the SSRI fluoxetine (Amitai et al., 2020). Higher tumor necrosis factor (TNF)-α protein levels at baseline predicted worsening suicidal ideation after 12 weeks (Choi et al., 2021). Another study found that lower levels of IL-1β (a pro-inflammatory cytokine) and plasma phospholipid levels of docosahexaenoic acid (an anti-inflammatory) were present in those with a history of suicide attempt compared with those with severe suicidal ideation (Ganança et al., 2021). Finally, a panel of 23 inflammatory markers identified a significant association between increased inflammation and suicide risk (as defined by the suicide module of the Mini International Neuropsychiatric Interview), particularly levels of the chemokine ligand 1 (Su et al., 2020). In contrast, Coryell and colleagues found no association between 5 different inflammatory markers and history of suicide attempt (Coryell et al., 2018).

Interestingly, previous research also observed that chemokines, a type of cytokine, affect neuroinflammation by modulating microglial activity, although they also affect the HPA axis and various neuroendocrine functions. For instance, studies found that levels of CCL-5 and CCL-17 were significantly lower in suicidal patients than non-suicidal patients (Grassi-Oliveira et al., 2012; Janelidze et al., 2013). In particular, the CC chemokines were most commonly downregulated in the brains of those who died by suicide (Shinko et al., 2020), a finding not mirrored in other neuropsychiatric disorders (Köhler et al., 2017; Leighton et al., 2018). While limited recent research has attempted to expand these findings, this is a promising area of study that warrants future efforts to differentiate suicidal from non-suicidal patients.

Studies measuring the neutrophil/lymphocyte ratio (NLR) have obtained mixed results. For instance, one study observed lower NLR in individuals who had attempted suicide than in those who had not, though this difference was not significant (Meydaneri and Meydaneri, 2018). In contrast, another study found that participants with MDD who had no history of suicide attempt had a significantly lower NLR than those who did (Velasco et al., 2020).

Despite these intriguing findings, it should be noted that multiple studies found no association between inflammatory markers and different measures of suicidal ideation (Chen et al., 2017; Bergmans et al., 2019; Bai et al., 2021), suicide attempt (Coryell et al., 2018), and death by suicide (Russell et al., 2021). However, the consistently higher levels of CRP expression and potential specificity of CC chemokines are quite promising. Both of these inflammatory markers have great potential for differentiating different suicide subtypes and further implicate the role of neuroinflammation in suicidal ideation, attempt, and death by suicide. Briefly, genetic research has also found that various inflammatory markers can be used to differentiate or predict potential suicide attempts, particularly increased levels of TNF-α mRNA and polymorphisms (reviewed in Serafini et al., 2020). Further research is needed to elucidate whether inflammation can be pursued as a biomarker of suicide risk, particularly with regard to the potentially clinically meaningful sex differences that appear across multiple studies.

Lipids

Lipids—hydrophobic and amphiphilic molecules such as polyunsaturated fatty acids and neuroactive steroids—have recently garnered attention as promising therapeutic targets. Lipid metabolism is particularly important in the brain, given its high demand for energy to maintain neurogenesis, synaptogenesis, and other essential functions (Hussain et al., 2020). Lipids are easily modifiable through drugs, lifestyle, and dietary changes. They are also strongly linked to the microbiome, making them a promising therapeutic target (Fu et al., 2015).

Recent research suggests that lipids may be a potentially valuable biomarker of suicide risk (Sublette, 2020). For instance, cholesterol reductions, which impact 5-HIAA levels, may lead to a serotonergic imbalance that could be linked to mood dysregulation and suicide risk (Gorwood, 2001). Such reductions in cholesterol and triglyceride levels were observed in individuals who died by suicide compared with healthy volunteers and non-attempters diagnosed with MDD (Messaoud et al., 2017). In veterans, significantly lower cholesterol levels were reported in individuals with suicidal ideation or suicide attempt compared with other individuals with depression, even when controlling for cholesterol medication (Reuter et al., 2017). While no significant differences were found between the suicidal ideation and suicide attempt groups, it was hypothesized that individual decreases in cholesterol levels might have contributed to a shift from suicidal ideation to suicide attempt. In support of this

hypothesis, the authors found that individual cholesterol levels dropped between a participant's non-suicidal and suicidal hospitalizations (Reuter et al., 2017). Furthermore, esterified cholesterol levels significantly overlapped with genetic risk for suicide attempt in a sample of Mexican Americans, a finding mediated by ABCA-1 cholesterol efflux capacity (Knowles et al., 2018). Another study found that suicide attempt and death by suicide were related to low-density lipoprotein cholesterol levels in a cohort of participants with first-episode psychosis (Ayesa-Arriola et al., 2018). Interestingly, total cholesterol and low-density lipoprotein levels (but not triglycerides) were significantly lower in individuals who attempted suicide (Eidan et al., 2019) compared with non-suicide MDD controls, particularly those who used a violent method (Capuzzi et al., 2020a). Although some studies found no association between cholesterol levels and suicide attempt (Bartoli et al., 2017; Bartoli et al., 2018; Capuzzi et al., 2018), the fact that most studies have consistently linked low cholesterol levels to suicidal ideation or shift from ideation to attempt suggests that monitoring cholesterol levels may ultimately serve as a simple, practical measure of suicide risk, particularly in at-risk individuals.

With regard to other lipids, a panel of apolipoprotein A1, high-density lipoprotein cholesterol, alpha 1-antitrypsin, and transferrin was able to effectively differentiate individuals with MDD with suicidal ideation from those without, demonstrating the power of multiple markers for clinical diagnosis (Bai et al., 2021). A recent meta-analysis found that individuals with a suicide attempt had decreased serum levels of leptin compared with both psychiatric and healthy controls in addition to some decreases in cholesterol (González-Castro et al., 2021). Leptin, an adipocyte hormone, affects lipid concentrations by reducing the synthesis of fatty acids. Leptin may also interact with serotonin levels in the CNS (Tomson et al., 2011; Sarkar et al., 2021). Another emerging area of research is the association between lipids and body mass index (BMI), although the link between BMI and suicide is currently complicated because studies have demonstrated both negative and positive correlations (Magnusson et al., 2006; Perera et al., 2016); additional research is needed to clarify any putative associations.

In addition, rates of nonlethal suicide attempts are significantly higher in women, and rates of death by suicide are much higher in men (Lenz et al., 2019). Although social factors contribute to these differences—for instance, men are more likely to use more lethal methods such as firearms (Callanan and Davis 2011)—biological differences should also be explored. The role of neuroactive steroids (e.g., testosterone, estradiol, and progesterone) in suicide attempt and death by suicide has been proposed to help explain this gender paradox of suicidal behaviors. Interestingly, in women, the use of hormonal contraceptives that significantly alter levels of neuroactive steroids was positively associated with both suicide attempt and death by suicide, both of which peaked in adolescence (Skovlund et al., 2018). Previous research also identified an increased number of suicide attempts among women during low estradiol and progesterone periods (Baca-Garcia et al., 2010); the same study found that individuals with a regular menstrual cycle were more likely to attempt suicide during the premenstrual period or the first days of the cycle.

Androgens have consistently been linked to increased risk-taking and aggressive behavior (Carré et al., 2011), which may explain the sex differences in suicide attempt and death by suicide (Lenz et al., 2019). However, a large, 9-year longitudinal study measuring testosterone, 5α-dihydrotestosterone, and androstenedione found no association between levels of androgens and suicide attempt or suicidal ideation (de Wit et al., 2020). Nevertheless, this finding may have been confounded by the fact that shifting levels of androgens across the lifespan were not accounted for by the limited baseline measurements.

Broadly, lipids encompass a great number of signaling molecules that have a large effect on many different systems. Despite this ubiquity, lipids appear to be some of the most promising predictors of suicide risk and therapeutic targets. In particular, low levels of cholesterol have consistently been linked to worsening suicidal ideation or shift from ideation to attempt. Genetic research has also supported the role of lipids in suicide risk, demonstrating the effects of certain polymorphisms that affect the biosynthesis of long-chain polyunsaturated fatty acids (reviewed in Sudol and Mann, 2017). Because it is a simple measure commonly obtained in many hospital settings, monitoring cholesterol levels may prove to be a practical test that could be conducted with many patients if future studies prove successful.

Endocannabinoids

Endocannabinoids have been explored in recent years as possible biomarkers for neuropsychiatric disorders and treatment responsiveness due to their role in the GC system and HPA axis through mediation of the negative feedback loop (Evanson et al., 2010). Endocannabinoid system blockade was also found to lead to depressive-like behavior in animal models (Martin et al., 2002).

Despite this burgeoning interest, few studies have explored the role of these retrograde neurotransmitters in suicidal ideation, suicide attempt, or death by suicide. Recent research found that serum levels of anandamide (AEA) and N-palmitoylethanolamide (PEA) were higher in suicide attempters compared with psychiatric controls (Herranz-Herrer et al., 2020). In a sample of combat veterans, 2-arachidonoylglycerol levels were higher in suicide attempters than non-attempters (Sher et al., 2020). While no significant differences were seen in AEA or PEA levels between groups, AEA levels in suicide attempters were negatively correlated with Scale for Suicide Ideation scores, an association not found in non-attempters (Sher et al., 2020).

In the larger endocannabinoid system, cannabinoid receptors (CB1 and CB2) may also help differentiate suicidal behavior (attempts and death). Both receptors accept endogenous and exogenous ligands, and the CB1 receptor is mainly present in the CNS. A recent systematic review of individuals diagnosed with alcohol use disorder found consistent increases in CB1 receptor density in individuals who died by suicide compared with those who did not (Colino et al., 2018). These findings suggest that endocannabinoid system hyperactivity may contribute to suicidal behavior, in contrast to the downregulation of activity found in other psychiatric disorders. Interestingly, a recent meta-analysis found no relationship between acute or chronic cannabis use and suicidal ideation, suicide attempt, or death by suicide, though the study did not directly measure endogenous cannabinoid levels (Borges et al., 2016). Given the small sample sizes and mixed results of the extant studies, further longitudinal research studies are necessary.

Overall, the existing evidence suggests that endogenous cannabinoids appear to help differentiate suicide attempters from non-attempters, though small sample sizes and mixed results have complicated generalizability. Further research into brain-region specific differences, differences between ideation and behavior, and longitudinal research to determine changes in endocannabinoids over time is essential.

Brain-Derived Neurotrophic Factor (BDNF)

Given its essential role in synaptic plasticity and neuronal signaling, BDNF has long been an area of interest in neuropsychiatric disorders (Autry and Monteggia, 2012). Mature BDNF (mBDNF) contributes to cell survival and differentiation, and pro BDNF facilitates apoptosis and dendritic pruning. An inverse relationship has been observed between BDNF levels and HPA axis activity in multiple neuropsychiatric disorders and in female suicide attempters (Ambrus et al., 2016).

Notably, while most neuropsychiatric cohorts display low BDNF levels, serum mBDNF levels in those with a previous suicide attempt were higher than those of individuals with MDD and bipolar disorder (Lin et al., 2021); however, this finding was associated with poor discrimination accuracy (65.5%), so it may be less clinically relevant. When measuring total BDNF, other studies found no association between serum BDNF levels and previous suicide attempt (Eisen et al., 2016) or suicidal ideation (Zheng et al., 2020), particularly compared with other neuropsychiatric conditions (Pedrotti Moreira et al., 2018). A recent meta-analysis found no association between serum BDNF levels and suicide attempt but did observe that lower levels of plasma BDNF identified those with previous suicide attempt (Salas-Magaña et al., 2017). In women, plasma BDNF levels were similarly significantly associated with a previous suicide attempt (Kudinova et al., 2019). Another recent study found an association between serum BDNF levels and non-active suicidal intent, suggesting that BDNF may be a better indicator of less severe suicidal ideation (Khan et al., 2019). Moreover, decreased levels of BDNF following infusion with the glutamatergic modulator and novel antidepressant ketamine were associated with reduced suicidal ideation (Grunebaum et al., 2017), suggesting that BDNF may be a biomarker of treatment responsiveness.

In genetic studies, the allele distributions of the BDNF *Val66met* allele were significantly associated with the severity of current suicidal ideation, with those carrying the *Met* allele more likely to experience suicidal ideation or a more severe presentation of ideation (Zhang et al., 2019). Taken together, the existing evidence suggests that BDNF may not be an ideal indicator of suicidal ideation or attempt, but further studies in plasma or that differentiate pro BDNF and mBDNF may provide additional insight. In addition, further studies are needed to establish whether BDNF can be used as a biomarker of treatment responsiveness. Ultimately, however, it is often difficult to measure BDNF levels in plasma, serum, or CSF samples; thus, it may not be practical to measure BDNF in a clinical setting regardless of its potential usefulness as a biomarker.

Biometals

Biometals, or metals that are naturally present in biology such as zinc, iron, and copper, are important to the function of biological systems. In neuropsychiatry, they became a topic of interest largely because of the efficacy of lithium in bipolar disorder and because some of these metals were found to play a role in neurotransmitter systems via their ability to influence serotonin and noradrenaline uptake (Komulainen and Tuomisto, 1981).

A small study of individuals who died by suicide found significant variability in 16 biometals across different areas of the cortex compared with those who had died of other causes (including psychiatric controls). For instance, in those who had died by suicide, lower levels of strontium, molybdenum, and ruthenium were evident across multiple areas of the cortex (Dean et al., 2019). Another study that measured levels of the proteins responsible for iron transport in the cortex found lower levels of holo-CP (copper-containing ceruloplasmin) and higher levels of β-amyloid precursor protein, TAU, and transferrin in individuals who died by suicide vs psychiatric and healthy controls (Dean et al., 2020). Given that these studies were conducted post-mortem, more information is needed to determine whether biometal measurements could ultimately predict suicidal behavior. However, the intertwining role of biometals in the serotonergic system, combined with evidence of lithium's efficacy, suggests that this research avenue holds promise.

Additional Biomarkers of Interest

Preliminary evidence also exists for several other promising biomarkers of interest. These include changes in non-coding microRNAs (Belzeaux et al., 2019), dopamine and norepinephrine metabolites (e.g., homovanillic acid and 3-methoxy-4hydroxyphenylglycol) (Hoertel et al., 2021), and uric acid levels (Peng et al., 2018). Despite the preliminary nature of the findings, the encouraging early results warrant further investigation.

Discussion

Suicide is a leading cause of psychiatric-related death, and biomarkers are critical for prediction and intervention. This review of studies published in the last 5 years highlights several promising biomarkers for suicide. These include (1) increased peripheral cortisol levels, which were able to differentiate suicidal ideation from suicide attempt; (2) lower tryptophan levels, which were able to differentiate suicidal ideation from other neuropsychiatric controls; (3) endocannabinoid levels (2-arachidonoylglycerol, AEA, and PEA), which were able to distinguish between previous suicide attempters and those experiencing current suicidal ideation and other neuropsychiatric disorders; and (4) increased CRP levels, which appear to be a good indicator of worsening symptoms of suicidal ideation, suicide attempt, and death by suicide. While fewer studies have examined biomarkers for death by suicide, varying levels of biometals and serotonin transporter binding in the cortex appeared to differentiate death by suicide from other non-suicidal psychiatric controls. Although replication is clearly necessary to confirm these findings, all are promising starting points for future research that could benefit both patients and clinicians.

Biomarkers provide invaluable information about many facets of neuropsychiatric disorders and symptom profiles, including disease presence, disease severity, and disease progression. These categories provide clinicians with tools to confirm diagnoses, predict disease course, and develop appropriate interventions. This toolbox is particularly important with regard to the prediction, diagnosis, and treatment of suicidal ideation, suicide attempt, and death by suicide, as putative intervention currently relies heavily on clinician observation and self-report measures that can be unreliable. In addition, individuals exhibiting suicidal ideation or behavior are quite heterogeneous, and different neuropsychiatric diagnoses and symptom presentations complicate clinical treatment. In this context, personalizing treatment by identifying reliable biomarkers is essential for targeting suicidal ideation, suicide attempt, and death by suicide.

While many promising avenues of research into suicide biomarkers exist, such work is associated with some limitations. First, post-mortem analyses cannot be correlated with current emotional state or cognition and may be confounded by biological changes caused by method of death, such as poisoning or hypoxia from strangulation. Second, small sample sizes in

post-mortem research also limit the power of data analyses. Third, studies conducted after suicide attempt cannot be correlated with psychological state at the time of the attempt. Finally, most studies conducted to date have not accounted for differences in sex, age, or BMI—3 variables shown to significantly affect suicide ideation, suicide attempt, and death by suicide.

Future research should focus on determining effective panels of multiple biomarkers, as this could help control for individual disparities between patients and provide a more complete summary of biological differences. Towards this end, developments in machine learning and precision medicine may help identify promising candidates for panels of different suicidal subtypes (Niculescu and Le-Niculescu 2020). An emphasis on practical biomarkers that are optimal for clinical settings is also important for future translation of these findings. Longitudinal analyses should be prioritized to observe changing levels of biomarkers across diagnoses and treatment. Sex differences in the different subgroups also need to be carefully considered given the aforementioned gender paradox in suicide. Finally, large-scale studies that replicate previous findings in many different populations are necessary before bringing these biomarkers into clinical practice. Determining correlations between varying biomarkers, self-report scales, and psychological scales would provide future clinicians a blueprint to incorporate these biomarkers into everyday practice.

CONCLUSION

Amalgamating research into biomarkers linked to suicide can provide crucial insight into which biological changes are associated with each of these indicators. As reviewed above, the identification and investigation of promising biomarkers are ultimately likely to fundamentally alter the field's ability to pinpoint diagnoses, improve prediction strategies, and help develop novel therapeutic targets for suicidal ideation, suicide attempt, and death by suicide. Targeting those at risk could help decrease the enormous public health toll associated with suicide—both in terms of the personal and societal impact and in terms of reducing healthcare expenses. Quantifiable biomarkers, in conjunction with the psychological scales currently in use, could dramatically improve clinician decision-making and patient outcomes, preventing innumerable deaths and significantly improving global mental health.

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Interest Statement

Dr Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R*,*S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

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