Current Topics in Behavioral Neurosciences 46

Enrique Baca-Garcia *Editor*

Behavioral Neurobiology of Suicide and Self Harm

Springer

Current Topics in Behavioral Neurosciences

Volume 46

Current Topics in Behavioral Neurosciences provides critical and comprehensive discussions of the most significant areas of behavioral neuroscience research, written by leading international authorities. Each volume in the series represents the most informative and contemporary account of its subject available, making it an unrivalled reference source. Each volume will be made available in both print and electronic form.

With the development of new methodologies for brain imaging, genetic and genomic analyses, molecular engineering of mutant animals, novel routes for drug delivery, and sophisticated cross-species behavioral assessments, it is now possible to study behavior relevant to psychiatric and neurological diseases and disorders on the physiological level. The Behavioral Neurosciences series focuses on translational medicine and cutting-edge technologies. Preclinical and clinical trials for the development of new diagnostics and therapeutics as well as prevention efforts are covered whenever possible. Special attention is also drawn on epigenetical aspects, especially in psychiatric disorders.

CTBN series is indexed in PubMed and Scopus.

More information about this series at http://www.springer.com/series/7854

Enrique Baca-Garcia
Editor

Behavioral Neurobiology of Suicide and Self Harm

Springer

Editor
Enrique Baca-Garcia
Fundacion Jimenez Diaz Psychiatry Department
Universidad Autonoma de Madrid
Madrid, Spain

ISSN 1866-3370 ISSN 1866-3389 (electronic)
Current Topics in Behavioral Neurosciences
ISBN 978-3-030-57573-1 ISBN 978-3-030-57574-8 (eBook)
https://doi.org/10.1007/978-3-030-57574-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Understanding what underlies a purely human, although paradoxical, behavior such as suicidal behavior remains to be as challenging as reversing a polyhedral puzzle. On the one hand, the cause of death depends totally on who suffers it. On the other hand, suicide is the cause of death in which we have made the least progress in terms of management and prevention as a species. Recently, the COVID-19 pandemic has shown that while we are able to devote enormous efforts to external threats, we do not appear to have the same capacity to modify a behavior which is theoretically under our control.

Although out of the scope of this volume, it is worth noting all the profound ethical and anthropological implications of suicide since ancient times. On purpose, this volume has omitted any reference to culture since plenty of work has been dedicated to this topic elsewhere and we aimed to focus on clinical and biological aspects of suicide and suicidal behavior.

Thankfully, true eminences and world leaders in suicide research have kindly agreed to collaborate and co-authored the following chapters. The reader will find this volume to be an up-to-date critical review of cutting-edge issues in suicide research, hence including authors' personal views.

Dr. Arles provides an updated overview of the epidemiology of suicide in the USA. Although the USA is the top world country in suicide research, it is one of the few countries, according to the World Health Organization, where there has been no decrease in suicidal behavior over the past few years, which makes this chapter particularly relevant.

Prof. Oquendo outlines the difficulties in research on the prevention and treatment of suicidal behavior. How far can we go? What are the problems that prevent us from progressing?

Prof. Turecki covers a subject which is absolutely topical and at the frontier of knowledge: the epigenetics of suicide. Not only is this area of ongoing research on the borderline between Darwinian and Lamarckian dogmas, but also it may shed some light on the understanding and treatment of other diseases such as cancer.

Epigenetics links exposure to the environment with the transmission of these changes to the next generations, which may therefore explain the mechanisms through which suicide risk may run between generations.

An unavoidable topic concerns the relationship between psychopathology of suicidal behavior (hopelessness, impulsiveness, and aggressiveness) and their biological correlates, which is dealt by Dr. Vaquero, which critically reviews the definition of these psychopathological characteristics and the extent to which they may be related to biological markers, thus becoming potential endophenotypes.

A very relevant issue for clinicians is the repetition of suicide attempts due to health services use and high risk of further suicidal acts. Although this topic has received little attention from previous research, Prof. Mendez has done an excellent update.

Although well established, we tend to ignore the association of suicidal behavior with a clear "sexual dimorphism." Dr. Barrigon has compiled epidemiological and clinical data to support this notion, namely relevant differences in suicidal behavior between men and women. Whether these differences could be attributable to cultural (gender) or biological factors (sex) requires further investigation.

As shown in the index, from this chapter onwards, the most novel lines of research, which may provide a new horizon in suicide research, are summarized.

Thus, Dr. Perez-Rodriguez has review neurocognition in suicide behavior to conclude that there is a neurocognitive endophenotype of suicidal behavior which is transdiagnostic. This hypothesis may be crucial when it comes to finding biological markers and proposing new explanatory mechanisms for suicidal behavior and alternative therapeutic approaches.

The role of lipids, especially fatty acids, in suicidal behavior opens a research area on nutrition and behavior as Prof. Sublette has reviewed.

Suicidal behavior, despite affecting several million people worldwide annually, lacks evidence-based treatments, particularly there are no targeted biological treatments. Rather, available treatments address other "core" mental disorders linked with suicidality. Therefore, the emergence of the glutamatergic hypothesis, which may not only have implications on treatment, represents a paradigm shift and an opportunity for the launch of therapeutic research. In this regard, the relationship between physical and psychological pain in suicidal behavior offers new therapeutic opportunities for crisis intervention as Prof Courtet and Prof Saiz have described.

In the two final chapters (by Prof Lopez-Castroman and Prof Artes), the reader will be provided with an overview on novel methodology for suicide research: the role of ecological monetary assessment in monitoring those at high risk of suicidal behavior, such as suicide attempters. For instance, sleeping, on which we spend one-third of our life, is essential for the correct functioning of our nervous system and therefore, implications on decision-making, including suicidal thoughts. Undoubtedly, this is a promising field which comes hand in hand with the technological revolution which will transform mental healthcare and psychiatric research.

This work is the result of the collaboration of top-level professionals in both authorship and editorial management. It is fair to acknowledge the excellent work of the series editor Charles Marsden and the production team at Springer (Alamelu Damodharan, Gerit Rother, Coral Zhou, and Susanne Dathe). In conclusion, we all hope that this book, while creating further controversy, will be an encouragement to continue advancing this fascinating and challenging research area.

Madrid, Spain Enrique Baca-Garcia

Contents

Why Are Suicide Rates Increasing in the United States? Towards a Multilevel Reimagination of Suicide Prevention

Gonzalo Martinez-Ales, Daniel Hernandez-Calle, Nicole Khauli, and Katherine M. Keyes

Contents

Abstract Suicide, a major public health concern, takes around 800,000 lives globally every year and is the second leading cause of death among adolescents and young adults. Despite substantial prevention efforts, between 1999 and 2017, suicide and nonfatal self-injury rates have experienced unprecedented increases across the United States – as well as in many other countries in the world. This chapter reviews the existing evidence on the causes behind increased suicide rates and critically evaluates the impact of a range of innovative approaches to suicide prevention. First, we briefly describe current trends in suicide and suicidal behaviors

G. Martinez-Ales (✉)
Columbia University Mailman School of Public Health, New York, NY, USA

Universidad Autónoma de Madrid School of Medicine, Madrid, Spain
e-mail: gm2794@cumc.columbia.edu

D. Hernandez-Calle
La Paz University Hospital, Madrid, Spain

N. Khauli and K. M. Keyes
Columbia University Mailman School of Public Health, New York, NY, USA

Curr Topics Behav Neurosci (2020) 46: 1–24
https://doi.org/10.1007/7854_2020_158
Published Online: 30 August 2020

and relate them to recent time trends in relevant suicide risk markers. Then, we review the existing evidence in suicide prevention at the individual and the population levels, including new approaches that are currently under development. Finally, we advocate for a new generation of suicide research that examines causal factors beyond the proximal and clinical and fosters a socially conscious reimagining of suicidal prevention. To this end, we emphasize the need for the conceptualization of suicide and suicidal behaviors as complex phenomena with causes at several levels of organization. Future interdisciplinary research and interventions should be developed within a multilevel causal framework that can better capture the social, economic, and political settings where suicide, as a process, unfolds across the life course.

Keywords Multilevel epidemiology · Prevention · Self-harm · Suicide

1 Introduction

Suicide, the "only one really serious philosophical problem" (Camus 1955), is a major public health concern that takes around 800,000 lives globally every year. Death by suicide is the second leading cause of death among youth and accounts for 57% of all violent deaths and roughly 1.5% of all mortality – more than malaria or breast cancer (World Health Organization 2019). Because suicide "is of all modes of death that which leaves in the hearts of the sorrowing survivors the most poignant and the most enduring sting" (Wade 1879), its impact on families and communities is far-reaching: grief, stigma, and subsequent increases in psychiatric conditions and suicide rates reverberate over generations. The question whether suicide is a preventable outcome has been present in the medical literature since the late nineteenth century, when the act of suicide started being considered as caused by mental illness rather than by moral failing (Maris 2000) and it became the subject of medical (Wade 1879; Pacheco 1936) and public health inquiry (Oliven 1954). This chapter outlines recent advances in suicide prevention and critically discusses how several innovative approaches to prevention efforts may potentially impact current trends in suicide and nonfatal self-injury, with a focus on the increasing burden of suicide in the United States. First, we describe recent data on trends in suicide and suicidal behaviors and relate them to recent time trends in relevant suicide risk markers. Then, we review the existing evidence in suicide prevention at the individual and the population levels, including new approaches that are currently under development. Last, we emphasize the need for the conceptualization of suicide and suicidal behaviors as a complex phenomenon, with causes at multiple levels of organization, which requires the development of interdisciplinary research and intervention initiatives within a multilevel causal framework.

2 Recent Trends in Suicide and Nonfatal Self-Harm

2.1 Global Trends in Suicide and Nonfatal Self-Harm

2.1.1 Global Trends in Suicide

Suicide ranks currently as the 18th leading cause of death worldwide – 2nd in ages 15 to 29 and 3rd in ages 15 to 45 (World Health Organization 2019). Given the fact that considerable limitations exist in the detection and registration, the number of deaths by suicide is likely underestimated (World Health Organization 2014; AbouZahr et al. 2015). Also of note, even though most research in the suicide prevention field comes from high-income countries, almost eight in every ten suicides take place in low- and middle-income countries (LMIC) (World Health Organization 2018a; Lopez-Castroman et al. 2015). In 2016, countries with the highest suicide rates included those in Eastern European and south sub-Saharan African countries such as Lithuania (31.0 suicides per 100,000 population), Russia (30.6), Lesotho (39.0), and Zimbabwe (27.8) which reported the highest suicide rates overall. High-income countries (HIC) with traditionally high rates include those in the Asia Pacific region, such as South Korea (25.1) and Japan (17.3). Countries with relatively low suicide rates include those in Latin American and East Asian countries, such as Jamaica (2.9), Peru (3.0), Lebanon (2.4), and Kuwait (2.7) (Naghavi 2019). North America and Western Europe show suicide rates that stand at around 11.0 suicides per 100,000, the global age-standardized rate (Turecki and Brent 2016).

While a recent study suggests that the global age-standardized mortality rate due to suicide has decreased by 32.7% between 1990 and 2016 (Naghavi 2019), trends in suicide rates vary substantially between countries. From 195 countries included in Naghavi et al.'s analysis, 63 registered noticeable decreases and 132 reported not significant differences and only 8 increases in suicide rates (Naghavi 2019). Notably, substantial declines in China (−64.1% decrease in age-standardized suicide mortality rate between 1990 and 2016), a country that had constant increases in suicide rates between years 1900 and 1970 (Phillips et al. 2002), and India (−15.2% decrease) drive most of the global decrease in suicide rates, given that these two countries account for approximately 36% of the world population (United Nations, Department of Economic and Social Affairs, Population Division 2017) and 44.2% of deaths by suicide globally in 2016. The countries with the highest observed recent increases in suicide rate are Zimbabwe (+96.2%), Jamaica (+70.9%), Paraguay (+70.4%), Uganda (+61.6%), several western sub-Saharan African countries like Liberia (+45.9%) or Cameroon (+37.6%), and Mexico (+35.6%).

Interestingly, the estimated global male to female ratio in suicide has seemingly increased in the recent decades from 1.40:1 in 1990 to 2.17:1 in 2016 (Naghavi 2019), and suicide mortality between ages 15 and 19, an age stratum where females traditionally displayed higher suicide rates, shows now virtually no age-specific differences (Rhodes et al. 2014; Wasserman et al. 2005). Age distribution of suicide

mortality varies considerably across the globe, but it generally distributes in a bimodal fashion, peaking first around adolescence and again in adults over 70 years of age. There are noticeable differences between low/middle- and high-income countries in this respect. Middle-aged males have higher suicide rates in HIC than their counterparts in LMIC, where suicide rates are higher among adolescents and elderly females (World Health Organization 2014).

2.1.2 Global Trends in Nonfatal Self-Harm

Finally, while suicidal behaviors constitute the most reliable predictor of subsequent suicide risk (Franklin et al. 2017), global nonfatal self-injury rates are difficult to study since no international entity has been able to maintain a systematic registry, and most nationwide or international suicide statistic reports do not include information on nonlethal self-injury (World Health Organization 2014). Based on data available from both regional studies using medical records or surveys and from the World Mental Health Surveys conducted in 21 countries between 2001 and 2007 and using the WHO Composite International Diagnostic Interview (CIDI) (Nock 2012; Kessler and Wang 2008), WHO estimates that over 20 suicide attempts take place globally for each death by suicide (World Health Organization 2018a). However, the number of estimated suicide attempts, as well as the relationship between attempted and completed suicide, varies remarkably across countries. For example, while the United States reported around a 5% 12-month prevalence of suicide attempts, in Italy, the prevalence was just 0.5% for the same time period (Borges et al. 2010). Further, Spain reports 174.4 attempts per death by suicide, a figure that lowers to 64.1 in Italy (Blasco-Fontecilla et al. 2018). Of note, Blasco-Fontecilla et al. have recently proposed the use of a ratio between attempted and completed suicides across countries as a means of evaluation of healthcare delivery for people at high risk of suicide (Blasco-Fontecilla et al. 2018).

2.1.3 Global Trends in Mood and Alcohol Use Disorders

Comorbid psychiatric and substance use disorders – in particular mood and alcohol use disorders – remain the most consistent modifiable predictors of suicide and suicidal behaviors worldwide (Nordentoft et al. 2011; Moscicki 1997; Nock 2012). Studies based on psychiatric autopsies of suicide decedents suggest that affective disorders, present in roughly half of those who die by suicide (Cavanagh et al. 2003; Arsenault-Lapierre et al. 2004), are a powerful independent risk factor for suicide, especially among the elderly (Conwell et al. 2002). Similarly, recent meta-analyses indicate that acute alcohol use increases the risk of suicide attempts by approximately seven times (Borges et al. 2017) and that the risk of suicidal ideation, suicidal attempts, and death by suicide are each increased by 2–3 times among people with alcohol use disorders (AUD), in comparison with the general population (Darvishi et al. 2015). Hence, global trends in the prevalence of mood disorders and AUD are

of interest when interrogating the evidence behind recent trends in suicide. Much like suicide, there is wide country-level heterogeneity in both the prevalence of psychiatric and substance use disorders, as well as their trends over time, and there is debate as to whether there exists an identifiable international pattern (Steel et al. 2014; Kessler et al. 2011; Whiteford et al. 2013a, b). However, there is consensus that both mood disorders (World Health Organization 2017) and AUD (Manthey et al. 2019) seem to be on the rise across the globe. Until 2025, total alcohol per capita consumption in persons aged 15 years and older is projected to increase in the Americas, Southeast Asia, and the Western Pacific (World Health Organization 2018b). In brief, available evidence indicates that the most salient drivers of prevalence and trends in mood disorders include country-level economic and employment opportunities as well as the morbidity and freedom of women in society (Seedat et al. 2009). Drivers of prevalence of alcohol and other substance use disorders include historical country culture (Skog 1985), and trends in substance use disorders are best predicted by changes in policies as laws such as trade policy, taxes, and restrictions on sales (Anderson et al. 2009; Manthey et al. 2019).

2.2 Trends in Suicide and Nonfatal Self-Harm in the United States

2.2.1 Trends in Suicide in the United States

Suicide rates in the United States declined between 1990 and 1999 (McKeown et al. 2006). However, from 1999 to 2016, suicide rates increased by 30% in 44 of 50 US states and across every age group, though most dramatic increments were observed in men aged 45 to 64 (Stone et al. 2018). This trend was maintained into 2017, with suicide rates increasing from 13.5 per 100,000 to 14.0 per 100,000 (Hedegaard et al. 2018). At the moment, suicide is the second leading cause of death among Americans aged 10 to 34 (Centers for Disease Control 2018a) and generates an estimated national cost of almost $100 billion per year (Shepard et al. 2016).

Within the United States, high suicide rates correlate with geographic factors such as high elevation (Cheng et al. 2018), as well as demographic factors such as high concentrations of indigenous populations (Leavitt et al. 2018). Occupational exposures also impact suicide risk: for example, risk is particularly heightened among US military members who have experienced active combat and traumatic events (Pompili et al. 2013). Historically, members of the armed forces showed lower death rates, including suicide, than the general population. Notwithstanding, suicide among the US military has escalated markedly since 2004 (Armed Forces Surveillance Center 2012). Following such unprecedented increases among civilians and army members, suicide rates in both populations are now comparable (Naifeh et al. 2012).

2.2.2 Trends in Nonfatal Self-Harm in the United States

Nonfatal self-injury is also increasing in the United States across age. Self-reported suicide attempts across two cross-sectional surveys of adults completed 10 years apart found an increase in prevalence from 0.62% in 2004–2005 to 0.79% in 2012–2013 (Olfson et al. 2017), with adults aged 21–34, those with high school or less education, and those with psychiatric disorders showing the highest increases. Analyses of hospitalization records also indicate that self-injury is on the rise (Mercado et al. 2017; Owens et al. 2006; Ting et al. 2012), especially among middle-aged adults (Olfson et al. 2015).

Adolescents and young adults are evidencing particularly high increases in nonfatal self-injury in the United States. The prevalence of adolescents reporting having "seriously considered attempting suicide" in the past 12 months increased from 14.5% in 2007 to 17.2% in 2017 (Centers for Disease Control 2018b), although we should point out that overall trends since the mid-1990s suggest declines. Emergency visits and hospital admissions coded for suicidal ideation or attempt across 49 children's hospitals in the United States increased almost tripled between 2008 and 2015 (Plemmons et al. 2018). While the largest increases were observed for 12–14- and 15–17-year-olds, girls, and non-Hispanic whites, significant increases can be identified across age, gender, and race. Burstein et al. (2019) reported that emergency department visits due to suicide attempts or ideation among children and adolescents doubled (from 580,000 to 1.12 million) over the 2007–2015 period.

2.2.3 Trends in Mood and Alcohol Use Disorders in the United States

As mentioned, examining time trends in the prevalence of mood disorders and AUD can provide additional insights when trying to contextualize trends in suicide and suicidal behaviors.

In the United States, mood disorders are also increasing among adolescents – in particular adolescent girls (Mojtabai et al. 2016). Further, a recent increase in depressive symptoms among American girls has been confirmed by studies using national representative US studies, with no or less change among boys (Keyes et al. 2019a). Also, young adults attending college have evidenced increases in anxiety and depressive disorders in the past decade (Oswalt et al. 2018). Whether a similar rise in affective disorders can be identified among adults is less clear. According to Case and Deaton, it seems that middle-aged men with low education have experienced increases in the prevalence of non-specific psychological distress over the 1997–2013 period (2015). Along those lines and during the same time, the socioeconomically disadvantaged experienced decreases in life satisfaction, positive affect, and psychological well-being and increases in negative affect (Goldman et al. 2018). Annual nationally representative surveys indicate recent increases in psychological distress and major depressive episodes among adults, especially

among those with low socioeconomic status (Twenge et al. 2019; Mojtabai et al. 2016), a finding in line with other national data (Weinberger et al. 2018). All in all, the small range of observed increases is inconsistent over the life course, and further, sustained surveillance is needed to clarify whether they reflect temporary, time-limited noise in the data or there is a real increasing trend that may underlie changes in suicide risk in the United States.

As for AUD, while some studies indicate slight recent decreases in rates (Center for Behavioral Health Statistics and Quality 2018; Cheng et al. 2018) and overall per capital alcohol consumption (Haughwout et al. 2016), other studies show rates of AUD to be on the rise (Grant et al. 2017). Keyes et al. (2011) have suggested that cohort effects might account for these apparent discrepancies when data are aggregated by time period. The identification of birth cohorts at high risk for alcohol-related problems is key for etiological research, as well as for public health planning (Keyes et al. 2011). For example, recent literature points to a particular increase of alcohol use, AUD, and alcohol-related mortality risk among older adults (Holahan et al. 2014; Han et al. 2017). Gender-specific differences are also present in AUD rates, with men showing higher prevalence of AUD across all life course stages (Grant et al. 2015), and might be experiencing recent changes over time: A recent review of studies on national trends in alcohol consumption suggests that these differences may be diminishing and even reversing for some birth cohorts (Keyes et al. 2019b).

2.3 Why Are Suicide Rates Increasing in the United States?

To sum up, there is substantial evidence that increases in suicide rates somewhat overlap with increases in mood and affective disorders, especially among adolescents. However, we can only speculate on the reasons underlying such increases. Considerable attention has been directed towards the relationship between suicide and opioid overdose, which increased exponentially, in tandem with suicide rates, since approximately 1999 in the United States (Scholl et al. 2018; Bohnert and Ilgen 2019). Opioid overdose and suicide deaths share some demographic and clinical correlates. For example, roughly one in four individuals with opioid use disorder (OUD) also meet criteria for AUD (Hser et al. 2017), and a strong relationship between mood disorders and opioids use/OUD has been documented in nationally representative studies (Martins et al. 2009; Martins et al. 2012). However, it should be noted that the trends are not entirely concordant, given that there are different demographic groups that have had the largest increase in suicide compared to opioid overdose. All in all, similar mechanisms may underlie both increasing trends: First, suicide risk among users of medical opioids increases with opioid dose (Ilgen et al. 2016). Second, communities ravaged by losses due to opioid overdoses may have higher levels of collective trauma and psychological distress that would, in turn, drive a higher risk of suicide (Case and Deaton 2017). Third, access to opioids entails access to a potentially lethal means. Notwithstanding, there is limited

evidence on the use of opioids for suicide completion: in the United States, poisoning accounts for less than 15% of suicides, and opioids are present in a minority of those poisonings (Stone et al. 2018). That said, providing an accurate estimate of the number of unintentional opioid overdoses that may have actually been suicides, especially among people with OUD, is challenging, given evident difficulties in determining the intentionality of death.

On another front, a brief discussion on recent trends in access to lethal means is warranted. Changes in access to means have been considered a faithful predictor of changes in suicide rates elsewhere (Gunnell and Eddleston 2003). Because firearm suicide is the most common method of suicide in the United States, accounting for one in two suicides among males and one in three among females, suicides would be expected to closely relate to access to firearms. However, even though this suicide method represents a plurality of suicide deaths in the United States, recent data suggest that firearm ownership is decreasing, rather than increasing, in the United States (Smith et al. 2015). In addition, between the 1999–2007 and the 2008–2015 periods, the increase in suicides by firearm was less pronounced than the increase in suicides by other means, such as suffocation (Centers for Disease Control 2018a). Given that no evidence suggests a recent increase in access to suffocation means in the United States, variations in access to lethal means do not seem to have had a tangible role in current increases in suicide.

Case and Deaton (2017) have suggested the provocative hypothesis that increases in suicide rates, OUD, opioid overdose, AUD, and alcohol-related deaths can be framed as the result of a long process of erosion of the American middle class, especially regarding middle-aged men and those with low educations, by means of the progressive loss of key components of the well-being of the working class, such as job stability. However, it has been difficult to provide compelling evidence to back such hypotheses. For example, Masters et al. (2018) found that the age groups where drug overdose rates have recently peaked do not mirror trends for the other contributors to America's "deaths of despair," such as suicide. Hence, it seems plausible that factors driving deaths by suicide may be at least partially different from those determining trends in opioid overdose. Further, while measures of economic decline at the county level, such as unemployment, can predict suicide, they explain less than 1% of the variation in rates over time (Ruhm 2018).

3 Individual-Level Suicide Prevention

Over the last decades, most of the attention in the field of suicide prevention has been directed towards either improving the ability of clinicians at identifying individuals at high risk of suicide and suicidal behaviors (individual-level suicide risk prediction) or developing and scaling up interventions to reduce the risk of suicide among those at high risk. Notwithstanding, suicide risk prevention remains a largely unmet clinical need. The following section reviews the existing evidence regarding

individual-level suicide risk prevention and interventions, discusses main existing challenges, and proposes potential next steps to overcome those challenges.

3.1 Individual-Level Suicide Risk Prediction

3.1.1 The Role of Clinical Expertise, Risk Factors, Scales, and Computer Science

In most clinical settings, mental health professionals are in charge of estimating the probability that a patient will attempt suicide in the future in order to inform appropriate clinical decision-making. The clinician's assessment of a patient's suicide risk is largely based on a combination of prior clinical expertise and a series of biological, behavioral, and social risk factors (Mann et al. 1999; Brent et al. 1993; Dube et al. 2001; Roy 1982; for a review, see Franklin et al. 2017). In addition, there is a range of available suicide assessment scales to support decision-making in the clinical context (e.g., Posner et al. 2011; Beck et al. 1997; for a review, see Runeson et al. 2017).

Pokorny (1960) pioneered the use of clinical and sociodemographic factors to predict suicide risk in a case-control study featuring 44 veterans who died by suicide. Several risk factors for suicide and suicidal behaviors have since been determined, including a range of psychiatric disorders (especially mood disorders), substance use disorders (especially those related to alcohol use), being admitted to a psychiatric hospital, having attempted suicide in the past, being male, widowed, living alone, etc. (Franklin et al. 2017). However, several limitations undermine the contribution of suicide risk factor identification to effective prevention efforts (Owens and Kelley 2017).

While most accepted risk factors for suicide are highly prevalent, suicide behaviors and especially death by suicide are relatively rare events, something Hawton (1987) famously referred to as the "base-rate problem". Hence, even among those classified as "high-risk," most will never engage in suicidal behaviors, and attempts to identify particular persons who will commit suicide tend to yield striking false-positive rates (Pokorny 1983). MacKinnon and Farberow (1976) calculated the positive predictive value (PPV) of a hypothetical test with 99% sensitivity and 99% specificity in a hypothetical sample with an incidence of 250 per 100,000. Their estimate of a PPV of just 0.25% indicates a false-positive rate of 99.75%. Of note, actual clinical scales have around 80% sensitivity and 46% specificity (Chan et al. 2016).

Although most mentioned attributes, such as substance use disorders or psychiatric conditions, are present in most people who attempt or die by suicide, they are also present to a variable extent among people who do not report engaging in suicidal behaviors. For example, while 90% people who die by suicide in Western countries have diagnosable mental disorders, only 2% of psychiatric patients actually die by suicide – 4% in the case of affective conditions (Bertolote et al. 2004; Bostwick and Pankratz 2000). Along those lines, Large et al. (2011) evaluated the

clinical utility of high-risk patient selection through a large meta-analysis. They found that 56% of suicides occurred in high-risk patient groups, while 44% occurred among low-risk ones, something near the 50–50% percent chance of flipping a coin. This is also true for the most accepted risk factor for death by suicide, namely, suicidal behaviors. Owens et al. (2002) reviewed 90 studies that followed cohorts of suicide attempters for a long period of time. They found that, while their relative risk of dying by suicide was remarkably high compared to the general population, the rate of suicide after a 9-year follow-up stood around just 7%.

Last, even most accepted suicide risk assessment scales seem to perform modestly when applied to clinical samples. A recent meta-analysis evaluating all available risk scales found that a pooled 96.3% of those who tested positive would never go on to die by suicide (Carter et al. 2017). As a result of the inherent limitation of using suicide risk factors and scales to estimate the probability of patients engaging in suicidal behaviors, Wang et al. (2016) concluded that even highly trained psychiatrists roughly achieve a 10.3% PPV when predicting subsequent suicide attempts in a 6-month longitudinal study of suicide attempters.

Computer science and the use of machine learning algorithms for clinical prediction have yielded a number of promising findings in the field of suicidology. Using clinical and administrative records to extract clinical, sociodemographic, and administrative data of 53,796 hospitalized soldiers who had psychiatric diagnoses, Kessler et al. (2017) obtained regression tree-driven estimates of suicide risk following hospital discharge, reporting an area under the curve (AUC) of 0.85. Other researchers have focused on less selected samples, used different statistical tools (e.g., neural network methods), and obtained comparable AUC values (DelPozo-Banos et al. 2018; Simon et al. 2018). In a recent comprehensive review, Belsher et al. (2019) ran several simulations to study the variation of the PPV of different developed algorithms in hypothetical populations with a variety of suicide rates. Even though these methods outperformed clinical assessments in terms of sensitivity and AUC, they concluded that their resulting false-positive rates remained too high to be currently useful for the clinical practice. Finally, further innovations in technology-aided suicide prevention, including techniques such as speech analysis or cell phone geolocation, are currently under development (Vahabzadeh et al. 2016).

3.1.2 When Is Suicide Risk Highest?

Time variations in suicide risk pose an additional challenge for prediction in suicidology. Even if we accepted that a suicide risk score can be derived from the combination of a set of the abovementioned characteristics, there is still a long way to go when it comes to determining *when* this risk is higher, a key limitation that greatly undermines effective intervention planning. Large et al. (2011) estimated that, if an ultra-high-risk patient has a 5.5% suicide mortality risk of over a period of 5 years, the probability of suicide per week is roughly 0.02%. In fact, many accepted risk factors remain stable over time, like family history of suicide or gender (Hawton

2002), or take a long time to establish and resolve, like a disadvantaged socioeconomic status (Glenn and Nock 2014). While most prospective studies have relied mainly on assessments of the association between characteristics of participants at baseline and subsequent suicide and suicidal behaviors, in real life these "risk factors" interact in hard-to-capture complex hierarchical networks and undertake dramatic variations over time. As an example, studies trying to understand the excess suicide risk among people living with schizophrenia have shown that, compared to counterparts with good premorbid functioning, patients with low premorbid life functioning may have higher suicide rates after disease onset but lower long-term risk (Madsen and Nordentoft 2012; Ayesa-Arriola et al. 2015).

One of the most targeted time-varying risk factors for suicide is suicidal ideation (SI), because it necessarily antecedes suicidal acts (Kessler et al. 1999). Notwithstanding the marked within-person variations that suicidal thoughts undertake over extremely short periods of time (Kleiman and Nock 2018), most studies have used single-point measurements of SI, leading to interestingly mixed results. For example, one study estimated that suicidal "ideation" entailed a lower risk of transitioning to an attempt than suicide "planning" (Kessler et al. 1999), while another study found the risk of "active" and "passive" suicidal ideation to be roughly the same (Baca-Garcia et al. 2010), and a third one concluded that attempting suicide was more frequent than planning it among suicidal ideators (Lee et al. 2007).

Ecologic momentary assessment (EMA), a novel technology that allows for the collection of data using smartphone-delivered assessments "in the natural contexts of daily life" (Husky et al. 2014), seems particularly promising to study the variation of suicidal thoughts and how they relate to suicide risk. By measuring a participant's domains of interest repeatedly, EMA can accurately characterize variations in SI and relate them to a range of potential triggers and subsequent outcomes (e.g., Rodriguez-Blanco et al. 2018; Davidson et al. 2017; Kleiman and Nock 2018). For example, Hallensleben et al. (2018) recently portrayed the mentioned variation of SI experienced by high-risk individuals over short periods of time, and Husky et al. (2017) linked suicidal thoughts to a range of daily life predictors.

3.2 Individual-Level Interventions for Suicide Risk Prevention

Developing, implementing, and scaling up effective suicide prevention strategies is critical to obtain improvements in individual-level suicide prevention efforts. In fact, a range of interventions in clinical settings, including psychotherapeutic as well as pharmacological strategies, have proved effective at lowering suicide risk in high-risk psychiatric patients (for comprehensive reviews, see Mann et al. 2005; van der Feltz-Cornelis et al. 2011; Zalsman et al. 2016). Here, we will focus on the role of brief contact interventions, a particularly cost-effective psychosocial approach to suicide risk reduction.

3.2.1 Brief Contact Interventions

Recently, an emerging body of literature suggests that evidence-based psychotherapeutic treatments (e.g., dialectical-behavior therapy or interpersonal therapy) (Linehan et al. 2006; Heisel et al. 2015) do not outperform more feasible programs simply seeking to ensure contact between the patient and treatment providers over a sustained period of time (Martínez-Alés et al. 2019). In a notable example, a meta-analysis of randomized controlled trials found that the WHO Brief Intervention and Contact program, a flexible schedule of telephone and in-person repeated follow-ups initiated shortly after discharge following a suicide attempt, was more effective at lowering subsequent suicide risk than an intervention based on cognitive-behavioral therapy (Riblet et al. 2017).

Because patients discharged from the hospital after a suicide attempt tend to experience low adherence rates to treatment during follow-up due to a variety of barriers in access to outpatient care, actively enhancing their contact with mental health providers seems intuitive. In a pioneer randomized trial including 843 suicide attempters who did not engage in follow-up treatment, Motto and Bostrom (2001) assigned half of participants to receive personalized letters over the following 5 study years. After just 2 years, the suicide rate among the control group doubled that of those assigned to the intervention. Variations of this approach include the use of short text messages, postcards, telephone calls, etc. (Hassanian-Moghaddam et al. 2011; Cebria et al. 2013; Kaput et al. 2014; Vaiva et al. 2018). The Safety Planning Intervention is an interesting evidence-based augmentation of brief contact strategies that is widely implemented across the globe that seeks to reduce the patient's access to lethal means, prioritize the most adequate coping strategies during suicidal crises, and enhance outreach to mental health providers (Stanley and Brown 2012).

4 Population-Level Suicide Prevention

4.1 Population-Level Suicide Risk Factors: The Logic in Ecological

Suicide rates are determined, at least partially, by causal factors that affect entire societies and thus operate beyond the level of the individual, but impact individuals within those societies. Durkheim's (1966) seminal book *Le Suicide* captured these "(causes) of suicide as a collective phenomenon," "whose action is felt by society as a whole". Rose (2001) discussed such population-level effects when discussing blood pressure with "why some individuals have high blood pressure is a different question than why some populations have more burden of high blood pressure?". Echoing Durkheim and Rose's work, while we term "individual-level factors" those that predict who will die by suicide and who will not within a population, we also term "group-level factors" those that predict which populations will have higher or

lower suicide rates. Over the twentieth century, these group-level factors have been commonly used to explain health outcomes in psychiatric epidemiology: Morris (1957) referred to this as the "ecology of mental disorders" in his *Uses of Epidemiology*. For instance, in a classic study, Faris and Dunham described a direct correlation between level of urbanicity and rate of schizophrenia in Chicago (1939), a finding that leads to a century of hypotheses and empirical data analysis regarding environmental risk factors of psychotic disorders (Plana-Ripoll et al. 2018).

Mervyn Susser coined the term "integral variables" (Susser 1994a) to refer to variables that are shared by a whole social group, such as economic downturns or urban dwelling. By definition, a comparison between individuals who comprise the target social group will not allow to estimate the causal effect of an integral variable. Instead, ecologic designs that consider the whole group as a legitimate unit of analysis and perform between-groups comparisons are required (Susser 1994b, 1972). In words of Durkheim (1966), "the social rate must be taken directly as the object of analysis". For example, the tenfold difference in suicide rates between Lithuania or Russia and Peru or Lebanon (Naghavi et al. 2019) can illustrate the need of the conceptualization of suicide using an ecological perspective. Similarly, remarkable differences can be found across countries within Europe (Organization for Economic Co-operation and Development 2019), states and regions within the United States (Kegler et al. 2017), or areas within the city of London (Rezaeian et al. 2005). Such variation prompts questions about how a region's political, socioeconomic, and cultural context might impact suicide risk.

Notwithstanding, traditional and innovative prediction efforts have characteristically approached suicide from an individual-level perspective (e.g., Roy 1982; Ursano et al. 2014; Vahabzadeh et al. 2016) and may be overlooking central determinants of risk that include country-level and area-level social and political factors, such as general area industry and employment, past suicide rates in the geographic area, and economic growth and contraction (Fountoulakis et al. 2016). Further, beyond geopolitical concerns are actual environmental factors that influence risk, including temperature, elevation, both synthetical and natural chemical exposures, and other topographical and toxicological features of the physical environment (Deisenhammer et al. 2003; Akkaya-Kalayci et al. 2017; Fountoulakis et al. 2016).

4.2 Population-Level Suicide Prevention

Several population-level interventions have proved effective for suicide risk reduction. In general terms, they fall within three main categories: education campaigns, regulations in mass media coverage, and restriction of access to means. Among evidence-based educational approaches, we would like to highlight the implementation of school-based programs for suicide prevention (Zenere 3rd and Lazarus 1997; Wasserman et al. 2015) and "gatekeeper training" strategies, directed towards individuals who have high probability of contacting suicidal individuals but are not

designated specifically as mental health professionals, such as teachers or general practitioners (Isaac et al. 2009).

Media reporting of high-profile suicides has a large evidence base as a causal catalyst to subsequent increases in population-level suicide rates (Sisask and Varnik 2012; Pirkis et al. 2006a, b; Fink et al. 2018). This phenomenon is sometimes referred to as the "Werther effect," after the protagonist of a 1774 German novel who dies by suicide, prompting so-called "copycat" suicides reported throughout Europe at the time. Increases in suicide after widespread media coverage of a suicide event are framed within the broader behavioral contagion theory (Gould 2001). Notably, recent studies point out the importance of the social context at shaping the harmful, neutral, or protective impact of suicide media portrayals (VanderWeele et al. 2019). Opportunities for effective suicide prevention at this level generally consist in a variety of reporting recommendation guidelines seeking to enhance responsible, non-sensationalist coverage of suicide and related events (American Association of Suicidology 2019).

Mass media also plays a role in the regulation of a population's "cognitive-access" to suicide means and methods (Florentine and Crane 2010; Fink et al. 2018). However, the term "means reduction" usually refers to evidence-based interventions aimed at preventing the population from physically accessing potentially lethal means (e.g., Gunnell and Eddleston 2003; for a review, see Pirkis et al. 2015). This approach builds on empirical studies providing a substantial body of evidence that ease of access greatly impacts the risk of attempting suicide (Marzuk et al. 1992) and the method choice (Eddleston and Gunnell 2006), especially in impulsive suicidal behaviors – the most frequent type (Hawton et al. 2013). Of note, Deisenhammer et al. estimated that half of suicide attempt survivors report an interval between the onset of a serious suicidal thought and subsequent suicide attempt of 10 min or less (Deisenhammer et al. 2009).

While reductions in access to lethal means are associated with lives saved, there remains concern about substitution of method as an additional risk for suicide. Indeed, reducing the access to lethal means is more effective if an alternative method available for substitution has a lower associated lethality – this can be due to a higher ability to abort mid-attempt or to a lower inherent deadliness. Firearms, present in almost 33% of homes in the United States and in 51% of total suicides in the United States, entail 50 times the potential lethality of drug overdose (Marzuk et al. 1992). A range of epidemiological studies have confirmed higher suicide rates in states with higher gun ownership levels (Miller et al. 2007) and higher suicide risk for people living in a household with firearms (Brent et al. 1993; Kellermann et al. 1992).

In sum, the contribution of population-level causes of suicide is significant, as well as in terms of their potential to reduce the burden of harm, quite influential when taken seriously. As suicide prevention efforts continue, a sustained and serious focus on population-level effects is critical.

5 Conclusion

Suicide is an avoidable tragedy with a devastating impact on individuals, families, and communities. Despite substantial prevention efforts, it remains a major global contributor to causes of death, especially among youth. Suicide and nonfatal self-injury are increasing at an unprecedented rate in the United States, as well as in many other places across the globe, raising questions about their causes and how to better intervene on them. As mentioned, prevention and treatment are often pointed towards high-risk groups, such as those with repeated suicide attempts, who are at increased risk of dying by suicide, but may miss the majority of suicide decedents who do not come into contact with the mental healthcare system and act impulsively. Moreover, even among those classified clinically as high-risk, little is known as to when is that risk actually higher – when should mental health professionals intensify their interventions? In addition, it seems eminently plausible that different effective clinical interventions, such as psychotherapy or brief contact programs, may not be equally useful for different profiles of individuals at high risk, and further research should enhance precision in clinical decision-making. Last, suicide prevention efforts tend to use an individual-level approach to understand and intervene on suicide risk (e.g., Roy 1982; Ursano et al. 2014; Vahabzadeh et al. 2016), probably failing to adequately acknowledge determinants at other, supra-individual levels. Potential future suicide prevention initiatives should acknowledge that suicide is a complex multilevel process.

5.1 Towards a Multilevel Approach to Suicide Prevention

To study the causes of suicide, researchers need to select a frame of reference that will define a finite set of potential causes (Susser 1972). Logically, each researcher's knowledge field will shape this frame of reference: for example, a sociologist and a psychiatrist will consider different sets of potential causes. The process of discarding all factors outside the frame of reference generates a useful asymmetry that permits cause-effect directionality (Pearl 2009). As a result, the way we consider potential causal relationships within our research field will be determined by our scope of interest and the frame of reference. Hence, although characterizing the entire field of risk is of interest, we usually reduce complex systems to simpler thought models and exclude dynamic interactions between ecological and individual factors. The fact that causal relations tend to be ascertained at a particular level of organization, usually the individual level, in the case of suicide (e.g., Roy 1982), limits their generalizability to other levels of organization, as well as the ascertainment of salient potential points of intervention.

In reality, "systems never exist in isolation" (Susser 1972), but they relate to each other in an enveloping hierarchy best represented by Susser and Susser's Chinese box metaphor (Susser and Susser 1996). As George Engel synthesized in his

celebrated bio-psycho-social model (Engel 1977), molecular, individual, and social levels of causation interact in shaping mental suffering, disease, and illness. More recently, Metzl and Hansen have used the notion of "structural competency" to encourage the recognition of how "institutions, neighborhood conditions, market forces, public policies, and healthcare delivery systems shape symptoms and disease" (Metzl and Hansen 2018).

Multilevel epidemiology has emerged as a response to the growing interest in the study of how macro-level characteristics affect outcomes independently of individual variables, as well as how both levels interact (Diez-Roux 1998). The arena of multilevel epidemiology, both a thinking framework and a set of analytical tools, allows for the careful consideration of a hierarchic range of levels of causation. We believe that innovative analytic tools for suicide risk prediction, such as those based on new technologies (Husky et al. 2014), data science initiatives (Torous et al. 2018), and machine learning approaches (Kessler et al. 2019), can be enhanced by partnering with broader conceptual models to include multiple levels of organization and capture the social, economic, and political settings where suicide, as a complex process, unfolds across the life course (Martínez-Alés and Keyes 2019). Examining causal factors beyond the proximal and clinical will be critical to allow for a socially conscious reimagining of suicide prevention.

References

Armed Forces Health Surveillance Center (AFHSC) (2012) Deaths by suicide while on active duty, active and reserve components, U.S. Armed Forces, 1998–2011. MSMR 19(6):7–10

AbouZahr C, de Savigny D, Mikkelsen L et al (2015) Towards universal civil registration and vital statistics systems: the time is now. Lancet 386(10001):1407–1418

Akkaya-Kalayci T, Vyssoki B, Winkler D et al (2017) The effect of seasonal changes and climatic factors on suicide attempts of young people. BMC Psychiatry 17(1):365

American Association of Suicidology (2019) Suicide reporting recommendations: media as partners toolkit. https://www.suicidology.org/Resources/Recommendations-for-Reporting-on-Suicide

Anderson P, de Bruijn A, Angus K et al (2009) Impact of alcohol advertising and media exposure on adolescent alcohol use: a systematic review of longitudinal studies. Alcohol Alcohol 44 (3):229–243

Arsenault-Lapierre G, Kim C, Turecki G (2004) Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 4:37

Ayesa-Arriola R, Alcaraz EG, Hernandez BV et al (2015) Suicidal behaviour in first-episode non-affective psychosis: specific risk periods and stage-related factors. Eur Neuropsychopharmacol 25(12):2278–2288

Baca-Garcia E, Perez-Rodriguez MM, Keyes KM et al (2010) Suicidal ideation and suicide attempts in the United States: 1991-1992 and 2001-2002. Mol Psychiatry 15(3):250–259

Beck AT, Brown GK, Steer RA (1997) Psychometric characteristics of the scale for suicide ideation with psychiatric outpatients. Behav Res Ther 35(11):1039–1046

Belsher BE, Smolenski DJ, Pruitt LD et al (2019) Prediction models for suicide attempts and deaths: a systematic review and simulation. JAMA Psychiatry 76:642

Bertolote JM, Fleischmann A, De Leo D et al (2004) Psychiatric diagnoses and suicide: revisiting the evidence. Crisis 25(4):147–155

Blasco-Fontecilla H, Artieda-Urrutia P, de Leon J (2018) A proposal for using the ratio of attempted to completed suicides across several countries worldwide. Epidemiol Psychiatry Sci:1–5
Bohnert ASB, Ilgen MA (2019) Understanding links among opioid use, overdose, and suicide. N Engl J Med 380:71–79. https://doi.org/10.1056/NEJMra1802148
Borges G, Nock MK, Haro Abad JM et al (2010) Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization world mental health surveys. J Clin Psychiatry 71(12):1617–1628
Borges G, Bagge CL, Cherpitel CJ et al (2017) A meta-analysis of acute use of alcohol and the risk of suicide attempt. Psychol Med 47(5):949–957
Bostwick JM, Pankratz VS (2000) Affective disorders and suicide risk: a reexamination. Am J Psychiatry 157(12):1925–1932
Brent DA, Perper JA, Moritz G et al (1993) Firearms and adolescent suicide. A community case-control study. Am J Dis Child 147(10):1066–1071
Burstein B, Agostino H, Greenfield B (2019) Suicidal attempts and ideation among children and adolescents in US emergency departments, 2007–2015. JAMA Pediatr 173(6):598–600. https://doi.org/10.1001/jamapediatrics.2019.0464
Camus A (1955) Myth of sisyphus, and other essays. Hamish Hamilton
Carter G, Milner A, McGill K et al (2017) Predicting suicidal behaviours using clinical instruments: systematic review and meta-analysis of positive predictive values for risk scales. Br J Psychiatry 210(6):387–395
Case A, Deaton A (2015) Rising midlife morbidity and mortality, US whites. Proc Natl Acad Sci 112(49):15078–15083. https://doi.org/10.1073/pnas.1518393112
Case A, Deaton A (2017) Mortality and morbidity in the 21(st) century. Brookings Pap Econ Act 2017:397–476
Cavanagh JT, Carson AJ, Sharpe M et al (2003) Psychological autopsy studies of suicide: a systematic review. Psychol Med 33(3):395–405
Cebria AI, Parra I, Pamias M et al (2013) Effectiveness of a telephone management programme for patients discharged from an emergency department after a suicide attempt: controlled study in a Spanish population. J Affect Disord 147(1–3):269–276
Center for Behavioral Health Statistics and Quality (2018) 2017 National survey on drug use and health: detailed tables. Substance Abuse and Mental Health Services Administration, Rockville, MD
Centers for Disease Control (2018a) Suicide rates in the United States continue to increase. https://www.cdc.gov/nchs/data/databriefs/db309.pdf
Centers for Disease Control (2018b) Trends in the prevalence of suicide-related behaviors national YRBS: 1997–2017. In: Youth risk behavior survey. Data summary and trends report, 2007–2017. https://www.cdc.gov/healthyyouth/data/yrbs/pdf/trendsreport.pdf
Chan MK, Bhatti H, Meader N et al (2016) Predicting suicide following self-harm: systematic review of risk factors and risk scales. Br J Psychiatry 209(4):277–283
Cheng N, Rahman MM, Alatawi Y et al (2018) Mixed approach retrospective analyses of suicide and suicidal ideation for brand compared with generic central nervous system drugs. Drug Saf 41(4):363–376
Conwell Y, Duberstein PR, Caine ED (2002) Risk factors for suicide in later life. Biol Psychiatry 52 (3):193–204
Darvishi N, Farhadi M, Haghtalab T et al (2015) Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. PLoS One 10(5):e0126870
Davidson CL, Anestis MD, Gutierrez PM (2017) Ecological momentary assessment is a neglected methodology in Suicidology. Arch Suicide Res 21(1):1–11
Deisenhammer EA, Kemmler G, Parson P (2003) Association of meteorological factors with suicide. Acta Psychiatr Scand 108(6):455–459
Deisenhammer EA, Ing CM, Strauss R et al (2009) The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? J Clin Psychiatry 70(1):19–24

DelPozo-Banos M, John A, Petkov N et al (2018) Using neural networks with routine health records to identify suicide risk: feasibility study. JMIR Ment Health 5(2):e10144
Diez-Roux AV (1998) Bringing context back into epidemiology: variables and fallacies in multilevel analysis. Am J Public Health 88(2):216–222
Durkheim E (1966) Suicide: a study in sociology. Free Press, New York
Eddleston M, Gunnell D (2006) Why suicide rates are high in China. Science 311 (5768):1711–1713
Engel GL (1977) The need for a new medical model: a challenge for biomedicine. Science 196 (4286):129–136
Faris REL, Dunham HW (1939) Mental disorders in urban areas: an ecological study of schizophrenia and other psychoses
Feltz-Cornelis CM, Sarchiapone M, Postuvan V et al (2011) Best practice elements of multilevel suicide prevention strategies: a review of systematic reviews. Crisis 32(6):319–333
Fink DS, Santaella-Tenorio J, Keyes KM (2018) Increase in suicides the months after the death of Robin Williams in the US. PLoS One 13(2):e0191405
Florentine JB, Crane C (2010) Suicide prevention by limiting access to methods: a review of theory and practice. Soc Sci Med 70(10):1626–1632
Fountoulakis KN, Chatzikosta I, Pastiadis K et al (2016) Relationship of suicide rates with climate and economic variables in Europe during 2000–2012. Ann General Psychiatry 15(1):19
Franklin JC, Ribeiro JD, Fox KR et al (2017) Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychol Bull 143(2):187–232
Franklin JC, Huang X, Fox KR et al (2018) What suicide interventions should target. Curr Opin Psychol 22:50–53
Glenn CR, Nock MK (2014) Improving the prediction of suicidal behavior in youth. Int J Behav Consult Ther 9(3):7–10
Goldman N, Glei DA, Weinstein M (2018) Declining mental health among disadvantaged Americans. Proc Natl Acad Sci U S A 115(28):7290–7295
Gould MS (2001) Suicide and the media. Ann N Y Acad Sci 932:200–221; discussion 221-204
Grant BF, Goldstein RB, Saha TD et al (2015) Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on alcohol and related conditions III. JAMA Psychiat 72(8):757–766
Grant BF, Chou SP, Saha TD et al (2017) Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on alcohol and related conditions. JAMA Psychiat 74 (9):911–923
Gunnell D, Eddleston M (2003) Suicide by intentional ingestion of pesticides: a continuing tragedy in developing countries. Int J Epidemiol 32(6):902–909
Hallensleben N, Spangenberg L, Forkmann T et al (2018) Investigating the dynamics of suicidal ideation. Crisis 39(1):65–69
Han X, Xiao L, Yu Y et al (2017) Alcohol consumption and gastric cancer risk: a meta-analysis of prospective cohort studies. Oncotarget 8(47):83237–83245
Hassanian-Moghaddam H, Sarjami S, Kolahi AA et al (2011) Postcards in Persia: randomised controlled trial to reduce suicidal behaviours 12 months after hospital-treated self-poisoning. Br J Psychiatry 198(4):309–316
Haughwout SP, Harford TC, Castle IJ et al (2016) Treatment utilization among adolescent substance users: findings from the 2002 to 2013 National Survey on drug use and health. Alcohol Clin Exp Res 40(8):1717–1727
Hawton K (1987) Assessment of suicide risk. Br J Psychiatry 150:145–153
Hawton K (2002) Studying survivors of nearly lethal suicide attempts: an important strategy in suicide research. Suicide Life Threat Behav 32:76–84
Hawton K, Casanas ICC, Haw C et al (2013) Risk factors for suicide in individuals with depression: a systematic review. J Affect Disord 147(1–3):17–28

Hedegaard H, Curtin SC, Warner M (2018) Suicide mortality in the United States, 1999-2017. NCHS Data Brief 330:1–8
Heisel MJ, Talbot NL, King DA et al (2015) Adapting interpersonal psychotherapy for older adults at risk for suicide. Am J Geriatr Psychiatry 23(1):87–98
Holahan CJ, Schutte KK, Brennan PL et al (2014) Episodic heavy drinking and 20-year total mortality among late-life moderate drinkers. Alcohol Clin Exp Res 38(5):1432–1438
Hser YI, Mooney LJ, Saxon AJ et al (2017) High mortality among patients with opioid use disorder in a large healthcare system. J Addict Med 11(4):315–319
Husky M, Olie E, Guillaume S et al (2014) Feasibility and validity of ecological momentary assessment in the investigation of suicide risk. Psychiatry Res 220(1–2):564–570
Husky M, Swendsen J, Ionita A, Jaussent I, Genty C, Courtet P (2017) Predictors of daily life suicidal ideation in adults recently discharged after a serious suicide attempt: a pilot study. Psychiatry Res 256:79–84
Ilgen MA, Bohnert AS, Ganoczy D et al (2016) Opioid dose and risk of suicide. Pain 157 (5):1079–1084
Isaac M, Elias B, Katz LY et al (2009) Gatekeeper training as a preventative intervention for suicide: a systematic review. Can J Psychiatr 54(4):260–268
Kaput J, van Ommen B, Kremer B et al (2014) Consensus statement understanding health and malnutrition through a systems approach: the enough program for early life. Genes Nutr 9 (1):378
Kegler SR, Stone DM, Holland KM (2017) Trends in suicide by level of urbanization – United States, 1999-2015. MMWR 66(10):270–273
Kellermann AL, Rivara FP, Somes G et al (1992) Suicide in the home in relation to gun ownership. N Engl J Med 327(7):467–472
Kessler RC, Wang PS (2008) The descriptive epidemiology of commonly occurring mental disorders in the United States. Annu Rev Public Health 29:115–129
Kessler RC, Borges G, Walters EE (1999) Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatry 56(7):617–626
Kessler RC, Aguilar-Gaxiola S, Alonso J et al (2009a) The global burden of mental disorders: an update from the WHO world mental health (WMH) surveys. Epidemiol Psichiatr Soc 18 (1):23–33
Kessler RC, Aguilar-Gaxiola S, Alonso J et al (2009b) The WHO world mental health (WMH) surveys. Psychiatrie (Stuttg) 6(1):5–9
Kessler RC, Cox BJ, Green JG et al (2011) The effects of latent variables in the development of comorbidity among common mental disorders. Depress Anxiety 28(1):29–39
Kessler RC, Stein MB, Petukhova MV et al (2017) Predicting suicides after outpatient mental health visits in the Army study to assess risk and resilience in Servicemembers (Army STARRS). Mol Psychiatry 22(4):544–551
Kessler RC, Bossarte RM, Luedtke A, Zaslavsky AM, Zubizarreta JR (2019) Machine learning methods for developing precision treatment rules with observational data. Behav Res Ther 120:103412. https://doi.org/10.1016/j.brat.2019.103412
Keyes KM, Hatzenbuehler ML, Hasin DS (2011) Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. Psychopharmacology 218(1):1–17
Keyes KM, Gary D, O'Malley PM et al (2019a) Recent increases in depressive symptoms among US adolescents: trends from 1991 to 2018. Soc Psychiatry Psychiatr Epidemiol 54:987
Keyes KM, Rutherford C, Miech R (2019b) Historical trends in the grade of onset and sequence of cigarette, alcohol, and marijuana use among adolescents from 1976-2016: implications for "gateway" patterns in adolescence. Drug Alcohol Depend 194:51–58
Kleiman EM, Nock MK (2018) Real-time assessment of suicidal thoughts and behaviors. Curr Opin Psychol 22:33–37
Large M, Sharma S, Cannon E et al (2011) Risk factors for suicide within a year of discharge from psychiatric hospital: a systematic meta-analysis. Aust N Z J Psychiatry 45(8):619–628

Leavitt RA, Ertl A, Sheats K et al (2018) Suicide among American Indian/Alaska natives – national violent death reporting system, 18 states, 2003-2014. MMWR 67(8):237–242
Lee S, Fung SC, Tsang A et al (2007) Lifetime prevalence of suicide ideation, plan, and attempt in metropolitan China. Acta Psychiatr Scand 116(6):429–437
Linehan MM, Comtois KA, Murray AM et al (2006) Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry 63(7):757–766
Lopez-Castroman J, Blasco-Fontecilla H, Courtet P et al (2015) Are we studying the right populations to understand suicide? World Psychiatry 14(3):368–369
MacKinnon DR, Farberow NL (1976) An assessment of the utility of suicide prediction. Suicide Life Threat Behav 6(2):86–91
Madsen T, Nordentoft M (2012) Suicidal changes in patients with first episode psychosis: clinical predictors of increasing suicidal tendency in the early treatment phase. Early Interv Psychiatry 6 (3):292–299
Mann JJ, Oquendo M, Underwood MD et al (1999) The neurobiology of suicide risk: a review for the clinician. J Clin Psychiatry 60(Suppl 2):7–11; discussion 18-20, 113-116
Mann JJ, Apter A, Bertolote J et al (2005) Suicide prevention strategies: a systematic review. JAMA 294(16):2064–2074
Manthey J, Shield KD, Rylett M et al (2019) Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. Lancet 393:2493
Maris RW (2000) Comprehensive textbook of suicidology. Guilford Press
Martínez-Alés G, Keyes K (2019) Fatal and non-fatal self-injury in the United States: current trends and innovations in prevention. Curr Psychiat Rep 21:104. https://doi.org/10.1007/s11920-019-1080-6
Martínez-Alés G, Angora R, Barrigon ML et al (2019) A real-world effectiveness study comparing a priority appointment, an enhanced contact intervention, and a psychotherapeutic program following attempted suicide. J Clin Psychiatry 80(2)
Martins SS, Keyes KM, Storr CL et al (2009) Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on alcohol and related conditions. Drug Alcohol Depend 103(1–2):16–24
Martins SS, Fenton MC, Keyes KM et al (2012) Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: longitudinal evidence from the National Epidemiologic Study on alcohol and related conditions. Psychol Med 42(6):1261–1272
Marzuk PM, Leon AC, Tardiff K et al (1992) The effect of access to lethal methods of injury on suicide rates. Arch Gen Psychiatry 49(6):451–458
Masters RK, Tilstra AM, Simon DH (2018) Explaining recent mortality trends among younger and middle-aged white Americans. Int J Epidemiol 47(1):81–88
McKeown RE, Cuffe SP, Schulz RM (2006) US suicide rates by age group, 1970-2002: an examination of recent trends. Am J Public Health 96(10):1744–1751
Mercado MC, Holland K, Leemis RW et al (2017) Trends in emergency department visits for nonfatal self-inflicted injuries among youth aged 10 to 24 years in the United States, 2001-2015. JAMA 318(19):1931–1933
Miller M, Lippmann SJ, Azrael D, Hemenway D (2007) Household firearm ownership and rates of suicide across the 50 United States. J Trauma 62(4):1029–1035. https://doi.org/10.1097/01.ta.0000198214.24056.40
Metzl JM, Hansen H (2018) Structural competency and psychiatry. JAMA Psychiat 75(2):115–116
Mojtabai R, Olfson M, Han B (2016) National trends in the prevalence and treatment of depression in adolescents and Young adults. Pediatrics 138(6):e20161878
Moscicki EK (1997) Identification of suicide risk factors using epidemiologic studies. Psychiatr Clin North Am 20(3):499–517
Motto JA, Bostrom AG (2001) A randomized controlled trial of postcrisis suicide prevention. Psychiatr Serv 52(6):828–833

Naghavi M (2019) Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the global burden of disease study 2016. BMJ 364:l94
Naifeh JA, Tull MT, Gratz KL (2012) Anxiety sensitivity, emotional avoidance, and PTSD symptom severity among crack/cocaine dependent patients in residential treatment. Cognit Ther Res 36(3):247–257
Nock MK (2012) Future directions for the study of suicide and self-injury. J Clin Child Adolesc Psychol 41(2):255–259
Nordentoft M, Mortensen PB, Pedersen CB (2011) Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry 68(10):1058–1064
Olfson M, Wang S, Blanco C (2015) National trends in hospital-treated self-harm events among middle-aged adults. Gen Hosp Psychiatry 37(6):613–619
Olfson M, Blanco C, Wall M et al (2017) National Trends in suicide attempts among adults in the United States. JAMA Psychiat 74(11):1095–1103
Oliven JF (1954) Suicide prevention as a public health problem. Am J Public Health Nat Health 44 (11):1419–1425
Organization for Economic Co-operation and Development (2019) Data: suicide rates. Accessible at: https://data.oecd.org/healthstat/suicide-rates.htm
Oswalt SB, Lederer AM, Chestnut-Steich K et al (2018) Trends in college students' mental health diagnoses and utilization of services, 2009-2015. J Am Coll Heal:1–11
Owens PL, Fingar KR, Heslin KC et al (2006) Emergency department visits related to suicidal ideation, 2006–2013: statistical brief #220, in healthcare cost and utilization project (HCUP) statistical briefs. Rockville, MD
Owens D, Horrocks J, House A (2002) Fatal and non-fatal repetition of self-harm. Systematic review. Br J Psychiatry 181:193–199. https://doi.org/10.1192/bjp.181.3.193
Owens D, Kelley R (2017) Predictive properties of risk assessment instruments following self-harm. Br J Psychiatry 210(6):384–386
Pacheco JNJ (1936) Suicide: its causes and prevention. Indian Med Gazette 71(12):720
Pearl J (2009) Causality. Cambridge University Press
Phillips MR, Yang G, Zhang Y, Wang L, Ji H, Zhou M (2002) Risk factors for suicide in China: a national case-control psychological autopsy study. Lancet 360(9347):1728–1736. https://doi.org/10.1016/S0140-6736(02)11681-3
Pirkis J, Blood RW, Beautrais A et al (2006a) Media guidelines on the reporting of suicide. Crisis 27(2):82–87
Pirkis JE, Burgess PM, Francis C et al (2006b) The relationship between media reporting of suicide and actual suicide in Australia. Soc Sci Med 62(11):2874–2886
Pirkis J, Too LS, Spittal MJ et al (2015) Interventions to reduce suicides at suicide hotspots: a systematic review and meta-analysis. Lancet Psychiatry 2(11):994–1001
Plana-Ripoll O, Pedersen CB, McGrath JJ (2018) Urbanicity and risk of schizophrenia-new studies and old hypotheses. JAMA Psychiat 75(7):687–688
Plemmons G, Hall M, Doupnik S et al (2018) Hospitalization for suicide ideation or attempt: 2008-2015. Pediatrics 141(6):e20172426
Pokorny AD (1960) Characteristics of forty-four patients who subsequently committed suicide. AMA Arch Gen Psychiatry 2(3):314–323
Pokorny AD (1983) Prediction of suicide in psychiatric patients. Report of a prospective study. Arch Gen Psychiatry 40(3):249–257
Pompili M, Sher L, Serafini G et al (2013) Posttraumatic stress disorder and suicide risk among veterans: a literature review. J Nerv Ment Dis 201(9):802–812
Posner K, Brown GK, Stanley B et al (2011) The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 168(12):1266–1277
Rezaeian M, Dunn G, St Leger S, Appleby L (2005) The ecological association between suicide rates and indices of deprivation in English local authorities. Soc Psychiatry Psychiatr Epidemiol 40(10):785–791

Rhodes AE, Boyle MH, Bridge JA et al (2014) Antecedents and sex/gender differences in youth suicidal behavior. World J Psychiatry 4(4):120–132
Riblet NBV, Shiner B, Young-Xu Y et al (2017) Strategies to prevent death by suicide: meta-analysis of randomised controlled trials. Br J Psychiatry 210(6):396–402
Rodriguez-Blanco L, Carballo JJ, Baca-Garcia E (2018) Use of ecological momentary assessment (EMA) in non-suicidal self-injury (NSSI): a systematic review. Psychiatry Res 263:212–219
Rose G (2001) Sick individuals and sick populations. Int J Epidemiol 30(3):427–432
Roy A (1982) Risk factors for suicide in psychiatric patients. Arch Gen Psychiatry 39 (9):1089–1095
Ruhm CJ (2018) Drug mortality and lost life years among U.S. midlife adults, 1999-2015. Am J Prev Med 55(1):11–18
Runeson B, Odeberg J, Pettersson A et al (2017) Instruments for the assessment of suicide risk: a systematic review evaluating the certainty of the evidence. PLoS One 12(7):e0180292
Scholl L, Seth P, Kariisa M et al (2018) Drug and opioid-involved overdose deaths – United States, 2013-2017. MMWR Morb Mortal Wkly Rep 67(5152):1419–1427
Seedat S, Scott KM, Angermeyer MC et al (2009) Cross-national associations between gender and mental disorders in the World Health Organization world mental health surveys. Arch Gen Psychiatry 66(7):785–795
Shepard DS, Gurewich D, Lwin AK et al (2016) Suicide and suicidal attempts in the United States: costs and policy implications. Suicide Life Threat Behav 46(3):352–362
Simon GE, Johnson E, Lawrence JM et al (2018) Predicting suicide attempts and suicide deaths following outpatient visits using electronic health records. Am J Psychiatry 175(10):951–960
Sisask M, Varnik A (2012) Media roles in suicide prevention: a systematic review. Int J Environ Res Public Health 9(1):123–138
Skog OJ (1985) The collectivity of drinking cultures: a theory of the distribution of alcohol consumption. Br J Addict 80(1):83–99
Smith PN, Currier J, Drescher K (2015) Firearm ownership in veterans entering residential PTSD treatment: associations with suicide ideation, attempts, and combat exposure. Psychiatry Res 229(1–2):220–224
Stanley B, Brown GK (2012) Safety planning intervention: a brief intervention to mitigate suicide risk. Cogn Behav Pract 19:256–264
Steel Z, Marnane C, Iranpour C et al (2014) The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. Int J Epidemiol 43(2):476–493
Stone DM, Simon TR, Fowler KA et al (2018) Vital signs: trends in state suicide rates – United States, 1999-2016 and circumstances contributing to suicide – 27 states, 2015. MMWR Morb Mortal Wkly Rep 67(22):617–624
Susser M (1972) Agent, host and Environment as an ecological system. Causal thinking in the health sciences
Susser M (1994a) The logic in ecological: II. The logic of design. Am J Public Health 84 (5):830–835
Susser M (1994b) The logic in ecological: I. The logic of analysis. Am J Public Health 84 (5):825–829
Susser M, Susser E (1996) Choosing a future for epidemiology: II. From black box to Chinese boxes and eco-epidemiology. Am J Public Health 86(5):674–677
Ting SA, Sullivan AF, Boudreaux ED et al (2012) Trends in US emergency department visits for attempted suicide and self-inflicted injury, 1993-2008. Gen Hosp Psychiatry 34(5):557–565
Torous J, Larsen ME, Depp C et al (2018) Smartphones, sensors, and machine learning to advance real-time prediction and interventions for suicide prevention: a review of current Progress and next steps. Curr Psychiatry Rep 20(7):51
Turecki G, Brent DA (2016) Suicide and suicidal behaviour. Lancet 387(10024):1227–1239
Twenge JM, Cooper AB, Joiner TE et al (2019) Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005-2017. J Abnorm Psychol 128(3):185–199

United Nations, Department of Economic and Social Affairs, Population Division (2017) World population prospects: the 2017 revision, key findings and advance tables. Working paper no. ESA/P/WP/248
Ursano RJ, Colpe LJ, Heeringa SG et al (2014) The Army study to assess risk and resilience in servicemembers (Army STARRS). Psychiatry 77(2):107–119
Vahabzadeh A, Sahin N, Kalali A (2016) Digital suicide prevention: can technology become a game-changer? Innov Clin Neurosci 13(5–6):16–20
Vaiva G, Berrouiguet S, Walter M et al (2018) Combining postcards, crisis cards, and telephone contact into a decision-making algorithm to reduce suicide reattempt: a randomized clinical trial of a personalized brief contact intervention. J Clin Psychiatry 79(6)
VanderWeele TJ, Mathur MB, Chen Y (2019) Media portrayals and public health implications for suicide and other behaviors. JAMA Psychiatry 76:891
Wade WF (1879) On the prevention of suicide. Br Med J 2(979):533
Wang Y, Bhaskaran J, Sareen J et al (2016) Clinician prediction of future suicide attempts: a longitudinal study. Can J Psychiatry 61(7):428–432
Wasserman D, Cheng Q, Jiang GX (2005) Global suicide rates among young people aged 15-19. World Psychiatry 4(2):114–120
Wasserman D, Hoven CW, Wasserman C et al (2015) School-based suicide prevention programmes: the SEYLE cluster-randomised, controlled trial. Lancet 385(9977):1536–1544
Weinberger AH, Gbedemah M, Martinez AM et al (2018) Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychol Med 48 (8):1308–1315
Whiteford HA, Degenhardt L, Rehm J et al (2013a) Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. Lancet 382 (9904):1575–1586
Whiteford HA, Harris MG, McKeon G et al (2013b) Estimating remission from untreated major depression: a systematic review and meta-analysis. Psychol Med 43(8):1569–1585
World Health Organization (2014) Preventing suicide: a global imperative. World Health Organization, Geneva
World Health Organization (2017) Depression and other common mental disorders: Global Health Estimates. World Health Organization, Geneva
World Health Organization (2018a) National suicide prevention strategies: progress, examples and indicators. World Health Organization, Geneva
World Health Organization (2018b) Global status report on alcohol and health. World Health Organization, Geneva
World Health Organization (2019) Latest data on suicide. https://www.who.int/mental_health/suicide-prevention/en/
Zalsman G, Hawton K, Wasserman D et al (2016) Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry 3(7):646–659
Zenere FJ 3rd, Lazarus PJ (1997) The decline of youth suicidal behavior in an urban, multicultural public school system following the introduction of a suicide prevention and intervention program. Suicide Life Threat Behav 27(4):387–402

Barriers for the Research, Prevention, and Treatment of Suicidal Behavior

Maria A. Oquendo and Alejandro Porras-Segovia

Contents

Abstract Efforts in research, prevention, and treatment of suicidal behavior have produced mixed results. One of the main barriers to combating suicidal behavior lies in the very conceptualization of suicide, a phenomenon that is at once sociological, psychiatric, and even philosophical, and one that has not always been included in the field of health care. There are also many barriers at the social level, ranging from stigma against people with suicidal behavior to stigma towards psychiatric care, as well as the controversial role of the media. The media plays an important role in society and depending on its attitude it can be either beneficial or harmful in our fight against suicidal behavior. Differences between countries – in the provision of

M. A. Oquendo (✉)
Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: moquendo@pennmedicine.upenn.edu

A. Porras-Segovia
Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain

Curr Topics Behav Neurosci (2020) 46: 25–40
https://doi.org/10.1007/7854_2020_159
Published Online: 29 September 2020

resources, in the way of understanding the phenomenon or in the manner of providing official figures – pose an additional challenge to suicide prevention on a global level. In the field of research, predicting suicidal behavior by identifying effective risk markers is severely hampered by the low occurrence of suicide in the population, which limits the statistical power of studies. The authors recommend combining various risk factors to build predictive models. This, in addition to employing increasingly precise machine learning techniques, is a step in the right direction, although there is still a long way to go before the expected results can be obtained. Finally, adequate training of health professionals, both specialized and non-specialized, as well as gatekeeper training, is crucial for implementing suicide prevention strategies in the population.

Keywords Suicide · Suicide attempt · Suicidal behavior · Suicide prevention

1 Introduction

Suicidal behavior is a public health challenge that resists the various efforts made toward its prevention and treatment. Suicide is one of the few leading causes of death that has not diminished in the USA in the past 10 years, whereas Eastern European and Asian countries exhibit the highest suicide rates worldwide (Barrigón and Baca-García 2018; Blasco-Fontecilla et al. 2012). While mortality for other causes, such as several conditions or vehicle crashes, has decreased in recent decades, suicide rates have not significantly changed in the past decades. Why are we failing?

The barriers for the research, prevention, and treatment of suicidal behavior begin with the difficult conceptualization of this phenomenon. Sometimes understood as a symptom of other mental illnesses, sometimes considered a disorder in itself, sometimes none of the above, suicide is a complex human behavior whose study does not correspond solely to psychiatry, but concerns fields such as anthropology, sociology, religion, or politics.

Suicide has complex legal ramifications, both for the subject as well as for the doctors in charge of its management. Society's interpretation of these behaviors, as well as the significance given to it in different cultures, can notably influence the management of this behavior at the public health level. One of the main reasons why it is so difficult to define and characterize suicide is because we still know very little about the neurobiological bases. The search for biomarkers of suicide has been so far unsuccessful, which complicates the already difficult process of risk assessment. Predicting a behavior whose intention is often not communicated remains one of the biggest challenges in psychiatry and hinders the implementation of effective preventive strategies.

2 Issues in the Conceptualization of Suicidal Behavior

2.1 Suicidal Behavior as a Mental Disorder

Lack of consensus about the definition and classification of suicidal behavior hinders the advance of suicidology, as it makes it difficult to compare results of different studies and quantify the impact of the issue on a global or even national scale (Silverman 2016). The very conception of suicidal behavior as pathological sometimes falters. Around 90% of cases of suicide are associated with a psychiatric diagnosis (Cavanagh et al. 2003). This epidemiological association, together with the evidence of specific neurobiological and genetic alterations in suicidal patients, has made psychiatry take charge of the study and prevention of suicide. But what about that other 10% in which we find no accompanying psychopathology? We can situate ourselves in scenarios in which voluntary death does not have to constitute a pathology. For example, the politician Salvador Allende took his own life in the face of the imminent arrival of his enemies, knowing that the death he might die would be much less cruel than the one that awaited him. But usually the line is much harder to draw. The decision to commit a suicidal act cannot be reduced to the context in which it takes place, since it is evident that not all people facing extreme circumstance are going to commit suicide. Understanding suicidal behavior in people without an identifiable psychiatric pathology adds complexity to the conception of suicide and is a pending task in suicidology.

Even if we agree to consider suicide under the umbrella of psychiatric illness, there remains the question of whether we should consider it as a disorder in itself or as the symptom of other mental disorders. In 2013, the DSM-5 included the notion "Suicidal behavior disorder" under the section "Conditions for further study." Thus, suicidal behavior is still remains in limbo. Several authors defend that suicidal behavior should be considered an independent diagnostic category. Suicidal behavior meets the requirements for diagnostic validity and reliability. Moreover, considering suicidal behavior as an independent mental disorder would facilitate proper assessment and documentation in clinical records, improve the comparability between studies, and boost attention and financial support for suicide research. It can also encourage the undertaking of randomized clinical trials to help develop new treatments for suicide (Oquendo and Baca-Garcia 2014).

However, other authors argue, keeping a transdiagnostic perspective adds flexibility to the concept. Another possibility is a dual consideration of suicidal behavior as symptom and disorder, in a similar fashion to insomnia, which may be considered a symptom of other psychiatric illnesses but can also constitute a disorder on its own.

2.2 Subgroups of Suicidal Behavior

Desire of death, active suicial ideation, suicidal plans, suicide attempts, death by suicide... The different elements of the suicidal process were once understood as necessary steps in the linear trajectory of suicide. However, reality is far more complex. Studies show that many suicide attempts occur without a previous plan, or even without a previous active suicidal ideation, jumping directly from wishing to be dead to trying to kill oneself (Baca-Garcia et al. 2011). Most people with suicide ideation will not progress to make a suicide attempt, many of those who attempt will never die by suicide. And, while a previous suicide attempt is the most important risk factor for dying by suicide, only minority of those who die by suicide have a history of a previous suicide attempt. In light of these findings, authors have proposed the existence of different – albeit overlapping – populations of suicidal patients.

One of the main distinctions is between suicide attempts and death by suicide. These two subtypes are not differentiated only by a result that depends on circumstantial factors, such as access to lethal means, although these also come into play. The sociodemographic factors associated with suicide attempts differ from those of completed suicide. For example, completed suicides are more prevalent in men than in women, while the opposite is true for suicide attempts (Centers for Disease Control and Prevention 2019). The overlap between these two populations appears to be greater in the case of medically serious suicide attempts.

Another basic distinction is that between suicide "ideators" and attempters. Other criteria to classify suicidal behavior are the level of planning, the method chosen, or the frequency. Lopez-Castroman et al. made a distinction between a more impulsive and less lethal suicidal behavior, versus a more planned and lethal one (Lopez-Castroman et al. 2015). Differential characteristics have also been found among suicides which opted for more violent methods. Another subtype frequently considered in the literature is that of major repeaters, who make multiple, low-lethal attempts along their lives. This subtype has been linked to specific sociodemographic and clinical traits, such as female gender, lower education, or a history of childhood abuse (Blasco-Fontecilla et al. 2012).

These subgroups could translate distinct neurobiological and genetic characteristics that could explain the differences between subpopulation. For instance, studies suggest that neurocognitive deficits can help explain the line drawn between ideas and actions, between those who only think about suicide and those who attempt it (Saffer and Klonsky 2018). The distinction of subtypes of suicidal behavior is relevant when it comes to finding effective treatments. Biological characterization of disorders is one of the crucial steps in identifying therapeutic targets. Effectiveness of interventions can vary depending on the subgroup in which we apply them. For instance, restriction to means can have special importance in impulsive and high-lethality suicidal behavior (Stone and Crosby 2014).

Heterogenous sample of suicidal patients in research may be causing us to lose power when it comes to finding associations, by stocking up together very dissimilar populations. Research that delves into the etiopathogenic bases of suicide should

take into account that, in the same way that the sociodemographic factors we already know are associated differently with each population, the same may also happen with those factors yet to discover. Mixing different subtypes in the same sample as if they were a homogeneous group may result in a decrease in statistic power in spite of bigger samples.

Mixing populations also diminishes the validity of the results when it comes to extrapolating them to clinical practice (Lopez-Castroman et al. 2015; Oquendo 2016). Conclusions extracted from studies performed in a certain suicide subpopulation may not be valid for others. A more nuanced distinction between different suicidal phenomena and the investigation of the most appropriate treatment in each of them may reveal novel preventive and therapeutic approaches (Oquendo 2016).

Death by suicide is, by comparison, a neglected area in suicide research, as most studies are conducted on people with suicidal ideation or suicide attempts, given that death by suicide much less common (O'Connor and Portzky 2018). Above all, we have to make sure that the prevention measures we develop are valid and applicable, which may call for a more selective sampling process. Otherwise, we may be trying to apply invalid conclusions to those most at risk of death by suicide.

3 Social Barriers to Suicide Prevention

Compromise of society is crucial in the battle against suicidal behavior. The stigma associated with mental illness can discourage suicidal people from seeking professional health. Both society's stigma and its internalization – called self-stigma – can influence perceptions about suicide-related issues, such as the need for help or the effectiveness of available treatments (Czyz et al. 2013).

One of the most influential factors is social media. Social media has the capacity to increase or decrease stigma depending on how they depict suicidal behavior. There has been concern about reporting of news related to suicide. Irresponsibility in reflecting the nature of suicidal behavior may favor factors involved in suicidal behavior, such as knowledge about suicide and access to means. It can also extend the conception of suicide as an escape route to the detriment of other alternatives. In contrast, adequate media reporting can contribute to suicide prevention by offering information about healthcare resources, support groups, and hotlines. Another way in which media can help suicide prevention is by sharing the stories of people who have overcome suicidal behavior rather on focusing on those who have succumbed to it (Acosta et al. 2017). The WHO has ushered recommendations for media advising not to report suicide in a sensationalist manner and not to give away detailed information about the act, such as method, place, or content of suicide notes.

The WHO recommends special caution when reporting the suicide of a celebrity, given the risks of suicide contagion (Acosta et al. 2017). Fictional works can also result in suicide contagion. Recently, the TV series *13 reasons why* has raised concerns about this potential effect (Bridge et al. 2019; Hong et al. 2019). Its detractors denunciate the glorification of the victim, the oversimplification of the

factors leading to suicide and the shallow treatment of the topic. Doubts remain as to whether these examples can actually increase the suicide rate or whether they influence other factors, such as the method chosen, or the accompanying circumstances.

Another social controversy than can influence suicide prevention is euthanasia and physician-assisted suicide, which has been legalized in four European countries and some US states. One of the arguments against euthanasia is that its boundaries can be progressively extended to include practices beyond the original concept (Sulmasy et al. 2016). Thus, in countries such as the Netherlands or Belgium, euthanasia has gained legal ground until it is accepted in certain contexts in which the capacity of patients is in question, as is the case of children or psychiatric patients (Schadenberg 2013). While the so-called rational suicide could be considered outside the scope of psychiatric care, the same does not occur when psychiatric patients come into play (Schadenberg 2013). While some authors contemplate psychiatric euthanasia in cases of unbearable suffering, others claim that this practice calls into question the very rationale for suicide care and may compromise funding for research, prevention, and treatment of suicidal behavior (Levy et al. 2012).

4 Suicide as a Global Challenge

Around 75% of suicides take place in low- and middle-income countries, with the highest rates occurring in Eastern Europe and Asia (Blasco-Fontecilla et al. 2012). However, most suicide research is carried out in developed countries (Phillips and Cheng 2012; Bertolote and Fleischmann 2002). Additionally, most suicides occur in rural areas, while studies' samples are usually taken from urban settings.

To be successful, prevention policies must be tailored to the characteristics of the population, in which they are implemented, but current suicide prevention programs are based on research from high-income countries and urban areas, disregarding the particular needs of different settings (Lopez-Castroman et al. 2015). We are not investigating suicide in areas where it occurs most frequently and the conclusions drawn from our studies may not be applicable in areas where suicide prevention is most needed (Barrigón and Baca-García 2018).

Countries that have made greater efforts in implementing suicide prevention policies have achieved a greater reduction in suicide rates. Government policies play a key role in preventing suicidal behavior, as there are actions that can only be undertaken from above, such as restrictions to means. Some governments and pressure groups may oppose restricting access to certain means of suicide, such as firearms, when it conflicts with other interests, even though these preventive measures have been shown to be effective in reducing suicide rates (Zalsman et al. 2016). Other population-level strategies that can reduce the incidence of suicide attempts are limiting the access to suicide-by-jumping hotspots by implementing structural barriers and legally restricting the size of acetaminophen packs. These have the effect of lowering attempts by jumping and self-poisoning respectively (Law et al.

2014; Sarchiapone et al. 2011). Increasing taxes on alcoholic beverages has also been found to be effective (Wagenaar et al. 2010).

We must also acknowledge that main suicide risk assessment tools were designed for Western populations and, despite validation efforts, may not be ideal for other populations. We also face the possibility that data on the epidemiology of suicide may not be entirely reliable. In certain countries, especially in parts of Asia and Africa, reported suicide figures are less reliable, due to shortcomings in epidemiological surveillance systems. A panel of 32 experts from 12 different countries noted that the unreliability of suicide data depending on the geographic area was one of the main challenges of suicide research (O'Connor and Portzky 2018). A joint research effort between different countries could contribute to closing this gap by homogenizing the methodology used. It could also help to fill another of the deficiencies of suicide research, which is the small sample size of most studies. However, the same cultural differences mentioned above make it difficult to carry out multi-center studies on suicidal behavior (Lopez-Castroman et al. 2015).

In addition to the geographical variations in suicide rates, some ethnic minorities, such as Native Americans, present an increased risk for suicidal behavior (Baca-Garcia et al. 2011). Cultural and religious beliefs can influence suicide-related phenomenon, from the perspective of the patients as well as the healthcare professionals (Chakraborty et al. 2017). The very meaning of suicide can change radically from one country to another. Under the Western prism, suicide appears strongly linked to depression, but this is not the case with other cultures. The low prevalence of depression in Asian countries contrasts with their high-suicide rates. It has been suggested that emotions different from sadness, such as shame or dishonor, would be more associated to suicide in these cultures (Pérez Sales 2004).

The different meanings attributed to suicidal behavior in each culture may limit its straightforward association with mental illness, at least with the Western concept of mental illness. In China, proportion of suicides without a history of mental disorder are estimated at 37%, nearly four times higher than the figures found in Western countries (Phillips et al. 2002). These difficulties are also present when it comes to many other mental illnesses. The expression of a pathology is highly influenced by the sociocultural context, so that the same neurobiological substrate can give rise to different symptoms, and vice versa. Risk factors for suicide are also influenced by cultural differences. For instance, the effect of life events on suicidal behavior may vary depending on the country's economic and social structure, since the impact this event will have in people's everyday life will change accordingly (Blasco-Fontecilla et al. 2012).

There are also important differences in the legal regulation of suicidal behavior between countries. There is still a significant stigma surrounding suicide, and these reactions are much more exacerbated in countries where suicide is not decriminalized (Behere et al. 2015). Beyond the legal framework, the stigmatization can cause families to try to conceal the cause of death by passing it off as an accident. This has two important consequences: first, it can affect the suicide figures reported in those countries, making suicide rates appear lower than they actually are. Second, it can promote self-stigma and reduce professional help-seeking.

5 Barriers to the Prediction of Suicide

In the last decades, there has been little progress in the search for novel risk factors and biomarkers for suicidal behavior. As showed by the meta-analysis of Franklin et al. (2017a, b), risk factors discovered so far are no more accurate in predicting suicidal behavior than flipping a coin. The few biomolecular markers associated with suicidal behavior present an effect size too small to be relevant in a clinical context (Chang et al. 2016). We are dealing with a behavior that can have a lethal result, leaving us without second chances, and we have not come closer to predicting it in the last 50 years.

To increase prediction ability, authors have tried to integrate different risk factors to create prediction models. But this strategy has yielded disappointed results. A systematic review of integrated suicide prevention models showed that they had low sensitivity and even lower specificity (Belsher et al. 2019). The best fitting model only reached a positive predictive value of 0.22 for suicide attempt. Results are especially disheartening when it comes to predict death by suicide, with most models providing positive predictive values below 0.01. The low incidence of death by suicide is one of the main obstacles in studying this behavior. Low specificity implies falsely identifying individuals as at high-suicide risk and applying unnecessary interventions and potentially stigmatizing labeling in addition to the high burden of healthcare cost. Low sensitivity means not being able to identify people at death risk, and thus not being able to implement needed interventions.

Machine learning has the potential to improve statistical modeling. Prediction models designed using machine learning algorithms showed a similar capability of prediction but using far less risk factors (Belsher et al. 2019). Further technological advances are expected to generate a more accurate risk prediction. However, routine use of new technologies in clinical practice is still far away.

5.1 Lack of Short-Term Risk Factors

Another reported weakness in current suicide research is the shortage of short-term risk factors (O'Connor and Portzky 2018). Most studies focus on long-term factors, which may not be producing the expected results in a pathology such as suicide, which has great variability over time and requires intensive short-term follow-up. In recent years, there has been an effort to study suicidal behavior in shorter time frames, facilitated by new tools such as the Ecological Momentary Assessment (EMA). The implementation of such approach is in turn facilitated by the use of new technologies. For instance, Littlewood et al. (2018) studied insomnia as a risk factor for suicidal ideation using a 1-week long EMA protocol and found that insomnia could increase the risk of suicide in only 24 h.

5.2 *Lack of Protective Factors*

There is also a gap in research on suicide protective factors compared to research on risk factors. Certain circumstances, such as increased social support, access to medical care, or problem-solving abilities can reduce suicide risk, and their promotion can be an effective strategy in the prevention of suicide. However, the identification and implementation of such factors have been insufficiently studied (Baca-Garcia et al. 2011; Stone and Crosby 2014).

5.3 *Lack of Specific Risk Factors*

Additionally, those that have been identified are predominantly risk factors for suicide ideation rather than suicide attempt or death by suicide (Saffer and Klonsky 2018). The knowledge of the risk factors of suicide ideation is not enough to prevent suicide attempts, since only a third of people will act on their suicidal thoughts. More research is needed into the factors that make possible the progression from suicidal ideation to suicide attempt. Neurocognition is one of the promising lines of research in differentiating these subtypes of suicidal behavior. Also, we must take into account that active suicide ideation is not a necessary step before an attempt, as evidence shows that people who had only experience a wish to be dead can progress directly to making a suicide attempt, without prior suicidal ideation (Baca-Garcia et al. 2011).

6 Barriers to the Development of Treatments for Suicidal Behavior

Research to identify specific treatments for suicidal behavior has produced poor results so far. Deficiencies in the neurobiological characterization of suicide limit the discovery of specific therapeutic targets. Exploring the biological underpinnings of suicidal behavior can help identify novel therapeutic targets. Promising lines of investigation include abnormalities in stress response and serotonergic systems (Oquendo et al. 2014). Endophenotypes of suicidal behavior – the internal factors that mediate the path between genes and their expression – are also an important focus of investigation, with the most promising being the traits of impulsivity and aggression (Courtet et al. 2011).

Randomized clinical trials of suicidal patients are a neglected area of research, partly because they pose a difficult ethical challenge. There are concerns about the construction of the comparison group, as well as about the general vulnerability of this population. In addition, clinical trials in suicidal patients usually have a modest sample size. Due to safety concerns, at high-risk patients are often excluded from

clinical trials. Balance between ethics and advances in research is difficult to sustain, but it is necessary to develop protocols that allow the inclusion of at-risk populations with the greatest possible guarantee of their safety, in order to advance the development of effective treatments in those patients who need it the most (Roberts et al. 2019).

The specific therapeutic tools available to treat suicide are scarce. However, there is a strong evidence of the anti-suicidal properties of clozapine in patients with schizophrenia, or lithium in patients with bipolar disorder (Benard et al. 2016). Recently, other avenues are being explored that could reveal more specific treatments for suicidal behavior, such as ketamine.

Research in nonpharmacological treatments is equally needed. Apart from psychotherapy, other interventions such as brief post-discharge contacts are promising. The delivery of such interventions can be made easier by the use of new technologies, such as short-messaging systems or smartphone apps (Larsen et al. 2016). Another possibility is real-time assessment of suicidal patients using smartphones (Kleiman and Nock 2018). The aim is combine the data collection and interpretation of machine learning with the ubiquity and 24/7 availability of smartphones to create pocket monitoring systems.

However, some authors also show concern about research trends using big data and machine learning because they believe that these methods can disregard case-specific circumstances of the person involved (O'Connor and Portzky 2018). The novelty of these approaches, together with the lack of training in new technologies, may be causing this suspicion. Authors behind the main research activity in machine learning applied to suicidology claim that the case is actually the opposite and that new technologies can facilitate the step into personalized medicine. Machine learning algorithms can avoid the ecological fallacy of traditional research, favoring the development of a more personalized medicine. Real-time risk monitoring algorithms can be applied to each individual separately so that longitudinal monitoring, with the progressive addition of data on the same individual, leads to a personalized prediction of risk. The system would alert when there is a factor in that person that may lead to clinical decompensation, regardless of what happens in the population to which he or she belongs. This is especially relevant in the secondary prevention of suicidal behavior, when patients are monitored after the first suicide attempt. Although such technologies are not yet fully functional, their implementation in clinical practice is expected in the near future (Torous et al. 2018).

7 Difficulties in the Management of Suicidal Behavior in the Clinical Practice

7.1 Suicide Risk Assessment Tools

Rating scales are an important element of suicide risk assessment and stratification. However, many authors criticize the validity and clinical utility of these scales,

especially when applied to the clinical practice (Quinlivan et al. 2016). Some authors point out that other data, such as sociodemographic factors or variables coded in electronic health records, can predict a suicide attempt more accurately than clinical assessment (Tran et al. 2014). Beyond the precision of these tools, scales, and questionnaires are mainly used in research, while their use in clinical practice is limited by lack of time and often dispensed in favor of the unstructured clinical interview.

However, several authors recommend the use of standardized forms as part of the follow-up plan for suicidal patients. Systematized risk assessment processes can help stratify risk, design tailored interventions and provide medicolegal support by objectifying the decision-making process (Oquendo and Bernanke 2017). One of the most supported assessment tools is the Suicide Status Form (SSF), framed within the clinical protocol Collaborative Assessment and Management of Suicidality (CAMS). This form has an abbreviated version to monitor progress and aims to encourage outpatient treatment and avoid involuntary hospitalizations.

A major barrier to suicide prevention is the lack of reliability of self-reported measures of suicide risk (Glenn et al. 2017). Many suicide attempters will hide their suicidal ideas or only communicate them indirectly, by, for instance, visiting their general practitioner for other motive in the few months prior to the attempt (Hauge et al. 2018). We must look for alternative approaches for the screening and ultimate prevention of suicidal behavior. Data mining and machine learning offer a potential for interpret data from other sources – such as electronic health records or passively collected smartphone data – and help guide medical decisions.

7.2 Medicolegal Aspects in Suicide Risk Assessment

Suicide risk involves not only the patients but also those in charge of taking care of them. Healthcare providers managing suicidal risk may see his professional integrity compromised if they discharge a patient who later commits suicide. Because of this, there is a risk of falling into defensive medicine and carry out more invasive measures such as a psychiatric admission, in order to protect itself from possible legal issues. This may also favor the opposite action: relaxation of measures in cases where there is no manifest intent to die, when we know that patients can also minimize symptoms with the aim, for example, of avoiding an unwanted psychiatric admission. Therefore, there may be a disproportion between the care required and that one provided.

However, adequate risk stratification should not result in relaxation of practices. Although the distinction of major repeaters evokes some control over their behavior, this is a delicate line to draw. Risk stratification does not imply that certain forms of suicidal behavior such as suicidal threats, low lethality attempts or self-harming gestures should not be taken seriously, as these carry a high risk of death. But we must acknowledge that the needs of subpopulations of suicidal patients may be different and therefore they may require a more tailored management in clinical practice.

7.3 Healthcare Professionals' Skills and Attitudes

Suicide prevention is a task that psychiatry has taken over for the most part, but prevention strategies cannot be implemented from mental healthcare only. Other areas such as primary care must be implicated, as well as non-health settings such as schools. Approximately 25% of those who commit suicide had previously contacted mental health services, leaving 75% of people on which prevention could not have been made from specialized care. It is therefore important to carry out multilevel prevention interventions. Managing suicide only from a psychiatric perspective can also increase stigma and reduce help-seeking.

Primary care is a key factor in the prevention of suicidal behavior. Nearly half of suicide victims contact their general physician in the few months before death (Hauge et al. 2018). However, physicians most often failed to notice any hint of suicidal ideation during these visits (Schulberg et al., 2004). Primary care professionals may have difficulties responding to patients who express suicidal ideation, and they may also not be able to detect suicide risk factors (Feldman et al., 2007). This can be more pronounced in countries where mental health care provision is scarce. In a survey of physicians from urban settings in India, more than half felt that suicide prevention was not within their competence, and almost half of the practitioners admitted that they did not ask questions about suicide even in the presence of symptoms of depression or anxiety (Eynan et al. 2015). The training of primary care professionals is essential to implement effective prevention measures, as this may be a less threatening and more stigma-free environment.

Emergency healthcare providers also report lack of confidence with some aspects of suicide prevention, such as creating a safety plan, or providing counseling. There is also the perception that suicide prevention is not a top priority at emergency departments (Betz et al., 2013). In another study, emergency department healthcare professionals highlighted the lack of time, the privacy issues, and their wish for a further collaboration with other professionals, as well as the implementation of standardized suicide risk assessment protocols (Petrik et al. 2015).

Another area of nonpsychiatric care in which suicide risk assessment is relevant is in the care of terminally ill patients. A study conducted among nursing professionals in an oncology ward revealed the perceived lack of training to deal with suicide-related matters, including deficiencies in communication skills with suicidal patients, which can result in a lack of assessment and intervention for fear of iatrogenic intervention. Among these professionals, there was still the widespread fear that asking about suicidal behavior would lead to it.

In addition to the lack of specific training, healthcare providers' beliefs can get in the way of an optimal suicide risk management. For some professionals, especially those caring for terminally ill patients or those working at nursing homes, the voluntary death of their patients can be an expression of autonomy and a means of liberation from suffering (Valente, 2011). Defending patient autonomy may conflict with ethical and legal duties to safeguard their physical integrity. To have an informed opinion in this regard, we must take into account the criteria that allow

us to say that a patient has full autonomy to make his decisions. Beyond the conception of suicide in itself, we must take into account the wish to be death can be an expression of physical or mental suffering, on which we can focus our efforts in a manner compatible with our individual beliefs.

Other psychosocial factors that can prevent healthcare professionals from delivering optimal care are the stigma associated with mental illness, the "burnout" syndrome, and the pessimistic conception that suicide is inevitable (Betz et al., 2013; O'Connor and Portzky 2018).

8 Conclusions

Suicidal behavior is one of the main challenges in global public health. There have been increasing efforts in understanding and preventing suicide, but research so far has not yielded the outcomes we hoped for. Instead of just increasing the volume of published work on the same lines, authors should explore new approaches and tackle the main weaknesses of current suicide research.

This effort must be global. The lack of data in non-Western settings is one of the main shortcomings of current suicide research. Suicide is being insufficiently studied in those countries where its prevalence is highest. The validity and universality of the results obtained in the leading Western research is therefore questionable. At the same time, it is an opportunity and a challenge for psychiatric research to extend our investigations to areas of high prevalence and low level of publication, to replicate results and check the validity of current models of suicidal behavior.

New approaches in research should take advantage of the latest advances available, such as machine learning. Although implementation in the clinical practice is still far, machine learning presents a great potential for improving prediction models, as well as for providing a more personalized approach to treatment. At the same time, some of the basic assumptions of suicidal behavior should be revisited, such as the conception of a linear trajectory of suicide. Instead, the existence of subgroups of suicidal patients should be given more attention as it can help focus research efforts to the populations most in need.

There is a shortcoming of specific anti-suicidal psychopharmacological treatments, as well as psychotherapeutic interventions. It is necessary to look for novel therapeutic approaches to get away from a stalled situation, exploring not only which strategies can be effective but also the potential synergies between different kinds of interventions.

There is still a long way to go in understanding and preventing suicidal behavior. Efforts cannot come exclusively from psychiatry but has to be implemented from different levels, including nonpsychiatric healthcare settings and also non-healthcare settings. Only through a coordinated effort will we be able to reduce morbidity and mortality caused by suicidal behavior.

References

Acosta J, Ramchand R, Becker A (2017) Best practices for suicide prevention messaging and evaluating California's "know the signs" media campaign. Crisis 38(5):287–299

Baca-Garcia E, Perez-Rodriguez M, Oquendo M et al (2011) Estimating risk for suicide attempt: are we asking the right questions? J Affect Disord 134(1–3):327–332. https://doi.org/10.1016/j.jad.2011.06.026

Barrigón M, Baca-García E (2018) Retos actuales en la investigación en suicidio. Revista de Psiquiatría y Salud Mental 11(1):1–3. https://doi.org/10.1016/j.rpsm.2017.10.001

Behere P, Sathyanarayana Rao T, Mulmule A (2015) Decriminalization of attempted suicide law: journey of fifteen decades. Indian J Psychiatry 57(2):122. https://doi.org/10.4103/0019-5545.158131

Belsher B, Smolenski D, Pruitt L (2019) Positive predictive values and potential success of suicide prediction models—reply. JAMA Psychiat 76(8):870

Benard V, Vaiva G, Masson M, Geoffroy P (2016) Lithium and suicide prevention in bipolar disorder. L'Encéphale 42(3):234–241. https://doi.org/10.1016/j.encep.2016.02.006

Bertolote JM, Fleischmann A (2002) Suicide and psychiatric diagnosis: a worldwide perspective. World Psychiatry 1(3):181–185

Betz M, Sullivan A, Manton AP, Espinola JA, Miller I, Camargo CA Jr, Boudreaux ED (2013) Knowledge, attitudes, and practices of emergency department providers in the care of suicidal patients. Depress Anxiety. https://doi.org/10.1002/da.22071

Blasco-Fontecilla H, Perez-Rodriguez MM, García-Nieto R et al (2012) Worldwide impact of economic cycles on suicide trends over 3 decades: differences according to level of development. A mixed effect model study. BMJ Open 2:e000785

Bridge J, Greenhouse J, Ruch D et al (2019) Association between the release of Netflix's 13 reasons why and suicide rates in the United States: an interrupted times series analysis. J Am Acad Child Adolesc Psychiatry 59:236. https://doi.org/10.1016/j.jaac.2019.04.020

Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM (2003) Psychological autopsy studies of suicide: a systematic review. Psychol Med 33(3):395–405

Centers for Disease Control and Prevention (2019) Web-based injury statistics query and reporting system. Cdc.gov. https://www.cdc.gov/injury/wisqars/nvdrs.html. Accessed 11 Aug 2019

Chakraborty R, El-Jawahri A, Litzow M, Syrjala K, Parnes A, Hashmi S (2017) A systematic review of religious beliefs about major end-of-life issues in the five major world religions. Palliat Support Care 15(5):609–622

Chang BP, Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM et al (2016) Biological risk factors for suicidal behaviors: a meta-analysis. Transl Psychiatry 6(9):e887

Courtet P, Gottesman I, Jollant F, Gould T (2011) The neuroscience of suicidal behaviors: what can we expect from endophenotype strategies? Transl Psychiatry 1(5):e7–e7

Czyz E, Horwitz A, Eisenberg D, Kramer A, King C (2013) Self-reported barriers to professional help seeking among college students at elevated risk for suicide. J Am Coll Heal 61(7):398–406. https://doi.org/10.1080/07448481.2013.820731

Eynan R, Reiss L, Links P, Shah R, Sathyanarayana Rao T, Parkar S et al (2015) Suicide prevention competencies among urban Indian physicians: a needs assessment. Indian J Psychiatry 57(4):397

Feldman M, Franks P, Duberstein P, Vannoy S, Epstein R, Kravitz R (2007) Let's not talk about it: suicide inquiry in primary care. Ann Fam Med 5(5):412–418

Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, Musacchio KM, Jaroszewski AC, Chang BP, Nock MK (2017a) Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychol Bull 143(2):187–232

Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X et al (2017b) Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychol Bull 143(2):187–232

Glenn J, Werntz A, Slama S, Steinman S, Teachman B, Nock M (2017) Suicide and self-injury-related implicit cognition: a large-scale examination and replication. J Abnorm Psychol 126 (2):199–211

Hauge L, Stene-Larsen K, Grimholt T, Øien-Ødegaard C, Reneflot A (2018) Use of primary health care services prior to suicide in the Norwegian population 2006–2015. BMC Health Serv Res 18 (1):619

Hong V, Ewell Foster C, Magness C, McGuire T, Smith P, King C (2019) 13 reasons why: viewing patterns and perceived impact among youths at risk of suicide. Psychiatr Serv 70(2):107–114. https://doi.org/10.1176/appi.ps.201800384

Kleiman E, Nock M (2018) Real-time assessment of suicidal thoughts and behaviors. Curr Opin Psychol 22:33–37. https://doi.org/10.1016/j.copsyc.2017.07.026

Larsen M, Nicholas J, Christensen H (2016) A systematic assessment of smartphone tools for suicide prevention. PLoS One 11(4):e0152285. https://doi.org/10.1371/journal.pone.0152285

Law C, Sveticic J, De Leo D (2014) Restricting access to a suicide hotspot does not shift the problem to another location. An experiment of two river bridges in Brisbane, Australia. Aust N Z J Public Health 38(2):134–138. https://doi.org/10.1111/1753-6405.12157

Levy T, Azar S, Huberfeld R, Siegel A, Strous R (2012) Attitudes towards euthanasia and assisted suidice: a comparison between psychiatrists and other physicians. Bioethics 27(7):402–408. https://doi.org/10.1111/j.1467-8519.2012.01968.x

Littlewood D, Kyle S, Carter L, Peters S, Pratt D, Gooding P (2018) Short sleep duration and poor sleep quality predict next-day suicidal ideation: an ecological momentary assessment study. Psychol Med 49(3):403–411

Lopez-Castroman J, Blasco-Fontecilla H, Courtet P, Baca-Garcia E, Oquendo M (2015) Are we studying the right populations to understand suicide? World Psychiatry 14(3):368–369. https://doi.org/10.1002/wps.20261

O'Connor R, Portzky G (2018) Looking to the future: a synthesis of new developments and challenges in suicide research and prevention. Front Psychol 9:2139

Oquendo M (2016) Subtyping suicidal behavior. J Clin Psychiatry 77(06):813–814. https://doi.org/10.4088/jcp.16f10933

Oquendo M, Baca-Garcia E (2014) Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations. World Psychiatry 13(2):128–130. https://doi.org/10.1002/wps.20116

Oquendo M, Bernanke J (2017) Suicide risk assessment: tools and challenges. World Psychiatry 16 (1):28–29

Oquendo M, Sullivan G, Sudol K et al (2014) Toward a biosignature for suicide. Am J Psychiatr 171(12):1259–1277. https://doi.org/10.1176/appi.ajp.2014.14020194

Pérez Sales P (2004) Psicología y psiquiatría transcultural, 1st edn. Desclée de Brouwer, Bilbao

Petrik M, Gutierrez P, Berlin J, Saunders S (2015) Barriers and facilitators of suicide risk assessment in emergency departments: a qualitative study of provider perspectives. Gen Hosp Psychiatry 37(6):581–586. https://doi.org/10.1016/j.genhosppsych.2015.06.018

Phillips M, Cheng H (2012) The changing global face of suicide. Lancet 379(9834):2318–2319

Phillips MR, Yang G, Zhang Y et al (2002) Risk factors for suicide in China: a national case-control psychological autopsy study. Lancet 360:1728–1736

Quinlivan L, Cooper J, Davies L, Hawton K, Gunnell D, Kapur N (2016) Which are the most useful scales for predicting repeat self-harm? A systematic review evaluating risk scales using measures of diagnostic accuracy. BMJ Open 6(2):e009297

Roberts L, Berk M, Lane-McKinley K (2019) Ethical considerations in research on suicide prediction. JAMA Psychiat 76:883. https://doi.org/10.1001/jamapsychiatry.2019.1228

Saffer B, Klonsky E (2018) Do neurocognitive abilities distinguish suicide attempters from suicide ideators? A systematic review of an emerging research area. Clin Psychol Sci Pract 25(1): e12227. https://doi.org/10.1111/cpsp.12227

Sarchiapone M, Mandelli L, Iosue M, Andrisano C, Roy A (2011) Controlling access to suicide means. Int J Environ Res Public Health 8(12):4550–4562. https://doi.org/10.3390/ijerph8124550

Schadenberg A (2013) Exposing vulnerable people to euthanasia and assisted suicide. Ross Lattner, London

Schulberg H, Bruce M, Lee P, Williams J, Dietrich A (2004) Preventing suicide in primary care patients: the primary care physician's role. Gen Hosp Psychiatry 26(5):337–345

Silverman M (2016) Challenges to defining and classifying suicide and suicidal behaviors. In: O'Connor R, Pirkins J (eds) The international handbook of suicide prevention. Wiley Blackwell, Oxford

Stone D, Crosby A (2014) Suicide Prevention. Am J Lifestyle Med 8(6):404–420. https://doi.org/10.1177/1559827614551130

Sulmasy D, Travaline J, Mitchell L, Ely E (2016) Non-faith-based arguments against physician-assisted suicide and euthanasia. Linacre Q 83(3):246–257. https://doi.org/10.1080/00243639.2016.1201375

Torous J, Larsen M, Depp C et al (2018) Smartphones, sensors, and machine learning to advance real-time prediction and interventions for suicide prevention: a review of current progress and next steps. Curr Psychiatry Rep 20(7). https://doi.org/10.1007/s11920-018-0914-y

Tran T, Luo W, Phung D, Harvey R, Berk M, Kennedy RL et al (2014) Risk stratification using data from electronic medical records better predicts suicide risks than clinician assessments. BMC Psychiatry 14:76

Valente S (2011) Nurses' psychosocial barriers to suicide risk management. Nurs Res Pract 2011:1–4. https://doi.org/10.1155/2011/650765

Wagenaar A, Tobler A, Komro K (2010) Effects of alcohol tax and Price policies on morbidity and mortality: a systematic review. Am J Public Health 100(11):2270–2278. https://doi.org/10.2105/ajph.2009.186007

Zalsman G, Hawton K, Wasserman D, van Heeringen K, Arensman E, Sarchiapone M et al (2016) Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry 3:646–659. https://doi.org/10.1016/S2215-0366(16)30030-X

The Role of Epigenetic Dysregulation in Suicidal Behaviors

Laura M. Fiori and Gustavo Turecki

Contents

Abstract Suicidal behaviors have been associated with both heritable genetic variables and environmental risk factors. Epigenetic processes, such as DNA methylation, have important roles in mediating the effects of the environment on behavior. Dysregulation of these processes has been observed in many psychiatric disorders, and evidence suggests that they may also be involved in suicidal behaviors. Herein, we have summarized candidate gene and epigenome-wide studies which have investigated DNA methylation in relation to suicidal behaviors, as well as discussed some of the limitations of the field to date.

Keywords DNA methylation · Epigenetics · EWAS · Suicidal behaviors · Suicide

L. M. Fiori and G. Turecki (✉)
McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Verdun, QC, Canada
e-mail: gustavo.turecki@mcgill.ca

Curr Topics Behav Neurosci (2020) 46: 41–62
https://doi.org/10.1007/7854_2020_160
Published Online: 24 July 2020

1 Introduction

Nearly one million people die by suicide each year (Saxena et al. 2014), with considerably higher numbers attempting suicide or experiencing suicidal ideation. While a history of psychiatric disorders is present in the majority of people who display suicidal behaviors, their transmission is independent, indicating that suicidal behaviors represent a distinct phenotype (Turecki and Brent 2016). Those suicidal behaviors possess a genetic component that has been demonstrated through numerous studies, with heritability estimated between 30 and 50% (Statham et al. 1998; McGuffin et al. 2001; Fu et al. 2002; Turecki and Brent 2016). Although efforts to identify biological pathways underlying the genetic risk for suicidal behaviors have been ongoing for decades, it has become clear that the etiology and pathology of these behaviors are the result of a complex relationship between genetic factors and the environment. Epigenetic processes play an important role in mediating the relationship between genetics and the environment, and their relationship to both behavior and psychopathology has been well established (Weaver et al. 2004; McGowan et al. 2009; Turecki 2014).

Epigenetics refer to molecular processes that alter gene expression without altering the underlying genomic sequence. The most commonly investigated epigenetic mechanisms are DNA methylation, posttranslational histone modifications, and noncoding RNA-mediated gene repression by microRNAs (miRNA). Each of these has been examined for their role in various psychiatric disorders, particularly mood disorders, anxiety disorders, and schizophrenia (for recent reviews, see Hoffmann et al. 2017; Dwivedi 2018; Punzi et al. 2018; Schiele and Domschke 2018; Brown et al. 2019). Although the environmental exposures responsible for the majority of these epigenetic differences have not been identified, one environmental factor which has been shown to be associated with psychopathology-related epigenetic alterations is early life adversity (ELA). Specifically, ELA, defined as childhood abuse and parental neglect, is associated with increased rates of anxiety, depression, and suicidal behaviors (McCauley et al. 1997; Gilbert et al. 2009; McLaughlin et al. 2010), as well as specific epigenetic alterations (e.g., see McGowan et al. 2009; Jawahar et al. 2015; Lutz et al. 2015; Turecki and Meaney 2016).

The most thoroughly investigated epigenetic mechanism is DNA methylation. DNA methylation involves the covalent addition of a methyl group to the 5′ position of cytosine nucleotides. In mammals, the majority of methylated cytosines are found at cytosine-guanine dinucleotides (CpG) (Maunakea et al. 2010). When found within gene promoter regions, DNA methylation is typically associated with repression of gene expression (Jones et al. 1998; Klose and Bird 2006), whereas gene body methylation can be linked to elevated levels of gene expression and the use of alternative promoters (Maunakea et al. 2010; Zemach et al. 2010; Jjingo et al. 2012). In addition to CpG methylation, non-CpG methylation and hydroxymethylation are important marks which display enriched levels in the brain and appear to play important roles in synaptic development (Lister et al. 2013). Moreover, it must be noted that while the relationship between methylation

and expression can often be predicted based on genomic location, the actual relationship between methylation and gene expression is far more complex, both in terms of the location of methylated sites (Spainhour et al. 2019) and the timing of expression changes (Pacis et al. 2019). Furthermore, as methylation patterns can be influenced by the underlying genetic sequence (Do et al. 2017), correlations between gene expression and methylation may not reflect a causal relationship.

Investigating the role of epigenetic factors in suicidal behaviors follows one of two strategies. Classically, researchers have used hypothesis-driven candidate gene approaches focusing on genes and/or pathways of interest to suicidal behaviors. More recently, large-scale approaches, investigating methylation across the whole genome, have revealed additional genes and pathways not previously implicated in this phenotype. In this chapter, we will first highlight the major findings resulting from candidate gene studies (Table 1), focusing on studies examining stress response pathways, neurotrophic factor signaling, and neurotransmitter signaling. Secondly, we will summarize findings from larger, epigenome-wide association studies (EWAS) (Table 2). Finally, we will discuss some of the limitations and implications of the studies to date.

2 Stress Response Pathways

Stress response systems are essential for survival. They initiate numerous behavioral and physiological changes in response to environmental stressors. Not surprisingly, dysregulated functioning of stress response systems can be highly detrimental. The stress-diathesis interaction is widely used to conceptualize risk for suicide. The model assumes that suicide results from a combination of stressors and predisposing factors. As such, two molecular systems related to stress response, the hypothalamic-pituitary-adrenal (HPA) axis and the polyamine system, have been investigated at the epigenetic level for their role in suicide.

Corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus activates the HPA axis, in turn, stimulating the release of adrenocorticotropic hormone from the pituitary gland, resulting in the release of glucocorticoids from the adrenal gland (Herman et al. 2003). These hormones travel systemically, acting to increase the expression of genes involved in metabolism and inflammation, resulting innumerous effects in the central nervous system. Dysregulation of this pathway has been found to play an important role in suicidal behaviors (Pfennig et al. 2005; O'Connor et al. 2016; Melhem et al. 2017). Moreover, numerous studies have shown that the early life environment can modify the reactivity of this stress system, leading to lifelong behavioral changes (Liu et al. 1997; Francis et al. 1999; Meaney and Szyf 2005). Consequentially, the relationship between the epigenetic effects of ELA and functioning of the HPA axis has been the focus of a number of studies of suicide.

The polyamine system is important for all organisms playing a key role in numerous cell functions including growth, division, and signaling cascades. It is

Table 1 Findings from targeted epigenetic studies in suicide. Genes displaying significant differences are in bolded type

System	Gene(s) examined	Phenotype	Tissue	Significant findings	Reference
Stress response	**NR3C1**	Abuse and non-abuse, suicide vs HC	Hippocampus	Hypermethylation in abused suicides	McGowan et al. (2009)
	NR3C1	Abuse and non-abuse, suicide vs HC	Hippocampus	Hypermethylation (exon 1B and 1C), hypomethylation (exon 1H)	Labonte et al. (2012a)
	NR3C1	Bulimia with suicidality vs bulimia without suicidality vs HC	Whole blood	Hypermethylation of exon 1C in patients with suicidality	Steiger et al. (2013)
	NR3C1, **BDNF**, **FKBP5**, **CRHBP**, CRHR1	Suicide ideation vs non-ideation, MDD	Peripheral blood mononuclear cells	Hypermethylation in suicide ideation	Roy et al. (2017)
	CRH,CRHBP, CRHR1, CRHR2, FKBP5, and NR3C1	High-risk suicide attempt vs low-risk attempt	Whole blood	Hypomethylation in high-risk attempters	Jokinen et al. (2018)
	SKA2	Suicide attempts, suicide ideation	Saliva, whole blood	Methylation predicted suicide attempts	Kaminsky et al. (2015)
	SKA2	Suicide ideation and attempts	Whole blood	Methylation predicted suicide attempts and ideation	Sadeh et al. (2016)
	SAT1	Suicide vs HC	BA11	NS	Guipponi et al. (2009)
	SAT1	Suicide vs HC	BA 8/9	NS	Fiori and Turecki (2011)

	SMS, SMOX	Suicide vs HC	BA 8/9	NS	Fiori and Turecki (2010)
	AMD1, ARG2, OAZ1, OAZ2	Suicide vs HC	BA44	Overall and site-specific differences in promoter methylation	Gross et al. (2013)
Neurotrophins	**BDNF**	Suicide vs HC	Wernicke area	Hypermethylation in suicides	Keller et al. (2010)
	BDNF	Suicide attempts, suicide ideation	Whole blood	Hypermethylation in attempters and ideators	Kang et al. (2013)
	BDNF	Suicide ideation, late life	Whole blood	Hypermethylation in suicidal ideation	Kim et al. (2014)
	BDNF	Suicide ideation, breast cancer	Whole blood	Hypermethylation associated with suicidal ideation and depressive symptoms	Kim et al. (2015)
	BDNF	Suicide ideation, acute coronary syndrome	Whole blood	Hypermethylation associated with suicidal ideation	Kang et al. (2018)
	TrkB	Suicide vs HC	BA8/9	Hypermethylation in suicides	Ernst et al. (2009)
	TrkB	Suicide vs HC	Wernicke area	NS	Keller et al. (2011)
	TrkB	Suicide vs HC	BA8/9	Hypermethylation in suicides	Maussion et al. (2014)
Neurotransmission	**HTR2A**	Schizophrenia and bipolar disorder, suicide attempt vs non-attempt	BA46, white blood cells	Hypermethylation in suicide attempters with schizophrenia	De Luca et al. (2009)

(continued)

Table 1 (continued)

System	Gene(s) examined	Phenotype	Tissue	Significant findings	Reference
	HTR2A	Schizophrenia, suicide attempt vs non-attempt	White blood cells	NS	Bani-Fatemi et al. (2016)
	HTR2A	Schizophrenia, suicide attempt vs non-attempt	Frontal cortex, saliva	NS	Bani-Fatemi et al. (2017)
	TPH2	MDD, suicide attempt vs non-attempt	Whole blood	Hypermethylation in suicide attempters	Zhang et al. (2015)
	GABAA	Suicide vs HC	BA10	Hypermethlation in suicide	Poulter et al. (2008)
	Galanin, **GALR3**, GALR1, GALR2	MDD suicide vs HC	Anterior cingulate cortex; dorso-lateral prefrontal cortex; dorsal raphe nucleus; locus coeruleus; medullary raphe nucleus	Brain region- and gender-specific alterations in methylation	Barde et al. (2016)
	KOR	Abuse and non-abuse, suicide vs HC	AI	Hypomethylation in abused suicides compared to non-abused suicides or controls	Lutz et al. (2018)
Other	QKI	MDD suicide vs HC	BAs 4, 6, 8/9, 10, 11,20, 21, 24, 29, 38, 44, 45, 46, and 47, hippo-campus, amygdala, nucleus accumbens	NS	Klempan et al. (2009)
	rRNA	Abused suicide vs HC	Hippocampus	Hypermethylation of rRNA promoters and 5′ regulatory regions	McGowan et al. (2008)

	CACNA1C	Suicide attempt vs non-attempt	Whole blood	Significant differences in two CpG sites in suicide attempters	Kim et al. (2017)
	ERBB3	Suicide vs HC	Hippocampus	NS	Mahar et al. (2017)
	ELOVL5, FADS1, FADS2	MDD, suicide attempt vs non-attempt	Buffy coat	Hypomethylation in downstream region, hypermethylation in upstream region	Haghighi et al. (2015)
	TNFα	Suicide vs HC	Prefrontal cortex	Hypomethylation in suicide	Wang et al. (2018)

BA Brodmann area, *HC* healthy control, *MDD* major depressive disorder, *NS* not significant

Table 2 EWAS investigating epigenetic differences related to suicidal behaviors

Highlighted genes	Phenotype	Tissue	Technology	Reference
ALS2, DGKZ, *HIST2H2AB*, *NR1D1*, *TAF5L*	Abuse and non-abuse Suicide vs HC	Hippocampus	MeDIP Promotor tiling array	Labonte et al. (2012b)
NR2E1, CHRNB2, GRM7, DBH	Suicide vs HC	Hippocampus	MeDIP Promotor tiling array	Labonte et al. (2013)
ATP8A1, KCNAB2, LOC153328, SKA2	Suicide, suicidal behaviors	BA9 BA10 BA46 White blood cells	HumanMethylation450K BeadChip	Guintivano et al. (2014)
EYA2, MEGF11, LMNA, GLUD1, ERBB3, SLC18A2	MDD suicide vs HC	BA47	HumanMethylation27 BeadChip	Haghighi et al. (2014)
BEGAIN, GRIK2	Suicide vs HC	BA8/9	MBD2 sequencing	Nagy et al. (2015)
LINGO3, POU3F1, ITGB1	Abuse and non-abuse Suicide vs HC	BA24	Reduced representation bisulfite sequencing	Lutz et al. (2017)
PSORS1C3, TAPBP, ATP5G2	MDD suicide vs HC	BA11 BA25	HumanMethylation450K BeadChip	Murphy et al. (2017)
MPP4, TBC1D16, NUP133	BD-high suicidal behavior vs BD-low suicidal behavior	White blood cells	HumanMethylation450K BeadChip	Jeremian et al. (2017)
NRIP3, ZNF714	Suicide vs HC	BA9 Hippocampus	Reduced representation bisulfite sequencing	Kouter et al. (2019)
None	Suicide vs HC	BA10	HumanMethylation450K BeadChip	Schneider et al. (2015)
None	Schizophrenia, suicide attempt vs non-attempt	White blood cells	HumanMethylation450K BeadChip	Bani-Fatemi et al. (2018)

BA Brodmann area, *HC* healthy control, *MDD* major depressive disorder

also a crucial system for stress responses, both at the cellular and behavioral levels (Tabor and Tabor 1984; Gilad and Gilad 2003; Minguet et al. 2008). The polyamine stress response (PSR) is activated after exposure to stressful stimuli, resulting in elevated levels of putrescine and agmatine in the brain and periphery (Fiori and Turecki 2008; Turecki 2014; Limon et al. 2016). Interestingly, the PSR appears to be developmentally regulated, and the emergence of the adult PSR is correlated with the cessation of the hyporesponsive period of the HPA system (Gilad et al. 1998). As with the HPA axis, dysregulation of this system has been observed in a number of

psychiatric disorders, including mood disorders, anxiety, and schizophrenia (Fiori and Turecki 2008). While the HPA and polyamine systems have distinct molecular effects on their biological targets, there is evidence for cross-talk at several levels (Cousin et al. 1982; Ientile et al. 1988; Gilad et al. 1998).

Suicidal behaviors in abused individuals have been investigated in three studies of glucocorticoid receptor (GR, NR3C1) promoter methylation (variable exon 1). Two studies, performed in the hippocampus of individuals who died by suicide, identified abuse-specific methylation differences associated with the expression of different GR isoforms (McGowan et al. 2009; Labonte et al. 2012a). The third study examined GR promoter methylation in the blood of individuals with bulimia nervosa finding that specific promoter methylation was associated with suicidal behavior, but not childhood abuse (Steiger et al. 2013). It is unclear if these differences are related to differences in tissue (brain, blood), severity of suicidal behavior (suicide vs attempt), or other factors. Nonetheless, altogether these three studies reinforce the importance of this gene in psychopathology.

Moving beyond GR, two studies have examined larger sets of stress- and HPA-related genes in the blood. The first examined suicidal ideation in individuals with major depressive disorder (MDD) and its relationship to methylation and expression of five stress-related genes in the blood (Roy et al. 2017). Four genes displayed hypermethylation related to suicidal ideation: GR, corticotropin-releasing hormone-binding protein (CRHBP), FK506 binding protein 5 (FKBP5), and the neurotrophin brain-derived neurotrophic factor (BDNF). The increased methylation was inversely correlated with expression of BDNF, FKBP5, and NR3C1. The fifth gene, corticotropin-releasing hormone receptor 1 (CRHR1), did not display differential methylation or expression in this cohort. A second study investigated methylation of CRH, CRHBP, CRHR1, CRHR2, FKBP5, and NR3C1 in the blood of individuals who had attempted suicide and found hypomethylation of two sites within CRH in relation to higher severity of suicide attempts (Jokinen et al. 2018). Interestingly, one of these sites was hypermethylated in adolescents with a high risk of psychiatric disorders, suggesting a complex relationship between this gene and psychopathology.

One of the most consistent findings emerging from epigenetic studies of suicidal behavior has been altered methylation in a polymorphic methylation site in the 3′ untranslated region of spindle and kinetochore associated complex subunit 2 (SKA2), which is involved in GR signaling (Rice et al. 2008). The importance of this site was first identified in an EWAS examining the prefrontal cortex of individuals who died by suicide (Guintivano et al. 2014). This site was found to be hypermethylated and correlated with expression in both the brain and blood. Methylation at this site was increased in the blood in relation to suicidal ideation, interacted with anxiety to influence suicidal ideation and attempts, and was associated with waking cortisol levels. A follow-up study found that methylation at this site, in both blood and saliva, interacted with trauma exposure to predict lifetime suicide attempts and mediated cortisol suppression in the dexamethasone suppression test (Kaminsky et al. 2015). Another group found that SKA2 methylation was associated with current, but not past, suicidal behaviors, as well as current and

lifetime internalizing symptoms (Sadeh et al. 2016). Finally, a biosignature comprised of methylated sites in discoidin domain receptor tyrosine kinase 1 (DDR1), rho guanine nucleotide exchange factor 10 (ARHGEF10), and protein tyrosine phosphatase, non-receptor type 6 (SHP1) was found to interact with SKA2 methylation to predict suicidal ideation (Clive et al. 2016).

In the original study identifying SKA2 methylation in suicidal behavior, methylation at the 3' UTR site in SKA2 was also found to interact with methylation at a GR-binding site in the spermidine/spermine N1-acetyltransferase (SAT1) promoter to associate with suicidal ideation, suggesting that epigenetic regulation of SAT1 may be stress-related (Guintivano et al. 2014). The involvement of SAT1 in suicidal behavior was first demonstrated in a gene expression study showing widespread downregulation of this catabolic enzyme in the brains of individuals who died by suicide (Sequeira et al. 2006). However, two studies examining methylation of the promoter region of SAT1 in the brain found no differences in relation to suicide (Guipponi et al. 2009; Fiori and Turecki 2011).

Additional polyamine-related genes have demonstrated differential expression in suicide (Fiori et al. 2011) and have been further assessed for epigenetic differences related to suicide. The first study examined two catabolic enzymes, spermine synthase (SMS) and spermine oxidase (SMOX), and found no significant differences in individuals who died by suicide (Fiori and Turecki 2010). However, a second study examining anabolic enzymes ornithine decarboxylase antizymes 1 (OAZ1) and 2 (OAZ2), arginase II (ARG2), and S-adenosylmethionine decarboxylase (AMD1) found differential promoter methylation, with methylation of ARG2 and AMD1 being significantly correlated with gene expression (Gross et al. 2013).

3 Neurotrophic Factor Signaling

Neurotrophins are a class of peptide growth factors secreted by specific cells to increase the growth and survival of neurons and include nerve growth factor (NGF), neurotrophin 3 (NT-3), neurotrophin 4 (NT-4), and brain-derived neurotrophic factor (BDNF). Both the expression of these growth factors and the BDNF receptor TrkB demonstrate dysregulated expression in suicide (Dwivedi et al. 2005; Pandey et al. 2008; Ernst et al. 2009; Sheldrick et al. 2017). To date, epigenetic studies examining neurotrophic factors have focused on BDNF and TrkB and, along with SKA2, have been the most consistent epigenetic findings related to suicidal behavior.

The first study investigating BDNF in suicide examined methylation of the promoter/exon IV regions in the brain Wernicke area of people who died by suicide and found hypermethylation, which was inversely correlated with expression (Keller et al. 2010). Hypermethylation of BDNF has also been repeatedly shown in the blood: in individuals with MDD who had previously attempted suicide (Kang et al. 2013), as well as suicidal ideation in people with MDD (Kang et al. 2013; Roy et al.

2017), the elderly (Kim et al. 2014), patients with breast cancer (Kim et al. 2015), and people with acute coronary syndrome (Kang et al. 2018).

Two studies have also found significant methylation differences in the TrkB.T1 isoform in suicide. The first study found hypermethylation at specific promoter sites in the prefrontal cortex of suicides, which was associated with decreased expression of this transcript (Ernst et al. 2009). The second study identified hypermethylation at several sites in the 3' UTR of TrkB.T1, which correlated with expression in the prefrontal cortex (Maussion et al. 2014). However, hypermethylation of TrkB appears to be brain-region specific, as no differences were found in the cerebellum (Ernst et al. 2009) or the Wernicke area (Keller et al. 2011).

4 Neurotransmitter Systems

Neurotransmitter systems are the main target for the majority of psychopharmaceutical agents currently in use and have been extensively explored in psychiatry. Serotonergic neurotransmission is the target of most antidepressants and has been the focus of several epigenetic studies of suicidal behavior. Three studies have examined methylation of a specific CpG site in exon 1 of the serotonin 2A receptor (HTR2A). Although one study found increased levels of methylation at this site in the blood of patients with schizophrenia who had attempted suicide relative to non-attempters (De Luca et al. 2009), follow-up studies by the same group were notable to fully replicate these findings (Bani-Fatemi et al. 2016, 2017). Furthermore, no differences were found in suicide attempters with bipolar disorder or in the brains of people who died by suicide (De Luca et al. 2009; Bani-Fatemi et al. 2017). Finally, one study examined tryptophan hydroxylase 2 (TPH2) and found hypermethylation in the blood of people with MDD who had previously attempted suicide relative to non-attempters (Zhang et al. 2015).

A few additional epigenetic studies of neurotransmitter systems have been performed and have identified methylation differences in $GABA_A$ α1 receptor subunit (Poulter et al. 2008), kappa opioid receptor (Lutz et al. 2018), and components of galanin signaling (Barde et al. 2016). However, these findings have yet to be replicated.

5 Epigenome-Wide Association Studies (EWAS)

Although candidate gene studies have provided important insight into the role of specific genes and methylation marks in psychiatric disorders, it has become increasingly clear that epigenetic reprogramming in response to the environment occurs on a much larger scale and that genome-wide patterns of altered methylation may be more relevant than quantifying levels at specific CpG sites. Furthermore, candidate gene studies lack the ability to assess relationships between altered

methylation across different biological pathways and how methylation at a specific locus may be influenced by that in nearby genomic regions. These issues can be better studied using epigenome-wide approaches, which also have the potential to identify genes and pathways not been previously implicated in suicide. A summary of EWAS examining suicidal behaviors is shown in Table 2.

Four EWAS have investigated suicidal behaviors within individuals diagnosed with mood disorders. The first study assessed methylation in the orbital prefrontal cortex of suicides with MDD relative to non-psychiatric controls (Haghighi et al. 2014). Their results showed a significant effect of age on methylation, with a significantly higher number of age-related CpGs in the depressed suicide group. Furthermore, these age-related genes were enriched for those associated with behavior, cell cycle, cell death and survival, and cellular and embryonic development. The second study also compared depressed suicides relative to non-psychiatric controls and evaluated methylation in two regions: the orbitofrontal cortex and the anterior cingulate cortex (Murphy et al. 2017). Three genes were found to be differentially methylated in both brain areas: psoriasis susceptibility 1 candidate 3 (PSORS1C3), TAP binding protein (TAPBP), and ATP synthase membrane subunit c locus 2 (ATP5G2). In an independent sample of depressed suicides, hypomethylation of PSORS1C3 was observed in sorted neuronal cells from the prefrontal cortex. Using a combination of polygenic risk scores (PRS) and weighted gene co-expression network analysis (WGCNA), they found enrichment for processes related to nervous system development and mitochondrial function. A third study examined methylation in the prefrontal cortex of an astrocytic dysfunction subgroup of depressed suicides relative to non-psychiatric controls (Nagy et al. 2015). They found 115 differentially methylated regions, with the most significant findings in the genes glutamate ionotropic receptor kainate type subunit 2 (GRIK2) and brain-enriched guanylate kinase-associated (BEGAIN), which was inversely correlated with gene expression. Methylation differences in GRIK2 were maintained in both neuronal and nonneuronal cells, whereas hypermethylation of BEGAIN was found only in nonneuronal cells. An in vitro study showed that this region of BEGAIN has a regulatory function, which is impacted by methylation. Finally, one study examined methylation in the blood of people with bipolar disorder and dichotomized their sample based on high or low levels of suicidal behaviors (Jeremian et al. 2017). They identified differential methylation in three genes: membrane palmitoylated protein 4 (MPP4), nucleoporin 133 (NUP133), and TBC1 domain family member 16 (TBC1D16). Additionally, they calculated DNA methylation age and found a weaker correlation with tissue age in people in the high suicidal behavior group.

Two studies have examined epigenome-wide methylation in groups with mixed psychiatric disorders, including MDD, bipolar disorder, or schizophrenia. The first study was described within the candidate gene studies earlier and identified four differentially methylated regions: ATPase phospholipid transporting 8A1 (ATP8A1), potassium voltage-gated channel subfamily A regulatory beta subunit 2 (KCNAB2), LOC153328, and SKA2, in the prefrontal cortex of depressed suicides (Guintivano et al. 2014). Differential methylation of SKA2 in the prefrontal cortex was replicated in two cohorts, comprised of suicides with bipolar disorder or

schizophrenia, as well as correlated with other important behavioral and physiological measures, as described earlier. A second study assessed the prefrontal cortex and the hippocampus in a small group of suicides who died by hanging and found differential methylation of a number of genes in both regions (Kouter et al. 2019). Two of these genes, nuclear receptor-interacting protein 3 (NRIP3) and zinc finger protein 714 (ZNF714), were also differentially expressed in the prefrontal cortex.

Finally, three postmortem studies have used a three-group design to disentangle the effects of ELA and suicide, by comparing non-psychiatric controls to suicide completers with or without a history of ELA. Similar to the previous section, suicides within these three studies were diagnosed with various psychiatric disorders, including MDD, bipolar disorder, or schizophrenia. The first study was performed in the hippocampus and examined genome-wide promoter methylation (Labonte et al. 2012b). They identified 362 promoters which were differentially methylated in abused suicides relative to non-psychiatric controls. Gene ontology analyses indicated that genes associated with neuronal plasticity were the most enriched among the differentially methylated regions and highlighted alsin (ALS2) as being of particular importance. Methylation differences in this promoter were found to be specific to neuronal cells and hypermethylated at a functional CpG site specifically in abused suicides relative to non-abused suicides and non-psychiatric controls. A follow-up study was performed using a larger sample, again examining promoter methylation in the hippocampus, specifically to identify suicide-related differences by controlling for a history of ELA (Labonte et al. 2013). Gene ontology analyses of differentially methylated promoters found enrichment for genes related to cognitive processes and neuronal communication, with the most significant differences in this cluster found within the genes nuclear receptor subfamily 2 group E member 1 (NR2E1), cholinergic receptor nicotinic beta 2 subunit (CHRNB2), glutamate metabotropic receptor 7, (GRM7), and dopamine beta-hydroxylase (DBH). Finally, a third study was performed in the anterior cingulate cortex and assessed epigenome-wide differences in abused suicides relative to non-psychiatric controls (Lutz et al. 2017). Differential methylation was enriched in genes related to oligodendrocytes, and both an impairment in transcription of myelin-related genes and a reduction in myelination were observed in depressed suicides with a history of childhood abuse. The three most differentially methylated regions were in leucine-rich repeat and Ig domain containing 3 (LINGO3), POU class 3 homeobox 1 (POU3F1), and integrin subunit beta 1 (ITGB1). Methylation differences in LINGO3 and POU3F1 were found to be specific to oligodendrocytes, with no changes in neuronal cells. Finally, suicides without a history of childhood abuse had similar methylation levels to non-suicides in these cells, indicating that these effects are specific to ELA, rather than suicide.

6 Discussion and Conclusions

As described above, a number of genes and biological pathways have now been shown to display altered methylation levels in relation to suicidal behaviors. However, many of these findings have been replicated across only a few studies, with relatively poor overlap between candidate gene studies and EWAS.

There are a number of factors which may explain the lack of consistency in epigenetic findings and which represent important elements to address in future studies. Firstly, very diverse phenotypes have been used in the studies to date. Although suicidal behaviors are believed to represent a continuum between ideation and completed suicide, they may possess both distinct and shared epigenetic risk factors. Moreover, studies have used cohorts diagnosed with a variety of Axis 1 disorders. Although suicidal behaviors are considered to be trans-diagnostic, it seems likely that at a biological level, epigenetic changes related to suicidal behaviors may interact with both epigenetic and genetic variations related to other psychopathologies. Additionally, epigenetic factors are susceptible to the underlying genetic sequence, as well as subtle environmental differences. As such, they can be easily confounded by sociodemographic variables such as age, gender, ethnicity, ELA, and smoking. Finally, the temporal relationship between environmental exposures, such as abuse, and the course of epigenetic alterations has not been clearly established. The stability of suicide-related epigenetic differences over time has yet to be addressed, nor has it been demonstrated that suicide-related epigenetic signatures in adulthood are identical to those that were present in childhood following adversity. Furthermore, there is some evidence that the age of experiencing abuse may be important in terms of defining the nature and extent of neurobiological alterations (Heim and Binder 2012).The use of larger and better characterized cohorts, with more refined suicide phenotypes, and appropriate control populations, will enhance our ability to disentangle effects specifically related to suicidal behaviors.

Secondly, studies have investigated a variety of both central (frontal cortex, anterior cingulate cortex, hippocampus) and peripheral samples (whole blood, white blood cells, saliva). Brain regions have been selected based on evidence implicating their involvement in psychiatric disorders. However it remains unclear whether these regions are the most appropriate or meaningful sites for suicide-related epigenetic changes. Additionally, some of the studies described above have identified epigenetic changes specific to particular cell types (neuronal, nonneuronal, oligodendrocyte, etc.). As the majority of studies in the brain have used tissue homogenates, significant epigenetic effects found only within a few cell types may have been diluted and/or undetectable. The use of brain tissue is not an option to investigate suicide attempts or ideation. Accordingly, studies which have focused on these behaviors have relied on peripheral samples. The concordance between methylation patterns in the brain and peripheral tissues has not been fully established. A number of studies have found that DNA methylation variance is more closely linked to tissue-specificity than to individual specificity, suggesting that variations in DNA

methylation in the blood do not necessarily capture variations in brain tissues (Hannon et al. 2015a, b; Schultz et al. 2015; Walton et al. 2015). Nonetheless, some findings, including those regarding SKA2, do appear to be present in both central and peripheral tissues, indicating that peripheral samples can be a viable option for some epigenetic marks. This consistency is very promising, as it indicates the presence of systemic changes in methylation which can be captured outside of the brain.

Future studies will be needed to determine the optimal cell types and tissues to use in these investigations and to identify and control for the most relevant clinical and sociodemographic variables. Further, both better-characterized cohorts and larger-scale epigenetic investigations will be needed to fully delineate the extent of methylation differences specifically related to suicidal behaviors.

In spite of the issues described above, there have been some consistent findings with regard to genes displaying methylation differences in relation to suicidal behaviors. What is particularly promising is studies which have demonstrated that epigenetic processes, including those targeting suicide-related genes, can be modified by antidepressant treatment. Specifically, differential methylation and histone modifications have been found in the promoter regions of BDNF following antidepressant treatment (D'Addario et al. 2013; Lopez et al. 2013; Tadic et al. 2014). Additionally, levels of histone modification enzymes have been found to be altered by antidepressant treatment (Iga et al. 2007), and a number of miRNAs have been shown to be altered by treatment and involved in clinical response (Fiori et al. 2017; Lopez et al. 2017). Finally, treatment with histone deacetylase inhibitors has been shown to elicit antidepressant-like effects in animals (Tsankova et al. 2006; Covington et al. 2009; Hobara et al. 2010). As such, while studies have definitively demonstrated the adverse effects of early childhood experiences, it appears that these environmental influences have the potential to be reversed, thus representing potential new targets for treatment of suicidal behaviors.

In conclusion, the studies described in this chapter have demonstrated a number of epigenetic alterations associated with suicidal behaviors. Methylation differences in some genes, including SKA2, NR3C1, and BDNF, have shown excellent reproducibility across populations and phenotypes. It is clear that the epigenome is an integral system for mediating the effects of the environment on gene function. Understanding its involvement in suicidal behaviors represents a key step in elucidating the molecular mechanisms underlying their development and for identifying new treatment targets and potential biomarkers for early diagnosis and prevention.

References

Bani-Fatemi A, Howe AS, Matmari M, Koga A, Zai C, Strauss J, De Luca V (2016) Interaction between methylation and CpG single-nucleotide polymorphisms in the HTR2A gene: association analysis with suicide attempt in schizophrenia. Neuropsychobiology 73:10–15

Bani-Fatemi A, Strauss J, Zai C, Wong AHC, de Luca V (2017) Multiple tissue methylation analysis of HTR2A exon I in suicidal behavior. Psychiatr Genet 27:219–224

Bani-Fatemi A, Jeremian R, Wang KZ, Silveira J, Zai C, Kolla NJ, Graff A, Gerretsen P, Strauss J, De Luca V (2018) Epigenome-wide association study of suicide attempt in schizophrenia. J Psychiatr Res 104:192–197

Barde S, Ruegg J, Prud'homme J, Ekstrom TJ, Palkovits M, Turecki G, Bagdy G, Ihnatko R, Theodorsson E, Juhasz G, Diaz-Heijtz R, Mechawar N, Hokfelt TG (2016) Alterations in the neuropeptide galanin system in major depressive disorder involve levels of transcripts, methylation, and peptide. Proc Natl Acad Sci U S A 113:E8472–E8481

Brown A, Fiori LM, Turecki G (2019) Bridging basic and clinical research in early life adversity, DNA methylation, and major depressive disorder. Front Genet 10:229

Clive ML, Boks MP, Vinkers CH, Osborne LM, Payne JL, Ressler KJ, Smith AK, Wilcox HC, Kaminsky Z (2016) Discovery and replication of a peripheral tissue DNA methylation biosignature to augment a suicide prediction model. Clin Epigenetics 8:113

Cousin MA, Lando D, Moguilewsky M (1982) Ornithine decarboxylase induction by glucocorticoids in brain and liver of adrenalectomized rats. J Neurochem 38:1296–1304

Covington HE, Maze I, LaPlant QC, Vialou VF, Yoshinori ON, Berton O, Fass DM, Renthal W, Rush AJ, Wu EY, Ghose S, Krishnan V, Russo SJ, Tamminga C, Haggarty SJ, Nestler EJ (2009) Antidepressant actions of HDAC inhibitors. J Neurosci 29:11451–11460

D'Addario C, Dell'Osso B, Galimberti D, Palazzo MC, Benatti B, Di Francesco A, Scarpini E, Altamura AC, Maccarrone M (2013) Epigenetic modulation of BDNF gene in patients with major depressive disorder. Biol Psychiatry 73:e6–e7

De Luca V, Viggiano E, Dhoot R, Kennedy JL, Wong AH (2009) Methylation and QTDT analysis of the 5-HT2A receptor 102C allele: analysis of suicidality in major psychosis. J Psychiatr Res 43:532–537

Do C, Shearer A, Suzuki M, Terry MB, Gelernter J, Greally JM, Tycko B (2017) Genetic-epigenetic interactions in CIS: a major focus in the post-GWAS era. Genome Biol 18:120

Dwivedi Y (2018) MicroRNAs in depression and suicide: recent insights and future perspectives. J Affect Disord 240:146–154

Dwivedi Y, Mondal AC, Rizavi HS, Conley RR (2005) Suicide brain is associated with decreased expression of neurotrophins. Biol Psychiatry 58:315–324

Ernst C, Deleva V, Deng X, Sequeira A, Pomarenski A, Klempan T, Ernst N, Quirion R, Gratton A, Szyf M, Turecki G (2009) Alternative splicing, methylation state, and expression profile of tropomyosin-related kinase B in the frontal cortex of suicide completers. Arch Gen Psychiatry 66:22–32

Fiori LM, Turecki G (2008) Implication of the polyamine system in mental disorders. J Psychiatry Neurosci 33:102–110

Fiori LM, Turecki G (2010) Genetic and epigenetic influences on expression of spermine synthase and spermine oxidase in suicide completers. Int J Neuropsychopharmacol 13:725–736

Fiori LM, Turecki G (2011) Epigenetic regulation of spermidine/spermine N1-acetyltransferase (SAT1) in suicide. J Psychiatr Res 45:1229–1235

Fiori LM, Bureau A, Labbe A, Croteau J, Noel S, Merette C, Turecki G (2011) Global gene expression profiling of the polyamine system in suicide completers. Int J Neuropsychopharmacol 14:595–605

Fiori LM, Lopez JP, Richard-Devantoy S, Berlim M, Chachamovich E, Jollant F, Foster J, Rotzinger S, Kennedy SH, Turecki G (2017) Investigation of miR-1202, miR-135a, and miR-16 in major depressive disorder and antidepressant response. Int J Neuropsychopharmacol 20:619–623

Francis D, Diorio J, Liu D, Meaney MJ (1999) Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 286:1155–1158

Fu Q, Heath AC, Bucholz KK, Nelson EC, Glowinski AL, Goldberg J, Lyons MJ, Tsuang MT, Jacob T, True MR, Eisen SA (2002) A twin study of genetic and environmental influences on suicidality in men. Psychol Med 32:11–24

Gilad GM, Gilad VH (2003) Overview of the brain polyamine-stress-response: regulation, development, and modulation by lithium and role in cell survival. Cell Mol Neurobiol 23:637–649

Gilad GM, Gilad VH, Eliyayev Y, Rabey JM (1998) Developmental regulation of the brain polyamine-stress-response. Int J Dev Neurosci 16:271–278

Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S (2009) Burden and consequences of child maltreatment in high-income countries. Lancet 373:68–81

Gross JA, Fiori LM, Labonte B, Lopez JP, Turecki G (2013) Effects of promoter methylation on increased expression of polyamine biosynthetic genes in suicide. J Psychiatr Res 47:513–519

Guintivano J, Brown T, Newcomer A, Jones M, Cox O, Maher BS, Eaton WW, Payne JL, Wilcox HC, Kaminsky ZA (2014) Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. Am J Psychiatry 171:1287–1296

Guipponi M, Deutsch S, Kohler K, Perroud N, Le Gal F, Vessaz M, Laforge T, Petit B, Jollant F, Guillaume S, Baud P, Courtet P, La Harpe R, Malafosse A (2009) Genetic and epigenetic analysis of SSAT gene dysregulation in suicidal behavior. Am J Med Genet B Neuropsychiatr Genet 150B:799–807

Haghighi F, Xin Y, Chanrion B, O'Donnell AH, Ge Y, Dwork AJ, Arango V, Mann JJ (2014) Increased DNA methylation in the suicide brain. Dialogues Clin Neurosci 16:430–438

Haghighi F, Galfalvy H, Chen S, Huang YY, Cooper TB, Burke AK, Oquendo MA, Mann JJ, Sublette ME (2015) DNA methylation perturbations in genes involved in polyunsaturated fatty acid biosynthesis associated with depression and suicide risk. Front Neurol 6:92

Hannon E, Lunnon K, Schalkwyk L, Mill J (2015a) Interindividual methylomic variation across blood, cortex, and cerebellum: implications for epigenetic studies of neurological and neuropsychiatric phenotypes. Epigenetics 10:1024–1032

Hannon E, Spiers H, Viana J, Pidsley R, Burrage J, Murphy TM, Troakes C, Turecki G, O'Donovan MC, Schalkwyk LC, Bray NJ, Mill J (2015b) Methylation QTLs in the developing brain and their enrichment in schizophrenia risk loci. Nat Neurosci 19:48–54

Heim C, Binder EB (2012) Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp Neurol 233:102–111

Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE (2003) Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol 24:151–180

Hobara T, Uchida S, Otsuki K, Yamagata H, Watanabe Y (2010) Molecular mechanisms of the antidepressant actions by histone deacetylase inhibitors. Neurosci Res 68(Suppl 1):e316

Hoffmann A, Sportelli V, Ziller M, Spengler D (2017) Epigenomics of major depressive disorders and schizophrenia: early life decides. Int J Mol Sci 18:1711

Ientile R, De Luca G, Di Giorgio RM, Macaione S (1988) Glucocorticoid regulation of spermidine acetylation in the rat brain. J Neurochem 51:677–682

Iga J, Ueno S, Yamauchi K, Numata S, Kinouchi S, Tayoshi-Shibuya S, Song H, Ohmori T (2007) Altered HDAC5 and CREB mRNA expressions in the peripheral leukocytes of major depression. Prog Neuro-Psychopharmacol Biol Psychiatry 31:628–632

Jawahar MC, Murgatroyd C, Harrison EL, Baune BT (2015) Epigenetic alterations following early postnatal stress: a review on novel Aetiological mechanisms of common psychiatric disorders. Clin Epigenetics 7:122

Jeremian R, Chen YA, De Luca V, Vincent JB, Kennedy JL, Zai CC, Strauss J (2017) Investigation of correlations between DNA methylation, suicidal behavior and aging. Bipolar Disord 19:32–40

Jjingo D, Conley AB, Yi SV, Lunyak VV, Jordan IK (2012) On the presence and role of human gene-body DNA methylation. Oncotarget 3:462–474

Jokinen J, Bostrom AE, Dadfar A, Ciuculete DM, Chatzittofis A, Asberg M, Schioth HB (2018) Epigenetic changes in the CRH gene are related to severity of suicide attempt and a general psychiatric risk score in adolescents. EBioMedicine 27:123–133

Jones PL, Veenstra GJ, Wade PA, Vermaak D, Kass SU, Landsberger N, Strouboulis J, Wolffe AP (1998) Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat Genet 19:187–191

Kaminsky Z, Wilcox HC, Eaton WW, Van Eck K, Kilaru V, Jovanovic T, Klengel T, Bradley B, Binder EB, Ressler KJ, Smith AK (2015) Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. Transl Psychiatry 5:e627

Kang HJ, Kim JM, Lee JY, Kim SY, Bae KY, Kim SW, Shin IS, Kim HR, Shin MG, Yoon JS (2013) BDNF promoter methylation and suicidal behavior in depressive patients. J Affect Disord 151:679–685

Kang HJ, Bae KY, Kim SW, Shin IS, Hong YJ, Ahn Y, Jeong MH, Yoon JS, Kim JM (2018) BDNF methylation and suicidal ideation in patients with acute coronary syndrome. Psychiatry Investig 15:1094

Keller S et al (2010) Increased BDNF promoter methylation in the Wernicke area of suicide subjects. Arch Gen Psychiatry 67:258–267

Keller S, Sarchiapone M, Zarrilli F, Tomaiuolo R, Carli V, Angrisano T, Videtic A, Amato F, Pero R, di Giannantonio M, Iosue M, Lembo F, Castaldo G, Chiariotti L (2011) TrkB gene expression and DNA methylation state in Wernicke area does not associate with suicidal behavior. J Affect Disord 135:400–404

Kim JM, Kang HJ, Bae KY, Kim SW, Shin IS, Kim HR, Shin MG, Yoon JS (2014) Association of BDNF promoter methylation and genotype with suicidal ideation in elderly Koreans. Am J Geriatr Psychiatry 22:989–996

Kim JM, Kang HJ, Kim SY, Kim SW, Shin IS, Kim HR, Park MH, Shin MG, Yoon JH, Yoon JS (2015) BDNF promoter methylation associated with suicidal ideation in patients with breast cancer. Int J Psychiatry Med 49:75–94

Kim YJ, Park HJ, Jahng GH, Lee SM, Kang WS, Kim SK, Kim T, Cho AR, Park JK (2017) A pilot study of differential brain activation to suicidal means and DNA methylation of CACNA1C gene in suicidal attempt patients. Psychiatry Res 255:42–48

Klempan TA, Ernst C, Deleva V, Labonte B, Turecki G (2009) Characterization of QKI gene expression, genetics, and epigenetics in suicide victims with major depressive disorder. Biol Psychiatry 66:824–831

Klose RJ, Bird AP (2006) Genomic DNA methylation: the mark and its mediators. Trends Biochem Sci 31:89–97

Kouter K, Zupanc T, Videtic Paska A (2019) Genome-wide DNA methylation in suicide victims revealing impact on gene expression. J Affect Disord 253:419–425

Labonte B, Yerko V, Gross J, Mechawar N, Meaney MJ, Szyf M, Turecki G (2012a) Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. Biol Psychiatry 72:41–48

Labonte B, Suderman M, Maussion G, Navaro L, Yerko V, Mahar I, Bureau A, Mechawar N, Szyf M, Meaney MJ, Turecki G (2012b) Genome-wide epigenetic regulation by early-life trauma. Arch Gen Psychiatry 69:722–731

Labonte B, Suderman M, Maussion G, Lopez JP, Navarro-Sanchez L, Yerko V, Mechawar N, Szyf M, Meaney MJ, Turecki G (2013) Genome-wide methylation changes in the brains of suicide completers. Am J Psychiatry 170:511–520

Limon A, Mamdani F, Hjelm BE, Vawter MP, Sequeira A (2016) Targets of polyamine dysregulation in major depression and suicide: activity-dependent feedback, excitability, and neurotransmission. Neurosci Biobehav Rev 66:80–91

Lister R et al (2013) Global epigenomic reconfiguration during mammalian brain development. Science 341:1237905

Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ (1997) Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 277:1659–1662

Lopez JP, Mamdani F, Beaulieu MM, Yang J, Berlim MT, Ernst C, Turecki G (2013) Epigenetic regulation of BDNF expression according to antidepressant response. Mol Psychiatry 18:398–399

Lopez JP et al (2017) MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes. Nat Commun 8:15497

Lutz PE, Almeida D, Fiori LM, Turecki G (2015) Childhood maltreatment and stress-related psychopathology: the epigenetic memory hypothesis. Curr Pharm Des 21:1413–1417

Lutz PE et al (2017) Association of a history of child abuse with impaired myelination in the anterior cingulate cortex: convergent epigenetic, transcriptional, and morphological evidence. Am J Psychiatry 174:1185–1194

Lutz PE, Gross JA, Dhir SK, Maussion G, Yang J, Bramoulle A, Meaney MJ, Turecki G (2018) Epigenetic regulation of the kappa opioid receptor by child abuse. Biol Psychiatry 84:751–761

Mahar I, Labonte B, Yogendran S, Isingrini E, Perret L, Davoli MA, Rachalski A, Giros B, Turecki G, Mechawar N (2017) Disrupted hippocampal neuregulin-1/ErbB3 signaling and dentate gyrus granule cell alterations in suicide. Transl Psychiatry 7:e1161

Maunakea AK et al (2010) Conserved role of intragenic DNA methylation in regulating alternative promoters. Nature 466:253–257

Maussion G, Yang J, Suderman M, Diallo A, Nagy C, Arnovitz M, Mechawar N, Turecki G (2014) Functional DNA methylation in a transcript specific 3'UTR region of TrkB associates with suicide. Epigenetics 9:1061–1070

McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, Ryden J, Derogatis LR, Bass EB (1997) Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA 277:1362–1368

McGowan PO, Sasaki A, Huang TC, Unterberger A, Suderman M, Ernst C, Meaney MJ, Turecki G, Szyf M (2008) Promoter-wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. PLoS One 3:e2085

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 12:342–348

McGuffin P, Marusic A, Farmer A (2001) What can psychiatric genetics offer suicidology? Crisis 22:61–65

McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC (2010) Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. Arch Gen Psychiatry 67:124–132

Meaney MJ, Szyf M (2005) Maternal care as a model for experience-dependent chromatin plasticity? Trends Neurosci 28:456–463

Melhem NM, Munroe S, Marsland A, Gray K, Brent D, Porta G, Douaihy A, Laudenslager ML, DePietro F, Diler R, Driscoll H, Gopalan P (2017) Blunted HPA axis activity prior to suicide attempt and increased inflammation in attempters. Psychoneuroendocrinology 77:284–294

Minguet EG, Vera-Sirera F, Marina A, Carbonell J, Blazquez MA (2008) Evolutionary diversification in polyamine biosynthesis. Mol Biol Evol 25:2119–2128

Murphy TM, Crawford B, Dempster EL, Hannon E, Burrage J, Turecki G, Kaminsky Z, Mill J (2017) Methylomic profiling of cortex samples from completed suicide cases implicates a role for PSORS1C3 in major depression and suicide. Transl Psychiatry 7:e989

Nagy C, Suderman M, Yang J, Szyf M, Mechawar N, Ernst C, Turecki G (2015) Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. Mol Psychiatry 20:320–328

O'Connor DB, Ferguson E, Green JA, O'Carroll RE, O'Connor RC (2016) Cortisol levels and suicidal behavior: a meta-analysis. Psychoneuroendocrinology 63:370–379

Pacis A, Mailhot-Leonard F, Tailleux L, Randolph HE, Yotova V, Dumaine A, Grenier JC, Barreiro LB (2019) Gene activation precedes DNA demethylation in response to infection in human dendritic cells. Proc Natl Acad Sci U S A 116:6938–6943

Pandey GN, Ren X, Rizavi HS, Conley RR, Roberts RC, Dwivedi Y (2008) Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. Int J Neuropsychopharmacol 11:1047–1061

Pfennig A, Kunzel HE, Kern N, Ising M, Majer M, Fuchs B, Ernst G, Holsboer F, Binder EB (2005) Hypothalamus-pituitary-adrenal system regulation and suicidal behavior in depression. Biol Psychiatry 57:336–342

Poulter MO, Du L, Weaver IC, Palkovits M, Faludi G, Merali Z, Szyf M, Anisman H (2008) GABAA receptor promoter hypermethylation in suicide brain: implications for the involvement of epigenetic processes. Biol Psychiatry 64:645–652

Punzi G, Bharadwaj R, Ursini G (2018) Neuroepigenetics of schizophrenia. Prog Mol Biol Transl Sci 158:195–226

Rice L, Waters CE, Eccles J, Garside H, Sommer P, Kay P, Blackhall FH, Zeef L, Telfer B, Stratford I, Clarke R, Singh D, Stevens A, White A, Ray DW (2008) Identification and functional analysis of SKA2 interaction with the glucocorticoid receptor. J Endocrinol 198:499–509

Roy B, Shelton RC, Dwivedi Y (2017) DNA methylation and expression of stress related genes in PBMC of MDD patients with and without serious suicidal ideation. J Psychiatr Res 89:115–124

Sadeh N, Wolf EJ, Logue MW, Hayes JP, Stone A, Griffin LM, Schichman SA, Miller MW (2016) Epigenetic variation at Ska2 predicts suicide phenotypes and internalizing psychopathology. Depress Anxiety 33:308–315

Saxena S, Krug EG, Chestnov O, World Health Organization. Department of Mental Health and Substance Abuse (2014) Preventing suicide : a global imperative. World Health Organization, Geneva

Schiele MA, Domschke K (2018) Epigenetics at the crossroads between genes, environment and resilience in anxiety disorders. Genes Brain Behav 17:e12423

Schneider E, El Hajj N, Muller F, Navarro B, Haaf T (2015) Epigenetic dysregulation in the prefrontal cortex of suicide completers. Cytogenet Genome Res 146:19–27

Schultz MD, He Y, Whitaker JW, Hariharan M, Mukamel EA, Leung D, Rajagopal N, Nery JR, Urich MA, Chen H, Lin S, Lin Y, Jung I, Schmitt AD, Selvaraj S, Ren B, Sejnowski TJ, Wang W, Ecker JR (2015) Human body epigenome maps reveal noncanonical DNA methylation variation. Nature 523:212–216

Sequeira A, Gwadry FG, Ffrench-Mullen JM, Canetti L, Gingras Y, Casero RA Jr, Rouleau G, Benkelfat C, Turecki G (2006) Implication of SSAT by gene expression and genetic variation in suicide and major depression. Arch Gen Psychiatry 63:35–48

Sheldrick A, Camara S, Ilieva M, Riederer P, Michel TM (2017) Brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) levels in post-mortem brain tissue from patients with depression compared to healthy individuals – a proof of concept study. Eur Psychiatry 46:65–71

Spainhour JC, Lim HS, Yi SV, Qiu P (2019) Correlation patterns between DNA methylation and gene expression in the cancer genome atlas. Cancer Inform 18:1176935119828776

Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, Slutske WS, Dunne MP, Martin NG (1998) Suicidal behaviour: an epidemiological and genetic study. Psychol Med 28:839–855

Steiger H, Labonte B, Groleau P, Turecki G, Israel M (2013) Methylation of the glucocorticoid receptor gene promoter in bulimic women: associations with borderline personality disorder, suicidality, and exposure to childhood abuse. Int J Eat Disord 46:246–255

Tabor CW, Tabor H (1984) Polyamines. Annu Rev Biochem 53:749–790

Tadic A, Muller-Engling L, Schlicht KF, Kotsiari A, Dreimuller N, Kleimann A, Bleich S, Lieb K, Frieling H (2014) Methylation of the promoter of brain-derived neurotrophic factor exon IV and antidepressant response in major depression. Mol Psychiatry 19:281–283

Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ (2006) Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci 9:519–525

Turecki G (2014) The molecular bases of the suicidal brain. Nat Rev Neurosci 15:802–816

Turecki G, Brent DA (2016) Suicide and suicidal behaviour. Lancet 387:1227–1239

Turecki G, Meaney MJ (2016) Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. Biol Psychiatry 79:87–96

Walton E, Hass J, Liu J, Roffman JL, Bernardoni F, Roessner V, Kirsch M, Schackert G, Calhoun V, Ehrlich S (2015) Correspondence of DNA methylation between blood and brain tissue and its application to schizophrenia research. Schizophr Bull 42:406–414

Wang Q, Roy B, Turecki G, Shelton RC, Dwivedi Y (2018) Role of complex epigenetic switching in tumor necrosis factor-alpha Upregulation in the prefrontal cortex of suicide subjects. Am J Psychiatry 175:262–274

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ (2004) Epigenetic programming by maternal behavior. Nat Neurosci 7:847–854

Zemach A, McDaniel IE, Silva P, Zilberman D (2010) Genome-wide evolutionary analysis of eukaryotic DNA methylation. Science 328:916–919

Zhang Y, Chang Z, Chen J, Ling Y, Liu X, Feng Z, Chen C, Xia M, Zhao X, Ying W, Qing X, Li G, Zhang C (2015) Methylation of the tryptophan hydroxylase2 gene is associated with mRNA expression in patients with major depression with suicide attempts. Mol Med Rep 12:3184–3190

Suicide: Genetics and Heritability

Concepcion Vaquero-Lorenzo and Manuel A. Vasquez

Contents

Abstract Nature vs nurture is, and has been, a never stopping debate since Lamarck and Darwin exposed their corresponding theories on evolution, and even before them, such discussion already existed. Is suicide a heritable conduct? Is it learnt? Maybe the answer is both and none, at the same time. From genetic twin studies to epigenetic and environmental influence on development, this chapter aims to take a look at different points of view and most relevant theories in one of the worlds

C. Vaquero-Lorenzo
Department of Biology, Autonoma University, Madrid, Spain

M. A. Vasquez (✉)
Department of Psychiatry, Fundación Jiménez Díaz Hospital, Madrid, Spain
e-mail: alfonso.vasquezg@quironsalud.es

Curr Topics Behav Neurosci (2020) 46: 63–78
https://doi.org/10.1007/7854_2020_161
Published Online: 14 August 2020

leading causes of death, specially for young individuals. We explore different studies aiming to find biomarkers for suicide, as well as other traits frequently encountered in individuals who engage in suicidal behavior, such as impulsivity, aggressivity, and hopelessness. Finally, this chapter also looks at some of the most recent approaches in treatment and prevention of suicidal behavior, in order to highlight what they have in common and try to explain (at least partially) why they could be effective.

Keywords Cognition · Environmental · Epigenetics · Heritability · Suicide

1 Biological Correlates of Hopelessness, Impulsivity, and Aggressivity in Suicidal Behavior

In a topic as broad as suicide, and with as little answers as we've been able to gather so far, speaking about biological factors implies defining them and explaining why we consider them so. In this chapter we will discuss how some behavioral characteristics can be developed, in some cases through life experiences, and then passed down to our descendants. Further ahead, we will also talk about how a factor that hasn't been taken enough into account in heritability studies could be the one holding us back from reaching better answers. That factor is timing.

1.1 Heritability in Suicidal Behavior

Heritability is the amount of variance in biological characters that can be accounted by genetic differences between individuals.

Epidemiologic and family studies estimate that there is a genetic component in suicide with a heritability that goes from 17% to 55% (Ruderfer et al. 2019).

Additive effect of genetic factors could account for 30–50% in the development of a wide suicidality phenotype, which includes ideation, planning, and attempts, and its heritability is, mostly, independent of other psychiatric illness (most people who attempt suicide suffer from a previous psychiatric condition). Heritability in non-mortal attempts has been estimated between 17 and 45% after controlling for psychiatric illness, and family studies show higher ratios among relatives of suicidal individuals (JJ Mann et al. 2009).

For less clearly defined phenotypes, such as suicidal ideation, it is harder to establish how much of a genetic influence there is, although it clearly exists, together with environmental and other individual factors (Strawbridge et al. 2019).

Twin studies have been one of the ways of comparing the influence of the environment vs. genetics in suicide, as well as in other psychiatric illnesses. A

study on suicidal conduct performed in 1991 by Roy studied 176 couples of twins and showed a level of agreement for suicide of 11.3% between monozygotic (MZ) twins, compared to 1.8% between dizygotic (DZ) twins. For suicide attempts however, the level of correlation was even higher, reaching 38% for MZ brothers (Roy et al. 1991), showing that both, suicidal attempts, as well as suicide, have heritable factors.

Different studies have observed that when one twin develops depression, there is a risk of 50–60% of the other one developing depression as well. On suicide, however, if one of the twins dies for this cause, the risk of the same thing happening to the other is around 13% (Wasserman et al. 2007), up to 24%, depending on the study (Mann et al. 2009). In DZ twins, the risk is only 0.7% (Roy et al. 1991) up to 2.8% (Mann et al. 2009).

2 Genetic Association Studies and Polygenic Risk Scores

There still exists a problem with general population studies, and that is the lack of wide enough samples, with enough statistical power. As Ruderfer highlights (Ruderfer et al. 2019), after performing a genome-wide association analyses (GWAS), they find a very low heritability, based on single nucleotide polymorphism (SNP), only 0.035 on UK population and 0.046 on Vanderbilt's clinically predicted phenotype. They describe two polymorphic variants, chromosome 5 (rs1297617) and chromosome 19 (rs1297618), but neither was statistically significant.

For complex conditions as high blood pressure and suicide as well, SNP and GWAS have shown to be lacking, and in the same way, polygenic risk scores (PRS) have progressively gained terrain.

A PRS is a number that estimates the probability of an individual for manifesting a trait, taking into account multiple genetic variants, at the same time. In psychiatry (although not with some deterrents), this kind of study seems to be the new way to go, in what is related to heritability. Still, some studies state that PRS can only be applied to the population they derive from, and some even describe that these scores have a higher relation with ascendency, than with the condition they try to predict.

Mullins' work with PRS and suicide behavior found a relation between heritability of suicidal ideation and other psychiatric disorders, but still suggested that carrying out this thoughts had some other independent genetic factors (Mullins et al. 2014). Since they could not find significant relation among the SNPs or GWAS studied by their group, their conclusion was that suicide must be highly polygenic; therefore, PRS are a better approach to study its heritability.

3 Individual Characteristics: The Diathesis-Stress Model

Debate about "what is and what is not" suicidal behavior is widely spread and takes into consideration philosophical and semantic elements, which are far from being the purpose of this chapter.

What does seem clear though is that not all suicides are the same, as suicide attempts aren't either. Individuals who indulge in suicide behavior may have very different characteristics, although they do have some in common. Things like aggressivity or impulsivity are consistently found as risk factors for suicide behavior, so much that there is a particular subtype of suicide attempters, determined by such characteristics (Stanley et al. 2019). This kind of differences between individuals, and the presence of some particular factions that allow to group them, is what brought the hypothesis of diathesis-stress as a clinical model for suicide (Mann et al. 2009).

JJ Man et al.'s work helped show that despite environmental events that may be happening at the moment of the attempt, there are "tendencies" particular to the individual making the attempt that make him or her more prone to such behavior.

"Hopelessness" would be another one of these tendencies, and it has been related to suicide just as much as aggression or impulsivity. Different from the other two, hopelessness is a completely subjective sensation, often present in individuals suffering from depression, and it can predict future suicide (not just attempts).

Later in this chapter, we will discuss how these three tendencies, very different in the way they present themselves, find common ground in the brain prefrontal cortex (PFC). This particular region is in charge of inhibition of conduct, and at the same time, being part of the default mode network (DMN), it also plays a role in our thoughts about the past, the future, and ourselves. It is not strange at all that Arango et al. (1995), or Audenaert et al. (2006), have found changes in the number and function of serotonin receptors in this area, in individuals who engaged in suicide behavior.

4 Serotonin as a Biomarker: Why and Why Not?

The serotoninergic system is composed by 14 different serotonin receptors (found so far), the serotonin transporter, synthesis enzymes TPH1 and 2, and also catabolic enzymes MAOA and MAOB. The function of each component varies from inhibitory to excitatory, depending on the region of the brain, the exact neuron the receptor is attached to, and whether they are located presynaptically or postsynaptically. All of these variations can give place to a multitude of confounding factors to take into account, even though there is no denying that one of the most consistent findings in relation to suicide and serotonin is the low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid of suicidal individuals.

Starting by the serotonin transporter (5HTT), it can be found in nerve endings and platelets. Its job consists mainly in retrieving serotonin (5HT) from synaptic clefts. There is a polymorphism in the promoting region proband 44 (44 bp ins/del). The short allele accounts for a lower expression of the gene and is associated with 40% less union of the transporter to serotonin.

Studies with statistical significance have shown that there is less of this transporter in cortical areas of depressive people who committed suicide (PFC, hypothalamus, raphe, etc.). Some studies have also associated the lesser union of this transporter to serotonin (specially at PFC) with depression and suicide attempts, while other studies have found the opposite.

4.1 So, How Is It That We Give People with Depression a Medication That Inhibits This Transporter Even Further? And Why Studies on 5HTT Can Be So Drastically Different?

A review carried out in 2013 focused on the relation of the different components of the serotoninergic system and their relation with suicidal behavior (Antypa et al. 2013). They report that associations between variation on the TPH1 gene and 5-HTTLPR gene and violent suicidal behavior are the most consistent findings (or, at least, the less inconsistent), but for some variations, negative results have also been reported and need further analyses. It's important to talk individually about the components of the serotoninergic system, in order to better understand where and possibly why these conflicting results emerge.

Serotonin receptor 1A (5HT1A) is an autoreceptor that regulates serotonergic synthesis and neurotransmission. Some studies have shown that there is less of this receptor in the hippocampus and amygdala of suicidal individuals. Polymorphism rs6295, as well as increased methylation of the gene promoter region in PFC, has been associated with depressed patients who committed suicide. These results have been reproduced, but there are also studies that couldn't find a significant relation between the said gene variation and suicide.

Serotonin receptor 2A (5HT2A) can be found in GABAergic neurons in the locus ceruleus. One of its functions is inhibiting noradrenergic neurons through activation of GABAergic cells. Studies on suicidal individuals haven't shown significant results, but studies on suicidal individuals with high scores of aggression show a positive correlation in all frontal areas examined. PET and SPECT studies show a reduction of union to this receptor in suicidal individuals with anxiety or depression, while there is an increase in impulsive attempters (Audenaert et al. 2006). Another study also found association between the T102C and C1354T (His452Tyr) polymorphisms of the 5-HT2a receptor gene and suicide attempts (Vaquero-Lorenzo et al. 2008). In that same study, there were no significant differences between suicide

attempters and psychiatric controls, leaving the possibility of this receptor as a common ground for both, suicide and other psychiatry conditions.

Tryptophan hydroxylase 1 (TPH1) is the enzyme in charge of peripheral synthesis of serotonin, with limited action within the brain. Although there are studies that show negative results, there are others that have related variations of this gene with completed suicide; such are the studies of Turecki et al. (2001), as well as Brezo et al. (2010), with positive results for the rs10488683 polymorphism. Other studies have also related the polymorphism A779C in the 7th intron of the gene with violent suicide attempts (Mann et al. 2001). These polymorphisms may affect the genes transcription, or the function of the enzyme, reducing its activity.

Tryptophan hydroxylase 2 (TPH2) is the rate-limiting enzyme in charge of serotonin synthesis within the brain, but studies relating this enzyme to suicide have, so far, shown conflicting results.

Ottenhof et al. (2018) reviewed in a meta-analysis 166 studies analyzing 69 *TPH2* polymorphisms, and many of these SNPs could be associated with suicide behavior, but the specific influence of these in suicide is really unclear.

Monoamine oxidase A (MAOA): As it happens with other components of the serotonergic system, there are studies that have found a positive relation between levels of this enzyme and suicide attempts, but also other studies with negative results. MAOA is the enzyme in charge of degrading norepinephrine as well as serotonin; it presents a polymorphism of the type variable number tandem repeat (VNTR) in the region 5 flanking the genes promoter, and the 4 repetition variation activates its expression, while other variants have the opposite effect. In a study by Courtet et al. (2005), they found that Caucasian males who had violent suicide attempts, had an increased expression of the allele with increased activity, as compared to nonviolent attempters.

As explained above, serotonin can carry completely different functions depending on the receptor it is activating and the location of the said receptor. That is why focusing on only one component of the system, be it the molecule itself, its transporter, or the enzymes that synthesize or degrade it, can yield conflicting results.

5 Epigenetics: When Nature Meets Nurture

We've already talked about different genetic studies related to suicide, but speaking about biology and heritability means speaking about epigenetics as well.

An article published in 2004 already stated that, as early as during pregnancy, environmental factors start having an impact on an individual's future life and that stressors during this period of time can increase the risk of suicidal behavior (Oquendo and Baca-Garcia 2004).

Epigenetics refers to the study of the epigenome, the chemical and physical modifications of the deoxyribonucleic acid (DNA) molecule that functionally regulate the collection of genes of an organism by altering the capacity of a gene to be

activated and produce the messenger ribonucleic acid (mRNA) it encodes (Petronis 2010).

It could be initially thought that epigenetics have to do exclusively with environmental influences; however, this point of view would be too reductionist, since epigenetic changes are also heritable. Twin studies (mentioned above) have been considered, as of today, the gold standard in what has to do with environment vs. heritability; the problem presents itself when we start looking at differences in genetic expression between the said twins. An article published on the *American Journal of Human Genetics* mentions a study carried out by Mill et al. (2006), where they found differences of up to 42% in methylation profile between MZ twins. "These new insights about epigenetic DNA modifications and their effects on gene expression and phenotype may increase our understanding of diverse phenotypes from personality traits to neuropsychiatric disease. The new paradigm is not one of nature vs. nurture, but complex and dynamic interaction between DNA sequence, epigenetic DNA modifications, environment, gene expression, and environmental factors that all combine to influence phenotype." To support this statement even further, there's one other study on identical twins who were discordant for schizophrenia (groups of twins where one had the disease and the other was healthy) (Mill et al. 2006). In this study, they measured epigenetic distance (the number of differences at each CpG site) and found that the patients were epigenetically more similar between them, than to their respective siblings.

5.1 So What Are These Changes "Produced by the Environment" That We Have Been Talking About?

Let's go back a little and discuss Stanley's study on suicidal subtypes. This study on impulsive and aggressive behavior used cortisol levels as a measure of response to stress. They found that suicide attempters with higher levels of impulsivity/aggression had a heightened cortisol response to stress, not seen in any of the other groups (Stanley et al. 2019).

5.2 How Are Cortisol Levels a Demonstration of Environmental Influence?

Cortisol (basal levels and reactivity) is controlled by the HPA axis. When exposed to psychological stress, the hypothalamus responds producing CRH, which stimulates production of ACTH from the pituitary gland. ACTH induces secretion of cortisol from the adrenal cortex. Cortisol performs different functions within the body, some have to do with metabolic response and some with the immune system (which in turn also affect the brain and behavior), and lastly, some of cortisol effects take place

within the brain. Glucocorticoid receptors (GR) are widely spread through the brain, and once cortisol reaches these receptors, they bind and relocate inside the cell. Once inside, they can interact with transcriptional factors and modify genetic expression of the cell (this also happens in other cells of the immune system).

Environmental factors, like childhood trauma and abuse, or maternal care, can modify HPA axis function by mediation of these receptors. There is a specific GR gene promoter that has been demonstrated to be modified by the said experiences. *NR3C1* gene is observed to have an increased methylation at the promoter region in depressed patients who experienced early sexual abuse and also in animal models with pups that received low care, leading to a lower GR expression. An increased NR3C1 has also been observed in suicide completers with a history of maternal deprivation and adults with child maltreatment. Individuals with a higher methylation of NR3C1 also show diminished cortisol responses in the dexamethasone suppression test (Chmielewska et al. 2019).

Lutz and Turecki also talked about differences in GR in an animal model of maternal grooming, where the offspring of mothers with high grooming during the first week of life had a higher hippocampal GR expression and also a lesser response to stress. This is due to an epigenetic variant of an exon 1 GR promoter, induced by maternal care (Lutz and Turecki 2014).

In his group's work, Turecki proposes a model of environmental influence on suicide based on three factors (Turecki 2014): 1 distal or predisposing factors, 2 developmental or regulating factors, and 3 proximal or precipitating factors. When these factors interact, it looks similar to Fig. 1.

There are other genetic variants related to early life stressors and adversity. *FKBP5* gene regulates a protein that allows GR receptors to translocate inside the cell, to carry its function. Hypermethylation of this gene decreases the presence of the said protein, stopping GR receptors to relocate and give negative feedback to the HPA axis.

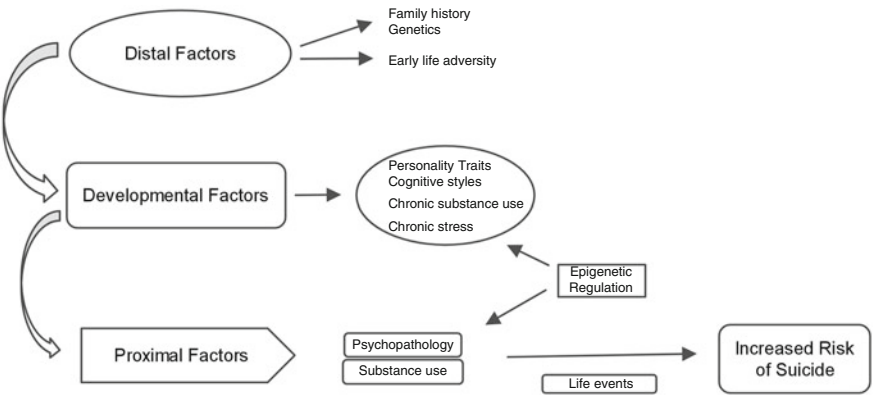


Fig. 1 Based on: Epigenetics and suicidal behavior research pathways. Gustavo Turecki. Am J Prev Med. 2014 September: 47(3 Suppl 2):S144–S151

Serotonin system may also suffer changes from early life experiences. *SLC6A4* (*5HTT*, serotonin transporter gene) has also been shown to present an increased methylation in relation to early life abuse, and in cases of hypermethylation, response of cortisol to stress was dull.

All of the above were examples of how early life experiences can shape genetic expression of individuals, making them more prone to conditions such as anxiety, or depression, and, in turn, making it more likely that they present suicide behavior.

Taking Stanley's group work on suicide subtypes (Stanley et al. 2019), and the evidence on modification of genetic expression from life events, we would like to propose a model for the subtype of stress responders, described in their work (Fig. 2).

In our model, stress responders (SR) and non-responders (NSR) would be placed at both ends of a spectrum. The closer an individual is to the SR end, the lesser a stimulus has to be to induce self-harming or suicidal behavior, while individuals on the NSR end could still act in such a way, if a strong enough stimulus appears. We also propose that life events, such as childhood trauma/abuse, parental neglect, drug abuse, damage to frontal cortex, and chronic stress (to name a few), can little by little move a NSR individual along the spectrum, toward the SR end. Since this is a spectrum, the opposite is also possible. Individuals in the SR end who receive adequate treatment, in time, would need a higher stimulus to engage in self-harming behavior.

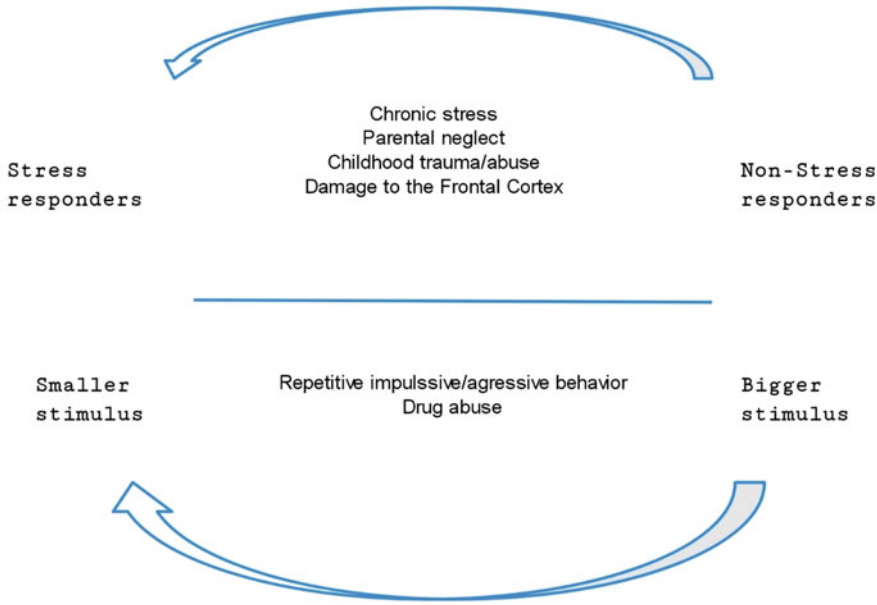


Fig. 2 Factors that contribute in transition from lesser to higher stress response

5.3 *Timing and Epigenetic Studies*

Since the very beginning of this chapter, we mentioned how timing was an important factor, probably not taken enough into account in genetic and epigenetic studies about different conditions (suicide not being an exception). The thing about epigenetics, besides their heritability, is that it changes. When an individual is studied together with their family for a genetic expression of a certain condition, that individual might not present it at the time of the test (it will make sense in a moment). Evidence suggests epigenetic changes that take place during childhood are carried all the way into adult life, and probably passed down (if they are still present), but there can also be changes that happen later into adulthood, after an individual has already had children. In this case, that person's descendants will not inherit the same pattern of gene expression that their progenitor had, giving place to additional confounding factors.

6 Prefrontal Cortex: (Maybe) the Most Important Correlate

In 2010, K. S. Kendler published an article talking about different pathways that lead to one outcome. In this article, using different risk factors (past adversity, current adversity, and psychiatric disorders, among others), Kendler showcases how ten different pathways can lead to suicide. In his closing argument, Kendler urges us to "avoid hard reductionism" but also prevents us from thinking that suicidal behavior is beyond our capacity to study or understand (Kendler 2010).

It might be possible that the ten pathways Kendler speaks about converge in a point prior to the said behavior. Through this chapter, we've already talked about most (if not all) of these pathways, in a way or another. From here on, we'll look for that "prior" convergence point, which might show us a way forward.

Ronald W Maris, in his article titled "Suicide," published in 2002, made reference to suicidal hopelessness in terms of cognitive inflexibility. Not exactly a definition, we will use his words to make sure we are not being misunderstood when speaking about hopelessness: "difficulty in believing that there are non-suicidal alternatives to life problems" (Maris 2002).

Maris hasn't been the only one relating suicide and cognition. Several articles published after his have studied the role of the prefrontal cortex in suicide. Monkul et al. (2007), Hwang et al. (2010), Wagner et al. (2012), and Keilp et al. (2013) studied different populations of suicide attempters and used different (image- or functional image-based) techniques; Keilp's group study was based on neuropsychological tests, instead of neuroimaging. Interestingly, they all found alterations in the prefrontal cortex of the population they studied.

To illustrate just how different their samples were, it would suffice to say that Hwang team's sample consisted of geriatric male patients (65 years or older)

(Hwang et al. 2010), while Monkul group's sample was formed by females, with a mean of age of 31 (Monkul et al. 2007). Both studies had different goals; the one with geriatric patients wanted to demonstrate that changes in gray matter (GM), as well as white matter (WM) (in this case due to vascular lesions), have a role in suicide behavior. They found a significant decrease in GM across several different brain areas (could be expected from their population of patients), with an even more prominent reduction in the medial frontal cortex, midbrain, cerebellum, and lentiform nucleus. They relate these findings to cognitive impairments seen in suicidal patients, including inflexibility, executive functioning, decision-making, and problem-solving.

In the study with adult female subjects, all depressed patients showed smaller orbitofrontal cortex volumes, and suicidal patients also showed larger right amygdala, than non-suicidal. It was statistically not significant (maybe due to lack of subjects), but suicidal subjects had more previous depressive episodes than non-suicidals, or an earlier age of illness onset. The explanation they give for this volume reduction also has to do with cortisol toxicity and chronic response to stress (as we already discussed above).

Orbitofrontal cortex has been described to play an important role in decision-making, and when it is damaged, subjects engage in more risky behaviors. The findings in this study correlate with previous findings showing that suicide attempters have poorer decision-making abilities. More aggressive suicidal individuals can even show a pattern of decision-making in the Iowa Gambling Task similar to that observed in patients with orbitofrontal lesions (Jollant et al. 2005).

Wagner also found reduction in cortical thickness in PFC in individuals with high risk for suicide, compared to non-high risk. His findings were in ventrolateral and dorsolateral PFC, both areas relating to inhibition of behavior.

In all, findings in these studies suggest that cognition plays a role in suicide, and its impairment, be it because of brain lesions, emotional trauma, congenital factors, or any other reason, which increases the likelihood of suicidal behavior. As Hwang expresses, in some cases it might be because of a difficulty in relocating attention away from preoccupied negative emotions or cognitions (giving way to hopelessness) (Hwang et al. 2010). In other cases, it might be because of a poorer decision-making and a lack of premeditation, as it might be the case in high aggression/impulsivity subtype described by Stanley (Stanley et al. 2019). In some cases it might be both.

Interesting enough this impaired-cognition model of suicide can also be applied to psychotic spectrum disorders. In investigations to determine psychosis biotypes, one of the most consistent findings has been brain volume reductions, with the largest effects in frontal, cingulate, temporal, and parietal cortex (Clementz et al. 2016), although these last findings on biotypes have yet to be related to suicidal behavior (Fig. 3).

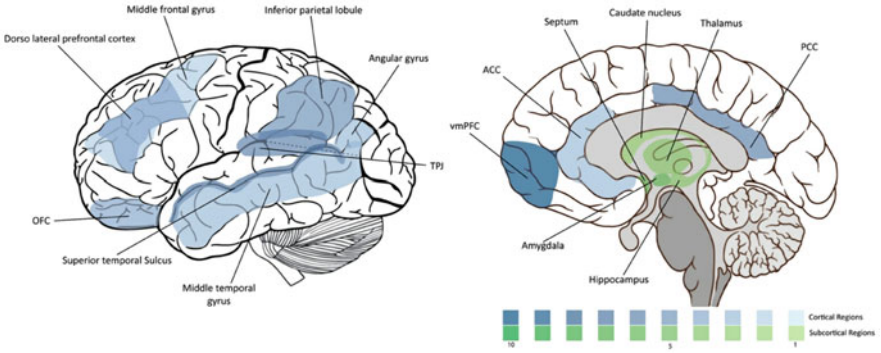


Fig. 3 Pascual L, Rodriques P and Gallardo-Pujol D (2013) How does morality work in the brain? A functional and structural perspective of moral behavior. Front Integr Neurosci 7:65. Doi: https://doi.org/10.3389/fnint.2013.00065. Image tagged for reuse

7 BDNF: Further Evidence of Cognitive Impairment in Suicide?

One more thing we have yet to talk about, but relates with the hypothesis of PFC dysfunction in suicide behavior, is the role of BDNF (brain-derived neurotrophic factor). Chmielewska's group research highlights the importance of BDNF as *1- a predictor of suicide ideation* and *2- a marker of depression* (Chmielewska et al. 2019).

Through several studies, BDNF has been related to fear conditioning, treatment response to antidepressants, and suicidal ideation and behavior. Depending on the context, and the region where BDNF is enhanced, it can act as a coding factor for memory and consolidation of fear learning. It appears that after a traumatic experience, there is an increase of BDNF in the CA1 region of the hippocampus. This would have to do with consolidation of memory. Extinction of the said conditioning also involves an increase of BDNF, but this time, it takes place in the PFC (Fuchikami et al. 2010). The same study also showed that, as it happens with cortisol, or serotonin, stressful events can also modify BDNF levels in the brain, through changes in genetic expression.

Low levels of BDNF have been related to suicidal ideation and behavior (Khan et al. 2019; Björkholm and Monteggia 2016), not only in depressed patients but also in patients with whole different conditions. One example might be a study relating *BDNF* hypermethylation in patients with acute coronary syndrome, with the presence of suicidal ideation, 1 year after the coronary event, although it is not possible knowing if the said hypermethylation already existed or was a result of the stressful situation (maybe both).

Polymorphism rs6265 (Val66Met) of the *BDNF* gene has been related with suicidal behavior as well. A study with patients who engaged in self-harming

behavior found an interaction between the said gene and the emotional environment while growing up, for homozygotic individuals, with the Val-Val variation. Homozygotic individuals, growing up in an emotionally challenging environment, were more likely to engage in harmful and life-threatening behavior. That same polymorphism has also been related to the presence of suicide thoughts (Sudol and Mann 2017).

The most important conclusion, from these and other studies, is that brain plasticity and connectivity seem to play a major role in the pathogenesis of depression and suicidal behavior (as well as other psychiatric conditions), but also in their recovery, and response to treatment. Considering these findings, if we could control in which regions BDNF is released, and enacts its function, we could open new paths for treatment.

8 Clinical Implications of an Impaired-Cognition Approach to Suicidal Behavior

At the current date, different psychological approaches and interventions for suicide prevention, in patients with borderline personality disorder, highlight the importance of mindfulness practice, some heavily relying on skills training of patients and mindfulness exercises.

8.1 Why Are We Talking About Mindfulness?

Aside from its meditation or oriental like approach (that may appeal or not to some people), mindfulness is, at its core, a style of cognitive training.

In our model, suicidal behavior would derive (in most cases) from impairments in cognition, impairments that, for some patients, would be equivalent as that seen in cases of structural brain damage. The volume reduction mentioned in the studies we already discussed would be the biological correlate of the said impairment.

Since life events and routines can negatively impact an individual brain structure, the opposite should also be true. If we believe that mindfulness training reduces risk of suicide, then individuals who undergo such training should show signs of it.

A review performed by Gotink et al. (2016) shows that after 8 weeks of mindfulness training, dorsomedial and dorsolateral PFCs show an increase in activity. There is also an increased functional connectivity of the salience network (SN), which is in charge of downregulation of the DMN, as well as directing attention to important stimuli. In all, aside from functional and volume increase in PFC, they found similar changes in the cingulate cortex, insula, and hippocampus. The amygdala also showed increased connection to the PFC and a reduction in activity and volume.

This review focused on findings after an 8-week training program, but there are studies that show changes as early as after 4 days of training. A study performed in Seoul, where they picked a group of healthy individuals, showed that after an intensive meditation program (mainly focused in mindfulness exercises) of only 4 days and 3 nights, there was increased activity in the ACC and DLPFC. They explain this finding as an improvement of functioning of the executive control network, but it is important remembering that the SN (which was not evaluated in this particular study) is responsible for directing and maintaining attention, both necessary when performing heavy focus-reliant tasks (Hwang et al. 2018).

We are not using these studies as a statement that mindfulness should be the one and only way of intervention in suicidal behavior. Quite the opposite, what we would like to relay is that interventions that increase PFC function and volume should have a positive impact in suicide prevention and that these interventions can show results in very small periods of time.

If we can accurately correlate brain volume reductions with cognitive symptoms via clinical evaluations, we could find better ways to predict suicidal behavior. Also, if we use these biological correlates as guidelines, we can pick specific interventions, better suited for each individual patient and his/her particular symptoms.

9 Conclusions

Environmental factors can modify an individual genetic expression, making them and their descendants prone to suicidal behavior.

Individuals exposed to chronic stress can become progressively less resilient to stressful situations, leading to a higher probability of them engaging in suicidal behavior.

Malfunction of the PFC, no matter the reason, could increase the probability of suicide behavior, even more so in depressed individuals.

Hopelessness, impulsivity, and aggressivity appear to have a common substrate in the PFC, although they are probably regulated by different specific areas.

In family studies of genetic expression, it is important to take timing into account.

References

Antypa N, Serretti A, Rujescu D (2013) Serotonergic genes and suicide: a systematic review. Eur Neuropsychopharmacol 23(10):1125–1142. https://doi.org/10.1016/j.euroneuro.2013.03.013

Arango V, Underwood MD, Gubbi AV, Mann JJ (1995) Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. Brain Res 688(1–2):121–133. https://doi.org/10.1016/0006-8993(95)00523-s

Audenaert K, Peremans K, Goethals I, van Heeringen C (2006) Functional imaging, serotonin and the suicidal brain. Acta Neurol Belg 106(3):125–131

Björkholm C, Monteggia LM (2016) BDNF – a key transducer of antidepressant effects. Neuropharmacology 102:72–79. https://doi.org/10.1016/j.neuropharm.2015.10.034

Brezo J, Bureau A, Mérette C, Jomphe V, Barker ED, Vitaro F, Hébert M, Carbonneau R, Tremblay RE, Turecki G (2010) Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. Mol Psychiatry 15(8):831–843. https://doi.org/10.1038/mp.2009.19

Chmielewska N, Szyndler J, Maciejak P, Płaźnik A (2019) Epigenetic mechanisms of stress and depression. Psychiatr Pol 53(6):1413–1428. https://doi.org/10.12740/PP/94375

Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, Keshavan MS, Tamminga CA (2016) Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry 173(4):373–384. https://doi.org/10.1176/appi.ajp.2015.14091200

Courtet P, Jollant F, Buresi C, Castelnau D, Mouthon D, Malafosse A (2005) The monoamine oxidase A gene may influence the means used in suicide attempts. Psychiatr Genet 15 (3):189–193. https://doi.org/10.1097/00041444-200509000-00009

Fuchikami M, Yamamoto S, Morinobu S, Takei S, Yamawaki S (2010) Epigenetic regulation of BDNF gene in response to stress. Psychiatry Investig 7(4):251–256. https://doi.org/10.4306/pi.2010.7.4.251

Gotink RA, Meijboom R, Vernooij MW, Smits M, Hunink MG (2016) 8-week mindfulness based stress reduction induces brain changes similar to traditional long-term meditation practice – a systematic review. Brain Cogn 108:32–41. https://doi.org/10.1016/j.bandc.2016.07.001

Hwang JP, Lee TW, Tsai SJ, Chen TJ, Yang CH, Lirng JF, Tsai CF (2010) Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. J Geriatr Psychiatry Neurol 23(3):171–184. https://doi.org/10.1177/0891988710363713

Hwang WJ, Lee TY, Lim KO, Bae D, Kwak S, Park HY, Kwon JS (2018) The effects of four days of intensive mindfulness meditation training (Templestay program) on resilience to stress: a randomized controlled trial. Psychol Health Med 23(5):497–504. https://doi.org/10.1080/13548506.2017.1363400

Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R, Castelnau D, Malafosse A, Courtet P (2005) Impaired decision making in suicide attempters. Am J Psychiatry 162(2):304–310. https://doi.org/10.1176/appi.ajp.162.2.304

Keilp JG, Gorlyn M, Russell M, Oquendo MA, Burke AK, Harkavy-Friedman J, Mann JJ (2013) Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. Psychol Med 43(3):539–551. https://doi.org/10.1017/S0033291712001419

Kendler KS (2010) Genetic and environmental pathways to suicidal behavior: reflections of a genetic epidemiologist. Eur Psychiatry 25(5):300–303. https://doi.org/10.1016/j.eurpsy.2010.01.005

Khan MS, Wu GWY, Reus VI, Hough CM, Lindqvist D, Westrin Å, Nier BM, Wolkowitz OM, Mellon SH (2019) Low serum brain-derived neurotrophic factor is associated with suicidal ideation in major depressive disorder. Psychiatry Res 273:108–113. https://doi.org/10.1016/j.psychres.2019.01.013

Lutz PE, Turecki G (2014) DNA methylation and childhood maltreatment: from animal models to human studies. Neuroscience 264:142–156. https://doi.org/10.1016/j.neuroscience.2013.07.069

Mann JJ, Brent DA, Arango V (2001) The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. Neuropsychopharmacology 24(5):467–477. https://doi.org/10.1016/S0893-133X(00)00228-1

Mann JJ, Arango VA, Avenevoli S, Brent DA, Champagne FA, Clayton P, Currier D, Dougherty DM, Haghighi F, Hodge SE, Kleinman J, Lehner T, McMahon F, Mościcki EK, Oquendo MA, Pandey GN, Pearson J, Stanley B, Terwilliger J, Wenzel A (2009) Candidate endophenotypes for genetic studies of suicidal behavior. Biol Psychiatry 65(7):556–563. https://doi.org/10.1016/j.biopsych.2008.11.021

Maris RW (2002) Suicide. Lancet 360(9329):319–326. https://doi.org/10.1016/S0140-6736(02)09556-9

Mill J, Dempster E, Caspi A, Williams B, Moffitt T, Craig I (2006) Evidence for monozygotic twin (MZ) discordance in methylation level at two CpG sites in the promoter region of the catechol-

O-methyltransferase (COMT) gene. Am J Med Genet B Neuropsychiatr Genet 141B (4):421–425. https://doi.org/10.1002/ajmg.b.30316

Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda AL, Sassi RB, Mallinger AG, Keshavan MS, Soares JC (2007) Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Mol Psychiatry 12(4):360–366. https://doi.org/10.1038/sj.mp.4001919

Mullins N, Perroud N, Uher R, Butler AW, Cohen-Woods S, Rivera M, Malki K, Euesden J, Power RA, Tansey KE, Jones L, Jones I, Craddock N, Owen MJ, Korszun A, Gill M, Mors O, Preisig M, Maier W, Rietschel M, Rice JP, Müller-Myhsok B, Binder EB, Lucae S, Ising M, Craig IW, Farmer AE, McGuffin P, Breen G, Lewis CM (2014) Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: a genome-wide association and polygenic scoring study. Am J Med Genet B Neuropsychiatr Genet 165B(5):428–437. https://doi.org/10.1002/ajmg.b.32247

Oquendo MA, Baca-Garcia E (2004) Nurture versus nature: evidence of intrauterine effects on suicidal behaviour. Lancet 364(9440):1102–1104. https://doi.org/10.1016/S0140-6736(04)17115-8

Ottenhof KW, Sild M, Lévesque ML, Ruhé HG, Booij L (2018) TPH2 polymorphisms across the spectrum of psychiatric morbidity: a systematic review and meta-analysis. Neurosci Biobehav Rev 92:29–42. https://doi.org/10.1016/j.neubiorev.2018.05.018

Pascual L, Rodrigues P, Gallardo-Pujol D (2013) How does morality work in the brain? A functional and structural perspective of moral behavior. Front Integr Neurosci 7:65. https://doi.org/10.3389/fnint.2013.00065

Petronis A (2010) Epigenetics as a unifying principle in the aetiology of complex traits and diseases. Nature 465(7299):721–727. https://doi.org/10.1038/nature09230

Roy A, Segal NL, Centerwall BS, Robinette CD (1991) Suicide in twins. Arch Gen Psychiatry 48 (1):29–32. https://doi.org/10.1001/archpsyc.1991.01810250031003

Ruderfer DM, Walsh CG, Aguirre MW, Tanigawa Y, Ribeiro JD, Franklin JC, Rivas MA (2019) Significant shared heritability underlies suicide attempt and clinically predicted probability of attempting suicide. Mol Psychiatry. https://doi.org/10.1038/s41380-018-0326-8

Stanley B, Michel CA, Galfalvy HC, Keilp JG, Rizk MM, Richardson-Vejlgaard R, Oquendo MA, Mann JJ (2019) Suicidal subtypes, stress responsivity and impulsive aggression. Psychiatry Res 280:112486. https://doi.org/10.1016/j.psychres.2019.112486

Strawbridge RJ, Ward J, Ferguson A, Graham N, Shaw RJ, Cullen B, Pearsall R, Lyall LM, Johnston KJA, Niedzwiedz CL, Pell JP, Mackay D, Martin JL, Lyall DM, Bailey MES, Smith DJ (2019) Identification of novel genome-wide associations for suicidality in UK biobank, genetic correlation with psychiatric disorders and polygenic association with completed suicide. EBioMedicine 41:517–525. https://doi.org/10.1016/j.ebiom.2019.02.005

Sudol K, Mann JJ (2017) Biomarkers of suicide attempt behavior: towards a biological model of risk. Curr Psychiatry Rep 19(6):31. https://doi.org/10.1007/s11920-017-0781-y

Turecki G, Zhu Z, Tzenova J, Lesage A, Séguin M, Tousignant M, Chawky N, Vanier C, Lipp O, Alda M, Joober R, Benkelfat C, Rouleau GA (2001) TPH and suicidal behavior: a study in suicide completers. Mol Psychiatry 6(1):98–102. https://doi.org/10.1038/sj.mp.4000816

Vaquero-Lorenzo C, Baca-Garcia E, Diaz-Hernandez M, Perez-Rodriguez MM, Fernandez-Navarro P, Giner L, Carballo JJ, Saiz-Ruiz J, Fernandez-Piqueras J, Baldomero EB, de Leon J, Oquendo MA (2008) Association study of two polymorphisms of the serotonin-2A receptor gene and suicide attempts. Am J Med Genet B Neuropsychiatr Genet 147B (5):645–649. https://doi.org/10.1002/ajmg.b.30642

Wagner G, Schultz CC, Koch K, Schachtzabel C, Sauer H, Schlösser RG (2012) Prefrontal cortical thickness in depressed patients with high-risk for suicidal behavior. J Psychiatr Res 46 (11):1449–1455. https://doi.org/10.1016/j.jpsychires.2012.07.013

Wasserman D, Geijer T, Sokolowski M, Rozanov V, Wasserman J (2007) Nature and nurture in suicidal behavior, the role of genetics: some novel findings concerning personality traits and neural conduction. Physiol Behav 92(1–2):245–249. https://doi.org/10.1016/j.physbeh.2007.05.061

Toward a Biosignature of Suicide Reattempt

Hilario Blasco-Fontecilla, Pablo Mendez-Bustos, and Javier David Lopez-Morinigo

Contents

Abstract Suicidal behaviour (SB) is a major public health issue, which encompasses both suicide attempts and suicide completions. Suicide tragically accounts for up to almost one million deaths across the world every year. So far, suicide prediction models have focused on the so-called *classic* risk factors (male gender, depression, alcohol-related problems, and so on). However, suicide is, thankfully, a very rare outcome. As a result, these suicide predictive models have performed very poorly due to the high number of false positives to pick up suicides.

However, a history previous suicide attempts has been consistently reported to be the strongest predictor of a future SB. Hence, suicide prevention strategies may prioritise high-risk groups such as those who reattempt/repeat suicide. More specifically, an alternative to the classic 'clinical' risk assessment approach, which is based on rating 'clinical' risk factors, may be to identify *biomarkers*, which may increase the specificity and sensitivity of the aforementioned suicide prediction models, thus helping clinicians to predict future SB.

H. Blasco-Fontecilla
Department of Psychiatry, IDIPHIM-Puerta de Hierro University Hospital, CIBERSAM, Autonoma University, Madrid, Spain

P. Mendez-Bustos (✉)
Department of Psychology, Universidad Católica del Maule, Maule, Chile

J. D. Lopez-Morinigo
Department of Psychiatry, Universidad Autónoma de Madrid, Madrid, Spain

Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
e-mail: javierd.lopez@uam.es

Curr Topics Behav Neurosci (2020) 46: 79–88
https://doi.org/10.1007/7854_2020_164
Published Online: 26 August 2020

Within this context, this chapter provides an up-to-date literature review literature on *biomarkers of repeated SB*. Three main conclusions can be drawn from our review. First, there is a paucity of studies on the role of biomarkers in repeated suicide attempts to date. Second, the vast majority of these studies focused on two biomarkers, which have been also more comprehensively researched in SB, namely, the serotonin system abnormalities and the HPA axis dysfunction. Finally, 'it seems to be unlikely that there is a single biomarker of (repeated) SB'. Rather, future research should look at the complex dynamic interaction of a wide range of biological, clinical and neuropsychological contributing risk factors leading up to SB.

Keywords Biomarker · Clinical factor · Suicide reattempt

1 Background

Almost one million people end their lives across the world every year (WHO 2019). Of major concern, suicide rates appear to have increased since the 2007/08 economic recession (Oyesanya et al. 2015). This said, it is worth noting that at least 79% of suicides occur in low-middle income countries, and this figure is likely to underestimate the real suicide rate in these countries according to the World Health Organization (WHO (Producer) 2019), where precisely research tends to be underfunded (Lopez-Castroman et al. 2015).

Suicide is undoubtedly the most tragic outcome in mental health and a leading cause of death worldwide (Patton et al. 2009). A history of previous suicide attempts has been reported to be the strongest clinical risk factor for suicide (Oquendo et al. 2006). Suicide *reattempters* may therefore represent a particularly high-risk suicide group. After an index suicide attempt, suicide reattempt rate ranges from 15 to 30% over the following 1 to 2 years of follow-up (Giraud et al. 2013; Heyerdahl et al. 2009). And up to 2% of these subjects were reported to end their lives at 1-year follow-up (Owens et al. 2002).

Predicting future suicidal behaviour (SB) has been a long-standing goal for suicide researchers and mental health professionals, which is particularly challenging due to a myriad of reasons, namely:

1. Thankfully, suicide (completion) is a very rare outcome, hence highly unpredictable from a statistical point of view (Pokorny 1983, 1993). On the other hand, there is a significantly higher rate of suicide attempts compared to suicide completion (Blasco-Fontecilla et al. 2018), which makes these non-fatal suicidal behaviours more predictable in the clinical setting than suicides (Artieda-Urrutia et al. 2015).
2. However, suicide attempters and suicide completers may be different, albeit overlapping, populations (Giner et al. 2013; Parra Uribe et al. 2013). In other

words, prediction of suicide attempts and suicide completion may have been hampered by the (wrong) assumption that these two populations share the same risk factors, which has been recently replicated by a recent investigation showing that (to paraphrase the authors): 'instruments that predicted non-fatal repeat suicide attempts did not predict suicide and vice-versa' (Lindh et al. 2019).

3. Until now, predicting SB has been based on gathering information concerning risk assessment from the individual at risk. However, those at high-risk for SB tend not to report suicidal ideation/plans (Isometsa et al. 1995; Smith et al. 2013), which makes this source of information of little, if any, value.
4. Current predictive models of SB, which are based on rating the presence/absence (and maybe the severity) of well-known risk factors for SB, have been consistently found to perform very poorly (Blasco-Fontecilla et al. 2012a, b), even in high-risk groups such as patients under secondary mental healthcare (Lopez-Morinigo et al. 2018), including those with schizophrenia spectrum disorders (Lopez-Morinigo et al. 2016).

Tackling suicide should therefore prioritise reducing risk of reattempting suicide, which can be, to a large extent, predictable (Hampton 2010; Hegerl et al. 2010). Previous suicide attempts, clinical factors such as major depression and alcohol-related problems, and life events have been reported to, to some degree, predict future SB (Blasco-Fontecilla et al. 2012a, b; Parra-Uribe et al. 2017). Nevertheless, the above risk factors can be considered 'clinical' variables.

An alternative approach may be to identify *biomarkers*, which may increase the specificity and sensitivity of suicide prediction models (Mann et al. 2006) and help to predict future SB (Blasco-Fontecilla et al. 2013).

Within this context, this chapter aims to narratively review up-to-date literature concerning biomarkers of repeated suicide attempts. Given the scarce literature published to date, we will first provide an overview on biomarkers of (single and repeated) SB, prior to which we will briefly review the concept of biomarker.

2 Definition of Biomarker

A *biomarker* can be defined as follows: (1) A test or molecule that is able to specifically and reliably identify those individuals displaying a determined behaviour, including SB or a condition (Jones 2010), or (2) 'A characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention' (Singh and Rose 2009). *Biomarkers* should therefore be (1) non-invasive, (2) easily applicable in routine clinical practice, and (3) inexpensive so they can be widely used from a cost-effectiveness perspective (Blasco-Fontecilla and Oquendo 2016).

Biomarkers can be classified as (1) *screening biomarkers* (characteristics that help in the identification of future patients), (2) *diagnostic biomarkers*

(characteristics of those who are ill), and (3) *prognostic biomarkers* (characteristics that may predict outcomes) (Gerszten and Wang 2008; Lee et al. 2011).

Biomarkers may also be divided into (1) *diathesis biomarkers* ('who is at risk?'), which is likely to yield a high number of false positives (i.e., at-risk individuals who will not go on to make a SB), and (2) *stress biomarkers* ('when will risk change?', i.e., 'when will the at-risk individual attempt to take his/her own life?') (Blasco-Fontecilla and Oquendo 2016; Mann et al. 1999), which is what clinically matters.

As alluded to above, prior to reviewing biomarkers of 'repeated' SB, briefly we will first comment on previous research findings on 'biomarkers of SB', i.e., irrespective of the number of attempts (one single episode or multiple suicide attempts). We think that this approach will provide the reader with a better understanding of the current evidence of 'biomarkers of repeated SB'.

3 Biomarkers of SB

Identification of 'biomarkers of SB' has received much attention from suicide researchers across the world since the early 1990s. Although there have been some promising results, which are summarised below, we can already anticipate that this is a field in which the main conclusion is that one that 'further research is needed'.

The first investigations focused on the role of the hyperreactivity of the stress-response system, that is, the non-suppression observed in the dexamethasone suppression test (DST), in SB (Coryell and Schlesser 2001; Jokinen et al. 2008a, b), which was found to correlate with dysfunctions in the stress-response system (Lee and Kim 2011). In line with this, postmortem elevated levels of the corticotropin-releasing hormone (CHR) in the locus coeruleus, frontopolar, dorsolateral prefrontal and ventromedial prefrontal cortices and reduced CHR levels at the dorsovagal system were also found in suicide completers (Merali et al. 2006). Consistent with this, previous research also demonstrated the role of dysregulations in the stress-response system, namely, the hypothalamus-pituitary-adrenal axis (HPA) (Oquendo et al. 2014) and the serotoninergic system, which both reflected diathesis (Mann 2003; Pandey 2013), in SB.

Dysfunctions on the serotonergic system have also been consistently linked with SB (Lee and Kim 2011). In particular, reduced serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) concentrations were found in the cerebrospinal fluid (CSF) of suicide attempters who had used violent methods (Lester 1995) and suicide completers (Mann and Currier 2007; Oquendo et al. 2014). Moreover, this biomarker -5-HIAA- was associated with a 4.5-fold suicide risk increase in individuals with mood disorders (Mann et al. 2006). In addition, one report showed high-lethality suicide attempters to have a blunted prolactin response to fenfluramine (Lee and Kim 2011).

Also, serum cholesterol and polyunsaturated fatty acids (PUFAs) plasma levels (Daray et al. 2018; Sublette et al. 2006), brain-derived neurotrophic factor (BDNF) (Jimenez-Trevino et al. 2017) and SAT1 (Le-Niculescu et al. 2013), among others,

have been suggested to be potential biomarkers of SB. More specifically, total cholesterol plasma levels were found to be a useful biological marker for assessing suicide risk (Kim and Myint 2004; Papadopoulou et al. 2013) since low cholesterol plasma levels were reported to predict more severe suicide attempts (Golier et al. 1995). In keeping with this, in a cohort of 6,393 middle-aged men both low plasma cholesterol levels and reduced cholesterol concentrations were associated with greater suicide risk (Zureik et al. 1996).

The investigation of the immune system in relation to suicide risk has also received some interest from research based on early observations of immunological abnormalities in suicide attempters (Bayard-Burfield et al. 1996). In particular, high plasma SB100 (Falcone et al. 2010) and S100A10 protein levels have been proposed to act as potential biomarkers of SB (Zhang et al. 2011). Interestingly, low concentrations of BDNF, which is involved in neural regeneration and decreases in response to stress (Duman and Monteggia 2006), were found in the brain of depressed suicide completers, which was replicated by two independent studies (Dwivedi et al. 2003; Lee and Kim 2011).

4 Biomarkers of Repeated SB

The lack of a clear definition of repetition of SB has significantly hampered this research area (Mendez-Bustos et al. 2013). Furthermore, research on risk factors for multiple suicide attempts has been focused on sociodemographic and clinical factors (Parra-Uribe et al. 2017) rather than on the neurobiological mechanisms underlying such a complex phenomenon.

In terms of biomarkers, once again the vast majority of previous research work has looked at either the serotonin system or the HPA axis abnormalities. Thus, reattempting suicide has been classically linked with decreased CSF 5-HIAA (Asberg et al. 1976; Nordstrom et al. 1994; Roy et al. 1989; Samuelsson et al. 2006; Traskman et al. 1981) and homovanillic acid plasma levels (Roy et al. 1992). Moreover, in a sample of ($n = 106$) suicide attempters with at least two previous lifetime suicide attempts, plasma serotonin levels were reported to play a relevant role in reattempting suicide over the 1-year follow-up study period (Verkes et al. 1998).

Also, findings from genetics research provide further support for the involvement of the serotonin dysfunction in repeated suicide attempts. In particular, higher frequencies of the serotonin transporter (5-HTTLPR) S allele and the SS genotype were found in those who reattempted suicide, compared with those who did not, in a 1-year follow-up cohort of ($n = 103$) inpatient suicide attempters from France (Courtet et al. 2004). Of note, these findings were consistent with an independent study from Italy with multiple suicide attempters, in which the LL genotype was shown to prevent from being a multiple suicide attempter (Schillani et al. 2009). In line with this, the frequency of the TT genotype in the tryptophan hydroxylase 2 (TPH2) polymorphism was reported to be significantly higher in ($n = 143$) suicide

completers, particularly in the suicide reattempters (53.3% vs. 8.6%; $p < 0.0001$), than in ($n = 162$) age- and sex-matched controls (Fudalej et al. 2010).

In addition, HPA dysfunction appears to be associated with repeated suicide attempts. Thus, a study of ($n = 61$) suicide attempters revealed that those who repeated SB after the index suicide attempt had low 24-h urinary cortisol levels more frequently than those suicide attempters who did not reattempt suicide (Traskman-Bendz et al. 1992). Consistent with this, based on a follow-up study of ($n = 106$) depressed patients with an index suicide attempt, a cut-off point of 3.3 microg/dL for the non-suppressor status in the DST identified 17 out of the 25 suicides (68%) (Jokinen et al. 2008a, b). In another follow-up study which compared ($n = 35$) suicide attempters with ($n = 16$) non-suicidal controls, repeated suicide attempts were related to low morning and lunch salivary cortisol in women (Lindqvist et al. 2008).

Also, we identified some investigations which were carried out in children. In particular, a small study compared nine adolescents admitted to hospital with a history of three or more suicide attempts and ten age-matched psychiatric inpatients with no suicidal antecedents in terms of platelet peripheral-type benzodiazepine receptors (PBR), which are 'responsible for mitochondrial cholesterol uptake, the rate limiting step of steroidogenesis'. Interestingly, the suicidal adolescents were found to have lower platelet PBR density (−35%) than controls ($p < 0.005$) (Soreni et al. 1999), hence becoming a potential biomarker for SB in this particular population, although replication studies are warranted.

5 Conclusions

To sum up, there is a paucity of studies on the role of biomarkers in repeated suicide attempts to date. In addition, most of previous studies focused on two biomarkers, which have been classically involved in SB, namely, the serotonin system abnormalities and the HPA axis dysfunction.

However, given the complexity of suicide as phenomenon, and thankfully, its low occurrence as outcome, it is highly unlikely that there is such 'single biomarker of SB'. Alternatively, a better understanding of the combination of the wide range of biological, clinical and neuropsychological contributing factors to suicide risk in relation to the individual's mental health problems and his/her social context and how these factors may change dynamically over time (Franklin et al. 2017) may be more helpful in assessing suicide risk than using biomarkers alone (Blasco-Fontecilla et al. 2013; Lee and Kim 2011; Mann et al. 2006). As we have anticipated above, indeed 'further research is needed' in this area.

References

Artieda-Urrutia P, Delgado-Gomez D, Ruiz-Hernandez D, Garcia-Vega JM, Berenguer N, Oquendo MA, Blasco-Fontecilla H (2015) Short personality and life event scale for detection of suicide attempters. Rev Psiquiatr Salud Ment 8(4):199–206. https://doi.org/10.1016/j.rpsm.2015.02.004

Asberg M, Traskman L, Thoren P (1976) 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Arch Gen Psychiatry 33(10):1193–1197. https://doi.org/10.1001/archpsyc.1976.01770100055005

Bayard-Burfield L, Alling C, Blennow K, Jonsson S, Traskman-Bendz L (1996) Impairment of the blood-CSF barrier in suicide attempters. Eur Neuropsychopharmacol 6(3):195–199. https://doi.org/10.1016/0924-977x(96)00020-x

Blasco-Fontecilla H, Oquendo MA (2016) Biomarkers of suicide: predicting the predictable? In: Courtet P (ed) Understanding suicide. Springer, London, pp 77–84

Blasco-Fontecilla H, Delgado-Gomez D, Legido-Gil T, de Leon J, Perez-Rodriguez MM, Baca-Garcia E (2012a) Can the Holmes-Rahe social readjustment rating scale (SRRS) be used as a suicide risk scale? An exploratory study. Arch Suicide Res 16(1):13–28. https://doi.org/10.1080/13811118.2012.640616

Blasco-Fontecilla H, Delgado-Gomez D, Ruiz-Hernandez D, Aguado D, Baca-Garcia E, Lopez-Castroman J (2012b) Combining scales to assess suicide risk. J Psychiatr Res 46(10):1272–1277. https://doi.org/10.1016/j.jpsychires.2012.06.013

Blasco-Fontecilla H, Lopez-Castroman J, Giner L, Baca-Garcia E, Oquendo MA (2013) Predicting suicidal behavior: are we really that far along? Comment on "discovery and validation of blood biomarkers for suicidality". Curr Psychiatry Rep 15(12):424. https://doi.org/10.1007/s11920-013-0424-x

Blasco-Fontecilla H, Artieda-Urrutia P, de Leon J (2018) A proposal for using the ratio of attempted to completed suicides across several countries worldwide. Epidemiol Psychiatr Sci:1–5. https://doi.org/10.1017/s2045796018000628

Coryell W, Schlesser M (2001) The dexamethasone suppression test and suicide prediction. Am J Psychiatry 158(5):748–753. https://doi.org/10.1176/appi.ajp.158.5.748

Courtet P, Picot MC, Bellivier F, Torres S, Jollant F, Michelon C et al (2004) Serotonin transporter gene may be involved in short-term risk of subsequent suicide attempts. Biol Psychiatry 55(1):46–51. https://doi.org/10.1016/j.biopsych.2003.07.004

Daray FM, Mann JJ, Sublette ME (2018) How lipids may affect risk for suicidal behavior. J Psychiatr Res 104:16–23. https://doi.org/10.1016/j.jpsychires.2018.06.007

Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59(12):1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013

Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2003) Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 60(8):804–815. https://doi.org/10.1001/archpsyc.60.8.804

Falcone T, Fazio V, Lee C, Simon B, Franco K, Marchi N, Janigro D (2010) Serum S100B: a potential biomarker for suicidality in adolescents? PLoS One 5(6):e11089. https://doi.org/10.1371/journal.pone.0011089

Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X et al (2017) Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychol Bull 143(2):187–232. https://doi.org/10.1037/bul0000084

Fudalej S, Ilgen M, Fudalej M, Kostrzewa G, Barry K, Wojnar M et al (2010) Association between tryptophan hydroxylase 2 gene polymorphism and completed suicide. Suicide Life Threat Behav 40(6):553–560. https://doi.org/10.1521/suli.2010.40.6.553

Gerszten RE, Wang TJ (2008) The search for new cardiovascular biomarkers. Nature 451(7181):949–952. https://doi.org/10.1038/nature06802

Giner L, Blasco-Fontecilla H, Mercedes Perez-Rodriguez M, Garcia-Nieto R, Giner J, Guija JA et al (2013) Personality disorders and health problems distinguish suicide attempters from completers in a direct comparison. J Affect Disord 151(2):474–483. https://doi.org/10.1016/j.jad.2013.06.029

Giraud P, Fortanier C, Fabre G, Ghariani J, Guillermain Y, Rouviere N et al (2013) Suicide attempts by young adolescents: epidemiological characteristics of 517 15-year-old or younger adolescents admitted in French emergency departments. Arch Pediatr 20(6):608–615. https://doi.org/10.1016/j.arcped.2013.03.024

Golier JA, Marzuk PM, Leon AC, Weiner C, Tardiff K (1995) Low serum cholesterol level and attempted suicide. Am J Psychiatry 152(3):419–423. https://doi.org/10.1176/ajp.152.3.419

Hampton T (2010) Depression care effort brings dramatic drop in large HMO population's suicide rate. JAMA 303:1903–1905

Hegerl U, Mergl R, Havers I, Schmidtke A, Lehfeld H, Niklewski G, Althaus D (2010) Sustainable effects on suicidality were found for the Nuremberg alliance against depression. Eur Arch Psychiatry Clin Neurosci 260(5):401–406. https://doi.org/10.1007/s00406-009-0088-z

Heyerdahl F, Bjornaas MA, Dahl R, Hovda KE, Nore AK, Ekeberg O, Jacobsen D (2009) Repetition of acute poisoning in Oslo: 1-year prospective study. Br J Psychiatry 194 (1):73–79. https://doi.org/10.1192/bjp.bp.107.048322

Isometsa ET, Heikkinen ME, Marttunen MJ, Henriksson MM, Aro HM, Lonnqvist JK (1995) The last appointment before suicide: is suicide intent communicated? Am J Psychiatry 152 (6):919–922. https://doi.org/10.1176/ajp.152.6.919

Jimenez-Trevino L, Saiz PA, Garcia-Portilla MP, Blasco-Fontecilla H, Carli V, Iosue M et al (2017) 5-HTTLPR-brain-derived neurotrophic factor (BDNF) gene interactions and early adverse life events effect on impulsivity in suicide attempters. World J Biol Psychiatry:1–13. https://doi.org/10.1080/15622975.2017.1376112

Jokinen J, Martensson B, Nordstrom AL, Nordstrom P (2008a) CSF 5-HIAA and DST non-suppression -independent biomarkers in suicide attempters? J Affect Disord 105 (1–3):241–245. https://doi.org/10.1016/j.jad.2007.04.008

Jokinen J, Nordstrom AL, Nordstrom P (2008b) ROC analysis of dexamethasone suppression test threshold in suicide prediction after attempted suicide. J Affect Disord 106(1–2):145–152. https://doi.org/10.1016/j.jad.2007.06.008

Jones R (2010) Biomarkers: casting the net wide. Nature 466(7310):S11–S12. https://doi.org/10.1038/466S11a

Kim YK, Myint AM (2004) Clinical application of low serum cholesterol as an indicator for suicide risk in major depression. J Affect Disord 81(2):161–166. https://doi.org/10.1016/s0165-0327(03)00166-6

Lee BH, Kim YK (2011) Potential peripheral biological predictors of suicidal behavior in major depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry 35(4):842–847. https://doi.org/10.1016/j.pnpbp.2010.08.001

Lee JM, Han JJ, Altwerger G, Kohn EC (2011) Proteomics and biomarkers in clinical trials for drug development. J Proteome 74(12):2632–2641. https://doi.org/10.1016/j.jprot.2011.04.023

Le-Niculescu H, Levey DF, Ayalew M, Palmer L, Gavrin LM, Jain N et al (2013) Discovery and validation of blood biomarkers for suicidality. Mol Psychiatry 18(12):1249–1264. https://doi.org/10.1038/mp.2013.95

Lester D (1995) The concentration of neurotransmitter metabolites in the cerebrospinal fluid of suicidal individuals: a meta-analysis. Pharmacopsychiatry 28(2):45–50. https://doi.org/10.1055/s-2007-979587

Lindh AU, Dahlin M, Beckman K, Stromsten L, Jokinen J, Wiktorsson S et al (2019) A comparison of suicide risk scales in predicting repeat suicide attempt and suicide: a clinical cohort study. J Clin Psychiatry 80(6). https://doi.org/10.4088/JCP.18m12707

Lindqvist D, Isaksson A, Traskman-Bendz L, Brundin L (2008) Salivary cortisol and suicidal behavior--a follow-up study. Psychoneuroendocrinology 33(8):1061–1068. https://doi.org/10.1016/j.psyneuen.2008.05.012

Lopez-Castroman J, Blasco-Fontecilla H, Courtet P, Baca-Garcia E, Oquendo MA (2015) Are we studying the right populations to understand suicide? World Psychiatry 14(3):368–369. https://doi.org/10.1002/wps.20261

Lopez-Morinigo JD, Ayesa-Arriola R, Torres-Romano B, Fernandes AC, Shetty H, Broadbent M et al (2016) Risk assessment and suicide by patients with schizophrenia in secondary mental healthcare: a case-control study. BMJ Open 6(9):e011929. https://doi.org/10.1136/bmjopen-2016-011929

Lopez-Morinigo JD, Fernandes AC, Shetty H, Ayesa-Arriola R, Bari A, Stewart R, Dutta R (2018) Can risk assessment predict suicide in secondary mental healthcare? Findings from the South London and Maudsley NHS foundation trust biomedical research centre (SLaM BRC) case register. Soc Psychiatry Psychiatr Epidemiol 53(11):1161–1171. https://doi.org/10.1007/s00127-018-1536-8

Mann JJ (2003) Neurobiology of suicidal behaviour. Nat Rev Neurosci 4(10):819–828. https://doi.org/10.1038/nrn1220

Mann JJ, Currier D (2007) A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. Arch Suicide Res 11(1):3–16. https://doi.org/10.1080/13811110600993124

Mann JJ, Waternaux C, Haas GL, Malone KM (1999) Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry 156(2):181–189

Mann JJ, Currier D, Stanley B, Oquendo MA, Amsel LV, Ellis SP (2006) Can biological tests assist prediction of suicide in mood disorders? Int J Neuropsychopharmacol 9(4):465–474. https://doi.org/10.1017/s1461145705005687

Mendez-Bustos P, de Leon-Martinez V, Miret M, Baca-Garcia E, Lopez-Castroman J (2013) Suicide reattempters: a systematic review. Harv Rev Psychiatry 21(6):281–295. https://doi.org/10.1097/hrp.0000000000000001

Merali Z, Kent P, Du L, Hrdina P, Palkovits M, Faludi G et al (2006) Corticotropin-releasing hormone, arginine vasopressin, gastrin-releasing peptide, and neuromedin B alterations in stress-relevant brain regions of suicides and control subjects. Biol Psychiatry 59(7):594–602. https://doi.org/10.1016/j.biopsych.2005.08.008

Nordstrom P, Samuelsson M, Asberg M, Traskman-Bendz L, Aberg-Wistedt A, Nordin C, Bertilsson L (1994) CSF 5-HIAA predicts suicide risk after attempted suicide. Suicide Life Threat Behav 24(1):1–9

Oquendo MA, Currier D, Mann JJ (2006) Prospective studies of suicidal behavior in major depressive and bipolar disorders: what is the evidence for predictive risk factors? Acta Psychiatr Scand 114(3):151–158. https://doi.org/10.1111/j.1600-0447.2006.00829.x

Oquendo MA, Sullivan GM, Sudol K, Baca-Garcia E, Stanley BH, Sublette ME, Mann JJ (2014) Toward a biosignature for suicide. Am J Psychiatry 171(12):1259–1277. https://doi.org/10.1176/appi.ajp.2014.14020194

Owens D, Horrocks J, House A (2002) Fatal and non-fatal repetition of self-harm. Systematic review. Br J Psychiatry 181:193–199. https://doi.org/10.1192/bjp.181.3.193

Oyesanya M, Lopez-Morinigo J, Dutta R (2015) Systematic review of suicide in economic recession. World J Psychiatry 5(2):243–254. https://doi.org/10.5498/wjp.v5.i2.243

Pandey GN (2013) Biological basis of suicide and suicidal behavior. Bipolar Disord 15(5):524–541. https://doi.org/10.1111/bdi.12089

Papadopoulou A, Markianos M, Christodoulou C, Lykouras L (2013) Plasma total cholesterol in psychiatric patients after a suicide attempt and in follow-up. J Affect Disord 148(2–3):440–443. https://doi.org/10.1016/j.jad.2012.11.032

Parra Uribe I, Blasco-Fontecilla H, Garcia-Pares G, Giro Batalla M, Llorens Capdevila M, Cebria Meca A et al (2013) Attempted and completed suicide: not what we expected? J Affect Disord 150(3):840–846. https://doi.org/10.1016/j.jad.2013.03.013

Parra-Uribe I, Blasco-Fontecilla H, Garcia-Pares G, Martinez-Naval L, Valero-Coppin O, Cebria-Meca A et al (2017) Risk of re-attempts and suicide death after a suicide attempt: a survival analysis. BMC Psychiatry 17(1):163. https://doi.org/10.1186/s12888-017-1317-z

Patton GC, Coffey C, Sawyer SM, Viner RM, Haller DM, Bose K et al (2009) Global patterns of mortality in young people: a systematic analysis of population health data. Lancet 374 (9693):881–892. https://doi.org/10.1016/s0140-6736(09)60741-8

Pokorny AD (1983) Prediction of suicide in psychiatric patients. Report of a prospective study. Arch Gen Psychiatry 40(3):249–257

Pokorny AD (1993) Suicide prediction revisited. Suicide Life Threat Behav 23(1):1–10

Roy A, De Jong J, Linnoila M (1989) Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients. A 5-year follow-up study. Arch Gen Psychiatry 46(7):609–612. https://doi.org/10.1001/archpsyc.1989.01810070035005

Roy A, Karoum F, Pollack S (1992) Marked reduction in indexes of dopamine metabolism among patients with depression who attempt suicide. Arch Gen Psychiatry 49(6):447–450. https://doi.org/10.1001/archpsyc.1992.01820060027004

Samuelsson M, Jokinen J, Nordstrom AL, Nordstrom P (2006) CSF 5-HIAA, suicide intent and hopelessness in the prediction of early suicide in male high-risk suicide attempters. Acta Psychiatr Scand 113(1):44–47. https://doi.org/10.1111/j.1600-0447.2005.00639.x

Schillani G, Goljevscek S, Carlino D, De Vanna M, Aguglia E, Giraldi T (2009) Repeated suicidal behaviour: stressful life events and 5-HTTLPR genetic polymorphism. Int J Psychiatry Clin Pract 13(3):229–232. https://doi.org/10.1080/13651500902785652

Singh I, Rose N (2009) Biomarkers in psychiatry. Nature 460(7252):202–207. https://doi.org/10.1038/460202a

Smith EG, Kim HM, Ganoczy D, Stano C, Pfeiffer PN, Valenstein M (2013) Suicide risk assessment received prior to suicide death by Veterans Health Administration patients with a history of depression. J Clin Psychiatry 74(3):226–232. https://doi.org/10.4088/JCP.12m07853

Soreni N, Apter A, Weizman A, Don-Tufeled O, Leschiner S, Karp L, Gavish M (1999) Decreased platelet peripheral-type benzodiazepine receptors in adolescent inpatients with repeated suicide attempts. Biol Psychiatry 46(4):484–488. https://doi.org/10.1016/s0006-3223(98)00342-4

Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ (2006) Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. Am J Psychiatry 163 (6):1100–1102. https://doi.org/10.1176/ajp.2006.163.6.1100

Traskman L, Asberg M, Bertilsson L, Sjostrand L (1981) Monoamine metabolites in CSF and suicidal behavior. Arch Gen Psychiatry 38(6):631–636. https://doi.org/10.1001/archpsyc.1981.01780310031002

Traskman-Bendz L, Alling C, Oreland L, Regnell G, Vinge E, Ohman R (1992) Prediction of suicidal behavior from biologic tests. J Clin Psychopharmacol 12(2 Suppl):21s–26s

Verkes RJ, Hengeveld MW, van der Mast RC, Fekkes D, van Kempen GM (1998) Mood correlates with blood serotonin, but not with glucose measures in patients with recurrent suicidal behavior. Psychiatry Res 80(3):239–248. https://doi.org/10.1016/s0165-1781(98)00075-4

WHO (Producer) (2019) Suicide in the world. Global Health Estimates

Zhang L, Su TP, Choi K, Maree W, Li CT, Chung MY et al (2011) P11 (S100A10) as a potential biomarker of psychiatric patients at risk of suicide. J Psychiatr Res 45(4):435–441. https://doi.org/10.1016/j.jpsychires.2010.08.012

Zureik M, Courbon D, Ducimetiere P (1996) Serum cholesterol concentration and death from suicide in men: Paris prospective study I. BMJ 313(7058):649–651. https://doi.org/10.1136/bmj.313.7058.649

Sex, Gender, and Suicidal Behavior

Maria Luisa Barrigon and Fanny Cegla-Schvartzman

Contents

Abstract This chapter reviews gender differences in suicide, commonly known as the gender paradox in suicide. While men are more likely to complete suicide, suicide attempts are more frequent in women. Although there are exceptions, this paradox occurs in most countries over the world, and it is partially explained by the preference of men for more lethal methods. Nevertheless, there are differences in the known risk factors for suicide between men and women, and this chapter summarizes the more relevant findings for the gender paradox. Apart from previous attempts, which still is the strongest predictor of death by suicide, with a higher rate in males than in females, we will emphasize in the role of male depression. It is

M. L. Barrigon (✉) and F. Cegla-Schvartzman
Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
e-mail: luisa.barrigon@fjd.es

Curr Topics Behav Neurosci (2020) 46: 89–116
https://doi.org/10.1007/7854_2020_165
Published Online: 30 August 2020

commonly recognized that over 90% of people who die by suicide had a psychiatric diagnosis, mostly depression, and male depression seems to be a distinct clinical phenotype challenging to recognize, which might contribute to the gender paradox. Finally, in light of all the information reviewed, some recommendations on prevention of suicide from a gender perspective in the clinical setting will be made.

Keywords Gender · Gender differences · Prevention · Risk factors · Sex · Suicide · Suicide attempted

1 Introduction

Suicide is a complex multifactorial phenomenon; the precise process underlying suicide involves many issues still unresolved. Suicide rates are different according to region, sex, age, time, ethnic origin, and, presumably, death registration methods (Hawton and van Heeringen 2009). One of the classic risk factors for suicide is male sex/gender, with men being more likely to complete suicide and women to try it; this is known as the gender paradox in suicide (Canetto and Sakinofsky 1998). Apart from China, Bangladesh, and Lesotho, where there are more deaths by suicide in women than in men, this is a demonstrated fact worldwide (Naghavi 2019; WHO, Suicide Data 2019).

Sex differences in suicidal behavior have been extensively studied, but most of the research in this topic is made assuming equivalence between sex and gender, and, furthermore, only in most recent times, research has also focused on suicidal behavior in a non-binary gender (Fox et al. 2018). Sex and gender are constructs that should be differentiated. Essentially, sex refers to biology while gender involves cultural constructs (Clayton and Tannenbaum 2016), and differences in suicidal behavior are probably more related to cultural issues (i.e., gender) than only to a biological basis (i.e., sex). In suicidology, both constructs should be taken into account, but by now it is difficult to perform a specific search on sex or gender exclusively; therefore, this chapter will use both terms interchangeably, with a preference for the term "gender," given the role of cultural factors in suicide phenomena.

In this chapter, we are going to review gender differences in suicide rates across different countries of the world. Then we will describe and reflect on gender differences in suicide methods. Next, suicide risk factors will be study focusing on the effect of male or female gender. Finally, different preventive approaches will be suggested in light of gender differences previously reviewed.

Across different sections of the chapter, it will be observed how the role of traditional masculinity is frequently involved in gender differences in suicide, and how men are a high-risk population, and specifical and tailored interventions are needed for them.

2 Terminology

2.1 Suicidal Behavior

In this chapter, we use the terminology for suicide based on the definition given by O'Carroll et al. in 1996 (O'Carroll et al. 1996) and later redefined by Silverman et al. in 2007 (Silverman et al. 2007). Thus, here we use the term *suicidal behavior* for denoting any type of suicidality, that is, suicidal ideation, suicidal plans, non-fatal suicide attempts, and deaths by suicide. Subsequently, we will use the term *suicidal ideation* for "unelaborated thoughts related to the wish and/or intention of taking one's life," *suicidal plan* for "an elaborated and structured suicidal ideation with decisions made as how to perform the suicide attempt," and *suicide attempts* for "any act of self-harm performed with the intention of taking one's life"; suicide attempts could lead to *non-fatal suicide attempts* or *death by suicide*. Hence, in this chapter, we will mostly refer to *death by suicide* or just *suicide.* Non-suicidal self-injuries (NSSI), a descriptive term employed in the DSM 5, will not be addressed in this chapter. Furthermore, extended and assisted suicide are not part of this chapter.

2.2 Sex and Gender

Sex and gender are terms frequently used interchangeably in ordinary speech. Indeed, in some languages there are not two different words for both constructs. Although in scientific terms, sex and gender are not strictly exchangeable, both terms are non-exclusive, but are related to each other and influence health in different ways (Clayton and Tannenbaum 2016). Primarily, while sex refers to biology, the term gender includes psychosocial factors (Clayton and Tannenbaum 2016).

Sex refers to the biological characteristics that define humans as female or male, which is determined by the genetic information of chromosomes, and includes cellular and molecular differences (Dunn et al. 2016). The World Health Organization (WHO) states that "sex refers to the biological and physiological characteristics that define men and women" and "'male' and 'female' are sex categories" (WHO, Defining Sexual Health 2019). Male or female sexual differentiation is based in karyotype at birth, 46XX for female sex and 46XY for males, and is physiologically characterized by the gonads (ovary or testes), sex hormones (testosterone and estrogen), external genitalia (e.g., penis or vulva), and internal reproductive organs (e.g., uterus or prostate gland) (Clayton and Tannenbaum 2016). People with mixed sex factors are intersex.

On the other hand, **gender** refers to the socially constructed characteristics of women and men and comprises the social, environmental, cultural, and behavioral factors that influence a person's identity of being a man or a woman (Clayton and Tannenbaum 2016). In the sphere of gender, several aspects must be distinguished: gender assignment, gender roles, and gender identity. *Gender assignment* is how an

infant is classified at birth, as either male or female based on external genitalia (WHO, Defining Sexual Health 2019). *Gender roles or gender norms* are unspoken rules in the family, workplace, institutions, or global culture that influence individual attitudes and behaviors (Schiebinger and Stefanick 2016). Finally, *gender identity* refers to how individuals and groups perceive and present themselves (Clayton and Tannenbaum 2016), but rather than a binary concept, there are gender identity gradations from masculinity to femininity (Fausto-Sterling 2008). When a mismatch between gender identity and gender assigned exists, we refer to "transgender," and so the term transgender includes people whose gender identity is the opposite of their assigned sex (trans men and trans women), but also includes people who feel not exclusively masculine or feminine (genderqueer, non-binary, bigender, pangender, genderfluid, or agender) (Fausto-Sterling 2008). Thus, gender identity is not an entirely fixed characteristic, and many transgender people move fluidly between identities over time, often without any specific labels (Haas et al. 2011).

Although, as it has been previously exposed, gender and sex are not equivalent, we should point out that in this chapter both terms will be used indistinctly since a specific search for each term is complicated due to the fact that previous scientific research has not generally made the distinction (Clayton and Tannenbaum 2016). A reflection on this should be made, and currently, many journals encourage authors to transparently report sex, gender, or even both in their works. Generally in research sex/gender are visually assigned to research participants without specifically asking, and even more, there are no validated tools for assessing gender, and an approach in which participants were asked first about sex assigned at birth and then about gender identity has been proposed (Clayton and Tannenbaum 2016).

Furthermore, transgender condition impacts death by suicide and suicide behavior, and it has been extensively studied, especially in recent years (Fox et al. 2018; Narang et al. 2018). Although highly interesting, this topic is beyond the scope of our review and will not be covered in this chapter.

3 Worldwide Suicide Rates by Gender

The World Health Organization (WHO) provides the most exhaustive and unbiased data on suicide rates from its member states and periodically updates them. Currently, the last available suicide data are from 2016 (WHO, Suicide Data 2019). According to WHO data, in 2016 the global male/female ratio of age-standardized suicide rates was 1.8, meaning that worldwide, men complete suicide almost twice more often than women (WHO, Suicide Rates (per 100 000 population) 2019). Interestingly, this ratio is particularly high in Europe (around 4:1) and in high-income countries but lower in low- and middle-income countries (around 1.6:1) (Saxena et al. 2014). Asian countries typically show much lower male/female ratios (Chen et al. 2012). Furthermore, comparing the information from the WHO countries, the male/female ratio ranged from 0.8 in Bangladesh and China to 12.2 in St. Vincent and the Grenadines (Bachmann 2018).

This is graphically shown in the map developed periodically by WHO, in which the lighter-colored countries represent those in which more women than men die by suicide and, on the contrary, the darker-colored ones represent those countries in which more men than women die by suicide (Fig. 1).

Similar figures are thrown by the Global Burden of Disease (GBD) Study (Naghavi 2019). According to GBD, male suicide age-standardized rate was higher (15.6 deaths/100,000, 95% uncertainty interval 13.7 to 17.2) than female rate (7.0 deaths/100,000, 95% uncertainty interval 6.5 to 7.4), However, the rate of decrease from 1990 to 2016 was lower for male (23.8%, 95% uncertainty interval 15.6% to 32.7%) than for female (49.0%, 42.6% to 54.6%). Figure 2 shows regional trends of age-standardized suicide rates for women and men.

Suicide rates vary in different countries throughout the world. Details of rates by country, according to WHO data (WHO, Suicide Rates (per 100 000 population) 2019), are shown in Table 1.

In this table, it could be observed how, in most countries, male suicide rates are higher than female, with Ukraine, Lithuania, or Russia among the top. Only in a limited number of countries, most from East Asia, the opposite happens. This is widely known for China (Simon et al. 2013), Bangladesh (Sharmin Salam et al. 2017), and Pakistan (Shekhani et al. 2018), but also consistently observed in African countries such as Morocco or Lesotho. Concerning Morocco, as in many other Arabic countries where suicide is a taboo act, there is a notable lack of national suicide rates, and studies on the topic are scarce (Bjegovic-Mikanovic et al. 2019). Finally, for Lesotho no specific studies about suicides have been found. Altogether, and in a simplistic approach, the highest male/female suicide rates are found in Eastern European countries and the lowest in the WHO Southeast Asia Region.

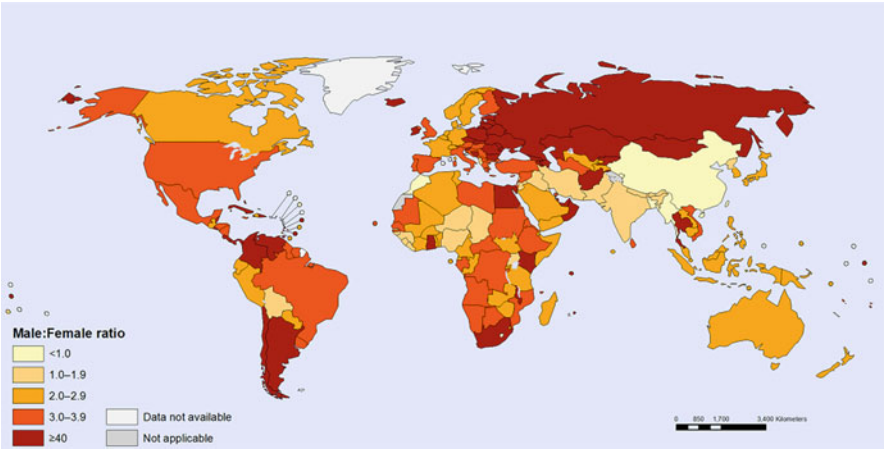


Fig. 1 2016 map of male/female ratio of age-standardized suicide rates from 2016. Picture obtained from WHO Global Health Observatory data repository

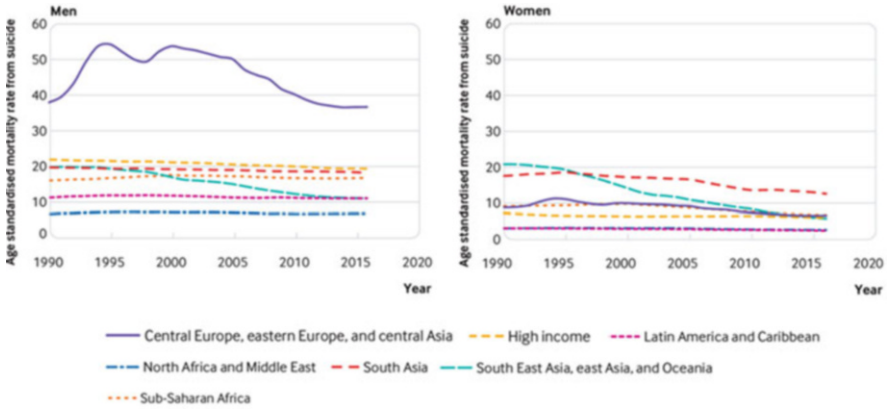


Fig. 2 Global Burden of Disease regions' age-standardized suicide rates for women and men (1990 to 2016). Modification of figure from the Global Burden of Disease Study 2016 (British Medical Journal, 2019; 364: l94)

Although there are many unanswered questions regarding these differences in the male/female suicide ratio across countries, probably cultural factors must be taken into account to understand them (Canetto 2008). In this sense, the review of Ahmed et al. highlighted how, in the United Kingdom, rates of self-harm among South Asian women are much higher than among their White counterparts (Ahmed et al. 2007).

Finally, it is worth to mention how the research investment in suicide does not correspond with the worldwide distribution of suicide, and we should point out that more research should be developed to better understand the male-female gap in suicide (Lopez-Castroman et al. 2015).

4 Gender Differences in Suicide Methods

Returning to the concept of gender paradox in suicide, men completed suicide up to three times more than women, while for suicide attempts, an inverse ratio is found (Bachmann 2018), and this difference is partially explained by the preference of men for more lethal methods (Ajdacic-Gross et al. 2008; Saxena et al. 2014). In the latest overview of suicide methods, in 2008, authors differentiated hanging, drowning, falls, pesticide poisoning, other poisoning, firearms, and others (Ajdacic-Gross et al. 2008). Globally, for both genders together, the most commonly used methods to complete suicide are hanging, self-poisoning with pesticides, and use of firearms (Saxena et al. 2014). Methods differ between world regions and between males and females. Next, is summarized the latest data on methods for males and females according to different world regions:

Table 1 Year 2016 age-standardized suicide rates (per 100,000 population)

Country	Both sexes	Male	Female
Afghanistan	6.4	10.6	2.1
Albania	5.6	7.0	4.3
Algeria	3.3	4.9	1.8
Angola	8.9	14.0	4.6
Antigua and Barbuda	0.5	0.0	0.9
Argentina	9.1	15.0	3.5
Armenia	5.7	10.1	2.0
Australia	11.7	17.4	6.0
Austria	11.4	17.5	5.7
Azerbaijan	2.6	4.3	1.0
Bahamas	1.6	2.8	0.5
Bahrain	5.7	7.9	2.1
Bangladesh	6.1	5.5	6.7
Barbados	0.4	0.8	0.3
Belarus	21.4	39.3	6.2
Belgium	15.7	22.2	9.4
Belize	5.9	9.9	2.0
Benin	15.7	22.6	9.6
Bhutan	11.6	13.8	8.9
Bolivia	12.9	16.9	8.9
Bosnia and Herzegovina	6.4	10.6	2.5
Botswana	11.5	18.3	5.7
Brazil	6.1	9.7	2.8
Brunei Darussalam	4.5	6.2	2.8
Bulgaria	7.9	13.1	3.2
Burkina Faso	14.8	22.4	9.1
Burundi	15.0	23.1	7.7
Cabo Verde	15.1	24.1	7.7
Cambodia	5.9	9.0	3.2
Cameroon	19.5	26.9	12.5
Canada	10.4	15.1	5.8
Central African Republic	11.6	18.0	6.0
Chad	15.5	17.1	13.8
Chile	9.7	16.0	3.8
China	8.0	7.9	8.3
Colombia	7.0	11.5	2.8
Comoros	11.1	17.6	5.4
Congo	9.3	13.9	5.0
Costa Rica	7.5	12.8	2.3
Cote d'Ivoire	23.0	32.0	13.0
Croatia	11.5	18.8	5.1
Cuba	10.1	16.4	4.1

(continued)

Table 1 (continued)

Country	Both sexes	Male	Female
Cyprus	4.5	7.2	1.9
Czechia	10.5	17.2	4.2
South Korea	10.6	14.8	8.0
Congo	9.7	15.0	4.9
Denmark	9.2	13.2	5.2
Djibouti	8.5	11.9	5.3
Dominican Republic	10.5	17.9	3.2
Ecuador	7.2	10.7	3.8
Egypt	4.4	7.2	1.7
El Salvador	13.5	24.8	4.3
Equatorial Guinea	22.0	31.3	10.8
Eritrea	13.8	22.4	6.1
Estonia	14.4	25.6	4.4
Eswatini	16.7	25.4	9.6
Ethiopia	11.4	18.7	4.7
Fiji	5.5	8.8	2.5
Finland	13.8	20.8	6.8
France	12.1	17.9	6.5
Gabon	9.6	15.0	4.3
Gambia	10.0	12.8	7.3
Georgia	6.7	12.3	1.9
Germany	9.1	13.6	4.8
Ghana	8.7	15.8	2.9
Greece	3.8	6.1	1.5
Grenada	1.7	2.1	1.0
Guatemala	2.9	4.4	1.7
Guinea	10.5	12.7	8.4
Guinea-Bissau	7.4	8.9	6.1
Guyana	30.2	46.6	14.2
Haiti	12.2	18.3	6.4
Honduras	3.4	5.3	1.7
Hungary	13.6	22.2	6.2
Iceland	13.3	21.7	4.7
India	16.5	18.5	14.5
Indonesia	3.7	5.2	2.2
Iran	4.0	4.9	3.1
Iraq	4.1	4.7	3.4
Ireland	10.9	17.6	4.2
Israel	5.2	8.2	2.4
Italy	5.5	8.4	2.6
Jamaica	2.0	3.2	0.9
Japan	14.3	20.5	8.1

(continued)

Table 1 (continued)

Country	Both sexes	Male	Female
Jordan	3.7	4.7	2.7
Kazakhstan	22.8	40.1	7.7
Kenya	5.6	9.7	2.1
Kiribati	15.2	25.9	5.4
Kuwait	2.2	2.5	1.7
Kyrgyzstan	9.1	14.8	3.7
Lao	9.3	12.9	6.1
Latvia	17.2	31.0	5.1
Lebanon	3.2	4.2	2.2
Lesotho	28.9	22.7	32.6
Liberia	13.4	13.8	13.0
Libya	5.5	8.7	2.3
Lithuania	25.7	47.5	6.7
Luxembourg	10.4	15.0	5.8
Madagascar	6.9	10.5	3.6
Malawi	7.8	13.7	3.2
Malaysia	6.2	8.7	3.6
Maldives	2.7	3.6	1.6
Mali	8.9	13.5	4.7
Malta	6.5	10.3	2.8
Mauritania	7.5	12.1	3.6
Mauritius	7.3	12.5	2.2
Mexico	5.2	8.2	2.3
Micronesia	11.3	16.2	6.2
Mongolia	13.3	23.3	3.8
Montenegro	7.9	12.6	3.6
Morocco	3.1	2.5	3.6
Mozambique	8.4	14.0	4.1
Myanmar	8.1	6.3	9.8
Namibia	11.5	19.4	4.9
Nepal	9.6	11.4	8.0
Netherlands	9.6	12.9	6.4
New Zealand	11.6	17.3	6.2
Nicaragua	11.9	19.2	5.0
Niger	9.0	11.5	6.7
Nigeria	17.3	17.5	17.1
Norway	10.1	13.6	6.5
Oman	3.5	4.8	0.9
Pakistan	3.1	3.0	3.1
Panama	4.4	7.6	1.2
Papua New Guinea	7.0	10.2	3.8
Paraguay	9.3	12.3	6.2

(continued)

Table 1 (continued)

Country	Both sexes	Male	Female
Peru	5.1	7.6	2.7
Philippines	3.7	5.2	2.3
Poland	13.4	23.9	3.4
Portugal	8.6	14.3	3.8
Qatar	5.8	7.3	1.1
North Korea	20.2	29.6	11.6
Moldova	13.4	24.1	3.8
Romania	8.0	13.9	2.4
Russia	26.5	48.3	7.5
Rwanda	11.0	16.9	0.0
Saint Lucia	7.3	12.7	2.1
Saint Vincent	2.4	3.9	0.9
Samoa	5.4	8.7	2.2
Sao Tome and Principe	3.1	4.2	2.1
Saudi Arabia	3.4	4.6	1.7
Senegal	11.8	20.3	5.2
Serbia	10.9	17.3	5.2
Seychelles	8.3	15.0	2.1
Sierra Leone	16.1	18.2	14.2
Singapore	7.9	11.1	4.9
Slovakia	10.1	18.4	2.6
Slovenia	13.3	22.4	4.5
Solomon Islands	5.9	8.5	3.2
Somalia	8.3	11.5	5.4
South Africa	12.8	21.7	5.1
South Sudan	6.1	8.3	4.1
Spain	6.1	9.3	3.1
Sri Lanka	14.2	23.3	6.2
Sudan	9.5	14.5	4.6
Suriname	23.2	36.1	10.9
Sweden	11.7	15.8	7.4
Switzerland	11.3	15.8	6.9
Syria	2.4	3.8	1.1
Tajikistan	3.3	5.0	1.7
Thailand	12.9	21.4	4.8
Macedonia	6.2	9.7	3.0
Timor-Leste	6.4	9.0	3.7
Togo	16.6	22.7	10.9
Tonga	4.0	5.2	2.9
Trinidad and Tobago	12.9	21.9	4.3
Tunisia	3.2	4.4	2.2
Turkey	7.2	11.3	3.2

(continued)

Table 1 (continued)

Country	Both sexes	Male	Female
Turkmenistan	7.2	11.0	3.7
Uganda	20.0	21.2	18.7
Ukraine	18.5	34.5	4.7
United Arab Emirates	2.7	3.5	0.8
United Kingdom	7.6	11.9	3.5
Tanzania	9.6	14.3	5.4
USA	13.7	21.1	6.4
Uruguay	16.5	26.8	7.1
Uzbekistan	7.4	10.3	4.6
Vanuatu	5.4	8.1	2.7
Venezuela	3.8	6.6	1.2
Vietnam	7.0	10.8	3.4
Yemen	9.8	13.4	6.2
Zambia	11.3	17.5	6.2
Zimbabwe	19.1	29.1	11.1

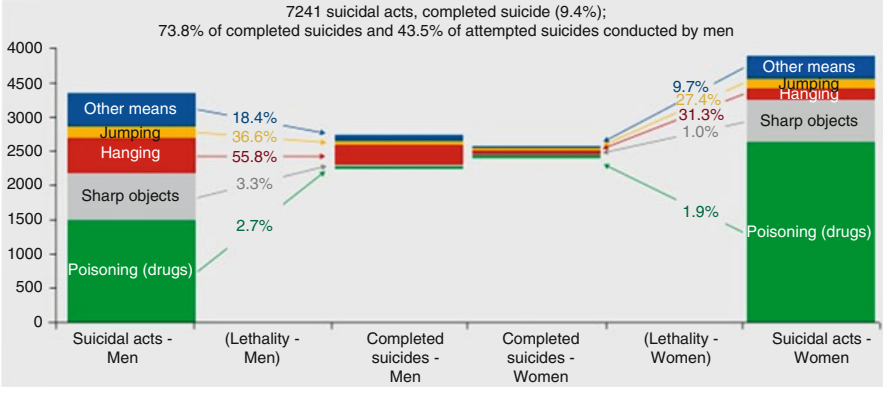
1. Africa: Suicide research in this continent is limited by a lack of systematic data collection; available data are from 60% of African population, which represents less than one third of African countries. The more common methods for suicide are hanging and poisoning, although across studies rates substantially varied (hanging 8–70%; poisoning 8–83%). Firearms are also a common method in some countries (range 0–32%). For both, suicides and suicide attempts, women have higher poisoning rates than males, whereas men tend to use violent methods such as hanging and firearms (Mars et al. 2014).
2. The Americas: Here, a distinction should be made between the United States and the rest of the countries, where significant differences are found in the last group. In the United States, suicides broadly occur by firearms in both genders (61% in males and 36% in females); furthermore poisoning represents 31% of suicide in women. In the other American countries, both men and women completed suicide by poisoning with pesticides (from 0.4% in Canada to 86% in El Salvador for men; from 1% in Canada to 95% in El Salvador for women) and hanging (from 8% in El Salvador to 77% in Chile for men; from 5% in Nicaragua to 63% in Chile for women) (Ajdacic-Gross et al. 2008; Fox et al. 2018).
3. Asia: globally, hanging and poisoning are the prevalent methods. In Hong Kong, people choose hanging (23% in men versus 48% in women) and falls (43% in men versus 23% in women). In the rest of Asian countries, females commit suicide by hanging (from 26% in South Korea to 60% in Japan) or by pesticide poisoning (from 4% in Japan to 43% in South Korea) (Jordans et al. 2014). China deserves a special mention, since more women die by suicide and poisoning with pesticides is the primary method, which reflects the role of women in rural China and the accessibility to pesticides here (Fox et al. 2018).

4. Europe: Globally, most common method, in both males and females, is hanging, except in Swiss males, were is firearm use. Men use firearm to commit suicide in second place in Finland, Norway, France, Austria, and Croatia (21–27%), while women poisoning or fall themselves. Slightly differences were found between countries (Bachmann 2018).
5. Australia and New Zealand: Hanging predominates in both male (45%) and females (36%), followed by firearms (12% in men versus 11% in women) and poisoning representing the third method of suicide (27% in men versus 20% in women) (Australian Institute of Health and Welfare 2014).

While globally these data point out how women who die by suicide choose methods with the same lethality than men, the same is not found for suicide attempts, and it has been shown how females survive suicide attempts more often than males because they use less lethal means (Cibis et al. 2012). Various studies developed in Europe illustrate these facts and explain the gender paradox by males choosing more lethal suicide methods and, in a minor extent, by a higher lethality of men's suicidal acts, even using the same method than women (Freeman et al. 2017)

This is graphically shown in Fig. 3 from the work of Hegerl with data from OSPI-Europe project ("Optimising Suicide Prevention Programmes and their Implementation in Europe") (Hegerl et al. 2009), where it is shown how women preferably choose drug overdose for attempting suicide with a less lethal outcome compared with men using poisoning with drugs as well. The same applies to all other methods, emphasizing that hanging is the most effective method in both men and women, with more lethal results in men (Hegerl 2016).

In Europe, more than 95% of people attempting suicide by poisoning survive, representing a low lethality of intoxications (Mergl et al. 2015). Nevertheless, in most low- and middle-income countries, poisoning is made with pesticides and other substances not available in Europe and more lethal than substances used in "European poisonings." So, many of the suicidal poisonings in these countries result



Open access graphic (Hegerl 2016)

Fig. 3 Differences in suicide methods in men and women

in a lethal outcome and tend to equal male/female suicide rates or even exceed them, as is in the case of China, where in rural areas young women have easy access to pesticides.

5 Gender Differences in Suicide Risk and Protective Factors

This section reviews the main suicide risk factors from a gender perspective, focusing on facts and findings that try to provide evidence for clarifying the gender paradox in suicide. Thus, we consider the known risk factors such as sociodemographic factors, sexual orientation, religiosity, suicide family history, previous suicide attempts, mental disorders, medical conditions, childhood trauma and stressful life events, help-seeking and coping strategies, and biological risk factors.

Here, it is essential to point out that a synergistic relationship is usually found between risk factors. Suicide is never the consequence of a single cause, and complex explanatory models have been proposed to better understand the path toward suicide behaviors (Turecki and Brent 2016; van Heeringen 2012). The stress-diathesis model proposes that direct or proximal stressors interact with distal risk factors (neurobiological and psychological susceptibilities) to predict suicidal behaviors (van Heeringen 2012). Thus, the interpretation of each single risk factor listed in this chapter should be cautiously made.

5.1 Demographics Risk Factors

Age is a relevant moderator factor for gender differences for suicide. Although no gender differences in suicide rates are found under the age of 14 (Fox et al. 2018), there is a consistent tendency for suicide rates to increase with age (Bertolote and Fleischmann 2002). Suicide is the second leading cause of death among 15–19-year-old females worldwide (Saxena et al. 2014) and the first one in Southeast Asia among young females aged 15–29 (Jordans et al. 2014). In most countries, suicide risk is highest in older males, and in younger females, the risk for suicide attempt is highest (Naghavi 2019; Saxena et al. 2014). Overall, female suicide rates are relatively stable with increasing age, whereas for males suicide rates increase with age, tend to plateau in midlife, and reach the highest point with men aged over 75. This final late-life peak is most evident for certain countries such as the United States, France, and Germany (Kiely et al. 2019).

Being unemployed, retired, and single were all significant risk factors for suicide in men, with no effect in females, although it should be acknowledged as a limitation that most studies on this topic come from Europe (Qin et al. 2000; Tóth et al. 2014).

In women, having a young child is identified as a protective factor (Qin et al. 2003). These differences could be explained by gender differences in burdensomeness perception according to Interpersonal-Psychological Theory of Suicidal Behavior (Donker et al. 2014).

Regarding employment, it should be noted how certain professions are more related to suicide, and a higher risk is found in physicians in most countries, more in female than in male doctors (Schernhammer and Colditz 2004). Also, female nurses have a high risk (Agerbo et al. 2002). In these professional groups, a crucial factor involved in the high rates of suicide is access to methods (Agerbo et al. 2002).

5.2 Sexual Orientation

Minority sexual orientations (i.e., being gay, lesbian, or bisexual) have been linked to suicidal behavior. Some authors propose that "minority stress theory" may explain this relationship, as homosexual or bisexual people are frequently exposed to external stressors (more significant stigma, discrimination, or victimization) or even internal stressors such as internalized homophobia that may predispose to suicidal behavior (Miranda-Mendizábal et al. 2017). However, as death records do not routinely include sexual orientation, there are no accurate rates of completed suicide in people with minority sexual orientation (Haas et al. 2011). Some researchers have approached this issue through psychological autopsies studies and have generally concluded that minority sexual orientations are not over-represented among suicide victims; nevertheless, these studies have limitations, especially small samples, and results should be cautiously interpreted (Haas et al. 2011).

It should be noted that suicide behavior in minority sexual orientations is more prevalent in young people (Haas et al. 2011). A meta-analysis of longitudinal studies in youths found that sexual orientation is significantly associated with suicide attempts, but the relationship is not clear for completed suicide, as until then it has been explored in only one longitudinal study. Regarding gender differences, sexual orientation was found to be an independent risk factor for suicide attempts among males, more than among females (Miranda-Mendizábal et al. 2017).

5.3 Religiosity

Beliefs and personal values strongly influence a possible decision to commit suicide. Higher levels of religiosity across the main religions (Christianity, Hinduism, Islam, and Judaism) are historically related to decreased suicide risk (Gearing and Alonzo 2018). Many factors have been postulated to be involved in this protective effect: religious beliefs, involvement in public religious practices by church attendance, moral objections to suicide, lower aggression level among religious individuals, spirituality, or less substance abuse (Kralovec et al. 2018).

To the best of our knowledge, no specific studies taking into account the gender role on the influence of religiosity in death by suicide have been developed. Regarding suicide thoughts and suicidal behavior, different studies have shown how religion in women seems to be a stronger protective effect than in men, either in the general population (Neeleman et al. 1997; Neeleman and Lewis 1999; Rasic et al. 2011), in clinical samples (Kralovec et al. 2018), or in special populations such as high-risk pregnant women (Benute et al. 2011). Only in one study, developed in college students, no significant interactions between gender, religiosity, and suicide ideation were found (Taliaferro et al. 2009).

5.4 Family History

It is well known that family history of suicide increases suicide risk independent of family psychiatric history, and this seems to be stronger in women than in men (Qin et al. 2003). Similarly, family transmission of suicide risk is especially important when suicide happens on the maternal side (Agerbo et al. 2002). Nevertheless, to the best of our knowledge, no systematic research has been developed on this topic.

5.5 Previous Suicide Attempts

The most robust predictor for complete suicide are previous suicide attempts. The effect with 38% of women who completed suicide had a previous suicidal behavior in men, the figure rises to 62% (Ayuso-Mateos et al. 2012).

5.6 Mental Disorders

The majority of deaths by suicide are related to underlying mental diseases, with depression on the top (Bertolote et al. 2004; Bertolote and Fleischmann 2002; Too et al. 2019). It is commonly recognized that over 90% of people who die by suicide had a psychiatric diagnosis and even higher figures (98%) are found in an extensive review of 15,629 cases (Bertolote and Fleischmann 2002). Among all diagnoses, mood disorders were found in 30.2% of suicides, followed by substance use disorders (17.6%), schizophrenia (14.1%), and personality disorders (13.0%) (Bertolote et al. 2004). Globally, females suffer more frequently mental disorders than males (Balta et al. 2019), and also gender differences are known for the more prevalent disorders involved in suicides. Here is again the gender paradox: women suffer more from mental disorders while more men die by suicide.

In psychological autopsies, it is shown that affective disorders prevail in suicide in both genders. Substance use and schizophrenia are more common in male

suicides, whereas in anorexia nervosa, most of patients who died by suicide are women (Hawton 2000).

Next, we summarize information regarding gender differences for the most frequent disorders underlying deaths by suicide: mood disorders (depression and bipolar disorders), substance use disorders, schizophrenia (and psychosis in general), and personality disorders. Also, it should be taken into account that comorbidity of mental disorders increases the suicide risk (Cavanagh et al. 2003).

Concerning **depression**, it is known that it doubles the risk of suicide in the 90 days after hospital discharge (Olfson et al. 2016). As women suffer from a major depressive disorder 2–3 more times than men (Alonso et al. 2000; Kessler et al. 1993), it might be expected more deaths by suicide in women than in men. Possible explanations for this paradox are the different expressions of depression in men and women and the interaction of depression with other risk factors such as alcohol use in men (Lenz et al. 2019). Although not recognized in classification systems, a "male depressive syndrome," widely supported by population studies and meta-analyses, has been proposed (Oliffe et al. 2019; Wålinder and Rutz 2001). This male depression would be a distinct clinical phenotype characterized by a range of externalizing symptoms not captured by diagnostic criteria and, consequently, underdiagnosed and undertreated (Genuchi 2015; Martin et al. 2013). Thus, depressive men are more likely than women to present irritability, anger, aggression, substance misuse, low impulse control, risk-taking, impulsivity, and over-involvement in work (Oliffe et al. 2019), and this depression appearance seems to be mainly influenced by men adjustment to masculine gender role norms (Genuchi and Valdez 2015). It should be noted how these "male traits" of depression are by themselves known suicide risk factors.

In **bipolar disorder**, a strong association with suicide has been found. In a large Danish register, the absolute risk of suicide in bipolar patients after their first hospitalization was around 8% for men and 5% for women (Nordentoft et al. 2011). The gender paradox of suicide is also present for bipolar disorders; however it might be less intense for bipolar disorder than for the general population (Beyer and Weisler 2016). The group of patients with higher suicide risk are young men in an early phase of the illness, especially those who have made a previous suicide attempt, those abusing alcohol, and those recently discharged from the hospital (Jamison 2000; Simpson and Jamison 1999). Among the risk factors specifically related to suicide in bipolar disorder, depressive polarity of the most recent mood episode, as well as depressive polarity of first episode, had the strongest association (Schaffer et al. 2015); this finding illustrates the gender paradox once again, as women tend to have a depressive polarity throughout the illness course.

In psychological autopsy studies, in 19% to 63% of suicides, there were found **substance use disorders (SUD)**, mostly **alcohol use disorders** (Schneider 2009), more commonly in male than in female suicides (Hawton 2000). However, only a limited number of observational studies have reported gender differences in SUD and suicide; therefore, in a recent meta-analysis on SUD and suicide, it was not possible to carry out a meta-analysis risk of suicide by gender (Poorolajal et al. 2016). Specifically for alcohol use, there is evidence from different studies on the

association of male gender, alcohol use, and suicide attempts (Boenisch et al. 2010). Acute alcohol use, or alcohol intoxication, deserves special mention, as it is related to suicide by itself (Bachmann 2018); according to a gender-stratified analysis (Kaplan et al. 2013), acute intoxication in deaths by suicide was more frequent in males than in females.

Comorbidity of SUD and other mental disorders seems to confer a heightened risk of suicide via impulsivity, hostility, and violence (Vijayakumar et al. 2011); all these are characteristically masculine traits (Lenz et al. 2019). Thus, although in the absence of evidence from meta-analysis (Poorolajal et al. 2016), the role of male gender should be taken into account in assessing the risk of suicide in men with mental disorders who also use drugs, especially alcohol.

In **schizophrenia,** male gender is traditionally considered a risk factor for suicide (Popovic et al. 2014). Therefore, the gender pattern of suicide in schizophrenia is similar to general population, and most studies have found higher suicide rates in men than in women (Hawton et al. 2005; Lester 2006), but differences between sex seem to be less marked than in general population (Carlborg et al. 2010) and there even are studies reporting no gender differences (Carlborg et al. 2008; Reutfors et al. 2009). The risk of suicide is highest within the first year after being diagnosed (Nordentoft et al. 2015), but in first-episode psychosis, the traditional gender pattern of suicide is not always found (Austad et al. 2015). Finally, in early-onset psychosis, which is psychosis starting before the age of 18, gender is not a consistent predictor of suicidality (Díaz-Caneja et al. 2015).

Personality disorders represent a high-risk group for suicide with 15% of inpatient and almost 12% of outpatient suicides (Bachmann 2018). Among personality disorders, in **borderline personality disorder (BPD)**, the association with suicide behavior is clear, even included as a diagnostic criterion (Vera-Varela et al. 2019). Nevertheless, in BPD, gender differences in suicidal behavior have been scarcely studied (Sher et al. 2019). In a recent meta-analysis of prospective studies, mean suicide rate ranged from 2% to 5%, but the effect of moderators, including gender, could not be studied due to the heterogeneity among studies (Álvarez-Tomás et al. 2019). Again, while most of BPD patients are women (Silberschmidt et al. 2015), almost 70% of BPD patients who completed suicide are men (Doyle et al. 2016); but contrary to general population, in BPD there are no gender differences in the proportion of suicide attempters or in lifetime number of suicide attempts (Sher et al. 2019). The second highest suicide risk group in personality disorders is **narcissistic personality disorder** (Bachmann 2018), but gender differences have not been studied in this subgroup.

5.7 Medical Conditions

The prevalence of suicide and suicide attempts is elevated not only in individuals with psychiatric illness but also in the context of physical health problems. Ultimately, any chronic disease may be associated with an elevated risk of suicide. An

essential issue in chronic physical illness is disability, which leads to an increase in suicidality. Studies show a variety of chronic diseases related to increased risk for suicide: chronic pain, heart disease, chronic obstructive pulmonary disease, stroke, cancer, congestive heart failure, and asthma (Bachmann 2018). Research also suggests that suffering from multiple physical health conditions confers an even greater risk for suicide (Juurlink et al. 2004).

In suicidality linked to cancer, a review has studied gender differences, concluding that also the gender paradox appears in this population. Thus, although there are exceptions, most studies found that suicide risk is higher in men than women (Robson et al. 2010). In other medical conditions, no systematic research on suicide gender differences has been found.

Nevertheless, an important issue to be taken into account when studying the relationship between somatic diseases and suicide is the role of comorbid psychiatric conditions. Many authors suggest that this comorbidity is what confers a higher risk for suicide in somatic diseases (Qin et al. 2014)

5.8 Childhood Trauma and Stressful Life Events

Suicide attempts and death by suicide are more frequent in people exposed to traumatic events in childhood compared with the general population, and this happens in both males and females (Zatti et al. 2017).

Concerning childhood trauma in a general sense, that is all kind of childhood trauma without distinctions. Some studies have found that suicidality is higher in women who have suffered childhood trauma than in men (Angst et al. 2014), but few works have separately study genders, so there is a lack of strong evidence (Zatti et al. 2017). In particular diagnoses, a recent review on the impact of gender and childhood abuse in psychosis found that women who suffered childhood abuse reported more suicide attempts compared to men (Comacchio et al. 2019).

The role of early sexual abuse on suicide and suicidal behavior has been extensively studied, and there is strong evidence about this relationship (Devries et al. 2014). Gender differences have been analyzed in at least two reviews. The first one is made with cross-sectional data, supporting previous knowledge of an increased odd of suicide in people (men and women) who have suffered childhood sexual abuse, and although sexual abuse was more frequent among females, the association between abuse and suicide attempts was higher in males (Rhodes et al. 2011). The second review is a meta-analysis of longitudinal studies (Devries et al. 2014) that found only two works which separately analyzed genders: in one of them, authors found higher risk of suicide attempts in males versus females (Brezo et al. 2008); the other revealed higher risk of death by suicides in females versus males (Cutajar et al. 2010). These findings are quite interesting, as in people who have suffered sexual abuses during childhood the gender paradox of suicide seems to be reversed.

While childhood trauma is a distal risk factor in explicative models of suicide, life stressors would be a proximal factor also playing a role in the suicide pathway.

Regarding life stressors, differences between genders are described; while men are more likely to experience different types of trauma, except for sexual and violent trauma, women tend to engage more in suicidal behaviors (Ásgeirsdóttir et al. 2018). Similarly, different types of stressors are more frequent according to gender; women tend to react to relational problems such as breakups and men to economic or work-related issues (Shaik et al. 2017). Here, traditional masculinity seems to play a critical role.

5.9 Coping Strategies and Help-Seeking

Men tend to respond to emotional stress with externalizing strategies like risk-taking, aggression, or substance use. Anger is also a negative emotion that men are culturally allowed to show. As previously exposed in this chapter, these coping strategies are related to traditional masculine traits, and, similarly, conformity to masculine norms is linked to a lower probability of help-seeking, as to be strong, resilient, and in control, also identified as male traits (Lenz et al. 2019; Seidler et al. 2016). Men often deny illness, suppress negative feelings, and refuse to admit depressive symptoms, waiting until late before seeking help (Oliffe and Phillips 2008). Thus, men are less likely than women to use healthcare services in general and mental healthcare services in particular; furthermore, men who look for help tend to delay service-seeking, to be reluctant to disclose health concerns, and worst to comply medical recommendations (Fox et al. 2018).

Help-seeking process involves, in addition to the initial act of seeking help, the patient's experience in consultation and subsequent treatment; and the effects of compliance with traditional male norms may also interfere with the therapy process, resulting in difficulties of attendance, compromise, or a non-stable therapeutic alliance (Seidler et al. 2016).

Nevertheless, contrary to the frequent assumption that men's engagement in help-seeking behaviors is rare, a recent review found that men do seek help if it is accessible, appropriate, and engaging (Seidler et al. 2016). This should be taken into account for designing resources tailored according patient gender.

Finally, it also should be noted that men tend to use emergency psychiatric services more than other healthcare facilities (Bachmann 2018). This situation turns emergency departments in critical spots for suicide treatment interventions, and when men with suicidal crisis attend to emergency departments, clinicians should make a special effort to initiate interventions in order to promote their commitment in a therapeutic plan.

5.10 Biological Risk Factors

A biological basis for suicide is known throughout brain post-mortem studies, genomic studies, and neuroimaging studies. Around 50% of suicide risk due to

diathesis is inherited, and this percentage might be higher in females compared to males (van Heeringen and Mann 2014). Despite a large number of studies on biological risk factors for suicide, the knowledge of biological mechanisms underpinning in suicide completion is limited, and the studies focusing on gender differences are scarce.

Genetic differences by gender have been reported in suicide in different samples: in a Portuguese sample, the 5-HTR6 gene 268 C/T SNP has a role in male suicide but not in females (Azenha et al. 2009); in a Japanese sample, men who died by suicide had a lower frequency of the minor allele of a single SNP in the NOS1 gene compared to controls and suicide in women (Cui et al. 2010). Also, a dysfunction in the serotoninergic system is probably the most consistent biological risk factor for suicide, and this is connected with aggression and violence, both considered male traits (Lenz et al. 2019).

Studies on the biology of suicide from a gender perspective often focus on the main biological difference between men and women: sexual hormones. From this perspective, an attractive explanatory model of suicide, "the androgen model of suicide completion" (Lenz et al. 2019), has been proposed. The authors of this model posit that taking into account that male gender is a specific risk factor for suicide, androgen effects might be implicated in the suicidal process and numerous studies are presented showing direct and indirect evidence that increased prenatal androgen levels and also increased androgen activity in adulthood are involved in death by suicide.

The fact that male traits such as aggression, violence, and impulsivity are related to suicide *s*upports the role of androgens in suicide (Lenz et al. 2019). Similarly, the finding of women attempting suicide more frequently during the follicular phase when there are higher testosterone levels also advocates this hypothesis (Baca-Garcia et al. 2010).

As far as biological factors are concerned, probably the most relevant fact to take into account is the role of the interaction of different distal suicide risk factors in the onset of epigenetic mechanisms. In this sense, the work of Turecki et al. is particularly enlightening when it states how sexual hormone activity and early-life stressful events interact and lead to a dysregulation of hypothalamic-pituitary-adrenal (HPA) axis which is known to be involved in suicide (Turecki 2014).

6 Toward a Tailored Prevention According to Gender

Suicide prevention programs include multilevel strategies to address population and individual suicide risk factors and generally include public awareness campaigns, training of community "gatekeepers," and educational initiatives for GPs (Saxena et al. 2014). In this section, we will focus on initiatives that take place in clinical settings, even though population and public health approaches are essential to suicide prevention.

Previous reviews of the effectiveness of prevention programs have recommended the development of tailor-made interventions for specific risk groups (Zalsman et al. 2016). As previously shown throughout this chapter, men are a particular risk group, but gender differences in response to preventive strategies have received little research attention, and specifical interventions focus in men are scarce (Struszczyk et al. 2019). The specificity of certain risk factors in men suggests that there is a need for specific interventions focusing on male factors. Some suggestions, based on previous research, are proposed below.

First of all, depression plays a crucial role in suicide behavior, and depression in men is poorly understood and, consequently, underdiagnosed and undertreated (Olfson et al. 2016). Results of Gotland study highlight how, after an educational program to enhance GP detection of depression, the overall rate of suicide decreased by 60%, but this change was related to female suicide reduction, whereas suicide males were not affected (Rutz et al. 1995). In many men, depression is manifested atypically, and their distress is undetected by the existing diagnostic tools (Seidler et al. 2016). All these findings reflect the necessity of specific tools for screening depression in men and changes in the training of GPs and mental health professionals, including a gender perspective. In response to the first requirement, some specific tools have been developed, such as the Gotland Male Depression Scale (Zierau et al. 2002) or the Masculine Depression Scale (Magovcevic and Addis 2008), the last one divided depression symptoms into internalizing and externalizing (e.g., aggression and irritability), with externalizing symptoms being more representative of depression in men.

The expression of traditional masculinity is closely related to the manifestation of depression in men (Wide et al. 2011), and depressive symptoms are contrary to male ideals, such as feelings of control, stoicism, strength, and success (Seidler et al. 2016). This contradiction usually causes men not to seek help and instead to have feelings of shame or weakness (Seidler et al. 2016). Here, psychotherapeutic and social approaches to redefine masculinity are useful. Reframing traditional male roles to a fluid and flexible masculinity according to contexts allows to cope better with depression and mental health problems (Seidler et al. 2016).

Furthermore, this masculinity, along with the difficulty to recognize depression in men, contributes to delay help-seeking (Seidler et al. 2016). Additionally, when men finally reach mental health services, therapies should be tailored according to most men's preferences. Studies have shown that men tend to prefer interventions based on problem-solving, short-term therapies, and group-based treatment options (Oliffe and Phillips 2008; Seidler et al. 2016). Gender differences in verbal abilities and the resistance of many men to share emotional problems may make talking therapies less attractive to some men (Hawton 2000). Also, sharing experiences with other suicide survivors has been shown to be helpful (Seidler et al. 2016).

Not only the therapeutic approach seems to be important for men but also the environment. Thus, many men demand less formal settings. In this sense, the use of interventions that promote social interaction and informal community-based support centers is highly valued by men. This is of particular interest in young men. Nevertheless, ultimately, and in order to avoid this stigmatization of mental health

facilities by men, incorporating mental health promotion strategies into the educational curriculum from a young age might be a solution (Seidler et al. 2016). Also, this strategy could help men to be more open and to recognize and express their feelings, helping to normalize the need for psychiatric care.

References

Agerbo E, Nordentoft M, Mortensen PB (2002) Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. BMJ 325:74

Ahmed K, Mohan RA, Bhugra D (2007) Self-harm in South Asian women: a literature review informed approach to assessment and formulation. Am J Psychother 61:71–81

Ajdacic-Gross V, Weiss MG, Ring M, Hepp U, Bopp M, Gutzwiller F, Rössler W (2008) Methods of suicide: international suicide patterns derived from the WHO mortality database. Bull World Health Organ 86:726–732

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lépine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martínez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacín C, Romera B, Taub N, Vollebergh WAM, ESEMeD/MHEDEA (2000) Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) project (2004) Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl:21–27

Álvarez-Tomás I, Ruiz J, Guilera G, Bados A (2019) Long-term clinical and functional course of borderline personality disorder: a meta-analysis of prospective studies. Eur Psychiatry 56:75–83

Angst J, Hengartner MP, Rogers J, Schnyder U, Steinhausen H-C, Ajdacic-Gross V, Rössler W (2014) Suicidality in the prospective Zurich study: prevalence, risk factors and gender. Eur Arch Psychiatry Clin Neurosci 264:557–565

Ásgeirsdóttir HG, Valdimarsdóttir UA, Þorsteinsdóttir ÞK, Lund SH, Tomasson G, Nyberg U, Ásgeirsdóttir TL, Hauksdóttir A (2018) The association between different traumatic life events and suicidality. Eur J Psychotraumatol 9

Austad G, Joa I, Johannessen JO, Larsen TK (2015) Gender differences in suicidal behaviour in patients with first-episode psychosis. Early Interv Psychiatry 9:300–307

Australian Institute of Health and Welfare (2014) Suicide and hospitalised self-harm in Australia: trends and analysis. Canberra, ACT, Australian Institute of Health and Welfare

Ayuso-Mateos JL, Baca-García E, Bobes J, Giner J, Giner L, Pérez V, Sáiz PA, Ruiz JS (2012) Recommendations for the prevention and management of suicidal behaviour. Revista de Psiquiatría y Salud Mental (English Edition) 5:8–23

Azenha D, Alves M, Matos R, Santa JF, Silva B, Cordeiro C, Vieira DN, Ambrósio AM (2009) Male specific association between the 5-HTR6 gene 267C/T SNP and suicide in the Portuguese population. Neurosci Lett 466:128–130

Baca-Garcia E, Diaz-Sastre C, Ceverino A, Perez-Rodriguez MM, Navarro-Jimenez R, Lopez-Castroman J, Saiz-Ruiz J, de Leon J, Oquendo MA (2010) Suicide attempts among women during low estradiol/low progesterone states. J Psychiatr Res 44:209–214

Bachmann S (2018) Epidemiology of suicide and the psychiatric perspective. Int J Environ Res Public Health 15:1425

Balta G, Dalla C, Kokras N (2019) Women's psychiatry. Adv Exp Med Biol 1192:225–249

Benute GRG, Nomura RMY, Jorge VMF, Nonnenmacher D, Fráguas R Jr, de Lucia MCS, Zugaib M (2011) Risk of suicide in high risk pregnancy: an exploratory study. Rev Assoc Med Bras 57:583–587

Bertolote JM, Fleischmann A (2002) Suicide and psychiatric diagnosis: a worldwide perspective. World Psychiatry 1:181–185
Bertolote JM, Fleischmann A, De Leo D, Wasserman D (2004) Psychiatric diagnoses and suicide: revisiting the evidence. Crisis 25:147–155
Beyer JL, Weisler RH (2016) Suicide behaviors in bipolar disorder: a review and update for the clinician. Psychiatr Clin North Am 39:111–123
Bjegovic-Mikanovic V, Abousbie ZAS, Breckenkamp J, Wenzel H, Broniatowski R, Nelson C, Vukovic D, Laaser U (2019) A gap analysis of SDG 3 and MDG 4/5mortality health targets in the six Arabic countries of North Africa: Egypt, Libya, Tunisia, Algeria, Morocco, and Mauritania. Libyan J Med 14:1607698
Boenisch S, Bramesfeld A, Mergl R, Havers I, Althaus D, Lehfeld H, Niklewski G, Hegerl U (2010) The role of alcohol use disorder and alcohol consumption in suicide attempts--a secondary analysis of 1921 suicide attempts. Eur Psychiatry 25:414–420
Brezo J, Paris J, Vitaro F, Hébert M, Tremblay RE, Turecki G (2008) Predicting suicide attempts in young adults with histories of childhood abuse. Br J Psychiatry 193:134–139
Canetto SS (2008) Women and suicidal behavior: a cultural analysis. Am J Orthopsychiatry 78:259–266
Canetto SS, Sakinofsky I (1998) The gender paradox in suicide. Suicide Life Threat Behav 28:1–23
Carlborg A, Jokinen J, Jönsson EG, Nordstrom A-L, Nördstrom P (2008) Long-term suicide risk in schizophrenia spectrum psychoses: survival analysis by gender. Arch Suicide Res 12:347–351
Carlborg A, Winnerbäck K, Jönsson EG, Jokinen J, Nordström P (2010) Suicide in schizophrenia. Expert Rev Neurother 10:1153–1164
Cavanagh JTO, Carson AJ, Sharpe M, Lawrie SM (2003) Psychological autopsy studies of suicide: a systematic review. Psychol Med 33:395–405
Chen Y-Y, Chien-Chang Wu K, Yousuf S, Yip PSF (2012) Suicide in Asia: opportunities and challenges. Epidemiol Rev 34:129–144
Cibis A, Mergl R, Bramesfeld A, Althaus D, Niklewski G, Schmidtke A, Hegerl U (2012) Preference of lethal methods is not the only cause for higher suicide rates in males. J Affect Disord 136:9–16
Clayton JA, Tannenbaum C (2016) Reporting sex, gender, or both in clinical research? JAMA 316:1863
Comacchio C, Lasalvia A, Ruggeri M (2019) Current evidence of childhood traumatic experiences in psychosis – focus on gender differences. Psychiatry Res 281:112507
Cui H, Supriyanto I, Asano M, Ueno Y, Nagasaki Y, Nishiguchi N, Shirakawa O, Hishimoto A (2010) A common polymorphism in the 3'-UTR of the NOS1 gene was associated with completed suicides in Japanese male population. Prog Neuro-Psychopharmacol Biol Psychiatry 34:992–996
Cutajar MC, Mullen PE, Ogloff JRP, Thomas SD, Wells DL, Spataro J (2010) Suicide and fatal drug overdose in child sexual abuse victims: a historical cohort study. Med J Aust 192:184–187
Devries KM, Mak JYT, Child JC, Falder G, Bacchus LJ, Astbury J, Watts CH (2014) Childhood sexual abuse and suicidal behavior: a meta-analysis. Pediatrics 133:e1331–e1344
Díaz-Caneja CM, Pina-Camacho L, Rodríguez-Quiroga A, Fraguas D, Parellada M, Arango C (2015) Predictors of outcome in early-onset psychosis: a systematic review. NPJ Schizophr 1:14005
Donker T, Batterham PJ, Van Orden KA, Christensen H (2014) Gender-differences in risk factors for suicidal behaviour identified by perceived burdensomeness, thwarted belongingness and acquired capability: cross-sectional analysis from a longitudinal cohort study. BMC Psychol 2:20
Doyle M, While D, Mok PLH, Windfuhr K, Ashcroft DM, Kontopantelis E, Chew-Graham CA, Appleby L, Shaw J, Webb RT (2016) Suicide risk in primary care patients diagnosed with a personality disorder: a nested case control study. BMC Fam Pract 17:106
Dunn AG, Coiera E, Mandl KD, Bourgeois FT (2016) Conflict of interest disclosure in biomedical research: a review of current practices, biases, and the role of public registries in improving transparency. Res Integr Peer Rev 1:1

Fausto-Sterling A (2008) Sexing the body: gender politics and the construction of sexuality. Hachette, London

Fox KR, Millner AJ, Mukerji CE, Nock MK (2018) Examining the role of sex in self-injurious thoughts and behaviors. Clin Psychol Rev 66:3–11

Freeman A, Mergl R, Kohls E, Székely A, Gusmao R, Arensman E, Koburger N, Hegerl U, Rummel-Kluge C (2017) A cross-national study on gender differences in suicide intent. BMC Psychiatry 17

Gearing RE, Alonzo D (2018) Religion and suicide: new findings. J Relig Health 57:2478–2499

Genuchi M (2015) Anger and hostility as primary externalizing features of depression in college men. Int J Mens Health 14:113–128

Genuchi MC, Valdez JN (2015) The role of anger as a component of a masculine variation of depression. Psychol Men Masculinity 16:149–159

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ (2011) Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. J Homosex 58:10–51

Hawton K (2000) Sex and suicide: gender differences in suicidal behaviour. Br J Psychiatry 177:484–485

Hawton K, van Heeringen K (2009) Suicide. Lancet 373:1372–1381

Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ (2005) Schizophrenia and suicide: systematic review of risk factors. Br J Psychiatry 187:9–20

Hegerl U (2016) Prevention of suicidal behavior. Dialogues Clin Neurosci 18:183–190

Hegerl U, Wittenburg L, Arensman E, Van Audenhove C, Coyne JC, McDaid D, van der Feltz-Cornelis CM, Gusmão R, Kopp M, Maxwell M, Meise U, Roskar S, Sarchiapone M, Schmidtke A, Värnik A, Bramesfeld A (2009) Optimizing suicide prevention programs and their implementation in Europe (OSPI Europe): an evidence-based multi-level approach. BMC Public Health 9:428

Jamison KR (2000) Suicide and bipolar disorder. J Clin Psychiatry 61:47–51

Jordans MJD, Kaufman A, Brenman NF, Adhikari RP, Luitel NP, Tol WA, Komproe I (2014) Suicide in South Asia: a scoping review. BMC Psychiatry 14:358

Juurlink DN, Herrmann N, Szalai JP, Kopp A, Redelmeier DA (2004) Medical illness and the risk of suicide in the elderly. Arch Intern Med 164:1179–1184

Kaplan MS, McFarland BH, Huguet N, Conner K, Caetano R, Giesbrecht N, Nolte KB (2013) Acute alcohol intoxication and suicide: a gender-stratified analysis of the national violent death reporting system. Inj Prev 19:38–43

Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB (1993) Sex and depression in the national comorbidity survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 29:85–96

Kiely KM, Brady B, Byles J (2019) Gender, mental health and ageing. Maturitas 129:76–84

Kralovec K, Kunrath S, Fartacek C, Pichler E-M, Plöderl M (2018) The gender-specific associations between religion/spirituality and suicide risk in a sample of Austrian psychiatric inpatients. Suicide Life Threat Behav 48:281–293

Lenz B, Röther M, Bouna-Pyrrou P, Mühle C, Tektas OY, Kornhuber J (2019) The androgen model of suicide completion. Prog Neurobiol 172:84–103

Lester D (2006) Sex differences in completed suicide by schizophrenic patients: a meta-analysis. Suicide Life Threat Behav 36:50–56

Lopez-Castroman J, Blasco-Fontecilla H, Courtet P, Baca-Garcia E, Oquendo MA (2015) Are we studying the right populations to understand suicide? World Psychiatry 14:368–369

Magovcevic M, Addis ME (2008) The masculine depression scale: development and psychometric evaluation. Psychol Men Masculinity 9:117–132

Mars B, Burrows S, Hjelmeland H, Gunnell D (2014) Suicidal behaviour across the African continent: a review of the literature. BMC Public Health 14:606

Martin LA, Neighbors HW, Griffith DM (2013) The experience of symptoms of depression in men vs women: analysis of the national comorbidity survey replication. JAMA Psychiat 70:1100–1106

Mergl R, Koburger N, Heinrichs K, Székely A, Tóth MD, Coyne J, Quintão S, Arensman E, Coffey C, Maxwell M, Värnik A, van Audenhove C, McDaid D, Sarchiapone M, Schmidtke A, Genz A, Gusmão R, Hegerl U (2015) What are reasons for the large gender differences in the lethality of suicidal acts? An epidemiological analysis in four European countries. PLoS One 10: e0129062

Miranda-Mendizábal A, Castellví P, Parés-Badell O, Almenara J, Alonso I, Blasco MJ, Cebrià A, Gabilondo A, Gili M, Lagares C, Piqueras JA, Roca M, Rodríguez-Marín J, Rodríguez-Jiménez T, Soto-Sanz V, Vilagut G, Alonso J (2017) Sexual orientation and suicidal behaviour in adolescents and young adults: systematic review and meta-analysis. Br J Psychiatry 211:77–87

Naghavi M (2019) Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. BMJ 364:l94

Narang P, Sarai SK, Aldrin S, Lippmann S (2018) Suicide among transgender and gender-nonconforming people. Prim Care Companion CNS Disord 20

Neeleman J, Lewis G (1999) Suicide, religion, and socioeconomic conditions. An ecological study in 26 countries, 1990. J Epidemiol Community Health 53:204–210

Neeleman J, Halpern D, Leon D, Lewis G (1997) Tolerance of suicide, religion and suicide rates: an ecological and individual study in 19 Western countries. Psychol Med 27:1165–1171

Nordentoft M, Mortensen PB, Pedersen CB (2011) Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry 68:1058–1064

Nordentoft M, Madsen T, Fedyszyn I (2015) Suicidal behavior and mortality in first-episode psychosis. J Nerv Ment Dis 203:387–392

O'Carroll PW, Berman AL, Maris RW, Moscicki EK, Tanney BL, Silverman MM (1996) Beyond the tower of babel: a nomenclature for suicidology. Suicide Life Threat Behav 26:237–252

Olfson M, Wall M, Wang S, Crystal S, Liu S-M, Gerhard T, Blanco C (2016) Short-term suicide risk after psychiatric hospital discharge. JAMA Psychiat 73:1119–1126

Oliffe JL, Phillips MJ (2008) Men, depression and masculinities: a review and recommendations. J Men's Health 5:194–202

Oliffe JL, Rossnagel E, Seidler ZE, Kealy D, Ogrodniczuk JS, Rice SM (2019) Men's depression and suicide. Curr Psychiatry Rep 21:103

Poorolajal J, Haghtalab T, Farhadi M, Darvishi N (2016) Substance use disorder and risk of suicidal ideation, suicide attempt and suicide death: a meta-analysis. J Public Health 38:e282–e291

Popovic D, Benabarre A, Crespo JM, Goikolea JM, González-Pinto A, Gutiérrez-Rojas L, Montes JM, Vieta E (2014) Risk factors for suicide in schizophrenia: systematic review and clinical recommendations. Acta Psychiatr Scand 130:418–426

Qin P, Agerbo E, Westergård-Nielsen N, Eriksson T, Mortensen PB (2000) Gender differences in risk factors for suicide in Denmark. Br J Psychiatry 177:546–550

Qin P, Agerbo E, Mortensen PB (2003) Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: a national register-based study of all suicides in Denmark, 1981-1997. Am J Psychiatry 160:765–772

Qin P, Hawton K, Mortensen PB, Webb R (2014) Combined effects of physical illness and comorbid psychiatric disorder on risk of suicide in a national population study. Br J Psychiatry 204:430–435

Rasic D, Kisely S, Langille DB (2011) Protective associations of importance of religion and frequency of service attendance with depression risk, suicidal behaviours and substance use in adolescents in Nova Scotia, Canada. J Affect Disord 132:389–395

Reutfors J, Brandt L, Jönsson EG, Ekbom A, Sparén P, Osby U (2009) Risk factors for suicide in schizophrenia: findings from a Swedish population-based case-control study. Schizophr Res 108:231–237

Rhodes AE, Boyle MH, Tonmyr L, Wekerle C, Goodman D, Leslie B, Mironova P, Bethell J, Manion I (2011) Sex differences in childhood sexual abuse and suicide-related behaviors. Suicide Life Threat Behav 41:235–254

Robson A, Scrutton F, Wilkinson L, MacLeod F (2010) The risk of suicide in cancer patients: a review of the literature. Psycho-Oncology 19:1250–1258

Rutz W, von Knorring L, Pihlgren H, Rihmer Z, Wålinder J (1995) Prevention of male suicides: lessons from Gotland study. Lancet 345:524

Saxena S, Krug EG, Chestnov O, World Health Organization (2014) Preventing suicide: a global imperative. World Health Organization, Geneva

Schaffer A, Isometsä ET, Azorin J-M, Cassidy F, Goldstein T, Rihmer Z, Sinyor M, Tondo L, Moreno DH, Turecki G, Reis C, Kessing LV, Ha K, Weizman A, Beautrais A, Chou Y-H, Diazgranados N, Levitt AJ, Zarate CA, Yatham L (2015) A review of factors associated with greater likelihood of suicide attempts and suicide deaths in bipolar disorder: part II of a report of the international society for bipolar disorders task force on suicide in bipolar disorder. Aust N Z J Psychiatry 49:1006–1020

Schernhammer ES, Colditz GA (2004) Suicide rates among physicians: a quantitative and gender assessment (meta-analysis). Am J Psychiatry 161:2295–2302

Schiebinger L, Stefanick ML (2016) Gender matters in biological research and medical practice. J Am Coll Cardiol 67:136–138

Schneider B (2009) Substance use disorders and risk for completed suicide. Arch Suicide Res 13:303–316

Seidler ZE, Dawes AJ, Rice SM, Oliffe JL, Dhillon HM (2016) The role of masculinity in men's help-seeking for depression: a systematic review. Clin Psychol Rev 49:106–118

Shaik S, Rajkumar RP, Menon V, Sarkar S (2017) Gender, life events, and depression: an exploratory study. Indian J Psychol Med 39:330–335

Sharmin Salam S, Alonge O, Islam MI, Hoque DME, Wadhwaniya S, Ul Baset MK, Mashreky SR, El Arifeen S (2017) The Burden of suicide in rural Bangladesh: magnitude and risk factors. Int J Environ Res Public Health 14

Shekhani SS, Perveen S, Hashmi D-E-S, Akbar K, Bachani S, Khan MM (2018) Suicide and deliberate self-harm in Pakistan: a scoping review. BMC Psychiatry 18:44

Sher L, Rutter SB, New AS, Siever LJ, Hazlett EA (2019) Gender differences and similarities in aggression, suicidal behaviour, and psychiatric comorbidity in borderline personality disorder. Acta Psychiatr Scand 139:145–153

Silberschmidt A, Lee S, Zanarini M, Schulz SC (2015) Gender differences in borderline personality disorder: results from a multinational, clinical trial sample. J Personal Disord 29:828–838

Silverman MM, Berman AL, Sanddal ND, O'carroll PW, Joiner TE (2007) Rebuilding the tower of Babel: a revised nomenclature for the study of suicide and suicidal behaviors. Part 2: suicide-related ideations, communications, and behaviors. Suicide Life Threat Behav 37:264–277

Simon M, Chang E-S, Zeng P, Dong X (2013) Prevalence of suicidal ideation, attempts, and completed suicide rate in Chinese aging populations: a systematic review. Arch Gerontol Geriatr 57:250–256

Simpson SG, Jamison KR (1999) The risk of suicide in patients with bipolar disorders. J Clin Psychiatry 60:53–56

Struszczyk S, Galdas PM, Tiffin PA (2019) Men and suicide prevention: a scoping review. J Ment Health 28:80–88

Taliaferro LA, Rienzo BA, Pigg RM, Miller MD, Dodd VJ (2009) Spiritual well-being and suicidal ideation among college students. J Am Coll Heal 58:83–90

Too LS, Spittal MJ, Bugeja L, Reifels L, Butterworth P, Pirkis J (2019) The association between mental disorders and suicide: a systematic review and meta-analysis of record linkage studies. J Affect Disord 259:302–313

Tóth MD, Ádám S, Birkás E, Székely A, Stauder A, Purebl G (2014) Gender differences in deliberate self-poisoning in Hungary: analyzing the effect of precipitating factors and their relation to depression. Crisis 35:145–153

Turecki G (2014) The molecular bases of the suicidal brain. Nat Rev Neurosci 15:802–816
Turecki G, Brent DA (2016) Suicide and suicidal behaviour. The Lancet 387:1227–1239
van Heeringen K (2012) Stress–diathesis model of suicidal behavior. In: Dwivedi Y (ed) The neurobiological basis of suicide, frontiers in neuroscience. CRC Press/Taylor & Francis, Boca Raton
van Heeringen K, Mann JJ (2014) The neurobiology of suicide. Lancet Psychiatry 1:63–72
Vera-Varela C, Giner L, Baca-García E, Barrigón ML (2019) Trastorno límite de personalidad: el reto del manejo de las crisis. Psiquiatr Biol 26:1–6
Vijayakumar L, Kumar MS, Vijayakumar V (2011) Substance use and suicide. Curr Opin Psychiatry 24:197–202
Wålinder J, Rutz W (2001) Male depression and suicide. Int Clin Psychopharmacol 16:S21
WHO, Defining Sexual Health (2019). WHO. http://www.who.int/reproductivehealth/topics/sexual_health/sh_definitions/en/ Accessed 27 Nov 2019
WHO, Suicide Data (2019) WHO. http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ Accessed 10 Nov 2019
WHO, Suicide Rates (per 100 000 population) (2019) WHO. http://www.who.int/gho/mental_health/suicide_rates_male_female/en/ Accessed 10 Nov 2019
Wide J, Mok H, McKenna M, Ogrodniczuk JS (2011) Effect of gender socialization on the presentation of depression among men: a pilot study. Can Fam Phys 57:e74–e78
Zalsman G, Hawton K, Wasserman D, van Heeringen K, Arensman E, Sarchiapone M, Carli V, Höschl C, Barzilay R, Balazs J, Purebl G, Kahn JP, Sáiz PA, Lipsicas CB, Bobes J, Cozman D, Hegerl U, Zohar J (2016) Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry 3:646–659
Zatti C, Rosa V, Barros A, Valdivia L, Calegaro VC, Freitas LH, Ceresér KMM, da Rocha NS, Bastos AG, Schuch FB (2017) Childhood trauma and suicide attempt: a meta-analysis of longitudinal studies from the last decade. Psychiatry Res 256:353–358
Zierau F, Bille A, Rutz W, Bech P (2002) The Gotland male depression scale: a validity study in patients with alcohol use disorder. Nord J Psychiatry 56:265–271

Neurocognition and the Suicidal Process

S. B. Rutter, N. Cipriani, E. C. Smith, E. Ramjas, D. H. Vaccaro, M. Martin Lopez, W. R. Calabrese, D. Torres, P. Campos-Abraham, M. Llaguno, E. Soto, M. Ghavami, and M. M. Perez-Rodriguez

Contents

Abstract Early thinking about cognitive process and suicidal behaviors tended to focus on the immediate situation surrounding the individual – typically the underlying psychiatric condition that was seen as leading to his or her distress. However, we now know that the cognitive processes involved in a range of suicidal thoughts and behaviors can exert a significant impact on the expression or development of these behaviors, even without an environmental stressor or psychiatric condition. In

S. B. Rutter, N. Cipriani, E. C. Smith, E. Ramjas, D. H. Vaccaro, M. Martin Lopez, W. R. Calabrese, D. Torres, P. Campos-Abraham, M. Llaguno, E. Soto, M. Ghavami, and M. M. Perez-Rodriguez (✉)
Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: Mercedes.perez@mssm.edu

Curr Topics Behav Neurosci (2020) 46: 117–154
https://doi.org/10.1007/7854_2020_162
Published Online: 29 August 2020

this chapter, we summarize theoretical perspectives that led to this realization and explore the current understanding of the link between cognition and suicide from recent research and clinical findings. We present these findings first by psychiatric disorder, then by cognitive domains, and finally by specific suicidal construct in order to highlight the importance of these factors in determining the role of cognition in the suicidal process.

Within and across psychiatric disorders, certain cognitive processes – negativistic thinking, impulsivity, cognitive rigidity, and altered emotional processing – are frequently found to be linked to suicidal thoughts and behaviors. Overall cognitive performance, decreased processing speed, executive dysfunction, and negative biases in memory and attention have also been linked to suicidal thoughts and behaviors. However, these findings do not hold true for all populations. There seems to be a role both for cognitive distortions (such as hopelessness) and neurocognitive deficits (such as poor overall cognitive performance, slower processing speed, and executive dysfunction) in the suicidal process, which warrant further exploration both separately and together.

Keywords Attempted suicide · Cognition · Neurocognition · Suicidal ideation · Suicide

1 Suicide and Cognition: An Introduction

1.1 History

It comes as no surprise that cognitive processes play a crucial role in a range of suicidal behaviors. However, where exactly in the suicidal process cognition is most important and what domains of cognition or cognitive styles are related to each construct within the suicidal process are up for debate. Early research into cognition and the suicidal process tended to assume that suicidal acts and suicidal ideation went hand in hand and that suicidal acts or behaviors were simply symptoms of disorders (see Ellis 2006). The emergence of the cognitive-mediational model (Rudd 2000), which suggests a causal relationship between cognition and behavior, shifted this perspective and allowed for clinical interventions beyond those aimed at altering the situation or alleviating the underlying psychiatric disorder the suicidal individual is suffering from.

The first formal exploration of the cognitive processes of suicidal individuals came from Edward Shneidman's analysis of suicide notes (Shneidman and Farberow 1957). He discovered that those who completed suicide often displayed an inability to consider a situation from a different perspective and often viewed their choices as black and white (either all good or all bad), representing a deficit in problem-solving. He also interpreted some of these thought patterns as "illogic," mainly resulting from

constriction and rigidity in their thinking. While Shneidman's was not an explicitly cognitive model, his early work would influence later research into cognitive processes and the suicidal process. However, he was much more interested in the importance of psychological pain (or "psychache") in suicidal ideation and behavior.

The first explicitly cognitive conception of suicide came from George Kelly (1961), who included other aspects of the suicidal process not explored by Shneidman, namely, self-injurious behavior (closely related to the current DSM-5 diagnostic category of non-suicidal self-injury) and passive suicidal ideation (although this term would be coined much later). His Personal Construct Psychology focused on the general process of generating patterns or themes about self, others, and the world through expectations and "experiments" which confirm or deny our expectations (Kelly 1955). These themes then allow us to make predictions about future events. This work led to a number of seminal studies regarding constructs of significant others (Landfield 1976), problem-solving strategies (Parker 1981), and cognitive predictors of risk (Hughes and Neimeyer 1993).

Following George Kelly came Charles Neuringer, who authored the first published review of research on cognition and suicide (Neuringer 1976). This early review identified the importance of imaginative resources, polarized value systems, rigid and constricted thinking, and present versus past or future orientations in the suicidal process. Neuringer compared suicidal individuals to control subjects in thought patterns and discovered a tendency for dichotomous thinking, cognitive rigidity, and impaired problem-solving in those with suicidal behaviors or suicidal ideation. His findings spurred further research into cognitive vulnerabilities in suicidal individuals.

Any discussion of cognition would be incomplete without mentioning the pioneering work of both Aaron T. Beck and Albert Ellis, whose cognitive theories and therapies sparked a cognitive revolution. With Beck came the first formal conceptions of suicidality and the suicidal process, which were later refined by O'Carroll et al. (1996), creating formal definitions of passive and active suicidal ideation, suicide attempts, and non-suicidal self-injury (Beck et al. 1973). Beck identified both the Hopelessness Theory of Suicide and the idea of a suicidal mode, discussed in more detail in the following section. While Ellis did not have a theory of suicide per se, his work has important implications for theoretical perspectives and treatments related to the suicidal process.

After the cognitive revolution came the work of Marsha Linehan and her Biosocial Theory and Dialectical Behavior Therapy, both grounded on her research and clinical observation of patients with borderline personality disorder (Linehan 1981, 1986, 1993). Biosocial Theory posits that suicidal behavior is a method of coping with emotional pain that arises due to skill deficits; the suicidal individual can think of no other methods of reducing his or her suffering. Linehan recognized that there are multiple pathways to suicidal behavior and ideation and emphasized the importance of context in the development of problematic emotions and behavior. Her theory and the related therapeutic modality, reviewed later in this chapter, was a key step towards current thinking about neurocognition and the suicidal process.

1.2 Current Theoretical Perspectives

1.2.1 Hopelessness Theory of Suicide

Aaron T. Beck in 1975 introduced the Hopelessness Theory of Suicide (Beck et al. 1975), which has been one of the predominant theories in the field. Beck and colleagues understood suicidal behavior as the result of a sense of hopelessness and/or impaired reasoning. The importance here was not only the presence of hopelessness but also the persistence of this feeling and its importance in the decision to make a suicide attempt. Impaired reasoning was thought to play a key role in the transition from suicidal ideation to suicide attempt, as these individuals are able to conceive of no other solution to their hopelessness. After nearly 20 years of research in the field, Beck refined his theory of suicide with the idea of the suicidal mode (Beck 1996). Here the modes are defined as networks of cognitive, motivation, physiological, affective, and behavioral schemas that are spontaneously activated by relevant events (both internal and external) to assist in achieving a goal (Beck 1996). When the suicidal mode is activated repeatedly, the threshold for activation is lowered, as the capacity for cognitive control is reduced with each activation. This idea was expanded upon by Rudd, who made explicit the implications for those with a history of suicidal behavior or multiple suicide attempters in his Fluid Vulnerability Theory (Rudd 2000; Rudd et al. 2001). This theory led to the development of targeted Cognitive Behavioral Therapy (CBT), with an emphasis on helplessness, poor problem-solving, impaired impulse control, noncompliance, and social isolation rather than treating on the underlying diagnosis (often thought to be depression). The emphasis on identifying triggering problems and the thoughts generated by them, the importance of thoughts related to hopelessness, and the focus on cognitive restructuring have guided cognitive theories of suicidal behavior and related research. Beck also helped develop a classification scheme that recognized differences between intent and lethality in completed suicide, attempted suicide, and suicidal ideation (Beck et al. 1973). He identified the importance of self-destructive thoughts, plans, and expectations regarding the suicidal ideation, including duration and frequency of the thoughts, their sense of control over making an attempt, the number of deterrents, and the amount of actual preparation for the suicide attempt (Beck et al. 1979). This suicide risk assessment was separate from the assessment of risk/symptoms of depression, unique for its time as most associated suicide and suicidal ideation with depressive symptoms (see Brown et al. 2006).

1.2.2 Rational Emotive Behavior Therapy: Theoretical Implications

Albert Ellis' Rational Emotive Behavior Therapy (REBT) and related theory emerged around the same time as the work of Beck (see Ellis 1973). While Ellis did not have an explicit theory regarding suicidal behavior, it's not difficult to see how his theory would be relevant. The concept of emotional responsibility offers a

link between environmental factors and cognition. Emotional responsibility is our tendency to believe that problems emerge from circumstances rather than our perception of these circumstances (Ellis and Ratliff 1986). The idea of low frustration tolerance comes from REBT and has been important in work on suicide (see Linehan 1993; Rudd et al. 2001). Thoughts about the situation are more readily accessible and modifiable to a clinician than the underlying environment, so this offered a path to early intervention. His ABC model suggests that irrational beliefs are the core of both mental illness and common emotional distress; under this model, there are activating events (A) that interact with our underlying beliefs and cognitive processes (B) to lead to certain emotional consequences (C; A. Ellis 1957). To bring about change, Ellis recommends clinicians focus on altering the clients' beliefs, which are often irrational, to bring about a change in the emotional consequences of events. The emphasis in the ABC model on the importance of changing dysfunctional beliefs, while not explicitly studied or always recognized as such, has been groundbreaking in the field of suicidality. Even if we are able to target and remove the suicidal thoughts and behavior in the short term, or resolve the events that directly lead to those behaviors, without addressing the cognitive aspects that linger, the individual is at high risk of subsequent suicidal ideation or suicide attempts at the next setback.

1.2.3 Biosocial Theory

Marsha Linehan's Biosocial Theory suggests that suicidal behavioral is a learned coping mechanism for acute emotional pain that results from a skill deficit, similar to the idea of impaired problem-solving (Linehan 1981, 1986, 1993). Linehan recognized that behaviors don't arise from a single cause; we have to analyze the complex interplay between environmental factors, cognition, emotion, and observable behavior to determine the causes of suicidal behavior. Common environmental causes include adverse events, lack of social support, modes of suicidal behavior (similar to Beck, but activated through observational learning of suicidal behavior in others), emotion dysregulation (characterized here by easily activated and unusually strong emotions), hopeless thinking, and self-invalidation and shame (which includes the idea of perfectionism). She also recognized the importance of combinations of biological vulnerabilities and individual factors (like temperament) that interact with environmental factors to confer increased risk for a variety of self-destructive behaviors, including suicidal behavior. Unique here was her emphasis on what was termed the Invalidating Environment, wherein chronic and pervasive invalidation by others reinforces the escalation of emotional behaviors and leads to increasing isolation.

1.2.4 Separation Theory

Robert Firestone's Separation Theory introduced the concept of the Voice, wherein self-destructive impulses arise out of critical or hostile messages from early figures that are internalized and become their own voice (Firestone 1986, 1997). In his concept, there exist self and anti-self systems which influence self-destructive thoughts, falling on a continuum from mildly self-critical to suicidal; these systems are part of the self-destructive thoughts which compromise the Voice, which in turn alters the continuum of self-destructive behaviors. The anti-self system is a protective element, designed to deal with painful or frustrating interpersonal interactions. Firestone's theory came from a Developmental Perspective, with a strong emphasis on attachment styles and emotion dysregulation. Among his 11 constructs on the continuum of self-destructive thoughts were isolation, addictions, hopelessness, and giving up. His Voice Therapy aimed to stop the progression along the continuum (which ended in self-harm and "suicide injunctions") by offering insight into the origins of these thoughts. In cases where thoughts are only partly conscious, reframing them in the second person may aid in revealing these thoughts and the behaviors they provoke.

1.2.5 Personal Construct Psychology: Theoretical Implications

George Kelly's theory also recognized the importance of the social environment in constructing as well as validating or invalidating an individual's conceptions of self and the world. In his seminal chapter, Kelly recognized three basic pathways to the suicidal choice (Kelly 1961). These include deterministic suicide, where the person feels there's no choice and no reason for waiting to see the outcome because he or she anticipates only pain; suicide as a dedicated act, where the person believes that his or her core beliefs (which may be under attack) will be taken up by others; and chaotic self-harm, where the persons' environment is so unpredictable that the only way to find certainty and clarity is in death.

1.2.6 Interpersonal Theory of Suicide

Robert Joiner's Interpersonal Theory of Suicide suggests there are three key aspects related to suicide attempts – "thwarted belongingness," "perceived burdensomeness," and the acquired ability ("capability") to overcome a fear of death (Joiner 2005). Thwarted belongingness here is the experience of an unmet need – the need to belong – and is closely related to social isolation, a common risk factor for suicide attempts (Van Orden et al. 2010). Perceived burdensomeness refers to both the perception that the "self is so flawed as to be a liability on others" and the "affectively-laden cognitions of self-hatred," commonly found in suicide victims and suicide attempters (Van Orden et al. 2010, p. 677). This sense of being a burden

on others is also thought to explain the relationship between events like physical illness and job loss on suicidal behavior. While thwarted belongingness and perceived burdensomeness are sufficient to produce hopelessness and eventually suicidal ideation, they do not lead to suicidal acts without the ability to overcome one's natural fear of dying (Joiner 2005; Van Orden et al. 2010). Given how strong this natural aversion is, Joiner suggests that only exposure to profoundly painful or traumatic experiences (such as childhood trauma or self-harm) would lead to insensitivity to pain and fearlessness (Van Orden et al. 2010). The Interpersonal Theory of Suicide is uniquely able to capture a majority of the risk factors (certain stressful life events, hopelessness, social isolation, trauma history, previous suicide attempts) identified by other theorists while at the same time offering an explanation for the transition from suicidal ideation to suicidal behavior (Van Orden et al. 2010). This theoretical perspective also lends itself well to empirical research, and many of the studies cited in the preceding sections operate from this perspective.

1.2.7 Ideation to Action Theories of Suicide

A growing body of work has attempted to explain the transition from suicidal ideation to suicidal action – together termed Ideation-to-Action Theories. These include Interpersonal Theory, Integrated-Motivational Model, Three-Step Theory, and Fluid Vulnerability Theory (Klonsky et al. 2018). Both Interpersonal Theory and Fluid Vulnerability Theory were discussed in the previous sections. Integrated-Motivation Model suggests that there are two phases in the suicidal process – a motivational phase and a volitional phase (O'connor 2011). In the motivational phase, a sense of entrapment results from a combination of defeat and humiliation (from certain life events) and individual factors (like impaired problem-solving or poor coping skills); this sense of entrapment leads the individual to view suicide as a solution (O'connor 2011). In the volitional phase, intent to commit suicide (developed during the motivational phase) combines with other factors (like access to lethal weapons, impulsivity, and capability) to lead to suicidal behavior (O'connor 2011). Three-Step Theory posits that, with stressful or painful circumstances, individuals are "punished" for being alive, which then leads to hopelessness and a desire to escape life (step 1; Klonsky and May 2015). Intensification of pain to the point where it overwhelms connectedness (to roles, others, or a sense of purpose) leads to an intensification of suicidal ideation from passive to active (step 2). Finally, with the capacity to attempt suicide (as described in the Interpersonal Theory section above), suicide becomes likely (step 3).

1.2.8 Summary and Current Theoretical Perspectives

The theories mentioned above comprise the main cognitive theories related to suicidal behavior (see O'Connor and Nock 2014 for a review of all current psychological theories of suicidal behavior). Currently, the field of cognition and suicide

has moved towards general theories of the impact of neurocognition on behavior, looking at these behaviors in a variety of disorders and in relationship to discrete neurocognitive domains. Given the general definition of neurocognition (cognitive abilities that support complex processes such as thought, action, emotion, and perception; see Lichtenberger and Kaufman 2009), it's not hard to conceive how this general theory can be applied in how certain thoughts are linked to suicidal ideation and behavior. In addition, the diathesis-stress model has proven to be an effective guiding principle for a number of disorders and concerning behaviors, including the suicidal process (Mann et al. 1999; see Schotte and Clum 1987). With advances in neuroscience, cognition has become enmeshed within the neurological or neurobiological theories of suicidal behavior. Strictly cognitive theories are mainly limited to exploration of cognitive domains as in neuropsychology. As our understanding of the suicidal process as separate from individual disorders advances, the work on suicide and cognition moves from general to disorder-specific work. What remains to be explored, however, is how neurocognitive factors influence the transition from suicidal ideation to behavior and from suicidal behavior to multiple suicide attempts, as described by Rudd (2006). Not explored here is the additional role of brain structure and network function in the relationship between neurocognition and behavior.

2 Suicide and Neurocognition in Psychiatric Disorders

2.1 Mood Disorders

2.1.1 Depression and Neurocognition

Depression is strongly associated with suicidal behaviors, and it is the primary cause of death by suicide worldwide (Brachman et al. 2016). Researchers have explored the relationship between depression and cognition for quite some time, supported by the hypothesis of a cognitive triad of depression, which is characterized by negative views of the self, the surrounding environment, and the future (Wetzel and Reich 1989). In keeping with Helplessness Theory, a tendency to make negative inferences about the self, others, and the environment is associated with suicidal behavior in this population (Beck et al. 1979). In both depression and suicide, negative cognitive biases are pervasive (Al-Mosaiwi and Johnstone 2018; Beck 1963; Chu et al. 2015). In fact, cognitive vulnerability (measured with the Cognitive Style Questionnaire) can account for both a higher risk of suicidality and hopelessness in depressed patients (Abramson et al. 1998). In addition, researchers have found a link between implicit biases towards depression-related words and the self and suicidal ideation and history of suicide attempt (Glashouwer et al. 2010). Recent work involving ketamine has confirmed the role of cognition and specifically helplessness in suicidal ideation in individuals with treatment-resistant depression. Ketamine (both as racemic compound and as its enantiomers esketamine and r-ketamine) has been shown to

have a strong anti-suicidal effect that seems to be driven by improvements in explicit and implicit suicidal cognition, as well as a reduction in hopelessness scores (Price et al. 2014). In fact, reductions in negative cognitions and improvements in cognitive functioning (memory, planning, behavioral inhibition, and flexibility) were associated with a decrease in suicidal ideation with ketamine treatment (Schwartz et al. 2016). Moreover, subjects who respond to ketamine infusion show an improvement in the go/no-go, an attentional performance test in which subjects are asked to indicate when a word matches the target category (either positive, negative, or neutral; Chen et al. 2018).

Impulsivity has also been shown to be a relevant cognitive risk factor for suicidal behaviors in depressed patients, acting as a moderator in the relationship between depression severity and suicidal ideation (Wang et al. 2015). Research into decision-making in depressed patients with a history of suicide attempt have led to controversial findings, with some suggesting lower performance at Iowa Gambling Test and riskier choices on the Game of Dice Task, both of which indicate greater impulsivity (Deisenhammer et al. 2018).

Recently, Roca et al. (2019) proposed a method for identifying longitudinal links between alterations in executive functioning and suicidal ideation and behavior. In a recent paper investigating performances in "cool" (processed without affective influence, e.g., logic) and "hot" (processed in an emotional setting, e.g., reward sensitivity) executive functioning, depressed suicide attempters showed deficits in general inhibition compared to depressed non-suicidal and healthy controls (Ho et al. 2018). This finding is in line with other studies in which self-reported impulsivity has been shown to predict suicidal behaviors (Ponsoni et al. 2018). Westheide et al. (2008) found suicide attempters with suicidal ideation to perform worse at Iowa Gambling Test, compared to healthy controls and attempters without current suicidal ideation, suggesting that executive functioning and decision-making deficits in these patients may be a possible reflection of the cognitive rigidity found in suicidal ideation. The relationship between suicidal behavior and cognitive rigidity is still controversial, with the latter associated with suicidal thinking at 6 months in subjects with previous attempts, when measured as number of perseverative errors at Wisconsin Card Sorting Test (Miranda et al. 2012), but without statistical significance when measured at the Embedded Figures Test (Fazakas-DeHoog et al. 2017).

Other cognitive domains related to suicidality have been investigated among depressed patients, with some findings suggesting that memory and working memory and selected attention may be compromised in suicide attempters (Keilp et al. 2013). While the cognitive rigidity hypothesis has been challenged by conflicting findings, the cognitive deficits found in suicidal subjects seem to act dynamically in time, with suicide attempter performing worse in mental sequencing and flexibility during aging compared to non-attempters (King et al. 2000).

2.1.2 Bipolar Disorder (BD) and Neurocognition

Compared to MDD, individuals with bipolar disorder (BD) tend to show higher rates of suicidal behavior, with 4–19% ending their life via suicide and 20–60% attempting at least once in their life (Rhimer et al. 2017). Regarding neurocognition, individuals in the depressive episode of bipolar disorder (BD) have been shown to have cognitive styles (e.g., overly pessimistic) that are at least as negativistic as individuals with unipolar depression (see Alloy et al. 2006a, b). Interestingly, although unipolar depressed and bipolar manic individuals differ in their *explicitly* measured cognitive styles [i.e., negative vs. positive styles on the Attributional Style Questionnaire (ASQ; Peterson et al. 1982)], both groups have been shown to have negative attributions when measured implicitly through the pragmatic inference task (PIT; Lyon et al. 1999). The PIT contained a set of hypothetical, self-referent scenarios derived from ASQ items, which were disguised as a memory test for various facts within the scenarios. Participants were then asked unexpected questions about the cause of the outcomes described in the scenarios. While subtle, alterations in emotion processing in BD may also play a role in the high rate of suicide. Given these findings, links between cognitive styles and suicide likely are similar across unipolar and bipolar depressed individuals. However, future research will need to directly test this hypothesis.

Despite these similarities, risk of suicide generally is higher in individuals with BD versus MDD, and some have speculated that this is due to greater illness severity (e.g., Baldessarini et al. 2019). Others have suggested that this is due to higher levels of aggressiveness and mania-related symptoms, like impulsivity (e.g., Diler et al. 2017; Oquendo et al. 2000, 2004). Specifically, research has shown that in addition to illness severity, impulsivity helped to differentiate patients with a history of suicide attempts as measured by both self-report (i.e., Barratt Impulsiveness Scale) and performance on behavioral tasks. This includes commission errors in an immediate memory task (Wu et al. 2009) and greater preference for the impulsive smaller-sooner choices on the Two-Choice Impulsivity Paradigm (Dougherty et al. 2009). However, more research is needed in light of contradictory findings showing that self-reported impulsivity was actually lower for individuals with BD with a prior suicide attempt (Gilbert et al. 2011). In studies using diffusion tensor imaging to measure white matter, results showed that BD participants with a previous suicide attempt reported more impulsivity than BD individuals without an attempt and that this effect may be due to abnormal orbital frontal white matter (Mahon et al. 2012) or white matter in the anterior limb of the internal capsule and anterior corona radiate (Reich et al. 2019). Studies like these hold promise for finding neurocognitive mediators for suicide in BD.

Taken together, when it comes to suicide, individuals with BD may have the worst of both worlds. Not only do they share the implicit negative attributional styles of depressed individuals, regardless of mood state, but also the impulsivity associated with hypomanic and manic symptoms which could increase their likelihood of engaging in risky suicidal acts. Further, research has shown that individuals with BD

may also share cognitive risk factors with individuals with schizophrenia, based on hierarchical clustering analyses showing similar levels of severity of cognitive impairment across disorders (Van Rheenen et al. 2017). A recent review of the literature has shown that these cognitive impairments are associated with increased inflammatory state, brain structural abnormalities, and reduced neuroprotection (Van Rheenen et al. 2019). Future research needs to look longitudinally and better control for general symptom severity in order to elucidate more specific neurocognitive mechanisms that predict suicide in individuals with BD and mood disorders, in general.

Malhi et al. (2019) recently responded to this call by examining neural responses to an Emotional Face-Word Stroop task in 79 mood disorder patients and 66 controls. Results revealed that after accounting for general depressive symptom severity, as well as diagnosis and gender, Dorsal Default Mode Network activity during incongruent face-word items (i.e., happy face-sad word) was negatively associated with past month suicidal behavior, and basal ganglia activity during sad face-happy word items was positively associated with past month suicidal ideation. These findings are in line with a review by Miskowiak et al. (2019) showing that aberrant processing of emotional faces was the most consistent finding across studies of affect (i.e., emotion-laden) cognition in BD. Because this finding was robust across illness states, the authors recommended that this "trait-related" impairment in facial recognition should be the focus of future study as a potential treatment target in BD. More studies like Malhi et al. (2019), along with research targeting these processes in moment-by-moment, in vivo paradigms, are required in order to clarify the sequential links between mood symptoms, cognitive functioning, neural activity, and suicidal ideation and behavior. Malhi et al. (2018) present an integrated neurocognitive model of suicide in BD, which can provide guidance for future research and treatment aiming to better understand suicide from "ideation to action."

2.2 Schizophrenia and Related Disorders

Suicide is the leading cause of death in patients with schizophrenia, especially in younger individuals early in course of the disease, shortly after onset of symptoms (Verma et al. 2016). It is estimated that 4–13% of patients with schizophrenia die prematurely due to suicide attempts, and up to 60% of individuals diagnosed with schizophrenia make at least one suicide attempt in their lifetime (Delaney et al. 2012). This high rate of suicide may at least in part be associated with cognitive deficits characteristic of the disorder. Schizophrenia spectrum disorders are marked by significant cognitive deficits in over 80% of patients (Reichenberg et al. 2009), including impairments in domains of neurocognition (e.g., processing speed, attention, working memory, verbal learning, visual learning, reasoning, and problem-solving) and social cognition (Bechi et al. 2017; Green 2006; Verma et al. 2016). Extensive cognitive deficits in conjunction with the chronicity of these disorders lead

to poor functional outcomes and an overall decreased quality of life (Bechi et al. 2017).

The high rate of suicide in schizophrenia spectrum disorders has sparked research into the genesis of suicidal ideation and suicide attempts in this population, including the role of neurocognition. Verma et al. (2016) proposed a triangular relationship between suicide, cognition, and insight. Insight is here defined as the ability to distinguish between real and unusual experiences. Lack of insight is a symptom of various psychiatric disorders, while increased insight alone is associated with an increased risk of suicide behaviors in schizophrenia spectrum disorders (Vrbova et al. 2017b). This is thought to be due to self-stigma, low self-esteem, and psychological trauma stemming from their realization of the severity of their disorder and its impact on their functioning (see Vrbova et al. 2017a, b). To investigate this relationship, Vrbova et al. (2017b) assessed suicide intent via Pierce's suicide intent scale (Pierce 1981) in subjects diagnosed with schizophrenia or schizoaffective disorder and examined associations with measures of executive functioning and cognitive insight on Beck's cognitive insight scale (Beck et al. 2004) and the Trail Making Test (Tombaugh 2004). They found that individuals with a history of a suicide attempt scored higher on these measures of cognitive ability and insight compared to those with no history of a suicide attempt. In keeping with this idea, Hewitt proposes that suicide may stem from a rational decision based on the individuals' insight into their situation and their own pragmatic assessment of the hardships that result from these types of disorders, rather than stemming from mental incapacity associated with the illness (Hewitt 2010). In addition, advanced cognitive functioning may facilitate the practice of goal-directed behavior, thus enabling these individuals to plan and initiate suicide attempts (Verma et al. 2016). These findings suggest that greater insight and higher executive functioning may be associated with a greater risk of lifetime suicide attempts in this population, through increased awareness of the impact of the disorder and related increased psychological burden (Verma et al. 2016).

Other research further explores the potential association between suicidal behavior and cognitive ability. For example, Delaney et al. (2012) compared neurocognition in suicide attempters and ideators with schizophrenia or schizoaffective disorder, speculating that observed differences in neurocognition may be related to variations in suicidal behavior. They found that suicide attempters and ideators did not differ in neuropsychological performance on tasks assessing episodic memory, working memory, or attentional control. However, these groups (attempters and ideators) significantly outperformed individuals without a history of either a suicide attempt or ideation on the same neuropsychological measures. These results demonstrate that suicidal ideation and a single lifetime suicide attempt appear to both relate to improved neurocognition in psychotic disorders. Kim et al. (2003) conducted a similar study, assessing the relationship between suicidality and measures of cognitive dysfunction (including hopelessness and insight) in this population. They found that schizophrenia patients with a lifetime history of suicidality exhibited increased cognitive function; specifically, those with a history of suicide performed better on tasks of psychomotor speed, attention, verbal working memory,

verbal fluency, verbal memory, and executive function. Villa et al. (2018) directly assessed the relationship between insight, self-reflection, and suicidal behavior in schizophrenia. In this study, global cognitive ability, verbal learning, and working memory were associated with higher rates of suicidal ideation. These studies provide evidence for an association between neurocognition and suicidality in schizophrenia and related disorders, with improved neurocognitive function related to a range of suicidal behaviors. Taken together, this suggests that greater mental capacity may increase psychosocial burden of the disease; combined with an improved ability to carry out goal-directed behavior, this facilitates suicidal behaviors (Delaney et al. 2012; Verma et al. 2016; Villa et al. 2018).

Despite compelling empirical evidence that supports an association between neurocognition and suicide in these disorders, the exact nature of this relationship is unclear. In addition, some studies still fail to find any association between the factors of suicide and cognition; therefore, the association is still under speculation. For example, Stip et al. (2017) measured suicidal ideation and cognitive ability in 30 patients with schizophrenia and found that suicidal ideation was associated with cognitive dysfunction. This is in direct opposition to the association with *increased* cognitive performance found in other studies (see Villa et al. 2018; Vrbova et al. 2017b). Another study that investigated differences in intelligence quotient (IQ) and neurocognition in suicide attempters versus non-attempters found no association (Barrett et al. 2011). Additionally, the study by Villa et al. (2018) found no association between passive suicidal ideation and cognitive ability or insight (as distinct from the positive association between cognitive ability, insight, and history of suicidal ideation, described above). In this same study, history of planned suicide attempts was associated with greater verbal learning, while a history of aborted attempts was associated with poorer reasoning and problem-solving (Villa et al. 2018). These conflicting results further emphasize the complexity of the association between neurocognitive ability, insight, and the suicidal process in schizophrenia spectrum disorders.

2.3 Borderline Personality Disorder

It is well-known that borderline personality disorder (BPD) is highly correlated with suicidal behavior: one in ten BPD patients will complete suicide and about 75% of sufferers will engage in self-injurious behavior (LeGris and van Reekum 2006). Recent findings have revealed that neurocognitive deficits may hasten the progression from suicidal thoughts to behavior (Saffer and Klonsky 2018), and thus it is believed that an understanding of neurocognition in BPD may lead to greater clarification of its links with suicidal behavior. While extensive research has been conducted on neurocognitive processes of schizophrenia and attention-deficit/hyperactivity disorder (ADHD), the role of neurocognitive deficits as it relates to suicidal behavior in BPD remains unclear (LeGris and van Reekum 2006).

Cognitive deficits in BPD associated with hyperarousal may relate to progression along the suicidal process. BPD is characterized by hypersensitivity to emotional stressors and emotion dysregulation (Soloff et al. 2017). Negative life events have been shown to trigger episodes of affective instability and behavioral disinhibition that are often characterized by impulsive aggression and suicidal and/or self-injurious behavior and are associated with high-lethality suicide attempts in individuals with BPD (Brodsky et al. 1997; Cackowski et al. 2014; Soloff et al. 2017; Yen et al. 2004). Under behavioral disinhibition (an inability to resist impulsive behavior), individuals with BPD may be more prone to aggressive self-destructive behavior in place of destructive behavior towards others (Cackowski et al. 2017). When compared to individuals with ADHD alone (a disorder characterized by behavioral disinhibition and related issues with impulsivity), individuals with BPD with or without ADHD showed significant stress-induced increases in self-reported state impulsivity (Krause-Utz et al. 2013). In BPD, impulsive behavior primarily occurs under acute stress; it has even been suggested that impulsive behavior in non-stressful conditions may be related to comorbid ADHD (see Krause-Utz et al. 2013). Related to impulsivity, individuals with BPD often display delay discounting, wherein the value of a reward is decreased with a delay in receipt of the reward; this is independent of comorbid ADHD and occurs even in the absence of acute stress (Krause-Utz et al. 2016).

Research into the neurological underpinnings of behavioral disinhibition, emotion dysregulation, and impulsivity under acute stress has revealed a key role for limbic hyperarousal and decreased cortical activation (Soloff et al. 2017). In stressful situations, individuals with BPD may become emotionally dysregulated to the point that it interferes with cognitive abilities key to making adaptive responses to negative life events, such as response inhibition, decision-making, directed attention, planning, and goal-directed behavior (Soloff et al. 2017). Affective interference with executive function facilitates emotion dysregulation. This combined with a lack of behavioral control ultimately contributes to suicidal and self-injurious behavior in individuals with BPD; increasing lethality of attempt is associated with decreased activation of the anterior cingulate cortex (ACC) during negative picture viewing, a region associated with key cognitive processes involved in impulse control, emotion, and decision-making (Soloff et al. 2017). Cognitive impairments predominantly associated with the dorsolateral prefrontal cortex (key in higher-order cognitive processes such as inhibitory control, working memory, and switching attention) have been shown to exist in BPD and may represent an important pathway to suicidal behavior (LeGris and van Reekum 2006). Impaired decision-making in suicide attempters and individuals with BPD may represent a shared inhibitory pathway (Bazanis et al. 2002; Dougherty et al. 1999; Dowson et al. 2004; Jollant et al. 2005). Specifically, individuals with BPD may exhibit disinhibited responses and poor planning, indicated by longer deliberation times, selecting the most unlikely outcomes, making a greater number of attempts, and placing earlier bets on whether their choices were correct in a decision-making task (Bazanis et al. 2002).

Some research suggests similar deficits in specific cognitive domains in both individuals with BPD and suicide attempters. Keilp et al. (2001) conducted a

comprehensive comparison of high- and low-lethality suicide attempts and found that high-lethality subjects performed more poorly on all tests of executive function compared to all other groups and were the only group to perform significantly worse on tests of general intellectual functioning, attention, and memory. A meta-analysis by Ruocco (2005) noted that BPD individuals performed poorly compared to controls across a series of neurocognitive domains, including attention, cognitive flexibility, learning and memory, planning, processing speed, and visuospatial abilities (Fincham et al. 2002; Lezak et al. 2004). This meta-analysis implicated executive function deficits in BPD that are similar to those which have been found in suicide attempters; however, it also suggests that these deficits are somewhat selective. However, others have found minimal to no impairment for BPD participants across a variety of neuropsychological domains (McClure et al. 2015; Moritz et al. 2011; Sprock et al. 2000).

It is difficult to conclude that both suicide attempters and individuals with BPD have identical cognitive deficits. There are issues with neuropsychological measures used to assess cognition in each case, the heterogeneous nature of BPD, and the high rates of comorbidity that are found among BPD patients. BPD is often comorbid with anxiety, depression, other Axis I, ADHD, substance use disorders, learning disorders, and medication effects, all of which are known to independently affect neurocognitive performance (LeGris and van Reekum 2006). Regardless, it seems that cognitive disinhibition and executive dysfunction secondary to emotional dysregulation may be a pathway from BPD to the suicidal process.

2.4 Transdiagnostic Effect of Cognition on Suicide

Mental disorders in general are strongly associated with suicidality, and this association seems to be mediated by a common psychopathological predisposition rather than by the singular disorder itself (Hoertel et al. 2015). Neurocognitive abnormalities in general psychiatric populations have been identified since the very first stages of the mental illness, including deficits in processing speed, working memory, attention, and problem-solving (Romanowska et al. 2018). Intelligence does not seem to be associated with suicide, with controversial findings showing association with both high and low QI as well as no association at all (Weiser et al. 2017). On the other hand, there are several components of cognition that seem to increase the risk for suicidal behaviors across psychiatric disorders.

In a recent study investigating the link between cognition and suicidality among prison inmates, cognitive deficits (in sustained attention, task switching, working memory, and processing speeds) were the strongest predictor of suicidal risk and lifetime suicide attempt, regardless of current or past psychiatric diagnosis (Vadini et al. 2018). Impairments in cognitive flexibility, meant as the individual's adaptability to switch between thought in different settings, have been studied as a potential vulnerability factor for suicide in psychiatric populations. Recent studies suggest that a lack in cognitive flexibility may be related to hopelessness and

negative expectations about the future, both associated with suicidality. The nonlinear association between cognitive flexibility and hopelessness found in other studies (wherein increased hopelessness was associated with decreases in cognitive flexibility, while low hopelessness was not related to cognitive flexibility; Yu and Lee 2016) may be explained by other mediating factors such as rumination. Miranda and colleagues suggested the existence of an indirect path between cognitive inflexibility and brooding, between brooding and hopelessness, and between hopelessness and suicidal ideation (Miranda et al. 2013). Brooding rumination showed an association with suicidal ideation and attempts through agitation, insomnia, and nightmares, suggesting overarousal as a potential link between rumination and suicidality among psychiatric outpatients (Rogers et al. 2017). Moreover, reflective rumination was associated with suicidal ideation only among suicide attempters, compared to non-attempters (Surrence et al. 2009).

Repetitive negative thinking has been addressed as a transdiagnostic vulnerability factor for suicide (Law and Tucker 2018). Repetitive negative thinking can also be associated with executive functioning (EF); EF deficits can lead to a wide range of difficulties, including trouble controlling emotions, thoughts, and actions. In addition, deficient EF may be related to difficulty controlling thoughts related to self-harm or to difficulty switching to more positive or adaptive thinking in response to stress. EF in suicidal subjects seem to differ across psychiatric disorders, with several studies suggesting lower EF performances in the general psychiatric population and in depressive-like disorders, but even higher EF performances in psychotic disorders (Bredemeier and Miller 2015). The most common cognitive measures assessed in those studies reporting a significant negative relationship between EF performances and suicidality focused on inhibition and shifting. It's interesting to note that cognitive distortions seem to be significantly associated with suicide attempts over and above hopelessness or depressive symptoms (Jager-Hyman et al. 2014).

In sum, almost all suicide victims suffer from psychiatric disorders, and cognitive abnormalities may represent a transdiagnostic endophenotype of suicidality. In one study, suicidal cognitions (cognitive distortions related to suicide) accounted for almost 40% of the variance in predicting suicidal ideation after discharge (Rufino and Ellis 2017). The major links between suicidal behavior and cognitive deficits seem to include attentional biases, cognitive inflexibility, impulsivity, as well as impairments in problem-solving and decision-making (da Silva et al. 2018). Cognitive distortions, such as hopelessness, may have a direct association with suicidality, while neurocognitive deficits (e.g., impaired problem-solving, rigidity) may have an indirect one, through their contribution to the development of cognitive distortions (Fazakas-DeHoog et al. 2017). Although cognitive intervention in psychiatric populations has already been shown to reduce suicidality (see Sher and Kahn 2019), further studies are needed to improve the therapeutic strategies and cognitive targets.

3 Cognitive Domains and Suicide

3.1 Overall Cognitive Ability

Empirical studies of global cognitive ability and the suicidal process are relatively limited, as studies typically focus on distinct cognitive domains, such as executive function and processing speed. The link between cognitive ability and the suicidal process is still unclear, with links between worse cognitive performance and suicide risk in some populations (depression; Pu et al. 2017), yet links between improved performance and suicide risk in others (schizophrenia; Vrbova et al. 2017b). In a recent meta-analysis, Saffer and Klonsky (2018) found only a small effect size in the difference between ideators and non-suicidal controls on measures of global cognitive functioning (Mini-Mental Status Examination and Dementia Rating Scale) and no significant differences between attempters and ideators on the same measures. Allen et al. (2019) suggest that overall neurocognitive dysfunction may be a common pathway explaining the influence of common risk factors on the suicidal process. Indeed, others have found that worse general cognition/intellect may be a common risk for suicidal *behavior*, irrespective of diagnosis (Canal-Rivero et al. 2018; Ho et al. 2018; Naifeh et al. 2017), while improved cognition/intellect may be a risk factor for suicidal *ideation* (Saffer and Klonsky 2018). As discussed in Allen and colleagues' review (2019), further research is needed to tease out how global cognitive ability is related to the entire "spectrum of suicidality."

3.2 Intelligence

The link between intelligence and suicide has been examined for decades with conflicting results, including associations between both low intelligence (Abel and Kruger 2005; Gunnell et al. 2005) and high intelligence (Voracek 2004, 2006) with increased risk of suicide, as well as a lack of association (Park et al. 2015). Saffer and Klonsky (2018) recently reviewed the literature comparing suicide ideators and attempters on intelligence, including 14 studies. Their results suggest overall higher full-scale IQ for ideators than non-suicidal individuals, as measured by the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), and Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI- II). They found no difference between attempters and ideators, except on premorbid IQ, with attempters showing slightly worse performance than ideators. The authors provided three interpretations for these findings. One is that there is no relation between intelligence and suicide. Another interpretation is that suicidal behavior requires both insight into the situation and planning; with severe cognitive impairment, individuals would neither be aware of their environment (which may be toxic enough to confer increased risk for suicide) nor be able to carry out a suicide attempt if they wished to. Lastly, in

recognition of previous mixed findings, intelligence might act as a moderator of other risk factors to suicide.

Either way, future research will need to be more fine-grained in their approach, as broad full-scale IQ likely is insufficient to elucidate the complexities of the relations between the construct of intelligence and the range of behaviors included in the suicidal process. In order to best examine these links, a comprehensive, valid conceptualization of intelligence will be required. There is rich debate in the field on how best to conceptualize intelligence, with arguments for (e.g., Gottfredson 2016) and against (e.g., Kan et al. 2019) a latent *g* factor for explaining intelligence. We offer up the following research-based three-factor Cognitive Performance Model (Taub and McGrew 2014) to help organize the literature on the hierarchical latent structure of intelligence; however, we refer readers to Kan et al. (2019) for evidence for and a discussion of the mutualism model of intelligence, which has important implications for future research in intelligence.

3.3 Executive Function

Executive functioning (EF) encompasses a series of cognitive traits that have an influence on one's ability to accomplish goals and in general guiding behavior to reach a goal (Bredemeier and Miller 2015). This includes reasoning and problem-solving, planning behavior, switching or cognitive flexibility, monitoring one's performance, and inhibiting inappropriate responses or behavior (Burton et al. 2011; Marzuk et al. 2005). When comparing healthy volunteers to individuals with suicidal ideation or history of suicide attempts, both groups performed slightly worse than average on overall EF compared to healthy controls. Attempters showed greater executive functioning and worse response inhibition as compared to ideators (Burton et al. 2011). A meta-analysis of 43 studies confirmed the association between suicidal behavior and deficits in EF (Bredemeier and Miller 2015; Jollant et al. 2005; Keilp et al. 2001; McGirr et al. 2012; Richard-Devantoy et al. 2013; Swann et al. 2005). However, the relationship between EF deficits and suicide varies between diagnostic groups and is influenced by other factors, such as the seriousness or lethality of the attempt (Bredemeier and Miller 2015). While deficits in EF were related to suicidal behavior in those with mood disorders, no association was found in those with psychosis spectrum disorders, with evidence suggesting that it may even be associated with improved EF (Bredemeier and Miller 2015).

There are differences across the lifespan in the relationship between EF and suicidal behavior. Adolescents with a history of suicide attempt display difficulty in EF, performing worse than adolescents with depressive disorders without a history of suicide attempt (Marzuk et al. 2005). However, in older adults executive dysfunction (and related cognitive impairment) is not directly related to suicidal ideation or suicide attempts; this is despite increasing lethality of suicide attempts in older populations (Gujral et al. 2014; O'Riley et al. 2014). In addition, older adults with a history of suicide attempt display greater difficulty in problem-solving as

compared to both euthymic and depressed older adults (Clark et al. 2011; Gibbs et al. 2009; Howat and Davidson 2002).

The link between executive dysfunction and suicidal behavior is likely related to rumination or brooding, as previously mentioned in this chapter. Those with executive dysfunction may have a hard time controlling suicidal impulses and less ability to switch from negative to positive thoughts, in addition to difficulty with problem-solving and predicting future outcomes (Polanco-Roman et al. 2015). These in turn may lead to helplessness, which as we know is an important factor in the suicidal process. On the other hand, difficulty planning may impede the ability to successfully plan and carry out a suicide attempt, which may explain the link between improved EF and suicide attempts in psychotic disorders discussed earlier. However, others have found that cognitive impairments alone are not associated with increased suicidal ideation (Harris and Barraclough 1997; Haw et al. 2009).

While not discussed here, there are important factors relating to brain health and function in various disorders related to suicidal behavior that may affect the role of EF. For example, decreased brain volume in the prefrontal cortex is associated with both executive dysfunction and suicidal behavior (see (Sudol and Mann 2017). In addition, computational cognitive models have allowed researchers to isolate decision-making biases in suicidal individuals. Millner et al. (2019) recently found that suicidal psychiatric patients demonstrated decision-making biases in response to aversive stimuli. When asked to choose between active or passive (go or no-go) responses, suicidal individuals showed a greater bias towards actively escaping negative stimuli rather than passively escaping, in comparison to a group of non-suicidal individuals.

3.4 Processing Speed

Processing speed is defined as the duration of time required to process a stimulus and generate a response. In addition to being a cognitive domain, processing speed is a key predictor of cognitive function (Foong et al. 2018). For example, targeted processing speed training has been shown to improve overall cognitive ability, and a large amount of the natural cognitive decline that is associated with age can be attributed to a decline in processing speed (Foong et al. 2018).

Few studies have examined the role of processing speed in suicidal ideation and behavior. Vadini et al. (2018) examined associations between specific subdomains of cognition and suicidal behavior in prison inmates. The neuropsychological battery administered to subjects included assessments of attention, task switching, working memory, and processing speed. They found that subjects with high suicide risk and overall suicide risk performed worse on assessments of all aspects of cognition, including processing speed, compared to those with no suicide risk (Vadini et al. 2018).

Researchers have also investigated the association between processing speed and suicidal behavior in subjects with various psychiatric disorders. Notably, Pu and

colleagues examined this relationship in patients with major depressive disorder (MDD) using the Brief Assessment of Cognition in Schizophrenia (BACS) which is an extensive neuropsychological battery that assesses verbal memory, working memory, motor speed, verbal fluency, attention, processing speed, and executive function (Pu et al. 2017). Patients with suicidal ideation scored worse on the BACS compared to patients without suicidal ideation and displayed similar differences in processing speed; however, these differences did not approach significance. Processing speed was found to be negatively correlated with suicidal ideation ($r = 0.09$), indicating that decreased processing speed was associated with an increase in suicidal ideation; however, this was not statistically significant (Pu et al. 2017). Furthermore, Comparelli et al. (2018) found that schizophrenia patients with suicidal ideation scored lower than patients without suicidal ideation on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery, which includes an assessment of processing speed.

Overall, the association between processing speed and suicidal behaviors remains unclear and requires further investigation. The literature looking specifically at processing speed is limited compared to the research examining executive functioning or cognitive performance as a whole. As a result, more research needs to be done in this area to elucidate the association between suicidal behavior and processing speed, which again may play a pivotal role in this relationship.

3.5 Memory

Increasing literature has demonstrated that individuals who have engaged in suicidal behavior exhibit impairments in memory (Dombrovski et al. 2008; Giner et al. 2016; Gujral et al. 2015; Keilp et al. 2013, 2014). These impairments impact the ability to develop long-term perspectives and the ability to solve problems, thereby facilitating suicidal acts (Richard-Devantoy et al. 2014). Considering that memory is complex and is comprised of different processes, there has been great variability in the manner of which memory has been defined and assessed by researchers. A review by Richard-Devantoy et al. (2014) identified four aspects of memory which have most commonly been measured in the literature evaluating cognitive functioning and suicidal processes: short-term memory, long-term memory, working memory, and autobiographical memory. Short-term memory is defined as temporarily storing small amounts of information in the mind, while long-term memory is defined as storing larger amounts of information in the mind for an extended period of time. Working memory refers to holding and manipulating pieces of transient information in the mind, and autobiographical memory involves collecting, storing, and retrieving information about an individual's life and personal experiences (Richard-Devantoy et al. 2014). Research has demonstrated that individuals who have attempted suicide exhibit impaired long-term and working memory when compared to patient populations and healthy controls who have not attempted suicide (Richard-Devantoy et al. 2014). However, this does not seem to be the case in patients

diagnosed with schizophrenia, as individuals diagnosed with schizophrenia who have attempted suicide appear to exhibit intact memory (Delaney et al. 2012). This is particularly surprising given that verbal memory and working memory are very commonly impaired in schizophrenia (e.g., Fatouros-Bergman et al. 2014). Further, research evaluating the impact of memories related to suicide (witnessing a suicide behavior of a relative or peer) found that individuals who have attempted suicide significantly recalled more memories of being exposed directly to suicide (Ventrice et al. 2010). This suggests that being directly exposed to suicidal acts, such as finding the dead person, may increase an individual's vulnerability to suicidal behavior (Ventrice et al. 2010).

3.6 Attention

Attention refers to how an individual processes incoming or attended-to information and is an important component of cognitive functioning (Lezak et al. 2004). Impairments in attention may be associated with suicidal constructs. Research has indicated that, compared to individuals who have never engaged in suicidal behaviors, patient populations who have had a suicidal attempt or have exhibited suicidal ideation demonstrated greater impairments in attention (Dombrovski et al. 2008; Juven-Wetzler et al. 2014; Keilp et al. 2013, 2014). However, not all available data support this conclusion, as some researchers have not found any significant differences in performance on attention tasks between individuals who have engaged in suicidal behaviors and those who have not (Gilbert et al. 2011; Saffer and Klonsky 2018). These inconsistencies may be due in part to the differences in measures used to assess attention, as studies have utilized tasks such as the Attention Network Task (Posner 1980), Continuous Performance Tests (CPT), Mattis Dementia Rating Scale (DRS; Mattis 1988), Wechsler Adult Intelligence Scale (WAIS), Digit Span (Wechsler 2008), and Stroop tasks which may all measure different aspects of attention. Moreover, the discrepancy in results may also be due to the heterogeneity of populations studied, which include patients of varying ages (adolescents, adults, and older adults, and diagnoses, i.e., depression, bipolar disorder, borderline personality disorder, schizophrenia; Barrett et al. 2011; Dombrovski et al. 2008; Gilbert et al. 2011; Gujral et al. 2015; Kim et al. 2003; Lara et al. 2015; LeGris and van Reekum 2006; Nangle et al. 2006; Olié et al. 2014; Olsson et al. 2016; Sommerfeldt et al. 2015). Moreover, studies on attentional bias have suggested that individuals with a history of attempted suicide likely attend more to suicidal thoughts and suicide-related information in their environment than patient and control populations who have not attempted suicide (Richard-Devantoy et al. 2017). Research has demonstrated that suicide attempters not only take longer to name suicide-related words on modified Stroop tasks than non-attempters, but they also take longer to name suicide-related words in comparison to neutral, positive, or negative words (Becker et al. 1999; Cha et al. 2010; Richard-Devantoy et al. 2017).

There is also evidence of implicit associations with death (as compared to life) in suicidal individuals, indicative of more automated attentional processes. Nock and Banaji's (2007) Self-Injury Implicit Association Test (SI-IAT) was able to distinguish between non-suicidal individuals, ideators, and attempters; results indicated that suicidal individuals may implicitly identify with self-injury irrespective of self-injurious behavior. Researchers have also found a significant association between performance on a modified "Death/Life" Implicit Association Test (d-IAT) and self-reported suicidal behavior, over and above self-reported risk for suicide (Podlogar et al. 2019). The implicit association with death in particular may be influenced by mood in ideators but not in non-suicidal controls, and association with death was predictive of suicidal ideation 6 months later (Cha et al. 2018).

Interestingly, while attention may be impaired in individuals who have engaged in suicidal behaviors across various diagnoses, it appears that attentional processes may be improved in individuals diagnosed with schizophrenia or other psychotic disorders who have attempted suicide. Several studies evaluating patients diagnosed with schizophrenia with a history of lifetime suicidality have found that they perform better on tasks of attention than patients without a lifetime history of suicidality (Barrett et al. 2011; Kim et al. 2003; Nangle et al. 2006). Psychotic disorders are generally associated with cognitive impairment; however, it may be that relatively intact cognitive functioning, such as attentional processes, is necessary to formulating plans for and initiating goal-directed behaviors such as attempting suicide (Barrett et al. 2011; Nangle et al. 2006).

Overall, it appears that attention may be associated with suicide attempts and suicidal ideation. However, due to the limited research specifically evaluating attentional and suicidal processes, the relationship between these constructs has yet to be elucidated.

3.7 Social Cognition

Social cognition refers to the neural processes utilized by individuals to engage with people around them (Frith and Frith 2007). These processes include recognizing, interpreting, and responding to verbal and nonverbal social cues. Impairments in social cognition have been implicated in numerous psychiatric conditions, including psychotic disorders, mood disorders such as depression, and personality disorders such as borderline personality disorder (Canal-Rivero et al. 2017). This section regards the role of social cognition in suicidality.

Research has shown that social connectedness is protective against suicide. Conversely, across demographic factors, social isolation is one of the strongest predictors of suicidal ideation and attempts (Conwell 1997; Dervic et al. 2008; Joiner and Van Orden 2008; Van Orden et al. 2010). According to the Interpersonal Theory of Suicide, risk for suicide is linked to an unmet "need to belong" (Van Orden et al. 2010). Social cognitive deficits may impair individuals' ability to form strong social connections with others, as evidenced in disorders including autism and

schizophrenia (Couture 2006; Hughes et al. 1997; Klin et al. 2002; Pinkham et al. 2003, 2008). Recent research assessing social cognition and suicide in veterans provides insight into how specific social cognitive impairments may impair social connectedness and increase suicide risk. Bulbena-Cabre, Fred-Torres, and colleagues found that veterans at high risk for suicide exhibited more errors in hypomentalization than the low-risk group, suggesting that specific social cognitive deficits may increase suicide risk through their detrimental effect on social relationships and connectedness (Bulbena-Cabre et al. n.d.).

Impairments in social cognition have been implicated in suicidality in psychotic disorders. King et al. (2000) assessed the role of social cognition in suicidality among 65 patients with first-episode psychosis. One metric included is theory of mind, which refers to a person's ability to comprehend the mental state of oneself and other individuals. Theory of Mind was evaluated using two false-belief stories and tasks. The study found that suicide attempts were associated with impairments in Theory of Mind, as measured by a first-order false belief task (OR = 4.26, 95% CI = 1.05–17.31).

Deficits in social cognition have also been linked to suicidality in patients with mood disorders such as major depression. One study found that among 90 older adults with depression, those who had attempted suicide showed greater impairment in emotion recognition (Szanto et al. 2012). Suicide attempters were also more likely than non-suicidal older adults to lack strong social networks and to have difficulty with problem-solving related to social interactions. Another study involved 391 adolescents hospitalized in inpatient psychiatric settings. 50.1% of the study population were diagnosed with a mood disorder, and 52.2% were diagnosed with an anxiety disorder. Excessive, distorted Theory of Mind was significantly associated with suicide attempt in the past year and suicidal ideation in the past 4 weeks (Hatkevich et al. 2019). Reduced Theory of Mind was significantly associated with lifetime suicide attempt, in addition to past 4 week and past year suicidal ideation. These findings provide insight into the role of social cognition in suicidality among individuals with mood and anxiety disorders.

Further research demonstrates the role of social cognition in suicidality in borderline personality disorder. Williams et al. (2015) found that impairments in social cognition were associated with self-injurious behavior that required medical attention and was potentially lethal. Individuals who exhibited such behavior experienced deficits in emotion recognition and discrimination of facial expressions.

It appears that social cognition plays a role in suicidal behavior across multiple psychiatric conditions. Further research would be helpful in providing greater insight into this relationship, which could also better inform future interventions and treatment.

4 Neurocognition and Specific Suicidal Behaviors

4.1 Comparing Ideators and Attempters

4.1.1 Attempters vs. Ideators

Neurocognitive deficits that differentiate suicidal ideators from suicide attempters have been the focus of various studies, as they are theorized to hasten the progression from suicidal thoughts to behaviors (Saffer and Klonsky 2018). In general, it is believed that the risk factors for suicidal ideation may be distinct from those of suicide attempt (Klonsky and May 2013; May and Klonsky 2016). A meta-analysis of 14 studies measured the effect size of differences between attempters and ideators across neurocognitive domains (Saffer and Klonsky 2018). They found that neurocognitive differences were negligible to small on most of the neurocognitive tasks (including those measuring intelligence, processing speed, memory, attention, cognitive flexibility, verbal fluency). However, two subdomains of executive functioning showed medium effect sizes; attempters scored significantly worse on both decision-making and inhibition than ideators. Interestingly, ideators did not differ significantly from non-suicidal controls on these measures. The authors note that definitive conclusions cannot be drawn due to the small number of studies, the limitations of these studies, and the methodological variation among them.

4.1.2 Ideators vs. Non-suicidal Controls

In the same review, it was demonstrated that ideators perform worse than non-suicidal psychiatric controls on measures of processing speed, whereas attempters performed slightly better than ideators, although still worse than controls. This suggests that impaired processing speed might be more closely related to suicidal ideation than to suicide attempt (Saffer and Klonsky 2018).

4.1.3 Attempters vs. Non-suicidal Controls

Among suicide attempters, the main findings in the literature suggest higher attention to specific emotional stimuli (in modified Stroop; bias towards suicide-related versus positive, neutral, and negative words), impaired decision-making, lower problem-solving abilities, reduced verbal fluency, and impaired reward/punishment reversal learning compared to non-suicidal controls (Becker et al. 1999; Jollant et al. 2011; Williams and Broadbent 1986). Several studies suggest that these neurocognitive abnormalities are independent of comorbid psychiatric disorder (Jollant et al. 2011). Impairment in executive function, which could not be fully accounted for by psychiatric disorders and psychological stress, has been found to be associated with a history of suicide attempt (Bredemeier and Miller 2015). Results

from various studies have shown that individuals with a history of suicide attempt present an attentional bias towards suicide-related words (Becker et al. 1999; Nock and Banaji 2007).

Suicide attempters also seem to have an impaired ability to assign value to external events. This has been suggested by a study that showed suicide attempters had a significantly greater response to angry faces in the ventrolateral prefrontal cortex (Jollant et al. 2008). This study also showed reduced response during risky vs. safe choices associated with poor decision-making in the same region. The inability to assign adequate value to long-term risk is a key cause of poor decision-making in attempters (Jollant et al. 2011). Additionally, the lateral orbitofrontal cortex may be implicated in signaling predicted value of expected outcomes in a given situation; in the suicidal process, alterations in this pathway may be involved in decision-making impairments and sensitivity to social stimuli (Jollant et al. 2011; Schoenbaum et al. 2009).

4.2 First-Degree Relatives of Suicide Attempters

Suicidal behaviors, including suicide ideation, planning, attempt, and completion, aggregate in families (Brent 1996) and seem to have a high rate of heritability, with a risk of suicide attempts increased by ten times among suicide's relatives (Kim et al. 2005).

The heritability of familial traits seems to include several cognitive deficits in decision-making that may account for the higher rate of suicidal behaviors among parents and siblings. Several studies reported a heritability of decision-making of up to 46% in certain periods of life (Tuvblad et al. 2013). Ding and colleagues, investigating the neural basis of decision-making in first-degree relatives of suicide completers, found an increased activation in medial orbitofrontal cortex and right dorsomedial prefrontal cortex during risky choices compared to healthy controls, along with a decreased activation during safe choices (Ding et al. 2017). They suggested that this impairment in the orbitofrontal cortex may lead to dysfunctional decision-making, thus representing a neurocognitive endophenotype of suicide. In another paper, Hoehne et al. (2015) assessed cognitive deficits in first-degree relatives of suicide attempters/completers with no personal history of suicidal behaviors, excluding confounding factors such as major depressive disorder. They discovered worse decision-making in the Iowa Gambling Test compared to controls. They also noticed a lower ability in improving score performance (i.e., adapting to their performance by changing their behavior or strategy) among subjects who eventually exhibited suicidal acts. Both factors seem to be partially heritable and may predispose individuals to suicidal behavior.

In a recent paper on a large population of young subjects, a significant association was found between suicidal ideation and inherited single nucleotide polymorphisms (SNPs) correlated with the speed in emotion identification (Brick et al. 2019). The rate of heritability was 24% for executive functioning and 23% for complex

cognition. They also suggested that abnormalities in memory (e.g., episodic memory) and in emotional recognition (e.g., increased sensitivity to angry faces at emotion identification task and attentive difficulties in processing positive stimuli) may be related to subject's hypersensitivity to disapproval from others, eventually compromising decision-making processes and leading to suicidal acts.

From a biological point of view, stressful events usually trigger a transient activation of the hypothalamus-pituitary axis (HPA) that, if appropriate in intensity and length, can be beneficial to physiologic response to stress (Sapolsky 2000). Relatives of suicide victims seem to be unable to mount a transient stress response along with showing a deficit in cognitive inhibition (McGirr 2010). In a more recent analysis (McGirr et al. 2013), healthy first-degree relatives of suicide completers exhibited deficits in cognitive control, displaying more frequent perseverative errors and lower conceptual responses while performing the Wisconsin Card Sorting Test, of which lower scores have been associated with suicidal behaviors.

Suicidality tends to aggregate not only in families sharing the same bloodline but even in adopted children, suggesting the existence of environmental factors increasing the vulnerability to engage in suicidal acts. According to Brent and colleagues, while imitation hasn't proven so far to be the most significant mechanism through which suicidality is transmitted to the offspring of suicidal parents, impulsivity and aggression can be transmitted, acting as vulnerability factors (Brent and Melhem 2008). Moreover, the relationships in a suicidal individual's family may be compromised, eventually leading to altered cognitive development; the resultant poor self-esteem, depressive traits, and increased neuroticism and impulsivity act as vulnerability factors for suicide. Cognitive vulnerability within suicidal families may also include the Hopelessness Theory, according to which there may be negative inferential styles worsening the individual's perception of life, and the Response Style Theory, such as brooding rumination, both of them showing a controversial association to suicidality (Tsypes and Gibb 2016).

5 Conclusions

The field of suicidology as it relates to cognition has made great strides since Shneidman's analysis of suicide notes. Since that time, researchers have characterized the role of hopelessness and negativistic thinking, cognitive rigidity, impulsivity, and altered emotional processing in the suicidal process across a variety of disorders. In addition, with the emergence of discrete neurocognitive domains, we have been able to parse out the moderators of these cognitive factors, including executive functioning, processing speed, memory, social cognition, and attention. Overall, findings support the idea that worse cognitive performance, executive dysfunction, slower processing speed, and biases in memory and attention, all related to suicidal ideation and behavior (albeit with mixed results in schizophrenia spectrum disorders and older populations). A number of theories have emerged that can account for common risk factors and cognitive processes, and with advances in

the field of neuroscience, the links to neurobiology are slowly coming to light. Further research is needed to elucidate the complex interplay between environment and individual factors, cognition, and neurobiology.

References

Abel EL, Kruger ML (2005) Educational attainment and suicide rates in the United States. Psychol Rep 97(1):25–28. https://doi.org/10.2466/pr0.97.1.25-28

Abramson LY, Alloy LB, Hogan ME, Whitehouse WG, Cornette M, Akhavan S, Chiara A (1998) Suicidality and cognitive vulnerability to depression among college students: a prospective study. J Adolesc 21(4):473–487. https://doi.org/10.1006/jado.1998.0167

Allen KJD, Bozzay ML, Edenbaum ER (2019) Neurocognition and suicide risk in adults. Curr Behav Neurosci Rep. https://doi.org/10.1007/s40473-019-00189-y

Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK (2006a) A cognitive vulnerability–stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. Dev Psychopathol 18(04). https://doi.org/10.1017/s0954579406060524

Alloy LB, Abramson LY, Walshaw PD, Neeren AM (2006b) Cognitive vulnerability to unipolar and bipolar mood disorders. J Soc Clin Psychol 25(7):726–754. https://doi.org/10.1521/jscp.2006.25.7.726

Al-Mosaiwi M, Johnstone T (2018) In an absolute state: elevated use of absolutist words is a marker specific to anxiety, depression, and suicidal ideation. Clin Psychol Sci 6(4):529–542. https://doi.org/10.1177/2167702617747074

Baldessarini RJ, Tondo L, Pinna M, Nuñez N, Vázquez GH (2019) Suicidal risk factors in major affective disorders. Br J Psychiatry 215(04):621–626. https://doi.org/10.1192/bjp.2019.167

Barrett EA, Sundet K, Simonsen C, Agartz I, Lorentzen S, Mehlum L et al (2011) Neurocognitive functioning and suicidality in schizophrenia spectrum disorders. Compr Psychiatry 52(2):156–163. https://doi.org/10.1016/j.comppsych.2010.06.001

Bazanis E, Rogers RD, Dowson JH, Taylor P, Meux C, Staley C et al (2002) Neurocognitive deficits in decision-making and planning of patients with DSM-III-R borderline personality disorder. Psychol Med 32(8):1395–1405. https://doi.org/10.1017/s0033291702006657

Bechi M, Bosia M, Spangaro M, Buonocore M, Cavedoni S, Agostoni G et al (2017) Exploring functioning in schizophrenia: predictors of functional capacity and real-world behaviour. Psychiatry Res 251:118–124. https://doi.org/10.1016/j.psychres.2017.02.019

Beck AT (1963) Thinking and depression: I. Idiosyncratic content and cognitive distortions. JAMA Psychiat 9(4):324–333. https://doi.org/10.1001/archpsyc.1963.01720160014002

Beck AT (1996) Beyond belief: a theory of modes, personality, and psychopathology. In: Frontiers of cognitive therapy. The Guilford Press, New York, pp 1–25

Beck AT, Davis JH, Frederick CJ, Perlin S, Pokorny AD, Schulman RE et al (1973) In: Hathorne HRB (ed) Suicide prevention in the 70's. US Government Printing Office, Washington, pp 7–12

Beck AT, Kovacs M, Weissman A (1975) Hopelessness and suicidal behavior: an overview. JAMA 234(11):1146–1149. https://doi.org/10.1001/jama.1975.03260240050026

Beck AT, Kovacs M, Weissman A (1979) Assessment of suicidal intention: the scale for suicide ideation. J Consult Clin Psychol 47(2):343

Beck AT, Baruch E, Balter JM, Steer RA, Warman DM (2004) A new instrument for measuring insight: the Beck cognitive insight scale. Schizophr Res 68(2-3):319–329. https://doi.org/10.1016/s0920-9964(03)00189-0

Becker ES, Strohbach D, Rinck M (1999) A specific attentional bias in suicide attempters. J Nerv Ment Dis 187(12):730–735. https://doi.org/10.1097/00005053-199912000-00004

Brachman RA, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C et al (2016) Ketamine as a prophylactic against stress-induced depressive-like behavior. Biol Psychiatry 79(9):776–786. https://doi.org/10.1016/j.biopsych.2015.04.022

Bredemeier K, Miller IW (2015) Executive function and suicidality: a systematic qualitative review. Clin Psychol Rev 40:170–183. https://doi.org/10.1016/j.cpr.2015.06.005

Brent DA (1996) Suicidal behavior runs in families. Arch Gen Psychiatry 53(12):1145. https://doi.org/10.1001/archpsyc.1996.01830120085015

Brent DA, Melhem N (2008) Familial transmission of suicidal behavior. Psychiatr Clin N Am 31 (2):157–177. https://doi.org/10.1016/j.psc.2008.02.001

Brick LA, Marraccini ME, Micalizzi L, Benca-Bachman CE, Knopik VS, Palmer RHC (2019) Overlapping genetic effects between suicidal ideation and neurocognitive functioning. J Affect Disord 249:104–111. https://doi.org/10.1016/j.jad.2019.02.003

Brodsky BS, Malone KM, Ellis SP, Dulit RA, Mann JJ (1997) Characteristics of borderline personality disorder associated with suicidal behavior. Am J Psychiatr 154(12):1715–1719. https://doi.org/10.1176/ajp.154.12.1715

Brown GK, Jeglic E, Henriques GR, Beck AT (2006) Cognitive therapy, cognition, and suicidal behavior. In: Ellis TE (ed) Cognition and suicide: theory, research, and therapy. American Psychological Association, Washington, pp 53–74

Bulbena-Cabre A, Fred-Torres S, Harris R, Goodman M, New A, Perez-Rodriguez MM (n.d.) Abnormal social cognition among veterans at high risk for suicide

Burton CZ, Vella L, Weller JA, Twamley EW (2011) Differential effects of executive functioning on suicide attempts. J Neuropsychiatry Clin Neurosci 23(2):173–179. https://doi.org/10.1176/appi.neuropsych.23.2.173

Cackowski S, Reitz AC, Ende G, Kleindienst N, Bohus M, Schmahl C, Krause-Utz A (2014) Impact of stress on different components of impulsivity in borderline personality disorder. Psychol Med 44(15):3329–3340. https://doi.org/10.1017/s0033291714000427

Cackowski S, Krause-Utz A, Van Eijk J, Klohr K, Daffner S, Sobanski E, Ende G (2017) Anger and aggression in borderline personality disorder and attention deficit hyperactivity disorder – does stress matter? Borderline Personal Disord Emot Dysregul 4:6. https://doi.org/10.1186/s40479-017-0057-5

Canal-Rivero M, Lopez-Moriñigo JD, Barrigón ML, Perona-Garcelán S, Jimenez-Casado C, David AS et al (2017) The role of premorbid personality and social cognition in suicidal behaviour in first-episode psychosis: a one-year follow-up study. Psychiatry Res 256:13–20. https://doi.org/10.1016/j.psychres.2017.05.050

Canal-Rivero M, López-Moríñigo JD, Setién-Suero E, Ruiz-Veguilla M, Ayuso-Mateos JL, Ayesa-Arriola R, Crespo-Facorro B (2018) Predicting suicidal behaviour after first episode of non-affective psychosis: the role of neurocognitive functioning. Eur Psychiatry 53:52–57. https://doi.org/10.1016/j.eurpsy.2018.06.001

Cha CB, Najmi S, Park JM, Finn CT, Nock MK (2010) Attentional bias toward suicide-related stimuli predicts suicidal behavior. J Abnorm Psychol 119(3):616–622. https://doi.org/10.1037/a0019710

Cha CB, O'Connor RC, Kirtley O, Cleare S, Wetherall K, Eschle S et al (2018) Testing mood-activated psychological markers for suicidal ideation. J Abnorm Psychol 127(5):448–457. https://doi.org/10.1037/abn0000358

Chen M-H, Li C-T, Lin W-C, Hong C-J, Tu P-C, Bai Y-M et al (2018) Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. J Affect Disord 241:1–7. https://doi.org/10.1016/j.jad.2018.07.033

Chu C, Klein KM, Buchman-Schmitt JM, Hom MA, Hagan CR, Joiner TE (2015) Routinized assessment of suicide risk in clinical practice: an empirically informed update. J Clin Psychol 71 (12):1186–1200. https://doi.org/10.1002/jclp.22210

Clark L, Dombrovski AY, Siegle GJ, Butters MA, Shollenberger CL, Sahakian BJ, Szanto K (2011) Impairment in risk-sensitive decision-making in older suicide attempters with depression. Psychol Aging 26(2):321–330. https://doi.org/10.1037/a0021646

Comparelli A, Corigliano V, Lamis DA, De Carolis A, Stampatore L, De Pisa E et al (2018) Positive symptoms and social cognition impairment affect severity of suicidal ideation in schizophrenia. Schizophr Res 193:470–471. https://doi.org/10.1016/j.schres.2017.07.027
Conwell Y (1997) Management of suicidal behavior in the elderly. Psychiatr Clin N Am 20 (3):667–683. https://doi.org/10.1016/s0193-953x(05)70336-1
Couture SM (2006) The functional significance of social cognition in schizophrenia: a review. Schizophr Bull 32(Suppl 1):S44–S63. https://doi.org/10.1093/schbul/sbl029
da Silva AG, Malloy-Diniz LF, Garcia MS, Figueiredo CGS, Figueiredo RN, Diaz AP, Palha AP (2018) Cognition as a therapeutic target in the suicidal patient approach. Front Psych 9. https://doi.org/10.3389/fpsyt.2018.00031
Deisenhammer EA, Schmid SK, Kemmler G, Moser B, Delazer M (2018) Decision making under risk and under ambiguity in depressed suicide attempters, depressed non-attempters and healthy controls. J Affect Disord 226:261–266. https://doi.org/10.1016/j.jad.2017.10.012
Delaney C, McGrane J, Cummings E, Morris DW, Tropea D, Gill M et al (2012) Preserved cognitive function is associated with suicidal ideation and single suicide attempts in schizophrenia. Schizophr Res 140(1-3):232–236. https://doi.org/10.1016/j.schres.2012.06.017
Dervic K, Brent DA, Oquendo MA (2008) Completed suicide in childhood. Psychiatr Clin N Am 31(2):271–291. https://doi.org/10.1016/j.psc.2008.01.006
Diler RS, Goldstein TR, Hafeman D, Merranko J, Liao F, Goldstein BI et al (2017) Distinguishing bipolar depression from unipolar depression in youth: preliminary findings. J Child Adolesc Psychopharmacol 27(4):310–319. https://doi.org/10.1089/cap.2016.0154
Ding Y, Pereira F, Hoehne A, Beaulieu MM, Lepage M, Turecki G, Jollant F (2017) Altered brain processing of decision-making in healthy first-degree biological relatives of suicide completers. Mol Psychiatry 22(8):1149–1154. https://doi.org/10.1038/mp.2016.221
Dombrovski AY, Butters MA, Reynolds CF, Houck PR, Clark L, Mazumdar S, Szanto K (2008) Cognitive performance in suicidal depressed elderly: preliminary report. Am J Geriatr Psychiatry 16(2):109–115. https://doi.org/10.1097/jgp.0b013e3180f6338d
Dougherty DM, Bjork JM, Huckabee HCG, Moeller FG, Swann AC (1999) Laboratory measures of aggression and impulsivity in women with borderline personality disorder. Psychiatry Res 85 (3):315–326. https://doi.org/10.1016/s0165-1781(99)00011-6
Dougherty DM, Mathias CW, Marsh-Richard DM, Prevette KN, Dawes MA, Hatzis ES et al (2009) Impulsivity and clinical symptoms among adolescents with non-suicidal self-injury with or without attempted suicide. Psychiatry Res 169(1):22–27. https://doi.org/10.1016/j.psychres.2008.06.011
Dowson J, Bazanis E, Rogers R, Prevost A, Taylor P, Meux C et al (2004) Impulsivity in patients with borderline personality disorder. Compr Psychiatry 45(1):29–36. https://doi.org/10.1016/j.comppsych.2003.09.013
Ellis A (1957) Rational psychotherapy and individual psychology. J Individ Psychol 13:38–44
Ellis A (1973) Humanistic psychotherapy: the rational emotive approach. Julian Press, New York
Ellis TE (2006) The study of cognition and suicide: beginnings and developmental milestones. In: Ellis TE (ed) Cognition and suicide: theory, research, and therapy. American Psychological Association, Washington, pp 13–28
Ellis TE, Ratliff K (1986) Cognitive characteristics of suicidal and nonsuicidal psychiatric inpatients. Cogn Ther Res 10:625–634
Fatouros-Bergman H, Cervenka S, Flyckt L, Edman G, Farde L (2014) Meta-analysis of cognitive performance in drug-naive patients with schizophrenia. Schizophr Res 158(1-3):156–162. https://doi.org/10.1016/j.schres.2014.06.034
Fazakas-DeHoog LL, Rnic K, Dozois DJA (2017) A cognitive distortions and deficits model of suicide ideation. Eur J Psychol 13(2):178–193. https://doi.org/10.5964/ejop.v13i2.1238
Fincham JM, Carter CS, van Veen V, Stenger VA, Anderson JR (2002) Neural mechanisms of planning: a computational analysis using event-related fMRI. Proc Natl Acad Sci 99 (5):3346–3351. https://doi.org/10.1073/pnas.052703399
Firestone RW (1986) The “inner voice” and suicide. Psychotherapy 23:439–447

Firestone RW (1997) Suicide and the inner voice: risk assessment, treatment, and case management. Sage, Thousand Oaks

Foong HF, Hamid TA, Ibrahim R, Haron SA (2018) Information processing speed as a mediator between psychosocial stress and global cognition in older adults. Psychogeriatrics 18(1):21–29. https://doi.org/10.1111/psyg.12279

Frith CD, Frith U (2007) Social cognition in humans. Curr Biol 17(16):R724–R732. https://doi.org/10.1016/j.cub.2007.05.068

Gibbs LM, Dombrovski AY, Morse J, Siegle GJ, Houck PR, Szanto K (2009) When the solution is part of the problem: problem solving in elderly suicide attempters. Int J Geriatr Psychiatry 24 (12):1396–1404. https://doi.org/10.1002/gps.2276

Gilbert AM, Garno JL, Braga RJ, Shaya Y, Goldberg TE, Malhotra AK, Burdick KE (2011) Clinical and cognitive correlates of suicide attempts in bipolar disorder. J Clin Psychiatry 72 (08):1027–1033. https://doi.org/10.4088/jcp.10m06410

Giner L, Blasco-Fontecilla H, De La Vega D, Courtet P (2016) Cognitive, emotional, temperament, and personality trait correlates of suicidal behavior. Curr Psychiatry Rep 18(11). https://doi.org/10.1007/s11920-016-0742-x

Glashouwer KA, de Jong PJ, Penninx BWJH, Kerkhof AJFM, van Dyck R, Ormel J (2010) Do automatic self-associations relate to suicidal ideation? J Psychopathol Behav Assess 32 (3):428–437. https://doi.org/10.1007/s10862-009-9156-y

Gottfredson LS (2016) A g theorist on why Kovacs and Conway's process overlap theory amplifies, not opposes, g theory. Psychol Inq 27(3):210–217. https://doi.org/10.1080/1047840x.2016.1203232

Green MF (2006) Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry 67(Suppl 9):3–8; discussion 36-42

Gujral S, Dombrovski AY, Butters M, Clark L, Reynolds CF 3rd, Szanto K (2014) Impaired executive function in contemplated and attempted suicide in late life. Am J Geriatr Psychiatr 22 (8):811–819. https://doi.org/10.1016/j.jagp.2013.01.025

Gujral S, Ogbagaber S, Dombrovski AY, Butters MA, Karp JF, Szanto K (2015) Course of cognitive impairment following attempted suicide in older adults. Int J Geriatr Psychiatry 31 (6):592–600. https://doi.org/10.1002/gps.4365

Gunnell D, Magnusson PK, Rasmussen F (2005) Low intelligence test scores in 18 year old men and risk of suicide: cohort study. BMJ 330(7484):167. https://doi.org/10.1136/bmj.38310.473565.8F

Harris EC, Barraclough B (1997) Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry 170:205–228. https://doi.org/10.1192/bjp.170.3.205

Hatkevich C, Venta A, Sharp C (2019) Theory of mind and suicide ideation and attempt in adolescent inpatients. J Affect Disord 256:17–25. https://doi.org/10.1016/j.jad.2019.05.051

Haw C, Harwood D, Hawton K (2009) Dementia and suicidal behavior: a review of the literature. Int Psychogeriatr 21(3):440–453. https://doi.org/10.1017/s1041610209009065

Hewitt J (2010) Schizophrenia, mental capacity, and rational suicide. Theor Med Bioeth 31 (1):63–77. https://doi.org/10.1007/s11017-010-9137-x

Ho M-C, Hsu Y-C, Lu M-L, Gossop M, Chen VC-H (2018) 'Cool' and 'Hot' executive functions in suicide attempters with major depressive disorder. J Affect Disord 235:332–340. https://doi.org/10.1016/j.jad.2018.04.057

Hoehne A, Richard-Devantoy S, Ding Y, Turecki G, Jollant F (2015) First-degree relatives of suicide completers may have impaired decision-making but functional cognitive control. J Psychiatr Res 68:192–197. https://doi.org/10.1016/j.jpsychires.2015.07.004

Hoertel N, Franco S, Wall MM, Oquendo MA, Kerridge BT, Limosin F, Blanco C (2015) Mental disorders and risk of suicide attempt: a national prospective study. Mol Psychiatry 20 (6):718–726. https://doi.org/10.1038/mp.2015.19

Howat S, Davidson K (2002) Parasuicidal behaviour and interpersonal problem solving performance in older adults. Br J Clin Psychol 41(Pt 4):375–386

Hughes SL, Neimeyer RA (1993) Cognitive predictors of suicide risk among hospitalized psychiatric patients: a prospective study. Death Stud 17(2):103–124. https://doi.org/10.1080/07481189308252609

Hughes C, Soares-Boucaud I, Hochmann J, Frith U (1997) Social behaviour in pervasive developmental disorders: effects of informant, group and theory-of-mind. Eur Child Adolesc Psychiatry 6(4):191–198. https://doi.org/10.1007/s007870050029

Jager-Hyman S, Cunningham A, Wenzel A, Mattei S, Brown GK, Beck AT (2014) Cognitive distortions and suicide attempts. Cogn Ther Res 38(4):369–374. https://doi.org/10.1007/s10608-014-9613-0

Joiner T (2005) Why people die by suicide. Harvard University Press, Cambridge

Joiner TE, Van Orden KA (2008) The interpersonal–psychological theory of suicidal behavior indicates specific and crucial psychotherapeutic targets. Int J Cogn Ther 1(1):80–89. https://doi.org/10.1680/ijct.2008.1.1.80

Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R et al (2005) Impaired decision making in suicide attempters. Am J Psychiatr 162(2):304–310. https://doi.org/10.1176/appi.ajp.162.2.304

Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D et al (2008) Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. Am J Psychiatry 165(6):740–748. https://doi.org/10.1176/appi.ajp.2008.07081239

Jollant F, Lawrence NL, Olie E, Guillaume S, Courtet P (2011) The suicidal mind and brain: a review of neuropsychological and neuroimaging studies. World J Biol Psychiatry 12(5):319–339. https://doi.org/10.3109/15622975.2011.556200

Juven-Wetzler A, Cohen H, Kaplan Z, Kohen A, Porat O, Zohar J (2014) Immediate ketamine treatment does not prevent posttraumatic stress responses in an animal model for PTSD. Eur Neuropsychopharmacol 24(3):469–479. https://doi.org/10.1016/j.euroneuro.2013.08.007

Kan K-J, van der Maas HLJ, Levine SZ (2019) Extending psychometric network analysis: empirical evidence against g in favor of mutualism? Intelligence 73:52–62. https://doi.org/10.1016/j.intell.2018.12.004

Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ (2001) Neuropsychological dysfunction in depressed suicide attempters. Am J Psychiatr 158(5):735–741. https://doi.org/10.1176/appi.ajp.158.5.735

Keilp JG, Gorlyn M, Russell M, Oquendo MA, Burke AK, Harkavy-Friedman J, Mann JJ (2013) Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. Psychol Med 43(3):539–551. https://doi.org/10.1017/s0033291712001419

Keilp JG, Beers SR, Burke AK, Melhem NM, Oquendo MA, Brent DA, Mann JJ (2014) Neuropsychological deficits in past suicide attempters with varying levels of depression severity. Psychol Med 44(14):2965–2974. https://doi.org/10.1017/s0033291714000786

Kelly GA (1955) The psychology of personal constructs. Norton, New York

Kelly GA (1961) Suicide: the personal construct point of view. In: Sneidman NLFES (ed) The cry for help. McGraw Hill, New York, pp 225–280

Kim C-H, Jayathilake K, Meltzer HY (2003) Hopelessness, neurocognitive function, and insight in schizophrenia: relationship to suicidal behavior. Schizophr Res 60(1):71–80. https://doi.org/10.1016/s0920-9964(02)00310-9

Kim CD, Seguin M, Therrien N, Riopel G, Chawky N, Lesage AD, Turecki G (2005) Familial aggregation of suicidal behavior: a family study of male suicide completers from the general population. Am J Psychiatr 162(5):1017–1019. https://doi.org/10.1176/appi.ajp.162.5.1017

King DA, Conwell Y, Cox C, Henderson RE, Denning DG, Caine ED (2000) A neuropsychological comparison of depressed suicide attempters and nonattempters. J Neuropsychiatry Clin Neurosci 12(1):64–70. https://doi.org/10.1176/jnp.12.1.64

Klin A, Jones W, Schultz R, Volkmar F, Cohen D (2002) Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry 59(9):809. https://doi.org/10.1001/archpsyc.59.9.809

Klonsky ED, May AM (2013) Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. Suicide Life Threat Behav 44(1):1–5. https://doi.org/10.1111/sltb.12068

Klonsky ED, May AM (2015) The three-step theory (3ST): a new theory of suicide rooted in the "ideation-to-action" framework. Int J Cogn Ther 8(2):114–129. https://doi.org/10.1521/ijct.2015.8.2.114

Klonsky ED, Saffer BY, Bryan CJ (2018) Ideation-to-action theories of suicide: a conceptual and empirical update. Curr Opin Psychol 22:38–43. https://doi.org/10.1016/j.copsyc.2017.07.020

Krause-Utz A, Sobanski E, Alm B, Valerius G, Kleindienst N, Bohus M, Schmahl C (2013) Impulsivity in relation to stress in patients with borderline personality disorder with and without co-occurring attention-deficit/hyperactivity disorder: an exploratory study. J Nerv Ment Dis 201(2):116–123. https://doi.org/10.1097/NMD.0b013e31827f6462

Krause-Utz A, Cackowski S, Daffner S, Sobanski E, Plichta MM, Bohus M et al (2016) Delay discounting and response disinhibition under acute experimental stress in women with borderline personality disorder and adult attention deficit hyperactivity disorder. Psychol Med 46(15):3137–3149. https://doi.org/10.1017/s0033291716001677

Landfield A (1976) A personal construct approach to suicidal behavior. In: Slater P (ed) Explorations of intrapersonal space. Wiley, London, pp 93–107

Lara E, Olaya B, Garin N, Ayuso-Mateos JL, Miret M, Moneta V, Haro JM (2015) Is cognitive impairment associated with suicidality? A population-based study. Eur Neuropsychopharmacol 25(2):203–213. https://doi.org/10.1016/j.euroneuro.2014.08.010

Law KC, Tucker RP (2018) Repetitive negative thinking and suicide: a burgeoning literature with need for further exploration. Curr Opin Psychol 22:68–72. https://doi.org/10.1016/j.copsyc.2017.08.027

LeGris J, van Reekum R (2006) The neuropsychological correlates of borderline personality disorder and suicidal behaviour. Can J Psychiatry 51(3):131–142. https://doi.org/10.1177/070674370605100303

Lezak MD, Howieson DB, Loring DW, Fischer JS (2004) Neuropsychological assessment. Oxford University Press, Oxford

Lichtenberger EO, Kaufman AS (2009) Essentials of WAIS-IV assessment. John Wiley & Sons, Hoboken, NJ

Linehan MM (1981) A social-behavioral analysis of suicide and parasuicide: implications for clinical assessment and treatment. In: Clarkin HGGJF (ed) Depression: behavioral and directive intervention strategies. Garland, New York, pp 229–294

Linehan MM (1986) Suicidal people. One population or two? Ann N Y Acad Sci 487:16–33. https://doi.org/10.1111/j.1749-6632.1986.tb27882.x

Linehan MM (1993) Cognitive-behavioral treatment of borderline personality disorder. Guilford Press, New York

Lyon HM, Startup M, Bentall RP (1999) Social cognition and the manic defense: attributions, selective attention, and self-schema in bipolar affective disorder. J Abnorm Psychol 108(2):273–282. https://doi.org/10.1037//0021-843x.108.2.273

Mahon K, Burdick KE, Wu J, Ardekani BA, Szeszko PR (2012) Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study. Bipolar Disord 14(1):80–89. https://doi.org/10.1111/j.1399-5618.2012.00984.x

Malhi GS, Outhred T, Das P, Morris G, Hamilton A, Mannie Z (2018) Modeling suicide in bipolar disorders. Bipolar Disord 20(4):334–348. https://doi.org/10.1111/bdi.12622

Malhi GS, Das P, Outhred T, Gessler D, John Mann J, Bryant R (2019) Cognitive and emotional impairments underpinning suicidal activity in patients with mood disorders: an fMRI study. Acta Psychiatr Scand 139(5):454–463. https://doi.org/10.1111/acps.13022

Mann JJ, Waternaux C, Haas GL, Malone KM (1999) Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry 156(2):181–189. https://doi.org/10.1176/ajp.156.2.181

Marzuk PM, Hartwell N, Leon AC, Portera L (2005) Executive functioning in depressed patients with suicidal ideation. Acta Psychiatr Scand 112(4):294–301. https://doi.org/10.1111/j.1600-0447.2005.00585.x

Mattis S (1988) Dementia rating scale: DRS: professional manual. PAR

May AM, Klonsky ED (2016) "Impulsive" suicide attempts: what do we really mean? Personal Disord Theory Res Treat 7(3):293–302. https://doi.org/10.1037/per0000160

McClure G, Hawes DJ, Dadds MR (2015) Borderline personality disorder and neuropsychological measures of executive function: a systematic review. Personal Ment Health 10(1):43–57. https://doi.org/10.1002/pmh.1320

McGirr A (2010) Dysregulation of the sympathetic nervous system, hypothalamic–pituitary–adrenal axis and executive function in individuals at risk for suicide. J Psychiatry Neurosci 35 (6):399–408. https://doi.org/10.1503/jpn.090121

McGirr A, Dombrovski AY, Butters MA, Clark L, Szanto K (2012) Deterministic learning and attempted suicide among older depressed individuals: cognitive assessment using the Wisconsin card sorting task. J Psychiatr Res 46(2):226–232. https://doi.org/10.1016/j.jpsychires.2011.10.001

McGirr A, Jollant F, Turecki G (2013) Neurocognitive alterations in first degree relatives of suicide completers. J Affect Disord 145(2):264–269. https://doi.org/10.1016/j.jad.2012.05.062

Millner AJ, den Ouden HEM, Gershman SJ, Glenn CR, Kearns JC, Bornstein AM et al (2019) Suicidal thoughts and behaviors are associated with an increased decision-making bias for active responses to escape aversive states. J Abnorm Psychol 128(2):106–118. https://doi.org/10.1037/abn0000395

Miranda R, Gallagher M, Bauchner B, Vaysman R, Marroquin B (2012) Cognitive inflexibility as a prospective predictor of suicidal ideation among young adults with a suicide attempt history. Depress Anxiety 29(3):180–186. https://doi.org/10.1002/da.20915

Miranda R, Valderrama J, Tsypes A, Gadol E, Gallagher M (2013) Cognitive inflexibility and suicidal ideation: mediating role of brooding and hopelessness. Psychiatry Res 210(1):174–181. https://doi.org/10.1016/j.psychres.2013.02.033

Miskowiak KW, Seeberg I, Kjaerstad HL, Burdick KE, Martinez-Aran A, Bonnin CM et al (2019) Affective cognition in bipolar disorder: a systematic review by the ISBD targeting cognition task force. Bipolar Disord. https://doi.org/10.1111/bdi.12834

Moritz S, Schilling L, Wingenfeld K, Köther U, Wittekind C, Terfehr K, Spitzer C (2011) Psychotic-like cognitive biases in borderline personality disorder. J Behav Ther Exp Psychiatry 42(3):349–354. https://doi.org/10.1016/j.jbtep.2011.02.003

Naifeh JA, Nock MK, Ursano RJ, Vegella PL, Aliaga PA, Fullerton CS et al (2017) Neurocognitive function and suicide in U.S. Army soldiers. Suicide Life Threat Behav 47(5):589–602. https://doi.org/10.1111/sltb.12307

Nangle J, Clarke S, Morris D, Schwaiger S, McGhee K, Kenny N et al (2006) Neurocognition and suicidal behaviour in an Irish population with major psychotic disorders. Schizophr Res 85 (1-3):196–200. https://doi.org/10.1016/j.schres.2006.03.035

Neuringer C (1976) Current developments in the study of suicidal thinking. In: Sneidman ES (ed) Suicidology: contemporary developments. Grune & Stratton, New York, pp 234–252

Nock MK, Banaji MR (2007) Prediction of suicide ideation and attempts among adolescents using a brief performance-based test. J Consult Clin Psychol 75(5):707–715. https://doi.org/10.1037/0022-006x.75.5.707

O'Carroll PW, Berman AL, Maris RW, Moscicki EK, Tanney BL, Silverman MM (1996) Beyond the tower of babel: a nomenclature for suicidology. Suicide Life Threat Behav 26(3):237–252

O'connor RC (2011) Towards an integrated motivational–volitional model of suicidal behaviour. In: O'Connor SPRC, Gordon J (eds) International handbook of suicide prevention, pp 181–198

O'Connor RC, Nock MK (2014) The psychology of suicidal behaviour. Lancet Psychiatry 1 (1):73–85. https://doi.org/10.1016/S2215-0366(14)70222-6

Olié E, Seyller M, Beziat S, Loftus J, Bellivier F, Bougerol T et al (2014) Clinical and neuropsychological characteristics of euthymic bipolar patients having a history of severe suicide attempt. Acta Psychiatr Scand 131(2):129–138. https://doi.org/10.1111/acps.12326

Olsson P, Wiktorsson S, Sacuiu S, Marlow T, Östling S, Fässberg MM et al (2016) Cognitive function in older suicide attempters and a population-based comparison group. J Geriatr Psychiatry Neurol 29(3):133–141. https://doi.org/10.1177/0891988715627015

Oquendo MA, Waternaux C, Brodsky B, Parsons B, Haas GL, Malone KM, Mann JJ (2000) Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. J Affect Disord 59(2):107–117. https://doi.org/10.1016/s0165-0327(99)00129-9

Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ (2004) Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am J Psychiatr 161(8):1433–1441. https://doi.org/10.1176/appi.ajp.161.8.1433

O'Riley AA, van Orden KA, He H, Richardson TM, Podgorski C, Conwell Y (2014) Suicide and death ideation in older adults obtaining aging services. Am J Geriatr Psychiatr 22(6):614–622. https://doi.org/10.1016/j.jagp.2012.12.004

Park S-J, Yi K, Lee JD, Hong JP (2015) There is no difference in IQ between suicide and non-suicide psychiatric patients: a retrospective case-control study. Psychiatry Investig 12 (3):330. https://doi.org/10.4306/pi.2015.12.3.330

Parker A (1981) The meaning of attempted suicide to young parasuicides: a repertory grid study. Br J Psychiatry 139:306–312. https://doi.org/10.1192/bjp.139.4.306

Peterson C, Semmel A, von Baeyer C, Abramson LY, Metalsky GI, Seligman MEP (1982) The attributional style questionnaire. Cogn Ther Res 6(3):287–299. https://doi.org/10.1007/bf01173577

Pierce DW (1981) The predictive validation of a suicide intent scale: a five year follow-up. Br J Psychiatry 139(5):391–396. https://doi.org/10.1192/bjp.139.5.391

Pinkham AE, Penn DL, Perkins DO, Lieberman J (2003) Implications for the neural basis of social cognition for the study of schizophrenia. Am J Psychiatr 160(5):815–824. https://doi.org/10.1176/appi.ajp.160.5.815

Pinkham AE, Hopfinger JB, Pelphrey KA, Piven J, Penn DL (2008) Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. Schizophr Res 99 (1-3):164–175. https://doi.org/10.1016/j.schres.2007.10.024

Podlogar MC, Gutierrez PM, Joiner TE (2019) Improving our understanding of the death/life implicit association test. J Pers Assess:1–13. https://doi.org/10.1080/00223891.2019.1663357

Polanco-Roman L, Jurska J, Quiñones V, Miranda R (2015) Brooding, reflection, and distraction: relation to non-suicidal self-injury versus suicide attempts. Arch Suicide Res 19(3):350–365. https://doi.org/10.1080/13811118.2014.981623

Ponsoni A, Branco LD, Cotrena C, Shansis FM, Grassi-Oliveira R, Fonseca RP (2018) Self-reported inhibition predicts history of suicide attempts in bipolar disorder and major depression. Compr Psychiatry 82:89–94. https://doi.org/10.1016/j.comppsych.2018.01.011

Posner MI (1980) Orienting of attention. Q J Exp Psychol 32(1):3–25. https://doi.org/10.1080/00335558008248231

Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ et al (2014) Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety 31(4):335–343. https://doi.org/10.1002/da.22253

Pu S, Setoyama S, Noda T (2017) Association between cognitive deficits and suicidal ideation in patients with major depressive disorder. Sci Rep 7(1). https://doi.org/10.1038/s41598-017-12142-8

Reich R, Gilbert A, Clari R, Burdick KE, Szeszko PR (2019) A preliminary investigation of impulsivity, aggression and white matter in patients with bipolar disorder and a suicide attempt history. J Affect Disord 247:88–96. https://doi.org/10.1016/j.jad.2019.01.001

Reichenberg A, Harvey PD, Bowie CR, Mojtabai R, Rabinowitz J, Heaton RK, Bromet E (2009) Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. Schizophr Bull 35(5):1022–1029. https://doi.org/10.1093/schbul/sbn044

Rhimer Z, Gonda X, Döme P (2017) The assessment and management of suicide risk in bipolar disorder. In: Carvalho EVAF (ed) The treatment of bipolar disorder: integrative clinical strategies and future directions. Oxford University Press, Oxford

Richard-Devantoy S, Olie E, Guillaume S, Bechara A, Courtet P, Jollant F (2013) Distinct alterations in value-based decision-making and cognitive control in suicide attempters: toward a dual neurocognitive model. J Affect Disord 151(3):1120–1124. https://doi.org/10.1016/j.jad.2013.06.052

Richard-Devantoy S, Berlim MT, Jollant F (2014) Suicidal behaviour and memory: a systematic review and meta-analysis. World J Biol Psychiatry 16(8):544–566. https://doi.org/10.3109/15622975.2014.925584

Richard-Devantoy S, Yang D, Gustavo T, Jollant F (2017) Attentional bias toward suicide-relevant information in suicide attempters: a cross-sectional study and a meta-analysis. Eur Psychiatry 41:S401. https://doi.org/10.1016/j.eurpsy.2017.02.471

Roca M, del Amo AR-L, Riera-Serra P, Pérez-Ara MA, Castro A, Roman Juan J et al (2019) Suicidal risk and executive functions in major depressive disorder: a study protocol. BMC Psychiatry 19(1). https://doi.org/10.1186/s12888-019-2233-1

Rogers ML, Schneider ME, Tucker RP, Law KC, Anestis MD, Joiner TE (2017) Overarousal as a mechanism of the relation between rumination and suicidality. J Psychiatr Res 92:31–37. https://doi.org/10.1016/j.jpsychires.2017.03.024

Romanowska S, MacQueen G, Goldstein BI, Wang J, Kennedy SH, Bray S et al (2018) Neurocognitive deficits in a transdiagnostic clinical staging model. Psychiatry Res 270:1137–1142. https://doi.org/10.1016/j.psychres.2018.10.030

Rudd DM (2000) The suicidal mode: a cognitive-behavioral model of suicidality. Suicide Life Threat Behav 30(1):18–33

Rudd MD (2006) Fluid vulnerability theory: a cognitive approach to understanding the process of acute and chronic suicide risk. In: Cognition and suicide: theory, research, and therapy. American Psychological Association, Washington, pp 355–368

Rudd MD, Joiner TE, Rajab MH (2001) Treating suicidal behavior: an effective, time-limited approach. Guilford Press

Rufino KA, Ellis TE (2017) Contributions of cognitions, psychological flexibility, and therapeutic alliance to suicidal ideation in psychiatric inpatients. Suicide Life Threat Behav 48(3):271–280. https://doi.org/10.1111/sltb.12353

Ruocco AC (2005) The neuropsychology of borderline personality disorder: a meta-analysis and review. Psychiatry Res 137(3):191–202. https://doi.org/10.1016/j.psychres.2005.07.004

Saffer BY, Klonsky ED (2018) Do neurocognitive abilities distinguish suicide attempters from suicide ideators? A systematic review of an emerging research area. Clin Psychol Sci Pract 25(1):e12227. https://doi.org/10.1111/cpsp.12227

Sapolsky RM (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 21(1):55–89. https://doi.org/10.1210/er.21.1.55

Schoenbaum G, Roesch MR, Stalnaker TA, Takahashi YK (2009) A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature reviews*. Neuroscience 10(12):885–892. https://doi.org/10.1038/nrn2753

Schotte DE, Clum GA (1987) Problem-solving skills in suicidal psychiatric patients. J Consult Clin Psychol *55*(1):49

Schwartz J, Murrough JW, Iosifescu DV (2016) Ketamine for treatment-resistant depression: recent developments and clinical applications. Evid Based Ment Health 19(2):35–38. https://doi.org/10.1136/eb-2016-102355

Sher L, Kahn RS (2019) Suicide in schizophrenia: an educational overview. Medicina (Kaunas) 55(7). https://doi.org/10.3390/medicina55070361

Shneidman ES, Farberow NL (1957) The logic of suicide. In: Farberow ESN (ed) Clues to suicide. McGraw-Hill, Toronto, pp 31–40

Soloff PH, Abraham K, Ramaseshan K, Burgess A, Diwadkar VA (2017) Hyper-modulation of brain networks by the amygdala among women with borderline personality disorder: network signatures of affective interference during cognitive processing. J Psychiatr Res 88:56–63. https://doi.org/10.1016/j.jpsychires.2016.12.016

Sommerfeldt SL, Cullen KR, Han G, Fryza BJ, Houri AK, Klimes-Dougan B (2015) Executive attention impairment in adolescents with major depressive disorder. J Clin Child Adolesc Psychol 45(1):69–83. https://doi.org/10.1080/15374416.2015.1072823

Sprock J, Rader TJ, Kendall JP, Yoder CY (2000) Neuropsychological functioning in patients with borderline personality disorder. J Clin Psychol 56(12):1587–1600. https://doi.org/10.1002/1097-4679(200012)56:12<1587::aid-9>3.0.co;2-g

Stip E, Caron J, Tousignant M, Lecomte Y (2017) Suicidal ideation and schizophrenia: contribution of appraisal, stigmatization, and cognition. Can J Psychiatry 62(10):726–734. https://doi.org/10.1177/0706743717715207

Sudol K, Mann JJ (2017) Biomarkers of suicide attempt behavior: towards a biological model of risk. Curr Psychiatry Rep 19(6):31. https://doi.org/10.1007/s11920-017-0781-y

Surrence K, Miranda R, Marroquín BM, Chan S (2009) Brooding and reflective rumination among suicide attempters: cognitive vulnerability to suicidal ideation. Behav Res Ther 47(9):803–808. https://doi.org/10.1016/j.brat.2009.06.001

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG (2005) Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. Am J Psychiatry 162(9):1680–1687. https://doi.org/10.1176/appi.ajp.162.9.1680

Szanto K, Dombrovski AY, Sahakian BJ, Mulsant BH, Houck PR, Reynolds CF, Clark L (2012) Social emotion recognition, social functioning, and attempted suicide in late-life depression. Am J Geriatr Psychiatry 20(3):257–265. https://doi.org/10.1097/jgp.0b013e31820eea0c

Taub GE, McGrew KS (2014) The Woodcock–Johnson tests of cognitive abilities III's cognitive performance model: empirical support for intermediate factors within CHC theory. J Psychoeduc Assess 32(3):187–201

Tombaugh TN (2004) Trail making test A and B: normative data stratified by age and education. Arch Clin Neuropsychol 19(2):203–214. https://doi.org/10.1016/S0887-6177(03)00039-8

Tsypes A, Gibb BE (2016) Cognitive vulnerabilities and development of suicidal thinking in children of depressed mothers: a longitudinal investigation. Psychiatry Res 239:99–104. https://doi.org/10.1016/j.psychres.2016.03.008

Tuvblad C, Gao Y, Wang P, Raine A, Botwick T, Baker LA (2013) The genetic and environmental etiology of decision-making: a longitudinal twin study. J Adolesc 36(2):245–255. https://doi.org/10.1016/j.adolescence.2012.10.006

Vadini F, Calella G, Pieri A, Ricci E, Fulcheri M, Verrocchio MC et al (2018) Neurocognitive impairment and suicide risk among prison inmates. J Affect Disord 225:273–277. https://doi.org/10.1016/j.jad.2017.08.030

Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE Jr (2010) The interpersonal theory of suicide. Psychol Rev 117(2):575–600. https://doi.org/10.1037/a0018697

Van Rheenen TE, Lewandowski KE, Tan EJ, Ospina LH, Ongur D, Neill E et al (2017) Characterizing cognitive heterogeneity on the schizophrenia-bipolar disorder spectrum. Psychol Med 47(10):1848–1864. https://doi.org/10.1017/s0033291717000307

Van Rheenen TE, Lewandowski KE, Bauer IE, Kapczinski F, Miskowiak K, Burdick KE, Balanza-Martinez V (2019) Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: an overview of evidence. Bipolar Disord. https://doi.org/10.1111/bdi.12821

Ventrice D, Valach L, Reisch T, Michel K (2010) Suicide attempters' memory traces of exposure to suicidal behavior. Crisis 31(2):93–99. https://doi.org/10.1027/0227-5910/a000013

Verma D, Srivastava MK, Singh SK, Bhatia T, Deshpande SN (2016) Lifetime suicide intent, executive function and insight in schizophrenia and schizoaffective disorders. Schizophr Res 178(1-3):12–16. https://doi.org/10.1016/j.schres.2016.08.009

Villa J, Choi J, Kangas JL, Kaufmann CN, Harvey PD, Depp CA (2018) Associations of suicidality with cognitive ability and cognitive insight in outpatients with schizophrenia. Schizophr Res 192:340–344. https://doi.org/10.1016/j.schres.2017.06.013

Voracek M (2004) National intelligence and suicide rate: an ecological study of 85 countries. Personal Individ Differ 37(3):543–553. https://doi.org/10.1016/j.paid.2003.09.025

Voracek M (2006) Regional intelligence and suicide rate in Denmark. Psychol Rep 98(3):671–674. https://doi.org/10.2466/pr0.98.3.671-674

Vrbova K, Prasko J, Ociskova M, Holubova M, Kamaradova D, Marackova M et al (2017a) Negative aspects of self-stigma in patients with schizophrenia spectrum disorders. Eur Psychiatry 41:S390. https://doi.org/10.1016/j.eurpsy.2017.02.437

Vrbova K, Prasko J, Ociskova M, Latalova K, Holubova M, Grambal A, Slepecky M (2017b) Insight in schizophrenia – a double-edged sword? Neuro Endocrinol Lett 38(7):457–464

Wang Y-Y, Jiang N-Z, Cheung EFC, Sun H-W, Chan RCK (2015) Role of depression severity and impulsivity in the relationship between hopelessness and suicidal ideation in patients with major depressive disorder. J Affect Disord 183:83–89. https://doi.org/10.1016/j.jad.2015.05.001

Wechsler D (2008) Wechsler adult intelligence scale, 4th edn. https://doi.org/10.1037/t15169-000

Weiser M, Fenchel D, Werbeloff N, Goldberg S, Fruchter E, Reichenberg A et al (2017) The association between premorbid cognitive ability and social functioning and suicide among young men: a historical-prospective cohort study. Eur Neuropsychopharmacol 27(1):1–7. https://doi.org/10.1016/j.euroneuro.2016.11.015

Westheide J, Quednow BB, Kuhn K-U, Hoppe C, Cooper-Mahkorn D, Hawellek B et al (2008) Executive performance of depressed suicide attempters: the role of suicidal ideation. Eur Arch Psychiatry Clin Neurosci 258(7):414–421. https://doi.org/10.1007/s00406-008-0811-1

Wetzel RD, Reich T (1989) The cognitive triad and suicide intent in depressed in-patients. Psychol Rep 65(3):1027–1032. https://doi.org/10.2466/pr0.1989.65.3.1027

Williams JM, Broadbent K (1986) Autobiographical memory in suicide attempters. J Abnorm Psychol 95(2):144–149. https://doi.org/10.1037/0021-843x.95.2.144

Williams GE, Daros AR, Graves B, McMain SF, Links PS, Ruocco AC (2015) Executive functions and social cognition in highly lethal self-injuring patients with borderline personality disorder. Pers Disord 6(2):107–116. https://doi.org/10.1037/per0000105

Wu C-S, Liao S-C, Lin K-M, Tseng MM-C, Wu EC-H, Liu S-K (2009) Multidimensional assessments of impulsivity in subjects with history of suicidal attempts. Compr Psychiatry 50 (4):315–321. https://doi.org/10.1016/j.comppsych.2008.09.006

Yen S, Shea MT, Sanislow CA, Grilo CM, Skodol AE, Gunderson JG et al (2004) Borderline personality disorder criteria associated with prospectively observed suicidal behavior. Am J Psychiatr 161(7):1296–1298. https://doi.org/10.1176/appi.ajp.161.7.1296

Yu J, Lee TMC (2016) Cognitive flexibility and changes in hopelessness across time: a moderation hypothesis. Appl Neuropsychol Adult 24(5):404–409. https://doi.org/10.1080/23279095.2016.1155991

Lipids and Suicide Risk

M. Elizabeth Sublette

Contents

Abstract In the search for biomarkers and modifiable risk factors for suicide, lipid status has garnered considerable interest, although the lipid-suicide connection is not without controversy. Major categories of lipids that have been reported as germane to suicide include sterols and polyunsaturated fatty acids (PUFAs). Research concerning lipid effects on mood and suicide risk includes epidemiologic approaches, cohort studies, and clinical trials. In general, current evidence suggests that higher n-3 relative to n-6 PUFA intake may have beneficial effects on depression and suicide risk, particularly in women, while low cholesterol may be detrimental in both sexes. Additionally, low estrogen in women has been associated with suicide attempts, whereas high androgen loads may contribute to the higher suicide

M. E. Sublette (✉)
Department of Psychiatry, Columbia University, New York, NY, USA

Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, NY, USA
e-mail: Elizabeth.Sublette@nyspi.columbia.edu

Curr Topics Behav Neurosci (2020) 46: 155–178
https://doi.org/10.1007/7854_2020_163
Published Online: 26 August 2020

completion rate in men. Basic and translational research provides strong evidence for several potential mechanisms that have been implicated in depression and suicide. Firstly, PUFAs, cholesterol, and estrogen can interact to influence structure and function of membrane microdomains ("lipid rafts"), with potential regulatory effects on inflammation and signal transduction, including monoaminergic signaling. Secondly, PUFAs bind to and activate peroxisome proliferator-activated receptors (PPARs), nuclear receptors that regulate gene expression, with resultant effects on inflammation and bioenergetics. Thirdly, PUFAs are both a target for and a hormetic regulator of oxidative stress. Critical to a greater understanding of lipid status as a suicide risk predictor and treatment target will be studies that map genomic and phenotypic characteristics of individuals whose emotional state is affected most by lipid status. Also important will be a more nuanced understanding of lipid-lipid interactions and the differential roles of lipid subclasses on suicide risk.

Keywords Androgen · Cholesterol · Estrogen · Lipids · Suicide · PUFA

1 Introduction

Suicidal behavior is a public health threat of alarming proportions, against which little progress has been made. Given the recalcitrant nature of this problem, it is important to evaluate a broad range of possible solutions, including innovative approaches. In terms of suicide prevention, one logical strategy is to identify and characterize measurable, modifiable suicide risk factors that singly or together account for a clinically significant proportion of the risk variance. In this chapter we discuss one putative risk domain for suicidal behavior: lipid status. Lipids are easily measured and particularly open to modification, as they are susceptible not only to drug or hormonal interventions but may also be directly affected by diet. Viewed in another light, a beneficial lipid balance could be a potentially inducible protective or resilience factor. An association of lipid status with suicide risk also carries important health implications with regard to the relevance of comorbid lipid-related conditions, such as obesity and hypertension, for suicide risk.

The neurobiology of lipids imparts considerable face validity to the concept that lipids may impact suicide risk, as lipids are in high concentration in brain tissue, and lipophilic substances can cross the blood-brain barrier (Suzuki 1981).

Against this backdrop, we will review the clinical literature relating to lipids and suicide and discuss neurobiological mechanisms that may subserve the translation of lipid functions into effects on suicidal behavior.

2 Lipid Classes

Lipids are hydrophobic or amphiphilic molecules that perform multiple structural and functional roles, particularly in the plasma membrane and with regard to bioenergetics. Lipids that have been implicated in suicide risk include polyunsaturated fatty acids, cholesterol, and neuroactive steroids.

2.1 Polyunsaturated Fatty Acids (PUFAs)

PUFAs are essential nutrients, i.e., they cannot be synthesized de novo by the body, although a minor source of PUFAs is the conversion of shorter-chain fatty acids such as alpha-linolenic acid (18:3n-3) or linoleic acid (18:2n-6) into longer-chain molecules including docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3) by a succession of elongation and desaturation steps. In developed countries where food animals are maintained on artificial diets low in n-3 PUFAs, its dietary acquisition primarily depends on fish intake, and the balance of n-3 to n-6 PUFAs is estimated to have deteriorated from ~1:1 to ~1:20 since the Industrial Age (Simopoulos 2006). Key components of phospholipids, PUFAs are attached to glycerophosphate at the *sn*-2 and *sn*-3 positions (see Fig. 1a), forming hydrophobic "tails" that face the interior of the lipid bilayer that comprises the biological membranes, while the hydrophilic phosphoglycerol moiety interacts with cytosolic and extracellular environments. The long carbon chains and presence of multiple double bonds impart flexibility to PUFA molecules and dictate their behavior in the

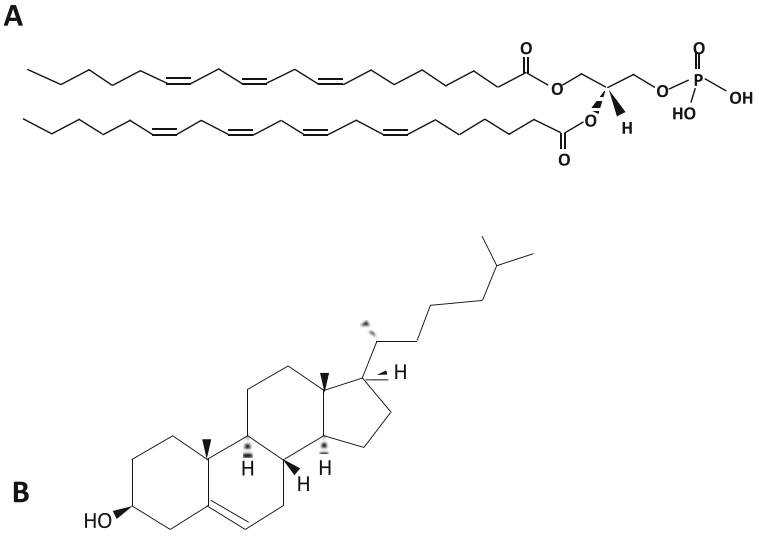


Fig. 1 Structure diagrams of a glycerophospholipid (**a**) and cholesterol (**b**)

plasma membrane. PUFAs also exist esterified to triacylglycerols stored in adipocytes and hepatocytes; in cholesteryl esters, such as in lipoproteins for transport; or in plasma in small quantities in a "free," unesterified state. (Reviewed in (Liu et al. 2015).)

2.2 *Sterols*

Cholesterol ($C_{27}H_{46}O$) is an organic compound found in virtually every cell in the body (see Fig. 1b). As much as 70% of cholesterol in the body is produced by de novo synthesis, and the remainder is obtained through the diet (Ikonen 2008). Cholesterol resides in cellular membranes and is carried in lipoproteins, either free or bound to long-chain fatty acids as cholesteryl esters, through an ester bond between the fatty acid carboxyl end and the cholesterol hydroxyl group. Cholesterol is the precursor for steroid production, which occurs in the brain as well as in the adrenals, gonads, and placenta.

The group of neuroactive steroids encompasses both endogenous and exogenous substances that may have inhibitory or excitatory effects on the central nervous system (Maninger et al. 2009). Herein we discuss endogenous neurosteroids, synthesized in the brain (Stoffel-Wagner 2001), that have been implicated in suicide risk, including estrogens and androgens (see Fig. 2). Estrogen can have direct central nervous system effects, as estrogen receptors are widespread in the brain including in the hypothalamus, prefrontal cortex, hippocampus, amygdala, raphe nucleus, locus coeruleus, and thalamus (reviewed in (Marin and Diaz 2018)). In contrast, little is known about androgen receptors in the human brain (Hofer et al. 2013).

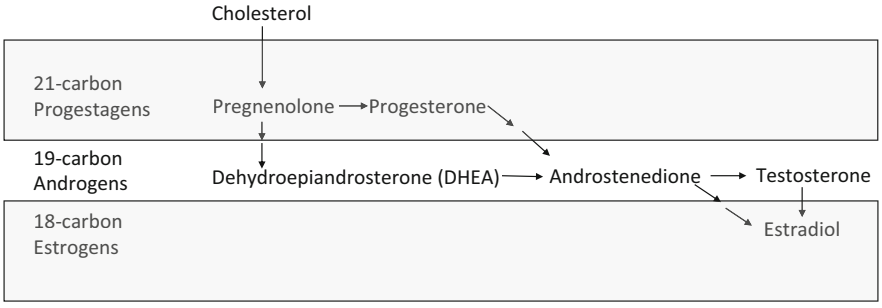


Fig. 2 Generation of neuroactive steroids from cholesterol

3 Evidence Linking Lipids and Suicide Risk

3.1 Cholesterol Levels and Suicide Risk

Interest in lipids with respect to suicide began to gain momentum in 1990 with a seminal paper by Muldoon et al. (1990), a meta-analysis of clinical trials studying cholesterol-lowering treatments comprising medication and dietary interventions. In this study of 24,847 male participants, although drug treatments were noted to reduce mortality from heart disease, among all treatments, an increase was observed in non-illness-related violent deaths, including suicide deaths. In a subsequent, larger meta-analysis by the same author 11 years later, dietary and non-statin treatments showed a trend ($p = 0.06$) toward non-illness-related violent deaths. These findings comport with studies in forensic populations in which violent behavior has been associated with low serum cholesterol (Virkkunen 1979, 1983; Repo-Tiihonen et al. 2002) and with primate studies finding that animals fed a low-cholesterol diet were more aggressive and less socially interactive (Kaplan et al. 1994).

The above reports stimulated additional cohort studies of cholesterol levels and suicidality. Two meta-analyses have been published concerning associations of cholesterol indices (total cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides) with markers of suicide risk (suicidal ideation, attempts, and "tendencies") (Wu et al. 2016; Bartoli et al. 2017). The study of Wu et al. (2016) encompassed 65 studies from 1992 to 2014, in a population of 510,392 participants with diverse psychiatric diagnoses. They concluded that suicidal patients had lower serum total cholesterol and triglyceride levels, compared to nonsuicidal patients, and lower total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels in comparison with healthy controls. Bartoli et al. (2017) focused on studies in bipolar disorder from 1994 to 2017, examining 11 studies in 1,042 participants, of which 8 studies were included in the Wu et al. meta-analysis; for analyses of specific lipids, data was only available in subsets of 5 (low-density lipoproteins) or 7 (triglycerides) studies. In contrast to Wu et al. (2016), Bartoli and colleagues found no significant association between any indices of serum lipid status and suicidality. Thus lipid involvement may differ in bipolar disorder due to differences in pathophysiology or medication history, or the sample may have been too small to have adequate statistical power.

Since the publication of these meta-analyses, we located 12 additional original studies of cholesterol levels and suicide risk (Mensi et al. 2016; Kavoor et al. 2017; Reuter et al. 2017; Shrivastava et al. 2017; Svensson et al. 2017; Capuzzi et al. 2018; Knowles et al. 2018; Mathew et al. 2018; Perera et al. 2018; Segoviano-Mendoza et al. 2018; Eidan et al. 2019; Suneson et al. 2019). Of these, total cholesterol was reported to be lower in suicide attempters compared with healthy controls in three studies (Kavoor et al. 2017; Mathew et al. 2018; Eidan et al. 2019) and compared with patient nonattempters in four studies (Mensi et al. 2016; Reuter et al. 2017; Segoviano-Mendoza et al. 2018; Eidan et al. 2019). In a large genetic/pedigree study in which psychiatric status was not an enrollment criterion, lower free cholesterol

was associated with increased suicide risk (Knowles et al. 2018). In veterans with a history of suicidal behaviors, total cholesterol levels were lower at visits when patients reported a suicide attempt or suicidal ideation (Reuter et al. 2017). Lower cholesterol was also seen to correlate negatively with aggression (Suneson et al. 2019) and impulsivity and suicidality (Kavoor et al. 2017). In contrast, no group differences were seen in three other studies (Shrivastava et al. 2017; Capuzzi et al. 2018; Perera et al. 2018). In one study of cholesterol and suicide death in 45,246 Japanese participants (Svensson et al. 2017), cholesterol was not associated with suicide in men, but *higher* levels of cholesterol were associated with higher suicide mortality in women (independently of menopause (Svensson et al. 2018)). Additionally, a couple of studies have identified genetic markers related to both suicide risk and cholesterol biosynthesis (Li et al. 2017) or cholesterol efflux capacity (Knowles et al. 2018).

3.2 Neuroactive Steroids and Suicide Risk

A 2006 nonquantitative review of literature ($N = 44$ studies) concerning associations between suicide risk and female reproductive steroid hormones acknowledged a caveat of methodological limitations, but suggested that those portions of the menstrual cycle with low estrogen appear to be associated with suicidal behaviors (Saunders and Hawton 2006). A later study (Baca-Garcia et al. 2010), of 431 women assessed within 24 h of a suicide attempt, employed hormonal blood levels as a precise method of menstrual cycle phase determination and concurred that in fertile women, suicide attempts occurred more frequently during menses and the early follicular phase of the menstrual cycle, during which estradiol and progesterone are lower. Moreover, suicide attempts at times of low estradiol/low progesterone were associated with higher suicide intent (Baca-Garcia et al. 2010). These findings are consistent with a postmortem study in females (Leenaars et al. 2009) reporting that 25% of 56 suicide decedents were menstruating compared to 4.5% of 44 control decedents.

Phasic differences in testosterone concentrations may also impact suicide risk in women. However, reports vary as to whether total and free testosterone levels are higher (Linton et al. 2016) or lower (Oka et al. 1988) in women during the follicular phase. One prospective study in female suicide attempters with bipolar disorder ($n = 51$) (Sher et al. 2014) found that baseline plasma testosterone levels correlated positively with the number of prior suicide attempts and higher testosterone predicted future suicide attempts; no attempt was made in this study to assess timing related to menses. Two studies that included both sexes (Chatzittofis et al. 2013; Stefansson et al. 2016) found no differences between CSF testosterone levels in female suicide attempters compared with female healthy controls; however, the sample sizes were small ($n = 10/6$ (Chatzittofis et al. 2013) and $n = 28/19$ (Stefansson et al. 2016)). Particularly in the case of women, in whom testosterone levels are much lower than in men, these discrepancies may relate to methodological

confounds in testosterone determination. The following factors have been noted to create bias: time of day, as circadian variation has been reported related to age; presence of other steroids that may interfere with the assay; menstrual phase; variation in sensitivity and accuracy of the assays used; and lack of age- and gender-corrected norms (Rosner et al. 2007).

In men, a number of studies report that activity of testosterone and other androgens is associated with aggression/violence and impulsivity (reviewed in (Lenz et al. 2019)), which may be mediators of androgen suicide effects (Lenz et al. 2019). Most studies report associations between elevated testosterone (Brower et al. 1989; Gustavsson et al. 2003; Tripodianakis et al. 2007; Markianos et al. 2009; Stefansson et al. 2016) and dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) (Butterfield et al. 2005; Chatzittofis et al. 2013) and suicide risk in men. Two negative studies also exist (Perez-Rodriguez et al. 2011; Sher et al. 2018). Lenz et al. (2019) propose that androgen effects are specifically associated with death by suicide, as opposed to nonlethal suicidal behaviors, and thus may explain the "gender paradox of suicidal behaviors" that suicide completion is much higher among males, while nonlethal suicide attempts are much higher among women. Their work implicates not only adult androgenic status but also prenatal androgen load.

3.3 Polyunsaturated Fatty Acid (PUFA) Dietary Intake and Suicide-Related Outcomes

Involvement of non-sterol lipids in suicide risk was proposed by Hibbeln and Salem in 1995 (Hibbeln and Salem 1995), who postulated that relationships between low cholesterol and aggression or violent acts including suicide may be confounded by the effects of cholesterol-lowering dietary interventions on the balance of n-3 to n-6 PUFAs. This hypothesis has been borne out in studies in humans with dyslipidemia, which find that gemfibrozil and, to a lesser extent, statins affect fatty acid composition, generally decreasing saturated fatty acids and increasing the n-6 to n-3 PUFA ratio (Nakamura et al. 1998; Harris et al. 2004; de Lorgeril et al. 2005; Nyalala et al. 2008; Nozue and Michishita 2015).

Several epidemiologic studies have examined relationships between dietary n-3 intake and depression (see Table 1a) (Tanskanen et al. 2001; Sanchez-Villegas et al. 2007; Murakami et al. 2008; Colangelo et al. 2009; Smith et al. 2014; Yang and Je 2018; Hakkarainen et al. 2004; Timonen et al. 2004). Studies of n-3 PUFA intake with respect to depression have relevance to suicide risk, given that major depression is a risk factor for suicide. One study in Spain ($N = 7{,}903$) found that moderate – but not low or high – fish consumption was associated with a lower rates of depression, anxiety, and stress (Sanchez-Villegas et al. 2007). They suggested that available fish in their locale may have had unacceptably high mercury content, which could explain the nonlinear results: too low n-3 intake or too high mercury intake could

Table 1 Epidemiologic studies of fish intake related to depression and suicide risk outcomes

Article	Population	Country	Study design	Covariates	Outcomes	Sex effects
(A) Fish intake associations with depression or other mental disorders						
Smith et al. (2014)	$N = 1{,}386$ adults aged 26–36 years	Australia	Prospective cohort study. Completed a food frequency questionnaire in 2004–2006. During 2009–2011, the CIDI was administered by telephone	Age, marital status, education, employment, accessibility/remoteness, smoking, medication use. For women, parous state	Higher fish intake associated with lower risk of *depression* at follow-up	Finding in *women* only
Yang and Je (2018)	$N = 9{,}183$ adults aged 19–64 years who participated in the 6th Korea National Health and Nutrition Examination Survey	Korea	Cross-sectional. Completed a food frequency questionnaire. Designated depressed if reported a physician diagnosis	Age, sex, marital status, household income, education, employment, smoking, alcohol consumption, physical activity, disease information	Highest rank of fish intake associated with lower risk of *depression*	Finding in *women* only
Sanchez-Villegas et al. (2007)	$N = 7{,}903$ participants	Spain	Prospective cohort study. Intake of n-3 PUFA and fish consumption calculated from a validated semiquantitative food frequency questionnaire	Age, BMI, physical activity, marital status, smoking, employment, presence of severe disease, energy intake, energy-adjusted folate, vitamin B12 and vitamin B6 intakes, alcohol intake, and consumption of stimulant beverages	Moderate consumption of fish associated with relative risk reduction of *total mental disorders* $> 30\%$	Finding in both sexes
Tanskanen et al. (2001)	$N = 3{,}204$ adult subjects	Finland	A single frequency question assessed fish consumption. Depressive symptoms assessed with the BDI	Age, marital status, employment, smoking, physical activity, sex, BMI, alcohol intake, coffee intake, education level, serum cholesterol	*Depressive symptoms* associated with infrequent fish consumption	Finding in *women* only

Colangelo et al. (2009)	$N = 3{,}317$ African-American and Caucasian participants from the Coronary Artery Risk Development in Young Adults study	USA	Diet assessed in year 7 and depressive symptoms measured with the CES-D in years 10 and 20	Age, race, education, income, marital status, employment, smoking, use of antidepressants, alcohol intake, physical activity	Lower n-3 PUFA intake associated with higher chronic *depressive symptoms*	Finding in *women* only
Murakami et al. (2008)	$N = 309$ male and $N = 208$ female municipal employees from two offices, 21–67 years	Japan	Cross-sectional study. Diet assessed with BDHQ. Depressive symptoms assessed using a 20-question Japanese version of the CES-D	BMI, marital status, job title, smoking, occupational and leisure physical activity (nonvalidated instruments), job stress	Prevalence of *depressive symptoms*	No associations with n-3 PUFA intake in both sexes
(B) Fish intake associations with suicide risk and depression						
Hirayama (1990)	$N = 265{,}000$ participants	Japan	Followed for 17 years	Did not adjust for covariates	Decreased *suicide risk* in those with daily fish consumption	Finding in both sexes
Timonen et al. (2004)	$N = 5{,}689$ participants in the Northern Finland 1966 Birth Cohort, aged 31	Finland	Cross-sectional data obtained by postal questionnaires	Body mass index, serum total cholesterol, and socioeconomic situation	Very low fish intake associated with *depression* and *suicidal ideation*	Finding in *women* only
Hakkarainen et al. (2004)	$N = 29{,}133$ men ages 50 to 69 years	Finland	Intake of n-3 PUFA and fish consumption calculated from a dietary questionnaire. Participants followed for up to 9 years. Self-reported depressed mood. Major depressive episodes derived from hospital discharge register. Suicides identified from death certificates	Age, body mass index, energy intake, serum total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, education, marital status, self-reported depression and anxiety, and smoking	No associations between dietary intake of n-3 PUFAs or fish and *depressed mood, major depressive episodes*, or *suicide*	No effects in an all-male sample

(continued)

Table 1 (continued)

Article	Population	Country	Study design	Covariates	Outcomes	Sex effects
Tsai et al. (2014)	$N = 42{,}290$ men enrolled in the Health Professionals Follow-Up Study; $N = 72{,}231$ women enrolled in the Nurses' Health Study; and $N = 90{,}836$ women enrolled in Nurses' Health Study II	USA	Intake of n-3 and n-6 PUFA and fish consumption calculated every 4 years using a validated food-frequency questionnaire. Suicide mortality ascertained through blinded physician review of death certificates and hospital or pathology reports	Smoking, body mass index, alcohol consumption, marital status, physical activity, coffee consumption, energy intake, trans fatty acids, saturated fatty acids, monounsaturated fatty acids, and the other n-3 and n-6 PUFAs. For women: menopausal status and use of hormone replacement therapy	No evidence that intake of n-3 PUFAs or fish lowered the risk of *suicide*	No effects in both sexes
Poudel-Tandukar et al. (2011)	$N = 47{,}351$ men and $N = 54{,}156$ women aged 40–69 years enrolled in the Japan Public Health Center-based Prospective Study	Japan	Completed a food frequency questionnaire in 1995–1999. Followed for death through December 2005	Age, area, BMI, alcohol consumption, smoking, physical activity, living alone, history of chronic disease, drug use, stress, and employment	Increased risk of *suicide* associated with very low intake of fish	Finding in *women* only

BDHQ brief diet history questionnaire, *BDI* Beck Depression Inventory, *BMI* body mass index, *CES-D* Center of Epidemiologic Studies Depression Scale, *CIDI* Composite International Diagnostic Interview, *DSM IV Diagnostic and Statistical Manual of Mental Disorders*, fourth edition

be detrimental to mental health. A second study, in Japanese office workers ($N = 517$), found no associations of n-3 consumption and depression (Murakami et al. 2008); the small sample size and the inclusion of only high-functioning (i.e., employed) adults may decrease the relevance of this finding for suicide risk. One study of men only did not find any relationship between n-3 intake and depression (Hakkarainen et al. 2004). Five studies from diverse locations did find associations between depressive symptoms and low fish consumption in adult women, but not men: in Finland ($N = 3{,}204$) (Tanskanen et al. 2001), ($N = 5{,}689$) (Timonen et al. 2004), in the USA ($N = 3{,}317$) (Colangelo et al. 2009), in Korea ($N = 9{,}183$) (Yang and Je 2018), and in Australia ($N = 1{,}386$) (Smith et al. 2014). Meta-analyses conclude there is an inverse relationship between n-3 PUFA intake and depression (Li et al. 2016; Yang et al. 2018), especially in women (Yang et al. 2018).

A small number of studies have assessed suicide-related outcomes in relation to n-3 PUFA dietary intake (see Table 1b) (Hirayama 1990; Hakkarainen et al. 2004; Timonen et al. 2004; Poudel-Tandukar et al. 2011; Tsai et al. 2014). In probably the earliest report of suicide relating to fish intake, decreased suicide risk was found in those with daily fish consumption in a large ($N = 265{,}000$), 17-year study (Hirayama 1990); however, this investigation has been criticized (Skrabanek 1992) for lack of a priori hypotheses and a large number of multiple comparisons (>1,000 relative risks computed). As with depression outcomes (Tanskanen et al. 2001; Colangelo et al. 2009; Smith et al. 2014; Yang and Je 2018), two studies reported very low fish intake as a predictor of suicide (Poudel-Tandukar et al. 2011) and suicidal ideation (Timonen et al. 2004) in women only. Two additional studies found no association between fish intake and suicide risk, although one (Hakkarainen et al. 2004) studied only men, and the other (Tsai et al. 2014), like the depression study by Murakami et al. (2008), may not be representative of the at-risk population since the study included only high-functioning subjects (health professionals).

Difficulties comparing epidemiologic studies of suicide risk and n-3 PUFA intake across countries include large geographic disparities in fish consumption. For example, an ecologic comparison of seafood intake across countries found average seafood intakes to be twofold higher in Spain and threefold higher in Japan, compared with the USA (Hibbeln 2002). Similarly, comparison of blood concentrations of the n-3 PUFA DHA in cross-sectional studies (Hibbeln and Gow 2014) reveals that the mean value of DHA in the lowest quartile in a study of Chinese suicide attempters (Huan et al. 2004) was greater than the highest octile in a study of US military suicide completers (Lewis et al. 2011). Thus individual studies may be susceptible to ceiling or floor effects. Additionally, there are many potential confounds related to location that likely correlate with differences in fish intake, such as genomic clustering and covarying dietary nutritional factors.

Given these confounds and the reporting bias inherent in analysis of dietary intake, a more straightforward index of PUFA status is the measurement of blood levels, assayed from red blood cells, total plasma, or plasma phospholipid or cholesteryl ester fractions. On meta-analysis (Lin et al. 2010), n-3 PUFA levels were lower in patients with depression, a major risk factor for suicide. More specific to suicide risk, two cross-sectional studies (Huan et al. 2004; Lewis et al. 2011) and

one small prospective study (Sublette et al. 2006) also found low n-3 PUFA levels to be associated with risk of suicidal behavior.

4 Potential Mechanisms of Action

4.1 Inflammation

The role of inflammation in depression and suicide risk is a current hot topic for investigation and debate, challenging in its complexity. One of the strongest findings in support of inflammation as etiologically relevant is that depression and suicidality are induced in medically ill individuals treated with the interferon (IFN)-α cytokine (Janssen et al. 1994; Sockalingam et al. 2011; Lucaciu and Dumitrascu 2015). Multiple studies have found other convincing evidence that cytokines are implicated in depression (reviewed in (Raison et al. 2006; Dantzer et al. 2008; Capuron and Miller 2011)). Human studies in a variety of inflammatory illnesses report n-3 PUFA attenuation of inflammatory cytokine activation (Maes et al. 2000; Rodriguez-Cruz et al. 2018; Hsiao et al. 2019).

Mechanisms of action for PUFA participation in inflammation include the generation of active PUFA metabolites that serve as homeostatic forces in inflammatory cascades. In brief, n-6 PUFA are primarily proinflammatory, with metabolites that include inflammatory prostaglandins, thromboxanes, and leukotrienes, but also anti-inflammatory lipoxins. N-3 PUFA metabolites include anti-inflammatory resolvins and protectins and less inflammatory prostaglandins, thromboxanes, and leukotrienes (reviewed in (Liu et al. 2015)).

In addition, n-3 PUFAs exercise inhibitory effects on the inflammation-promoting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in two ways. In cell cultures, n-3 PUFA activation of peroxisome proliferator-activated receptor (PPAR)γ reduced lipopolysaccharide (LPS)-induced NF-κB activation (Li et al. 2005; Rao and Lokesh 2017) (also see Sect. 4.3 below). Additionally, n-3 PUFAs inhibit the dimerization and lipid raft presence of the NF-κB activator, Toll-like receptor (TLR)4 (Wong et al. 2009). In the latter pathway, cholesterol levels may also play a role, since cholesterol and lipid rafts are prerequisites for activation of TLR4 (Sadikot 2012).

4.2 Lipid Raft-Mediated Effects

We propose that one major pathway whereby PUFAs, cholesterol, and estrogen may influence behavioral outcomes is via their demonstrated effects on lipid microdomains that mediate signal transduction, as detailed below.

4.2.1 Lipid Rafts and PUFAs

By virtue of their location in biological membranes and their multiple double bonds and long fatty acid chains, PUFA species such as DHA (22:6n-3) and EPA (20:5n-3) have physicochemical effects on membrane fluidity (Williams et al. 2012; Leng et al. 2018). For example, in model membrane paradigms, DHA has been observed to influence size and clustering of lipid microdomains ("lipid rafts") (Wassall et al. 2018), spatially and temporally dynamic membrane regions that contain sphingolipids and cholesterol as major constituents. Controversy exists about lipid raft structure and function and about precise mechanisms of PUFA effects on membrane microdomains (reviewed in (Liu et al. 2018)). However, the basic theory posits an aversion between the disordered, rapidly conformationally changing polyunsaturated chains of PUFAs and the highly ordered, rigid conformations of cholesterol, preventing close packing between the two lipid types, i.e., creating phase separation between membrane domains (Wassall et al. 2004; Wassall and Stillwell 2008, 2009). Chain length and degree of saturation are moderators of the n-3 PUFA effects on membrane order (Leng et al. 2018). Thus specific characteristics of DHA vs. EPA account for differential effects on the plasma membrane, effects that may translate into some of the clinical differences that have been reported between these PUFA species (Leng et al. 2018), such as a greater efficacy of EPA-rich supplements in treatment of depression (Martins 2009; Sublette et al. 2011; Lin et al. 2012; Martins et al. 2012).

n-3 PUFA effects on membrane fluidity and lipid microdomains contribute to their anti-inflammatory abilities. For example, in vitro studies show that PUFA effects on glycerophospholipids and membrane microdomains modulate B-cell (Whelan et al. 2016) and T-cell (Fan et al. 2018) functioning and that proliferating T cells incorporate long-chain PUFAs and increase the expression of the very long-chain fatty acid elongase protein ELOVL5 (Robichaud et al. 2018). One epigenetic study has demonstrated that DNA methylation in *Elovl5* gene regulatory regions explained PUFA associations with suicide attempt status (Haghighi et al. 2015).

4.2.2 Lipid Rafts and Sterols

Lipid rafts serve as a nexus for multimolecular complexes, or signalosomes, that include transmembrane proteins, G-proteins, and numerous adaptor proteins (Bjork and Svenningsson 2011). Transmembrane proteins affected include serotonin and norepinephrine transporters and multiple serotonin, dopamine, and adrenergic receptors (reviewed in (Liu et al. 2018)), with obvious implications for depression and anxiety and therefore suicide risk. Utilizing depletion, substitution, and repletion techniques, studies of cholesterol effects in the membrane have found that cholesterol depletion affects the serotonin transporter by significantly reducing the transport rate (V_{max}) and affinity (K_m) of serotonin for the transporter (Scanlon et al. 2001; Magnani et al. 2004). Similarly, depleting cholesterol lowers both agonist and

antagonist binding to serotonin receptors 1A and 7 (Pucadyil and Chattopadhyay 2004; Sjogren et al. 2006, 2008) and alters responses of serotonin 2A receptors (Dreja et al. 2002; Sommer et al. 2009).

Lipid microdomains are also crucial for estrogen signaling. Palmitoylated estrogen receptors take part in raft-associated signaling in the brain (Marin and Diaz 2018) and are thought to be neuroprotective, e.g., against amyloid-β-related toxicity (Marin et al. 2012). Estrogen's neuroprotective effects depend on the levels of cholesterol (Peri et al. 2011), and synergism occurs between estrogen and DHA effects on membrane (Marin and Diaz 2018). For example, in the hippocampus in ovariectomized (non-estrogen-producing) mice, DHA incorporation is enhanced in the presence of estradiol (Diaz et al. 2016). Moreover, estrogens participate in the genetic regulation of lipid biosynthesis in the brain: in both human neuroblastoma cells and rat brain cortex, 17β-estradiol induces the synthesis of DHA from linolenic acid (18:3n-3) through effects on expression of desaturases (Marin et al. 2012). These mechanistic relationships are particularly interesting in light of findings that both low estrogen states and low n-3 PUFA intake in women have been associated with suicide risk.

4.3 Bioenergetics

Formation of reactive oxygen species (ROS) in excess of ROS inactivation is known as oxidative stress and results in cumulative cell damage. ROS can be produced in mitochondria when excess electron leak occurs across the electron transport chain (Ramzan et al. 2010). Dysfunction in electron transport is hypothesized to drive many of the classic depression symptoms related to bioenergetics, such as fatigue, low motivation, psychomotor slowing, and amotivational states (Morris and Berk 2015). Via a free radical chain reaction, ROS degrade lipids via lipid peroxidation, with deleterious effects on membrane function and denaturing of enzymes and other proteins. Lipid peroxidation is associated with a variety of chronic diseases including neurodegenerative conditions and depression (Maes et al. 2011).

Connections between oxidative stress and suicide risk also have been reported. In one study, suicide attempters ($n = 141$) had higher levels of lipid hydroperoxides and lowered levels of plasma antioxidants compared to individuals without suicide attempts ($N = 201$) (Vargas et al. 2013). Similarly, in patients with major depressive disorder ($N = 114$), bipolar disorder ($N = 133$), and healthy controls ($N = 50$), increased lipid peroxidation markers predicted mood diagnoses and current suicidal ideation (Sowa-Kucma et al. 2018).

PUFAs are particularly susceptible to lipid peroxidation due to the configuration of multiple double bonds separated by methylene bridging groups containing highly reactive hydrogen atoms. Therefore, it has been proposed that high concentrations of PUFAs could constitute a greater risk for chronic illness, and some studies did find evidence that n-3 PUFA intake increased lipid peroxidation (Sarsilmaz et al. 2003; Casos et al. 2010). Increasingly, however, multiple in vitro and in vivo studies have

demonstrated that n-3 PUFA effects are actually protective against oxidative stress (Sarsilmaz et al. 2003; Altinkilic et al. 2010; Casos et al. 2010; Arunagiri et al. 2014; Giordano and Visioli 2014; Shichiri et al. 2014) and that, as in PUFA effects on lipid rafts, these protective abilities may vary according to the particular PUFA species (Di Nunzio et al. 2016). This protective phenomenon may be due to a hormesis mechanism, whereby non-toxic level doses of n-3 PUFAs induce mild increases in ROS that trigger an antioxidant response, thereby priming the cell's defenses against subsequent, more powerful oxidative stresses. A mechanism for this was shown in rodents in which, although an n-3 PUFA-rich diet caused increased fatty acid peroxidation, it also resulted in a robust chronic increase in endogenous antioxidant activity (by mitochondrial superoxide dismutase) and consequent inhibition of oxidative stress-related tissue damage (Abdukeyum et al. 2016). Consistent with neuroprotective benefits of n-3 PUFAs against deleterious effects of lipid peroxidation, secondary analyses of n-3 PUFA supplementation in patients with coronary artery disease found that late-stage lipid peroxidation at baseline predicted greater improvement in immediate recall (Mazereeuw et al. 2017a) and greater improvement in depressive symptoms (Mazereeuw et al. 2017b) after 12 weeks of n-3 PUFA treatment.

Another pathway for fatty acid effects on bioenergetics is that n-3 PUFAs bind as agonists and activate all PPAR isoforms (α, β/δ, γ), members of the nuclear receptor superfamily that join with retinoid X and regulate gene expression through binding to conserved DNA sequences in promoter regions of target genes. PPARs may be thought of as lipid sensors that in turn regulate fatty acid metabolism and play an essential role in metabolic adaptation to fasting by triggering utilization of long-chain fatty acids stored in triglycerides during times of low glucose (Nakamura et al. 2014). PPARs also demonstrate anti-inflammatory effects, notably by inhibiting the activation of the proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) as shown in animal studies. Thus lack of stimulation of PPARs due to low n-3 PUFA levels could contribute to inflammation- and bioenergetic-related depression symptoms, which map closely onto the concepts of neurovegetative symptoms and sickness behaviors (Smith et al. 2012; Low et al. 2014).

Both n-3 PUFAs (Sullivan et al. 2018) and estrogen (Marin and Diaz 2018) can have effects not only on plasma membranes but also on the mitochondrial phospholipidome. For instance, estrogen promotes improved bioenergetic functioning (Williams et al. 2012; Leng et al. 2018).

4.4 Receptor-Mediated Androgen Effects in the Brain

In animal studies, highly abundant androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) exhibit beneficial effects on neuroprotection and neurogenesis (reviewed in Butterfield et al. (2005)); mechanisms include noncompetitive antagonism of γ-aminobutyric acid (GABA)A, positive allosteric

modulation of *N*-methyl-D-aspartic acid (NMDA), and agonism on sigma-1 receptors (reviewed in (Maninger et al. 2009)). These beneficial functions are difficult to reconcile with multiple reports (reviewed in post-traumatic stress disorder (PTSD) (Maninger et al. 2009) and two reports in suicide attempters (Butterfield et al. 2005; Chatzittofis et al. 2013) of elevated DHEA/DHEAS, unless said elevations are compensatory in nature. Testosterone has been reported to upregulate alpha-2A adrenergic transcription, specifically in the prefrontal cortex (Agrawal et al. 2019). Additional work is needed to understand mechanisms of action whereby androgens may affect suicide risk.

5 Conclusions

Multiple lines of clinical investigation point to connections between lipid status and suicide risk. Findings with the greatest consensus include associations between suicide risk and (1) low n-3 PUFA intake and low estrogen states in women, (2) low cholesterol in both sexes, and (3) higher testosterone in men. A logical emerging research direction is to discover genomic (Li et al. 2017; Knowles et al. 2018) and epigenetic (Haghighi et al. 2015) biomarkers related to both lipid metabolism and suicide risk, toward the identification of individuals with the greatest potential to benefit from lipid optimization.

To traverse the conceptual distance between lipid biochemistry and behavioral outcomes, we have described two major mechanisms, effects on lipid microdomains and agonist binding to PPARs, whereby lipids are known to exert regulatory effects on dynamic processes implicated in depression and suicide risk, including inflammation, receptor-mediated signaling, oxidative stress, and bioenergetics (see Fig. 3). Studying pathophysiology in this context is challenging due to the complex, interactive, and often homeostatic nature of these processes. Areas for more detailed future investigation include lipid-lipid interactions and the roles of different lipid species. Also, most of the existing mechanistic evidence is based on preclinical/translational work. Therefore studies in humans are needed to confirm and elaborate on the clinical relevance of the mechanisms described, which may illuminate new potential treatment targets for the reduction of suicide risk.

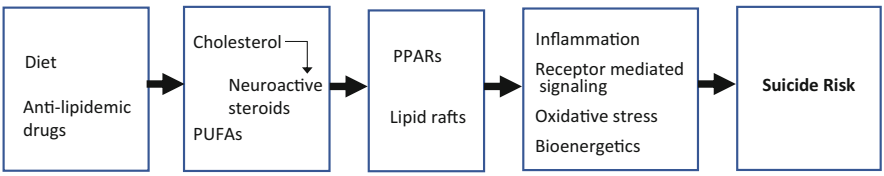


Fig. 3 Schematic of mechanisms contributing to lipid effects on suicide risk

References

Abdukeyum GG, Owen AJ, Larkin TA, McLennan PL (2016) Up-regulation of mitochondrial antioxidant superoxide dismutase underpins persistent cardiac nutritional-preconditioning by long chain n-3 polyunsaturated fatty acids in the rat. J Clin Med 5(3):32

Agrawal J, Ludwig B, Roy B, Dwivedi Y (2019) Chronic testosterone increases impulsivity and influences the transcriptional activity of the alpha-2A adrenergic receptor signaling pathway in rat brain. Mol Neurobiol 56(6):4061–4071

Altinkilic S, Naziroglu M, Uguz AC, Ozcankaya R (2010) Fish oil and antipsychotic drug risperidone modulate oxidative stress in PC12 cell membranes through regulation of cytosolic calcium ion release and antioxidant system. J Membr Biol 235(3):211–218

Arunagiri P, Rajeshwaran K, Shanthakumar J, Tamilselvan T, Balamurugan E (2014) Combination of omega-3 fatty acids, lithium, and aripiprazole reduces oxidative stress in brain of mice with mania. Biol Trace Elem Res 160(3):409–417

Baca-Garcia E, Diaz-Sastre C, Ceverino A, Perez-Rodriguez MM, Navarro-Jimenez R, Lopez-Castroman J, Saiz-Ruiz J, de Leon J, Oquendo MA (2010) Suicide attempts among women during low estradiol/low progesterone states. J Psychiatr Res 44(4):209–214

Bartoli F, Di Brita C, Crocamo C, Clerici M, Carra G (2017) Lipid profile and suicide attempt in bipolar disorder: a meta-analysis of published and unpublished data. Prog Neuropsychopharmacol Biol Psychiatry 79(Pt B):90–95

Bjork K, Svenningsson P (2011) Modulation of monoamine receptors by adaptor proteins and lipid rafts: role in some effects of centrally acting drugs and therapeutic agents. Annu Rev Pharmacol Toxicol 51:211–242

Brower KJ, Blow FC, Eliopulos GA, Beresford TP (1989) Anabolic androgenic steroids and suicide. Am J Psychiatry 146(8):1075

Butterfield MI, Stechuchak KM, Connor KM, Davidson JR, Wang C, MacKuen CL, Pearlstein AM, Marx CE (2005) Neuroactive steroids and suicidality in posttraumatic stress disorder. Am J Psychiatry 162(2):380–382

Capuron L, Miller AH (2011) Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther 130(2):226–238

Capuzzi E, Bartoli F, Crocamo C, Malerba MR, Clerici M, Carra G (2018) Recent suicide attempts and serum lipid profile in subjects with mental disorders: a cross-sectional study. Psychiatry Res 270:611–615

Casos K, Zaragoza MC, Zarkovic N, Zarkovic K, Andrisic L, Portero-Otin M, Cacabelos D, Mitjavila MT (2010) A fish-oil-rich diet reduces vascular oxidative stress in apoE(−/−) mice. Free Radic Res 44(7):821–829

Chatzittofis A, Nordstrom P, Hellstrom C, Arver S, Asberg M, Jokinen J (2013) CSF 5-HIAA, cortisol and DHEAS levels in suicide attempters. Eur Neuropsychopharmacol 23 (10):1280–1287

Colangelo LA, He K, Whooley MA, Daviglus ML, Liu K (2009) Higher dietary intake of long-chain omega-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. Nutrition 25(10):1011–1019

Dantzer R, O'Connor J, Freund G, Johnson R, Kelley KW (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9(1):46–56

de Lorgeril M, Salen P, Guiraud A, Zeghichi S, Boucher F, de Leiris J (2005) Lipid-lowering drugs and essential omega-6 and omega-3 fatty acids in patients with coronary heart disease. Nutr Metab Cardiovasc Dis 15(1):36–41

Di Nunzio M, Valli V, Bordoni A (2016) PUFA and oxidative stress. Differential modulation of the cell response by DHA. Int J Food Sci Nutr 67(7):834–843

Diaz M, Fabelo N, Casanas-Sanchez V, Marin R, Gomez T, Quinto-Alemany D, Perez JA (2016) Hippocampal lipid homeostasis in APP/PS1 mice is modulated by a complex interplay between dietary DHA and estrogens: relevance for Alzheimer's disease. J Alzheimers Dis 49(2):459–481

Dreja K, Voldstedlund M, Vinten J, Tranum-Jensen J, Hellstrand P, Sward K (2002) Cholesterol depletion disrupts caveolae and differentially impairs agonist-induced arterial contraction. Arterioscler Thromb Vasc Biol 22(8):1267–1272

Eidan AJ, Al-Harmoosh RA, Al-Amarei HM (2019) Estimation of IL-6, INFgamma, and lipid profile in suicidal and nonsuicidal adults with major depressive disorder. J Interferon Cytokine Res 39(3):181–189

Fan YY, Fuentes NR, Hou TY, Barhoumi R, Li XC, Deutz NEP, Engelen M, McMurray DN, Chapkin RS (2018) Remodelling of primary human CD4+ T cell plasma membrane order by n-3 PUFA. Br J Nutr 119(2):163–175

Giordano E, Visioli F (2014) Long-chain omega 3 fatty acids: molecular bases of potential antioxidant actions. Prostaglandins Leukot Essent Fatty Acids 90(1):1–4

Gustavsson G, Traskman-Bendz L, Higley JD, Westrin A (2003) CSF testosterone in 43 male suicide attempters. Eur Neuropsychopharmacol 13(2):105–109

Haghighi F, Galfalvy H, Chen S, Huang YY, Cooper TB, Burke AK, Oquendo MA, Mann JJ, Sublette ME (2015) DNA methylation perturbations in genes involved in polyunsaturated fatty acid biosynthesis associated with depression and suicide risk. Front Neurol 6:92

Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J (2004) Is low dietary intake of omega-3 fatty acids associated with depression? Am J Psychiatry 161(3):567–569

Harris JI, Hibbeln JR, Mackey RH, Muldoon MF (2004) Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients. Prostaglandins Leukot Essent Fatty Acids 71 (4):263–269

Hibbeln JR (2002) Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. J Affect Disord 69(1-3):15–29

Hibbeln JR, Gow RV (2014) The potential for military diets to reduce depression, suicide, and impulsive aggression: a review of current evidence for omega-3 and omega-6 fatty acids. Mil Med 179(11 Suppl):117–128

Hibbeln JR, Salem N Jr (1995) Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. Am J Clin Nutr 62(1):1–9

Hirayama T (1990) Life style and mortality. A large scale census-based cohort study in Japan. In: Contributions to epidemiology and biostatistics, vol 6. Karger, New York

Hofer P, Lanzenberger R, Kasper S (2013) Testosterone in the brain: neuroimaging findings and the potential role for neuropsychopharmacology. Eur Neuropsychopharmacol 23(2):79–88

Hsiao CC, Lin HC, Chang YJ, Yang SP, Tsao LY, Lee CH, Chen HN, Chen JY, Tsai YG (2019) Intravenous fish oil containing lipid emulsion attenuates inflammatory cytokines and the development of bronchopulmonary dysplasia in very premature infants: a double-blind, randomized controlled trial. Clin Nutr 38(3):1045–1052

Huan M, Hamazaki K, Sun Y, Itomura M, Liu H, Kang W, Watanabe S, Terasawa K, Hamazaki T (2004) Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. Biol Psychiatry 56(7):490–496

Ikonen E (2008) Cellular cholesterol trafficking and compartmentalization. Nat Rev Mol Cell Biol 9 (2):125–138

Janssen HL, Brouwer JT, van der Mast RC, Schalm SW (1994) Suicide associated with alfa-interferon therapy for chronic viral hepatitis. J Hepatol 21(2):241–243

Kaplan JR, Shively CA, Fontenot MB, Morgan TM, Howell SM, Manuck SB, Muldoon MF, Mann JJ (1994) Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. Psychosom Med 56(6):479–484

Kavoor AR, Mitra S, Kumar S, Sisodia AK, Jain R (2017) Lipids, aggression, suicidality and impulsivity in drug-naive/drug-free patients of schizophrenia. Asian J Psychiatr 27:129–136

Knowles EEM, Curran JE, Meikle PJ, Huynh K, Mathias SR, Goring HHH, VandeBerg JL, Mahaney MC, Jalbrzikowski M, Mosior MK, Michael LF, Olvera RL, Duggirala R, Almasy L, Glahn DC, Blangero J (2018) Disentangling the genetic overlap between cholesterol and suicide risk. Neuropsychopharmacology 43(13):2556–2563

Leenaars AA, Dogra TD, Girdhar S, Dattagupta S, Leenaars L (2009) Menstruation and suicide: a histopathological study. Crisis 30(4):202–207
Leng X, Kinnun JJ, Cavazos AT, Canner SW, Shaikh SR, Feller SE, Wassall SR (2018) All n-3 PUFA are not the same: MD simulations reveal differences in membrane organization for EPA, DHA and DPA. Biochim Biophys Acta Biomembr 1860(5):1125–1134
Lenz B, Rother M, Bouna-Pyrrou P, Muhle C, Tektas OY, Kornhuber J (2019) The androgen model of suicide completion. Prog Neurobiol 172:84–103
Lewis MD, Hibbeln JR, Johnson JE, Lin YH, Hyun DY, Loewke JD (2011) Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. J Clin Psychiatry 72(12):1585–1590
Li H, Ruan XZ, Powis SH, Fernando R, Mon WY, Wheeler DC, Moorhead JF, Varghese Z (2005) EPA and DHA reduce LPS-induced inflammation responses in HK-2 cells: evidence for a PPAR-gamma-dependent mechanism. Kidney Int 67(3):867–874
Li F, Liu X, Zhang D (2016) Fish consumption and risk of depression: a meta-analysis. J Epidemiol Community Health 70(3):299–304
Li J, Yoshikawa A, Meltzer HY (2017) Replication of rs300774, a genetic biomarker near ACP1, associated with suicide attempts in patients with schizophrenia: relation to brain cholesterol biosynthesis. J Psychiatr Res 94:54–61
Lin PY, Huang SY, Su KP (2010) A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry 68(2):140–147
Lin PY, Mischoulon D, Freeman MP, Matsuoka Y, Hibbeln J, Belmaker RH, Su KP (2012) Are omega-3 fatty acids antidepressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression. Mol Psychiatry 17 (12):1161–1163
Linton L, Taylor M, Dunn S, Martin L, Chavez S, Stanitz G, Huszti E, Minkin S, Boyd N (2016) Associations of serum levels of sex hormones in follicular and luteal phases of the menstrual cycle with breast tissue characteristics in young women. PLoS One 11(10):e0163865
Liu JJ, Green P, John Mann J, Rapoport SI, Sublette ME (2015) Pathways of polyunsaturated fatty acid utilization: implications for brain function in neuropsychiatric health and disease. Brain Res 1597:220–246
Liu JJ, Hezghia A, Shaikh SR, Cenido JF, Stark RE, Mann JJ, Sublette ME (2018) Regulation of monoamine transporters and receptors by lipid microdomains: implications for depression. Neuropsychopharmacology 43(11):2165–2179
Low CA, Bovbjerg DH, Jenkins FJ, Ahrendt SA, Choudry HA, Holtzman MP, Jones HL, Pingpank JF, Ramalingam L, Zeh HJ, Zureikat AH, Bartlett DL (2014) Preoperative inflammatory biomarkers and neurovegetative symptoms in peritoneal carcinomatosis patients. Brain Behav Immun 42:65–68
Lucaciu LA, Dumitrascu DL (2015) Depression and suicide ideation in chronic hepatitis C patients untreated and treated with interferon: prevalence, prevention, and treatment. Ann Gastroenterol 28(4):440–447
Maes M, Christophe A, Bosmans E, Lin A, Neels H (2000) In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. Biol Psychiatry 47(10):910–920
Maes M, Galecki P, Chang YS, Berk M (2011) A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry 35(3):676–692
Magnani F, Tate CG, Wynne S, Williams C, Haase J (2004) Partitioning of the serotonin transporter into lipid microdomains modulates transport of serotonin. J Biol Chem 279(37):38770–38778
Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH (2009) Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol 30(1):65–91
Marin R, Diaz M (2018) Estrogen interactions with lipid rafts related to neuroprotection. impact of brain ageing and menopause. Front Neurosci 12:128

Marin R, Marrero-Alonso J, Fernandez C, Cury D, Diaz M (2012) Estrogen receptors in lipid raft signalling complexes for neuroprotection. Front Biosci (Elite Ed) 4:1420–1433

Markianos M, Tripodianakis J, Istikoglou C, Rouvali O, Christopoulos M, Papageorgopoulos P, Seretis A (2009) Suicide attempt by jumping: a study of gonadal axis hormones in male suicide attempters versus men who fell by accident. Psychiatry Res 170(1):82–85

Martins JG (2009) EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr 28(5):525–542

Martins JG, Bentsen H, Puri BK (2012) Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. Mol Psychiatry 17(12):1144–1149

Mathew B, Srinivasan K, Pradeep J, Thomas T, Mandal AK (2018) Suicidal behaviour is associated with decreased esterified cholesterol in plasma and membrane fluidity of platelets. Asian J Psychiatr 32:105–109

Mazereeuw G, Herrmann N, Andreazza AC, Scola G, Ma DWL, Oh PI, Lanctot KL (2017a) Baseline oxidative stress is associated with memory changes in omega-3 fatty acid treated coronary artery disease patients. Cardiovasc Psychiatry Neurol 2017:3674371

Mazereeuw G, Herrmann N, Andreazza AC, Scola G, Ma DWL, Oh PI, Lanctot KL (2017b) Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. Brain Behav Immun 60:136–141

Mensi R, Messaoud A, Mhallah A, Azizi I, Salah WH, Douki W, Najjar MF, Gaha L (2016) The association between altered lipid profile and suicide attempt among Tunisian patients with schizophrenia. Ann Gen Psychiatry 15:36

Morris G, Berk M (2015) The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. BMC Med 13:68

Muldoon MF, Manuck SB, Matthews KA (1990) Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. BMJ 301(6747):309–314

Murakami K, Mizoue T, Sasaki S, Ohta M, Sato M, Matsushita Y, Mishima N (2008) Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. Nutrition 24(2):140–147

Nakamura N, Hamazaki T, Jokaji H, Minami S, Kobayashi M (1998) Effect of HMG-CoA reductase inhibitors on plasma polyunsaturated fatty acid concentrations in patients with hyperlipidemia. Int J Clin Lab Res 28(3):192–195

Nakamura MT, Yudell BE, Loor JJ (2014) Regulation of energy metabolism by long-chain fatty acids. Prog Lipid Res 53:124–144

Nozue T, Michishita I (2015) Statin treatment alters serum n-3 to n-6 polyunsaturated fatty acids ratio in patients with dyslipidemia. Lipids Health Dis 14:67

Nyalala JO, Wang J, Dang A, Faas FH, Smith WG (2008) Hypertriglyceridemia and hypercholesterolemia: effects of drug treatment on fatty acid composition of plasma lipids and membranes. Prostaglandins Leukot Essent Fatty Acids 78(4-5):271–280

Oka K, Hirano T, Noguchi M (1988) Changes in the concentration of testosterone in serum during the menstrual cycle, as determined by liquid chromatography. Clin Chem 34(3):557–560

Perera S, Eisen RB, Bhatt M, Dennis BB, Bawor M, El-Sheikh W, DeJesus J, Rangarajan S, Sholer H, Iordan E, Mackie P, Islam S, Dehghan M, Brasch J, Meyre D, de Souza R, Thabane L, Samaan Z (2018) Exploring metabolic factors and health behaviors in relation to suicide attempts: a case-control study. J Affect Disord 229:386–395

Perez-Rodriguez MM, Lopez-Castroman J, Martinez-Vigo M, Diaz-Sastre C, Ceverino A, Nunez-Beltran A, Saiz-Ruiz J, de Leon J, Baca-Garcia E (2011) Lack of association between testosterone and suicide attempts. Neuropsychobiology 63(2):125–130

Peri A, Benvenuti S, Luciani P, Deledda C, Cellai I (2011) Membrane cholesterol as a mediator of the neuroprotective effects of estrogens. Neuroscience 191:107–117

Poudel-Tandukar K, Nanri A, Iwasaki M, Mizoue T, Matsushita Y, Takahashi Y, Noda M, Inoue M, Tsugane S (2011) Long chain n-3 fatty acids intake, fish consumption and suicide

in a cohort of Japanese men and women – the Japan Public Health Center-based (JPHC) prospective study. J Affect Disord 129(1-3):282–288

Pucadyil TJ, Chattopadhyay A (2004) Cholesterol modulates ligand binding and G-protein coupling to serotonin(1A) receptors from bovine hippocampus. Biochim Biophys Acta 1663 (1-2):188–200

Raison CL, Capuron L, Miller AH (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27(1):24–31

Ramzan R, Staniek K, Kadenbach B, Vogt S (2010) Mitochondrial respiration and membrane potential are regulated by the allosteric ATP-inhibition of cytochrome c oxidase. Biochim Biophys Acta 1797(9):1672–1680

Rao YP, Lokesh BR (2017) Down-regulation of NF-kappaB expression by n-3 fatty acid-rich linseed oil is modulated by PPARgamma activation, eicosanoid cascade and secretion of cytokines by macrophages in rats fed partially hydrogenated vegetable fat. Eur J Nutr 56 (3):1135–1147

Repo-Tiihonen E, Halonen P, Tiihonen J, Virkkunen M (2002) Total serum cholesterol level, violent criminal offences, suicidal behavior, mortality and the appearance of conduct disorder in Finnish male criminal offenders with antisocial personality disorder. Eur Arch Psychiatry Clin Neurosci 252(1):8–11

Reuter C, Caldwell B, Basehore H (2017) Evaluation of cholesterol as a biomarker for suicidality in a veteran sample. Res Nurs Health 40(4):341–349

Robichaud PP, Munganyiki JE, Boilard E, Surette ME (2018) Polyunsaturated fatty acid elongation and desaturation in activated human T-cells: ELOVL5 is the key elongase. J Lipid Res 59 (12):2383–2396

Rodriguez-Cruz M, Cruz-Guzman ODR, Almeida-Becerril T, Solis-Serna AD, Atilano-Miguel S, Sanchez-Gonzalez JR, Barbosa-Cortes L, Ruiz-Cruz ED, Huicochea JC, Cardenas-Conejo A, Escobar-Cedillo RE, Yam-Ontiveros CA, Ricardez-Marcial EF (2018) Potential therapeutic impact of omega-3 long chain-polyunsaturated fatty acids on inflammation markers in Duchenne muscular dystrophy: a double-blind, controlled randomized trial. Clin Nutr 37(6 Pt A):1840–1851

Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H (2007) Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab 92(2):405–413

Sadikot R (2012) The role of cholesterol and lipid rafts in regulation of TLR receptors. In: Levitan I, Barrantes FJ (eds) Cholesterol regulation of ion channels and receptors. Wiley, Hoboken

Sanchez-Villegas A, Henriquez P, Figueiras A, Ortuno F, Lahortiga F, Martinez-Gonzalez MA (2007) Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. Eur J Nutr 46(6):337–346

Sarsilmaz M, Songur A, Ozyurt H, Kus I, Ozen OA, Ozyurt B, Sogut S, Akyol O (2003) Potential role of dietary omega-3 essential fatty acids on some oxidant/antioxidant parameters in rats' corpus striatum. Prostaglandins Leukot Essent Fatty Acids 69(4):253–259

Saunders KE, Hawton K (2006) Suicidal behaviour and the menstrual cycle. Psychol Med 36 (7):901–912

Scanlon SM, Williams DC, Schloss P (2001) Membrane cholesterol modulates serotonin transporter activity. Biochemistry 40(35):10507–10513

Segoviano-Mendoza M, Cardenas-de la Cruz M, Salas-Pacheco J, Vazquez-Alaniz F, La Llave-Leon O, Castellanos-Juarez F, Mendez-Hernandez J, Barraza-Salas M, Miranda-Morales E, Arias-Carrion O, Mendez-Hernandez E (2018) Hypocholesterolemia is an independent risk factor for depression disorder and suicide attempt in Northern Mexican population. BMC Psychiatry 18(1):7

Sher L, Grunebaum MF, Sullivan GM, Burke AK, Cooper TB, Mann JJ, Oquendo MA (2014) Association of testosterone levels and future suicide attempts in females with bipolar disorder. J Affect Disord 166:98–102

Sher L, Flory J, Bierer L, Makotkine I, Yehuda R (2018) Dehydroepiandrosterone and dehydroepiandrosterone sulfate levels in combat veterans with or without a history of suicide attempt. Acta Psychiatr Scand 138(1):55–61

Shichiri M, Adkins Y, Ishida N, Umeno A, Shigeri Y, Yoshida Y, Fedor DM, Mackey BE, Kelley DS (2014) DHA concentration of red blood cells is inversely associated with markers of lipid peroxidation in men taking DHA supplement. J Clin Biochem Nutr 55(3):196–202

Shrivastava A, Johnston M, Campbell R, De Sousa A, Shah N (2017) Serum cholesterol and Suicide in first episode psychosis: a preliminary study. Indian J Psychiatry 59(4):478–482

Simopoulos AP (2006) Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. Biomed Pharmacother 60(9):502–507

Sjogren B, Hamblin MW, Svenningsson P (2006) Cholesterol depletion reduces serotonin binding and signaling via human 5-HT(7(a)) receptors. Eur J Pharmacol 552(1-3):1–10

Sjogren B, Csoregh L, Svenningsson P (2008) Cholesterol reduction attenuates 5-HT1A receptor-mediated signaling in human primary neuronal cultures. Naunyn Schmiedebergs Arch Pharmacol 378(4):441–446

Skrabanek P (1992) Book reviews: T. Hirayama life style and mortality a large-scale census-based cohort study in Japan. Indoor Environ 1(2):126

Smith KJ, Norris S, McKiernan S, Hynes B, O'Dwyer AM, O'Mara SM (2012) An exploration of depressive symptoms in hepatitis C patients taking interferon-alpha: increase in sickness behaviors but not negative cognitions. J Clin Exp Hepatol 2(3):218–223

Smith KJ, Sanderson K, McNaughton SA, Gall SL, Dwyer T, Venn AJ (2014) Longitudinal associations between fish consumption and depression in young adults. Am J Epidemiol 179 (10):1228–1235

Sockalingam S, Links PS, Abbey SE (2011) Suicide risk in hepatitis C and during interferon-alpha therapy: a review and clinical update. J Viral Hepat 18(3):153–160

Sommer B, Montano LM, Carbajal V, Flores-Soto E, Ortega A, Ramirez-Oseguera R, Irles C, El-Yazbi AF, Cho WJ, Daniel EE (2009) Extraction of membrane cholesterol disrupts caveolae and impairs serotonergic (5-HT2A) and histaminergic (H1) responses in bovine airway smooth muscle: role of Rho-kinase. Can J Physiol Pharmacol 87(3):180–195

Sowa-Kucma M, Styczen K, Siwek M, Misztak P, Nowak RJ, Dudek D, Rybakowski JK, Nowak G, Maes M (2018) 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 81:372–383

Stefansson J, Chatzittofis A, Nordstrom P, Arver S, Asberg M, Jokinen J (2016) CSF and plasma testosterone in attempted suicide. Psychoneuroendocrinology 74:1–6

Stoffel-Wagner B (2001) Neurosteroid metabolism in the human brain. Eur J Endocrinol 145 (6):669–679

Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ (2006) Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. Am J Psychiatry 163 (6):1100–1102

Sublette ME, Ellis SP, Geant AL, Mann JJ (2011) Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry 72(12):1577–1584

Sullivan EM, Pennington ER, Green WD, Beck MA, Brown DA, Shaikh SR (2018) Mechanisms by which dietary fatty acids regulate mitochondrial structure-function in health and disease. Adv Nutr 9(3):247–262

Suneson K, Asp M, Traskman-Bendz L, Westrin A, Ambrus L, Lindqvist D (2019) Low total cholesterol and low-density lipoprotein associated with aggression and hostility in recent suicide attempters. Psychiatry Res 273:430–434

Suzuki K (1981) Chemistry and metabolism of brain lipids. In: Siegel D, Albers R, Agranoff B, Katzman R (eds) Basic neurochemistry. Little, Brown and Co., Boston, pp 355–370

Svensson T, Inoue M, Sawada N, Charvat H, Mimura M, Tsugane S, JPHC Study Group (2017) High serum total cholesterol is associated with suicide mortality in Japanese women. Acta Psychiatr Scand 136(3):259–268

Svensson T, Inoue M, Sawada N, Mimura M, Tsugane S (2018) High serum total cholesterol is associated with suicide mortality in Japanese women independently of menopause. Acta Psychiatr Scand 137(1):80–81

Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamaki H, Lehtonen J, Vartiainen E (2001) Fish consumption and depressive symptoms in the general population in Finland. Psychiatr Serv 52(4):529–531

Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Rasanen P (2004) Fish consumption and depression: the Northern Finland 1966 birth cohort study. J Affect Disord 82(3):447–452

Tripodianakis J, Markianos M, Rouvali O, Istikoglou C (2007) Gonadal axis hormones in psychiatric male patients after a suicide attempt. Eur Arch Psychiatry Clin Neurosci 257(3):135–139

Tsai AC, Lucas M, Okereke OI, O'Reilly EJ, Mirzaei F, Kawachi I, Ascherio A, Willett WC (2014) Suicide mortality in relation to dietary intake of n-3 and n-6 polyunsaturated fatty acids and fish: equivocal findings from 3 large US cohort studies. Am J Epidemiol 179(12):1458–1466

Vargas HO, Nunes SO, Pizzo de Castro M, Bortolasci CC, Sabbatini Barbosa D, Kaminami Morimoto H, Venugopal K, Dodd S, Maes M, Berk M (2013) Oxidative stress and lowered total antioxidant status are associated with a history of suicide attempts. J Affect Disord 150 (3):923–930

Virkkunen M (1979) Serum cholesterol in antisocial personality. Neuropsychobiology 5(1):27–30

Virkkunen M (1983) Serum cholesterol levels in homicidal offenders. A low cholesterol level is connected with a habitually violent tendency under the influence of alcohol. Neuropsychobiology 10(2–3):65–69

Wassall SR, Stillwell W (2008) Docosahexaenoic acid domains: the ultimate non-raft membrane domain. Chem Phys Lipids 153(1):57–63

Wassall SR, Stillwell W (2009) Polyunsaturated fatty acid-cholesterol interactions: domain formation in membranes. Biochim Biophys Acta 1788(1):24–32

Wassall SR, Brzustowicz MR, Shaikh SR, Cherezov V, Caffrey M, Stillwell W (2004) Order from disorder, corralling cholesterol with chaotic lipids. The role of polyunsaturated lipids in membrane raft formation. Chem Phys Lipids 132(1):79–88

Wassall SR, Leng X, Canner SW, Pennington ER, Kinnun JJ, Cavazos AT, Dadoo S, Johnson D, Heberle FA, Katsaras J, Shaikh SR (2018) Docosahexaenoic acid regulates the formation of lipid rafts: a unified view from experiment and simulation. Biochim Biophys Acta Biomembr 1860(10):1985–1993

Whelan J, Gowdy KM, Shaikh SR (2016) N-3 polyunsaturated fatty acids modulate B cell activity in pre-clinical models: Implications for the immune response to infections. Eur J Pharmacol 785:10–17

Williams JA, Batten SE, Harris M, Rockett BD, Shaikh SR, Stillwell W, Wassall SR (2012) Docosahexaenoic and eicosapentaenoic acids segregate differently between raft and nonraft domains. Biophys J 103(2):228–237

Wong SW, Kwon MJ, Choi AM, Kim HP, Nakahira K, Hwang DH (2009) Fatty acids modulate Toll-like receptor 4 activation through regulation of receptor dimerization and recruitment into lipid rafts in a reactive oxygen species-dependent manner. J Biol Chem 284(40):27384–27392

Wu S, Ding Y, Wu F, Xie G, Hou J, Mao P (2016) Serum lipid levels and suicidality: a meta-analysis of 65 epidemiological studies. J Psychiatry Neurosci 41(1):56–69

Yang Y, Je Y (2018) Fish consumption and depression in Korean adults: the Korea National Health and Nutrition Examination Survey, 2013-2015. Eur J Clin Nutr 72(8):1142–1149

Yang Y, Kim Y, Je Y (2018) Fish consumption and risk of depression: epidemiological evidence from prospective studies. Asia Pac Psychiatry 10(4):e12335

Glutamine and New Pharmacological Targets to Treat Suicidal Ideation

Luis Jimenez-Trevino, Leticia Gonzalez-Blanco, Clara Alvarez-Vazquez, Julia Rodriguez-Revuelta, and Pilar A. Saiz Martinez

Contents

Abstract Glutamate is the major excitatory neurotransmitter in the central nervous system, and it is linked with the amino acid glutamine through a metabolic relationship of enzymatic compound interconversion and transportation, also known as the glutamate-glutamine cycle.

L. Jimenez-Trevino, L. Gonzalez-Blanco, and P. A. Saiz Martinez (✉)
Department of Psychiatry, University of Oviedo, Oviedo, Spain

Biomedical Research Networking Centre in Mental Health (CIBERSAM), Oviedo, Spain

Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain

Mental Health Services of Principado de Asturias (SESPA), Oviedo, Spain
e-mail: frank@uniovi.es

C. Alvarez-Vazquez
Mental Health Services of Principado de Asturias (SESPA), Oviedo, Spain

J. Rodriguez-Revuelta
Department of Psychiatry, University of Oviedo, Oviedo, Spain

Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain

Mental Health Services of Principado de Asturias (SESPA), Oviedo, Spain

Curr Topics Behav Neurosci (2020) 46: 179–196
https://doi.org/10.1007/7854_2020_168
Published Online: 15 September 2020

A growing body of evidence suggests involvement of the glutamatergic neurotransmitter system in suicidal behaviours. The initial evidence comes from the pathophysiology of neuropsychiatric disorders, as disruptions in glutamate neurotransmission have been found underlying pathology in multiple suicide-related psychiatric conditions such as major depressive disorder, schizophrenia, post-traumatic stress disorder, and bipolar disorder.

Existing data from experimental animal models and human in vivo studies also demonstrate that glutamate plays a key role in suicide-related personality traits including aggression and impulsive aggression.

Further studies on glutamate system dysfunction underlying suicidal behaviours have focused on the different steps of the glutamate-glutamine cycle: an inflammation-mediated reduction of glutamine synthetase activity has been found in depressed suicide attempters, phosphate-activated glutaminase genes are reduced in suicide completers, and gene expression abnormalities in NMDA receptors have also been discovered in suicide victims.

Evidence of a role of the glutamate-glutamine cycle in suicidal behaviours unveils new targets for anti-suicide interventions. Lithium's mechanism to reduce the risk of suicide in people with mood disorders may be related to its ability to increase glutamine synthetase, whereas novel NMDA antagonists such as ketamine [or its S(+) enantiomer esketamine] have already demonstrated positive results in reducing suicidal ideation.

Keywords Esketamine · Glutamate · Glutamine · Ketamine · NMDA antagonist · Suicidal behaviour · Suicide prevention

1 The Glutamate-Glutamine Cycle

Glutamate is the major excitatory neurotransmitter in the central nervous system, and it is linked with the amino acid glutamine through a metabolic relationship of enzymatic compound interconversion and transportation, also known as the glutamate-glutamine cycle (Fig. 1): vesicular glutamate transporters load glutamate into synaptic vesicles at presynaptic terminals. An action potential propagated to a presynaptic terminal triggers glutamate release into the synaptic clefts (Hayashi 2018). Glutamate activates metabotropic and ionotropic receptors. The ionotropic receptors are further divided into N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors (Fudalej et al. 2017). It is then removed by glutamate transporters to prepare for another signal. The glutamate clearance also prevents neuronal excitotoxicity caused by excess activation of glutamate receptors. Both neurons and astrocytes express glutamate transporters for glutamate uptake (Hayashi 2018). Within astrocytes, glutamate is converted into glutamine by an energy-demanding process involving the enzyme glutamine synthetase. Glutamine is then released by

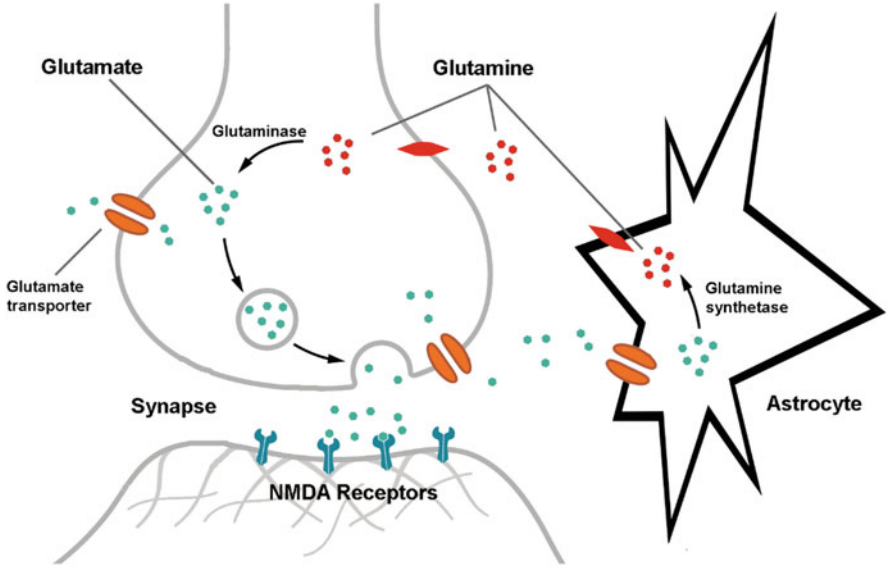


Fig. 1 The glutamate-glutamine cycle

the astrocytes and taken up by neuronal terminals where it is reconverted to glutamate by the enzyme glutaminase to replenish neurotransmitter pools (Kalkman 2011).

2 Glutamate-Glutamine Cycle and Psychopathology of Suicide

A growing body of evidence suggests involvement of the glutamatergic neurotransmitter system in suicidal behaviours (Bernstein et al. 2013).

The initial evidence comes from the pathophysiology of neuropsychiatric disorders. Mounting data indicate that disruptions in glutamate neurotransmission are a common underlying pathology in multiple suicide-related psychiatric conditions such as major depressive disorder (MDD), schizophrenia (SCZ), post-traumatic stress disorder (PTSD), and bipolar disorder (BD) (O'Donovan et al. 2017; Parkin et al. 2018; Wickens et al. 2018).

Existing data from experimental animal models and human in vivo studies demonstrate that glutamate plays a key role in suicide-related personality traits including aggression and impulsive aggression (Coccaro et al. 2013; Masugi-Tokita et al. 2016; Takahashi et al. 2015). Animal studies of glutaminergic activity suggest a facilitator role for central glutamate in the modulation of aggression. Glutamate

input in the dorsal raphe nucleus seems to be enhanced during escalated aggression in male mice (Takahashi et al. 2015).

The first study to investigate the relationship between central nervous system glutamate levels and aggression and/or impulsivity in human subjects found statistically significant direct correlations between cerebrospinal fluid (CSF) glutamate levels and composite measures of aggression, impulsivity, and impulsive aggression in healthy subjects as well as patients with personality disorders (Coccaro et al. 2013). CSF glutamate concentration also correlates with impulsive aggression in human subjects (Coccaro et al. 2013). More recent data from MR spectroscopy studies have provided new human in vivo evidence for the role of glutamate in impulsivity and aggression (Ende et al. 2016).

Courtet et al. have included glutamatergic neurotransmission in a comprehensive model suggesting how inflammation may contribute to the pathophysiology of suicidal behaviour: suicidal behaviour occurs due to an interaction between suicidal vulnerability and stressors. Considering suicidal vulnerability, childhood maltreatment leads to a systemic inflammatory state, promoting HPA axis dysregulation; sleep disturbances induce an inflammation response characterized by increases in cytokine serum level and C-reactive protein; and *T. gondii* infection (increased in suicidal patients) promotes a low chronic inflammatory state. This leads to indoleamine-2,3-dioxygenase (IDO) activation, which produces kynurenine from tryptophan. Then, microglial activation (i.e. dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), mediodorsal thalamus (MDT)) leads to increased quinolinic acid production and decreased kynurenic acid production from kynurenine, which increases NMDA stimulation. The inflammatory state also induces decrease in neurotrophins and in particular diminished levels of brain-derived neurotrophic factor (BDNF) leading to decreased neuronal repair, decreased neurogenesis, and increased activation in glutamatergic pathways, which also contributes to neuronal apoptosis. Additionally, enhanced metabolism of tryptophan results in depleted serotonin levels, which are involved in the personality dimension of suicidal vulnerability (i.e. impulsive aggression, pessimism). This increased consumption of tryptophan also induces the production of detrimental tryptophan catabolites with neurotoxic effects. Furthermore, stressors – psychiatric diseases and adverse life events (social isolation and rejection) – act on suicidal vulnerability to induce suicidal behaviour, through an activation of inflammatory response (Courtet et al. 2016).

3 Evidence of Glutamate-Glutamine Cycle Changes in Suicidal Behaviours

Further studies on glutamate system dysfunction underlying suicidal behaviours have focused on the different steps of the glutamate-glutamine cycle, providing new targets for anti-suicide interventions.

3.1 Glutamine Synthetase

The enzyme glutamine synthetase, mainly located in the astroglia, is required to synthesize the non-toxic glutamine from the re-uptake of glutamate. Due to this central position in the glutamate-glutamine cycle, possible changes in brain glutamine synthetase activity and expression came early into the focus of neuropsychiatric research (Bernstein et al. 2013).

Glutamine synthetase activity was found to be reduced in depressed suicide attempters as well as in non-depressed suicide attempters (Klempan et al. 2009; Sequeira et al. 2009). To find out if there is a suicide-specific pattern of brain glutamine synthetase expression, Sequeira et al. analysed samples from suicide completers who died during an episode of major depressive disorder (MDD), suicide completers with no history of depression, and healthy controls. They found a down-regulation of glutamine synthetase in suicidal MDD patients compared with controls, while in suicide completers without MDD, glutamine synthetase was down- or up-regulated in different brain regions. They observed the highest number of suicide-specific changes in prefrontal cortical areas and the hippocampus and concluded that glutamine synthetase changes may be different in suicide completers with and without MDD (Sequeira et al. 2009).

Glutamine synthetase was also found to be significantly less expressed in SCZ patients who died from suicide as compared with those who died from other causes. Densities of glutamine synthetase expressing glial cells in the mediodorsal thalamus as well as in the dorsolateral prefrontal and orbitofrontal cortex of SCZ suicide completers were significantly elevated compared with controls and non-suicidal SCZ patients, suggesting that cerebral glutamine synthetase deficit is indicative of suicidal behaviour (Bernstein et al. 2013; Kim et al. 2007).

3.1.1 Glutamine Synthetase and Inflammation

These glutamine synthetase changes may also be mediated by inflammation. For instance, inflammatory cytokines inhibit glutamine synthetase activity (Hu et al. 1994, 2000). Also in human astrocyte cultures, TNFa and IL-1 concentration-dependently inhibit glutamate uptake and suppress the enzymatic activity of glutamine synthetase (Huang and O'Banion 2002). Taken together, these data suggest that pro-inflammatory cytokines suppress glutamine synthesis in astrocytes, which potentially negatively affects the production of glutamate (Kalkman 2011).

3.2 Phosphate-Activated Glutaminase

Phosphate-activated glutaminase (PAG) converts glutamine to glutamate as part of the glutamate-glutamine cycle. Relatively little is known about the implications of

PAG involvement in suicide. A global brain gene expression analysis found that neocortical PAG genes were significantly reduced in non-depressed suicide completers but expression was normal in those with MDD (Sequeira et al. 2009). In a recent study, the gene expression of PAG was significantly increased in the anterior cingulate cortex of suicidal MDD patients (Zhao et al. 2018).

3.3 Glutamate Receptors

Glutamate receptors are situated on pre- and postsynaptic neurons as well as on astroglial cells. Glutamate signalling activates a family of receptors consisting of metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). Furthermore, the ionotropic receptor family includes the N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptor subfamilies. The iGluR subfamilies all share a common voltage-gated ion channel function. On the contrary, mGluRs are G-protein-coupled receptors (GPCRs) containing the classic 7 transmembrane domain structure and initiate signalling cascades or cation influx upon Glu binding. Based on sequence homology, pharmacology, and second messenger associations, mGluRs are further categorized into group I, II, and III subfamilies (Willard and Koochekpour 2013).

3.3.1 NMDA Receptors

Binding to NMDA-type receptors appears to be reduced in suicide completers, which might be the result of either impaired binding properties or an indication of receptor deficit (Holemans et al. 1993; Nowak et al. 1995; Sowa-Kućma et al. 2013). However, these results should be interpreted with some caution, since NMDA receptor deficit in depression (and also in suicide completers with MDD) may in part reflect chronic treatment effects (Nudmamud-Thanoi and Reynolds 2004).

Gene expression abnormalities in NMDA receptors have been discovered in suicide completers with MDD (Dean et al. 2016; Zhao et al. 2018) as well as in alcohol-dependent individuals (Fudalej et al. 2017; Sokolowski et al. 2013), suggesting that the glutamatergic system influences susceptibility to suicide attempts in these types of patients.

3.3.2 AMPA Receptors

Some authors have reported a pronounced increase in total AMPA binding in the caudate nucleus of suicide completers (Freed et al. 1993; Noga and Wang 2002). When comparing expression patterns of suicide completers with and without MDD and controls, there was an up-regulation of the genes and increased expression of the

corresponding proteins for AMPA receptors GRIA1, GRIA2, GRIA3, and GRIA4 among suicide completers with MDD vs controls and suicide completers without MDD (Sequeira et al. 2009; Zhao et al. 2018). GRIA3 has been also associated with suicidal ideation during citalopram therapy (Laje et al. 2007).

3.3.3 Kainate Receptors

There are positive data regarding an association of GRIK1 and GRIK2 genes and suicide. The gene coding for GRIK1 was found to be differentially expressed in suicide completers compared with controls in a global brain gene expression analysis of glutamatergic and GABAergic changes in MDD (Sequeira et al. 2009) and specifically in the anterior cingulate cortex (Zhao et al. 2018). Lastly, markers within GRIK2 genes were associated with treatment-emergent suicidal ideation during citalopram therapy (Laje et al. 2007).

3.3.4 Metabotropic Receptors

The genes encoding metabotropic receptors have also been associated with suicide in several studies. Gene expression of GRM1, GRM2, and GRM3 was significantly increased in the anterior cingulate cortex of suicidal MDD patients (Zhao et al. 2018), while GRM3 expression was found to be down-regulated in suicide completers with and without MDD (Fiori and Turecki 2012; Klempan et al. 2009; Laje et al. 2007; Sequeira et al. 2009).

3.4 Glutamate Transporters

Five types of glutamate transporters are known. These transporters keep the extracellular levels of GABA and excitatory amino acids low and provide amino acids for metabolic purposes. The various transporters have different properties both with respect to their transport functions and with respect to their ability to act as ion channels. Furthermore, they are differentially regulated (Zhou and Danbolt 2013). Two of them (glial glutamate and aspartate transporter, GLAST/EAAT1, and glial glutamate transporter, EAAT2) are expressed predominantly in astroglia and the other three in neurons (excitatory amino acid carrier, EAAC1/EAAT3, and excitatory amino acid transporters 4 and 5, EAAT 4 and EAAT 5 (Choudhury et al. 2012)).

The most important and most abundant transporters for removal of transmitter glutamate in the brain are EAAT2 (GLT-1) and EAAT1 (GLAST). Due to their high uncoupled anion conductance, EAAT4 and EAAT5 seem to act more like inhibitory glutamate receptors than as glutamate transporters. EAAT3 (EAAC1) does not

appear to play a role in signal transduction, but plays other roles (Zhou and Danbolt 2013).

Polymorphisms in EAAT2 and EAAT3 genes have been shown to be associated with a diathesis for suicidal acts (Murphy et al. 2011). Decreased EAAT3 expression has been observed in brains of suicide completers (Kim et al. 2007). Differentially expressed EAAT2 and EAAT3 have also been reported in suicide completers (Sequeira et al. 2009). Interestingly, certain gene variants of glutamate transporters EAAT2 and EAAT3 may even be protective with regard to suicidal behaviour (Murphy et al. 2011).

4 Glutamine-Glutamate as the Target of New Anti-suicide Drugs

Evidence of a role of the glutamate-glutamine cycle in suicidal behaviours unveils new targets for therapeutic interventions focused on different stages of the glutamate-glutamine cycle.

4.1 Glutamine Synthetase

Lithium is an effective treatment for reducing the risk of suicide in people with mood disorders (Cipriani et al. 2013). Although the molecular basis for lithium's therapeutic effects has yet to be fully elucidated, animal experiments showing that lithium may increase glutamine synthetase (GS) activity in the brain stem suggest that the therapeutic effect on suicide is related to an increase in GS expression (Kalkman 2011). It is known that, at therapeutic concentrations, lithium immediately inhibits glycogen synthase kinase-3 (GSK3), a key component of Wnt signalling that exerts effects on neurotransmission, neuroplasticity, and neuronal growth and metabolism, whose inhibition has been related to an increase in GS transcription (Jiménez et al. 2013). Thus, other GSK3 inhibitors (already used in an experimental Alzheimer's treatment) may be potential drugs for suicide treatment by increasing GS transcription (Bhat et al. 2004).

It has been also suggested that the consequences of glutamine synthetase dysfunction might be limited by a simple intervention such as supplementing the diet with glutamine. This would replenish neuronal glutamate levels (Kalkman 2011). Glutamine supplements are broadly used by endurance athletes, are well tolerated, and seem to have no harmful effects (Gleeson 2008).

4.2 NMDA Receptor

The NMDA receptor is the main target of fast-acting antidepressants and anti-suicide drugs. Table 1 shows the most relevant studies on these drugs to date.

4.2.1 Ketamine (NMDA Receptor Antagonist)

There is mounting evidence to suggest that the NMDA receptor antagonist ketamine, which induces schizophrenia-like behavioural and neuroanatomical changes in rats similar to those found in humans, has considerable antidepressant efficacy in MDD and BD patients and significantly reduces suicidal ideation (Bernstein et al. 2013).

In the last decade, several small clinical trials have demonstrated that sub-anaesthetic doses of ketamine have rapid-acting antidepressant properties (Berman et al. 2000; DiazGranados et al. 2010b; Murrough et al. 2013; Zarate et al. 2006) as well as potential anti-suicidal properties (Ballard et al. 2014; DiazGranados et al. 2010a; Grunebaum et al. 2018; Ionescu et al. 2016; Larkin and Beautrais 2011; Murrough et al. 2013, 2015; Price et al. 2014) in patients with mood disorders (both MDD and BD). In these trials, ketamine improved depressive symptoms and reduced suicidal ideation within hours of intravenous administration. Likewise, pooled analyses of placebo-controlled single-dose studies of ketamine suggest a substantial reduction in suicidal ideation in patients with treatment-resistant unipolar or bipolar depression (Canuso et al. 2018).

A recent meta-analysis examining the effects of a single dose of ketamine on suicidal ideation in ten identified comparison intervention studies (using either saline or midazolam as a control) found that ketamine rapidly (in 1 day) reduced suicidal ideation in both clinician-administered and self-reported outcome measures. Effect sizes were moderate to large at all time points post-dose. The authors concluded that ketamine rapidly reduced suicidal thoughts within 1 day and for up to 1 week in depressed patients with suicidal ideation. Ketamine's effects on suicidal ideation were partially independent of its effects on mood, although subsequent trials in transdiagnostic samples are required to confirm that ketamine exerts a specific effect on suicidal ideation (Wilkinson et al. 2018).

4.2.2 Esketamine (NMDA Receptor Antagonist)

The S(+) enantiomer of ketamine, esketamine, a powerful NMDA receptor antagonist that modulates glutamatergic transmission, has been developed as an intranasal formulation for treatment-resistant depression (Molero et al. 2018). Rapid onset of antidepressant effects has been observed in patients with treatment-resistant depression as early as 2 h (Singh et al. 2016) and 24 h after administration of a single dose of intranasal esketamine (Daly et al. 2018).

Table 1 Most relevant studies on NMDA receptor targeting drugs and suicide

Drug	Author (year)	Type of study (duration)	Sample	Results
Ketamine	Lascelles et al. (2019)	Qualitative study (hours)	14 patients with MDD, treatment resistant, and SI at the initiation of treatment	SI reduced following ketamine treatment in 12 out of 14 participants for periods of a few hours following a single treatment to up to three years with ongoing treatment
Ketamine	Zhan et al. (2019)	Prospective, open-label, single center (12 days)	86 unipolar and bipolar depressive patients	57.0% patients relief of SI after first infusion and 65.1% after six infusions
Ketamine	Wilkinson et al. (2018)	Meta-analysis, 10 studies	298 subjects who participated in the 10 included ketamine trials	Patients who received ketamine had lower scores on clinician-rated scores of suicidality on days 1 and 7 using HDRS or MADRS
Ketamine	Grunebaum et al. (2018)	Randomized controlled, double-blind, single center (24 h–6 weeks)	80 MDD inpatients, score of 16 or greater on HDRS, score of 4 or greater on SSI	Ketamine: SSI was reduced 4.96 points greater than comparator; 55% SSI responders for ketamine group vs 30% in midazolam group
Ketamine	Bartoli et al. (2017)	Meta-analysis, 5 studies	99 subjects with SI	Ketamine decreased SI. Nonsignificant higher effect with ketamine bolus vs infusion
Ketamine	Grunebaum et al. (2017)	Pilot, randomized, controlled trial (24 h)	16 patients with bipolar depression and SI	Suicidal thoughts were lower after ketamine than after midazolam at a trend level of significance
Ketamine	Fan et al. (2017)	Randomized controlled (7 days)	37 Newly diagnosed cancer patients with symptoms of depression and suicidality	BSSI and MADRS-SI reduced in ketamine vs midazolam groups 9.5 vs 16.8 and 1.7 vs 3.4; $P < 0.05$, respectively
Ketamine	Vande Voort et al. (2016)	Single arm, open-label (10 weeks)	12 patients with MDD, treatment resistant, hospitalized for SI	MADRS suicide item reduced from 2.9 at baseline to 1.7 after phase I
Ketamine	Price et al. (2014)	Randomized controlled (24 h)	57 patients with MDD, treatment-resistant, moderate to severe depression	53% of ketamine patients scored 0 on all 3 explicit suicide measures (BSSI, MADRS, QIDS) compared to 24% in midazolam group
Ketamine	Thakurta et al. (2012)	Prospective, open-label, single center (2 days)	27 patients with MDD, treatment-resistant	Mean decrease in SSI score from 5 to 1 maintained from minute 40 to 230. HDRS-SI score from 1.4 to 0.4 after 40-min infusión

Ketamine	Price et al. (2009)	Prospective single arm (24 h)	26 patients with MDD, treatment-resistant, moderate to severe depression	MADRS-SI reduced average of 2.08 points, 81% of patients achieved a 0 or 1 rating 24 h postinfusion
Ketamine	Kudoh et al. (2002)	Randomized controlled (5 days)	95 patients with MDD treated with antidepressant, undergoing orthopedic surgery	Suicide item on HDRS decreased from 1.3 to 0.3 in ketamine group vs 1.1 to 1.1 in comparator
Esketamine	Canuso et al. (2018)	Multicenter, randomized, double-blind controlled (25 days)	68 patients with MDD requiring inpatient hospitalization due to imminent risk of suicide, score of 22 or greater on MADRS	MADRS-SI reduced at 4 h, but not remaining significant at 24 h or at day 25. No differences in clinical global judgment of suicide risk scores at any time
Esketamine	Singh et al. (2016)	multicenter, randomized, placebo-controlled trial (7 days + open-label 4 weeks)	30 patients with MDD, treatment-resistant	C-SSRS-SI scores either improved or were maintained from screening through the open-label treatment phase for 29/30 esketamine patients
Esketamine	Popova et al. (2019)	double-blind, active-controlled, esketamine + ATD vs. placebo + ATD (4 weeks)	197 adults with moderate to severe nonpsychotic depression and a history of nonresponse to at least two antidepressants in the current episode	The percentage of patients reporting suicidal ideation (C-SSRS scores of 1–3 decreased from baseline to the endpoint in both treatment groups)

SI suicidal ideation, *SSI* scale for suicide ideation, *MDD* major depressive disorder, *HDRS* Hamilton depression rating scale, *MADRS* montgomery-asberg depression rating scale, *ATD* antidepressant, *C-SRSS* Columbia-suicide severity rating scale

Esketamine has shown potential for rapid reduction of suicidal ideation in patients at imminent risk for suicide (Canuso et al. 2018; Popova et al. 2019). In a double-blind, multicentre, proof-of-concept study, the esketamine group showed greater improvement on the Montgomery-Åsberg Depression Rating Scale (MADRS) suicidal thoughts item score at 4 h, but not at 24 h or at day 25. Of particular interest in this study was the nearly 35% between-group difference, favouring esketamine, in the proportion of participants achieving resolution of suicide risk 24 h after the first dose. The authors concluded that intranasal esketamine may be useful in depressed patients at imminent risk for suicide (Canuso et al. 2018).

4.2.3 Rapastinel (NMDA Receptor Modulator)

Rapastinel, an investigational NMDA receptor modulator for major depressive disorder, has shown promising results in a limited number of clinical studies in terms of providing rapid, reliable, and robust antidepressant effects as well as beneficial effects on measures of cognition and suicidality (Ragguett et al. 2019). Unfortunately, the failure of three phase III trials of rapastinel has led to the cancellation of its development in this indication. Several trials of rapastinel are however continuing, including those evaluating it for suicidality prevention and as a monotherapy in depression.

4.2.4 Lanicemine (NMDA Channel Blocker)

Lanicemine (AZD6765) is a low-trapping, parenterally administered NMDA channel blocker that shares many of the same pharmacological effects as ketamine on the NMDA receptor (Emnett et al. 2013; Sanacora et al. 2014).

A phase IIb study of 152 patients reported that lanicemine was associated with a significant improvement of depressive symptoms in patients with treatment-resistant MDD over placebo infusions after 3 weeks (Sanacora et al. 2014), but another phase IIb study of 302 patients failed to find a significant difference between lanicemine and placebo treatment on any outcome measures related to MDD after 12 weeks (Sanacora et al. 2017). There is as yet no data on the effect of lanicemine on suicide.

4.2.5 Other NMDA Receptor Targeting Drugs

There are some fast-acting NMDA receptor targeting drugs in different development stages (phase II and phase III) such as NRX-100 and apimostinel (partial agonists of the glycine site of the NMDA receptor); traxoprodil, EVT-101, and rislenemdaz (selective antagonists of the NR2B subunit of the NMDA receptor); and AGN-241751 (a NMDA receptor modulator). Table 2 shows the newest glutamate targeting drugs in development.

Table 2 Glutamate targeting drugs in development

Mechanism of action	Drug	Medical condition	Stage of development
NMDA receptor antagonist	Esketamine	TRD	FDA approved for TRD in conjunction with oral ATD. EMA approval expected in 2020 Development in MDD and TRD with imminent risk of suicide ongoing
	Dextromethadone (REL-1017)	MDD TRD	Phase IIa
	Nitrous oxide	MDD Suicidal Ideation	Phase I
Low-trapping NMDA receptor antagonist	Lanicemine	TRD MDD PTSD	Phase IIb
Partial NMDA receptor agonist	Rapastinel	MDD	Failed Phase III trials. Development in suicidality ongoing
	Ketamine HCL (NRX-100)	Bipolar Depression Suicidal Ideation	Phase III
	D-Cycloserine	TRD Schizophrenia	Phase II / Phase IV
	Sarcosine (N-methylglycine)	MDD OCD Schizophrenia	Phase II
	4-chlorokynurenine (AV-101)	MDD	Phase II
	Apimostinel	TRD MDD	Phase II (intravenous) Phase I (oral)
NMDA receptor modulator	AGN-241751	MDD	Phase II
NR2B antagonist	Traxoprodil (CP-101,606)	MDD	Phase II
	Deuterium Modified Dextromethorphan Hydrobromide/ Quinidine Sulfate (AVP-786)	TRD Schizophrenia IED	Phase II
	Rislenemdaz (CERC-301, MK-0657)	MDD	Phase II
	EVT-101	TRD	Phase II
	EVT-103, ENS-103	MDD	Phase I
Negative modulator of metabolic glutamate receptor	Basimglurant	MDD	Phase IIb
	Decoglurant	MDD	Failed Phase II trials. Discontinued
AMPA receptor modulator	Tulrampator (S-47445, CX-1632)	MDD	Phase II

(continued)

Table 2 (continued)

Mechanism of action	Drug	Medical condition	Stage of development
Glutamate release inhibitor	Riluzole	MDD PTSD Autism SAD	Phase II

Source: clinicaltrials.gov

NR2B NMDA receptor subunit 2B, *TRD* treatment resistant depression, *MDD* major depressive disorder, *PTSD* post-traumatic stress disorder, *OCD* obsessive-compulsive disorder, *IED* intermittent explosive disorder, *SAD* social anxiety disorder, *FDA* U.S. Food and Drug Administration, *EMA* European Medicines Agency

5 Conclusion

The glutamate-glutamine cycle seems to play an important role in the biological basis of suicidal behaviours.

Research data suggest that glutamate contributes to the aetiology of suicide indirectly, through its involvement in the pathophysiology of suicide-related disorders (i.e. MDD, SCZ, BD, and PTSD) or as part of the inflammation cascade, as well as directly by increasing impulsive aggression.

Genetic expression and receptor studies have demonstrated changes at different stages of the glutamate-glutamine cycle in suicidal patients, showing a path for anti-suicide drug development.

The promising results of glutamate targeting drugs, such as ketamine and esketamine, in reducing suicidal ideation have opened new prospects for suicide prevention-oriented drugs through the glutamate-glutamine cycle.

References

Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA et al (2014) Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. https://doi.org/10.1016/j.jpsychires.2014.07.027

Bartoli F, Riboldi I, Crocamo C, Di Brita C, Clerici M, Carrà G (2017) Ketamine as a rapid-acting agent for suicidal ideation: a meta-analysis. Neurosci Biobehav Rev https://doi.org/10.1016/j.neubiorev.2017.03.010

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. https://doi.org/10.1016/S0006-3223(99)00230-9

Bernstein H-G, Tausch A, Wagner R, Steiner J, Seeleke P, Walter M et al (2013) Disruption of glutamate-glutamine-GABA cycle significantly impacts on suicidal behaviour: survey of the literature and own findings on glutamine synthetase. CNS Neurol Disord Drug Targets. https://doi.org/10.2174/18715273113129990091

Bhat RV, Budd Haeberlein SL, Avila J (2004) Glycogen synthase kinase 3: a drug target for CNS therapies. J Neurochem. https://doi.org/10.1111/j.1471-4159.2004.02422.x

Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P et al (2018) Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatr. https://doi.org/10.1176/appi.ajp.2018.17060720

Choudhury PR, Lahiri S, Rajamma U (2012) Glutamate mediated signaling in the pathophysiology of autism spectrum disorders. Pharmacol Biochem Behav. https://doi.org/10.1016/j.pbb.2011.06.023

Cipriani A, Hawton K, Stockton S, Geddes JR (2013) Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. https://doi.org/10.1136/bmj.f3646

Coccaro EF, Lee R, Vezina P (2013) Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects. J Psychiatr Res. https://doi.org/10.1016/j.jpsychires.2013.05.001

Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D (2016) Neuroinflammation in suicide: toward a comprehensive model. World J Biol Psychiatry. https://doi.org/10.3109/15622975.2015.1054879

Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC et al (2018) Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiat. https://doi.org/10.1001/jamapsychiatry.2017.3739

Dean B, Gibbons AS, Boer S, Uezato A, Meador-Woodruff J, Scarr E, McCullumsmith RE (2016) Changes in cortical N-methyl-d-aspartate receptors and post-synaptic density protein 95 in schizophrenia, mood disorders and suicide. Aust N Z J Psychiatry. https://doi.org/10.1177/0004867415586601

DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA et al (2010a) Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. https://doi.org/10.4088/JCP.09m05327blu

Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S et al (2010b) A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. https://doi.org/10.1001/archgenpsychiatry.2010.90

Emnett CM, Eisenman LN, Taylor AM, Izumi Y, Zorumski CF, Mennerick S (2013) Indistinguishable synaptic pharmacodynamics of the N-methyl-D-aspartate receptor channel blockers memantine and ketamine. Mol Pharmacol. https://doi.org/10.1124/mol.113.089334

Ende G, Cackowski S, van Eijk J, Sack M, Demirakca T, Kleindienst N et al (2016) Impulsivity and aggression in female BPD and ADHD patients: association with ACC glutamate and GABA concentrations. Neuropsychopharmacology. https://doi.org/10.1038/npp.2015.153

Fan W, Yang H, Sun Y, Zhang J, Li G, Zheng Y, Liu Y (2017) Ketamine rapidly relieves acute suicidal ideation in cancer patients: a randomized controlled clinical trial. Oncotarget. https://doi.org/10.18632/oncotarget.13743

Fiori LM, Turecki G (2012) Broadening our horizons: gene expression profiling to help better understand the neurobiology of suicide and depression. Neurobiol Dis. https://doi.org/10.1016/j.nbd.2010.11.004

Freed WJ, Dillon-Carter O, Kleinman JE (1993) Properties of [3H]AMPA binding in postmortem human brain from psychotic subjects and controls: increases in caudate nucleus associated with suicide. Exp Neurol. https://doi.org/10.1006/exnr.1993.1070

Fudalej S, Klimkiewicz A, Mach A, Jakubczyk A, Fudalej M, Wasilewska K et al (2017) An association between genetic variation in the glutamatergic system and suicide attempts in alcohol-dependent individuals. Am J Addict. https://doi.org/10.1111/ajad.12571

Gleeson M (2008) Dosing and efficacy of glutamine supplementation in human exercise and sport training. J Nutr. https://doi.org/10.1093/jn/138.10.2045S

Grunebaum MF, Ellis SP, Keilp JG, Moitra VK, Cooper TB, Marver JE et al (2017) Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. Bipolar Disord. https://doi.org/10.1111/bdi.12487

Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS et al (2018) Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatr. https://doi.org/10.1176/appi.ajp.2017.17060647

Hayashi MK (2018) Structure-function relationship of transporters in the glutamate–glutamine cycle of the central nervous system. Int J Mol Sci. https://doi.org/10.3390/ijms19041177

Holemans S, De Paermentier F, Horton RW, Crompton MR, Katona CLE, Maloteaux JM (1993) NMDA glutamatergic receptors, labelled with [3H]MK-801, in brain samples from drug-free depressed suicides. Brain Res. https://doi.org/10.1016/0006-8993(93)90202-X

Hu S, Martella A, Anderson WR, Chao CC (1994) Role of cytokines in lipopolysaccharide-induced functional and structural abnormalities of astrocytes. Glia. https://doi.org/10.1002/glia.440100309

Hu S, Sheng WS, Ehrlich LC, Peterson PK, Chao CC (2000) Cytokine effects on glutamate uptake by human astrocytes. Neuroimmunomodulation. https://doi.org/10.1159/000026433

Huang TL, O'Banion MK (2002) Interleukin-1β and tumor necrosis factor-α suppress dexamethasone induction of glutamine synthetase in primary mouse astrocytes. J Neurochem. https://doi.org/10.1046/j.1471-4159.1998.71041436.x

Ionescu DF, Swee MB, Pavone KJ, Taylor N, Akeju O, Baer L et al (2016) Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. J Clin Psychiatry. https://doi.org/10.4088/JCP.15m10056

Jiménez E, Arias B, Mitjans M, Goikolea JM, Roda E, Sáiz PA et al (2013) Genetic variability at IMPA2, INPP1 and GSK3β increases the risk of suicidal behavior in bipolar patients. Eur Neuropsychopharmacol. https://doi.org/10.1016/j.euroneuro.2013.01.007

Kalkman HO (2011) Circumstantial evidence for a role of glutamine-synthetase in suicide. Med Hypotheses. https://doi.org/10.1016/j.mehy.2011.03.005

Kim S, Choi KH, Baykiz AF, Gershenfeld HK (2007) Suicide candidate genes associated with bipolar disorder and schizophrenia: an exploratory gene expression profiling analysis of post-mortem prefrontal cortex. BMC Genomics. https://doi.org/10.1186/1471-2164-8-413

Klempan TA, Sequeira A, Canetti L, Lalovic A, Ernst C, Ffrench-Mullen J, Turecki G (2009) Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. Mol Psychiatry. https://doi.org/10.1038/sj.mp.4002110

Kudoh A, Takahira Y, Katagai H, Takazawa T (2002) Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg. https://doi.org/10.1097/00000539-200207000-00020

Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, McMahon FJ (2007) Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. Am J Psychiatr. https://doi.org/10.1176/appi.ajp.2007.06122018

Larkin GL, Beautrais AL (2011) A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol. https://doi.org/10.1017/S1461145711000629

Lascelles K, Marzano L, Brand F, Trueman H, McShane R, Hawton K (2019) Effects of ketamine treatment on suicidal ideation: a qualitative study of patients' accounts following treatment for depression in a UK ketamine clinic. BMJ Open. https://doi.org/10.1136/bmjopen-2019-029108

Masugi-Tokita M, Flor PJ, Kawata M (2016) Metabotropic glutamate receptor subtype 7 in the bed nucleus of the stria terminalis is essential for intermale aggression. Neuropsychopharmacology. https://doi.org/10.1038/npp.2015.198

Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sánchez E, Gutiérrez-Rojas L, Meana JJ (2018) Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. CNS Drugs. https://doi.org/10.1007/s40263-018-0519-3

Murphy TM, Ryan M, Foster T, Kelly C, McClelland R, O'Grady J et al (2011) Risk and protective genetic variants in suicidal behaviour: association with SLC1A2, SLC1A3, 5-HTR1B &NTRK2 polymorphisms. Behav Brain Funct. https://doi.org/10.1186/1744-9081-7-22

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM et al (2013) Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatr. https://doi.org/10.1176/appi.ajp.2013.13030392

Murrough JW, Soleimani L, Dewilde KE, Collins KA, Lapidus KA, Iacoviello BM et al (2015) Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med. https://doi.org/10.1017/S0033291715001506

Noga JT, Wang H (2002) Further postmortem autoradiographic studies of AMPA receptor binding in schizophrenia. Synapse. https://doi.org/10.1002/syn.10106

Nowak G, Ordway GA, Paul IA (1995) Alterations in the N-methyl-d-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. Brain Res. https://doi.org/10.1016/0006-8993(95)00057-W

Nudmamud-Thanoi S, Reynolds GP (2004) The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. Neurosci Lett. https://doi.org/10.1016/j.neulet.2004.09.035

O'Donovan SM, Sullivan CR, McCullumsmith RE (2017) The role of glutamate transporters in the pathophysiology of neuropsychiatric disorders. NPJ Schizophr. https://doi.org/10.1038/s41537-017-0037-1

Parkin GM, Udawela M, Gibbons A, Dean B (2018) Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders. World J Psychiatry. https://doi.org/10.5498/wjp.v8.i2.51

Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P et al (2019) Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatr. https://doi.org/10.1176/appi.ajp.2019.19020172

Price RB, Nock MK, Charney DS, Mathew SJ (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry. https://doi.org/10.1016/j.biopsych.2009.04.029

Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ et al (2014) Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. https://doi.org/10.1002/da.22253

Ragguett RM, Rong C, Kratiuk K, McIntyre RS (2019) Rapastinel – an investigational NMDA-R modulator for major depressive disorder: evidence to date. Expert Opin Investig Drugs. https://doi.org/10.1080/13543784.2019.1559295

Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC (2014) Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. Mol Psychiatry. https://doi.org/10.1038/mp.2013.130

Sanacora G, Johnson MR, Khan A, Atkinson SD, Riesenberg RR, Schronen JP et al (2017) Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and history of inadequate response to antidepressants: a randomized, placebo-controlled study. Neuropsychopharmacology. https://doi.org/10.1038/npp.2016.224

Sequeira A, Mamdani F, Ernst C, Vawter MP, Bunney WE, Lebel V et al (2009) Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. PLoS One. https://doi.org/10.1371/journal.pone.0006585

Singh JB, Fedgchin M, Daly E, Xi L, Melman C, de Bruecker G et al (2016) Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry. https://doi.org/10.1016/j.biopsych.2015.10.018

Sokolowski M, Ben-Efraim YJ, Wasserman J, Wasserman D (2013) Glutamatergic GRIN2B and polyaminergic ODC1 genes in suicide attempts: associations and gene-environment interactions with childhood/adolescent physical assault. Mol Psychiatry. https://doi.org/10.1038/mp.2012.112

Sowa-Kućma M, Szewczyk B, Sadlik K, Piekoszewski W, Trela F, Opoka W et al (2013) Zinc, magnesium and NMDA receptor alterations in the hippocampus of suicide victims. J Affect Disord. https://doi.org/10.1016/j.jad.2013.08.009

Takahashi A, Lee RX, Iwasato T, Itohara S, Arima H, Bettler B et al (2015) Glutamate input in the dorsal raphe nucleus as a determinant of escalated aggression in male mice. J Neurosci. https://doi.org/10.1523/JNEUROSCI.2450-14.2015

Thakurta RG, Das R, Bhattacharya AK, Saha D, Sen S, Singh OP et al (2012) Rapid response with ketamine on suicidal cognition in resistant depression. Indian J Psychol Med. https://doi.org/10.4103/0253-7176.101793

Vande Voort JL, Morgan RJ, Kung S, Rasmussen KG, Rico J, Palmer BA et al (2016) Continuation phase intravenous ketamine in adults with treatment-resistant depression. J Affective Disord. https://doi.org/10.1016/j.jad.2016.09.008

Wickens MM, Bangasser DA, Briand LA (2018) Sex differences in psychiatric disease: a focus on the glutamate system. Front Mol Neurosci. https://doi.org/10.3389/fnmol.2018.00197

Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A et al (2018) The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. Am J Psychiatr. https://doi.org/10.1176/appi.ajp.2017.17040472

Willard SS, Koochekpour S (2013) Glutamate, glutamate receptors, and downstream signaling pathways. Int J Biol Sci. https://doi.org/10.7150/ijbs.6426

Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA et al (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. https://doi.org/10.1001/archpsyc.63.8.856

Zhan Y, Zhang B, Zhou Y, Zheng W, Liu W, Wang C et al (2019) A preliminary study of anti-suicidal efficacy of repeated ketamine infusions in depression with suicidal ideation. J Affective Disord. https://doi.org/10.1016/j.jad.2019.03.071

Zhao J, Verwer RWH, Gao SF, Qi XR, Lucassen PJ, Kessels HW, Swaab DF (2018) Prefrontal alterations in GABAergic and glutamatergic gene expression in relation to depression and suicide. J Psychiatr Res. https://doi.org/10.1016/j.jpsychires.2018.04.020

Zhou Y, Danbolt NC (2013) GABA and glutamate transporters in brain. Front Endocrinol. https://doi.org/10.3389/fendo.2013.00165

The Role of Opiates in Social Pain and Suicidal Behavior

Benedicte Nobile, Pierre-Eric Lutz, Emilie Olie, and Philippe Courtet

Contents

Abstract With more than 800,000 deaths by suicide each year and 20 to 30 times more suicide attempts worldwide, suicide is a major public health problem. Current treatments of SB are mainly based on pharmacological treatments that are not specific of SB (e.g. antidepressants), and new therapeutic targets are urgently needed. Recent data strengthen the ancient conception pain (social, psychic, physical) that is at the core of the suicidal process and should be incorporated in the clinical assessment of suicide risk. Then, the mechanisms involved in the regulation of pain may open new avenues regarding therapeutic perspectives. Opiates appear to be a promising candidate in treatment of SB. Indeed, since the last two decades, growing evidences suggest an implication of the opioid system in the pathophysiology of SB, this conduct to the elaboration of randomized controlled trials (RCTs)

B. Nobile, E. Olie, and P. Courtet (✉)
Department of Emergency Psychiatry and Acute Care, CHU, Montpellier, France

PSNREC, Univ Montpellier, INSERM, CHU de Montpellier, Montpellier, France

University Montpellier, Montpellier, France
e-mail: p-courtet@chu-montpellier.fr

P.-E. Lutz
Centre National de la Recherche Scientifique, Université de Strasbourg, Institut des Neurosciences Cellulaires et Intégratives, Strasbourg, France

Fédération de Médecine Translationnelle de Strasbourg (FMTS), Strasbourg, France

Curr Topics Behav Neurosci (2020) 46: 197–210
https://doi.org/10.1007/7854_2020_167
Published Online: 1 September 2020

using opiates in patients with SB. Results suggesting an anti-suicidal effect of buprenorphine and the potential opioidergic-related anti-suicidal effect of ketamine both contribute to the growing interest in opiates use in SB. In this review, we will summarize a large part of the evidence that leads researchers and clinicians to be interested in the use of opiates for SB treatment and discuss on new opioid pharmacological options for suicidal patients.

Keywords Opiates · Opioid system · Pain · Suicidal behavior · Therapeutics

1 Introduction

Suicide is a major public health problem. Indeed, there are more than 800,000 deaths by suicide each year and 20–30 times more suicide attempts (SA) worldwide (Zalsman et al. 2016). With the entry in DSM-5 of suicidal behavior (SB) as a disorder proposed for complementary studies, suicide is now regarded as an entity with its own physiopathology. Current treatments of SB are based on psychotherapy (e.g., cognitive behavioral therapy, dialectical behavioral therapy) (Ducasse et al. 2018a; Calati and Courtet 2016) and on pharmacological therapeutics (antidepressants, clozapine, and lithium) (Courtet and Olié 2014). Yet, these pharmacological treatments are not specific of SB, and new therapeutic targets are urgently needed. Opiates appear to be a promising candidate in treatment of SB. Until now, opiates, defined as exogenous compounds that interfere with endogenous opioid signaling, were principally used for the treatment of chronic pain (Choi 2016), substance use disorder (Klein 2016), and anesthesia (Kubica-Cielińska and Zielińska 2015). Since the last two decades, growing evidence has suggested an implication of the opioid system in the pathophysiology of SB, driving researchers and clinicians to conduct randomized controlled trials using opiates in patients with SB, such as buprenorphine (Yovell et al. 2016; Ahmadi et al. 2018). The results on the anti-suicidal potential of buprenorphine are instead in line with both human and animal studies that linked suicidal behavior with social pain (i.e., the unpleasant experience associated with actual or potential damage to one's sense of social connection or social value (Eisenberger 2012)).

In this review, we will summarize a large part of the evidence that leads researchers and clinicians to be interested in the use of opiates for SB treatment. First, we will discuss on common pathways of social and physical pain. Then, we will review studies on link between social pain and opioid system. Therefore, we will examine social pain as a risk factor of SB following by reviews of studies on opioid consumption in relation to SB. Thus, we will consider opioid dysfunction within patients with SB. Finally, we will discuss new opioid pharmacological options for suicidal patients.

2 Physical and Social Pains Are Sharing Common Pathways

For more than 30 years now, the opioid system has been studied for its implication in social interactions. Indeed, many animal studies (notably in mice and primates) have demonstrated its role in mediating socio-emotional responses (Herman and Panksepp 1981; Kalin et al. 1988; Panksepp et al. 1980a, b). More recently, neuroimaging studies have shown that physical pain and social pain (triggered by a paradigm of social exclusion or loss) share a common neuronal circuitry (Eisenberger 2012). Neuroimaging studies have shown that experiences of social pain rely on affective pain-related neural regions: the dorsal portion of the anterior cingulate cortex (dACC) and the anterior insula (Peyron et al. 2000). Using the Cyberball task (a virtual ball-tossing game; during which the participant is playing with two others players, before being excluded from the game), Eisenberger et al. found that exclusion (vs. inclusion) condition enhanced activation of the dACC and the anterior insula (Eisenberger et al. 2003). Those results were then replicated using other forms of socially painful experiences (Masten et al. 2011, 2012; Eisenberger et al. 2011). Another study has highlighted an additional involvement of posterior insula and secondary somatosensory cortex (Apkarian et al. 2005; Kross et al. 2011), whereas these regions were initially known to process the sensory dimension of physical pain. Nevertheless, several phenomenological and imaging dissociations among social and physical pain are currently being evaluated. Feelings of social pain seem to be more easily re-experienced than those of physical pain, and the neuro-circuits underlying it may be more divergent during pain revival than during the primary experience (Meyer et al. 2015). Moreover recent multivariate analyses suggest that within common brain structures, the two types of pain recruit distinct sets of voxels (Cacioppo et al. 2013; Woo et al. 2014), which may correspond to different neuronal populations (Rogachov et al. 2015). Finally, beyond its role in response to exclusion, the social pain network may also contribute to the encoding of social inclusion (Dalgleish et al. 2017) and perhaps even more generally to that of social evaluation (Perini et al. 2018). Despite those elements, globally, we can consider that physical and social pains are sharing common pathways, and since physical pain is regulated by the opioid system, it seems logical to hypothesize that social pain might also be under opioid regulation.

2.1 Social Pain and Opioid System

It has been hypothesized that responses to social rejection are regulated by endogenous opioids and possibly the μ-opioid receptor (MOR), which alleviates physical pain, but is also known to regulate social distress in several nonhuman species. Factors known to reduce sensitivity to social pain and associated with opioid system, such as social support (Masten et al. 2012; Eisenberger et al. 2007) and avoidant

attachment (DeWall et al. 2012), have been associated with reduced dACC and/or anterior insula activity to social exclusion. In this context, Hsu et al. (2013) measured the availability of MOR during social rejection and acceptance using positron emission tomography in healthy volunteers. Social rejection was associated with significant decreases in MOR availability in the ventral striatum, amygdala, midline thalamus, and periaqueductal gray (PAG), suggesting MOR activation. Furthermore, greater trait resiliency was positively correlated with MOR activation during rejection in the amygdala, PAG, and subgenual anterior cingulate cortex (sgACC). Finally, MOR activation in the ACC was correlated with reduced negative affect during social rejection. These data suggest that endogenous opioids have a role in reducing the experience of social pain and that MOR activation is protective or adaptive.

Genetic studies also support results from neuroimaging studies showing an involvement of the opioid system in mediating response to social exclusion. In particular, genetic studies on the opioid system and sensitivity to social exclusion focused on the single nucleotide polymorphism (SNP) A118G from the *OPRM1* (Opioid receptor mu 1) gene, which encodes MOR. This SNP results in an amino acid exchange (N40D), whose molecular impact has been difficult to disentangle (Kroslak et al. 2007; Zhang et al. 2005; Mague and Blendy 2010), but that has been extensively investigated at behavioral level. Studies on postoperative pain have shown that carriers of the minor G allele require greater morphine doses to release their pain compared to carriers of the A allele (Chou et al. 2006; Sia et al. 2008). A study on children aged 8–10 years explored this SNP implication in predicting childhood withdrawal (a predictor of sensitivity to social rejection), using scores on the Withdrawn Scale of the Child Behavior Checklist (CBCL) and the face-specific N170 event-related potential (cerebral visual event-related potentials, ERP) waveform in response to facial expression (six black and white pictures displaying three emotions: happiness, anger, and neutral). Results showed that children carrying the G allele had higher CBCL Withdrawn scores and strengthened N170 amplitudes in response to emotional expressions, suggesting that those children were more likely to develop social withdrawal (Bertoletti et al. 2012). Another study, in adults, found similar results. The G allele was associated with dispositional sensitivity to rejection (assessed by self-report) and with a greater activity in dACC and anterior insula during Cyberball game (Way et al. 2009). In another study, participants received an electrical stimulation to the dorsum of non-dominant hand, to investigate physical pain, and played Cyberball game, to investigate social pain. A Go/NoGo task with an increased risk of self-dependent erroneous performance was also used as a control task to investigate the effects of negative feedback (a feedback (correct, wrong) appeared after the participant's answer). Target and distracter of the Go/NoGo task were combined either congruent or incongruent (e.g., incongruent Go trial targets were flanked by visually similar NoGo targets). G allele carriers showed an increased activation within the pain matrix during electrical stimulation, Cyberball exclusion, and negative feedback upon erroneous response (Bonenberger et al. 2015). Considering these studies, the A118G seems to be predictive of the reactivity to social rejection.

Based on results from animal studies demonstrating beneficial effects of opiates on social interactions (Stein et al. 2007; Falcon et al. 2015), the effect on social rejection of buprenorphine, a partial mu agonist and kappa antagonist, was evaluated in humans. A randomized controlled trial was performed in healthy adults. Participants received either placebo or 0.2 mg sublingual buprenorphine in randomized order, under double-blind conditions, followed by three behavioral tasks: Cyberball game, an attention task in which there were shown pairs of emotional faces, and a picture viewing task, in which they rated (using an evaluative space grid) images with or without social content. During Cyberball game, buprenorphine intake was associated with a decrease of perceived social rejection. During the attention task there was a reduction of initial attention to fearful faces. The ratings of positivity of social images were enhanced (Bershad et al. 2016). Altogether, these results suggest a positive effect of buprenorphine on sensibility to social rejection.

2.2 Social Pain and Suicidal Risk

Social pain is strongly linked to SB (Courtet and Olié 2019). Having a low social integration is a risk factor for SB (Tsai et al. 2015), and a large majority of suicide victims face adverse life events in the months preceding their suicidal act (Foster 2011). Interpersonal conflict is at the greatest risk of suicidal act followed by relationship breakdown, forensic events, unemployment, job problems, financial problems, bereavement, and domestic violence. Some of the risk associated with such events is independent of mental disorder (Foster 2011). All these factors are related to social features and threat social status of the individual. Accordingly, more and more studies are interested in the role of psychological pain in SB. The definition of psychological pain or "psychache" is complex. Shneidman defined it as "the introspective experience of negative emotions such as dread, despair, fear, grief, shame, guilt, frustrated love, loneliness and loss" (Shneidman 1998). More recently, Meerwijk et al. defined it as "a lasting, unsustainable and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self" (Meerwijk and Weiss 2014). Social pain is part of psychological pain, and psychological pain has a strong relationship with SB (Conejero et al. 2018). A study conducted by Olié et al. (2010) found that higher psychological pain in patients with major depressive disorder (MDD) may be a vulnerability factor for SB. In a very recent study within euthymic females with a history of depression and SB, they demonstrated that those patients had an impaired brain response to social exclusion (tested with the Cyberball task) in comparison with healthy controls and euthymic females with a history of depression but no history of SB in regions implicated in pain tolerance (e.g., insula) (Olié et al. 2017). Those results suggest sustained brain dysfunctions in relation to social perception in suicide attempters. More recently, in a study in people with suicidal ideation (SI), tolerance for psychological pain was significantly higher for participants who never attempted suicide (Meerwijk and Weiss 2018), suggesting that persons with low tolerance to psychological pain were more inclined to SB. In a

review of literature, they identified psychological pain as a potential predictor of suicidal risk (Rizvi et al. 2017). Finally, in a meta-analysis conducted by Ducasse et al. (2018b), psychological pain was significantly associated with SI and suicidal acts.

Considering the relationship between social pain and opioid system and the link between social pain (which is a part of psychological pain) and SB, it seems legitimate to consider that the opioid system could have an involvement in the pathophysiology of SB.

2.3 Opioid Consumption in Relation to Suicidal Behavior

Suicides and drug overdoses kill American adults at twice the rate today as they did just 17 years ago, and opioids are a key contributor to that rise. Using data from Centers for Disease Control and Prevention databases, the researchers show that the sheer number of deaths from suicides and unintentional overdoses together rose from 41,364 in the year 2000 to 110,749 in 2017. Opioids were implicated in one-third of all overdose-related suicides (Bohnert and Ilgen 2019). In 2010, the Department of Veterans Affairs and Department of Defense Clinical Practice Guideline for the Management of Opioid Therapy described high suicide risk as a relative contraindication for opioid therapy. In a retrospective study using treatment records from Veteran Affairs healthcare system and the National Death Index, the risk of suicide was greater among individuals receiving higher doses of opioids (Ilgen et al. 2016). Opioid prescription (but not non-opioid analgesic use) was associated with a previous history of suicide attempt in an elderly sample from the general population (Olié et al. 2013). In this sample, suicidal risk was independent of physical pain level. In a longitudinal study on 355 patients with chronic non-cancer pain, the more important the opioid daily doses, the more important depressive rates were (Scherrer et al. 2015), depression being one of the leading causes of SB (Greden 2001). Yet, in a study including patients treated by opioid substitution therapy for substance use disorders, those discontinuing prescription had higher rates of suicidal ideation and act (Demidenko et al. 2017). We can hypothesize that opiate consumption may be driven by the need to relief physical or psychological pain, but when this pain is no longer relieved, even with high doses, suicidal acts become the mean to get relief from an intolerable pain. Considering those data and elements seen previously, it appears that opioid system has an implication in SB.

3 Suicidal Behavior and Opioid System

Some studies reported dysfunction of the opioid system in depressed and suicidal patients. Foremost, significantly lower levels of endorphins were found in patients suffering from major depressive disorder (MDD) (Ehrich et al. 2015). Using positron

emission tomography and the selective MOR radioligand [^{11}C]-carfentanil, the induction of a sadness state was associated with larger reductions in MOR availability in MDD females than in healthy controls in the anterior insular cortex, anterior and posterior thalamus, ventral basal ganglia, amygdala, and PAG cortex (Kennedy et al. 2006). A more recent study similarly showed differences of MOR availability in medication-free MDD patients and healthy controls when experiencing social rejection or acceptance. During rejection MDD patients had a decrease in MOR activation in opposite with controls that had MOR activation in the right nucleus accumbens, bilateral amygdala, midline thalamus, and PAG. Furthermore, while during acceptance both groups reported increased positive affect, MOR deactivation was observed in the nucleus accumbens in MDD as opposed to MOR activation in controls. It suggests opioid involvement in the motivation for positive social interactions in controls but not in MDD patients (Hsu et al. 2015).

Genetic studies were also conducted on the A118G SNP and suicidal event in depressed subjects. A study on a large naturalistic cohort of depressed patients beginning tianeptine treatment (a MOR agonist) showed that AA genotype of A118G was significantly associated with emergence of suicidal ideation (Nobile et al. 2019). Interestingly, patients with alcohol use disorders carrying G allele responded better to naltrexone (a MOR antagonist) than A carriers (Berrettini 2016). Yet, studies on social pain reported that G carriers were more sensitive to social exclusion. Even speculative, it is possible that G carriers of A118G SNP would be more sensitive to medications acting on MOR than A carriers.

Then, the hypothalamic-pituitary-adrenocortical axis (HPA) is known to be dysregulated in SB with an increase of its activation (O'Connor et al. 2016). HPA axis is partly regulated by the opioid system (Bilkei-Gorzo et al. 2008) as a MOR antagonist would increase HPA axis activation (Drolet et al. 2001), while a MOR agonist would modulate this activation (Lovallo et al. 2012). A recent genetic study found that G carriers were less reactive to stress compared to A carriers of A118G SNP (Lovallo et al. 2015).

Finally some post-mortem studies on suicide victim's brains showed a significant increased density of MOR in brains of suicide victims in the frontal cortex and caudate in comparison with healthy controls (Gabilondo et al. 1995; Gross-Isseroff et al. 1990; Zalsman et al. 2005), possibly as a consequence of a compensatory mechanism. The A118G SNP was found to be associated with completed suicide (G allele being protective of completed suicide) (Hishimoto et al. 2008) without being replicated in patients with substance use disorder (Icick et al. 2014; Arias et al. 2012; Lutz et al. 2018a).

Most studies were performed on MOR, but studies on kappa opioid receptor (KOR) are emerging. Initial post-mortem reports indicated that the dynorphin-kappa opioid receptor signaling pathway may contribute to suicide, with increased (Hurd et al. 1997) and decreased (Hurd 2002) expression found in the caudate nucleus and amygdala, respectively (Lutz et al. 2017). More recently, decreased expression and epigenetic modifications of the KOR gene were identified in depressed patients with a history of severe child abuse as opposed to both depressed patients with no such history and controls. These modifications may contribute to increased risk of suicide

associated with child abuse (Lutz et al. 2018b). Another study suggested an association between an insertion-deletion in the KOR promoter (rs 35,566,036) and the epigenetic status of this highly stress-responsive gene (Lutz et al. 2018c). More studies are needed in order to better understand the mechanisms underlying the implication of KOR in SB.

4 To New Pharmacological Treatments for SB

Even clinicians should be cautious to assess suicidal risk when prescribing available opioid drugs, it is possible to speculate that opioid system could help to develop treatments for SB. Historically, opiates were used for treating depression before modern antidepressants in the 1950s (Tenore 2008). In the 1980s, five clinical studies were performed in order to evaluate antidepressant effects of intravenous infusions of beta-endorphin. They showed a significant and rapid effect on depressive symptoms (Halbreich and Endicott 1981).

More recently, interest in tianeptine (a MOR agonist), buprenorphine (a partial MOR agonist and a KOR antagonist), and methadone (a MOR agonist) for the treatment of depression and SB has been growing.

Tianeptine has been shown to be a MOR agonist and that its antidepressants effects may be mediated by this receptor (Samuels et al. 2017; Gassaway et al. 2014). In a large naturalistic cohort of depressed outpatients, patients on tianeptine were significantly less prone to have a worsening of suicidal ideation during follow-up compared to patients taking other antidepressants (Nobile et al. 2018). Yet, studies on this antidepressant remain scarce as its commercialization is currently not allowed in several countries (e.g., the United States), notably due to the risk of dependence.

Regarding buprenorphine, growing evidence demonstrates its interest in treating depression and SB. In severely depressed patients with treatment-resistant depression, buprenorphine was administered at low doses (0.2–1.6 mg per day) during 8 weeks. At the end, after discontinuation of buprenorphine, most patients reached remission without side effects (Karp et al. 2014). A multisite randomized double-blind placebo-controlled trial was conducted on ultra-low-dose sublingual buprenorphine (maximal daily dose of 0.8 mg) for 1 month as an adjunctive treatment in depressed suicidal patients (64.5% had made at least one suicide attempt). Patients receiving buprenorphine had a greater reduction of suicidal ideation according to Beck Scale of Suicidal Ideation scores than patients on placebo at 2 weeks and 4 weeks of treatment. Concurrent use of antidepressants did not affect response to buprenorphine (Yovell et al. 2016). In another recent randomized controlled trial within patients with MDD, opioid dependence, and suicidal ideation (assessed by the Beck Scale of Suicidal Ideation), results have shown a significant decrease of suicidal ideation with a single-dose administration of buprenorphine (from 32 to 96 mg) (Ahmadi et al. 2018). It has been hypothesized that buprenorphine's "anti-suicidal" effect may be driven by MOR agonism (Yovell et al. 2016) and its antidepressant effect by KOR antagonism (Falcon et al. 2016).

Indeed, a randomized double-blind placebo-controlled trial with buprenorphine combined with samidorphan (a MOR antagonist, resulting in an unclear overall effect on MOR signaling) as adjunctive treatment was conducted in patients with MDD during 4 weeks. Patients were divided into three groups: 2/2 mg of buprenorphine/samidorphan, 8/8 mg of buprenorphine/samidorphan, or placebo. In comparison to patients on placebo, patients receiving 2/2 mg had greater improvement of depression, while tolerance was good with no opioid withdrawal during treatment discontinuation (Fava et al. 2016).

Methadone has been rarely studied in depressed or suicidal subjects. In a randomized controlled trial in depressed patients with methadone maintenance, fluoxetine was added to methadone in one group in order to compare improvement of depression in comparison to methadone use only. Both groups showed a significant reduction in depressive symptoms suggesting an antidepressant effect of methadone (no supplementary effect by adding fluoxetine) (Dean et al. 2002). Another randomized controlled trial was performed in severely depressed patients receiving methadone or buprenorphine. Depression severity significantly decreased in both groups, suggesting similar antidepressant effects of these opiates (Dean et al. 2004). Unfortunately, there is no clinical study using methadone in SB. Yet, in view of the antidepressant effect of methadone and the interest of opiates in treating SB, it would be interesting to conduct such studies in the future.

Recently, many studies demonstrated the efficacy of ketamine (an NMDA antagonist) to quickly reduce suicidal ideation in depressed patients (Canuso et al. 2018; Wilkinson et al. 2018). This effect would be partially explained by antidepressant efficacy but not only (Wilkinson et al. 2018). Yet, the mechanism of action by which ketamine acts on depression and suicidal ideation is still unclear. It is possible that this effect may come partly from an action on the opioid system. Indeed, it has been shown that ketamine increases the effectiveness of the signaling induced by opiates (Gupta et al. 2011). Moreover, a recent randomized controlled trial showed that reduction of depressive symptoms was lower when naltrexone vs. placebo was administered before ketamine (Williams et al. 2018). Those results suggest that the effect of ketamine requires opioid system activation. More studies are needed to confirm this hypothesis and to better understand opioid mechanisms contributing to ketamine action.

5 Conclusions

In summary, a vast majority of the studies reviewed here demonstrated an involvement of opioid system in mediating responses to social pain, which is an important risk factor of SB. Moreover, a link between opioid consumption and suicidal risk has been shown in many studies. Finally, some studies suggest that suicidal patients seem to have opioid system dysfunction. Yet, opioid mechanisms underlying depression and associated SB remain poorly understood and will require additional investigations, notably in relation to KOR and possibly the delta opioid receptor.

Finding effective pharmacological treatment for SB is a major health concern and is urgently needed. Results from studies on opiate use in treating depression and SB are really encouraging. More clinical trials are needed, and results should be more explored to better understand mechanisms underlying potential beneficial effects on SB of opiates.

References

Ahmadi J, Jahromi MS, Ehsaei Z (2018) The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: a randomized, double-blind, clinical trial. Trials 19:462

Apkarian AV, Bushnell MC, Treede R-D, Zubieta J-K (2005) Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain Lond Engl 9:463–484

Arias AJ, Chan G, Gelernter J, Farrer L, Kranzler HR (2012) Variation in OPRM1 and risk of suicidal behavior in drug-dependent individuals. Am J Addict 21:5–10

Berrettini W (2016) Alcohol addiction and the mu-opioid receptor. Prog Neuro-Psychopharmacol Biol Psychiatry 65:228–233

Bershad AK, Seiden JA, de Wit H (2016) Effects of buprenorphine on responses to social stimuli in healthy adults. Psychoneuroendocrinology 63:43–49

Bertoletti E, Zanoni A, Giorda R, Battaglia M (2012) Influence of the OPRM1 gene polymorphism upon children's degree of withdrawal and brain activation in response to facial expressions. Dev Cogn Neurosci 2:103–109

Bilkei-Gorzo A et al (2008) Control of hormonal stress reactivity by the endogenous opioid system. Psychoneuroendocrinology 33:425–436

Bohnert ASB, Ilgen MA (2019) Understanding links among opioid use, overdose, and suicide. N Engl J Med 380:71–79

Bonenberger M, Plener PL, Groschwitz RC, Grön G, Abler B (2015) Polymorphism in the μ-opioid receptor gene (OPRM1) modulates neural processing of physical pain, social rejection and error processing. Exp Brain Res 233:2517–2526

Cacioppo S et al (2013) A quantitative meta-analysis of functional imaging studies of social rejection. Sci Rep 3:1–3

Calati R, Courtet P (2016) Is psychotherapy effective for reducing suicide attempt and non-suicidal self-injury rates? Meta-analysis and meta-regression of literature data. J Psychiatr Res 79:8–20

Canuso CM et al (2018) Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatry 175:620–630

Choi CY (2016) Chronic pain and opiate management. Dis Mon 62:334–345

Chou W-Y et al (2006) Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. Anesthesiology 105:334–337

Conejero I, Olié E, Calati R, Ducasse D, Courtet P (2018) Psychological pain, depression, and suicide: recent evidences and future directions. Curr Psychiatry Rep 20:33

Courtet P, Olié É (2014) Antidepressants do prevent suicide, at least pending something better. Bull Acad Natl Méd 198:881–892

Courtet P, Olié E (2019) Social pain at the core of suicidal behavior. L'Encephale 45(Suppl 1):S7–S12

Dalgleish T et al (2017) Social pain and social gain in the adolescent brain: a common neural circuitry underlying both positive and negative social evaluation. Sci Rep 7:42010

Dean AJ, Bell J, Mascord DJ, Parker G, Christie MJ (2002) A randomised, controlled trial of fluoxetine in methadone maintenance patients with depressive symptoms. J Affect Disord 72:85–90
Dean A, Bell J, Christie M, Mattick R (2004) Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. Eur Psychiatry 19:510–513
Demidenko MI et al (2017) Suicidal ideation and suicidal self-directed violence following clinician-initiated prescription opioid discontinuation among long-term opioid users. Gen Hosp Psychiatry 47:29–35
DeWall CN et al (2012) Do neural responses to rejection depend on attachment style? An fMRI study. Soc Cogn Affect Neurosci 7:184–192
Drolet G et al (2001) Role of endogenous opioid system in the regulation of the stress response. Prog Neuro-Psychopharmacol Biol Psychiatry 25:729–741
Ducasse D et al (2018a) Acceptance and commitment therapy for the management of suicidal patients: a randomized controlled trial. Psychother Psychosom 87:211–222
Ducasse D et al (2018b) Psychological pain in suicidality: a meta-analysis. J Clin Psychiatry 79:16r10732. https://doi.org/10.4088/JCP.16r10732
Ehrich E et al (2015) Evaluation of opioid modulation in major depressive disorder. Neuropsychopharmacology 40:1448–1455
Eisenberger NI (2012) The neural bases of social pain: evidence for shared representations with physical pain. Psychosom Med 74:126–135
Eisenberger NI, Lieberman MD, Williams KD (2003) Does rejection hurt? An FMRI study of social exclusion. Science 302:290–292
Eisenberger NI, Taylor SE, Gable SL, Hilmert CJ, Lieberman MD (2007) Neural pathways link social support to attenuated neuroendocrine stress responses. NeuroImage 35:1601–1612
Eisenberger NI et al (2011) Attachment figures activate a safety signal-related neural region and reduce pain experience. Proc Natl Acad Sci 108:11721–11726
Falcon E, Maier K, Robinson SA, Hill-Smith TE, Lucki I (2015) Effects of buprenorphine on behavioral tests for antidepressant and anxiolytic drugs in mice. Psychopharmacology 232:907–915
Falcon E et al (2016) Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. Neuropsychopharmacology. https://doi.org/10.1038/npp.2016.38
Fava M et al (2016) Opioid modulation with buprenorphine/Samidorphan as adjunctive treatment for inadequate response to antidepressants: a randomized double-blind placebo-controlled trial. Am J Psychiatry 173:499–508
Foster T (2011) Adverse life events proximal to adult suicide: a synthesis of findings from psychological autopsy studies. Arch Suicide Res 15:1–15
Gabilondo AM, Meana JJ, García-Sevilla JA (1995) Increased density of mu-opioid receptors in the postmortem brain of suicide victims. Brain Res 682:245–250
Gassaway MM, Rives M-L, Kruegel AC, Javitch JA, Sames D (2014) The atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist. Transl Psychiatry 4:e411
Greden JF (2001) The burden of recurrent depression: causes, consequences, and future prospects. J Clin Psychiatry 62(Suppl 22):5–9
Gross-Isseroff R, Dillon KA, Israeli M, Biegon A (1990) Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Res 530:312–316
Gupta A, Devi LA, Gomes I (2011) Potentiation of μ-opioid receptor-mediated signaling by ketamine: opioid-ketamine interactions. J Neurochem 119:294–302
Halbreich U, Endicott J (1981) Possible involvement of endorphin withdrawal or imbalance in specific premenstrual syndromes and postpartum depression. Med Hypotheses 7:1045–1058
Herman BH, Panksepp J (1981) Ascending endorphin inhibition of distress vocalization. Science 211:1060–1062
Hishimoto A et al (2008) A functional polymorphism of the micro-opioid receptor gene is associated with completed suicides. J Neural Transm 115:531–536

Hsu DT et al (2013) Response of the μ-opioid system to social rejection and acceptance. Mol Psychiatry 18:1211–1217
Hsu DT et al (2015) It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. Mol Psychiatry 20:193–200
Hurd YL (2002) Subjects with major depression or bipolar disorder show reduction of prodynorphin mRNA expression in discrete nuclei of the amygdaloid complex. Mol Psychiatry 7:75–81
Hurd YL et al (1997) Prodynorphin mRNA expression is increased in the patch vs matrix compartment of the caudate nucleus in suicide subjects. Mol Psychiatry 2:495–500
Icick R et al (2014) OPRM1 polymorphism and lifetime suicide attempts among stabilized, methadone-maintained outpatients. Psychiatry Res 218:259–260
Ilgen MA et al (2016) Opioid dose and risk of suicide. Pain 157:1079–1084
Kalin NH, Shelton SE, Barksdale CM (1988) Opiate modulation of separation-induced distress in non-human primates. Brain Res 440:285–292
Karp JF et al (2014) Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry 75:e785–e793
Kennedy SE, Koeppe RA, Young EA, Zubieta J-K (2006) Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. Arch Gen Psychiatry 63:1199–1208
Klein JW (2016) Pharmacotherapy for substance use disorders. Med Clin North Am 100:891–910
Kroslak T et al (2007) The single nucleotide polymorphism A118G alters functional properties of the human mu opioid receptor. J Neurochem 103:77–87
Kross E, Berman MG, Mischel W, Smith EE, Wager TD (2011) Social rejection shares somatosensory representations with physical pain. Proc Natl Acad Sci U S A 108:6270–6275
Kubica-Cielińska A, Zielińska M (2015) The use of nalbuphine in paediatric anaesthesia. Anaesthesiol Intensive Ther 47:252–256
Lovallo WR et al (2012) Naltrexone effects on cortisol secretion in women and men in relation to a family history of alcoholism: studies from the Oklahoma family health patterns project. Psychoneuroendocrinology 37:1922–1928
Lovallo WR et al (2015) Cortisol stress response in men and women modulated differentially by the Mu-opioid receptor gene polymorphism OPRM1 A118G. Neuropsychopharmacology 40:2546–2554
Lutz P-E, Mechawar N, Turecki G (2017) Neuropathology of suicide: recent findings and future directions. Mol Psychiatry 22:1395–1412
Lutz P-E, Courtet P, Calati R (2018a) The opioid system and the social brain: implications for depression and suicide. J Neurosci Res. https://doi.org/10.1002/jnr.24269
Lutz P-E et al (2018b) Epigenetic regulation of the kappa opioid receptor by child abuse. Biol Psychiatry 84:751–761
Lutz P-E, Almeida D, Belzeaux R, Yalcin I, Turecki G (2018c) Epigenetic regulation of the kappa opioid receptor gene by an insertion-deletion in the promoter region. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol 28:334–340
Mague SD, Blendy JA (2010) OPRM1 SNP (A118G): involvement in disease development, treatment response, and animal models. Drug Alcohol Depend 108:172–182
Masten CL et al (2011) Subgenual anterior cingulate responses to peer rejection: a marker of adolescents' risk for depression. Dev Psychopathol 23:283–292
Masten CL, Telzer EH, Fuligni AJ, Lieberman MD, Eisenberger NI (2012) Time spent with friends in adolescence relates to less neural sensitivity to later peer rejection. Soc Cogn Affect Neurosci 7:106–114
Meerwijk EL, Weiss SJ (2014) Toward a unifying definition: response to 'the concept of mental pain'. Psychother Psychosom 83:62–63
Meerwijk EL, Weiss SJ (2018) Tolerance for psychological pain and capability for suicide: contributions to suicidal ideation and behavior. Psychiatry Res 262:203–208
Meyer ML, Williams KD, Eisenberger NI (2015) Why social pain can live on: different neural mechanisms are associated with reliving social and physical pain. PLoS One 10:e0128294

Nobile B et al (2018) Tianeptine is associated with lower risk of suicidal ideation worsening during the first weeks of treatment onset compared with other antidepressants: a naturalistic study. J Psychiatr Res 96:167–170
Nobile B et al (2019) Polymorphism A118G of opioid receptor mu 1 (OPRM1) is associated with emergence of suicidal ideation at antidepressant onset in a large naturalistic cohort of depressed outpatients. Sci Rep 9:2569
O'Connor DB, Ferguson E, Green JA, O'Carroll RE, O'Connor RC (2016) Cortisol levels and suicidal behavior: a meta-analysis. Psychoneuroendocrinology 63:370–379
Olié E, Guillaume S, Jaussent I, Courtet P, Jollant F (2010) Higher psychological pain during a major depressive episode may be a factor of vulnerability to suicidal ideation and act. J Affect Disord 120:226–230
Olié E et al (2013) History of suicidal behaviour and analgesic use in community-dwelling elderly. Psychother Psychosom 82:341–343
Olié E et al (2017) The experience of social exclusion in women with a history of suicidal acts: a neuroimaging study. Sci Rep 7:89
Panksepp J, Bean NJ, Bishop P, Vilberg T, Sahley TL (1980a) Opioid blockade and social comfort in chicks. Pharmacol Biochem Behav 13:673–683
Panksepp J, Herman BH, Vilberg T, Bishop P, DeEskinazi FG (1980b) Endogenous opioids and social behavior. Neurosci Biobehav Rev 4:473–487
Perini I et al (2018) The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. Sci Rep 8:1–9
Peyron R, Laurent B, García-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin Clin Neurophysiol 30:263–288
Rizvi SJ, Iskric A, Calati R, Courtet P (2017) Psychological and physical pain as predictors of suicide risk: evidence from clinical and neuroimaging findings. Curr Opin Psychiatry 30:159–167
Rogachov A, Cheng JC, DeSouza DD (2015) Discriminating neural representations of physical and social pains: how multivariate statistics challenge the "shared representation" theory of pain. J Neurophysiol 114:2558–2560
Samuels BA et al (2017) The behavioral effects of the antidepressant tianeptine require the Mu-opioid receptor. Neuropsychopharmacology 42:2052–2063
Scherrer JF et al (2015) Change in opioid dose and change in depression in a longitudinal primary care patient cohort. Pain 156:348–355
Shneidman ES (1998) The suicidal mind. Oxford University Press, Oxford
Sia AT et al (2008) A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 109:520–526
Stein DJ, van Honk J, Ipser J, Solms M, Panksepp J (2007) Opioids: from physical pain to the pain of social isolation. CNS Spectr 12(669–670):672–674
Tenore PL (2008) Psychotherapeutic benefits of opioid agonist therapy. J Addict Dis 27:49–65
Tsai AC, Lucas M, Kawachi I (2015) Association between social integration and suicide among women in the United States. JAMA Psychiat 72:987–993
Way BM, Taylor SE, Eisenberger NI (2009) Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. Proc Natl Acad Sci U S A 106:15079–15084
Wilkinson ST et al (2018) The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. Am J Psychiatry 175:150–158
Williams NR et al (2018) Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry 175:1205–1215
Woo C-W et al (2014) Separate neural representations for physical pain and social rejection. Nat Commun 5:1–12
Yovell Y et al (2016) Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. Am J Psychiatry 173:491–498

Zalsman G et al (2005) Postmortem mu-opioid receptor binding in suicide victims and controls. J Neural Transm 112:949–954
Zalsman G et al (2016) Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry 3:646–659
Zhang Y, Wang D, Johnson AD, Papp AC, Sadee W (2005) Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 280:32618–32624

Sleep Disturbances and Suicidal Behavior

Jorge Lopez-Castroman and Isabelle Jaussent

Contents

Abstract Sleep disturbances, particularly insomnia, nightmares, and excessive daytime sleepiness (EDS), are significant, proximal, and modifiable risk factors for suicidal ideation and behaviors (SIB) and could be targeted for preventative interventions. In this chapter, we review the evidence supporting the association of insomnia, nightmares, and EDS with SIB. We also describe these sleep disturbances in the general population, as well as their association with psychiatric disorders. A PubMed search was conducted to identify the relevant literature. Insomnia is very frequent across mental disorders, but SIB patients are particularly exposed. Specific interventions focused on insomnia are useful in contending suicidal ideation.

J. Lopez-Castroman (✉)
PSNREC, University of Montpellier, INSERM, Montpellier, France

Nimes University Hospital, Nimes, France

CIBERSAM, Madrid, Spain

I. Jaussent
PSNREC, University of Montpellier, INSERM, Montpellier, France

Curr Topics Behav Neurosci (2020) 46: 211–228
https://doi.org/10.1007/7854_2020_166
Published Online: 28 August 2020

Nightmares seem to constitute an independent risk factor for SIB, beyond insomnia, particularly in young people and when experienced frequently. The evidence regarding the association of EDS and SIB is less clear and probably explained by the reduction of health-related quality of life and comorbid depression. The mechanisms underlying the relationship between sleep disturbances and SIB as well as the role of potential confounders and future perspectives in this field are also discussed.

Keywords Dyssomnias · Self-injurious behavior · Sleep deprivation · Sleep disorders · Sleep hygiene · Suicide attempt

1 Introduction

Suicidal ideation and behaviors (SIB) are part of a complex, multifactorial phenomenon that spans over biological, social, and psychological mechanisms. The prevention of SIB has become a public health priority in many countries, but to date the results of prevention programs are insufficient (Hedegaard et al. 2018). If there is to be any progress in understanding suicide, significant, proximal, and modifiable risk factors should be identified.

Through the last decades, numerous studies suggest that sleep disturbances, particularly insomnia, nightmares, and excessive daytime sleepiness (EDS), are among such factors (Porras-Segovia et al. 2019; Littlewood et al. 2017; Bernert et al. 2015; Pigeon et al. 2012). First, sleep disturbances are strongly associated with all the different components of the suicidal process. Second, they very often constitute a proximal factor that immediately precedes the emergence of SIB. They can thus be considered a warning sign with potential applicability for prevention. Third, as it is often highlighted, sleep patterns can be modified through a number of treatments such as better sleep hygiene, different kinds of psychological interventions, or pharmacological treatments. In the present, wearable devices have made possible a feasible and relatively accurate assessment of sleep patterns and disturbances in both clinical and ecological settings. In the future, sleep assessment might be regularly used first to detect individuals at risk of SIB and then to implement preventive measures or adequate treatment (Chaïb et al. 2020).

2 Method

In this chapter, the focus is placed on insomnia, nightmares, and EDS since the evidence of an association with SIB is strongest for these three conditions. We start by describing these sleep disturbances in the general population and subsequently their association with psychiatric disorders and with SIB. A PubMed search was

conducted to identify the relevant literature on the topic. The following terms provided a total of 659 matches from 1955 to 2019: ("suicidal ideation" [MeSH Terms] OR "suicide, attempted" [MeSH Terms]) OR "suicide" [MeSH Terms] OR "suicide, attempted" [MeSH Terms]) AND ("sleep" [MeSH Terms] OR "sleep wake disorders" [MeSH Terms] OR "sleep initiation and maintenance disorders" [MeSH Terms] OR "disorders of excessive somnolence" [MeSH Terms] OR "nightmares" [MeSH Terms]). The bibliography in the most important studies was screened to select other papers of interest. Several systematic reviews and meta-analyses (Porras-Segovia et al. 2019; Littlewood et al. 2017; Pigeon et al. 2012; Liu et al. 2019a) have been published on this topic; the intent of this chapter is to provide the reader with an updated overview of different aspects connecting SIB and sleep disturbances.

3 Sleep Complaints in the General Population

3.1 Insomnia

Insomnia is characterized by one or more complaints of unsatisfactory sleep associated with daytime repercussions. The nature of night complaints concerns difficulties in initiating sleep, maintaining sleep, or waking up early with an inability to fall asleep again. In clinical practice, insomnia complaints can be difficult to assess objectively because there are significant differences between the individual's sleep, perception, and expectations. Significant differences exist between subjective sleep assessment reported by the patient and the objective assessment achieved during a polysomnography recording: poor sleepers tend to overestimate their sleep latency and underestimate their total sleep duration.

Although studies in the general population confirm that insomnia remains the most common sleep disorder, prevalence estimates vary widely depending on the definition (Ohayon 2002). The presence of insomnia complaints in the population is very high, ranging from 10 to 48%, but insomnia symptoms with diurnal consequences such as sleepiness, irritability, anxiety, or depressed mood that may lead to a medical consultation are much lower, from 9% to 15%. Subjects that define themselves as poor sleepers or as suffering from insomnia range similarly from 7% to 12%. Finally, if we also take into account the impact on daytime functioning, in agreement with international diagnostic criteria for insomnia, the rates then range from 5% to 11%. The variability found within each definition can be explained by differences according to demographic and cultural/geographical factors but also inconsistencies in study design, sample size, and the subjective nature of the complaints.

In any case, most epidemiological studies report that the prevalence of symptoms and insomnia syndrome is higher in women than in men and that it increases gradually with age and is reported to be twice as high in people over 65 years of age as in young people.

3.2 Excessive Daytime Sleepiness

Sleepiness is defined as the propensity to doze or fall asleep when intending to remain awake, to be distinguished from subjective feelings of "tiredness" or "fatigue" that are not always related to sleepiness.

Epidemiological surveys in the general population approach excessive sleepiness using different definitions. Most of them focus on the response to one single question: "do you sleep too much?" (excessive sleep). The idea of frequency and/or duration appears in some studies, but few distinguish daytime sleepiness from nighttime sleep. Prevalence estimates range from 0.3% to 16% (Breslau et al. 1996; Karacan et al. 1976). Other studies are interested in sudden sleep episodes defined by a question on either uncontrollably falling asleep during the day or falling asleep when it is not the time (e.g., while driving). The prevalence of sudden sleep episodes ranges from 3% to 9% (Bixler et al. 2005; Kaneita et al. 2005). Finally, EDS, i.e., hypersomnolence, is the object of a growing interest. The definition of EDS in epidemiological surveys is also highly variable. Studies that investigate the presence or absence of EDS during the day without further clarification report a prevalence ranging from 8% to 25% (Enright et al. 1996; Foley et al. 2001). A similar range, between 10% and 33%, is obtained from studies using a standardized self-report questionnaire to estimate the severity of EDS (Jaussent et al. 2017; Klink and Quan 1987).

Ohayon et al. emphasized the importance of considering the frequency, duration, and quality of naps, but also the distress associated with the complaint of sleepiness (Ohayon 2012). In their study, 27.9% of participants complained about EDS in the month prior to the interview, but only 4.7% of them reported EDS at least three times a week for at least 3 months, despite a normal night sleep duration ($\geq$7 h). Of these 4.7%, only 1.5% had hypersomnia.

The majority of studies do not find a significant association between EDS and gender, except for studies conducted among those over 65 years of age, which report an increased prevalence among men. With respect to the relationship between age and EDS, some studies do not find a significant association (Baldwin et al. 2004; Whitney et al. 1998), while others show a high proportion of EDS in adults under 30 years of age and in adults over 75 years of age (Bixler et al. 2005).

3.3 Nightmares

Nightmares are parasomnias consisting of unpleasant dreams that occur during late-night rapid eye movement (REM) sleep. Awakenings produced by nightmares often leave the person in a state of distress and unable to return to sleep (American Psychiatric Association 2013; American Academy of Sleep Medicine 2014). Fear is the most frequently reported emotion being reported in 62% to 85% of the nightmares, but other emotions, such as sadness, despair, anxiety, anger, or

confusion, are common (Robert and Zadra 2014). Approximately 0.9% to 6.8% of the general population report current nightmares (at least once a week) (Sandman et al. 2015). They are more frequent among women than among men, and they tend to weaken with age, being more common in young people. However, studies about nightmares are mostly retrospective and have potential sources of bias, in particular the recall bias, and confounding (Robert and Zadra 2008). Nightmares are often associated with depressive and anxiety symptoms, neuroticism, posttraumatic stress disorder (PTSD), and other sleep problems such as prolonged sleep latencies, poorer sleep quality, and daytime sleepiness (Germain 2013; Li et al. 2010a). They usually begin within 3 months of a psychological trauma and are present in more than 80% of patients with PTSD (American Academy of Sleep Medicine 2014).

4 Sleep Disturbances in Psychiatric Conditions

Sleep problems are very common in psychiatric conditions and even part of the diagnostic criteria in some cases. Within the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), insomnia/hypersomnia and short sleep duration are core diagnostic criteria of major depressive disorder and bipolar disorder, respectively. Sleep disturbances, such as difficulties in initiating sleep, difficulties in maintaining sleep, or poor sleep, are part of the clinical features of generalized anxiety disorder (GAD) and PTSD. Relative to controls, polysomnographic studies of patients with psychiatric disorders showed abnormalities in sleep architecture including decreased total sleep time and sleep efficiency, shorter REM latency, greater REM density, and greater percentage of REM sleep (Benca et al. 1992; Krystal et al. 2008). Indeed, sleep disorders have a negative impact on the course and treatment of psychiatric illness. They can increase the incidence of mood and anxiety events, trigger manic episodes in bipolar disorder, and facilitate the onset of psychotic symptoms or suicidal ideation. Insomnia seems also to mediate the effect on suicide risk of borderline personality disorder traits (DeShong and Tucker 2019).

5 Effects of Insomnia on SIB

The results of recent research studies highlight the existence of a prominent link between insomnia and SIB. In longitudinal studies, insomnia has been found to be a risk factor for suicidal ideation (McCall et al. 2010; Ribeiro et al. 2012), for suicide attempts (Ribeiro et al. 2012; Li et al. 2010b), and also for suicide deaths in both patients with mood disorders (Fawcett et al. 1990) and adult samples of the general population (Fujino et al. 2005; Turvey et al. 2002) over follow-ups ranging from 1 month (Ribeiro et al. 2012) to 14 years (Fujino et al. 2005). The associations remained significant even after adjustment for the presence of psychiatric disorders and/or symptoms of these disorders, such as hopelessness or anhedonia (McCall

et al. 2010; Ribeiro et al. 2012; Li et al. 2010b). In adolescents, the independence of this relationship seems to be less clear. According to a meta-analytic review, insomnia predicts the risk of suicidal thoughts in adolescents independent of depression, but the same conclusion cannot be applied to suicide attempts (Liu et al. 2019a). However, a large majority of suicide attempters in clinical settings, including both adolescents (Tishler et al. 1981) and adult attempters (Sjöström et al. 2007), seem to report insomnia symptoms. Moreover, insomnia symptoms are also very often present when retrospectively assessing suicides, especially in the days close to the time of death, in adolescent and adult samples (Drapeau and Nadorff 2017). This symptomatic increase near the attempts suggests that sleep disturbances may facilitate the transition from ideation to action. It should be noted however that most studies are based on self-reported symptoms of insomnia, rather than clinical diagnoses.

Connected with insomnia, sleep duration has been correlated with the severity of SIB. Short sleep ($\leq$5 h) seems to be several times more prevalent among suicide attempters that among healthy controls (Blasco-Fontecilla et al. 2011). According to a meta-analysis exploring this question among adolescents, sleep time is inversely correlated with the emergence of suicide plans and shows a U-shaped relationship with suicidal ideation and suicide attempts independent of depression severity and other mental disorders (Chiu et al. 2018). A similar correlation between sleep duration and suicidality has been reported in a representative adult sample from the community that was followed longitudinally over 30 years (Rössler et al. 2018). This latter study reported also that sleep disturbances and suicidal outcomes were bidirectionally related during follow-up, but ecological data in clinical samples suggests that sleep disturbances precede suicidal ideation (Littlewood et al. 2019). It should also be noted that the intensity of sleep problems affects the risk of SIB. Specific symptoms of insomnia, such as nonrestorative sleep or difficulties falling asleep, doubled the prospective risk of suicide compared to subjective poor sleep in a large community sample of older adults followed for 10 years (Bernert et al. 2014). In adolescents, the odds of SIB seem to augment with just an hour less of sleep during the week and increasingly so with fewer hours of sleep (Winsler et al. 2015).

As we have seen, insomnia is very frequent across mental disorders, but suicidal patients are particularly exposed. A population-based cohort study examined retrospectively data on about half a million hospitalizations in Taiwan and compared the rates of suicide attempts in patients with and without insomnia (Lin et al. 2018). According to their results, the risk of having made a suicide attempt was 18 times higher among patients with a mental disorder and insomnia compared to those without any of these conditions. Women and patients aged 25–44 years with insomnia were four to five times more likely to attempt suicide than those without, after adjustment for other factors including psychiatric conditions (Chiu et al. 2018). The effect of insomnia on suicide risk among depressed patients, which is one of the mental disorders more frequently associated with SIB, was examined in a large and well-characterized clinical cohort of patients suffering from major depression and followed up for 6 years in the Netherlands (Eikelenboom et al. 2019). Insomnia was

found to be one of the seven independent predictors of incident suicide attempts, but the odds were relatively small in multivariate analyses (OR = 1.42; CI = 1.06–1.89).

From a therapeutic point of view, some recent reports suggest that specific interventions focused on insomnia are useful in contending suicidal ideation. For instance, a cognitive behavioral therapy specifically designed against insomnia (CBT-I) reduced suicidal ideation in war veterans (Trockel et al. 2015). A proof-of-concept study that tested a brief CBT-I for primary care patients suffering from insomnia also found a reduction in the severity of suicidal ideation, but the effect size was found to be small (0.26) (Pigeon et al. 2019). Concerning the use of hypnotics, a randomized clinical trial has shown that using zolpidem, compared to placebo, as add-on to an open-label sertraline treatment for depressed adult patients with insomnia reduced the intensity of suicidal thoughts, along with the improvement in insomnia symptoms (McCall et al. 2019).

6 Effects of Nightmares on Suicidality

The accumulated evidence to date strongly suggests that nightmares are an independent factor for SIB. The meta-analysis by Pigeon et al. (2012) found that experimenting nightmares was associated with an increased risk (OR = 1.72, CI = 1.18–2.52) of any suicidal outcome, including suicide death, after adjustment for any other sleep disturbance (Pigeon et al. 2012). The association might be mediated by psychological factors and past traumatic experiences. In a study with 91 participants with PTSD symptoms, those who reported nightmares were more frequently associated with SIB, independent of comorbid insomnia and depression (Littlewood et al. 2016). The authors found also that feelings of defeat, entrapment, and hopelessness mediated this relationship. In another paper, nightmares, together with dysfunctional beliefs about sleep, were found to mediate the relationship between insomnia and suicidal ideation (Chiu et al. 2018; Rössler et al. 2018).

Nightmares might play different roles in the emergence of SIB depending on the population. In a cross-sectional study with older adults (≥65 years), the effect of insomnia on suicidal ideation was independent of the presence of nightmares (Nadorff et al. 2013). A similar finding was reported in a sample with borderline personality disorder traits (DeShong and Tucker 2019). However, a survey among undergraduate students in the USA found that nightmares were an independent predictor of suicidal ideation, even after controlling for insomnia, anxiety, depression, and PTSD (Nadorff et al. 2011). Similarly, a large adolescent survey in Scotland reported that nightmares were associated with suicidal ideation independent of insomnia (Russell et al. 2018). A recent meta-analysis based on observational studies in depressed patients found that the overall risk of SIB was higher with nightmares (OR = 4.47; CI = 2.00–9.97) than with insomnia (OR = 2.29; CI = 1.69–3.10) (Wang et al. 2019).

The effects on SIB of nightmares seem also to be determined by their features. A longitudinal study with suicide attempters reported that the frequency of nightmares

at baseline, but not the difficulties initiating or maintaining sleep, predicted the repetition of the attempt in the next 2 years (Sjöström et al. 2009). Another study, issued from an online survey, found that participants reporting less frequent nightmares were more likely to be single suicide attempters rather than multiple attempters even after adjusting for confounding factors such as depression or insomnia. The frequency of nightmares also differentiated attempters from non-attempters, but the severity of nightmares did not (Speed et al. 2018).

7 Effects of Excessive Daytime Sleepiness on Suicidality

Little is known about the relationship between EDS and suicide. Cross-sectional studies reported that EDS is associated with depressive symptoms but also with suicide ideation and suicide attempts in depressed children and adolescents (Lopes et al. 2016). Still among adolescents, a longitudinal study reinforced this result reporting that daytime sleepiness was associated with subsequent suicidal thoughts and suicide plans over a 1-year follow-up even after adjustment for depression/anxiety and sleep-related complaints (Liu et al. 2019a). However, no association was shown between EDS and suicide risk in adults admitted to an emergency department of a general or psychiatric hospital who presented passive or active suicide ideation over 1 month follow-up (Mirsu-Paun et al. 2017).

Concerning hypersomnia disorders, it has been reported that hypersomnia is frequent in suicidal patients (Bernert and Joiner 2007). Depressed patients with hypersomnia were more likely to attempt suicide compared to those without (Agargun et al. 1997). Interestingly, the co-occurrence of insomnia and hypersomnia may be linked with past-year suicide thoughts and suicide attempt planning (Soehner et al. 2014). In narcoleptic patients, one study reported that narcolepsy was associated with a 7.35-fold increase in mortality due to suicide (Ohayon et al. 2014).

The mechanisms for the association between suicidal behaviors and hypersomnia could be explained first by the reduction of health-related quality of life and comorbid depression, but the role of serotonin could also be important (see Sect. 9 for more details).

8 Role of Confounders in the Relationship Between Sleep Disturbances and SIB

A considerable body of literature confirms an association between sleep disorders and suicidality indexes (Porras-Segovia et al. 2019) although to date several aspects hinder the interpretability of this literature. Many studies have used cross-sectional designs, and the assessment of sleep disturbances and SIB, as well as the populations studied, are heterogeneous. Nonetheless, longitudinal studies are available to explore

the temporal pathways that connect both conditions. A large number of factors can modulate the relationship, but mental disorders should be mentioned first. According to the meta-analysis by Pigeon et al. (2012), the association between sleep disturbances and SIB is independent of psychiatric diagnoses and concerns all the steps of the suicidal process, from suicidal thoughts to completed suicide (Pigeon et al. 2012). Within populations affected by mental disorders, a systematic review revealed that the comorbidity with sleep disorders increased slightly the risk of completed suicide, doubled the risk of presenting suicidal ideation, and multiplied by four the risk of attempting suicide (Malik et al. 2014). However, although existing studies often adjust their analyses for the presence of depression or anxiety disorders, separating the contribution of insomnia on suicidality is still difficult. Depression/anxiety symptoms often fail to reach the cutoff of clinical diagnoses, their severity varies largely from one person to the other, and sleep disturbances are often listed among the diagnostic criteria (e.g., in depression or generalized anxiety disorder).

Winsper and Tang (2014) signaled two other conditions that had been so far neglected in the sleep-suicide literature: borderline personality disorder (BPD) and chronic pain (Winsper and Tang 2014). Recent studies seem to confirm the mediating effect of sleep disturbances in both cases: (1) increasing SIB in persons with BPD traits according to an online survey (DeShong and Tucker 2019) and (2) increasing the risk of suicide death among people suffering from chronic pain according to a large case-control study (Owen-Smith et al. 2019). Indeed, suicidality and disrupted sleep are defining features of BPD, as well as two psychological factors that seem to mediate the relationship between sleep disturbances and SIB: emotional dysregulation (Ward-Ciesielski et al. 2018) and impulsivity (Winsper and Tang 2014). Other psychological factors, such as hopelessness (Lamis et al. 2018), maladaptive sleep cognitions (i.e., dysfunctional beliefs about sleep) (McCall et al. 2013), and decision-making impairments (Noh et al. 2012; Jollant et al. 2005), may also play a significant role given their association to sleep disturbances and SIB. Feelings of entrapment and defeat have been found to mediate the emergence of suicidal ideation in adolescents and adults with PTSD suffering insomnia (Littlewood et al. 2016; Russell et al. 2018). Finally, two important non-clinical factors should be considered. The first is the socioeconomic level, often disregarded but strongly and independently associated with the incidence of SIB (Lin et al. 2018; Eikelenboom et al. 2019), as well as with poor sleep quality and duration (Lallukka et al. 2012). The second is the experience of stressful life events. Insomnia has been found to mediate the association between life events and SIB in a large adolescent sample in China (Liu et al. 2019b). All the abovementioned factors should be taken into account to clarify the extent to which sleep disturbances are an independent factor for suicidality (Littlewood et al. 2017; Bernert et al. 2015).

The role of these factors in the relationship between sleep and suicidality varies according to the sleep disturbances experienced. Future studies should adopt a rigorous methodology for the establishment of potential confounders in the relationship between sleep disorders and suicidality.

9 Mechanisms Underlying the Association Between Sleep Disturbances and SIB

Even though the results of several systematic reviews and meta-analysis have confirmed that sleep disturbances are closely associated with SIB, there is yet no clear understanding of the mechanisms that underlie the association. Several hypotheses, including psychological impairments and physiological conditions, have been proposed to explain the relationship between insomnia and SIB (Fig. 1) (Porras-Segovia et al. 2019; Woznica et al. 2015; McCall and Black 2013; Perlis et al. 2016):

1. *Altered psychological functioning.* Sleep disturbances, and particularly insomnia, may exacerbate impairments in psychological functioning, such as feelings of being hopelessness or disconnected and the propensity to ruminate, that facilitate the emergence of SIB. These three psychological factors are strong predictors of SIB and may help to maintain sleep disturbances through inflexible beliefs (Morin et al. 1993). Other psychological changes caused by poor sleep that may facilitate the emergence of SIB include emotional dysregulation and cognitive impairments (Winsper and Tang 2014).

   (a) The feeling of being disconnected (also called thwarted belongingness) mediated the relationship between insomnia and suicidal ideation across different military samples (Hom et al. 2017). Conversely, changes in hopelessness and beliefs about suicide predicted the improvement of sleep disturbances among active military personnel treated with a brief CBT (Roberge et al. 2019). The feelings of defeat and entrapment might facilitate the ideation into action transition according to recent psychological theories about suicidal behavior (O'Connor and Portzky 2018). In the same vein, feelings of hopelessness and defeat are directly linked to rumination, a fruitless but perseverant tendency to focus on stressful thoughts or symptoms. Interestingly, rumination about the causes of stress (reflective rumination) but not just perseverative thinking or actions (brooding rumination) mediated the effect of poor sleep on suicidal ideation in a large sample of American college students (Holdaway et al. 2018).

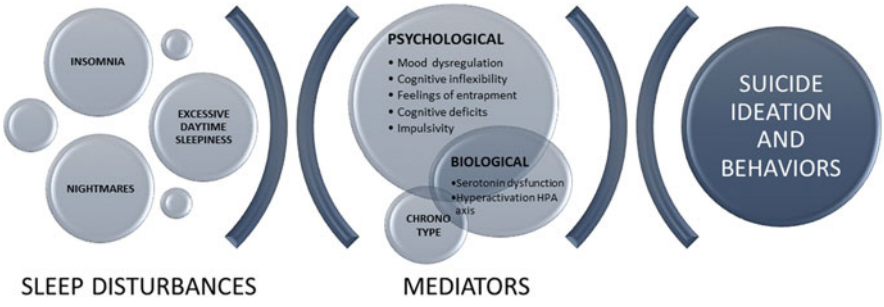


Fig. 1 Mediators between sleep disturbances and SIB

(b) Insomnia and more generally the reduction of sleep time are associated with changes in cognitive abilities (Brownlow et al. 2017), memory impairments (Fortier-Brochu et al. 2012), decision-making (Noh et al. 2012), and deficient problem-solving (Fortier-Brochu et al. 2012). A very similar neuropsychological profile has been found in suicidal patients. Cognitive deficits emerging from poor sleep would facilitate impulsive actions such as suicide attempts (Anderson and Platten 2011). Impulsive aggression is indeed a known risk factor for SIB (Lopez-Castroman et al. 2014), and sleep disturbances have been linked to both state and trait impulsivity (Winsper and Tang 2014). One study suggests that early morning awakening might be particularly linked to unplanned-impulsive suicide attempts (Wojnar et al. 2009).

(c) Emotional dysregulation is one of the most common symptoms among insomnia patients and also particularly frequent among individuals with SIB (Baglioni et al. 2010; de Klerk et al. 2011). A potential bidirectional mechanism would involve altered sleep-wake cycles disrupting mood regulation and in turn emotional reactivity maintaining insomnia through increased arousal. According to a diathesis-stress model, insomnia induces high stress-related sleep reactivity and greater emotional dysregulation. In this model, resilience could be an important factor partially determined by sleep quality (Williams et al. 2018). Palagini et al. (2018) found that patients with insomnia were less resilient compared to good sleepers, and this was related to high stress-related sleep reactivity, emotional dysregulation, and hyperarousal (Palagini et al. 2018). Individuals with less resilience would have a diminished capacity to successfully adapt to stressful events and have an increased vulnerability for developing insomnia and, by extension, mental health disorders and SIB.

2. *Biological factors.* Serotonin plays also an important and complex role in the induction and the continuity of sleep. Indeed, serotonin deficiency may decrease the duration of slow-wave sleep and exacerbate hypersomnia. In parallel, serotonin dysfunction is also one of the biological factors most strongly associated with SIB. It has been reported that patients who attempt or complete suicide had impaired serotonergic function (Ursin 2002). One study reported more frequent recourse to violent methods among attempters with insomnia compared to those without (Pompili et al. 2013). The relationship between insomnia and suicidal behavior may also involve biomarkers of stress. Insomnia is associated with the hyperactivation of the hypothalamic-pituitary-adrenal axis (Vgontzas et al. 2001), this marker being associated with an increased risk of suicidal behavior. Another biological mechanism exists for the association between SIB and EDS. The reduction of orexin levels is involved in the etiology of specific psychiatric symptoms, such as lassitude and a decreased motor activity (Brundin et al. 2007). This neuropeptide does regulate not only appetite but also arousal and wakefulness. The destruction of orexin production cells in the brain leads to the most common form of narcolepsy, cataplexic narcolepsy. Orexin levels seem to

be reduced in the cerebrospinal fluid of suicide attempters and recover after the attempt (Brundin et al. 2007).

3. *The chronotype*, which is defined by an individual's circadian preference, seems to be an important factor in the relationship between insomnia and suicide, as well as the alterations of the circadian rhythms (Matsumoto et al. 2016). While the morning chronotype appears to reduce the risk of SIB, the eveningness chronotype, which is more associated with impulsive features, may lead to more severe SIB (McCall and Black 2013). However, in another study, a vigorous chronotype, less prone to morning sleep inertia, was associated with suicide attempts in euthymic bipolar patients (Benard et al. 2019).

10 Perspectives

In the context of SIB, sleep disturbances have frequently been considered along the last decades more as a consequence of underlying diagnoses than a risk factor "per se." The lack of any kind of sleep assessment items in many scales or epidemiologic datasets examining suicide risk is a clear evidence of this fact. Now, the arrival of new technologies, notably wearable devices, allows the concretization of subjective complaints about sleep often reported by patients in suicidal crisis and points out the need to address sleep problems, specially since there is good evidence about effective psychotherapeutic and pharmacological interventions for insomnia and nightmares (McCall et al. 2019; Singh et al. 2016). It should also be noted that treatment-emergent suicidal ideation after the introduction of an antidepressant treatment was recently found to be strongly associated with sleep disturbances (OR = 8.42; CI = 5.78–12.30) (Lopez-Castroman et al. 2020). Indeed, sleep disturbances are part of the so-called activation syndrome.

Ecological assessments make possible the monitoring of patients at risk (Berrouiguet et al. 2019). The real-time detection of suicidal risk using sleep monitoring in clinical practice is nonetheless still far since the ethical concerns have to be confronted and the necessary adaptation in clinical care have not yet been designed. An unanswered question so far was the possibility of a two-sided relationship between suicidal ideation and sleep disturbances, i.e., that suicidal ideation might also cause sleep disturbances. A recent paper has provided some insight into this matter by showing that, when suicidal patients were followed with ecological momentary assessment and actigraphic measures for 1 week, sleep disturbances predicted suicidal ideation but not the opposite (Littlewood et al. 2019). In this study, the effect of pre-sleep feelings of entrapment on next morning suicidal ideation was moderated by the subjective quality of sleep.

The use of mobile phone applications to monitor sleep is a very promising avenue of suicide prevention. Currently, suicide prevention programs are confronted to a very large number of potential patients that could be at-risk. In 2017, almost one and a half million persons attempted suicide in the USA (American Foundation for Suicide Prevention 2016). Wearable devices could provide real-time proximal information about warning signs and particularly about sleep disturbances in this

population. However, several challenges lie ahead, starting with the clinical concerns on how to plan and implement efficient interventions in real-time and the ethical concerns on how to follow patients in their real-life while protecting sensitive data. The increasingly large and time-lagged sets of data will also require specific methods of analysis. The assessment of sleep disturbances in vulnerable populations by using wearable technology opens a window for ecological momentary intervention in SIB (Berrouiguet et al. 2019).

The cumulating evidence demonstrates the importance of sleep disturbances as independent, proximal, and modifiable factors for SIB. This evidence concerns not only patients with psychiatric conditions. Recent studies include a broad range of samples issued from vulnerable minorities, primary care, or the general population. Their results confirm the existence of a relationship in clinical and non-clinical samples (Woznica et al. 2015). Future studies are probably bound to explore longitudinally the underlying psychological mechanisms in this relationship before and after a suicidal crisis, the role of specific symptoms in both sleep and SIB (mediating mechanisms might be different for suicidal thoughts and suicide attempts, for instance), and the implementation of preventive efforts and interventions through ecological monitoring of sleep disturbances in vulnerable populations.

References

Agargun MY, Kara H, Solmaz M (1997) Sleep disturbances and suicidal behavior in patients with major depression. J Clin Psychiatry 58(6):249–251

American Academy of Sleep Medicine (2014) International classification of sleep disorders, 3rd edn. American Academy of Sleep Medicine, Darien

American Foundation for Suicide Prevention (2016) Suicide statistics. AFSP. https://afsp.org/about-suicide/suicide-statistics/. Accessed 26 Dec 2019

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. APA, Arlington

Anderson C, Platten CR (2011) Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. Behav Brain Res 217(2):463–466. https://doi.org/10.1016/j.bbr.2010.09.020

Baglioni C, Spiegelhalder K, Lombardo C, Riemann D (2010) Sleep and emotions: a focus on insomnia. Sleep Med Rev 14(4):227–238. https://doi.org/10.1016/j.smrv.2009.10.007

Baldwin CM, Kapur VK, Holberg CJ, Rosen C, Nieto FJ (2004) Associations between gender and measures of daytime somnolence in the sleep heart health study. Sleep 27(2):305–311

Benard V, Etain B, Vaiva G et al (2019) Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: an actigraphy study. J Affect Disord 244:1–8. https://doi.org/10.1016/j.jad.2018.09.054

Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992) Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry 49:651–668

Bernert RA, Joiner TE (2007) Sleep disturbances and suicide risk: a review of the literature. Neuropsychiatr Dis Treat 3(6):735–743

Bernert RA, Turvey CL, Conwell Y, Joiner TE (2014) Association of poor subjective sleep quality with risk for death by suicide during a 10-year period: a longitudinal, population-based study of late life. JAMA Psychiat 71(10):1129–1137. https://doi.org/10.1001/jamapsychiatry.2014.1126

Bernert RA, Kim JS, Iwata NG, Perlis ML (2015) Sleep disturbances as an evidence-based suicide risk factor. Curr Psychiatry Rep 17(3):554

Berrouiguet S, Barrigón ML, Castroman JL, Courtet P, Artés-Rodríguez A, Baca-García E (2019) Combining mobile-health (mHealth) and artificial intelligence (AI) methods to avoid suicide attempts: the Smartcrises study protocol. BMC Psychiatry 19(1):277. https://doi.org/10.1186/s12888-019-2260-y

Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A (2005) Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab 90(8):4510–4515

Blasco-Fontecilla H, Alegria AA, Lopez-Castroman J et al (2011) Short self-reported sleep duration and suicidal behavior: a cross-sectional study. J Affect Disord 133(1–2):239–246. https://doi.org/10.1016/j.jad.2011.04.003

Breslau N, Roth T, Rosenthal L, Andreski P (1996) Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 39(6):411–418

Brownlow JA, Klingaman EA, Boland EM, Brewster GS, Gehrman PR (2017) Psychiatric disorders moderate the relationship between insomnia and cognitive problems in military soldiers. J Affect Disord 221:25–30. https://doi.org/10.1016/j.jad.2017.06.023

Brundin L, Petersen A, Bjorkqvist M, Traskman-Bendz L (2007) Orexin and psychiatric symptoms in suicide attempters. J Affect Disord 100(1–3):259–263

Chaïb LS, Segovia AP, Baca-Garcia E, Lopez-Castroman J (2020) Ecological studies of sleep disturbances during suicidal crises. Curr Psychiatry Rep 14;22(7):34

Chiu H-Y, Lee H-C, Chen P-Y, Lai Y-F, Tu Y-K (2018) Associations between sleep duration and suicidality in adolescents: a systematic review and dose-response meta-analysis. Sleep Med Rev 42:119–126. https://doi.org/10.1016/j.smrv.2018.07.003

de Klerk S, van Noorden MS, van Giezen AE et al (2011) Prevalence and correlates of lifetime deliberate self-harm and suicidal ideation in naturalistic outpatients: the Leiden routine outcome monitoring study. J Affect Disord 133(1–2):257–264. https://doi.org/10.1016/j.jad.2011.03.021

DeShong HL, Tucker RP (2019) Borderline personality disorder traits and suicide risk: the mediating role of insomnia and nightmares. J Affect Disord 244:85–91. https://doi.org/10.1016/j.jad.2018.10.097

Drapeau C, Nadorff M (2017) Suicidality in sleep disorders: prevalence, impact, and management strategies. NSS 9:213–226. https://doi.org/10.2147/NSS.S125597

Eikelenboom M, Beekman ATF, Penninx BWJH, Smit JH (2019) A 6-year longitudinal study of predictors for suicide attempts in major depressive disorder. Psychol Med 49(6):911–921. https://doi.org/10.1017/S0033291718001423

Enright PL, Newman AB, Wahl PW, Manolio TA, Haponik EF, Boyle PJ (1996) Prevalence and correlates of snoring and observed apneas in 5,201 older adults. Sleep 19(7):531–538

Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D (1990) Time-related predictors of suicide in major affective disorder. Am J Psychiatry 147(9):1189–1194

Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L (2001) Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. J Am Geriatr Soc 49(12):1628–1632

Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, Morin CM (2012) Insomnia and daytime cognitive performance: a meta-analysis. Sleep Med Rev 16(1):83–94

Fujino Y, Mizoue T, Tokui N, Yoshimura T (2005) Prospective cohort study of stress, life satisfaction, self-rated health, insomnia, and suicide death in Japan. Suicide Life Threat Behav 35(2):227–237

Germain A (2013) Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry 170(4):372–382

Hedegaard H, Curtin SC, Warner M (2018) Suicide rates in the United States continue to increase. NCHS Data Brief 309:1–8

Holdaway AS, Luebbe AM, Becker SP (2018) Rumination in relation to suicide risk, ideation, and attempts: exacerbation by poor sleep quality? J Affect Disord 236:6–13. https://doi.org/10.1016/j.jad.2018.04.087

Hom MA, Chu C, Schneider ME et al (2017) Thwarted belongingness as an explanatory link between insomnia symptoms and suicidal ideation: findings from three samples of military service members and veterans. J Affect Disord 209:114–123. https://doi.org/10.1016/j.jad.2016.11.032

Jaussent I, Morin CM, Ivers H, Dauvilliers Y (2017) Incidence, worsening and risk factors of daytime sleepiness in a population-based 5-year longitudinal study. Sci Rep 7(1):1372

Jollant F, Bellivier F, Leboyer M et al (2005) Impaired decision making in suicide attempters. Am J Psychiatry 162(2):304–310. https://doi.org/10.1176/appi.ajp.162.2.304

Kaneita Y, Ohida T, Uchiyama M, Takemura S, Kawahara K, Yokoyama E (2005) Excessive daytime sleepiness among the Japanese general population. J Epidemiol 15(1):1–8

Karacan I, Thornby JI, Anch M, Holzer CE, Warheit GJ, Schwab JJ (1976) Prevalence of sleep disturbance in a primarily urban Florida County. Soc Sci Med 10(5):239–244

Klink M, Quan SF (1987) Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 91(4):540–546

Krystal AD, Thakur M, Roth T (2008) Sleep disturbance in psychiatric disorders: effects on function and quality of life in mood disorders, alcoholism, and schizophrenia. Ann Clin Psychiatry 20(1):39–46

Lallukka T, Sares-Jäske L, Kronholm E et al (2012) Sociodemographic and socioeconomic differences in sleep duration and insomnia-related symptoms in Finnish adults. BMC Public Health 12(1):565. https://doi.org/10.1186/1471-2458-12-565

Lamis DA, Innamorati M, Erbuto D et al (2018) Nightmares and suicide risk in psychiatric patients: the roles of hopelessness and male depressive symptoms. Psychiatry Res 264:20–25. https://doi.org/10.1016/j.psychres.2018.03.053

Li SX, Zhang B, Li AM, Wing YK (2010a) Prevalence and correlates of frequent nightmares: a community-based 2-phase study. Sleep 33(6):774–780

Li SX, Lam SP, Yu MW, Zhang J, Wing YK (2010b) Nocturnal sleep disturbances as a predictor of suicide attempts among psychiatric outpatients: a clinical, epidemiologic, prospective study. J Clin Psychiatry 71(11):1440–1446

Lin H-T, Lai C-H, Perng H-J et al (2018) Insomnia as an independent predictor of suicide attempts: a nationwide population-based retrospective cohort study. BMC Psychiatry 18(1):117. https://doi.org/10.1186/s12888-018-1702-2

Littlewood DL, Gooding PA, Panagioti M, Kyle SD (2016) Nightmares and suicide in posttraumatic stress disorder: the mediating role of defeat, entrapment, and hopelessness. J Clin Sleep Med 12(3):393–399. https://doi.org/10.5664/jcsm.5592

Littlewood D, Kyle SD, Pratt D, Peters S, Gooding P (2017) Examining the role of psychological factors in the relationship between sleep problems and suicide. Clin Psychol Rev 54:1–16

Littlewood DL, Kyle SD, Carter L-A, Peters S, Pratt D, Gooding P (2019) Short sleep duration and poor sleep quality predict next-day suicidal ideation: an ecological momentary assessment study. Psychol Med 49(3):403–411. https://doi.org/10.1017/S0033291718001009

Liu JW, Tu YK, Lai YF, Lee HC, Tsai PS, Chen TJ (2019a) Associations between sleep disturbances and suicidal ideation, plans, and attempts in adolescents: a systematic review and meta-analysis. Sleep

Liu B-P, Wang X-T, Liu Z-Z, Wang Z-Y, Liu X, Jia C-X (2019b) Stressful life events, insomnia and suicidality in a large sample of Chinese adolescents. J Affect Disord 249:404–409. https://doi.org/10.1016/j.jad.2019.02.047

Lopes MC, Boronat AC, Wang YP, Fu IL (2016) Sleep complaints as risk factor for suicidal behavior in severely depressed children and adolescents. CNS Neurosci Ther 22(11):915–920

Lopez-Castroman J, Jaussent I, Beziat S et al (2014) Increased severity of suicidal behavior in impulsive aggressive patients exposed to familial adversities. Psychol Med 44(14):3059–3068. https://doi.org/10.1017/S0033291714000646

Lopez-Castroman J, Jaussent I, Gorwood P, Courtet P (2020) Activation syndrome induced by the antidepressant tianeptine and suicidal ideation: evidence from a large depressed outpatient

sample. Prog Neuro-Psychopharmacol Biol Psychiatry 97:109762. https://doi.org/10.1016/j.pnpbp.2019.109762
Malik S, Kanwar A, Sim LA et al (2014) The association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses: a systematic review and meta-analysis. Syst Rev 3:18. https://doi.org/10.1186/2046-4053-3-18
Matsumoto Y, Uchimura N, Ishida T et al (2016) Day workers suffering from a wider range of sleep problems are more likely to experience suicidality. Sleep Biol Rhythms 14(4):369–376. https://doi.org/10.1007/s41105-016-0067-5
McCall WV, Black CG (2013) The link between suicide and insomnia: theoretical mechanisms. Curr Psychiatry Rep 15(9):389
McCall WV, Blocker JN, D'Agostino R Jr, Kimball J, Boggs N, Lasater B (2010) Insomnia severity is an indicator of suicidal ideation during a depression clinical trial. Sleep Med 11(9):822–827
McCall WV, Batson N, Webster M et al (2013) Nightmares and dysfunctional beliefs about sleep mediate the effect of insomnia symptoms on suicidal ideation. J Clin Sleep Med 9(2):135–140. https://doi.org/10.5664/jcsm.2408
McCall WV, Benca RM, Rosenquist PB et al (2019) Reducing suicidal ideation through insomnia treatment (REST-IT): a randomized clinical trial. Am J Psychiatry 176(11):957–965. https://doi.org/10.1176/appi.ajp.2019.19030267
Mirsu-Paun A, Jaussent I, Komar G, Courtet P, Lopez-Castroman J (2017) Sleep complaints associated with wish to die after a suicide crisis-an exploratory study. J Sleep Res 26 (6):726–731
Morin CM, Stone J, Trinkle D, Mercer J, Remsberg S (1993) Dysfunctional beliefs and attitudes about sleep among older adults with and without insomnia complaints. Psychol Aging 8 (3):463–467. https://doi.org/10.1037//0882-7974.8.3.463
Nadorff MR, Nazem S, Fiske A (2011) Insomnia symptoms, nightmares, and suicidal ideation in a college student sample. Sleep 34(1):93–98. https://doi.org/10.1093/sleep/34.1.93
Nadorff MR, Fiske A, Sperry JA, Petts R, Gregg JJ (2013) Insomnia symptoms, nightmares, and suicidal ideation in older adults. J Gerontol B Psychol Sci Soc Sci 68(2):145–152. https://doi.org/10.1093/geronb/gbs061
Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D (2012) The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. J Clin Neurol 8 (2):130–138
O'Connor RC, Portzky G (2018) The relationship between entrapment and suicidal behavior through the lens of the integrated motivational-volitional model of suicidal behavior. Curr Opin Psychol 22:12–17. https://doi.org/10.1016/j.copsyc.2017.07.021
Ohayon MM (2002) Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev:97–111
Ohayon MM (2012) Operational definitions and algorithms for excessive sleepiness in the general population: implications for DSM-5 nosology. Arch Gen Psychiatry 69(1):71. https://doi.org/10.1001/archgenpsychiatry.2011.1240
Ohayon MM, Black J, Lai C, Eller M, Guinta D, Bhattacharyya A (2014) Increased mortality in narcolepsy. Sleep 37(3):439–444
Owen-Smith AA, Ahmedani BK, Peterson E et al (2019) The mediating effect of sleep disturbance on the relationship between nonmalignant chronic pain and suicide death. Pain Pract 19 (4):382–389. https://doi.org/10.1111/papr.12750
Palagini L, Moretto U, Novi M et al (2018) Lack of resilience is related to stress-related sleep reactivity, Hyperarousal, and emotion Dysregulation in insomnia disorder. J Clin Sleep Med 14 (5):759–766. https://doi.org/10.5664/jcsm.7100
Perlis ML, Grandner MA, Chakravorty S, Bernert RA, Brown GK, Thase ME (2016) Suicide and sleep: is it a bad thing to be awake when reason sleeps? Sleep Med Rev 29:101–107. https://doi.org/10.1016/j.smrv.2015.10.003
Pigeon WR, Pinquart M, Conner K (2012) Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J Clin Psychiatry 73(9):1160–1167

Pigeon WR, Funderburk JS, Cross W, Bishop TM, Crean HF (2019) Brief CBT for insomnia delivered in primary care to patients endorsing suicidal ideation: a proof-of-concept randomized clinical trial. Transl Behav Med 9(6):1169–1177. https://doi.org/10.1093/tbm/ibz108

Pompili M, Innamorati M, Forte A et al (2013) Insomnia as a predictor of high-lethality suicide attempts. Int J Clin Pract 67(12):1311–1316. https://doi.org/10.1111/ijcp.12211

Porras-Segovia A, Perez-Rodriguez MM, Lopez-Esteban P, Courtet P, Barrigon MM, Lopez-Castroman J (2019) Contribution of sleep deprivation to suicidal behaviour: a systematic review. Sleep Med Rev 44:37–47

Ribeiro JD, Pease JL, Gutierrez PM, Silva C, Bernert RA, Rudd MD et al (2012) Sleep problems outperform depression and hopelessness as cross-sectional and longitudinal predictors of suicidal ideation and behavior in young adults in the military. J Affect Disord 136(3):743–750

Roberge EM, Bryan CJ, Peterson A, Rudd MD (2019) Variables associated with reductions in insomnia severity among acutely suicidal patients receiving brief cognitive behavioral therapy for suicide prevention. J Affect Disord 252:230–236. https://doi.org/10.1016/j.jad.2019.04.045

Robert G, Zadra A (2008) Measuring nightmare and bad dream frequency: impact of retrospective and prospective instruments. J Sleep Res 17(2):132–139

Robert G, Zadra A (2014) Thematic and content analysis of idiopathic nightmares and bad dreams. Sleep 37(2):409–417

Rössler W, Angst J, Ajdacic-Gross V et al (2018) Sleep disturbances and Suicidality–a longitudinal analysis from a representative community study over 30 years. Front Psych 9:320. https://doi.org/10.3389/fpsyt.2018.00320

Russell K, Rasmussen S, Hunter SC (2018) Insomnia and nightmares as markers of risk for suicidal ideation in Young people: investigating the role of defeat and entrapment. J Clin Sleep Med 14 (5):775–784. https://doi.org/10.5664/jcsm.7104

Sandman N, Valli K, Kronholm E, Revonsuo A, Laatikainen T, Paunio T (2015) Nightmares: risk factors among the Finnish general adult population. Sleep 38(4):507–514

Singh B, Hughes AJ, Mehta G, Erwin PJ, Parsaik AK (2016) Efficacy of Prazosin in posttraumatic stress disorder: a systematic review and meta-analysis. Prim Care Companion CNS Disord 18 (4). https://doi.org/10.4088/PCC.16r01943

Sjöström N, Waern M, Hetta J (2007) Nightmares and sleep disturbances in relation to suicidality in suicide attempters. Sleep 30(1):91–95. https://doi.org/10.1093/sleep/30.1.91

Sjöström N, Hetta J, Waern M (2009) Persistent nightmares are associated with repeat suicide attempt: a prospective study. Psychiatry Res 170(2–3):208–211. https://doi.org/10.1016/j.psychres.2008.09.006

Soehner AM, Kaplan KA, Harvey AG (2014) Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. J Affect Disord 167:93–97

Speed KJ, Drapeau CW, Nadorff MR (2018) Differentiating single and multiple suicide attempters: what nightmares can tell us that other predictors cannot. JCSM 14(05):829–834. https://doi.org/10.5664/jcsm.7116

Tishler CL, McKenry PC, Morgan KC (1981) Adolescent suicide attempts: some significant factors. Suicide Life Threat Behav 11(2):86–92. https://doi.org/10.1111/j.1943-278x.1981.tb00907.x

Trockel M, Karlin BE, Taylor CB, Brown GK, Manber R (2015) Effects of cognitive behavioral therapy for insomnia on suicidal ideation in veterans. Sleep:259–265

Turvey CL, Conwell Y, Jones MP, Phillips C, Simonsick E, Pearson JL (2002) Risk factors for late-life suicide: a prospective, community-based study. Am J Geriatr Psychiatry 10(4):398–406

Ursin R (2002) Serotonin and sleep. Sleep Med Rev 6(1):55–69

Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A (2001) Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 86(8):3787–3794

Wang X, Cheng S, Xu H (2019) Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behaviour in patients with depression. BMC Psychiatry 19(1):303. https://doi.org/10.1186/s12888-019-2302-5

Ward-Ciesielski EF, Winer ES, Drapeau CW, Nadorff MR (2018) Examining components of emotion regulation in relation to sleep problems and suicide risk. J Affect Disord 241:41–48. https://doi.org/10.1016/j.jad.2018.07.065

Whitney CW, Enright PL, Newman AB, Bonekat W, Foley D, Quan SF (1998) Correlates of daytime sleepiness in 4578 elderly persons: the cardiovascular health study. Sleep 21(1):27–36

Williams SG, Collen JF, Lettieri CJ (2018) More than just a good night's sleep. J Clin Sleep Med 14 (5):709–710. https://doi.org/10.5664/jcsm.7084

Winsler A, Deutsch A, Vorona RD, Payne PA, Szklo-Coxe M (2015) Sleepless in Fairfax: the difference one more hour of sleep can make for teen hopelessness, suicidal ideation, and substance use. J Youth Adolesc 44(2):362–378. https://doi.org/10.1007/s10964-014-0170-3

Winsper C, Tang NKY (2014) Linkages between insomnia and suicidality: prospective associations, high-risk subgroups and possible psychological mechanisms. Int Rev Psychiatry 26 (2):189–204. https://doi.org/10.3109/09540261.2014.881330

Wojnar M, Ilgen MA, Wojnar J, McCammon RJ, Valenstein M, Brower KJ (2009) Sleep problems and suicidality in the National Comorbidity Survey Replication. J Psychiatr Res 43(5):526–531. https://doi.org/10.1016/j.jpsychires.2008.07.006

Woznica AA, Carney CE, Kuo JR, Moss TG (2015) The insomnia and suicide link: toward an enhanced understanding of this relationship. Sleep Med Rev 22:37–46. https://doi.org/10.1016/j.smrv.2014.10.004

Ecological Momentary Assessment for Monitoring Risk of Suicide Behavior

Patricia Carretero, Juan Jose Campana-Montes, and Antonio Artes-Rodriguez

Contents

Abstract In recent years the involvement of technology in psychiatric treatment and its usefulness is increasing. The main advantages of its use lie in the possibility of collecting passively data with greater temporal granularity from each patient individually, since these devices are in direct contact almost every minute of the day with them. The variety of data collected by the all the smartphone sensors allows for a better understanding of the patient behavior through what is called the digital phenotype. So the use of a continuous monitoring system for patients at risk of

P. Carretero and J. J. Campana-Montes
Evidence-Based Behavior, Madrid, Spain

A. Artes-Rodriguez (✉)
Evidence-Based Behavior, Madrid, Spain

Department of Signal Theory and Communications, Universidad Carlos III de Madrid, Madrid, Spain
e-mail: aartes@ing.uc3m.es

Curr Topics Behav Neurosci (2020) 46: 229–246
https://doi.org/10.1007/7854_2020_170
Published Online: 15 August 2020

suicide becomes a very useful tool for improving the quality of life of patients and for the early detection of suicide attempts.

Keywords Big data · Digital footprint · Digital phenotype · Ecological momentary assessment · e-Health · Machine learning · Mobile health · Suicidal risk · Wearable devices

1 Suicidal Risk Behavior Assessment

1.1 Assessment

According to the World Health Organization, every 40s a person in the world dies because of suicide (https://www.who.int/mental_health/prevention/suicide/suicideprevent/en/). It was the 18th cause of death in 2016, thus implying a percentage of 1.4% of all deaths worldwide. On average, it takes a person 20 suicide attempts to finally commit suicide, which describes the importance of a good follow-up that enables intervention before this event occurs.

The classical and most frequent protocol to assess the suicide risk of a person is through episodic visits to the hospital where the health status is reported using some questionnaires that measure the suicidal risk such as the Modified SAD PERSONS scale, revised Beck Depression Inventory, Beck Anxiety Inventory, Beck Hopelessness Scale, Beck Scale for Suicidal Ideation (BSS), and the High-Risk Construct Scale (NEW) (Cochrane-Brink et al. 2000). If a person is classified as high risk, an intervention process starts where the subject may be hospitalized or medicated.

The main problem of this procedure is that visits must be on-hospital for the clinician to check how is the person, and a high frequency of visits would incur high costs that may not be affordable. Consequently, the periodicity of these visits is low, which means large blind periods where clinicians do not know anything about the person's life or even if they are at risk of committing suicide.

1.2 Ecological Momentary Assessment

To solve the problem of lack of information, a complementary way of assessment was proposed called Ecological Momentary Assessment (EMA) (Husky et al. 2014). With EMA, information can be collected in a daily period and using some simple questions items as suicide ideation (Rath et al. 2019), emotional status, follow-up of medication (Berrouiguet et al. 2016), or sleep or eating disorders can be measured (Duhem et al. 2018). In this paradigm, there are two sources of information: one is included by the clinician when the patient goes to the hospital and some the

questionnaires are passed, and another one are the self-reported questionnaires that the monitored person has to fulfill day by day.

This way of assessment can be used to implement automatic alarms that in some conditions such as high scores in suicidal ideation or bad sleep patterns send a message to the urgencies department to intervene before the suicide attempt occurs, or even to understand better how suicide ideation evolves and how is related with people's behavior.

EMA also changes the traditional and reactive way that questionnaires have been fulfilled not only in terms of frequency but also in relevance. Asking a patient about something that happened 2 weeks ago may imply unclear memories or subjective opinions that bias the original response. With an intelligent implementation of this protocol is not required to ask all questions every day but measures when these answers are providing more information because something is changing, and in those cases, look into this dimension (sleep, mood) that is changing and ask more specific questions. This flexible structure that asks the right questions at the right moment may be beneficial for the correct follow-up of the patient and to the own patient, that feels that something is listening to him when he needs it.

But people in suicide risk are months or even years being monitored and supervised, so answering questions or fulfilling the questionnaires day by day along many months may cause a loss of interest and lower adherence. And even if the subject is still active, some information can be biased or not precise for a subjective opinion. One way of solving this issue lies in observing not what the person says, but how he behaves. This is called Behavior Ecological Assessment (Berrouiguet et al. 2018) or passive EMA, an implicit and passive methodology that captures a new source of information about the patient called digital phenotype.

1.3 Digital Phenotype

In recent years, the growth of technology and the digitalization of medical systems have given rise to new practices in medicine such as telemedicine and m-health. All these new features are included in what is called electronic health or e-health. e-Health implies the acquisition of new technologies into the daily medical routine, generating benefits to clinicians and patients. With the transition from handwritten reports to digital information, all the patient information is stored in the electronic health record (EHR), which can be easily portable and used anywhere. There are tons of data that due to the new big data technologies can be processed and a new set of information and statistical correlations can be found using machine learning techniques like deep learning (Shickel et al. 2017). Furthermore, the cost reduction of sensors has allowed a better ambulatory patient monitorization of physiological signals like heart rate (Bär et al. 2007), galvanic skin response (Ahuja et al. 2003), temperature (Vinkers et al. 2013), etc. Making all this information is embedded into the EHR, and accessible for the clinicians is a new way of improving the treatment

and follow-up, complementing the classical source of information provided by questionnaires.

e-Health goes one step ahead and takes advantage of a set of devices that have become a new extension of the human body, the smartphone and wearable devices. The field of medicine that uses these devices for patient monitoring is called mobile health or m-health. Nowadays, the number of smartphones in the world is higher than three billion (https://www.statista.com/statistics/330695/number-of-smartphone-users-worldwide/). People carry the smartphone everywhere and anytime and use it to maintain a conversation, to look for information, to control their physical activity, for entertainment, and is a popular way to access to the baking account, the bills, or the healthcare medical appointments. Besides, smartphones have extensions such as smartwatches, smart bands, and activity trackers that extend the information that can be retrieved like sleep patterns, heart rate, skin resistance, or more precise activity like swimming or working out.

It can be easily seen that mobile technologies are the best and most spread human sensors. Accessing anyone's smartphone is probably the best way to know how is this person and, more important, how is his behavior during the whole day. With Behavior Ecological Assessment, the main source of information is not provided by a questionnaire, but the digital phenotype (Insel 2018) of the person. The main advantage of using this digital phenotype as source of information is that it is passive (Doryab et al. 2019) because all the data collection process is automatic and does not depend on the patient interaction, continuous in time, not stigmatizing as the person already uses these sensors and doesn't change his daily routine, and objective: the data is not biased by a patient opinion or distorted by the patient's memory or perception.

Specifically in this chapter, we are focusing on suicide risk patients monitoring. One important item to monitor this population is to detect some disturbance in any dimension of his behavior. For example, it has been demonstrated that the emergence of some sleep disorders can be a good indicator of a suicide attempt (Chellappa and Araújo 2007). Changes in eating habits also can be a symptom of a worse health status of the patient. A decrease in the patient's physical activity is tentative to be a warning symptom (Simon et al. 2004). This would suggest that a change in one or more dimensions of the patient's behavior, and the possibility to intervene in this precise moment would be a promising way of avoiding some of the possible future suicide attempts of the patient.

Lately, it has appeared some solutions that take advantage of all this amount of digital data to provide a suicide warning based on the whole digital phenotype of the patient and not only one or two sources of data. One of them is being tested in a project to develop reliable and informative indicators for a suicide prevention framework funded by the American Foundation for Suicide Prevention (AFSP) (https://afsp.org/) called Smartcrises (Berrouiguet et al. 2019). It is a pragmatic multisite trial that involves two countries, France with the University Hospital of Nimes and Spain with Jimenez Diaz Foundation. In this trial, the clinical information is mixed with an active and passive EMA protocol. The active EMA is captured by a smartphone app called MeMind (https://www.memind.net/) where some scales like

the Suicide Status Form (Jobes et al. 2009), the Perceived Social Support Questionnaire (PSSQ), and the Interpersonal Needs Questionnaire (Parkhurst et al. 2016) are filled by the patient, in addition to other questions related with sleep, eating habits, or mood. The passive EMA is captured by another smartphone app called eB2 mobile Logger that will be more deeply described in the next section. All this active and passive information is compared afterward with the clinical history of the patient in order to obtain objective and reliable indicators that can be used for an easy suicidal risk patient monitorization.

2 Continuous and Objective Monitoring: eB2 System

2.1 Description and Structure

Eb2 system (Fig. 1) has been designed to enhance the quality of mental health patient treatment and consequently the improvement of quality patient's life. This is possible due to the use of Artificial Intelligence (AI) techniques and continuous data collection, which is done with the help of a mobile application (eB2 Mobile Logger) developed for Android and iOS platforms to its use for the patient. This automatic and continuous collection of data has great benefits, but first of all, the system must ensure that patient data records are compliant with the general data protection regulation. Therefore, the data included in the system must be anonymized or pseudonymized, and the patient must signify the explicit consent of the data collected and the end thereof.

Once the application has been installed, it uploads data passively collected by its own sensors or by third-party applications and smart bands connected to it. This type of storage has the advantage that user interaction is not necessary, neither the opening of the application or the unlocking of the phone. There is also some information that the user can enter manually (emotions, sleep duration, quality of sleep), so the eb2 system can obtain two types of data from de application: passive and active data. The combination of both types of information allows to obtain patient's activity (Nazabal et al. 2016) that are used to estimate the health and behavioral states of users.

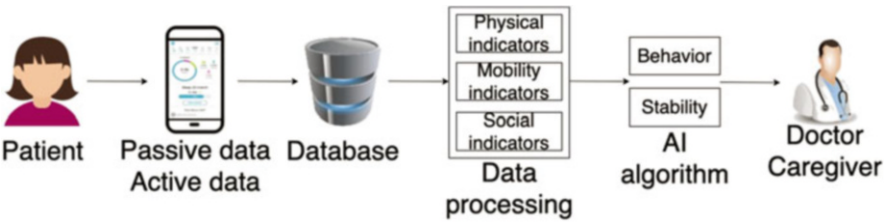


Fig. 1 Eb2 system

The total amount of information of each user is stored in a database waiting for being processed. A series of transformations on the data like missing data, grouping in time slots, and group location in work and home are carried out to obtain physical, mobility, and social indicators. Then they will be used as inputs to the algorithm that gets stability and functionality indicators of behavioral habits. These indicators are provided to the patient (in the mobile application), medical staff or caregivers (on a web platform) as useful information about the patient's condition and as a warning of the need for attention (too unstable behavior or a change in functionality). The system provides individualized indicators of behavior that warn of the possible need for patient care, thus contributing to improve attention to them and the control and self-management of mental pathologies.

In the next section it will be presented an analysis of the possible data sources, data type collected, and their use in mental health.

2.2 Data Sources

As mentioned in the previous section, eb2 system collects two types of data: passive data and active data. Passive data are those that do not need action from the patient to be gathered. This type of data is objective and usually may require a large database to be stored, and there are three possible sources provide this data: mobile sensors, wearables, and third-party applications. Eb2 mobile application has an option that allows the patient to connect and disconnect other platforms and devices: Fitbit, Google Fit, Garmin, Facebook, and Instagram. The patient has to accept the permission for every data type and platform to decide what type of data give to the system. In Table 1, we can see all passive data that eb2 mobile application gathers.

On the other hand, active data are those that required manual input and usually, they are based on the subjective perception of the patient. This type of data has a lot of limitations because you cannot ask for them every time, and the patient doesn't spend much time entering data. Table 2 shows data inserted by patients in eb2.

Once all these data are collected, we can see how to related with behavioral indicators Fig. 2.

Eb2 system uses location data provided by the GPS sensor making transformations on them. These transformations are carried out since it is not necessary to know the exact point location of patients. That is, we need to know what kind of mobility the patient has and if he spends a lot of time at home and the distance traveled inside the house (daily) or the distance traveled outside the house. The location information together with steps, distance, the list of nearest Wi-Fi networks and Bluetooth devices allow determining if one point belongs to home or an outside place. Once this is known, it can be used related to the type of places the patient visits daily (shops, theaters, education places, restaurants) and the radius of gyration to compute a mobility indicator which is useful to determine the geographical mobility of the patient and has been used in other works to identify some mental problems like depression (Saeb et al. 2016) and bipolar disorder (Osmani 2015).

Table 1 Passive data

Sensor name	Data collected	Source
GPS	Location (altitude, longitude, latitude, accuracy)	Smartphone
Wi-Fi	Wi-Fi networks near the user	Smartphone
Bluetooth	List of the Bluetooth near the user	Smartphone
Light sensor	Environmental light detected	Smartphone
Microphone	Voice	Smartphone
Accelerometer, actigraphy	Physical activity	Smartphone, Fitbit, Garmin, Health, Google Fit
Google places	Place type	Google places
Pedometer/ accelerometer	Steps	Smartphone, wearables, Health, Google Fit
Keyboard	Typing patterns	Smartphone
Call log	Duration call, type of call the destination number	Smartphone
Contacts	Contacts	Smartphone
Applications	Applications usage time	Smartphone
Light sensitive photodiodes, actigraphy, accelerometer	Sleep	Wearable, Health, Google Fit
Notifications	Notifications	Smartphone
Unlocks	Screen unlocks	Smartphone
Light sensitive photodiodes	Heart rate	Google Fit, wearable, Health
Pedometer, accelerometer	Distance walked	Smartphone, Google Fit, wearable, Health
Pedometer, accelerometer	Calories	Wearable, Google Fit, Health
Light sensitive photodiodes	Stress	Wearable
Light sensitive photodiodes	Blood oxygen level	Wearable
Facebook	General information about patient activity (number of comments, likes, reactions, the total number of posts, total number of friends)	Facebook
Instagram	General information about Instagram stories (number of comments, likes, the total number of stories, total number of followers and the total number of people followed by the patient)	Instagram

[a]Health: iOS health app
[b]Google Fit: Android health app

Table 2 Active data

Type data	Specific data
Medication	Name, frequency, and quantity of the intake
Emotions	How the patient feels at that moment (sad, happy, angry)
Sleep	Duration and quality

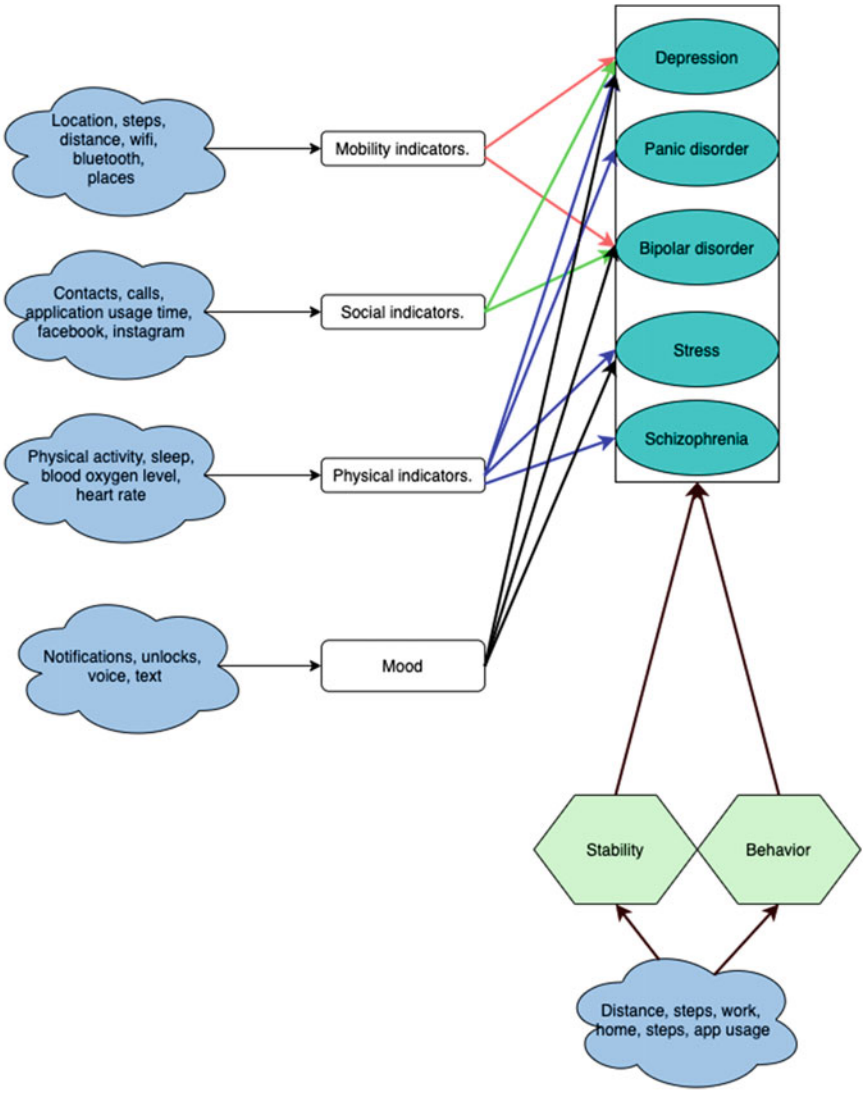


Fig. 2 Relation between data and indicators

In addition, the information related to social app usage joint with the percentage of outgoing calls during the whole day represents a daily social indicator. Moreover the entropy, the number of new contacts, and the moments of the day where the calls occur are relevant information to determine the social activity. This information is useful to detect anomalies in patient's social rhythms. Changes in a patient's social indicate a symptomatic worsening in some diseases such as bipolarity (Abdullah et al. 2016), which suggests the importance of capturing the social activity of a patient.

The environmental light level detected by the light sensor, the actigraphy data and the number of steps is used to estimate the sleeping hours with smartphone sensors. Also, data collected by wearables and health applications are used to determine the most accurate estimation of sleep duration and quality. Some studies (Malik et al. 2014) show that patients with sleep disorders tend to represent more suicidal behaviors than patients without sleep disorders (Kim et al. 2015). In addition, this relationship has been demonstrated in several disorders such as stress, depression, panic disorder, and schizophrenia. This is because a lack of sleep in patients can cause an increase in impulsive acts. So we can say that sleep indicators alone constitute a marker for impulsiveness. Tracking this data passively, we can predict suicidal behaviors.

Smartphone provides information on the type of activity the patient is performing at each moment (walking, cycling, running). This data allows knowing if the patient is active during the day. In addition to the actigraphy data, indicators about the patient's mobility such as the time of day that the patient has the most activity, the average daily activity and the difference between the average activity and the maximum activity can be created. Analogously of the social activity case, the physical activity of a person follows patterns that, if altered, it can be a warning that something is happening. This change may be a sign of a possible episode of depression, stress, or bipolarity, so changes in physical activity are used for the prevention or management of the patient's disease. Some studies linked physical activity with suicidal ideation and attempts (Andriessen and Krysinska 2009; Lester et al. 2010).

The continuous reception of notifications in the patient's mobile phone can cause adverse effects on the patient's health (Kanjo et al. 2017). The average of the total notifications received together with the time of day when the highest number of notifications are received can be used as an indicator of the affective state of the patient and stress (Westermann et al. 2016). This also applies to the number of unlocks screens made during the day. If a user unlocks the mobile screen a lot of times maybe he feels nervous, stressed, or impatient.

Another data collected by the eb2 system is the heart rate. It has been shown in some studies that patients with depression have a decrease in heart rate as well as a minor difference between the level of heart rate during the day and night (Taillard et al. 1993). Besides, heart rate and blood oxygen level can also be related to stress markers. And stress is inversely related to mental health.

The human being can capture the mood of a person in a conversation. This fact suggests that an analysis of the voice of a patient should contain information about

the emotional state. This analysis can be semantic (words) or acoustic (tone, flow). The diversity of expressions used can be a sign of creativity in patients, and the lack of such creativity can be an indicator of disease (Lauronen et al. 2004). Autistic children have semantic speech deficits until adulthood (Simmons and Baltaxe 1975). Also, voice recognition can be used to detect depressive episodes (Muñoz et al. 1999). As for the acoustic analysis, different features are extracted to get the mood of the patient (happy, sad, undecided, angry). This type of analysis has the advantage of being independent of the audio language and presents fewer privacy problems since the audio is not stored but its features. Through the features of pitch and jitter, the mood of bipolar patients can be determined (Vanello et al. 2012). Both analyses offer the possibility of making assumptions about the current mood of each patient. Another way to infer the patient's behavior is extracting writing features like typing speed, correction rate and keypress time (Reinertsen and Clifford 2018), so it can be measured the way the patient includes the text into the application. For example, if a patient enters the text in an impulsive or indecisive way.

2.3 Data Consolidation

These indicators are direct transformations on data that do not have any kind of medical quality, so the main challenge is to transform them into robust and solid data with high medical quality. This transformation is achieved with the use of artificial intelligence on the data on a daily basis resulting in some behavioral indicators or digital biomarkers. Those indicators are the core of the eB2 solution, whose main utility is to provide quick and interpretable information to clinicians and even include an alarm system to enable better patient attention.

3 Digital Biomarkers

As has been shown in the previous section, the spectrum of digital data that can be retrieved from a patient is huge. Nonetheless, it is not viable for a human to follow how all these data evolves over time, and a single data source may not be sufficiently robust to trigger an alarm or to be indicative of a close suicide attempt. There is a need to transform all this set of data into a more summarized and integrated set of indicators that englobes different data sources, easy to interpret, and fast to compute to bring a real-time framework. These indicators will be built using Artificial Intelligence, specifically, machine learning techniques. Machine learning is a collection of algorithms created to take advantage of the statistical properties of the data to solve a problem. In this scenario, the algorithms will be used to create indicators with the power of determining if it is likely a suicide attempt to happen. Most general indicators are presented in this section, giving a brief explanation about how are they built and their usefulness.

3.1 Behavioral Changes

Every individual is unique. In fact, it is quite complicated to create an algorithm that can explain every human behavior, as behavior is modeled by biological, psychological, cultural, and environmental factors, and there does not exist a golden rule to model how people behave. But the question is, is it possible to create an algorithm that "learns" how a single person behaves to detect patterns in this behavior or predict what this person will do?

To learn a person's behavior, the first thing that is needed is observations. It is required a window of at least 20 days of data to reach enough evidence that a machine learning model has learned this behavior. The number of behaviors can indeed be at least unlimited, but the days of a normal person are not so different. A normal person has a more or less stable routine where days are quite similar: it may be working days, resting days, tourism days, social days... but the pattern is usually the same during some time. Let's see it in an example.

Imagine a person whose routine is working from Monday to Friday in the morning, high smartphone use when this person arrives home, and more or less the same sleep patterns. At the weekend, maybe this person spends more time at home or decides to go to the country, or even visit his family. If each day is categorized with one label, from Monday to Friday this person has a day with type "1" that belongs to a working day profile, Saturday is profile "2," that is day to stay at home, and Sunday is day to go to the country, with a high level of physical activity, type "3." For the machine learning model, it is easy to identify that the baseline behavior is the sequence of 1,111,123. If we assume that this person falls into a depression that makes him or her unable to work. Suddenly, the type "1" and "3" days disappear, getting a sequence of 2,222,222. This example is shown in Fig. 3. If the moment when behavior 1 changes into behavior 2 is detected, early intervention is possible before this person is getting worse and worse.

The algorithm used for the identification of the moment where the behavior changes is called change-point detection algorithm and it's described in Moreno-Muñoz et al. (2018). The algorithm is composed in two different parts, the first process is to determine the type of day of the user (1,2,3,etc.), and the second one is responsible for learning the pattern of days and choose the moment where this pattern changes.

Preliminary results of the Smartcrises protocol suggest that behavioral changes detection algorithms built over personalized models are a good estimator of a near suicide attempt in a 7 days window. As behavior is a multidimensional item, changes are sometimes detected over a mobility dimension, other times in the social dimension, or other on the sleep patterns dimension. A general behavioral change detector over all these dimensions is being developed to make it easy for a clinician to monitor the status of the patient, and in case of an alert for a sudden change, evaluate in which set of dimensions was produced and if it is really in danger.

Behavioral changes indicator is nonspecific in terms of suicide risk assessment since it only measures changes, not the implications. If a patient's medication is

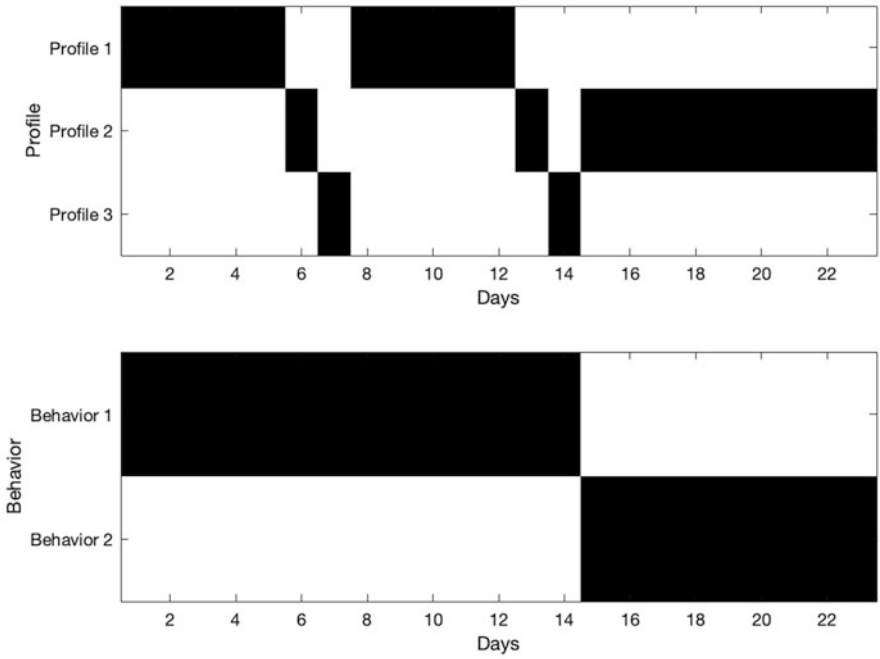


Fig. 3 Profile sequence and behavioral change

adjusted or starts a new therapy that improves his well-being, sleep time, or physical activity, the algorithm will detect a change. In these cases, taking into account this information can also be positive from the clinical point of view because this patient can be moved to a less risk group which will have more spaced medical check-ups, offloading the hospital.

3.2 Behavior Stability

In some cases, behavioral changes are an accurate indicator of a near suicide attempt. This happens when the behavior has a clear new pattern, so the patient has changed his habits. But in some other cases, this change of pattern does not occur, but it is followed by a suicide attempt. In this scenario, it has been observed that the suicide attempt can be preceded by a time period where the behavior is unstable, in other words, there is not a fixed pattern of habits that can be determined by an algorithm. This can happen due to a chaotic or unbalanced period where hours of sleep are dissimilar, and in different moments of the day, mobility in some days is infimal, others too high, etc. As these kinds of behaviors are interesting to detect from the clinical point of view, a different measure called stability was designed.

Fig. 4 Stability period

Stability is a measure that arises from the change-point detection algorithm and identifies periods where algorithm does not have enough evidence to determine that there is a new and clear pattern, but in the current pattern some fluctuations are observed. Three modalities can be identified, no fluctuations, low fluctuations, and high fluctuations. The first type is identified as "stable," the second one as "slightly unstable" and the third one as "unstable." They are usually represented in a timeline graph using traffic light colors where green is stable, yellow is slightly unstable, and red is unstable. Days tagged as unstable requires clinical supervision and the patient should be contacted to check if everything is ok. An example of this indicator can be found in Fig. 4.

3.3 Disability Assessment

Besides critical moments of alert where direct life-threatening is a risk, it is also interesting to know how patients deal with life. Are they functional to go out of home, to maintain social relationships, are they sleeping well? Conversely, what is the level of disability that this patient has?

Disability assessment questionnaires are frequently used in mental health to evaluate how is the disease or the diseases impacting on patient's daily life. One example is the WHODAS 2.0 questionnaire (Üstün et al. 2010), which splits the functionality in six different domains: mobility, cognition, self-care, getting along, life activities, and participation. The questionnaire gives a single score for each domain and a global one. The single score is based on the sum of the scores of each question for a single domain, and the score to each question can be "none" (0), "mild" (1), "moderate" (2), "severe" (3), and "extreme" (4). Then the global one can be computed with the sum of the scores of the six domains resulting in a value between 0 (no disability) and 100 (full disability). But the main problem with this kind of questionnaire is that it takes some time to fulfill them (WHODAS takes around 20 min). If a clinician wants to follow the status of the functionality of a patient once a month over a year, and he or she has more than 500 hundred patients, 2,000 h will be spent in a year only to pass the questionnaire. To solve this issue, eB2 has been working to develop automatic assessment algorithms that can give a score of the functionality of a patient in five domains: mobility, social, sleep, cognition, and emotional. The granularity of this score has been fixed to 15 days since a lower value might capture noisy scores that may not correspond with the general status of the patient.

Using disability continuous assessment, it is easier to evaluate with objective information how is the health status of the patient, and even if the patient is responding to some treatment or therapy, and adjust it or take action early. The main advantage of this continuous assessment is that provides a general view of how is the patient over many dimensions, and not only the ones that are supposed to be affected. Furthermore, as the disability score is obtained periodically, it enables not only to check how is the patient at a certain time but to follow how this functionality evolves over time.

The disability assessment algorithm has also a great potential for patient management and monitoring since some alarms can be configured for each patient to send warnings when some domain changes its score. For instance, a patient who has had previous suicide attempts where he was progressively decreasing the physical activity until he was at home during the whole day. An alarm can be configured to trigger when the mobility score passes a defined threshold, so the professionals can intervene in an early stage, avoiding a possible future suicide attempt.

3.4 Synchronic Indicators

The indicators that have been described in the previous sections are grouped in the category of diachronic, as they have a single value in a whole day, and it makes sense to analyze them in a long period as weeks, months, or even years. But there are other kinds of indicators whose temporal dimension is much shorter as they are designed for an intraday environment. These indicators are called synchronic.

Synchronic indicators are very specific, and they can be used, apart from the clinical objective information task, to be a source of data of other more general indicators. They have multiple values per day, but they can be summarized with statistical values as mean, standard deviation, maximum, minimum, or median to provide fast and interpretable information in one sight.

Affect: Arousal and Valence According to the classical approach of the affect, it can be divided into two separate dimensions: arousal and valence (Yik et al. 2011). Arousal is related to the level of activation or energy of the person, and valence is related to the attractiveness or averseness. Characterizing the score of a person in these two dimensions is very useful to understand the mood or the current status of a disease. For instance, depression is related to low arousal and negative valence and anxiety with high arousal and negative valence.

Arousal is an indicator that is directly related with some of the data mentioned before: changes in the physical activity or actigraphy, sleep patterns, the rate of screen unlocks per hour, keyboard press patterns, and voice features like pronunciation rate and number of silences are useful data to give an estimation of the arousal level of a person.

Valence can also be related to behavioral data as physical activity, voice features, and keyboard patterns, but it is more accurate if the text content is analyzed and not only the way the person types.

Mood As a secondary indicator mood can be registered by the patient using the application, and also it can be estimated using arousal and valence. For example, there are emotions like anger that are related to high arousal and negative valence, or sleepy, that has low arousal and neutral valence, or happy, that has a positive valence but medium arousal. Individual behavioral models can be useful to understand patient by patient how mood is reflected in behavior, and after some user interaction with the app registering the emotional status, the models can predict which is the current one without any interaction.

Attention Attention is a relevant synchronic indicator as is closely related to cognition. This indicator is created using sources of data such as the use of the apps in the smartphone, the time and continuity performing some activity, number of silences in a conversation, and cadence and errors typing in the keyboard.

Affability Affability indicator is related to the level of aggressiveness or hostility of the patient. It is obtained from some sources like vocal features, the text that the patient writes, and the activity in social networks.

4 Conclusions

The eB2 system that has been described in this chapter represents an innovative way of assessment called Behavior Ecological Assessment or passive EMA. This methodology provides an objective, automatic, continuous, and unobtrusive behavioral assessment in daily life conditions. With the emergence of mobile technologies, the concept of digital phenotype and its use in e-health has gained worldwide relevance as it establishes a new bridge between healthcare professionals and ambulatory care.

Moreover, through developments in Artificial Intelligence, all these amount of data that is unmanageable by a human and in many cases noisy and with a poor quality are converted into digital biomarkers that are more robust, reliable, and interpretable by a healthcare professional. In addition, the ability to forecast in serious situations make this type of system fundamental tool to avoid major consequences and to provide greater well-being for patients, which can have a great impact on the future of psychiatry.

References

Abdullah S, Matthews M, Frank E, Doherty G, Gay G, Choudhury T (2016) Automatic detection of social rhythms in bipolar disorder. J Am Med Inform Assoc 23(3):538–543

Ahuja ND, Agarwal AK, Mahajan NM, Mehta NH, Kapadia HN (2003) GSR and HRV: its application in clinical diagnosis. In: Proceedings of 16th IEEE symposium computer-based medical systems, IEEE, pp 279–283

Andriessen K, Krysinska K (2009) Can sports events affect suicidal behavior? A review of the literature and implications for prevention. Crisis 30(3):144–152

Bär KJ, Boettger MK, Koschke M, Schulz S, Chokka P, Yeragani VK, Voss A (2007) Non-linear complexity measures of heart rate variability in acute schizophrenia. Clin Neurophysiol 118 (9):2009–2015

Berrouiguet S, Barrigón ML, Brandt SA, Ovejero-García S, Alvarez-Garcia R, Carballo JJ et al (2016) Development of a web-based clinical decision support system for drug prescription: non-interventional naturalistic description of the antipsychotic prescription patterns in 4345 outpatients and future applications. PLoS One 11(10):e0163796

Berrouiguet S, Ramirez D, Barrigón ML, Moreno-Munoz P, Carmona Camacho R, Baca-García E et al (2018) Combining continuous smartphone native sensors data capture and unsupervised data mining techniques for behavioral changes detection: a case series of the evidence-based behavior (eB2) study. JMIR Mhealth Uhealth 6(12):e197

Berrouiguet S, Barrigón ML, Castroman JL, Courtet P, Artés-Rodríguez A, Baca-García E (2019) Combining mobile-health (mHealth) and artificial intelligence (AI) methods to avoid suicide attempts: the Smartcrises study protocol. BMC Psychiatry 19(1):1–9

Chellappa SL, Araújo JF (2007) Sleep disorders and suicidal ideation in patients with depressive disorder. Psychiatry Res 153(2):131–136

Cochrane-Brink KA, Lofchy JS, Sakinofsky I (2000) Clinical rating scales in suicide risk assessment. Gen Hosp Psychiatry 22(6):445–451

Doryab A et al (2019) Identifying behavioral phenotypes of loneliness and social isolation with passive sensing: statistical analysis, data mining and machine learning of smartphone and fitbit data. JMIR Mhealth Uhealth 7(7):e13209

Duhem S, Berrouiguet S, Debien C, Ducrocq F, Demarty AL, Messiah A et al (2018) Combining brief contact interventions (BCI) into a decision-making algorithm to reduce suicide reattempt: the VigilanS study protocol. BMJ Open 8(10):e022762

Husky M, Olié E, Guillaume S, Genty C, Swendsen J, Courtet P (2014) Feasibility and validity of ecological momentary assessment in the investigation of suicide risk. Psychiatry Res 220 (1–2):564–570

Insel TR (2018) Digital phenotyping: a global tool for psychiatry. World Psychiatry 17(3):276

Jobes DA, Kahn-Greene E, Greene JA, Goeke-Morey M (2009) Clinical improvements of suicidal outpatients: examining suicide status form responses as predictors and moderators. Arch Suicide Res 13(2):147–159

Kanjo E, Kuss DJ, Ang CS (2017) NotiMind: utilizing responses to smart phone notifications as affective sensors. IEEE Access 5:22023–22035

Kim J-H, Park E-C, Lee SG, Yoo K-B (2015) Associations between time in bed and suicidal thoughts, plans and attempts in Korean adolescents. BMJ Open 5(9):e008766

Lauronen E, Veijola J, Isohanni I, Jones PB, Nieminen P, Isohanni M (2004) Links between creativity and mental disorder. Psychiatry 67(1):81–98

Lester D, Battuello M, Innamorati M, Falcone I, Simoni E, Bono S, Tatarelli R, Pompili M (2010) Participation in sports activities and suicide prevention. Int J Sport Psychol 41:58–72

Malik S, Kanwar A, Sim LA, Prokop LJ, Wang Z, Benkhadra K et al (2014) The association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses: a systematic review and meta-analysis. Syst Rev 3:18

Moreno-Muñoz P, Ramírez D, Artés-Rodríguez A (2018) Change-point detection on hierarchical circadian models. arXiv preprint arXiv:1809.04197

Muñoz RF, McQuaid JR, González GM, Dimas J, Rosales VA (1999) Depression screening in a women's clinic: using automated Spanish-and english language voice recognition. J Consult Clin Psychol 67(4):502

Nazabal A, Garcia-Moreno P, Artes-Rodriguez A, Ghahramani Z (2016) Human activity recognition by combining a small number of classifiers. IEEE J Biomed Health Inform 20 (5):1342–1351

Osmani V (2015) Smartphones in mental health: detecting depressive and manic episodes. IEEE Pervas Comput 14(3):10–13

Parkhurst KA, Conwell Y, Van Orden KA (2016) The interpersonal needs questionnaire with a shortened response scale for oral administration with older adults. Aging Ment Health 20 (3):277–283

Rath D, de Beurs D, Hallensleben N, Spangenberg L, Glaesmer H, Forkmann T (2019) Modelling suicide ideation from beep to beep: application of network analysis to ecological momentary assessment data. Internet Interv 18:100292

Reinertsen E, Clifford GD (2018) A review of physiological and behavioral monitoring with digital sensors for neuropsychiatric illnesses. Physiol Meas 39(5):05TR01

Saeb S, Lattie EG, Schueller SM, Kording KP, Mohr DC (2016) The relationship between mobile phone location sensor data and depressive symptom severity. PeerJ 4:e2537

Shickel B, Tighe PJ, Bihorac A, Rashidi P (2017) Deep EHR: a survey of recent advances in deep learning techniques for electronic health record (EHR) analysis. IEEE J Biomed Health Inform 22(5):1589–1604

Simmons JQ, Baltaxe C (1975) Language patterns of adolescent autistics. J Autism Child Schizophr 5(4):333–351

Simon TR, Powell KE, Swann AC (2004) Involvement in physical activity and risk for nearly lethal suicide attempts. Am J Prev Med 27(4):310–315

Taillard J, Lemoine P, Boule P, Drogue M, Mouret J (1993) Sleep and heart rate circadian rhythm in depression: the necessity to separate. Chronobiol Int 10:63–72. https://doi.org/10.3109/07420529309064483

Üstün TB, Kostanjsek N, Chatterji S, Rehm J (eds) (2010) Measuring health and disability: manual for WHO disability assessment schedule WHODAS 2.0. World Health Organization

Vanello N, Guidi A, Gentili C, Werner S, Bertschy G, Valenza G, Lanata A, Scilingo E (2012) Speech analysis for mood state characterization in bipolar patients. In: IEEE engineering in medicine and biology society (EMBC)

Vinkers CH, Penning R, Hellhammer J, Verster JC, Klaessens JH, Olivier B, Kalkman CJ (2013) The effect of stress on core and peripheral body temperature in humans. Stress 16(5):520–530

Westermann T, Wechsung I, Möller S (2016) Smartphone notifications in context: a case study on receptivity by the example of an advertising service. In: Proceedings of the 2016 CHI conference extended abstracts on human factors in computing systems (CHI EA '16). Association for Computing Machinery, New York, pp 2355–2361

Yik M, Russell JA, Steiger JH (2011) A 12-point circumplex structure of core affect. Emotion 11 (4):705