Philippe Courtet *Editor*

Understanding Suicide

From Diagnosis to Personalized Treatment

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Preface

After several decades of scientific work, the field of suicidology has mainly evolved, and this begins with recent advances in the definition of the suicidal phenotypes, the description of the "suicidal behavior disorder," and the large implementation of validated scales for assessment of suicidal risk, such as the C-SSRS. The first part of this book will focus on these aspects related to the clinical evaluation, which is at core of management of suicidal patients. These clinical aspects will cover the description of the suicidal process across the suicidal crisis and the influence of the temperamental features. Innovative tools may help clinicians to detect high-risk subjects and those engaged in suicidal crisis to prevent suicidal act. The contribution of neurosciences in suicidology will help to better understand suicidal pathophysiology and to identify potential biomarkers. These results will enrich the clinical evaluation to explore beyond the risk factors and suicidal ideation. Indeed semiology based on neuroscience will enable clinicians to approach the complexity of suicidal behaviors. Innovative semiology, such as considering the existence of suicidal addiction, offers new perspectives for personalized therapeutic strategies. We also wished to give a place to the definition of a potential new entity, the suicidal addiction, so such recent works suggest the existence of this subgroup of patients who would deserve specific management.

The second part is devoted to advances in biology of suicide. The aim is to confirm that suicidal behavior is an independent clinical entity with its specific pathophysiology. Since Asberg's seminal works identifying the first trait marker of suicidal vulnerability, numerous biological and molecular systems have been involved in suicidal vulnerability. On the one hand, experts in suicidology will update our knowledge coming from prospective studies to biochemistry, genetics, epigenetics, brain imaging, and neuropsychology. Evidence suggests that we will soon have suicidal risk biomarkers that will benefit to diagnosis and therapeutic innovations. On the other hand, we will promote an argument throughout this manuscript, which aims to highlight the future needs of social neurosciences in suicidal behavior. In this part, we suggest that having a social approach of suicidal behavior in light of psychache introduced by E. Shneidman, may also contribute to the identification of new biomarkers. Indeed, the most recent data suggest that the vulnerability to suicidal act includes an increased sensitivity to social exclusion, which

leads to social pain and related inflammatory activation. Another contribution of recent advances in biological research stands in animal models. If suicide is observed only in humans, animal models may help to study biological or behavioral abnormalities underlying suicidal behaviors. Each component would then be likely to facilitate the dissection of a specific molecular pathway in order to identify biomarkers, which need to be tested in humans based on translational research.

In the third part, specificities of assessment and management of suicidal risk according to psychiatric disorders, including personality disorders will be discussed. The hierarchical attitude leads psychiatrists to first consider psychiatric disorder diagnoses before suicidal risk. But the role of personality dimensions to influence suicidal risk will be presented. This part will adopt a neo-Durkheimian approach. The reason is related to the fact that although suicide is a medical issue, and if we consider that the vulnerability is central to the suicidal process, the most recent work constantly reminds us that the social environment is at core of occurrence of psychiatric disorder and suicide. Economic crisis and unemployment are scourge. More and more mentally ill individuals go to prison. Ethnic discrimination and tragedy of migrants in Europe concerns everyone us as human beings, as citizens, and as health professionals. Religion, which nowadays poorly interferes in the public domain, may also protect against suicide through moral values, which deserves more attention for suicidal prevention. We also wanted to remind strongly that society must fight against the scourge of suicide with optimism. The outstanding example of the struggle by activists of humanism in Japan should be known, recognized, and followed all over the world: the will to fight against suicide can find a political and legal existence. This is a model to follow.

The doctors should not remain alone in fighting suicide. However, they are in first line. Clinical evaluation is central in suicidal prevention, and therapeutic alternatives are growing. As the editor of this book, I appeal to the compassion of readers. As we live in an ongoing innovative period, advances have been probably made since the authors proposed their chapters including the most recent developments at this time. The fourth part focused on therapeutic strategies of suicidal behaviors in a modern and heuristical way. Antidepressants, antipsychotics, and lithium salts are widely prescribed. Thus, it is important to discuss their role in reducing or increasing suicidal risk. Indeed, warnings and black boxes involving many drugs have been multiplied during the last decade, causing confusion among patients and care professionals. Yet treated patients are more likely to survive. Even if psychopharmacology becomes complex, guidelines may be proposed. Psychotherapy is often overlooked in the treatment of subjects at risk of suicide. It was necessary to review the interests of different psychotherapies specifically focused on suicidal behavior, to find that this field is flourishing with many innovations to expect in the coming years. Medicine too is experiencing the digital revolution. The Internet and smartphones represent tools for assessment, treatment, and prevention. Their intrusion in suicidology is remarkable as the demonstration of the effectiveness of e-health is

bright, opening up endless opportunities for progress. Returning to a guiding thread of this book, the problematic of social exclusion in suicidal behaviors, connected medicine is precious by facilitating development of close links with patients. Callback strategies have shown evidence in preventing suicidal recurrence. Suicidal patients need to be socially reconnected, and it works. Should be given as an example another citizens' initiative from a group of wonderful people of devotion in promoting suicide in Hungary. Based on the idea that citizens are primarily concerned with the battle against suicide, and that the Internet offers a unique strike force, they developed a suicide prevention platform accessible to everyone. It requires to be copied and exported.

Suicidal process develops in some individuals when they are facing a social adversity in a context of psychiatric suffering. Each element represents a potential area for developing specific care and preventive actions. But suicidology cannot ignore the development of precision medicine. The fifth part considers personalized strategies in the field of suicidology. One of the perspectives consists of pharmacogenetics. What do we know about the association between genes and drug metabolism in suicidal risk prediction? If genes are related to drug metabolism, are they new hints to understand suicidal vulnerability? They are certainly not part of our heritage with the unique role of degrading psychotropic drugs. Beyond the role of genomics, each part of this book has implicitly emphasized the social part and the individual part in the different phenomena related to suicide. Each edge, top and side, of the diamond is important in jewelry. It is the same when it comes to stop the suicidal process in a given subject. No aspect of its existence must be neglected. The use of "big data" and "learning machine" techniques will probably help to produce algorithms allowing us to integrate these huge levels of complexity. To date, we can consider other ways to customize the management of suicidal patients. With an assumed bias, the role of early development of the individual and the family being so crucial to the future of the individual, we propose that personalized suicidology is born with the management of childhood maltreatment and familial environment. Another demonstration of required personalized suicidology is the paradox of gender. Generally, women attempt suicide but men die by suicide, opening a reflection on the specific actions to promote according to gender, but also sexual orientation. Pharmacoepidemiology is included in this part focusing on personalized suicidology because of the potential deleterious consequences of warnings regarding drug use on medical practice and suicide rates. This is not a simple alliance of opposites, to celebrate the centenary of "Dada." But it strengthens the observation that general comments should not mechanically be applied to the individual.

With humility, the last chapter explains how we take care of patients engaged in suicidal crisis for 30 years, since the birth of one of the first specialized units for suicidal patients at Academic hospital in Montpellier, South of France. At that time, Pr Didier Castelnau, based on his clinical knowledge and his humanist listening, understood that suicidal patients deserved very specific management. Going a step

further, we suggest that care for suicidal patients must be very unique and very different from those commonly given to psychiatric patients. We propose in this closing chapter an attempt to integrate current concepts and specific modalities of management. The main objective is to offer an "outstretched hand" full of updated medical knowledge to our patients to relieve pain instead of suicide.

Montpellier, France

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Part I

Diagnostic and Clinical issues

Nomenclature and Definition of Suicidal Behavior

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Lucas Giner, Julio A. Guija, Christopher W. Root, and Enrique Baca-Garcia

Abstract

Today we understand suicidal behavior as a spectrum of actions and thought processes. This framework is the result of centuries of thought and study on the subject. This chapter will provide a historical context for attempts to classify and understand the various manifestations of suicidal behavior. This chapter traces the evolution of the study of suicidal behavior from the first appearances of the word "suicide" in text up to the present state of our conceptualization. Various models for classifying suicidal behavior will be described. This chapter aims to provide the reader with a thorough understanding of both the historical and the contemporary definitions of the terms suicidal behavior, suicide, suicide attempt, and suicidal ideation. The impact of the theories of a diverse group of thinkers will be discussed, especially the framework described in the DSM-5. Multiple contemporary and historic diagnostic criteria will be described, as well as the intersections of suicidal behavior and other mental disorders.

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The tremendous impact of suicide is clear when one considers the high number of suicides that occur annually across the globe and the consequences that accompany suicide. These consequences have been studied from various clinical, economical, statistical, and public health perspectives. The objective of this chapter is to provide the reader a theoretical and conceptual approach to the study of suicidal behavior. The following pages will attempt to catalog the evolution of our understanding of suicidal behavior both nosologically and philosophically and to discuss the current state of our understanding.

1.1 History of the Conceptualization, Definition, and Classification of Suicidal Behavior

The neologism suicide first appeared in the seventeenth century. It comes from the Latin words *sui* and *occidere*. Some cite Brown as the first using the word in the 1635 edition of *Religio Medici*, but others say the word was first used by Charleton in 1651. Some French historians credit its first use to either the Abbé Prevot in 1734 or the Abbé Desfontaines in 1737. Officially the word entered the dictionary of the French academy in 1762 and the English language dictionary, Blount's Glossographia, in 1656.

The term suicide has had several distinct meanings. Esquirol, for example, felt suicide was an act that could take place in a moment of madness, using madness in a sense similar to folie. In the introduction of his book *Le suicide*, Durkheim defined it as "all types of death that result, directly or indirectly, from an act, positive or negative, committed by the victim himself, knowing full well the intended result." Durkheim further defined a suicide attempt saying, "an attempt is the same act that we have defined, stopped at some point along its path before it was able to result in death" (Durkheim 1982). For his part, Freud understood suicide according to his psychoanalytical theory as a murder in reverse. Lacan saw suicide as a displacement of the object of aggression; before the impossibility of releasing it upon the other, it is released upon oneself.

For centuries there have been many distinct approaches to the conceptual problem of suicide. Initially religious and philosophical approaches predominated. From a scientific standpoint, it was sociology that initiated the study and conceptualization of suicide throughout Europe in the fourteenth century: Morselli in Italy; de Masaryk in Austria; Guerry, Étoc-Demazy, and Lisle in France; Winslow in England; and Casper, Müller, and Wagner in Germany. The seminal work on the topic is recognized to be Emile Durkheim's *Le Suicide*, published in 1897. Durkheim classified the act of suicide according to the grade of social integration of the individual and the social regulation of individual desires. In his classification, he distinguished three types of suicide: egoistic suicide, altruistic suicide, and anomic suicide. Since then, other authors have continued to define suicide from a sociological perspective. Halbwachs stands out for his work, *The Causes of Suicide*, in which he compared the differences in suicidal behavior between urban and rural societies (Halbwachs 1930). The social theory is best summarized by the idea that social disorganization produces individual disorganization (Uña Juárez 1985).

Psychoanalytic theory also made inroads into the conceptualization of suicide. Freud was the first to highlight ambivalence in suicide. He also noted the importance of aggression, relating it to homicide through the allure of death (Rodriguez Pulido et al. 1990). To a still greater extent along these lines, Menninger's work *Man Against Himself* (Menninger 1972) identifies three aggressive elements in the act of suicide: killing, being killed, and dying. According to these, the suicidal impulse can be subdivided into the wish to kill, the wish to be killed, and the wish to die. Afterward, Hendin identified six motives for suicide attempts (Hendin 1963): retaliatory abandonment, retroflexed murder, reunion with a loved one, rebirth of the self after death, self-punishment, and seeing oneself as already dead.

Until the end of the 1960s, suicide attempts were considered failed suicides; therefore, suicide and suicide attempt were considered parts of the same psychiatric subset. In light of this, some European authors introduced terms with the objective of formalizing and describing the study of the act of attempting suicide. Among these new terms were parasuicide (Kreitman et al. 1969), pseudosuicide (Kessel 1965), and deliberate self-harm (Morgan 1979). These terms originate from a psychological orientation toward death. The objective of these acts is to produce the subject's desired change by way of the actual or desired consequences of his actions (Kreitman et al. 1969). In general, American authors use the term "suicide attempt" and European authors use the terms "deliberate self-harm" and "parasuicide."

The definitions of suicide have evolved toward more operative conceptions. Shneidman stated that "Suicide is an intended act of self-inflicted cessation." Similarly Motto wrote: "Suicide is self-inflicted, self-intentioned death." In 1988 the Center for Disease Control (CDC) developed a series of terms to designate suicidal behaviors called "Operational Criteria for the Determination of Suicide" (OCDS) which defined suicide as "death as a result of an intentional, self-inflicted harm." It recognized three components: death by harm, acts against oneself, and intentionality. This initiative has given rise to other criteria that rest on concepts of self-infliction (ascertainment of the existence of self-provoked injuries by the subject) and intention (implicit or explicit evidence of a conscious decision or desire to kill oneself) (Operational criteria for determining suicide 1988).

This idea opened the possibility that suicidal behavior was not homogenous and that the definition ought to move toward a classification system. As such, in the classifications of suicidal behavior, we can find the causes, the intentionality, and the consequences. In 1986, the WHO, following this conceptualization, avoided the terms "suicide" and "suicide attempt" and instead used the collective "suicidal acts." Within this framework, suicide is described as "an act with a fatal outcome which the deceased, knowing or expecting a fatal outcome had initiated and carried out with the purpose of provoking the changes he desired." A suicide attempt was described as "an act with a nonfatal outcome in which an individual deliberately initiates a non-habitual behavior that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognized therapeutic dosage, and which is aimed at realizing changes which the subject desired, via the actual or expected physical consequences" (World Health Organization 1986).

Since then there have been numerous attempts to classify suicidal conduct from a theoretical perspective. Initially Hyman (1990) proposed a basic classification to describe what can be observed clinically. He divided subjects with suicidal behavior in terms of the behavior itself. He stated that, there are those deaths attributed to or suspected of being suicide; subjects that survive a suicide attempt; subjects that seek treatment for suicidal ideas or impulses; subjects that seek treatment for other causes, but admit to suicidal ideas or impulses; and subjects that deny suicidal intent, but whose behavior seems to demonstrate the potential for suicide to the observer or relatives. Since then other classifications have been published, among which the proposals of Marris and Diekstra stand out. Maris (1992) proposed three axes for classifying the type of suicidal behavior. Axis I specifies the type of behavior (ideation, attempt, or suicide). Axis II is for recording characteristics secondary to the act such as the medical lethality, the intentionality, the circumstances, the method, sex, age, race, marital status, and occupation. Finally, Axis III measures the presence or absence of chronic, indirect, self-destructive behavior (substance abuse, previous self-mutilation, or eating disorders). That same year, Diekstra proposed a classification system to classify suicidal behavior as either suicide, suicide attempts, or parasuicide (Diekstra 1992). Yet another attempt at classification is based in a cluster analysis of different populations with distinct patterns of suicidal behavior. The most impactful of these classification efforts have sought to group the similarities in completed suicides from the 1970s to the present. From these studies, three groups were identified: those with little suicidal intention comprised of young women, another comprised of older men with suicide attempts characterized by a high degree of violence and intentionality, and a third group intermediate between the two in terms of composition (Bagley et al. 1976; Kiev 1976; Paykel and Rassaby 1978; Rapeli and Botega 2005; Sinyor et al. 2014). A more modern analysis utilizes data mining, which requires older samples and seems to offer promising results (Oquendo et al. 2012) on the subject of suicidal behavior (Kuroki 2015).

1.2 Current Definitions of Types of Suicidal Behavior

Presently, the WHO defines suicide as the act of deliberately killing oneself and suicide attempt as "any non-fatal suicidal behavior and refers to intentional self-inflicted poisoning, injury or self-harm which may or may not have a fatal intent or outcome." Therein, the WHO also specifies that nonfatal self-harm without suicidal intent is included. The WHO explains that this is because of the problem of evaluating suicidal intentionality due to ambivalence or even concealment on the part of the patient. On the other hand, suicidal behavior can be "a range of behaviors that include thinking about suicide (or ideation), planning for suicide, attempting suicide and suicide itself" (World Health Organization 2014).

The DSM-5 defines suicidal ideation as "thoughts about self-harm, with deliberate consideration or planning of possible techniques of causing one's own death," defines suicide as "the act of intentionally causing one's own death," and defines suicide attempt as "an attempt to end one's own life, which may lead to one's death."

Likely the most complete classification is that of O'Carroll et al. (1996). O'Carroll proposed a nomenclature for the most basic epiphenomena of suicidal behavior through a clear and unambiguous definition. Initially they distinguished three large groups: suicidal ideation, behavior related to suicide, and completed suicide (Table 1.1). Later, they also came to consider self-inflicted wounds (with unknown intention) and behaviors with the intention of dying. Within each group they distinguish the result of the said behavior following the existence and gravity of the wounds. This nomenclature, proposed by O'Carroll et al., has been utilized in numerous studies and to develop the Columbia Classification Algorithm for Suicide Assessment (C-CASA) (Posner et al. 2007).

In critiquing these classifications, Barber and his colleagues called attention to aborted suicide attempts, which he defined as a first step to a suicide attempt in which the act is not completed, and therefore physical harm does not occur (Barber et al. 1998). They defined the characteristics of this behavior as having the intention of killing oneself but changing one's mind at the last moment before committing the act, along with the absence of physical injury. Later, Silverman et al. made an important revision (Silverman et al. 2007a, b) to this classification. In addition to factoring intentionality into the classification, they added a type of suicidal behavior, known as suicidal communication. This act can be verbal or nonverbal and can be defined as threatening suicide (possible suicidal behavior in the near future) or as a suicide plan (a proposed method for possible suicidal behavior) (Tables 1.2).

Presently, the DSM-5 includes suicidal behavioral disorder and nonsuicidal self-injury in Section III of the manual. Section III includes clinical situations that require a more in-depth investigation to determine if a formal diagnosis of a mental disorder should be considered along with a proposed set of diagnostic criteria (Table 1.3). Throughout the DSM-5 numerous disorders are described as being associated with suicide. However, there are disorders for which the epigraph specifically references the risk for suicide, such as schizophrenia, schizoaffective disorder, psychotic disorder due to another medical condition, bipolar I disorder, bipolar II disorder, major depressive disorder, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, separation anxiety disorder, specific phobia, panic disorder, obsessive-compulsive disorder, body dysmorphic disorder, posttraumatic stress disorder, dissociative identity disorder, dissociative amnesia, anorexia nervosa, bulimia nervosa, other hallucinogen intoxication, and opioid use disorder. Likewise this epigraph regarding risk of suicide is included for various disorders within Section III including depressive episodes with short-duration hypomania, persistent complex bereavement disorder, and neurobehavioral disorder associated with prenatal alcohol exposure.

The DSM-5 outlines two forms of psychopathological evaluation that evaluate suicidal ideation and suicide attempts concretely, one for the adult population and one for those between 6 and 17 years of age. The adult DSM-5 self-rated Level 1 Cross-Cutting Symptom Measure has 13 domains, among which Domain VI indicates suicidal ideation. The parent/guardian-rated DSM-5 Level 1 Cross-Cutting Symptom Measure for children aged 6–17 has 12 domains, among which Domain XII explores suicidal ideation/suicide attempt.

As it does with other disorders, the DSM-5 has included specifiers. Under suicidal behavior, these specifiers relate to the violence of the method employed, the

Table 1.1 Nomenclature of self-injurious thoughts and behaviors de O'Carroll et al. (1996)

Risk-taking thoughts and behaviors	
With immediate risk (high-risk sports)	With remote risk (smoking)

Suicide-related thoughts and behaviors									
Suicide ideation			Suicide-related behaviors						
Casual ideation	Serious ideation		Instrumental suicide-related behavior (ISRB)				Suicidal acts		
	Transient	Persistent	Suicide threat		Other ISRB	Accidental death associated with ISRB	Suicide attempt		Suicide
			Passive	Active			With no injuries	With injuries	

Table 1.2 Nomenclature suicide-related thoughts and behaviors de Silverman et al. (2007a)

Suicide-Related Ideation			Suicide-related Communications***				Suicide-Related Behaviors***			
Intention to suicide				Intention to suicide				Intention to suicide		
No	?	Yes	Type	No	?	Yes	Outcome	No (Self-harm)	? (Undetermined Suicide-related Behavior)	Yes (Suicide Attempt)
casual (2) transient			Suicide Threat*	Type I	Type II	Type III	No injuries	Type I	Type I	Type I
(3) passive (4) active (5) persistent			Suicide Plan**	Type I	Type II	Type III	Injuries	Type II	Type II	Type II
							Death	Self-Inflicted Unintentional Death	Self-Inflicted Death with Undetermined Intent	Suicide

*Suicide Threat: verbal or nonverbal; passive or active
**Suicide Plan: a proposed method of achieving a potentially self-injurious outcome
***Additional Modifiers
A. Intrapersonal focus—to change internal state (escape/release)
B. Interpersonal focus—to change external state (attachment/control)
C. Mixed focus

Table 1.3 Suicidal behavior disorder proposed criteria in DSM-5

A. Within the last 24 months, the individual has made a suicide attempt
Note: A suicide attempt is a self-initiated sequence of behaviors by an individual who, at the time of initiation, expected that the set of actions would lead to his or her own death. The "time of initiation" is the time when a behavior took place that involved applying the method
B. The act does not meet criteria for nonsuicidal self-injury – that is, it does not involve self-injury directed to the surface of the body undertaken to induce relief from a negative feeling/cognitive state or to achieve a positive mood state
C. The diagnosis is not applied to suicidal ideation or to preparatory acts
D. The act was not initiated during a state of delirium or confusion
E. The act was not undertaken solely for a political or religious objective
Specify if:
Current: not more than 12 months since the last attempt
In early remission: 12–24 months since the last attempt

medical consequences, and the degree of planning involved. The specifiers also account for possible cultural differences and the functional consequences of the act, which the clinician should remember to consider.

1.3 Suicidal Behavior as a Symptom, Syndrome, Complication, Disorder, or Diagnostic Axis

From the psychiatric point of view, suicidal behavior has been conceptualized variously as a symptom, a syndrome, a complication of a psychiatric illness, a psychiatric disorder, or a diagnostic axis.

As a symptom, suicidal behavior is present in various mental disorders. The diagnostic criteria for major depression include thoughts of suicide, and a history of suicide attempts is among the criteria for borderline personality disorder. In a somatic context, there are certain incapacitating and/or painful medical pathologies in which thoughts of suicide are common. Along these lines, the evaluation and treatment of suicide risk should be considered a secondary feature of the pathology that is causing it. As such, when the mental disorder or medical pathology improves, the suicidal ideation should improve as well. This vision of suicidal behavior does not permit a treatment or prevention plan unless it is incorporated into the treatment of the causative illness. It also assumes a parallel evaluation, without taking into account the specifics of the presenting subject. Furthermore, we are left without adequate consideration of much of what is now known about suicidal behavior, such as the recognized heritability of suicidal behavior independent of mental disorder.

The presuicidal syndrome, described by Riegel in 1958, was based on a specific psychological state (Ringel 1976). In this state preceding suicide, three aspects are present: constriction, inhibited aggression turned inward toward the self, and suicidal fantasies. This syndrome is characterized by a narrowing and diminishing of

the psychic life in general, along with the inhibition of aggressive impulses. At the same time, the desire for death and self-destructive fantasies begin to develop.

From another point of view, Pöldinger understood that the appearance of the act of suicide would develop secondary to an underlying disease or coincide with the onset of that disease. The chief among these underlying diseases are depression, schizophrenia, and alcoholism (Poldinger 1983). In this state there can be a depressive affect, with hopelessness and anhedonia owing to depressive symptoms that can be combined with the fatal intentionality described by Klerman (1987). The evolution of suicidal ideation and its transition into action depends on the precipitating disease and the individual history. As such the action can take an impulsive, planned, or ambivalent form (Poldinger 1983). Factors influencing the precipitation of suicidal behavior may include concurrent psychosocial events along with biological and genetic factors (Poldinger and Holsboer 1989). Shneidman interprets the evolution from suicidal ideation to the act of committing suicide in cognitive terms, basing it in what he calls suicidal logic. According to the threefold model he proposed (Shneidman 1976), a suicidal person experiences an unbearable psychogenic pain or suffering, a negative pressure of lived experiences, and a state of perturbation. The development of suicidal behavior will continue to surge from these three planes. Frustrated with the need to bear his continued suffering, the individual considers himself in the context of previous experiences, with a negative effect on the individual, and moves toward a state of rigid and dichotomous reasoning. The result is an unbearable suffering with inability to see other possibilities or solutions to his problems. This is how the presuicidal state evolves into suicidal act.

Suicide has also been understood as a complication of a mental illness. Presently more than 90 % of subjects that exhibit suicidal behavior also present with comorbid mental disorders, including personality disorders. Nonetheless, the presence of mental illness is not on its own sufficient to predict self-destructive behavior. Clearly, 10 % of subjects who present with suicidal behavior present with no other mental illness. However, it is important to consider that this 10 % figure is taken from western cultures. In China, for example, this figure approaches 60 % (Phillips et al. 2002). This figure also does not correspond to the clinical gravity or intrinsic severity of each pathology.

According to the DSM-IV, a mental disorder is a behavioral or psychological pattern of clinical significance that, whatever its cause, manifests itself in the individual in the form of a behavioral, psychological, or biological dysfunction. This manifestation is considered a symptom when it appears to be associated with discomfort, disability, or a significantly elevated risk of death, suffering, disability, or loss of liberty. Although mental illness and suicide are closely linked, suicidal behavior is not present in all subjects that suffer from a psychiatric pathology. In fact, it is only present in a minority of cases. For example, only one third of patients with bipolar disorder attempt suicide at some point in their life (Chen and Dilsaver 1996). In light of this, suicidal behavior cannot be considered an intrinsic characteristic of mental pathology (Oquendo and Baca-Garcia 2014).

Given the lack of findings based on diagnostic exams, Robins and Guze (1970) established widely accepted criteria delineating psychiatric illness based on clinical

Table 1.4 Validators to be used in the DSM-5 process (Kendler et al. 2009)

I. Antecedent validators
A. [a]Familial aggregation and/or co-aggregation (i.e., family, twin, or adoption studies)
B. Sociodemographic and cultural factors
C. Environmental risk factors
D. Prior psychiatric history
II. Concurrent validators
A. Cognitive, emotional, temperament, and personality correlates (unrelated to the diagnostic criteria)
B. Biological markers, e.g., molecular genetics, neural substrates
C. Patterns of comorbidity [note – while categories A and B would most typically be assessed after illness onset, they also could be assessed prior to illness onset as premorbid characteristics]
III. Predictive validators
A. [a]Diagnostic stability
B. [a]Course of illness
C. [a]Response to treatment

[a]Highest priority and greatest emphasis in decisions about the overall validity of diagnosis

description, laboratory studies, shadowing patients, and family interviews. Later, Krishnan (2005) condensed these criteria into two: the risk of incapacitation or death and the presence of environmental, pathological, or genetic factors. In cases where the second criterion is insufficient, the diagnosis can be based on the prognostic course, family history, and/or response to treatment.

Oquendo and Baca point out (2014) that suicidal behavior meets the criteria for a psychiatric diagnosis in Guidelines for Making Changes to DSM-5 (Kendler et al. 2009). That is (a) a behavioral or psychological syndrome or pattern that occurs in an individual, (b) associated with clinically significant distress or disability, (c) diagnostically valid, (d) clinically useful, and (e) reflective of an underlying psychobiological disturbance. Furthermore, the diagnosis cannot simply be a manifestation of social deviance or conflicts with the society. Oquendo and Baca also required three validators: antecedent validators, concurrent validators, and predictive validators (Table 1.4) (Regier et al. 2013). Following the reasoning of Oquendo and Baca, suicidal behavior fulfills four categories of antecedent validators, two categories of concurrent validators, and three categories of predictive validators. The authors express concern regarding only one of the categories of predictive validators, diagnostic stability, though they argue that diagnostic stability is highly variable between mental disorders and the same is true for suicidal behavior, which can range from just one attempt to multiple attempts or even completed suicide. In terms of diagnostic fallibility, the definition used in the Classification Algorithm for Suicide Assessment (C-CASA) (Posner et al. 2007) and the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2011) demonstrates an inter-rater reliability coefficient (C-CASA) and a sensitivity and specificity (C-SSRS) above 95 %, respectively, for predicting suicide attempts.

Finally, considering suicidal behavior as a diagnostic axis, as they were established in the multiaxial diagnosis in the DSM-IV, favors the perspective that it

is a situation that can affect a majority of mental disorders. In practice this view also facilitates assessment of suicide risk remaining fixed within the evaluation of mental status. This helps complete future evaluations for suicide risk, as it is now known that previous suicidal behavior is the best predictor for suicide risk. In the actual classification of illnesses, suicidal behavior is only included as a symptom of depressive disorders and borderline personality disorder, as discussed earlier. It is absent among the recognized symptoms that may accompany other conditions with known risk of suicide, such as schizophrenia or alcohol and other substance abuse. What's more, in cases where risk of suicidal behavior is identified, this does not affect the diagnosis or emphasize the potential risk.

1.4 Consideration of the Suicidal Spectrum for Its Classification

Studies on the characteristics of suicidal populations (number of attempts, methods of completed suicide) observe that there is little specificity of the risk factors, owing in part to the heterogeneity of these populations (Innamorati et al. 2008). According to some authors, suicidal behavior should be defined for two different populations, differentiated by the intent to die, with some overlapping risk factors shared between them (Linehan 1986; Beautrais 2001). The questions then should be, "What is the relationship between these two populations?" "Are they two groups on a continuum depending on the severity of the behavior?" "Should they be best categorized as two distinct but related populations?" Some data exists to support each idea.

Following the first idea, a continuum from suicidal ideation to completed suicide, the severity of the clinical situation would determine the outcome of suicidal behavior. One could determine the position on the suicidal spectrum based on intentionality, though this poses a problem due to the ambivalence many subjects show in suicide attempts regarding outcome (Hendin 1963). When suicide attempts are divided on a three-point scale according to the intentionality of the attempt, one can observe a similarity between the group of maximum intentionality and those who actually complete suicide, something that is not observed with the group of lowest intentionality (Menninger 1972; Hendin 1950). Alternatively intentionality can be analyzed based on the results of the act; a sample of suicide attempts can be divided into those who had had a serious suicide attempt (based on the medical consequences) or violent suicide attempt (based on the method employed) versus those who had not had a violent or serious attempt. Those with violent or serious attempts share characteristics with the population who complete suicide, such as a higher percentage of males, a history of prior attempts, a family history of suicidal behavior, and advanced age (Giner et al. 2014).

In the 1980s Linehan (1986) distinguished two types of populations with suicidal behavior according to the intensity of the intent. There are certain social and demographic differences between the populations that have attempted suicide and those that have completed suicide. Those who complete suicide are more likely to be male

and are typically of a more advanced age than those who survive a suicide attempt (Tuckman and Youngman 1963; Fushimi et al. 2006). Clinically, differences can also be observed between suicides and suicide attempts (Innamorati et al. 2008; Gladstone et al. 2001; Holmstrand et al. 2006; Giner et al. 2013), even though they may not be apparent in younger patients (Beautrais 2003; Brent et al. 1988). Beautrais (2001) continued this theory regarding the existence of two distinct but overlapping groups within the continuum of suicidal behavior. For her, both populations shared certain risk factors. This idea is supported by a study conducted with two clinical groups and one control group ($n=984$). The first group consisted of 202 subjects who completed suicide and the second of 275 subjects who had survived a suicide attempt. The data collection was accomplished using the same methodology employed in psychological autopsies.

The results indicated that attempted suicides of high lethality were similar to completed suicides in regard to mood, prior suicide attempts, outpatient psychiatric treatment, and psychiatric admission in the previous year. The precipitating events were typically classified as problems of an interpersonal, legal, or occupational nature. Nonetheless, differences did exist between the two groups. The group that completed suicide had a high percentage of men, subjects of advanced age, and a higher prevalence of a non-affective psychiatric diagnosis. The suicide attempt group showed a larger proportion of diagnosed anxiety disorder and socially isolated individuals. The diagnosis of anxiety disorder was particularly frequent among those adolescents with more than one suicide attempt compared to those with only one prior attempt (Pagura et al. 2008).

This differential vision can be criticized in light of the fact that the most significant risk factor for completion of suicide is a previous suicide attempt (Mann et al. 2005; Nordstrom et al. 1995; Tejedor et al. 1999; Suokas et al. 2001; Suominen et al. 2004; Gibb et al. 2005). It is estimated that between 10 and 20 % of those who have attempted suicide will complete suicide eventually (Monk 1987). The relative risk of suicide between those with prior suicide attempt versus the general population is 66 (CI 95 % 52–82); in the first year it is 0.7 % (CI 95 % 0.6–0.9 %), increasing to 1.7 %, 2.4 %, and 3.0 % after 5, 10, and 15 years, respectively (Hawton et al. 2003).

There also exists the possibility of an intermediate approach. As Lester proposed (Lester 1987) among subjects with prior suicide attempts, there will be a subgroup with a tendency toward repeated attempts. This subgroup will be distinct in clinical presentation and social relationships from both those who complete suicide and those who attempt suicide only once or twice (Rudd et al. 1996). This idea is similar to the one described by Blasco-Fontecilla (2012) regarding the theory on the addiction to suicide (Tullis 1998).

Conclusions

The classification of suicidal behavior has been an objective of study since the beginning of medicine and psychology. At present, despite an enormous quantity of studies from various perspectives, a definitive classification explaining suicidal behavior in its various incarnations has still not been achieved. The closest we have come would be a descriptive classification that includes intentionality as the

crucial factor. More studies are needed in which social, demographic, psychological, clinical, and biological characteristics of the subjects are compared according to presently accepted classifications in order to ascertain the validity of these classifications. Finally, including suicidal behavior as a nosological entity or diagnostic axis will promote research into unique characteristics within presentations of distinct evolutions and severity.

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A Modern Semiology of Suicidal Behavior

2

Jorge Lopez-Castroman, Emilie Olié, and Philippe Courtet

Abstract

The epidemiology, risk factors, and biological basis of suicidal behaviors have been the object of an ever-increasing research in the last three decades. During this period, researchers all over the world have identified potential biomarkers of risk and developed several theories about the mechanisms leading to suicidal behavior. However, the lack of common terminology, instruments, and cooperation has been a major deterrent. Today, the community has established the bases for this collaboration and evidence coming from neuroscientific studies can already be applied to the field of suicidology. We present here a potential semiology based on current evidence coming from biological, clinical, and neuroimaging studies.

Let them think what they liked, but I didn't mean to drown myself. I meant to swim till I sank – but that's not the same thing. –Joseph Conrad (1857–1924)

2.1 Introduction

Suicidal behavior has been present throughout human history but the usual definition of "self-death," even if eternal and universal, is not quite enough to appraise its concept. In recent years, several authors have tried to establish more specific definitions and operational criteria, especially since pioneer studies in the 1970s unveiled a biological ground for these behaviors (Åsberg et al. 1976). These studies opened a new research field that tries to identify biomarkers of risk for future suicidal behaviors, as well as potential treatments that could reduce specifically the suicidal vulnerability.

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Suicidal research has long suffered the absence of common criteria to describe the different phenomena associated to the suicidal spectrum, which classically ranges from suicidal ideas of gradual intensity to actual suicide attempts and completed suicide (Silverman et al. 2007). The lack of clarity and specificity in the suicidal nosology hampers the communication with health professionals, patients, and relatives and also the development of clinical guidelines and research protocols. A powerful example of this problem comes from the controversial effects of antidepressants on suicidal risk. The prevention of suicide by an adequate treatment of depression is debated because a non-defined suicidality, often self-declared suicide ideas, appears at the beginning of the treatment among the young and has given rise to a public concern (Courtet et al. 2014). However, epidemiological data in different countries show an inverse correlation between antidepressant use and suicide deaths (Isacsson et al. 2010). Indeed, a recent review by a group of international experts has explicitly claimed that the term "suicidality" should be banned from clinical trials (Meyer et al. 2010). Thus, the Federal Drug Administration (FDA) in the USA recommends now the use of a classificatory algorithm of suicidal and non-suicidal phenomena, the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The C-CASA enables the classification of the different types of suicidal behaviors, such as preparatory acts, suicidal ideation, self-harm behaviors of unknown intention, non-suicidal self-harm, the lack of information about a lethal or nonlethal behavior, suicide attempts (interrupted, aborted, or actual attempts), or completed suicide. This classification can be used for clinical trials and observational studies alike (Meyer et al. 2010).

Besides, certain features of the suicidal behaviors are frequently used to characterize and evaluate their importance. For instance, the violence of an attempt, its potential and actual lethality, or the intentionality and planning behind it are commonly reported. But the type of suicidal behavior should be defined before proceeding to characterize it in order to avoid clinical traps. A patient may change his view about the intentionally of a recent suicide attempt, but the act should still be considered an attempt: a potentially self-injurious act committed with *at least* some wish to die (Giner et al. 2014). We should always bear in mind that suicide attempters are frequently ambivalent with regard to their own acts, even those patients that have made serious or violent attempts.

Another important step forward in the scientific understanding of suicidal behavior is the presence of a "Suicidal behavior disorder" in DSM-5 (American Psychiatric Association 2013). This category designed for research includes those patients that have attempted suicide in the two preceding years, marking the period at high risk of recurrence. The operational criteria of "Suicidal behavior disorder" need to be validated, modified, or rejected by future research, but they are based on a specific formulation of suicide attempt and establish the main differential diagnoses (particularly with non-suicidal self-harm, suicidal ideation, and preparatory acts). Now, we have a common instrument by which to compare suicidal vulnerability throughout the world.

The development of valid methods to evaluate suicidal risk and the accurate identification of the risk stage of any given patient are needed to improve the

prevention of suicide. These advancements will help to construct personalized models of care, more appropriate to measure the actual risk, instead of the probabilistic models that are currently used. Indeed, for the moment we can just list risk factors when we try to establish if a patient is at light, moderate, or high risk.

2.2 Suicidal Ideation

The progression of the patients along the suicidal process is well known. This progression can be illustrated by a recent epidemiological study of the World Health Organization (WHO) that comprised 85,000 persons of 17 developed and developing countries (Nock et al. 2008). They observed that during the last year, suicidal ideation was present in 2 % of the sample, a suicidal plan was endorsed by 0.6 %, and 0.3 % had made a suicide attempt. In other words, approximately one third of the persons with suicidal ideas progress to a suicidal plan and in turn another third will progress to a suicide attempt. Most of these transitions (about 60 %) happened in the year following ideation onset. Suicidal ideation is thus the first element that can be identified in the suicidal process. An individual with suicidal ideas is at risk of attempting suicide within a year and should be subject of particular surveillance. Numerous instruments, including questionnaires, scales, or interview guidelines, exist for the standard evaluation of suicidal risk. The FDA currently promotes the use of a screening questionnaire for the different categories of suicidal behavior in all clinical trials: the Columbia Suicide Severity Rating Scale (C-SSRS). Recent evidence supports the validity of this instrument (Gipson et al. 2015), which is easy to use after a short training course and examines the essential features of suicidal thoughts: their frequency and duration, the mastery over the thoughts, the existence of deterrents, and the alleged purpose for a potential act. For instance, the presence of active suicidal ideation in the C-SSRS, but not in Beck's suicide ideation scale, predicts the occurrence of a suicide attempt in teen or adult patients (Posner et al. 2011). Moreover, the electronic version of the C-SSRS allows longitudinal and ecological self-assessment that alerts in case of high risk.

Indeed, the access and use of smartphones and new technologies by a large proportion of the population make now feasible a connected healthcare for (suicidal) patients. This is the paradigm of ecological momentary assessment (EMA), where patients respond to simple questions, often using Likert scales in their smartphones, and provide a real-time in vivo outline of their situation. EMA can also serve to optimize regular clinical consultations, because patients will find easier to discuss the specifics of their state. In a pilot study, we tested a questionnaire that popped up in the smartphones of the patients five times a day for 1 week (Husky et al. 2014). The sample included healthy participants, euthymic patients with a history of depression with or without a history of suicidal behavior, and patients discharged from the hospital after an admission for a suicide attempt. The result of this feasibility and validity study was encouraging since the acceptance and completion rate of the questionnaires were very high (68–88 %). In addition, the repeated evaluation of negative thoughts and suicidal ideas did not show any iatrogenic effect, because the

occurrence of these cognitions was unrelated to the duration of the study or to the multiple daily assessments.

A good description of the characteristics of suicidal ideation is not the only feature to be considered in the semiology of suicidal behavior. The warning signs for suicide include a number of observed signs and reported symptoms that indicate an imminent (in minutes or hours) passage to the act: hopelessness and feeling of being overwhelmed or trapped, the lack of reasons for living, increasing alcohol or drug use, social isolation, anxiety/agitation, reckless behaviors, sleep disorders, or dramatic mood changes (Rudd 2008). The identification of these warning signs facilitates clinical decisions and, importantly, reveals the need for acute treatments. The acute administration of drug therapies aims at preventing a short-term passage to the act through sedation, anxiolytic effects, and the reduction of aggressiveness.

2.3 Suicidal Vulnerability

During the evaluation of suicidal risk in a patient, it is important to determine the stage along the suicidal process in which the patient can be located. Consistent evidence, clinical, epidemiological, and biological, demonstrates the existence of a suicidal vulnerability (Lopez-Castroman et al. 2014b). In the Dunedin cohort, the main suicidal factors associated with this vulnerability were described for an adolescent population followed from their infancy to the age of 21 (Fergusson et al. 2003). The vulnerability factors identified were childhood abuse, family history of suicidal behavior, high scores of neuroticism or impulsivity, low self-esteem, school failure, and bad companies. Interestingly, suicidal risk was particularly high among patients that suffered a depression and presented also some factor of suicidal vulnerability. Participants that had either a depression or a suicidal vulnerability factor did not show such a large risk. The findings of the Dunedin cohort illustrate the stress-vulnerability model, which has sustained a successful research on suicidal behavior in the last years. Most individuals that attempt suicide present a conjunction of a proximal factor that triggers the crisis (stresses such as mental disorders or psychic pain) and a distal liability (such as having suffered a severe trauma). We should remember one important vulnerability factor that was not mentioned in this study, the personal history of suicide attempts, which is the main risk factor for future suicide attempts or completed suicides.

The effect of life events on suicide risk needs to be taken into consideration for the semiology of suicidal behavior. This has been particularly studied in the case of childhood maltreatment; any form of maltreatment is strongly associated with suicidal behavior in adulthood but the more severe, the higher the risk. Importantly, in clinical samples of suicide attempters, the rates of reported childhood abuse are usually over 50 % (Lopez-Castroman et al. 2012). Early life events are linked to later suicidal behavior probably through the mediation of personality traits, such as impulsive aggression (Lopez-Castroman et al. 2014a), but the trace left by these adverse events can be located in specific brain regions (Oquendo et al. 2013) and mediates probably a large share of the risk, indirectly through personality and

mental disorders or directly creating a specific vulnerability to suicide. The extent to which brain dysfunctions (neuroimaging and neurocognitive) associated with the suicidal vulnerability are caused by external events or inherited from our genes is still to be determined. This is all the more truth since biology and environment interplay; for instance, epigenetic changes result from adverse experiences (McGowan et al. 2009), and personality traits may increase suicidal vulnerability through a more frequent risk exposure (Williams 2007).

Many studies have also signaled two personality dimensions that are associated to suicidal vulnerability: impulsive aggression and hopelessness or pessimism (Oquendo et al. 2004). Hopelessness is repeatedly found in suicide studies, including prospective ones, as a good and independent predictor of suicidal ideas and lethal attempts. Impulsivity is usually seen as a catalyst for episodes of acting out in persons who think about suicide. However, the evidence in the literature does not clearly support this idea of impulsivity. For instance, the impulsivity of the suicidal act (planned, thoughtless) does not correlate with the impulsivity of the attempter (Baca-García et al. 2004). Moreover, meta-analytic results suggest that the relationship between trait impulsivity and suicidal behavior is rather small (Anestis et al. 2014). A cohort study compared three groups of adolescents: those who planned suicide but had never attempted, those who had attempted suicide without planning it, and those who had attempted suicide after planning it (Witte et al. 2008). The impulsivity of the adolescents was highest in the last group (planned attempts). This observation could suggest that impulsivity acts as a distal factor in the suicidal process (Anestis et al. 2014). Impulsivity facilitates harmful behaviors, such as substance abuse or antisocial acts, which in turn will eventually expose impulsive individuals to psychosocial adversity, an environmental risk factor of suicidal behavior. Besides the disruptive behaviors that are relatively easy to detect, a recent study unveils an important new target group of adolescents at risk, called the "invisible" risk group by the authors (Carli et al. 2014). Indeed, teenagers with antisocial traits and substance abuse usually trigger the alert of community gatekeepers, but another group characterized by high media consumption (especially on the web), sedentary behaviors, and reduced sleep time is also at risk. These young people tend to be isolated and silenced and require proactive teams that promote reach-out and prevention strategies.

Suicidal vulnerability could be outlined with neuropsychological tests. For instance, suicidal patients take disadvantageous decisions independently of any comorbid psychiatric disorder they may present. Several studies have shown how adolescent and adult suicide attempters appear to ignore past experiences in reward/punishment tasks such as the Iowa gambling task. Importantly, impaired decision-making is associated with emotional dysregulation (i.e., affective lability trait and skin conductance responses). Other neuropsychological findings suggest that suicide attempters pay higher attention to specific emotional stimuli and show lower problem-solving abilities, reduced verbal fluency, and reversal learning (Richard-Devantoy et al. 2013).

The complex picture of cognitive processes that interplay in suicidal behavior needs to be integrated. One interesting effort in this direction is the interpersonal theory of suicide, devised by Joiner and his team (Joiner et al. 2005). According to

this theory (Van Orden et al. 2010), the desire for death is mediated by unmet interpersonal needs reflected by the feelings of being a burden for others, being worthlessness, or being socially disconnected. These feelings would lead to despair and isolation. However, the desire for death is not enough to attempt suicide and requires a "suicidal capability." The suicidal person reduces the inherent fear of death by gradually getting used to the prospect of pain and challenging the cognitive and volitional obstacles to suicide. The more previous suicide attempts, the easier it will be to acquire the capacity to reattempt. The interaction of perceived burdensomeness and thwarted belongingness with the gradually acquired capability for suicide may explain the transition from suicidal ideation to suicide attempt.

2.4 Neuroscience-Based Semiology

Neuroscience in the field of suicidal behavior has been largely developed in recent years and should help to improve the identification of suicidal vulnerability factors beyond the clinical indicators we have just seen (Courtet et al. 2011). A suicidal vulnerability state could then be called "suicidotypy" like schizotypy was proposed as a state of vulnerability leading to schizophrenia. Cognitive models, such as the "cry of pain" by Williams and Pollock (Williams and Pollock 2008), need to be updated. In a series of studies, these authors proposed that the suicidal process is based on the succession of three steps: (1) vulnerable subjects are more sensitive to defeat signals, this being demonstrated by abnormalities in a suicide-specific Stroop test (Williams and Broadbent 1986); (2) the impaired problem-solving abilities of suicidal patients lead to the feeling of being trapped ("no escape") and correlates also with a lack of specific autobiographical memory (Raes et al. 2005); (3) suicidal persons feel hopeless and see no possibility of rescue, and following this line, the verbal fluency deficits observed in suicidal patients correlate with despair (MacLeod et al. 1993).

To advance our understanding of the neural processes and neuroanatomical bases involved in suicidal behavior, we need now to integrate neuropsychology and brain imaging. Thus, we propose a neurocognitive model of suicidal behavior based on the results of structural and functional brain imaging studies (Jollant et al. 2010; Van Heeringen et al. 2011). Brain imaging has revealed, for instance, that suicidal behavior is associated with changes of reactivity to different stimuli at the bilateral orbitofrontal cortex and anterior cingulate and right ventromedial and left dorsolateral prefrontal cortex. The functional connectivity between the anterior cingulate and posterior insula is also decreased (Van Heeringen et al. 2011). These correlates of suicidal behavior are part of the brain circuitry involved in cognitive reappraisal, mood regulation, and decision-making. Disturbances in this circuitry could lead to overestimate social rejection signals, to show deficits in the control of emotional responses (and consequently psychological pain), and to have a limited number of choices when making decisions. More specifically, we suggest the existence of three dysfunctional neurocognitive processes localized in three large prefrontal brain regions (ventrolateral, dorsolateral, and medial). These dysfunctions might be responsible for three stages of the suicidal crisis, from negative emotions to suicidal ideation and acting out.

The difficulties of suicidal individuals to evaluate external events, which are associated to the dysfunctions of the ventrolateral prefrontal cortex, might explain their acute sensibility to social exclusion. Automatic negative emotions can also be generated in the orbitofrontal lateral cortex. Thus, when confronted with specific social situations, suicidal individuals might react with anger and anxiety. These emotions, together with an impaired decision-making, can lead these persons to contemplate suicide as the only solution to stop their psychic pain.

The second step in the suicidal process (suicidal ideas) implies an impaired regulation of the emotional state. Dysfunctions of the mediodorsal and anterior cingulate cortex are associated with deficits in problem solving and verbal fluency, which in turn increase the feeling of hopelessness. This can explain the worsening and duration of negative emotional states and psychic pain and facilitate the emergence of suicidal ideas. Once the suicidal ideas have emerged as a solution, these cerebral regions modulate the intensity of suicidal intent, as has been demonstrated in a recent positron emission tomography study (Sullivan et al. 2015).

In the last step, prefrontal cortex dysfunctions facilitate the acting out through a defective inhibition of responses in emotional contexts (impaired decision-making) and a higher sensitivity to social rejection (Jollant et al. 2011). Clearly, this theoretical framework has to be tested.

Besides, the role of decision-making impairments and emotional dysregulation in suicidal vulnerability opens new avenues of psychotherapeutic interventions, such as cognitive or emotional remediation, to be explored. Some of these strategies could be developed: (i) improve decision-making, training the patients to make adequate attributions when facing multiple choices; (ii) decrease sensibility to reject from others; (iii) increase attention to positive stimuli in the environment; and (iv) decrease the sensibility to psychological and social pain.

2.5 Pain

The question of social pain could be placed right in the middle of the suicidal process. Durkheim (1897) already mentioned that the problems in social or moral integration were one of the social elements that characterized suicide. More recently, Schneidman considered that suicide was caused by a "psychache," or psychological pain (Shneidman 1993), and this is very frequently the emotion reflected in suicidal notes (Valente 1994). Updating their terms, we propose that the sensitivity to social exclusion, followed by social pain, could be a key component of suicidal vulnerability. Several findings in cognitive and neuroanatomical studies support this idea (Mee et al. 2006). Depressed patients with a history of suicide attempts express more psychic pain that depressed patients without such a history. Using a simple analogic scale, similar to the ones used by algologists, we found that the increased psychological pain in depressed patients with a history of suicide attempts was correlated with the frequency and intensity of suicidal ideas (Olie et al. 2010).

In addition, evidence coming from neuroscience studies suggests the existence of common neuroanatomical pathways across different types of pain, physic, or

psychological. Following this line, we hypothesized that patients with a suicidal vulnerability, having an increased perception of pain, would be frequently taking analgesics. This hypothesis was demonstrated in an epidemiological study of 850 individuals aged 65 years or older, with no evidence of cognitive decay. We distinguished three groups of persons: with a history of suicide attempts, with a history of depression but no suicide attempts, and healthy controls (Olie et al. 2013). After adjustment for potential confounders, we observed that those persons with a past history of suicide attempts took more opioid analgesics than the other groups (OR = 2). Although these results need to be replicated in independent samples, they bring to our attention the importance of analgesic use among suicidal patients and the possibility of treating suicidal vulnerability and psychic pain with this kind of drugs. In a pilot study, we have seen how Acceptance and Commitment Therapy (ACT) could reduce suicidal ideas in depressed suicide attempters by an improvement in psychological pain, rather than in depression (Ducasse et al. 2014).

2.6 Social Connectedness

Suicidal vulnerability represents an important obstacle for healthcare. The follow-up of suicide attempters, either by general practitioners or psychiatrists, is frequently irregular or nonexistent (Bolton 2015). Considering that suicidal vulnerability is related with impulsivity, hostility, decision-making impairments (correlated with interpersonal problems), emotional dysregulation, hypersensibility to social rejection, and a diminished perception of social support, we can easily understand why suicidal patients often continue their follow-up not longer than a week (Hunt et al. 2009; Dana Lizardi and Barbara Stanley 2010; Courtet et al. 2011). We may be in need of therapeutic strategies that reach out for these patients, since they will not take the steps to be treated or do not accept the usual frames of healthcare. Accordingly, reach-out prevention programs using telephone calls or postcards have proven their utility to reduce the risk of reattempts (Vaiva 2006).

In summary, a new semiology for suicidal behavior is ready to make entrance. The recognition of the specificity of suicidal physiopathology invites clinicians to discover new elements that could be useful for the assessment of suicidal risk, even if its core continues to be the evaluation of suicidal ideas. Several aspects of the suicidal vulnerability, especially the neurocognitive processes, can be integrated in the semiology of suicidal patients. Improving the assessment will also open new targets for suicide prevention. In the short term some of these targets await us: standard protocols for evaluation of risk, healthcare continuity, implication of the family/caregivers, and mitigation of social or psychological pain.

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Asking about Suicide as Suicide Prevention: The Columbia Suicide Severity Rating Scale (C-SSRS)

3

Kseniya Yershova, Adam Lesser, Katherine Logan, and Kelly Posner

Abstract

Suicide has long resisted prevention efforts and continues to be a major cause of mortality and morbidity worldwide. Improving methods for identifying and predicting suicide risk is critical to suicide prevention. Historically, variability in definitions, terminology and assessment methods stymied suicide risk identification and communication. Uniform language and guidelines for characterizing suicidal thoughts and behaviors can render suicide risk assessment reliable independent of the setting, accessible to non-mental health professionals, and can unlock the possibility of nationwide suicide prevention programs built on communication across all sectors of society. The Columbia Suicide Severity Rating Scale (C-SSRS) was developed to distinguish the domains of suicidal ideation, suicidal and non-suicidal self-injurious behavior, differentiate types of thoughts and behaviors and provide standard definitions and suggested questions to guide assessment. The scale has helped mitigate some of the weaknesses of the traditional open-ended clinical inquiry, improved screening accuracy and predictive validity of risk estimates relative to several other measures that combine the ideation and behavior domains. The growing utilization of the scale across clinical practice, research and public health is changing the way we accumulate knowledge about the etiology, epidemiology and treatment of suicide and is beginning to affect suicidal behavior rates. Examples of successful implementation programs in healthcare, the military and research are discussed.

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3.1 The Columbia Suicide Severity Rating Scale (C-SSRS): Implementation and Impact on Suicide Prevention

Suicide is one of the world's greatest public health crises, claiming more lives each year than war, homicide, and natural disasters combined. Every 40 s someone in the world dies by suicide, and in 2012, the World Health Organization (WHO) reported that in 58 of its member states, including many high-income states, deaths by suicide outnumbered road fatalities (World Health Organization 2012, 2014). Suicide is now the primary cause of death among adolescent girls around the world and is the second leading cause of death in people under the age of 25 (Centers for Disease Control and Prevention [WISQARS] 2013; World Health Organization 2014). The rate of suicide is higher than ever in groups where silence is expected and the stigma surrounding suicide is the costliest. Among active-duty US servicemen and women, deaths by suicide have surpassed combat deaths (National Center for Telehealth & Technology 2014); among law enforcement officers, suicide is a leading cause of death (Aamodt and Stalnaker 2006); and in the US jails, one in three inmate deaths is ruled a suicide (Noonan et al. 2015).

As disturbing as these facts are, they shed light on only part of the problem. Beneath the surface lie the unimaginable intergenerational, social, and economic costs of suicide. Each death by suicide intimately affects at least six other people, and this scope widens when one considers the ratio of suicide deaths to suicide attempts – 1:24 – and the connection between suicide and other forms of violence (Drapeau and McIntosh 2014). Among the US high school-aged children alone, the annual rate of suicide attempts is 8 % (Centers for Disease Control and Prevention [YRBSS] 2013). Deaths by suicide and suicide attempts also contribute significantly to the global burden of disease (World Health Organization 2012). Self-directed violence is closely related to other forms of violence: A review of 37 incidents of school violence between 1974 and 2000 found that 78 % of the perpetrators had a history of suicidal thoughts or attempts (Vossekuil et al. 2004). Economically, the US Centers for Disease Control and Prevention estimated that in 2010, medical and work-loss costs related to suicide amounted to 44.7 billion USD (Centers for Disease Control and Prevention [WISQARS] 2010). Worldwide in 2008, deaths due to suicide cost 141 billion USD in years of life lost (American Cancer Society and Livestrong 2010).

Fortunately, unlike many other common causes of death, suicide is preventable, but suicide prevention depends first and foremost upon appropriate identification and screening of at-risk individuals. Uniform definitions of suicidal thinking and behavior and the knowledge of how to ask about them are of paramount importance to the success of any suicide prevention effort. A group of clinical scientists at several US universities has been pursuing this objective. The resultant instrument, the Columbia Suicide Severity Rating Scale (C-SSRS), has been successful in helping professionals and gatekeepers across many disciplines to accurately identify the history, presence, and future risk of suicide-related events and in changing the cultural context for the study and prevention of suicide more broadly (Posner et al. 2011). The development, implementation, and impact of this suicide assessment methodology in a variety of settings are discussed herein.

3.2 Suicide Screening: Challenges and Solutions

Recent findings underscore the gaps in suicide screening, including under- and overidentification of those at risk, as well as the success of certain screening strategies. Nearly half of those who die by suicide see their primary care provider in the month before they die (Luoma et al. 2002), and 90 % of adolescents do so in the year before their death (McCarty et al. 2011). Many adolescent suicide attempters present to the hospital emergency departments for nonpsychiatric reasons (King et al. 2009). The natural conclusion is that suicide screening should be done as ubiquitously and regularly and with as universal a methodology as the monitoring of blood pressure. Screening for suicide risk can be effective in detecting at-risk individuals, facilitating treatment engagement and lowering rates of suicidal behavior in high-school, college, adult, and older populations (Callahan et al. 1996; Haas et al. 2008; Mann et al. 2005; Scott et al. 2009). In particular, training of gatekeepers in suicide risk identification, especially primary care physicians, reduces access to lethal means and suicide rates (Aseltine et al. 2007; Knox et al. 2003; Mann et al. 2005), and has added economic benefits (e.g., reduced medical costs, wages not lost) (Ashwood et al. 2015).

Many factors contribute to the lack of routine and reliable suicide risk screening in medical and nonmedical settings. Historically, conceptual ambiguity in characterizing suicide-related phenomena and inconsistency in suicide terminology in the medical community were among the most formidable obstacles to understanding and preventing suicide (O'Carroll et al. 1996; Posner et al. 2007). In both clinical and research settings, different terms were frequently applied to the same behavior, and markedly different behaviors were grouped under a nonspecific term. Many of these terms were vague and pejorative, such as "gesture" or "nonserious" act as references to suicide (Crosby et al. 2011). Not surprisingly, comparison and interpretation of suicide-related assessment information among individuals and across settings has been very difficult (Goldsmith et al. 2002).

Conversely, standard language and rules for identifying and describing suicidal thoughts and behaviors make suicide risk assessment reliable independent of the setting and accessible to nonmental health professionals. This, in turn, unlocks the possibility of developing a national suicide prevention program, which is built on; communication across all sectors of society (World Health Organization 2014).

3.3 The Columbia Suicide Severity Rating Scale (C-SSRS): towards Reliable Screening across Settings

The Columbia Suicide Severity Rating Scale (C-SSRS) was designed by a group of leading clinical scientists at Columbia University, the University of Pennsylvania, and the University of Pittsburgh during the course of a National Institute of Mental Health treatment study of adolescent suicide attempters (TASA; Brent et al. 2009a). The work emerged out of the need for a measure that clearly defined and differentiated the full range of suicidal ideation and behavior, could be used to characterize their frequency, density, and severity and to track

change over time. Historically, conceptualization of suicidal ideation and behavior overlapped, which is problematic for a number of reasons, e.g., they do not always co-occur and have distinct predictive patterns depending on other factors (for review, see Posner et al. 2014). In some studies, severe suicidal ideation has been shown to confer a greater risk of suicidal behavior than the lifetime history of suicidal behavior without severe ideation (King et al. 2012; Mundt et al. 2013). Another problem with characterizing ideation was that thoughts of being better off dead or life not being worth living were historically considered suicidal ideation. Instead, these are more characteristic of depression but do not necessarily reflect a person's desire or a wish to die (Brown et al. 2008). Another significant gap in suicide assessment was that certain behaviors on the suicidal spectrum were not adequately measured. Among these were preparatory behaviors such as collecting pills, writing a suicide note, or purchasing a gun and self- or other-interrupted attempts, all of which are predictive of future suicidal behavior or death by suicide (Beck et al. 1999; Marzuk et al. 1997; Mundt et al. 2013; Steer et al. 1988). In one study of almost 35,000 C-SSRS administrations, these other types actually constituted the majority (87 %) of 542 suicidal behaviors and only 13 % were actual attempts among high-risk patients (Mundt et al. 2011) (Barber et al. 1998; Marzuk et al. 1997; Steer et al. 1988).

The C-SSRS was created to distinguish the domains of suicidal ideation and suicidal behavior and provide standard definitions to guide assessment. This has helped mitigate the weaknesses of the traditional open-ended clinical inquiry, which often misses important history of suicidal risk such as 20–40 % of suicidal attempts, and, for the purposes of documenting suicidal events, remove the need for specialized training (Arias et al. 2014; Bongiovi-Garcia et al. 2009). Clearer demarcation of ideation and behavior also reduces overidentification of risk seen with measures that combine the two domains and do not distinguish suicidal and non-suicidal behavior. In one study, screening with the "suicide question" on the well-established depression screener, as is the case with a widely used screening tool for depression, PHQ-9 while some cases that were positive on the C-SSRS were missed by the PHQ-9 question (Katzan et al. 2013; Viguera et al 2015).

Suicidal ideation was subdivided into several types of thoughts of increasing severity, from thoughts about wanting to die to intent to act on thoughts of killing oneself with a specific plan (http://cait.cumc.columbia.edu/dept/cssrs/Nomenclature_000.html). The most severe thoughts are characterized by their intensity, which is a sum of several features: frequency (how frequent are the thoughts?), duration (how long do the thoughts last?), controllability (how difficult is it to control these thoughts?), deterrents (can anything stop one from acting on the thoughts?), and reasons for ideation (is thinking about dying mostly out of hope to get attention or to stop suffering?). The typology of *suicidal behavior* does not assume a severity hierarchy and was expanded to include behaviors beyond suicide attempt. Any behavior that is self-directed, has a potential for harm and is carried out with at least some ("nonzero") intent to die, was included in the taxonomy. These criteria originated in the definitions developed for the Columbia Suicide History Form (Oquendo et al. 2003). The full range of behaviors included preparatory acts, self-or-other-interrupted attempts, actual attempt, and death by suicide.

Suicidal behavior is also distinguished from any potentially self-injurious behavior with no intent to die or "non-suicidal self-injurious behavior." Presence of injury was explicitly removed from the criteria for determining suicidal and non-suicidal self-injurious behavior. Instead, the degree of injury in suicide attempts and non-suicidal self-injurious behavior is characterized in terms of actual lethality, in cases where injury is observable, and potential lethality in the absence of observable physical injury. The assessment time frames are purposefully left flexible to accommodate different clinical contexts and populations, with a general guideline of assessing lifetime history and longer time frames for suicidal behavior than ideation. The scale, based on empirical evidence, is intended to capture both the present events and the history of the most severe type of lifetime ideation, which it emphasizes as an important indicator of suicidal risk. Although researchers and clinicians have traditionally focused on assessing current levels of ideation to identify risk, worst point lifetime ideation has been shown to be a better predictor of death by suicide (Beck et al. 1999).

3.4 The C-SSRS: Applications and Results

Unique to the C-SSRS research, public health, and implementation program is a set of broader suicide prevention goals: (1) to improve risk identification by making risk assessment accessible and standardized across all public contexts, (2) to facilitate linking of systems in risk management, and (3) to optimize care delivery and service utilization. With these goals in mind, particular consideration is given to the practical parameters of the risk assessment tool: short administration time, versatility of delivery methods (paper, electronic, etc.), and descriptive terminology with clear definitions that eliminate the need for specialized clinical training.

To be successful, suicide prevention requires a complete linking of service systems grounded in the common understanding of risk and in the uniformity of assessment. An efficient assessment with the C-SSRS using only the essential questions with guidelines for risk formulation facilitates development of clinical alert and monitoring procedures, as well as utilization of innovative service methods. The C-SSRS suggests several guidelines for risk formulation based on the level of suicidal ideation and presence or history of suicidal behavior (e.g., recent ideation with any intent to act or intent and plan or recent history of suicidal behavior suggests acute risk and points to expeditious clinical intervention with the highest level of alert and monitoring). These guidelines can be embedded in a set of clinical management procedures specific to a given context. Then, an optimal linking of emergency medical care and primary care may start, for example, with an emergency medical technician using an app on a tablet to administer the C-SSRS to a patient on location. When that patient is brought to the hospital, the attending physician trained in the C-SSRS enters this information into the patient's electronic medical record, which is designed to automatically generate suicide risk alerts depending on the patient's responses. When the patient then visits his or her primary care doctor months later, the information is instantly accessible and the doctor can reassess the patient's suicide risk.

The C-SSRS questions and guidelines have been incorporated into existing assessment tools in many settings in order to streamline suicide risk screening and triage: intake and monitoring assessments such as nursing mental status checklists in hospitals, jails, the military, and behavioral health clinics list specific options for the next steps (e.g., referral for mental health services, one-to-one observation, etc.), depending on the responses (http://cssrs.columbia.edu/documents/C-SSRStriageexampleguidelines_001.pdf). This ability to more accurately triage individuals helps avoid unnecessary interventions and redirects resources to those with the greatest need. In one hospital setting, the rate of one-to-one monitoring of patients who were considered high-risk dropped significantly following the hospital-wide adoption of the C-SSRS, leading to more targeted use of resources (Stavarski et al. 2011). When risk screening is done uniformly with clear guidelines, even in high-risk populations, the number of patients requiring intervention is low. To illustrate, out of 2962 US military veterans screened with the C-SSRS at John D. Dingle VA Medical Center, only 14 screened positive (0.47 %), and of those, only 5 (0.17 %) required more acute care (Posner et al. 2013).

Many systems, including states and countries, have developed top-down policies to optimize implementation of screening programs using the C-SSRS. The state of Tennessee has adopted the scale as a statewide crisis assessment tool. Similarly, following the State Senate Commission Hearing on emergency room overuse, Rhode Island instituted a statewide implementation of the tool to help healthcare workers with the determination of placement in emergency department or alternative settings. In one of the US states, Georgia, the C-SSRS was introduced statewide, and it embodies the vision of provider by provider implementation in all services, between all services and in systems of care, thereby optimizing the linking of systems. Thus far, the C-SSRS risk assessment method has been adopted across a variety of settings and systems, including primary care, clinical practice, surveillance, hospitals, managed care organizations, behavioral health organizations, community agencies, faith-based institutions, hospices, schools, police, fire, and EMT departments, substance abuse treatment centers, prisons, courts, and the US Military. When implemented as part of a comprehensive suicide prevention program, the C-SSRS is beginning to demonstrate remarkable impact on public health and economic cost of suicidal behavior. Three cases illustrate these developments: (1) the implementation of the C-SSRS as part of the US National Strategy for Suicide Prevention, (2) total force rollout in the US Marine Corps, and (3) the use of the C-SSRS in research.

3.4.1 The C-SSRS in Community Mental Health Care: Translating the National Strategy for Suicide Prevention

In 2012 the Office of the US Surgeon General issued the National Strategy for Suicide Prevention as a guide to suicide prevention in the USA over the next decade. The National Strategy was the result of a joint effort with the National Action Alliance for Suicide Prevention. In an effort to translate the National Strategy, the Action Alliance launched the “Zero Suicide in Health and Behavioral

Healthcare" initiative, which, among other recommendations, indicates that universal screening for suicide risk should be routine in all primary, hospital, behavioral healthcare, and crisis response settings (e.g., help lines, mobile teams, first responders, crisis chat services), and that anyone who screens positive for possible suicide risk should be formally assessed for suicidal ideation, plans, availability of means, and presence of acute risk factors (Clinical Care and Intervention Task Force 2011). The "Zero Suicide" initiative offers a "tool kit" (www.zerosuicide.sprc.org/toolkit) that includes resources on risk assessment using the C-SSRS and complimentary intervention strategies such as the Safety Plan Intervention (Stanley and Brown 2012); www.suicidesafetyplan.com. In just one example, the largest provider of community-based outpatient mental healthcare in the USA, Centerstone has adopted the "Zero Suicide" initiative, and the C-SSRS is now administered to every client at every service delivery point. Centerstone's Tennessee facilities saw a nearly 65 % reduction in the suicide rate, from 3.1 per 10,000 clients to 1.1 in the first 20 months since the beginning of the program (Esposito 2015).

3.4.2 The C-SSRS in the Military: Total Force Rollout in the US Marine Corps

Militaries around the world have recently begun to recognize and address the issue of suicide among their active duty servicemen and women (Reisch et al. 2013; Shelef et al. 2015). In the US Military, the C-SSRS has become an integral component of a comprehensive screening and suicide prevention initiative. It is being used in the Army Behavioral Health Data Portal, throughout primary care in the Navy and by many National Guards and Veterans Affairs Hospitals. The Assistant Secretary of Defense has recommended the scale to the Tri-Service Surgeon Generals and one comprehensive example comes from Connecticut, where their Army National Guard uses the C-SSRS as part of nearly every soldier-to-soldier and commander-to-soldier communication and in the Periodic Health Assessment.

In the US Marine Corps (USMC), training was provided to all support staff: counselors, clinicians, chaplains, defense counsels, and legal services at 16 USMC installations, including Okinawa, Japan (Hedge 2015). Special attention was given to training for and mandatory screening by the non-healthcare personnel, including legal services, who are often the first to come in contact with at-risk servicemen (Department of the Navy 2012). Following implementation of suicide screening with the scale, suicides in the USMC dropped by 22 %, from 45 in 2013 to 34 in 2014, and represented the lowest number of suicides in any branch of the armed forces in 2014 (Hedge 2015).

3.4.3 The C-SSRS in Research: Standardizing Measurement

Many organizations and institutions in the public sector have adopted the C-SSRS framework for the study and monitoring of suicide risk. The ongoing NIMH

project for creating a uniform approach to data collection in suicide research has deemed the C-SSRS as one of the essential measures to be included in the standard repository of research tools (Hamilton et al. 2011). Using a "toolbox" approach similar to the one implemented in public health, researchers in biomedical sciences are working towards a centralized access to well-established, low-burden, standardized measures that can be used in ongoing or new large-scale studies. The US Food and Drug Administration (FDA), in its most recent 2012 guidelines for monitoring of suicidal events in drug development trials, noted that "the use of different instruments is likely to increase measurement variability […and that…] this type of imprecision is particularly problematic in dealing with events that have a low incidence, as is the case for suicidal ideation and behavior occurring in clinical trials" (Food and Drug Administration 2012). The FDA is now requiring drug development trials to document safety of any medication or medical device under development according to the 11 types of suicidal events found on the C-SSRS (http://www.fda.gov/downloads/Drugs/…/Guidances/UCM225130.pdf). Similarly, the US Centers for Disease Control are using the C-SSRS suicidal behavior types for surveillance of suicide-related behaviors (Crosby et al. 2011).

Multiple reviews have included the scale among the most evidence supported, leading to its widespread use in research (Meyer et al. 2010) (Fig. 3.1; for the full review of psychometrics, please see http://www.cssrs.columbia.edu/psychometric_cssrs.html). The scale has been extensively used in research settings to measure clinical outcomes (e.g., Pangallo et al. 2011), treatment safety (e.g., Skljarevski et al. 2010), treatment-dependent clinical change (e.g., Brent et al. 2009b), as well as present, proximal, and distal suicide risk (e.g., Brent et al. 2009a) in a range of clinical populations. Of special importance to clinical research and practice is the difficulty of predicting future suicidal events, yet studies show that the scale can be used to predict short-term risk of suicidal behavior (Posner et al. 2011). The scale also shows sensitivity to population-specific predictors of suicidal behavior (Gipson et al. 2015). In large-scale medication studies and outpatient settings, the scale is able to identify patients who will engage in suicidal behaviors with significant accuracy (Mundt et al. 2013; Viguera et al. 2015).

The number of studies examining psychometric properties of the scale in specific populations and settings is also growing, including cross-culturally (e.g., Teti et al. 2014). Linguistic validation of the scale is occurring on a large scale with 116 country-specific language versions available as of 2015 (Grataloup et al. 2013). Since its development for use with adolescent suicide attempters (Brent et al. 2009b), the use of the scale with pediatric populations has been growing. There are now a considerable number of studies in youth ages 6 and older across many clinical settings that are using the scale – from juvenile justice to emergency departments to treatment studies of depression and ADHD (Findling et al. 2013; Kerr et al. 2014; King et al. 2015; Prakash et al. 2012).

Psychometric property	Adults	Children	Study
Convergent validity	x	x	Posner et al. (2011) Kerr et al. (2014)
Divergent validity	x	x	Posner et al. (2011) Kerr et al. (2014)
Predictive validity	x	x	Brent et al. (2009) Posner et al. (2011) Mundt et al. (2013) Gipson et al. (2015) Horwitz et al. (2015)
Sensitivity to change	x	x	Posner et al. (2011)
Internal consistency	x	x	Posner et al. (2011)
Inter-rater reliability	x	x	Kerr et al. (2014) Brent et al. (2009) Hesdorffer et al. (2013) Arias et al. (2014)
Sensitivity and specificity	x	x	Posner et al. (2011) Mundt et al. (2013) Viguera et al. (2015)
Positive predictive value (PPV)	x	x	Mundt et al. (2013) Viguera et al. (2015)
Negative predictive value (NPV)	x	x	Mundt et al. (2013) Viguera et al. (2015)

Fig. 3.1 The C-SSRS: psychometric properties

Conclusion

In advancing suicide prevention, it is difficult to overemphasize the importance of a uniform method for suicide risk identification. The wide implementation of the C-SSRS is changing the way we accumulate knowledge about the etiology, epidemiology, and treatment of suicide. If until recently at-risk patients were excluded from studies, steps are now being taken towards the standardization of

risk assessment and facilitation of their inclusion, thereby improving generalizability of research findings to a wider range of patients (McCall et al. 2015). With the new appreciation for standard descriptive language, there is a current trend towards developing centralized banks of measures with a long-term goal of creating large-scale data sharing that is necessary in the study of rare lethal conditions such as suicide.

Our ability to name some of the most difficult human experiences in plain words with definitions that are understandable to all, regardless of their age, education, profession, and nationality, creates an entirely new culture of communication and understanding. Asking becomes less of a taboo, sharing information is normalized, and the barriers of isolation and silence become more permeable. Decisions about what can be done to help become clearer across all sectors of society. This is the significance of an easily mastered, cost-effective, and empirically supported tool such as the C-SSRS.

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Temperament in Suicidal Behaviour

4

Zoltan Rihmer and Xenia Gonda

Abstract

Suicide shows a very strong association with affective illnesses, yet not all mood disorder patients commit suicide; therefore analysing affective pathology for those characteristics which differentiate suicidal and non-suicidal patients would be a key step in understanding the pathology of suicidal behaviour. One such phenomenon associated with affective illnesses and suicidal behaviour as well is affective temperaments. While the different affective temperamental types (depressive, anxious, irritable, cyclothymic, and hyperthymic) have all been shown to have some pattern of association with suicidal behaviour, results most consistently point to a key role for cyclothymic temperament for increasing the risk of suicide and suicide attempts via multiple mechanisms and not only in case of mood disorders but also in other psychiatric illnesses and in healthy samples. Hyperthymic temperament, on the other hand, seems to have a protective effect. Although the biological substrate of the association between affective temperaments and suicidality is not well understood, one possible factor may be the presence of the 5-HTTLPR s allele, which is associated with affective temperaments carrying a depressive component and also violent suicidal behaviour. Understanding the role of affective

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temperaments in the development of suicidal behaviour may bring us closer not only to understanding the etiopathology of suicide and may provide us with important new research models but may also mean new targets for screening and intervention.

4.1 Introduction

Suicidal behaviour, a complex multicausal human phenomenon aimed at self-destruction, is the most tragic event of our human life, deleterious not only for its victim but also causing serious distress among relatives and friends as well as among treating doctors, at least in cases when the victim was in contact with medical care. Because suicide is a rare event in the community, its precise prediction in individual cases is very difficult. However, suicidal behaviour (completed suicide and suicide attempt) is quite frequent among psychiatric patients who contact different levels of healthcare some weeks or months before their death (Luoma et al. 2002). Untreated unipolar or bipolar major depressive episode is the main clinical substrate of completed suicide, accounting for 56–87 % of the cases (Rihmer 2007; Hawton and van Heeringen 2009). What is most important in this respect is that suicidal behaviour in mood disorder patients is a state- and severity-dependent phenomenon and that suicidality decreases/vanishes after the clinical recovery (Rihmer 2007; Rihmer and Gonda 2013). This underscores the importance of early recognition and appropriate acute and long-term treatment/care of patients with mood disorder in preventing suicidal behaviour. However, as the majority of depressed patients never complete suicide and about half of them never attempt it, special clinical (agitated/mixed depression, insomnia, hopelessness, etc.), psychological (premorbid personality, coping style, etc.), and psychosocial risk factors (early and current adverse life events, permanent stressors, etc.) also play a significant contributory role (Rihmer 2007; Hawton and van Heeringen 2009). Suicide risk factors are additive in their nature and a constellation of these factors may help identify those patients who are at an especially high risk for suicide.

4.2 Personality Features and Suicidal Behaviour

As for psychological characteristics, it is well known for many decades that suicidality is also associated with certain personality features, such as aggressive/impulsive traits, hopelessness, and pessimism, and the risk increases if these traits are present in combination (Mann et al. 1999; Oquendo et al. 2004; MacKinnon et al. 2005). Impulsivity, a characteristic trait in bipolar patients, was associated with nonlethal suicide attempts in general samples, and in case of affective patients, it is also associated with severe suicide attempts and completed suicide (Swann et al. 2005). Impulsivity distinguishes suicidal and non-suicidal affective inpatients and controls and in bipolar patients suicidal intent correlated with impulsivity even when controlling for aggression. Impulsivity increases suicide risk when combined

with depression, and even modest manic symptoms during bipolar depressive episodes are associated with a greater level of impulsivity and higher rates of suicide attempts (Swann et al. 2005). Several studies have shown that suicidal behaviour was also associated with aggressive traits in the case of major depression and bipolar disorder (Mann et al. 1999; Grunebaum et al. 2006; Hawton and van Heeringen 2009). Bipolar patients with a family history of suicidal behaviour and exposed to childhood physical and/or sexual abuse are at greater risk for suicide attempts (Carballo et al. 2008) and impulsivity seems to be the link between childhood abuse and suicidal behaviour (Braquehais et al. 2010). In a study on bipolar patients, harm avoidance and persistence as measured by Cloninger's TCI were significantly related to prior suicide attempts (Engstrom et al. 2004). Hostility was also found to be a suicide attempt risk factor, while optimistic personality features and many reasons for living an important protective factor in bipolar disorder (Chaudhury et al. 2007).

4.3 Affective Temperaments and Suicidal Behaviour

However, only in the last decade did it become evident that affective temperaments, known to be subclinical manifestations and precursors of major mood disorders (Akiskal et al. 2003; Kochman et al. 2005; Pompili et al. 2008), are also predisposing (risk) factors for suicidal behaviour. Classically, temperament carries the temporally stable biological "core" of personality and plays a role in establishing an individual's activity levels, rhythms, moods, and related cognitions as well as their variability, while personality, a broader phenotype, refers also to acquired characterologic determinants and interpersonal operations (Akiskal et al. 1983; Bouchard 1994). The concept that different kinds of temperament are constitutionally based types of behaviour can be traced back to the ancient humoral theory of Hippocrates (Akiskal 1996). About 100 years ago, Kraepelin described four basic affective dispositions (depressive, manic, cyclothymic, and irritable) which he believed were subclinical forms and many times precursors of major affective disorders and had their roots in adolescence. He also described that these four basic affective dispositions could be frequently found in blood relatives of manic-depressive patients (Kraepelin 1915). The modern concept of affective temperaments, as operationalized in research originally conducted at the University of Tennessee, Memphis, USA, by Akiskal and his coworkers (Akiskal and Mallya 1987; Akiskal et al. 1977) was based primarily on the works of Kraepelin (1915) and Kretschmer (1936) and was derived from both theoretical considerations and clinical observations yielding five affective temperaments (depressive, cyclothymic, hyperthymic, irritable, and anxious). This concept was turned into an instrument called as TEMPS-A (Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire version) for assessing depressive, cyclothymic, hyperthymic irritable, and anxious temperaments. This autoquestionnaire version requiring just simple "yes" or "no" answers contains 110 items (109 for males) (Akiskal et al. 2005a, b).

While the role of temperamental factors in suicidal behaviour has been known for decades (Maser et al. 2002), recent studies on this field have shown a strong

relationship between specific affective temperament types and suicidal behaviour. Compared to bipolar II patients without cyclothymic temperament ($n = 120$), bipolar II patients with such temperament ($n = 74$) reported significantly more frequent lifetime suicide attempts (38 % vs 49 %) and experienced more current hospitalization for suicidal risk (50 % vs 61 %) (Akiskal et al. 2003). Other studies have also shown that bipolar I, bipolar II, and unipolar major depressive disorder patients with a cyclothymic temperament have a significantly higher rate of prior suicide attempts and lifetime/current suicidal ideation than noncyclothymic patients (Young et al. 1995).

Recent studies have found that in contrast to hyperthymic temperament which seems to be a protective factor against suicidal behaviour (Vazquez et al. 2010; Pompili et al. 2008, 2012; Rihmer et al. 2009a), cyclothymic, irritable, depressive, and anxious affective temperaments were significantly overrepresented in suicide attempters or in mood disorder inpatients with high current suicide risk (Rihmer et al. 2009a; Pompili et al. 2008, 2012). Pompili et al. (2008) investigated the affective temperament profile of 150 consecutively hospitalized psychiatric patients; 80 % of them have had unipolar, bipolar I, or bipolar II major depressive episode and 41 % have had current suicidal risk at admission. They found that the 62 suicidal patients scored significantly higher on depressive, cyclothymic, irritable, and anxious and significantly lower on hyperthymic subscales of the TEMPS-A than the 88 patients with no suicidal risk. Using the same instrument, we also compared the affective temperament types of 150 consecutively investigated nonviolent suicide attempters (106 females) and 302 age-, sex-, and education-matched controls. Compared to controls, both female and male suicide attempters scored significantly higher in the four of the five affective temperaments, containing more or less of a depressive component (depressive, cyclothymic irritable, and anxious), while no significant difference was found for the hyperthymic temperament. Consequently, the dominant forms of depressive, cyclothymic, irritable, and anxious temperaments were significantly more common and hyperthymic temperament was (nonsignificantly) less frequent among the attempters (Rihmer et al. 2009a). Our recent study on 346 adult inpatients with major mood disorders, 81 % of patients with prevailing cyclothymic-depressive-anxious temperament had mild to severe suicidal risk on the M.I.N.I. versus only 42 % of those with a prevailing hyperthymic temperament. Sixty-four percent of patients with cyclothymic-depressive-anxious temperament had high suicide risk according to the Beck Hopelessness Scale versus only 13 % of patients with hyperthymic temperament (Pompili et al. 2012). The findings of these three studies (Pompili et al. 2008, 2012; Rihmer et al. 2009a) support the strong relationship between depression and suicidal behaviour even on temperamental level and suggest a possible protective role of hyperthymic temperament at least in the case of suicide attempts or mood disorder patients with current suicidality. The significantly higher cyclothymic and irritable scores among suicide attempters with childhood abuse also (Rihmer et al. 2009b) show the modifying role of early adverse events on the personality development in general and on the affective temperament in particular. The significantly higher cyclothymic and irritable scores among suicide attempters with childhood abuse also show the modifying role of early adverse

events on the personality development in general and on the affective temperament in particular.

In addition, cyclothymic temperament significantly predicted future bipolar transformation and suicide attempts in adult (Goto et al. 2011) and juvenile depressives (Kochman et al. 2005). In a large-scale French study, it has also been found that cyclothymic temperament was one of the eight risk factors (such as young age at onset, depressive or mixed polarity of first episode, stressful life events, etc.) statistically significantly associated with lifetime suicide attempts in patients with bipolar I disorder (Azorin et al. 2009).

Affective temperaments seem to be related to suicidal behaviour also in non-clinical samples. Investigating the affective temperamental profile, as measured by TEMPS-A, among 1381 college students in Austria it has been found that lifetime suicidal ideation was associated with the depressive, cyclothymic, and anxious temperament in both sexes and the irritable temperament in males and no relationship was found regarding hyperthymic temperament (Skala et al. 2012). In a sample of public school students ($N = 1713$, aged between 12 and 20 years) in Portugal, the history of prior self-harm was associated, in both genders, with a significant deviation on depressive, cyclothymic, and irritable dimensions of the TEMPS-A, and again, hyperthymic temperament was unrelated to self-harm (Guerreiro et al. 2013). However, marked affective temperaments that can be detected in about 15–20 % of the general population (Rihmer et al. 2010; Gonda et al. 2011b) become suicide risk factors only during major depressive episode as persons with marked affective temperament have a much higher chance to develop major mood episodes and particularly the combination of cyclothymic or irritable personality traits and major depressive episode results in a mixed depressive episode that carries very high suicide risk (Rihmer 2007; Rihmer et al. 2010). Suicide attempters with cyclothymic and irritable affective temperaments report significantly more frequently childhood physical and/or sexual abuse (Rihmer et al. 2009b) suggesting that besides impulsivity (Braquehais et al. 2010), cyclothymic or irritable temperaments are further mediating variables between these early negative life events and adult suicidal behaviour (Rihmer et al. 2009b).

4.4 How Can a Specific Affective Temperament Predispose for Suicidal Behaviour?

Currently, we have limited understanding concerning what mediates the how effects of these affective temperament on suicidal behaviour. Cyclothymic temperament may influence suicide risk on multiple levels, from determining emotional reactivity in stressful situations at the level of the personality, through determining illness and illness course characteristics, to influencing within-episode dynamics. Cyclothymic temperament is associated with rapid mood fluctuations, mood reactivity, and emotional instability contributing to extreme distress. Furthermore, cyclothymic temperament makes adapting to environmental changes and adversities difficult. Combined with other traits, cyclothymic temperament also contributes to a darker

and more risk-taking impulsive side of hypomania, and this, as well as the instability associated with this affective temperament, increases the risk of encountering stressful life events and comorbid conditions which play a role in triggering mood episodes and suicide. The temperamental reactivity embodied in cyclothymia also seems to be a stable trait constituting a basis for rapid shifts between inhibition and disinhibition providing the drive and energy for the suicidal act (Pompili et al. 2012). The relationship between affective temperaments and suicidal behaviour is, however, more complex than the simple additive effect of depressive personality components and current major depressive episode, as cyclothymic temperament seems to be also a contributor to suicidality in patients with other diagnosis than major depression, The presence of cyclothymic temperament increases suicide risk not only in affective disorders but in other illnesses as well, such as obsessive-compulsive disorder (Hantouche et al. 2003). The central role of cyclothymic oscillations of mood, thinking, and behaviour in the evolution of suicidal process has been shown by studies reporting that history of rapid mood switching was associated with increased likelihood of prior suicidal ideation or attempt (MacKinnon et al. 2005), and variability of suicidal ideation was a significantly better predictor of prior suicide attempts than duration and intensity of ideation (Witte et al. 2005).

Hyperthymic temperament, on the other hand, may be protective through being associated with lower levels of hopelessness, as well as high energy, lifelong drive, ambition, and such social-interpersonal skills which enables more effective coping with inner and outer events and make the individual less vulnerable to mood changes contributing to more effective defence against impulses toward suicide (Pompili et al. 2008; Vazquez et al. 2010). It should be also noted that recently a strong relationship has been found between psychological resilience and hyperthymic temperament both in depressive and healthy individuals (Kesebir et al. 2013).

Furthermore, the biological substrate of the association between affective temperaments and suicidality may be carried by the presence of the "s" or short allele of the 5-HTTLPR polymorphism of the serotonin transporter gene, known to be associated with suicidal behaviour (Gonda et al. 2011b) and affective temperaments as well (Gonda et al. 2006). Even more interestingly, the s allele is also associated with other endophenotypes related to suicidal behaviour, such as aggressiveness (Gonda et al. 2011a) or neuroticism (Gonda et al. 2009); therefore this genetic polymorphism seems to convey some kind of general vulnerability, which, depending on complex gene x gene and longitudinal and cross-sectional gene x environment interactions, may be expressed in various forms predisposing to suicidal behaviour, including the marked manifestation of affective temperaments (Gonda et al. 2011a). Affective temperaments, especially the frequency of their presentation in dominant form, show a characteristic geographical distribution, which also shows and excitingly parallel pattern to the distribution of the score of cultural indexes described by Hofstede, which in turn has been related to prevalence of affective illness (Gonda et al. 2011c). Hofstede's individualism-collectivism score was also found to show a parallel geographical distribution to the 5-HTTLPR s allele (Chiao and Blizinsky 2010). These above factors already outline a complex and delicate network of important and yet unidentified and undetected etiological factors in the background

of suicidal behaviour, determining its biological as well as psychosocial factors. However, affective temperaments seem to play a central role in this multilevel network, mediating the effects of a possible genetic background and psychosocial determinants of suicidal behaviour both on the individual and possibly on a higher and more complex social level.

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The Addiction to Suicidal Behavior

5

Hilario Blasco-Fontecilla

Abstract

Addictions have traditionally been restricted to substance use disorders. In the context of behavioral addictions, some individuals could also be addicted to the repetition of suicidal behavior (SB). In 1998, Tullis proposed a theory of suicide addiction, suggesting that individuals addicted to SB might have three characteristics: the presence of childhood trauma, mood disorder, and multiple addictions. In a series of recent studies, we have refined the addictive hypothesis of SB and confirmed that around 10 % of suicide attempters can develop an addiction to SB. In addition to presenting our studies, we briefly review the psychological and neurobiological mechanisms underlying the addiction to SB. Additionally, we suggest that the most evident targets to halt the development of the addiction to SB are the opioid, stress (corticotropin-releasing factor, CRF), and dopaminergic systems.

5.1 Introduction

Addictions have traditionally been restricted to substance use disorders. However, Goodman adapted and merged the DSM-IV criteria of substance dependence with those of pathological gambling (Goodman 1990). Thus, he expanded the focus of addictions by defining a behavioral addiction "as a process whereby a behavior […] is employed in a pattern characterized by loss of control and continuation despite significant negative consequences. It is not the type of behavior, its frequency or its social acceptability that determines whether a behavior pattern qualifies as an addiction […]." His statement preceded a Copernican change that allowed expanding addictions to include behavioral addictions such as shopping, gambling, suntanning, internet use, work, exercise, or even love and sex (Cassin and von Ranson

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2007; Favazza 1989; Goodman 1992; Kourosh et al. 2010; Reynaud et al. 2010; Sanchez-Carbonell et al. 2008; Tantam and Whittaker 1992; Tao et al. 2010). Indeed, behavioral addictions are frequent and share many characteristics with substance addictions (i.e., tolerance, withdrawal, and relapse) (Grant et al. 2006). Substance and behavioral addictions share common neurobiological and genetic underpinnings, and psychosocial factors may account for the variability of expressions of addictions within individuals (Ibanez Cuadrado 2008; Shaffer et al. 2004). In this context, it is surprising to find the paucity of studies testing the hypothesis that some individuals could also be addicted to the repetition of suicidal behavior (SB). The purpose of this chapter is to briefly examine the literature and to offer an explanatory model on the addiction to SB.

5.2 Background

In contrast with the lack of studies addressing a putative addiction to SB, there is substantive literature suggesting that non-suicidal self-injury (NSSI) could be viewed as an addictive behavior (Victor et al. 2012). For instance, Faye suggested that the heightened negative emotional state preceding NSSI is similar to the aversive withdrawal clinical symptoms experienced by drug users (Faye 1995). More recently, Washburn et al. (2010) reported that individuals displaying NSSI often have strong urges to self-injure (Washburn et al. 2010). Furthermore, although literature on this issue is still controversial, some authors have reported that endogenous opioids might be reduced in individuals who engage in NSSI (see Victor et al. 2012 for a review).

As for SB, in 1998, Tullis proposed a theory of suicide addiction (Tullis 1998) that described individuals addicted to SB as having three characteristics: the presence of childhood trauma, mood disorder, and multiple addictions. Until recently, the only study that tested this compelling hypothesis was a report of three cases (Mynatt 2000). One can review the literature on repeated SB that was collected without the influence of Tullis's model to explore whether Tullis's proposed characteristics are related to the repetition of SB or not. Our reading of the literature supports Tullis's hypothesis for two characteristics; both childhood abuse and addictions are associated with repetition of SB (Monnin et al. 2011; Mynatt 2000; Ystgaard et al. 2004). The evidence for mood disorders is, however, more controversial. For instance, Kreitman and Casey (1988) reported that the presence of mood disorders was negatively associated with repetition of SB. Furthermore, one of our studies recently found that both childhood abuse and substance dependence, but not mood disorders, were associated with major repetition of suicide attempts (Blasco-Fontecilla et al. 2014b).

In 2012, we refined Tullis's theory of suicide addiction by proposing that major repetition of SB could also be considered as another behavioral addiction within Goodman's paradigm (Blasco-Fontecilla 2012). Major repeaters (individuals with ≥5 lifetime suicide attempts) represent approximately 10 % of all suicide attempters (Barnes 1986; Bille-Brahe et al. 1996; Kreitman and Casey 1988). These individuals are at higher risk of suicide completion (King et al. 1995; Lewinsohn et al. 1994), are heavy consumers of health resources, and pose a challenge to clinicians (Kreitman

and Casey 1988). We have recently proposed that many of these individuals are addicted to SB (Blasco-Fontecilla et al. 2014b). In the first study comparing with non-major repeaters (<5 suicide attempts), major repeaters were more likely to be female and more likely diagnosed with anorexia nervosa or substance dependence and had higher levels of trait anger with lower levels of anger expression-out. In a second study, we demonstrated that major repeaters provided different reasons than non-major repeaters for the more lethal suicide attempts. Major repeaters significantly more frequently endorsed automatic positive reinforcement ("To feel something, because you felt numb or empty") as an explanation for their SB than the remaining suicide attempters. We found that relieving emptiness may be an important, but not the only, pathway to major repetition of suicide attempts (Blasco-Fontecilla et al. 2015). This is important because, in contrast with other authors who have suggested that NSSI is perpetuated primarily through negative reinforcement (i.e., the removal of negative emotions) (Victor et al. 2012), our findings suggest that major repetition of suicide attempts is perpetuated mainly through positive reinforcement (i.e., the generation of emotions). Finally, in a third study, we explored whether major repeaters are addicted to SB or not using seven criteria: tolerance (Criterion 1), withdrawal (Criterion 2), loss of control (Criterion 3), problems in quitting/cutting down (Criterion 4), much time spent using (Criterion 5), substantial reduction in activities (Criterion 6), and adverse physiological/physical consequences (Criterion 7) (Blasco-Fontecilla et al. 2014a). Total dependence on SB was indicated by the presence of three or more of the seven criteria in the last 12 months. This cross-sectional study at Puerta de Hierro University Hospital (Madrid, Spain) recruited 118 suicide attempters including 8 major repeaters (7 %, 8/118), who were all females. The association between each SB addiction criterion, physiological dependence and total dependence with major repeater status was tested for significance and for effect size with odds ratios (ORs) and their 95 % confidence intervals. As hypothesized, major repeaters met significantly higher frequency of criteria for total dependence on SB, OR = 62.9 (6.4–615). Indeed, 83 % of major repeaters met criteria for dependence on SB. Interestingly, in a similar study focused on NSSI, 98 % of individuals endorsed at least three of the addictive criteria; and 81 % endorsed more than five criteria (Nixon et al. 2002). In our study, a backward stepwise logistic regression model was used to provide an OR between major repeater status and total dependence status corrected by confounding variables (Blasco-Fontecilla et al. 2014a). Age, panic disorder without agoraphobia, borderline personality disorder, history of psychiatric inpatient admission, and total dependence on SB were introduced as independent variables with major repeater status as the dependent variable. The model selected total dependence and age as the remaining significant variables in the last step. Accordingly, we concluded that major repeaters appear to be addicted to SB (Blasco-Fontecilla et al. 2014a).

5.3 Psychological Mechanisms

The cathartic effect of SB (Farberow 1950) and Beck's "sensitizing" hypothesis of SB (Beck 1996) may explain some aspects of the addiction to SB. Beck (1996) suggested that previous SB sensitizes suicidal thoughts and behaviors, such that they

become more autonomous and easily precipitated. Self-aggression ameliorates the physical and emotional tension that precedes SB, depressive and anxiety symptoms, and painful emotions (i.e., hopelessness, emptiness) (Davis 1990; Jallade et al. 2005; Sarfati et al. 2003; van Praag and Plutchik 1985; Walker et al. 2001). In a pilot fMRI study with eight female individuals, mental pain triggering SB was associated with decreased prefrontal activity, whereas "planning and acting out suicidal impulses in response to mental pain" was related to increased activity in the frontal cortex, suggesting that SB reduces mental pain (Reisch et al. 2010). The cathartic effect might be explained by either emotional venting of an unbearable physical and/or emotional state (Jallade et al. 2005; van Praag and Plutchik 1985) or mobilization of interpersonal support (e.g., caring family, medical attention) (Jallade et al. 2005; Walker et al. 2001). Indeed, SB can be used as a signaling strategy within the "bargaining model" of depression, which suggests that SB is a way to impose costs to the social group – family, friends, and colleagues – where there is a conflict (Hagen 2003). In this context, some suicide attempters might raise support from their relatives and, therefore, gain a positive reinforcing effect from SB.

In this regard, Stanley and colleagues suggested that suicide attempters with a history of self-mutilation are a unique subpopulation of suicide attempters who use self-mutilation to deal with mental pain (Stanley et al. 2001). Others suggested that multiple suicide attempters may use self-mutilating behaviors as a way of self-regulating their negative emotions in the short term (Esposito et al. 2003). In the long term, however, self-mutilating behaviors increase negative affectivity and become another stressor (Linehan 1993). Esposito et al. (2003) suggested that suicide attempts may then replace self-mutilation as a way of modulating negative emotions in multiple suicide attempters. In a study comparing 35 suicide ideators and 32 attempters, suicide attempters, relative to suicide ideators, were less likely to display anger after an acute suicidal episode (Negron et al. 1997). Thus, after an initial suicide attempt, suicide repetition may become a coping strategy for dealing with anger, anxiety, and other painful emotions. Beck (1996) suggested that previous SB sensitizes suicidal thoughts and behaviors, such that they become more autonomous and easily precipitated. As suicidal episodes become more easily triggered by stressful life events, they also become more severe and persistent. In other words, repetition of SB may have a sensitization effect. Beck's "sensitizing" hypothesis of SB has gained some empirical support (Bradvik and Berglund 2011; Joiner and Rudd 2000; Joiner et al. 2000). And even after prolonged suicide-free periods, there is the risk of relapse, often precipitated by the same suicide-associated life events, probably in a similar way to that of drug addiction (Hyman 2005).

5.4 Neurobiological Mechanisms

Humans and animals share major neurobiological changes in substance use disorders, including a compromised reward system (dopamine and opioid peptides), overactivated brain stress system (corticotropin-releasing factor, CRF), and

dysregulation of orbitofrontal/prefrontal cortex function and amygdala (Koob 2006; Wise and Koob 2014). All three systems, opioid, dopaminergic, and hypothalamic-pituitary (HPA) axis, interact in the forebrain (Lovallo 2006; Volkow and Wise 2005) and can be activated either by psychoactive drugs or behaviors (Shaffer et al. 2004).

In the light of our previous findings, it is reasonable to hypothesize that the addiction to SB might also involve a compromised functioning of the brain's motivational systems, including the mesocortical dopamine reward system, the endogenous opioid systems (Grigson 2002; Volkow and Wise 2005; Wise and Koob 2014), and an overactivation of the stress system (Lovallo 2006; Wise and Koob 2014). Immediate relief of psychological (mental) pain is probably associated with endogenous opioid release in the central nervous system, as is the case in self-mutilation (Hicks and Hinck 2008). Indeed, in a recent systematic review, the authors suggested that neuropeptides are involved in the pathophysiology of SB (Serafini et al. 2013). The authors concluded that there was an association between SB and some neuropeptides such as CRF, VGF, and neuropeptide Y (NPY), which are key neuromodulators of emotional processing. Moreover, several authors have demonstrated elevated endogenous opioid release following stressful events. For instance, Christie and Chesher (1982) showed that chronic stress in mice produces opioid dependence. Coid et al. (1983) also reported that prolonged mutilating elevates met-enkephalins. This opioid release may ultimately produce tolerance and addiction in vulnerable subjects (Blasco-Fontecilla 2012). In addition, both acute and chronic stress increase the risk of taking drugs (Volkow and Wise 2005), and CRF is involved in the vulnerability of relapse (Sarnyai et al. 2001) and drug withdrawal (Kreek and Koob 1998). CRF is central to both stress and drug withdrawal responses. Indeed, gene polymorphisms of the CRF receptors have been related to exacerbated stress responses and the vulnerability to develop drug addiction (Logrip et al. 2011).

Here, we would like to stress that while dopaminergic and serotonergic dysfunction have been related to SB (Mann and Currier 2007), there is surprisingly little information about the relationship between the endogenous opioid system – i.e., beta-endorphins- and SB. This is somewhat surprising given the role of psychological pain in suicide (Tossani 2012) and the growing evidence linking self-harm and self-injurious behaviors, behaviors closely related to suicide attempts, with the stress and opioid system (Stanley et al. 2010). Indeed, β-endorphin and ACTH, which controls cortisol secretion, are derived from the same precursor, pro-opiomelanocortin (POMC) (Dent et al. 1986; Oquendo et al. 2014). Furthermore, in a recent study of patients displaying repetitive self-injurious behavior (SIB), the authors found that higher probabilities of sequential SIB – in other words, what they called "sequential dependence" to SIB – were associated with lower levels of ACTH measured in the morning or evening (Sandman et al. 2008). Additionaly, there is a strong correlation between the HPA stress system (CRH, ACTH) and beta-endorphins (Traskman-Bendz et al. 1992) (See Fig. 5.1).

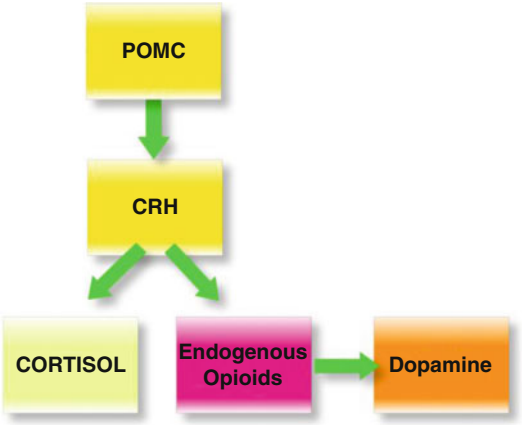

Fig. 5.1 Basic neurobiological mechanisms involved in the addiction to SB

5.5 Significance

There is limited understanding of the factors contributing to suicide attempt repetition and the hypothesis of the addiction to SB offers a plausible explanation for major repetition of SB. This hypothesis may have an important impact in the way we treat suicide attempters characterized by major repetition of attempts. Based on our previous studies, we estimate that around 10 % of suicide attempters become dependent on SB. They are heavy healthcare consumers and pose a challenge for clinicians. If the hypothesis of addiction to SB is further confirmed, this may allow changes in their treatment and help in reducing the associated economic cost associated to the repetition of SB.

As said before, the opioid, dopaminergic, and hypothalamic-pituitary (HPA) axis systems interact in the forebrain. Accordingly, the most evident targets to halt the development of the addiction to SB are the opioid, stress (CRF), and dopaminergic systems. Regarding opioids, yet in 1989, some advocated for clinical trials of opiate antagonists – i.e., naltrexone and buprenorphine – in treating patients with personality disorders and self-injurious behavior (SIB), as they have been found to have elevated levels of plasma beta-endorphin (Konicki and Schulz 1989). Furthermore, the CRF (stress) system has huge potential as a target for pharmacological development (Kreek and Koob 1998). Thus, CRF receptor antagonists, particularly CRF1 antagonists – i.e., antalarmin – show promise for the development of pharmacological treatments for drug abuse and addiction (Logrip et al. 2011). Importantly, CRF1 antagonists could have a lasting effect to blunt the increased stress sensitivity in dependent individuals (Logrip et al. 2011). As for the dopaminergic system, many animal models for SIB share a compromised striatal dopamine system, and the same accounts in several human conditions (Visser et al. 2000). Given that striatal dopamine receptors are coupled to L-type calcium channels, Blake et al. (2007) confirmed their hypothesis that blockers of these channels, such as nifedipine, suppress

SIB in four unrelated animal models (Blake et al. 2007). Unfortunately, 7 years later there is not a single study testing this compelling hypothesis in human beings.

Additionally, given the heterogeneity of SB, other treatments might also be helpful to halt the development of the addiction to SB. Following our model, any treatment alleviating psychological pain might halt the development of the addiction to SB. For instance, lithium, known to have a specific "antisuicidal effect" independently of mood-stabilizing effect (Ahrens and Muller-Oerlinghausen 2001), has an antinociceptive ("anti-psychological pain") action probably mediated through the opioid system (Banafshe et al. 2012). Finally, a recent but promising avenue of research is the use of medications with effects on glutamatergic transmission such as gabapentin, lamotrigine, topiramate, acamprosate, memantine, modafinil, D-cycloserine, and N-acetylcysteine (Olive et al. 2012). As these authors stressed, "substantial evidence has accumulated indicating that ligands acting on glutamatergic transmission are also of potential utility in the treatment of drug addiction, as well as various behavioral addictions such as pathological gambling" (Olive et al. 2012).

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Suicidal Crisis in the Digital Age

6

L. Jehel, R. Arnal, D. Carmelo, and N. Howard

Abstract

Suicide is a growing problem around the world. A suicidal crisis is a situation where a person attempts to kill himself/herself or contemplating to do so. The digital age has played a role in increasing suicidal crisis not only because of cyberbullying but also because of the loss of interpersonal connection that can happen as a result of a digitalized society. This situation requires various methods of prevention and intervention to protect people from harming themselves. There is a great need to identify warning signs as early as possible. Prevention factors such as community support or medical or psychiatric intervention can help patients who are heading toward a crisis. We suggest that novel detection methods that leverage everyday technology and are widely accessible should be developed.

6.1 Introduction

A suicidal crisis is an intense period of imbalance. Intense emotional and physical pain and suffering that can lead to an emergence of suicidal ideation and planning an act of self-harm (Karch et al. 2012). The state leading up to a suicidal crisis is fragile, wherein a single event at work or with family can accelerate the process and trigger suicidal thoughts. This vulnerable situation makes it difficult to identify warning signs because symptoms of distress may not be outwardly noticeable. The progression of a suicidal crisis is illustrated by Fig. 6.1.

In France, where the suicide rate is higher than all of Europe and twice that of the UK and Spain, suicide is the second leading cause of death among 25–34-year-olds and the third most common cause of death among 15–24-year-olds (Centers for

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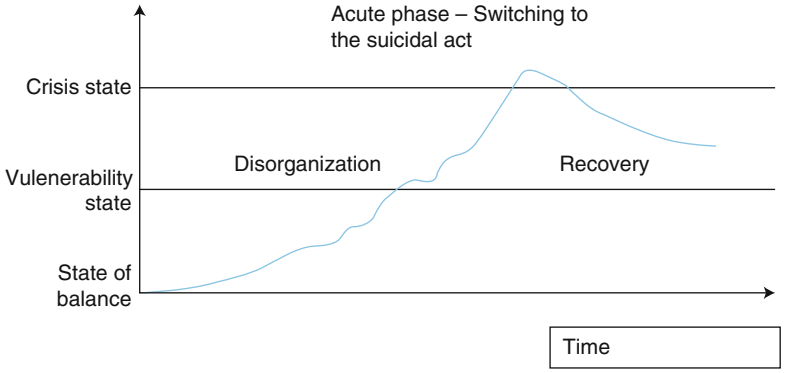

Fig. 6.1 Model of the evolution of the psychological state of the suicidal crisis (Séguin and Terra 2004)

Disease Control and Prevention 2007; Karch et al. 2012). Among French farmers, suicide is the third leading cause of death, overall (Brossard et al. 2013). In the USA, suicide is the tenth leading cause of death, averaged across all age groups (CDC 2013). Males commit suicide at four times the rate of females, representing 77.9 % of all suicides (CDC 2013). In 2012 suicide was the second leading cause of death among ages 15–29 globally (WHO). In the USA suicide is the third leading cause of death for ages 10–14 and the second among ages 15–34 (CDC 2013). Even higher rates exist within particular risk categories. Veterans are at 41–61 % higher risk of suicide relative to the US general population (Kang et al. 2015). Although youth and veterans both represent high-risk groups, the highest rate of suicide in the USA is actually among white males 45–64 years old.

It is estimated that over 90 % of people who commit suicide had a mental illness at the time of their death (Bertolote and Fleischmann 2002; Sharma 2015), depression being the most common. Sadly, these disorders are often unrecognized, undiagnosed, or treated inadequately. After depression, the most common disorders among those who commit suicide are mood disorders, substance use disorders, schizophrenia, and personality disorders (Bertolote and Fleischmann 2002). Most of these findings regarding the connection between underlying mental disorders and suicide have come from "autopsy" studies. This is because detection of mental illness before suicide occurs presents many challenges, one being refusal of the patient to seek help and another being the subjective methods of diagnosis used by clinicians today. The most common cause of suicide is depression, often accompanied by the loss of connection to others, employment, or a loved one (Sharma 2015). Patients with neurological disorders such as schizophrenia, bipolar disorder, Huntington's disease, PTSD, TBI, epilepsy, and countless others are at a significantly higher risk of suicide. The period of vulnerability that precedes a suicide attempt requires the identification of psychiatric disorders, sexual addictive behaviors, and a history of aggression. Courtet et al. (2010) remind us that these are important because they constitute priority risk factors and areas for effective therapeutic intervention.

In our globalized world of today, most perspectives concerning the issue of suicide are homogenized across societies. However, there are some distinct ethnic groups that attach a different meaning to suicide that differs from the westernized ideation of suicide. The prevalence of suicide in these populations shows that under the term "suicidal behavior," multiple realities can coexist depending on the patient's culture. Take the example of Japan, which today still has a very rich vocabulary to describe suicide: "kobara" suicide for the sake of children, "inseki jisatsu" suicide to avoid shame, or "funshi" suicide to express revolt.

6.2 The Effect of the Digital Age

Today, technology is a driving force of the ever-increasing pace of change in the world. Cultural, and geopolitical shifts follow in its wake. The world is changing more rapidly than ever before in history and this rate of change will only continue to accelerate.

Social media, mobile phones, smart tablets, and smart watches – the list continues to grow. What is the effect of technology on suicide? Certainly technology has advanced medicine and psychiatry; with the advent of telemedicine, patient-physician relations are being transformed as new and more personalized therapies are being implemented (Agius-Muscat 2000; Ahmed et al. 2014; Singhroha 2014). Technology has also had a significant influence on education, social interaction, the workplace, and even family life (Chen and Tseng 2012; Greenwood et al. 2012; Mears 2012). Communication has probably been most affected by the digital age as we now live in a hyper-loquacious network of e-mailing, texting, Facebook, Instagram, Twitter, and other forms of social media that are nonstop 24/7.

Most of the suicide literature to date has focused on the effect of social media on suicide rates in youth, particularly cyberbullying (Alao et al. 2006; Keith and Martin 2005; Vandebosch and Van Cleemput 2008; Wang et al. 2011). Not only has there been an increase in chatrooms and forums about preventing suicide, there are also resources that encourage and aid in committing suicide suggesting that the internet may even be a source of suicide contagion (Robertson et al. 2012). Bonanno and Hymel (2013) found that involvement in cyberbullying, as either a victim or a bully, significantly contributed to the prediction of both depressive symptomatology and suicidal ideation, far more than involvement in traditional forms of bullying (physical, verbal, relational).

As technology continues to proliferate, manufacturing will keep getting more automated, transportation is becoming automated, construction will be more automated, and as a result countless people will find themselves jobless. Without a clear, contributive position in society, depression can develop and grows as financial dominos fall, one after the other, until a new job/career is found or some other kind of life break. This is evidenced in the fact that globally middle-aged men show a suicide rate that is 3.0–7.5 times higher than women (Nock et al. 2008). The largest demographic for suicide in the USA is white males between the ages of 45 and 59 (Hu et al. 2008). Being in pre-retirement age, these groups of men are likely to be working or actively looking for employment, but in far too many cases, those who are eligible and wanting a job, find themselves unemployed. Therefore society is faced with a group of experienced, yet decreasingly valued

workers, many of whom are still responsible for their family, mortgages, etc. Unfortunately, it seems that the number of these dispossessed workers will only continue to grow in the years to come. Suicide rates will increase in step with the number of these dispossessed in society, as hopelessness comes from an inability to see any positive future.

This problem is not unique to the developed world – the steady advance of society has also impacted native peoples as rainforests and other lands have been cleared to farm cattle, bananas, sugar, coffee, or other commodities for outsourcing. Clearing these lands has deeply affected the local ecosystems and indigenous peoples for many miles in every direction. Not only have hunting grounds disappeared but the security of isolation has as well. Tribal children grow up seeing things on TV that seem so much more spectacular than what they have in their village and so ultimately want to leave their community, family, and culture behind to pursue another lifestyle. An uneducated native has very little chance of making it big in the city, so they often become a homeless beggar, addict, or thief. While a lifetime of hunting and fishing and singing within the tribe seemed more than enough just a few years ago, the allure of modern society can infect the native mind. Rates of suicide in these encroached cultures are among the highest in the world, as they can no longer see a future for themselves.

6.2.1 Aboriginal and Torres Strait

In Australia the rates of suicide are significantly higher in Aboriginal and Torres Strait Islander peoples. The standardized suicide rate from 2001 to 2010 for Aboriginal and Torres Strait Islanders (21.4 per 100,000) was more than double the non-indigenous rate (10.3 per 100,000) (ABS 2012 Op. Cit.). The Australian Board of Statistics 2012 report found that 1 in 20 of all Aboriginal and Torres Strait Islanders will die from suicide.

6.2.2 French Guiana

French Guiana is an overseas region of France on the North Atlantic coast of South America. The Amerindians are the indigenous peoples of Guiana with a population between 3500 and 7000 people. These indigenous people lead a lifestyle based on subsistence activities: hunting, fishing, and slash-and-burn agriculture. Some communities living along the coast have been exposed to westernization but maintain strong links with their culture of origin. In 2013, Action for Development, Education and Research (ADER) published a data report collected from 2009 to 2013 regarding rates of suicide and attempted suicide among the indigenous populations of the Maroni people. The average annual rate was 2.6 suicides and 8.6 attempted suicides among a population of 1200 inhabitants, in other words a rate 13 times higher than the French national average. Young people under the age of 25 accounted for more than half of all cases. The most commonly used methods used were shooting and hanging. Some have suggested that illegal gold washing, river contamination, an inappropriate education system, addiction, a generation gap, and difficulties in accessing the health system are all factors that may have been influential.

Tribal man still very much exists within modern man, as we are conditioned to have an identity within a relatively small set of people, a family, small group of friends, or tribe. However online (or when competing for a job), we exist among billions of others and so whatever was special or unique about ourselves in our small group/family quickly fades into nothing special, once seen against the macro. We simply can't ever be the smartest, funniest, strongest, or best looking in a group of billions, so identities are more difficult to define than ever before. With times changing so quickly, we need to be ready for an epidemic of dispossessed people and conduct more research to understand and develop more effective treatments for depression. The world will be spinning even faster tomorrow than it is today and millions of people will find themselves displaced as this rate of change accelerates causing widespread vulnerability to depression and possibly even higher rates of suicide.

6.3 Adolescence

Attempted suicide remains a significant problem in adolescence, distinct from that of a child or an adult. Adolescence is a stage of life characterized by various changes and requires great adaptability. Adolescence is often synonymous with changes at a mental and physical level, curiosity in sexuality, exploration of identity, and redefining relationships to others. Emotions occupy the entire field of inner experience. Teenagers seek to find and define their place in the world. Their path has a series of ups and downs, doubts and uncertainties, anxiety, and trust issues.

However, there is hope after an adolescent experiences a suicidal crisis. F Ligier et al. (2009) conducted a ten-yearlong study on the personal and professional well-being of patients who attempted suicide in their adolescence. They found that over three quarters of patients later reported that they were happy in their personal lives and more than half considered themselves to be satisfied or very satisfied with their professional lives. About 17.2 % of the patients reported a chronic psychiatric condition sometimes accompanied by repeated suicide attempts. In a more recent study, Fabienne Ligier et al. (2015) collected 10 years of data on a cohort of 249 patients who attempted suicide during adolescence. They found that the most significant risk factor of suicidal attempt reoccurrence was losing contact early (LCE) with clinicians. Furthermore, they found that most of those who LCE were female and had a psychiatric comorbidity. These results emphasize the importance of detection and early treatment of psychiatric disorders in preventing suicide in young adults.

6.4 Warning Signs and Risk Behaviors

Suicide is most often the final stage of a progressive depression, spawned from either the inability to live with a past trauma or a feeling of hopelessness in the face of an uncertain future (or both). To be mentally healthy, people need to have something to look forward to. Hope is a condition necessary for life. Studies have shown that a predominance of reference to past events over future ones is an indicator of

Table 6.1 Indicators and signs of suicidal crisis (Séguin and Roy 2005)

Behavioral signs	Psychological signs	Direct and indirect verbal messages
Any radical or unusual changes in terms of moods, attitudes, or behaviors	Pessimism	"Soon I will have peace with you"
Dangerous driving or "accidents" frequently	Conflicting emotions: angry outbursts, tears	"I'm going on a long trip"
Isolation: withdrawal, loneliness exaggerated	Spontaneous remission: better to be radical without proper reason after a period of depression	"This is no longer important to me"
Thoughts concerning death	Boredom, guilt feeling	"I give you this. I will not need it anymore"
Donations significant items: letters, gifts	State of indecision, discouragement	"In a few days I will be quiet"
Reconciliation with relatives	Sudden changes in mood	"Sometimes I tell myself that I would be better off dead"
Sudden interest in weapons	Loss of emotional control	
Unusual addictive behavior	Difficulty in attention and concentration	"I lost the joy of living"
Dissociation	Memory loss	"Sometimes I think about killing myself"
Neglected dress	Depersonalization	"I'm afraid to go there"
Imprecise painful complaint	State aggressive, rage	"Is that you're already happened to you, think of the suicide"
Planning means of suicide	Low self-esteem	"If something happens to me, my will is here"
	Fear of suicide	"I'm going to kill myself… "

mental health, which may allow for the development of linguistic analysis methods to identify potential suicide risks.

Warning signs of suicidal thoughts or tendencies include individuals talking about any of the following: wanting to hurt themselves; feeling trapped and/or in unbearable pain; being a burden to others; feeling hopeless, helpless, or worthless with no reason to live; or expressly saying that they want to die, perhaps even how they would do it. Nonverbal warning signs take place over time and include: withdrawing from friends or social activities, showing an increased use of alcohol or other substances, acting anxious or agitated, showing rage or talking about revenge, behaving recklessly, and/or having extreme changes in mood, diet, or sleeping patterns (Rasmussen et al. 2014; Séguin and Terra 2004; Stanley and Brown 2012). Table 6.1 gives common behavioral and psychological warning signs of suicide ideation.

If anyone you know exhibits a combination of these symptoms, you should pay close attention to them and consider contacting a specialist. They will often be able to perform more specific tests and recommend a treatment including changes in diet, behavior, and the increase of activities that strengthen connections among people, families, and communities. Medicinal and counseling therapies may also be prescribed. The primary challenge is one of awareness and proper diagnosis, as most people suffering from depression never recognize it themselves and so live with the condition undiagnosed and untreated. The good news is 80–90 % of the people who seek treatment for depression can be treated successfully (Essau and Petermann 1999; Valente and Saunders 1997). Many great resources are available online.

When symptoms of crisis are identified, prevention is often built around suicide ideation and therapies that focus on acts of self-harm. However, the majority of those who express suicidal thoughts (66 %) will not seek help (Koslow et al. 2014). In some cases the individual will deny having thoughts of suicide to avoid hospitalization or treatment.

6.5 Prevention

Prevention factors, such as social support, can play a major role in suicidal crisis. Studies have shown that when an individual is integrated within a community, they are less likely to accelerate toward suicidal crisis (Chehil and Kutcher 2012; Christensen et al. 2013). In contrast, difficulty "finding their place" in a community and experiencing isolation have been recurring themes of suicidal patients (Gitlin 2014). Being able to integrate into a family unit or a community where it is necessary to play a role in its operation seems to be at the core of social support. Many suicidal patients display qualities of isolation and a lack of family or community support. Fostering social support is a prevention factor that should be emphasized more often.

Another prevention factor is spirituality and religion. As Moron (2000) said, "'Religion' may well incidentally produce the best effects on both the spiritual health and on mental balance, the aim is not healing the psyche, but the salvation of the soul." It is a powerful factor and often a successful method of prevention for many suffering from suicidal crisis (Dervic et al. 2014; Wu et al. 2015). Spirituality, and all that it implies, suggests a search for greater meaning of life. Many religions even condemn the idea of choosing to end your own life, which can have a great influence on someone who is thinking suicidal thoughts.

The suicidal crisis can be conceptualized as an integrative model in which vulnerability factors, precipitating factors, and prevention factors interact (Terra and Le Vinatier 2003). Under this model, vulnerability and protective factors are opposed, creating a dynamic balance. Suicidal crisis arises from an imbalance in the relationship of forces induced by the addition of a third vector: the precipitating event. Schematically, the arrival of an extra psychological stress upsets the status quo of protective factors and vulnerability. One can then observe psychic tensions, which can lead to suicidal crisis. To avoid acts of suicide, the three factors mentioned

Table 6.2 Main protective factors (Terra 2011)

Factors identified for adult protection:
Support from family and social relationships
Presence of a family member, a spouse, a confidant
Pregnancy, children living at home
Family responsibilities
Integration into the community and society
Strong religious belief
Culture severely punishes suicide
Resilience and problem-solving ability

above are therapeutic areas of work for the clinician. These three dimensions should be explored in order to become aware of the full situation, which may help to prevent a suicidal crisis (Table 6.2).

Given the progressive nature of depression and self-destructive thoughts and behavior, it is critical to be able to diagnose and treat the condition early. According to a 2006 report from the National Center for Health Statistics, 90 % of the suicide victims studied in postmortem had a diagnosable psychiatric disorder at the time of their death. More advanced methods of diagnosing and tracking the progression of mental disease are needed, both clinically and at home. So perhaps the most effective method of prevention is earlier detection.

6.6 Detection

Suicide as a result of depression is incredibly tragic, even more so knowing that 80–90 % of these cases could have been successfully treated. The condition is treatable. If more people were aware of the warning signs and were more knowledgeable of the condition and causes, far more people would be seeking and receiving proper treatment.

Clinical interviews and testing are useful but highly subjective methods of diagnosing states of mind, especially since the severity of these conditions changes over time, due to any number of dietary, environmental, or hormonal factors. A patient can seem upbeat and healthy 1 min and then crash into a dark spiral the next – if the physician doesn't witness the patient (and condition) at the right time or know exactly what to look for, it can often be missed. Depression doesn't show up on an MRI. Once more advanced methods for automated diagnosis are developed; neuropsychological examinations could become a regular part of any doctor visit or even be seamlessly integrated into smartphones.

However, neuroscience may end up providing us with an answer to this diagnostic problem, as initial studies of brainwave data suggest biomarkers may be found to predict and correct many abnormal behaviors. Peripheral tissues focused on the levels of neurotransmitters and their metabolites have been found to predominantly show functional abnormalities of these in many cases of suicide. Receptors and receptor-linked signaling systems for serotonin and norepinephrine have great

potential as biomarkers for suicidal behavior, as do platelet 5HT2A receptors and CSF 5HIAA. Other useful biomarkers, such as HPA-axis components and cytokines, have potential as biomarkers for suicide, but need to be studied further.

Other potential methods for clinically detecting the disease (and its degree of severity) would include neuroendocrinal examination of serotonin function and transport throughout the body and noradrenergic examination of norepinephrine and MHPG. Genetics could also provide a greater understanding of risk, as depression and suicide have both been known to run in families. Victims of suicide who had suffered a major depressive disorder have been shown to have a reduction of QKI mRNA levels in their cortical, hippocampic, and amygdala regions, as compared to control subjects (Klempan et al. 2009).

6.7 New Methods of Detection

As the suicidal crisis epidemic continues, it is necessary to develop clinical tools that can detect mental disorders as early as possible in order to manage or intervene before an act of suicide is committed. Accessible, nonintrusive methods would allow for more widespread and effective detection, perhaps even tools that don't require a clinician to administer. Taking EEG, MEG, and skin conductivity readings while performing specific tasks could be used to develop disease biomarkers. Howard et al. (2014) suggest that the most effective way to detect suicidal ideation would be to access rich modes of expression such as language and facial features.

Linguistic analysis likely provides the greatest opportunity for automating the process of diagnosing mental health, as verbal expression is a direct correlate to internal dialogue (Howard 2012; Howard and Guidere 2011). With the explosion of conversational text available for digital analysis (emails, text messages, social media, etc.) and accessibility of speech input from phone calls, recorded therapy sessions and live ambient speech enable vocal and linguistic analysis. Methods of determining the state of mind of an individual through automated lexical analysis have already been developed, but aren't yet in widespread use, clinically or otherwise. One day it may be possible to quickly screen for suicide warning using a smartphone or tablet. More effective screening could be integrated into military health, public schools, and even the workplace. Perhaps detection of suicidal crisis could not only detect suicidal thoughts or behaviors but also give a personalized recommendation of what method of prevention would be most effective.

Conclusion

In conclusion, if we can improve diagnostic technologies and increase the awareness of depression, we will be able to change a significant number of potential suicides into positive outcomes, for so many people and their families. Left undiagnosed and unattended, this condition will only continue to destroy millions of lives and waste billions of dollars, every year. Communities such as schools or veteran associations have to be instructed and educated on how to detect signs of suicidal crisis and how to initiate prevention. A more accessible method of

detecting suicide may also lessen the stigmatization that is associated with having a mental disorder. Although technology may recently have played a role in increased rates of suicide, particularly among adolescents, the mental health community should seize the opportunity to use technology for earlier detection and prevention.

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Part II

Biomarkers of Suicide (Advances in Biology of Suicide)

Biomarkers of Suicide: Predicting the Predictable?

7

Hilario Blasco-Fontecilla and Maria A. Oquendo

Abstract

To date, the identification of individuals at risk of suicide is based on subjective reports. Given that individuals at risk often do not disclose their suicidal thoughts, the introduction of objective measures – such as biomarkers – of suicide risk might help in predicting which individuals will eventually die by suicide. Biomarkers have a potentially relevant role in the prediction of suicide, as an adjunct to, rather than a substitute for, current clinical practice. Within the context of the stress-diathesis model of suicidal behavior, the most relevant biomarkers for estimating suicide risk are non-suppression in the dexamethasone suppression test (DST) – a biomarker of stress – and reduced concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF), a biomarker of diathesis. Given the multi-determined nature of suicide, a combination of biological, clinical, neuropsychological, and neuroimaging factors might yield a better estimate of suicide risk than using biomarkers alone and help overcome current limitations in the prediction of suicide.

7.1 Introduction

Suicide, a major cause of death worldwide, has distinct biological underpinnings (Oquendo et al. 2014). A reasonable first step for suicide prevention is the detection of individuals at risk (predicting the predictable). Unfortunately, this is not an easy task (Davis and Schrueder 1990), and thus far, it relies "on the subjective reports of

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the individual at risk" (Blasco-Fontecilla et al. 2013). Furthermore, individuals at risk often do not disclose their suicidal thoughts (Smith et al. 2013). For those reasons, the introduction of objective measures of suicide risk might help in predicting which, among individuals at risk, will eventually attempt suicide. As a matter of fact, biological tests could substantially increase the specificity and sensitivity of suicide prediction models (Mann et al. 2006) and improve risk assessment and management strategies (McIntyre et al. 2008). Indeed, the identification of reliable biomarkers and the development of more accurate models for suicide prediction, probably by combining biomarkers, clinical and neuropsychological data will have implications for clinical evaluation, intervention, and treatment (Mann et al. 2006).

The purpose of this chapter is to briefly examine the role of biomarkers in the prediction of the most severe manifestation of suicidal behavior, suicide itself (Oquendo et al. 2014). Given that retrospective and cross-sectional studies can, by definition, neither predict nor ascertain causal relationships (Mann et al. 2006), we will focus on a selection of the most relevant literature addressing the problem of prediction of suicide within the stress-diathesis framework.

7.2 What Is a Biomarker?

The search for a biomarker of suicide risk is a long-standing pursuit in clinical psychiatry. A biomarker can be defined either as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (Singh and Rose 2009) or as a molecule or test able to reliably and specifically predict which individuals will show a disease or behavior (e.g., suicidal behavior) (Jones 2010). In order to generalize its use, they should be simple to apply, noninvasive, and inexpensive.

Biomarkers can be divided into *screening biomarkers* (characteristics that assist in the identification of patients yet to manifest the disease), *diagnostic biomarkers* (characteristics of those subjects who have the disease), and *prognostic biomarkers* (those characteristics which are informative for clinical outcomes) (Gerszten and Wang 2008; Lee et al. 2011). Within the context of the stress-diathesis model of suicidal behavior (Mann et al. 1999), biomarkers could also be divided into *diathesis biomarkers* (answer the question: who is at risk?) and *stress biomarkers* (answer the question: when will the individual attempt suicide?).

7.3 Predictive Biomarkers within the Stress-Diathesis Model

To date, the most relevant biomarkers for estimating suicide risk are non-suppression in the dexamethasone suppression test (DST) – reflecting hypothalamic-pituitary-adrenal (HPA) axis dysfunction, a marker of acute stress response – and reduced concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in

cerebrospinal fluid (CSF), as a marker of the diathesis (Coryell and Schlesser 2001; Mann et al. 2006; Oquendo et al. 2014).

One of the main elements of the stress response system is the HPA axis (see Oquendo et al. 2014). Most data devoted to the role of altered HPA axis functioning in suicide come from studies exploring the failure to respond to the DST (Oquendo et al. 2014), which might reflect an overactive HPA axis. The expected response to the 11 pm administration of an external steroid, in this case dexamethasone, would be activation of the negative feedback loop of the HPA axis, leading to a lower than normal blood cortisol level the following morning. Such failure to suppress has been examined as a putative predictor of suicide risk. For instance, in a depressed cohort followed for 15 years, DST non-suppression at baseline increased the risk of eventual suicide by a 14-fold higher odds (Coryell and Schlesser 2001). In another study of depressed inpatients, Jokinen et al. reported that suicide attempters with DST non-suppression were more likely to die by suicide (Jokinen et al. 2007). However, the effect of an altered HPA axis response on suicidal behavior may be mediated by mental disorders (Sunnqvist et al. 2008). In this sense, HPA axis dysfunction appears to indicate a physiological sensitivity to stress which translated into increased risk for suicidal behaviors during acute depressive episodes or when experiencing adverse life events (Braquehais et al. 2012; Jollant et al. 2011).

Dysfunctions of the serotonergic system at several levels have also been associated with suicide. For instance, postsynaptic serotonin receptors 5-HT1A and 5-HT2A are upregulated in the prefrontal cortex of suicides, possibly reflecting serotonergic hypoactivity (Sher et al. 2006). Furthermore, several studies have reported a blunted prolactin response to fenfluramine challenge – a measure reflecting the activity of the serotonergic system – in subjects that had attempted suicide, particularly if it was a high-lethality attempt (Lee and Kim 2011). But perhaps, the most relevant finding is that low CSF levels of 5-HIAA, an index of serotonin turnover (Jokinen et al. 2009) found in suicide attempters using violent methods (Lester 1995), predict suicide (Oquendo et al. 2014; Traskman et al. 1981; Asberg et al. 1976; Mann and Currier 2007). Indeed, reduced CSF 5-HIAA may increase suicide risk by a 4.5-fold, at least in individuals diagnosed with mood disorders (Mann et al. 2006).

In addition to DST non-suppression and 5-HIAA, recent research has also targeted other putative biomarkers of suicide such as reduced cholesterol or brain-derived neurotrophic factor (BDNF) in the serum. Low serum cholesterol levels have been linked to medically serious suicide attempts and suggested to be a putative biomarker of suicide risk (Golier et al. 1995). For instance, in a cohort of 6393 middle-aged working men, both low serum cholesterol and declining cholesterol concentration were related to increased risk of suicide (Zureik et al. 1996). Indeed, total serum cholesterol level might be a useful biological marker for evaluating the risk of suicide (Kim and Myint 2004; Papadopoulou et al. 2013; Coryell and Schlesser 2007). But some have stressed that the relationship between serum cholesterol and suicide is significant only when age is controlled for (Coryell and Schlesser 2007; Lindberg et al. 1992). Furthermore, low omega-3 proportions of serum lipids predicted future attempts among depressed subjects in a 2-year follow-up study (Sublette et al. 2006). This finding is notable because low omega-3 fatty

acids have been associated with both lower serotonergic function (diathesis) and HPA axis hyperactivity (stress) (Coryell and Schlesser 2001), and omega-3 fatty acids have anti-inflammatory effects (Oquendo et al. 2014). Unfortunately, two epidemiological studies considering the association between intake of polyunsaturated fatty acids (PUFAs) – including omega-3 or fish, a major source of PUFAs, and suicide yielded negative results (Poudel-Tandukar et al. 2011; Tsai et al. 2014). Therefore, the predictive capacity of either serum cholesterol or PUFAs for predicting suicide deserves further study.

Based on immunological anomalies and blood-brain barrier leakage present in suicide attempters (Bayard-Burfield et al. 1996), some have suggested that high serum SB100 levels might be a marker of severity of suicidal ideation (Falcone et al. 2010). In another study, the authors reported that P11 (S100A10), another member of the S100 family of proteins, could be a biomarker of suicide risk in patients with psychiatric disorders (Zhang et al. 2011). Though intriguing, both studies suffer from important shortcomings and should be considered exploratory.

Finally, neuroplasticity or neurogenesis may also have a role in suicide risk (Oquendo et al. 2014). BDNF is involved in neural maintenance and regeneration, which may be important for stress adaptation processes. Stress decreases the expression of BDNF (Duman and Monteggia 2006), and reduced BDNF levels in blood serum or plasma may be associated with impaired brain plasticity. Moreover, BDNF plays an important role in the growth of serotonergic neurons during childhood (Banerjee et al. 2013). Accordingly, some investigators suggest that BDNF is a good candidate for studies about suicide. Indeed, there is converging evidence suggesting that there are impairments in neurogenesis as expressed by lower BNDF in the prefrontal cortex and hippocampus of suicides (Dwivedi et al. 2003). Moreover, depressed individuals who die by suicide present reduced mRNA expression and protein levels of BDNF in the brain, regardless of prior mental disorders (Lee and Kim 2011; Dwivedi et al. 2003). This is important because some antidepressants increase BDNF production (Duman and Monteggia 2006). In any case, the predictive capability of BDNF for suicide risk remains unexplored.

7.4 Combination of Biomarkers

For a biomarker to be clinically useful, it must have high sensitivity (>90 %), specificity (>90 %) (Brower 2011), and a strong predictive value (Jones 2010). To date, biomarkers, used alone, have yielded disappointing results with regard to their predictive capability (Coryell and Schlesser 2001; Jokinen et al. 2008). Indeed, it is very unlikely that any single factor will gauge the risk of suicide.

But even the combination of some biological markers has been discouraging to date. For instance, some have suggested that the combination of a small number of unrelated biomarkers might provide a better prediction of suicide when compared to a larger sample of related biomarkers (Gerszten and Wang 2008). But despite the bidirectional relationship between the serotonin system and the HPA axis (Meijer and de Kloet 1998) and that these indices are relatively independent (Mann et al. 2006;

Fawcett et al. 1997; Oquendo et al. 2014; Jokinen et al. 2008), a prediction model requiring both DST and CSF 5-HIAA tests to be positive showed 37.5 % sensitivity and 88 % specificity in predicting suicide (Mann et al. 2006). In another study, mood-disordered patients with low serum cholesterol and DST non-suppression presented a 40 % higher probability of committing suicide in the survival analysis than individuals without these alterations, and the combination of both biomarkers was more powerful in predicting suicide than the use of either biomarker alone (Coryell and Schlesser 2007). These studies demonstrate that even combinations of biomarkers fall short in terms of meeting the necessary sensitivity and specificity expected for clinically useful predictive tests.

Conclusion

Current limitations of biomarkers for predicting suicide underscore the importance of identifying novel biomarkers. Biomarkers have a potentially relevant role in the prediction of suicide, as an adjunct to, rather than a substitute for, current clinical practice (Mann et al. 2006). To date, however, the few biomarkers measurable in vivo – i.e., DST and CSF 5-HIAA levels – lack the positive predictive value critical for clinical use (Oquendo et al. 2014). Given that different systems – HPA axis, the serotonin and opioid system, lipid status, inflammatory pathways, and neuroplasticity or neurogenesis – are involved in suicide, combining different biomarkers might provide a better prediction of suicide (Gerszten and Wang 2008; Oquendo et al. 2014).

Furthermore, given the multi-determined nature of suicide, the combination of biological, clinical, neuropsychological, and neuroimaging factors might yield a better estimate of suicide risk than using biomarkers alone and help to overcome current limitations in the prediction of suicide (Lee and Kim 2011; Mann et al. 2006; Blasco-Fontecilla et al. 2013). Indeed, Le-Niculescu and colleagues enhanced the prediction of hospitalizations caused by suicidal behavior by combining genetic and clinical factors (Le-Niculescu et al. 2013). Unfortunately, although results from these studies are encouraging, to date, the prediction of suicide still "depends on the subjective reports of the individual at risk" (Blasco-Fontecilla et al. 2013).

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Genetics and Suicide

8

Eugene Lin and Shih-Jen Tsai

Abstract

Strong evidence suggests a genetic susceptibility to suicidal behavior, including familial heritability and common occurrence in twins. In the recent advent of scientific research, the genome-wide association study (GWAS), an alternative to the candidate-gene approach, is widely utilized to examine hundreds of thousands of SNPs by high-throughput genotyping technologies. In addition to the candidate-gene approach, the GWAS approach has recently been employed to study the determinants of suicidal behavior. Several recent findings have demonstrated that some SNPs and genes are closely associated with suicidal behavior. This chapter addresses recent molecular genetic studies in suicidal behavior. First, we surveyed the SNPs and genes identified as genetic markers that are correlated and associated with suicidal behavior in the candidate-gene association studies. Next, we reviewed the SNPs and genes that have been suggested as contributors to suicidal behavior in the GWAS studies. Finally, we summarized the limitations and future directions. Future research with independent replication in large sample sizes is needed to confirm the role of the SNPs and genes identified in the candidate-gene and GWAS studies in suicidal behavior.

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8.1 Introduction

Numerous studies over the last three decades have reported that abnormalities in the functioning of the central serotonergic system are linked to the pathogenesis of suicidal behavior (Ryding et al. 2008). To date, most of the molecular genetic studies focused on the serotonergic pathway as the basis of established biological correlations of suicidal behavior, and thus, the candidate genes were primarily related to the serotonergic system (Bondy et al. 2006). Genetic association studies using genetic variants such as single nucleotide polymorphisms (SNPs) have shown that genes contribute to suicide risks and have suggested several genes such as *serotonin transporter* related to suicidal behavior, but not all reports support these findings (Tsai et al. 2011).

In addition, evidence from other research designs (such as adoption, family, geographical, immigrant, surname, and twin studies of suicide) suggested genetic contributions to suicide risk (Baldessarini and Hennen 2004). Further, the contribution of additive genetic factors is estimated to be 30–50 % for suicidal behavior including ideation, plans, and attempts (Voracek and Loibl 2007). Twin and family studies also documented a higher concordance rate for suicide in monozygotic than dizygotic twins (24.1 % vs. 2.8 %) and nearly fivefold greater relative risk of suicidal acts in the relatives of individuals who die by suicide, even after adjusting for psychiatric disorder.

8.2 Candidate-Gene Association Studies

Genes that code for proteins involved in regulating serotonergic neurotransmission have been major candidate genes for the association studies of suicidal behavior. Among them, genes for serotonergic receptors, serotonin transporter, tryptophan hydroxylase, and other monoaminergic systems have received the most research attention.

8.2.1 Brain-Derived Neurotrophic Factor Pathway

The protein encoded by the *brain-derived neurotrophic factor* (*BDNF*) gene is a member of the neurotrophin family and plays an important role in neuronal survival and brain plasticity (Dwivedi 2010). In the past decade, evidence is accumulating to suggest *BDNF* and its relevant genes such as the *neurotrophic tyrosine kinase receptor type 2* (*NTRK2*) and *nerve growth factor receptor* (*NGFR*) genes in the pathogenesis of suicidal behavior and major depression from clinical studies and postmortem studies. The functional Val66Met (rs6265) SNP in *BDNF* has attracted much attention in suicide research. However, evidence for assessing the risk of *BDNF* Val66Met in suicidal behavior is currently controversial. *BDNF* Val66Met has been reported to predispose to suicidal behavior in Japanese, Taiwanese, Korean, and Italian populations (Tsai et al. 2011). On the contrary, this association with suicide behavior has not been replicated in Taiwanese, Slovenian, Caucasian, and German studies (Tsai et al. 2011). Regarding the conflicting findings in these studies, a meta-analysis may

help to elucidate the role of *BDNF* Val66Met in suicidal behavior. Zai et al. (2012) performed the meta-analysis of BDNF Val66Met in suicidal behavior using data from 12 studies and suggested that *BDNF* Val66Met is involved in suicidality.

In addition to the aforementioned findings, a report failed to find an association between the *BDNF* SNPs and suicidal behavior but found the associations of SNPs in *NTRK2* with suicide attempt in depressed German patients, which were also replicated in the African American population (Kohli et al. 2010). McGregor et al. (2007) also investigated three SNPs in *NGFR* for an association with suicide behavior in childhood-onset mood disorder, and the results did not support an association of the *NGFR* SNPs with suicide risk.

8.2.2 Dopaminergic System

Genes in the dopaminergic system could be candidates for suicidal behavior study due to the fact that the striatal dopaminergic activity is related to impulsivity, a character of suicidal behavior. In a Japanese report, Suda et al. (2009) implicated possible involvement of the TaqIA and − 141C insertion/deletion variants of the *dopaminergic D2 receptor* (*DRD2*) gene in the biological susceptibility to suicidal behavior. Furthermore, this finding is in line with an earlier report that linked the *DRD2* − 141C insertion/deletion variant with attempted suicide in German alcoholics (Johann et al. 2005).

Catechol-O-methyltransferase (COMT), the postsynaptic enzyme that metabolizes released dopamine, is a critical enzyme in the metabolic degradation of dopamine in the prefrontal cortex. Kia-Keating et al. (2007) conducted a meta-analysis using six studies and demonstrated evidence of a modest significant association between the *COMT* Val158Met SNP and suicidal behavior. In addition, two following studies identified the role of *COMT* Val158Met in suicidal behavior among the male subjects in Korean (Lee and Kim 2011) and Caucasian (Pivac et al. 2011) populations. These findings are in line with a report associating *COMT* Val158Met with attempted suicide in Caucasian alcoholics (Nedic et al. 2011).

Monoamine oxidase (MAO) is a mitochondrial outer membrane enzyme that degrades biogenic amines, including neurotransmitters such as dopamine. The *MAOA* gene contains a functional variable number tandem repeat (or VNTR) in the upstream regulatory region (*MAOA*-uVNTR). Hung et al. (2012) indicated that there was no association between *MAOA*-uVNTR and suicidal behaviors in the meta-analysis using data from seven case-control association studies. However, Antypa et al. (2013) found that the *MAOA* rs909525 SNP was associated with suicidality after examining the following markers: *MAOA* rs909525, *MAOA* rs6323, *MAOA* rs2064070, and *MAOB* rs1799836.

8.2.3 Hypothalamic–Pituitary–Adrenal (HPA) Axis

The HPA axis is a neuronal and endocrine system that regulates the body's response to stress. Dysregulation of the HPA axis may be related to the risk of suicidal

behavior owing to the fact that stress plays a major role in the various pathophysiological processes associated with suicidal behavior (Pompili et al. 2010). De Luca et al. (2010) tested the HPA axis-related genes including the *corticotrophin-releasing hormone* (*CRH*), the *corticotrophin-releasing hormone receptor 1* (*CRHR1*), *CRHR2*, *CRH binding protein* (*CRHBP*), and *melanocortin 2 receptor* (*MC2R*) genes in a cohort of schizophrenia subjects with attempted suicide. The genotype analyses yielded a significant association between *CRHBP* and suicide attempt. They also demonstrated a significant interaction between *CRHR1* and *CRHBP* in influencing suicide attempt and the severity of suicidal behavior, suggesting that SNPs in the HPA-axis-related genes could be associated with suicidal behavior in schizophrenia. Wasserman et al. (2008) also reported *CRHR1* rs4792887 for suicidality in depressed males exposed to low stress. In addition, Roy et al. (2012) showed an interaction between *CRHBP* and childhood trauma on suicidal behavior. Moreover, there was an additive effect with the *FK506 binding protein 5* (*FKPB5*) gene.

The protein encoded by *FKBP5* is a member of the immunophilin protein family, which plays a role in causing subsensitivity of the glucocorticoid receptor. In a study with seven *FKBP5* SNPs in families with bipolar offspring, Willour et al. (2009) suggested that *FKBP5* may influence attempted suicide and number of depressive episodes in the bipolar subjects. In addition, Supriyanto et al. (2011) reported that the haplotypes (comprised of rs3800373 and rs1360780) in *FKBP5* were associated with completed suicide in the Japanese population. Furthermore, Roy et al. (2012) showed that an interaction between *FKBP5* and childhood trauma may increase the risk for attempting suicide.

8.2.4 Serotonergic Receptors

Suicide genetic studies mostly investigated the *5-hydroxytryptamine receptor 1A* (*HTR1A*) and *5-hydroxytryptamine receptor 2A* (*HTR2A*) genes that encode two of the serotonin receptors, which have opposing functions in a variety of cellular and behavioral processes.

HTR1A C-1019G (rs6295) has attracted considerable interest in suicidal behavior research because this SNP influences serotonergic neurotransmission. Angles et al. (2012) performed a meta-analysis of a possible correlation between *HTR1A* C-1019G and suicidal behavior with 4 studies and found no association. Similarly, González-Castro et al. (2013) performed another meta-analysis with nine studies and confirmed no association.

There are many genetic association studies of the *HTR2A* gene with suicidal behavior. Li et al. (2006) have made a good summary of these reports with a meta-analysis of 73 association studies for *HTR2A* and suicidal behavior. They detected a significant association between *HTR2A* A-1438G and suicidal behavior. However, they failed to find a significant association of *HTR2A* T102C with suicidal behavior.

In addition, a meta-analysis utilizing seven studies demonstrated no significant association between the G861C (rs6296) SNP in the *5-hydroxytryptamine receptor 1B* (*HTR1B*) gene and suicidal behavior (Kia-Keating et al. 2007).

8.2.5 Serotonin Transporter

The *solute carrier family 6 member 4* (*SLC6A4*) gene codes for the serotonin transporter. Following serotonin release, the serotonin transporter is the major site of serotonin reuptake into the presynaptic neuron. By regulating the reuptake of the released serotonin, the serotonin transporter is central to fine-tuning the serotonergic neurotransmission.

Among the genetic variants in *SLC6A4*, a 44-base pair (bp) insertion–deletion in the promoter region (serotonin-transporter-linked polymorphic region; 5-HTTLPR) polymorphism and a 17-bp VNTR in the second intron of *SLC6A4* have been extensively studied for an association with suicidal behavior. Li and He (2007) reviewed 39 studies that examined the association between the functional 5-HTTLPR polymorphism and suicidal behavior in groups with psychiatric diagnoses. Their report suggested a significant association ($P = 0.0068$) with S allele as the risk allele for suicidal behavior. For the *SLC6A4* VNTR polymorphism, they demonstrated no significant association for both the 10-repeat allele and 12-repeat allele, either in allelic or genotypic analysis.

8.2.6 Tryptophan Hydroxylase

The encoded proteins by the *tryptophan hydroxylase 1* (*TPH1*) and *tryptophan hydroxylase 2* (*TPH2*) genes are the rate-limiting enzymes in the biosynthesis of serotonin. In humans, as well as in other mammals, there are two isoforms of TPH, referred to as TPH1 and TPH2.

Numerous studies have tested for an association between the genetic variants in *TPH1* and suicidal behavior but produced contradictory results. Li and He (2006) reported a meta-analysis with published 22 studies. They demonstrated a significant overall association between suicidal behavior and the *TPH1* A218C/A779C SNPs, suggesting the involvement of *TPH1* in the pathogenesis of suicidal behavior. In contrast, a following meta-analysis is conflicting and does not support *TPH1* A218C/A779C being a susceptibility locus for suicidal behavior (Saetre et al. 2010). However, a recent meta-analysis with 37 studies provided evidence that *TPH1* A218C/A779C may be a risk factor to manifest suicidal behavior at the clinical level (González-Castro et al. 2014).

The *TPH2* gene has attracted much attention for its role in suicidal behavior pathophysiology since its identification. Several studies have tested *TPH2* in recent years for associations with suicidal behavior with positive findings, although some studies found negative findings (Tsai et al. 2011). A meta-analysis of these studies may help to clarify the role of *TPH2* in suicidal behavior. González-Castro et al. (2014) performed a meta-analysis with 37 studies and could not find an association with suicidal behavior with regard to the *TPH2* SNPs (including G-703T, A-473T, and G19918A).

8.2.7 Gene–Gene Interaction

Because suicidal behavior may be related to multiple genes, several studies have investigated gene–gene interaction in suicidal behavior. Studies have tested the gene–gene interaction between *MAOA* and *COMT* in suicide attempt history in families with at least one member having bipolar disorder (De Luca et al. 2005) and in patients with schizophrenia (De Luca et al. 2006); however, these studies found no additive effect in conferring suicidal behavior risk. Another report showed no association among the *HTR2C* and *MAOA* intergenic haplotype combination and suicide attempt in bipolar patients (De Luca et al. 2008).

Moreover, Murphy et al. (2011) identified a three-locus gene–gene interaction (including *HTR1B* rs6296, *SLC1A2* rs4755404, and *NTRK2* rs1659400) as a significant predictor of suicidal behavior after controlling for possible confounders such as age, gender, alcohol abuse, and schizophrenia. They also found four SNPs (including *SLC1A2* rs4755404, *SLC1A3* rs2269272, *HTR1B* rs6296, and *NTRK2* rs1659400), which showed evidence of association with suicidal behavior compared to a non-attempter control group.

Souza et al. (2011) evaluated whether genetic variants in *HTR3A* and *HTR3B* were susceptibility SNPs for suicidal behavior in Caucasian subjects with schizophrenia. Although *HTR3A* and *HTR3B* may not play a major role in the susceptibility for suicidal behavior, there were two nominally significant gene–gene interactions.

8.3 Genome-Wide Association Study

The genome-wide association study (GWAS) is an alternative to the candidate-gene approach (Christensen and Murray 2007). Unlike the candidate-gene approach, there is no a priori hypothesis about the involved genes in the GWAS studies, which examine common genetic variations (500,000 to 2 million SNPs) across the entire human genome in an attempt to identify genetic associations with observable traits by using high-throughput genotyping technologies.

8.3.1 GWAS by Perlis and Colleagues

In a GWAS study, Perlis et al. (2010) examined the association between common genome-wide variation and lifetime suicide attempts in bipolar I and II disorder as well as major depressive disorder. Strongest evidence of association for suicide attempt in bipolar disorder was observed for the rs1466846 SNP without known gene within 400 kb. In major depression, strongest evidence of association was shown for the rs2576377 SNP in the ABI family member 3 binding protein (*ABI3BP*) gene. Replication samples did not provide further support for these two SNPs.

However, they conducted a meta-analysis incorporating all available mood disorder subjects ($N=8737$) and identified ten SNPs in four loci, including the sorbin and SH3 domain containing 1 (*SORBS1*) and protein kinase C epsilon (*PRKCE*) genes.

The *SORBS1* gene has been indicated in insulin signaling (Perlis et al. 2010). Knockout mice for the *PRKCE* gene have been shown to exhibit reduced anxiety behavior. In addition, a study found differences in expression of multiple protein kinases, including the one encoded by the *PRKCE* gene, in individuals with depression relative to control subjects.

8.3.2 GWAS by Willour and Colleagues

Willour et al. (2012) conducted a GWAS study that compared the genotypes of 1201 bipolar subjects with a history of suicide attempts to the genotypes of 1497 bipolar subjects without a history of suicide attempts. Genotyping was performed using the Affymetrix 6.0 array. Their analysis produced an association with the rs300774 SNP at the threshold of genome-wide significance ($P=5.07\times10(-8)$). The associated rs300774 SNP is within a large linkage disequilibrium block that includes the SH3 and SYLF domain containing 1 (*SH3YL1*), acid phosphatase 1 (*ACP1*), and family with sequence similarity 150 member B (*FAM150B*) genes.

Expression in the *ACP1* gene was significantly elevated in bipolar subjects who have completed suicide (Willour et al. 2012). Furthermore, the protein encoded by the *ACP1* gene is a tyrosine phosphatase that influences the Wnt signaling pathway regulated by lithium, indicating *ACP1* as a functional candidate for involvement in suicidal behavior. Little is known about the potential functional contribution in the brain for *SH3YL1* and *FAM150B*.

8.3.3 GWAS by Perroud and Colleagues

Suicidal ideation or suicidal plans that emerge during the course of antidepressant treatment have received considerable public attention. A small subset of patients with major depressive disorder develops this uncommon adverse event. Perroud et al. (2012) conducted a GWAS study to identify SNPs involved in increasing suicidal ideation during antidepressant treatment, where the subjects ($n=706$) were either treated with escitalopram ($n=394$) or nortriptyline ($n=312$). They utilized high-quality Illumina Human610-quad chip genotyping data. There were 244 subjects who experienced an increase in suicidal ideation during follow-up.

Perroud et al. (2012) revealed that the rs11143230 SNP ($P=8.28\times10(-7)$) in the guanine deaminase (*GDA*) gene was significantly associated with increasing suicidality. The *GDA* gene encodes an enzyme responsible for the hydrolytic deamination of guanine and found to be differentially expressed in thalami from patients with schizophrenia.

8.3.4 Limitations in GWAS

With respect to the aforementioned GWAS studies, there were several limitations. First, the small size of the sample does not allow drawing definite conclusions. Small sample sizes can result in none of the findings reaching genome-wide significance due to insufficient statistical power (Spencer et al. 2009). In future work, independent replications in large sample sizes are needed to confirm the role of the polymorphisms found in these GWAS studies.

In addition, most of the loci found in the GWAS studies are not immediately informative because they are noncoding variants, which have incomplete annotation and unknown mechanisms (Ward and Kellis 2012). Therefore, extensive experimental work is needed to uncover the molecular mechanisms responsible for suicidal behavior. Moreover, the GWAS studies did not replicate across studies or populations, causing us to question the validity of novel associations, especially when the loci found are noncoding (Nebert et al. 2008).

8.4 Future Perspective

Future research may benefit from examining gene–gene interactions with novel computational techniques such as generalized multifactor dimensionality reduction (Lin et al. 2009). It is essential to address these interactions in order to describe complex traits in genetics. Epistasis analysis for gene–gene interactions has been advocated for deciphering complex mechanisms, particularly when each involved factor only demonstrates a minor marginal effect. Association studies based on individual SNPs or haplotypes, using a locus-by-locus or region-by-region approach, may overlook associations that can only be found when gene–gene interactions are investigated (Lane et al. 2012). To assess gene–gene interactions, there are many promising methods available, including regression models, multifactor dimensionality reduction, generalized multifactor dimensionality reduction, Bayesian approaches, and artificial neural network algorithms.

In addition, epigenetic approaches, which are modulated by environmental factors, should be considered to obtain clinically meaningful prediction of suicide owing to the fact that suicide may involve effects of the environment, genes, and their interaction. Guintivano et al. (2014) conducted an epigenome-wide association study using Illumina Infinium Human Methylation (HM) 450 BeadChip and generated a prediction model for suicidal behaviors with the rs7208505 SNP in the *spindle and kinetochore-associated complex subunit 2* (*SKA2*) gene. However, their results were limited by the small size of the cohort. Future epigenetic studies with a much larger cohort of patients are needed to better assess sensitivity and specificity of the proposed predictive models and biomarkers.

Other approaches such as transcriptomics should also be employed to identify and prioritize biomarkers of relevance to suicidality. Le-Niculescu et al. (2013) investigated whole-genome gene expression profiling in the blood samples using Affymetrix HG-U133 Plus 2.0 GeneChips and found four biomarkers (including the

spermidine/spermine N1–acetyltransferase 1 (*SAT1*), *phosphatase and tensin homolog* (*PTEN*), *myristoylated alanine-rich protein kinase C substrate* (*MARCKS*), and *mitogen-activated protein kinase kinase kinase 3* (*MAP3K3*) genes) to be predictive of suicidality in bipolar disorder and psychosis. However, their results should be interpreted with caution because of small sample sizes, and future transcriptome-based studies with large sample sizes should be carried out to further evaluate their findings.

Furthermore, studies in future work can examine the contributions of genetic markers by whole-genome sequencing (Ng and Kirkness 2010) or exome sequencing (Bamshad et al. 2011). It has been suggested that gene variants with relatively large effects on drug efficacy or side effects are rare rather than common ones because of additive effects of significant loci (Tucker et al. 2009). Rare variants can only be discovered through whole-exome and whole-genome sequencing or family-based studies, instead of GWAS studies. Whole-genome sequencing represents a new era of scientific research and provides the most comprehensive collection of an individual's genetic variation owing to the reduced cost and the increased throughput of next-generation sequencing technologies. Exome sequencing, which selectively sequences the nucleotides of protein-coding exons in an individual, has recently been introduced as an alternative and efficient approach for Mendelian disorders and common diseases (Bamshad et al. 2011). In summary, combining whole-genome approaches with novel computational tools may potentially lead to a better understanding on suicide.

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Epigenetics

9

Gustavo Turecki

Abstract

While the aetiology of suicide is complex and not completely understood, early-life adversity plays an important role in increasing lifetime risk for suicide. It is clear that the early-life environment has important influences on behavioural development, and only recently have we begun to better understand the molecular mechanisms through which early-life adversity may induce such profound effects on later behaviour, and as such, epigenetic processes have been implicated as one important mechanism. Epigenetics refers to the dynamic molecular processes that are involved in the regulation of gene expression through modifications of the chemical composition or physical structure of DNA or chromatin without affecting the DNA sequence. Since the epigenome is responsive to the environment, it is thought that through epigenetic regulation early-life adversity may affect behavioural development, augmenting the risk for psychopathology including suicide. This chapter will review the data supporting this view describing epigenetic changes that are associated with early-life adversity and suicide.

9.1 The Association between Early-Life Adversity and Suicide

A number of models have been proposed over the years in attempting to understand the risk for suicide. The most current models describe suicide as resulting from the interaction of several distal and proximal risk factors. Risk factors acting more distally are those believed to increase predisposition, while risk factors acting more proximally are regarded as precipitants (Turecki et al. 2012). Some of the proximal factors include recent life events and last 6-month psychopathology including

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current substance abuse, while some of the distal factors that are commonly investigated include genetics and early-life adversity. The latter is the distal factor with the strongest association with increased risk for suicide (Brezo et al. 2007a, b; Fergusson et al. 2000).

There is substantial evidence to suggest that early-life experiences including childhood abuse can have a significant impact on an individual's susceptibility to suicide and suicidal behaviours. Although most individuals who display suicidal behaviour do not necessarily have a history of early-life adversity, a significant minority of up to 40 %, depending on the type of abuse, frequency and suicide phenotype, does (Fergusson et al. 2008; Brezo et al. 2008; Cutajar et al. 2010; Martin et al. 2004; Plunkett et al. 2001; Fanous et al. 2004). In accordance with these findings, several longitudinal studies conducted in epidemiologically representative samples consistently show that children who have histories of sexual and physical abuse during childhood are more likely to exhibit suicidal behaviour in adulthood (Brezo et al. 2007a, b; Fergusson et al. 2000; Fanous et al. 2004; Juon and Ensminger 1997; Galera et al. 2008). In fact, child trauma, and particularly child sexual and physical abuse, is associated with a higher risk for psychiatric disorders including depression, anxiety, bipolar disorder, substance abuse and suicide (Evans et al. 2005; Molnar et al. 2001; Santa Mina and Gallop 1998; Heim and Nemeroff 2001; Kendler et al. 2000, 2004; Kaplan and Klinetob 2000; Agid et al. 1999; Fergusson et al. 1996).

While there is significant evidence to support the association between early-life adversity and development of psychopathology in adulthood, it remains unknown what long-lasting molecular changes occur as a result of adverse early-life experience that could increase suicide risk. This chapter will review the data suggesting that changes at the molecular level are occurring in response to variation in the early-life environment focusing on epigenetic processes as they are believed to regulate expression levels of genes that affect response systems and, in turn, modulate behaviour. There is indeed substantial evidence suggesting that epigenetic changes in several key genes are occurring as a result of early-life adversity which may be contributing to increased suicide risk. However, before continuing further some of the basic concepts of epigenetics need to be discussed.

9.2 Regulating Gene Expression by Epigenetic Mechanisms

The genome contains the entire genetic information required to express all the proteins of an entire organism; however, only a fraction of this information is expressed in a given cell at a given time. Epigenetics refers collectively to the chemical and physical processes that programme the genome to express its genes in a time- and cell-dependent manner. These are dynamic molecular processes that can regulate gene expression by altering the chemical composition or physical structure of DNA or chromatin without modifying the DNA sequence. These also include the modifications that affect the availability of mRNA products. The epigenome can respond to developmental, physiological and environmental cues, and in this way epigenetics

provides a basis for understanding how the environment may regulate the genome. Epigenetic regulation of gene function allows for genomic plasticity or, in other words, the adaptation of the genome according to the needs of the organism. It is understood that epigenetic processes occur as a result of physical and chemical environmental signals, but only recently has it been revealed that the social environment also triggers epigenetic responses (Labonte and Turecki 2010; Nagy and Turecki 2012; Petronis 2010). Therefore, it is possible to envision the epigenome providing an interface through which the environment may modify genetic processes and, as a result, regulate behaviour at least partially in response to environmental needs (Turecki et al. 2012).

DNA methylation is the best characterized and most investigated among the variety of known epigenetic processes. It is a post-transcriptional modification referring mainly to the transfer of a methyl group (CH_3) from an *S*-adenosyl-l-methionine donor to the 5′ carbon of the cytosine from dinucleotide sequences of cytosine-guanine (CpG). This process requires the enzymatic activity of DNA methyltransferase (DNMT) proteins among which DNMT3a and DNMT3b are de novo methylases as they add methyl groups to cytosines that were not previously methylated (Hata et al. 2002; Okano et al. 1998). DNA methylation occurring in the promoter region of a gene is associated with transcriptional repression of that gene through interference with the ability of transcription factors or similar proteins from binding to their target DNA regulatory sequences (Lutz and Turecki 2014). Another form of DNA methylation is DNA hydroxymethylation, which refers to the oxidation of pre-existing 5′ methylcytosine to 5′ hydroxymethylation by enzymes in the TET family (Tahiliani et al. 2009; Ito et al. 2010). 5-Hydroxymethylcytosine is an intermediate in DNA demethylation, and its concentrations positively correlate with gene transcription (Nestor et al. 2012). Moreover, different cell types exhibit different methylation and hydroxymethylation patterns that confer a specificity of expression based on the requirement of each cell type (Mellen et al. 2012; Iwamoto et al. 2011).

Nucleosomes, which make up the fundamental units of chromatin, are formed when DNA is wrapped around an octamer of histone proteins (H2A, H2B, H3 and H4). Histones are globular structures that have a tail of amino acids which can undergo modifications by the addition or removal of chemical residues. Chromatin has two structures: euchromatin, the active state associated with gene transcription and its counterpart, heterochromatin, the inactive state corresponding to gene repression. The chromatin state is dynamically regulated by the recruitment of proteins carrying intrinsic enzymatic activity leading to histone modifications (Clements et al. 2003; Fischle et al. 2005; Nelson et al. 2006; Pray-Grant et al. 2005; Santos-Rosa et al. 2003). These modifications lead to chromatin opening or closing favouring, respectively, active or inactive state of chromatin (Wysocka et al. 2005, 2006). Histone acetyltransferases (HAT) add acetyl groups to certain amino acid residues on histones, while histone deacetylases (HDAC) catalyze the removal of acetyl groups (Tsankova et al. 2007). Hyperacetylation of histone proteins leads to chromatin decondensation, making it looser and more accessible. Eight types of histone modifications have been characterized including methylation (lysine, arginine), acetylation, phosphorylation, ubiquitination, sumoylation, deimination, ADP

ribosylation and proline isomerization. While all these marks may affect gene expression, lysine methylation and acetylation have received the most attention. Methylation at specific lysines (K) of the third histone (H) as in H3K4, H3K36 and H3K79 is correlated with active transcription (Kirmizis et al. 2007; Salcedo-Amaya et al. 2009; Barrera et al. 2008; Pokholok et al. 2005; Wang et al. 2008; Xiao et al. 2007), whereas methylation at H3K9, H3K27 and H4K20 is associated with transcriptional repression (Wang et al. 2008; Barski et al. 2007; Bannister et al. 2001; Botuyan et al. 2006; Lan et al. 2007; Nielsen et al. 2001; Sanders et al. 2004; Swigut and Wysocka 2007).

There is emerging evidence to suggest that differential gene expression patterns may result from the action of non-coding RNAs (ncRNAs) that are capable of activating or repressing genes (Smalheiser et al. 2011; O'Connor et al. 2012; Omran et al. 2012). Among the different species of ncRNAs, microRNAs (miRNAs) have been gaining significant interest as they are implicated in the post-transcriptional regulation of mRNA and, thus, can regulate gene expression. MicroRNAs are small, non-coding, single-stranded, 19–24-based RNA transcripts that bind to mRNAs and target them for degradation. They form complexes that target complementary mRNA leading to either translational repression or the degradation of the targeted transcript which also results in gene repression (Saetrom et al. 2007).

9.3 Changes in the Epigenetic Regulation of Hypothalamic-Pituitary-Adrenal (HPA) Axis-Related Genes

In part through alterations in the neural circuits involved in stress regulation, child abuse has been proposed to impose long-term effects on behaviour (Heim et al. 2008a). The hypothalamic-pituitary-adrenal (HPA) axis is the major stress regulatory system (Pariante and Lightman 2008), and there is evidence to suggest that early-life adversity is associated with structural and functional alterations to several brain regions implicated in the stress response (Bremner et al. 1997; Stein et al. 1997; Driessen et al. 2000; Carrion et al. 2001; De Bellis et al. 2002; Bremner et al. 2003). In addition, individuals with a history of child abuse exhibited altered stress responses (Heim et al. 2000, 2008a) and increased corticotropin-releasing factor (CRH) levels (Heim et al. 2008b; Carpenter et al. 2004). There are several changes occurring in the HPA axis, and these changes may be contributing to alterations in behaviour that may increase suicide risk later in life.

The first evidence to suggest that the early-life environment induces changes in stable epigenetic states that regulate gene expression and ultimately, complex neural functions was demonstrated in studies investigating the effect of variations in maternal care in rats on stress reactivity. Rodent and nonhuman primate studies have shown that the early-life environment can regulate the hypothalamus-pituitary-adrenal (HPA) axis function in adulthood (Weaver et al. 2004; Meaney 2001; Higley et al. 1991; Levine et al. 1994). Meaney and colleagues conducted landmark studies demonstrating that variations in the early social environment, as modelled by

maternal care in the rat (the frequency of pup licking/grooming (LG) over the first week of life), programme the expression of genes that regulate behavioural and endocrine responses to stress. Pups raised by mothers that displayed increased frequency of pup licking/grooming (i.e. high LG mothers) compared to the offspring of low LG mothers exhibited in adulthood greater expression of hippocampal glucocorticoid receptors (GR; *NR3C1*), greater negative feedback regulation over hypothalamic CRF and more modest responses to stress (Weaver et al. 2004; Francis et al. 1999; Liu et al. 1997). Variations in maternal LG were found to be linked to an epigenetic modification of a neuron-specific exon 1_7 promoter of GR (Weaver et al. 2004) such that increased maternal care associates with decreased methylation of the $GR1_7$ promoter and increased hippocampal GR expression. This research underlines the profound and persistent impact that differential early-life experiences can have on gene expression and behaviour through epigenetic mechanisms and DNA methylation changes, thus, providing strong support for the ability of the early environment to stably influence neurodevelopment and complex behavioural traits.

The GR methylation findings reported in rats were subsequently translated to humans. It is quite possible that these changes contribute to the emergence into adulthood of maladaptive stress responses and potentiate the risk of suicide. The methylation state of the GR gene was investigated in the hippocampus of individuals who died by suicide and had histories of child abuse. Early-life adversity in humans was found to reprogram the DNA methylation patterns of one particular GR gene transcript variant, $GR1_F$ ($GR1_7$ homologue in rats) promoter such that increased methylation in the $GR1_F$ promoter region and decreased expression of $GR1_F$ were found in the hippocampus of suicide completers with a history of child abuse compared to non-abused suicide completers and healthy controls (McGowan et al. 2009). This hypermethylation led to the reduction in binding of the transcription factor NGFI-A, which is likely responsible for the decreased GR expression. Since decreased GR expression is known to result in HPA axis hyperactivity, there is strong evidence implicating the role of childhood abuse in the disruption of this key stress response system, and thus, the evidence highly implicates HPA axis dysregulation in the aetiology of suicide following a history of severe early-life adversity.

Changes in DNA methylation of other transcripts of GR were also subsequently reported. The GR gene is preceded by non-coding exons, and in humans, nine first exon variants each possessing their own promoter region have been identified: $1_{A, I, D, J, E, B, F, C \text{ and } H}$ (Turner and Muller 2005). In an investigation in the hippocampus of suicide completers with a history of childhood abuse, expression of the non-coding exons 1_B, 1_C and 1_H was found to be significantly decreased compared to non-abused suicides and controls (Labonte et al. 2012a). $GR1_C$ promoter methylation levels were found to be inversely correlated with $GR1_C$ expression in accordance with the previous finding on $GR1_F$ variant, whereas the $GR1_H$ promoter showed site-specific hypomethylation that was positively correlated with $GR1_H$ expression. These findings suggest that active demethylation may also be a functional mechanism affected by child abuse and suicide. Although this is a mechanism that has received less attention, further work is required to comprehend its potential implications in the context of early-life adversity.

Several groups have also investigated in peripheral blood samples from different populations of individuals that were exposed to varying forms of early-life adversity and have reported changes in DNA methylation of GR. Infants of mothers that endured intimate partner violence during pregnancy exhibited higher levels of methylation in the promoter of $GR1_F$ compared to those from mothers without such exposure (Radtke et al. 2011). Another study reported significant correlations between $GR1_F$ promoter methylation levels and parental loss, child maltreatment and parental care such that diminished care was associated with increased methylation of this gene (Tyrka et al. 2012). The severity of the type of abuse and frequency were found to be positively correlated with $GR1_F$ promoter methylation levels in another study investigating childhood maltreatment (Perroud et al. 2014, 2011). In sum, the evidence so far suggests that early-life adversity is capable of inducing specific long-lasting epigenetic alterations ultimately affecting gene expression.

Further to this, in a different study examining the expression of several GR exon 1 variants expressed in tissue from limbic regions of depressed suicide completers, hippocampal expression of the exon variants $GR1_F$ and $GR1_C$ was found to be significantly decreased without any changes in promoter methylation (Alt et al. 2010). However, this study examined DNA methylation only in a limited region of the gene, and the levels of promoter methylation that were detected were quite low. In addition, presence of early-life adversity was not a factor that was accounted for in this study, so it is possible that different molecular pathways are implicated in suicide completers without histories of early-life adversity.

9.4 Changes in the Epigenetic Regulation of the Brain-Derived Neurotrophic Factor (BDNF) Gene

There has been significant interest in neurotrophins or neurotrophic factors as candidate molecules to study in association with the development of psychopathology. These molecules play an important role in neuronal survival and plasticity and are expressed in the limbic regions of the brain, where the processing of emotions and related behaviours occurs. Among neurotrophic factors, there has been significant interest in brain-derived neurotrophic factor (BDNF), a neurotrophin involved in neuronal growth and development, in its involvement in psychiatric conditions such as depressive disorders and suicide (Brunoni et al. 2008; Dwivedi et al. 2003; Pandey et al. 2008). Roth and colleagues examined the role of early-life adversity in the epigenetic regulation of the BDNF gene in a rat model of maternal care studying the effect of repeatedly exposing pups for a short duration to non-biological mothers exhibiting abusive maternal behaviours which included pup avoidance and rough pup handling (Roth et al. 2009). They reported site-specific hypermethylation in the promoter region of transcripts IV and IX and decreased BDNF expression in the prefrontal cortex of the adult rats from the maltreated group compared to controls. The effects on BDNF expression could be reversed by intra-cerebroventricular injection of a DNA methyltransferase inhibitor, suggesting that epigenetic mechanisms are involved in the regulation of BDNF expression.

Several investigations into the methylation state of BDNF resulting from exposure to early-life adversity have been completed in humans. In one study, Keller and colleagues assessed in post-mortem tissues obtained from the Wernicke area from suicide completers the methylation levels in a region encompassing part of the non-coding exon IV and its promoter and found that methylation in four CpGs that are located downstream from the promoter IV transcription initiation site was significantly increased in suicide completers compared to controls (Keller et al. 2010). In another study, peripheral blood leucocytes were obtained from borderline personality patients who were assessed for childhood maltreatment, and in this population of patients, peripheral levels of methylation in the BDNF gene promoter increased as a function of the number of childhood traumas experienced, suggesting that methylation of BDNF associates with early-life adversity (Perroud et al. 2013). Another study using blood samples obtained from patients being treated for major depressive disorder who were also assessed for suicidal behaviours reported that greater BDNF promoter methylation was highly correlated with history of suicidal attempts and suicidal ideation (Kang et al. 2013a). Moreover, BDNF methylation levels were found to predict the likelihood of improvement from suicidal ideation during the treatment period such that patients with greater BDNF methylation exhibited less improvement on suicide ideation compared to those with lower BDNF methylation levels.

9.5 Changes in the Epigenetic Regulation of Serotoninergic Genes

The serotonin system, which has been highly implicated in major depressive disorders and behavioural regulation, has also been the focus of study in relation to epigenetic changes associated with early-life adversity and suicide. Several alterations including lower concentration, binding, neurotransmission and reuptake of serotonin and its metabolites have been reported in association with suicidality and major depression (Cronholm et al. 1977; Bhagwagar and Cowen 2008). The serotonin receptor subtype 2A (5-HT_{2A}) and its gene have been largely investigated in association studies of suicidal behaviour (Du et al. 2001; Turecki et al. 1999). In particular, the 102 C/T polymorphism has been commonly investigated (Du et al. 2000; De Luca et al. 2007), and methylation in the C allele variant is associated with higher expression of DNMT1 (Polesskaya et al. 2006). One study reported increased methylation of this variant in leucocytes from suicide ideators and a non-significant decrease in methylation in the prefrontal cortex of suicide completers carrying the C allele (De Luca et al. 2009), suggesting that methylation patterns may be different between individuals who committed and those planning suicide.

The serotonin transporter (5-HTT) gene has also been implicated in the interaction between early-life stress and the risk of depression in human and primate models (Caspi et al. 2003). An early study that examined peripheral blood samples from rhesus macaques reported that enhanced methylation of the 5-HTT promoter was associated with increased reactivity to stress in maternally deprived, but not mother-reared, infants (Capitanio et al. 2005). Several studies in humans have also found

associations between early-life adversity and DNA methylation of the 5-HTT gene. Investigating in lymphoblast DNA samples from subjects of the Iowa Adoption Study, Beach and colleagues reported a significant association between childhood sexual abuse and overall DNA methylation of the 5-HTT gene promoter region (Beach et al. 2010, 2011). Moreover, they revealed that the DNA methylation patterns observed in this gene were associated with the emergence of antisocial personality disorder in adulthood (Beach et al. 2011). Using the same cohort of subjects, another study reported a correlation between childhood abuse and DNA methylation at four CpG sites in the nonpromoter regions of the 5-HTT gene (Vijayendran et al. 2012). Another study investigating the methylation status of the 5-HTT promoter in peripheral blood samples of patients with major depressive disorders reported significantly higher DNA methylation levels in those who experienced early-life adversity (Kang et al. 2013b). However, a more recent study conducted in peripheral blood from a German cohort did not observe any site-specific changes in methylation associated with childhood trauma (Wankerl et al. 2014). The apparent discrepancy in results among these studies could have been attributed to the fact that different cell types were investigated and different promoter subregions were examined and, as well, different methods were applied to measure methylation, which are all important factors to take into consideration when making such comparisons.

9.6 Investigating Genome-Wide Epigenetic Changes

The studies described above have all focused on the epigenetic changes occurring on a specific gene, but it is possible that early-life adversity may induce epigenetic changes across the whole genome. One of the first genome-wide investigations was performed by Labonté and colleagues investigating promoter DNA methylation in post-mortem hippocampal tissue collected from individuals with a history of severe childhood abuse (Labonte et al. 2012b). The methylation profiles of individuals that experienced severe child abuse and non-abused controls were compared, and a total of 362 promoters were found to be differentially methylated in the abused group with 248 exhibiting hypermethylation and 114 hypomethylation. The greatest DNA methylation changes were reported to be occurring mainly in neurons and in genes that are involved in neural plasticity. More recently, a genome-wide DNA methylation study in post-mortem ventral prefrontal cortex tissues obtained from individuals suffering from major depression who died by suicide was conducted in which a total of 15,249 CpG sites were examined. This study reported eightfold more CpG sites showing hypermethylation in the suicide group compared to controls, and these CpG sites were located within genes implicated in behaviour, cell cycle, cell death and survival and cellular and embryonic development (Haghighi et al. 2014). Although in these individuals information on history of childhood abuse was not available, the findings combined with those from Labonté and colleagues do suggest that DNA hypermethylation in the brain may be a common feature associated with suicide.

In addition to studies conducted on brain tissues, there have been several genome-wide studies performed in peripheral samples obtained from individuals that experienced childhood abuse. Although these studies did not investigate suicidal

behaviour, they address the epigenetic regulation of early-life adversity. One study that examined peripheral blood samples obtained from post-traumatic stress disorder (PTSD) patients reported significant differences in the expression of several genes as well as more DNA methylation profile differences in the same genes in those who experienced childhood abuse than those without such histories (Mehta et al. 2013). Another genome-wide promoter DNA methylation investigation conducted in peripheral blood from subjects of the 1958 British cohort reported that childhood abuse was associated with significant differential methylation in 997 gene promoters – 311 of which exhibited hypermethylation and 686 hypomethylation (Suderman et al. 2014). Most of the methylation differences in this study were located in genes implicated in key cell signalling pathways related to transcriptional regulation and development. In addition, this investigation revealed significant DNA methylation differences in several genes that code for microRNAs in subjects with histories of child abuse compared to those without. In another study examining genome-wide DNA methylation in saliva samples from abused or neglected children, 2,868 CpG sites were found to be significantly differentially methylated in maltreated children compared to controls (Yang et al. 2013). In addition, the identified CpG sites were located within genes implicated in not only psychiatric disorders but also in several other health conditions commonly associated with childhood abuse including heart disease, stroke, respiratory disorders, among others. In sum, these findings provide ample evidence to suggest that childhood abuse is associated with numerous epigenetic adaptations occurring within the whole genome.

Conclusion

The data reviewed in this chapter provide strong evidence suggesting that early-life adversity and, in particular, childhood abuse can affect molecular processes involved in the regulation of emotion and behaviour. Through changes in the epigenetic regulation of genes involved in critical neuronal processes, changes in early-life environment may be capable of inducing behavioural changes during development that can have significant consequences later in life. The findings reviewed in this chapter point to several environmentally induced epigenetic changes occurring in the regulatory regions of genes involved in the stress response, neuroplasticity and neurotransmission in individuals that committed suicide and had histories of childhood abuse. Altogether, the data suggest that epigenetics may be a mechanism through which early environmental factors can act to induce long-term changes in behavioural responses, which could have a negative impact and increase the risk for suicide.

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Neuroinflammation in Suicide

10

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Abstract

Recent findings suggest the existence of a chronic low-grade inflammation in suicidal behavior. Postmortem studies demonstrated associations between suicide and inflammatory cytokines in the orbitofrontal cortex, a brain region involved in suicidal vulnerability. Also, microgliosis and monocyte–macrophage system activation may be a useful marker of suicide neurobiology. Kynurenine may influence inflammatory processes, and related molecular pathways may be involved in SB pathophysiology. Studies associated inflammatory markers with several indicators of suicidal vulnerability: serotonin dysfunction, impulsivity, and childhood trauma. Furthermore, the perception of threat that leads suicidal individuals to contemplate suicide may activate biological stress responses, including inflammatory responses. This new line of evidence involving inflammation along the development of a suicidal vulnerability should foster translational projects aimed at identifying potential biomarkers of suicidal behavior. These researches might lead to new biomarkers and novel directions for therapeutic strategies.

10.1 Introduction

"Over the past decade, it has become widely accepted that inflammation is a driving force behind chronic diseases" (Couzin-Frankel 2010). Psychiatric diseases are in the same line, as evidence supports inflammatory alterations in major depressive disorder (MDD) (Dowlati et al. 2010; Valkanova et al. 2013), schizophrenia (Potvin

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et al. 2008), and bipolar disorder (Modabbernia et al. 2013). What are suicidal behaviors about?

The aims of the recent World Health Organization (WHO) report, highlighting that every 40 s a person dies from suicide somewhere in the world, are to increase awareness on the public health significance of suicide and make suicide prevention a greater priority within the global public health agenda. The commonly accepted "stress-diathesis" model suggests that the suicidal act results from a complex interaction between vulnerability factors (diathesis) and environmental events or psychiatric diseases (stress) (Courtet et al. 2011). Suicidal behavior disorder, defined by the presence of a suicide attempt within 2 years, has been included in the DSM-5 as an independent clinical entity (American Psychiatric Association 2013) due to the large amount of evidence demonstrating a specific suicidal pathophysiology of suicidal behavior (SB). SB refers to a continuum of behaviors from completed suicide and suicidal attempt (public suicidal behavior) to suicidal ideation (private suicidal behavior) (O'Carroll et al. 1996; Harris 2013). Despite a robust increase in efficient pharmacological treatments for psychiatric diseases associated with increased risk of suicide, the rates of suicide ideation, suicide attempts, and completed suicides have not decreased substantially over recent years (Kessler et al. 2005). Thus, new hypotheses to better understand SB are needed and may lead to improved therapeutic strategies because efficient treatments to prevent suicide are still lacking. One of the proposals on the research agenda of the National Action Alliance for Suicide Prevention (www.suicide-research-agenda.org) is to explore the role of inflammation in depression and suicide risk.

10.2 SB Inflammation Hypothesis: Epidemiological and Clinical Observations

Immune system activation via cytokine therapy was reported to yield psychiatric side effects, such as depression. An increased suicide risk was validated in patients treated with cytokines for various pathologies such as melanoma, hepatitis C (HCV), HIV infections, and multiple sclerosis (MS) (Fragoso et al. 2010; Fukunishi et al. 1998; Janssen et al. 1994; Lana-Peixoto et al. 2002; Baron et al. 1993). The first 12 weeks of INF-α therapy in HCV patients represents a high-risk period and the onset of SB symptoms was specifically linked to serotonin depletion (Sockalingam et al. 2011). Furthermore, 11 cases of severe SB depression were reported in patients with MS treated by IFN-β with no previous psychiatric history. INF-β withdrawal led to complete remission (Fragoso et al. 2010). Peripheral administration of IFN-α for HCV treatment was shown to activate the dorsal anterior cingulate cortex (dACC) (Capuron et al. 2005), a region involved in SB (Jollant et al. 2011).

Associations were reported between allergy, asthma, and SB, with seasonal variation of suicide rates unveiling a suicide peak during spring and early summer (Christodoulou et al. 2012; Woo et al. 2012), in persons with and without prior history of mood disorders (Postolache et al. 2010). Several studies blamed allergies for this seasonal effect. Based on a 13-year database covering all suicides in Northern Finland, there was a significantly higher proportion of suicides among atopic patients during the first half of the year (Timonen et al. 2004). Spring tree pollen peaks were

associated with increased nonviolent suicide among women (Postolache et al. 2005). A history of allergy (Qin et al. 2011) predicted a greater risk of suicide completion among persons with MDD history. In an ecological study on patients with allergic rhinitis, intranasal corticosteroids (CS) were associated with reduced suicide risks. Conversely antihistamines were related to higher risks (Woo et al. 2011) since CS reduces the production of local airway Th2 cell-type cytokines, while antihistamines only secondarily affect cytokine production. Otherwise, associations between asthma and increased SB were reported among adults in the community and young people hospitalized for asthma (Goodwin and Eaton 2005; Goodwin et al. 2005).

Strong evidence of an association between *T. gondii* and SB (Okusaga and Postolache 2012) was also unveiled in cross-sectional studies (Arling et al. 2009; Ling et al. 2011; Okusaga et al. 2011; Yagmur et al. 2010; Zhang et al. 2012). A prospective cohort study on 45,788 women showed a predictive association between *T. gondii* IgG antibody levels and self-directed violence, violent suicide attempts, and suicide in later life (Pedersen et al. 2012). It could be mediated by elevated inflammatory cytokines (Aliberti and Bafica 2005) but also linked to the ability of *T. gondii* to modify testosterone, dopamine, and impulsive aggression and disinhibition (Okusaga and Postolache 2012).

The existence of a common inflammation-related cause was suggested as a strong connection between somatic diseases, particularly cardio-metabolic ones, and depression. The same reasoning may apply to SB. A recent cohort study reported that premature deaths from natural causes were twice more common in people who self-harm (Bergen et al. 2012). Artero et al. reported that coronary artery disease risk was increased severalfold in subjects with SB, independently of depression (Artero et al. 2006). Frequency of somatic diseases in patients at risk for suicide might also be linked to a common cause related to immune activation (Danesh et al. 2000).

The increasing issue of SB in patients with chronic systemic inflammatory diseases has been addressed (Asano et al. 2013). Data derived from WHO mortality statistics showed that suicide rate was four to five times higher than expected in SLE patients (Harris and Barraclough 1994) and suicidal thoughts were described in 8–34 % of SLE patients (Xie et al. 2012), i.e., four to eight times higher than in the general population. Cardiovascular damages (Mok et al. 2014) and uncontrolled disease activity (Matsukawa et al. 1994) were correlated to the intensity of SI. Generally, population-based studies reported a two- to sevenfold increased risk of suicide for MS patients after adjustment for age (Brønnum-Hansen et al. 2005; Fredrikson et al. 2003; Sadovnick et al. 1991; Stenager et al. 1992), although no significant association was observed in a recent North American study based on death certificate data (Goodin et al. 2014). Suicide risk might be particularly high in the first year following MS diagnosis and among young men (Fredrikson et al. 2003), and over a quarter of MS patients might have SI (Feinstein 2011, 2002). In a cohort study of 445 military veterans with MS (Turner et al. 2006) reported that 29.4 % of them had SI and 7.9 % had persistent SI in the past 2 weeks. SI was independently associated with depression severity and bowel disability. A community-based clinic registry study on 188 MS patients (Viner et al. 2014) reported SI prevalence at 8.3 %. The demographic variable found to be associated with SI was age >65. Pattern et al. found that hopelessness was higher in secondary progressive

MS than in relapsing–remitting MS patients, increasing over time in the former. Finally, few data on SB are available in RA yet suggesting increased SI prevalence (11 %) particularly in women (14 % vs. 3 % in men) (Gettings 2010; Treharne et al. 2000). A prospective study based on a 13-year follow-up database with linkage to national hospital discharge registers of all committed suicides (1,296 males, 289 females) in northern Finland (Timonen et al. 2003) found that females were significantly overrepresented among RA patients who committed suicide (52.6 % RA women vs. 17.3 % control women, $p<0.001$). A recent study on 105 RA patients found that SI was lower in RA patients treated with strong anti-inflammatory properties drugs (methotrexate or leflunomide) vs. other drugs (Pinho de Oliveira Ribeiro et al. 2013).

10.3 Peripheral Inflammatory Markers

Cytokines, C-reactive protein (CRP), and chemokines are inflammatory markers, which can be sampled peripherally.

Two recent meta-analysis suggested cytokine alterations in suicidal behavior (Black and Miller 2014; Ducasse et al. 2015b). Notably, IL-2 blood levels were decreased in suicidal patients as compared to both non-suicidal patients and healthy controls. Previous meta-analyses did not find altered IL2 levels in patients with major depression, suggesting that it may act as a marker of SB. Moreover, retrospective cohort study reported lower levels of IL2 in attempters who completed suicide when compared to those who did not (Isung et al. 2012).

Because of the short half-life of cytokines, C-reactive protein (CRP) is a relevant alternative for research, because of its long half-life and detectability at lower levels. Courtet et al. analyzed fasting hsCRP levels in 600 patients upon admission for MDD (Courtet et al. 2015b). Patients with CRP levels >10 mg/l and those receiving CRP-altering treatment were excluded. An association was highlighted between CRP levels and SA history, after adjusting for several potential confounders. Taking CR ≤1 as a reference, the OR of SA for CRP levels between 1 and 3 was 2.26, 95 % CI [1.17; 4.36], and 2.48, 95 % CI [1.13; 5.46] for CRP levels >3. CRP was neither associated with time between sampling and last suicide attempt nor with current SI at time of CRP sampling. Results suggested that CRP may represent a trait marker of SA, with a substantial risk of SB in patients presenting low-grade inflammation with CRP >3 mg/l. In a representative birth cohort of 1,000 depressed patients with history of childhood maltreatment, they were twice more likely to show high peripheral blood concentrations of hsCRP (>3 mg/l) vs. depressed individuals without history of childhood abuse (Danese et al. 2008). SB data were not reported; the association of childhood abuse with depression may substantially increase the risk of suicide. However, Ducasse et al. (2015a) failed to find association between history of SB and CRP levels in a bipolar disorder cohort. This may be explained by the frequent inflammatory state in bipolar patients (leading to no difference between those with and without SB comorbidity) or by mood stabilizers that might have an anti-inflammatory action; indeed, lithium, lamotrigine, valproic acid, and atypical

antipsychotics reduce oxidative stress (Berk et al. 2011; Malhi et al. 2013). Some atypical agents, such as olanzapine, have been associated with a reduction of inflammatory markers (Berk et al. 2011). Interestingly, a study on 106 suicide attempters and 517 healthy controls (Suchankova et al. 2013) reported an association between the CRP gene (+1444C>T, rs1130864) and SB. The +1444T allele, previously linked to elevated CRP levels, was significantly more common among suicide attempters and associated with impulsiveness (Suchankova et al. 2009). The correlation between CRP levels and inherent heart disease in suicidal patients should be further evaluated.

Chemokines may regulate neurobiological processes relevant in psychiatric disorders: pro/anti-inflammatory effects, neurotransmitter-like effects, neuromodulation, modulation of stem/progenitor cells, and developmental effects (Stuart and Baune 2014). Some chemokines were associated with the psychopathology across entities of psychiatric disorders (Stuart and Baune 2014). MCP-1/CCL-2 and eotaxin/CCL-11 were not statistically significant between patients with or without suicidality (Black and Miller 2014). However, it is premature to propose a relevant conclusion.

10.4 Markers in the Brain of Suicide Victims

Immune alterations in the brain of suicide victims suggest that cytokines might be emerging from the brain and leaking to its periphery or are produced by peripheral immune cells and having an effect in the brain.

Between the peripheral and central nervous system, the neuroinflammation pathway involves microglial cell activation. Microglial cells are macrophage living in the brain, producing cytokines, and are important for the cross talk between the immune and nervous systems (Ransohoff and Cardona 2010). These cells are involved in neurotransmission (e.g., serotonergic and glutamatergic), expressing GABA and 5HT2B receptors (McNally et al. 2008; Bevilacqua et al. 2010). Moreover, proinflammatory cytokines induce 5HT2B receptor expression on microglial cells, permitting inflammatory regulation in turn. Thus, a Finnish study pointed out an association between stop codon HTR2B (resulting in decreased expression of 5HT2B) and impulsivity, which is known as a major suicidal vulnerability trait (Bevilacqua et al. 2010).

Several studies found increased microglial activation in brain tissues of suicide victims (Steiner et al. 2006, 2008; Torres-Platas et al. 2011, 2014; Schnieder et al. 2014), whatever psychiatric diagnosis associated. It suggests that SB might be associated with altered microglial activity and low-grade cerebral neuroinflammation, regardless of the psychiatric diagnosis. Thus, microgliosis activation might represent a useful marker of disease acuity/severity or point to a distinct neurobiology of suicide.

Microglial activation could lead to increased CNS cytokine production, known to modulate noradrenergic or serotonergic neurotransmission, and could potentially trigger suicidality (Steiner et al. 2008). Microglia, neurons, and astroglia abnormally express Toll-like receptors (TLRs) (Hanke and Kielian 2011); among them

TLR3 and TLR4 appear to be unique and important in brain functions. A study (Pandey et al. 2014) found increased protein expression of TLR3 and TLR4 in DLPFC of depressed and nondepressed suicide victims vs. controls suggesting that TLR3 and TLR4 protein expression could be dysregulated in suicide victims. Considering lithium's mechanisms of action (Cipriani et al. 2013), with its strong anti-inflammation effects, it suppresses microglial activation, reduces IL-6 and TNF-α production from activated microglia (Dong et al. 2014), and attenuates overexpression of proinflammatory cytokines and chemokines in vivo (Li et al. 2011). Lithium inhibits induced upregulation of TLR4 in microglia by activating the PI3K/Akt/FoxO1 signaling pathway.

Conversely, circulating cytokines can impact brain physiology and stimulate microglia via direct/indirect pathways. Brains from suicide victims are more exposed to peripheral cytokines crossing the BBB. Recent findings challenged the dogma of the brain's stringent impermeability to outside molecules in suicide (Bayard-Burfield et al. 1996; Falcone et al. 2010). Serum S100B levels were positively correlated with the severity of suicidality, independently of psychiatric diagnosis (Falcone et al. 2010). BBB disruption may precede or follow a peripheral or central immune response, leading to an influx of peripheral immune cells, many found within or in contact with vascular walls. If peripheral and CNS immune cells increase both cytokine secretion and exchanges across the BBB, it could trigger a feed-forward inflammatory prelude to suicide, where microglial priming would constitute part of the cerebral macrophage's response to peripheral stimuli.

10.5 Inflammation, Kynurenine Pathway, and Glutamate Neurotransmission

Several mechanisms can explain how cytokines may affect brain function and behavior: interactions with the hypothalamic-pituitary-adrenal (HPA) axis and the enzyme indoleamine-2, 3-dioxygenase (IDO). In the former, cytokines can activate the HPA axis resulting in altered cortisol levels having detrimental effects on neurons. The latter relates to activation or inhibition of the IDO enzyme resulting in altered serotonin metabolism and production of neuroactive substances (Hsu et al. 2014).

Plasma kynurenine levels are elevated in SA with depression vs. healthy controls and depressed patients who never attempted suicide (Sublette et al. 2011). Kynurenine might be involved in other types of violent behavior: antisocial violent offenders (Tiihonen et al. 2001) and alcoholics with a history of blacked-out violent impulsive behaviors (Vignau et al. 2010). Microglial activation results in an increased production of quinolinic acid (QUIN) (NMDA agonist). Indeed, increased QUIN immunoreactivity in microglia was observed in the anterior cingulate gyrus of suicide victims (Steiner et al. 2011). Elevated CSF QUIN levels were found in SA, but not kynurenic acid (KYNA) (Erhardt et al. 2013). Interestingly, QUIN levels were correlated with suicidal intent and higher levels of CSF IL-6 (meant to induce the kynurenine pathway through IDO activation). Recently Bay-Richter

et al. (2015) reported that CSF QUIN levels remained permanently elevated in patients vs. healthy controls >2 years post-suicide attempt. Serotonin levels might be depleted by activated microglia enhancing tryptophan metabolism to QUIN via the kynurenine pathway, inducing a reduced availability of serotonergic neurotransmission, a trait of suicidal vulnerability (Courtet et al. 2011). KYNA levels appear to be decreased in SB. In a study on schizophrenic patients, lower concentrations of CSF KYNA were found in SB patients (Carlborg et al. 2013). Similarly, Bay-Richter et al. (2015) reported decreased CSF KYNA levels in suicide attempters vs. healthy individuals, and CSF KYNA was negatively associated with SI and depression symptoms. Thus, elevated QUIN levels, particularly in combination with reduced KYNA levels (Schwarcz et al. 2010), might lead to excessive NMDA receptor stimulation, providing a neurobiological rationale for ketamine-induced alleviation of depression and suicidality (Nowak et al. 1995). It was reported that a single ketamine infusion quickly improved SI (as early as 40 min post-administration) (Ballard et al. 2014; Berman et al. 2000; DiazGranados et al. 2010; Kudoh et al. 2002; Larkin and Beautrais 2011; Price et al. 2009, 2014; Thakurta et al. 2012; Zarate et al. 2012), yet this component might not be completely driven by improvements in depression and anxiety (Ballard et al. 2014). These data might open new areas to treat SI in the ER. A recent study found IL-6 levels to be predictors of ketamine's efficacy in treatment-resistant depression (Yang et al. 2015). Baseline serum levels of IL-6 in responders were significantly higher vs. non-responders illustrating what might be expected from inflammatory-based biomarkers in the perspective of stratified medicine. Further studies are needed to evaluate it in SB.

10.6 Environmental Stressors and Inflammation

Environmental stressors and SB. Most suicide victims did experience at least one adverse life event in the year before their death (Isometsä et al. 1995). In Finland, a nationwide suicide population involving 1,067 persons found that the most frequent life events during the last 3 months were job problems (28 %), family discord (23 %), somatic illness (22 %), financial trouble (18 %), unemployment (16 %), separation (14 %), death (13 %), and illness in family (12 %) (Heikkinen et al. 1994). Most of these events lead to social exclusion feeling. Notably, a large cohort of western Canadian sawmill workers ($n = 28{,}794$) found that low social support at the workplace was a risk factor for attempted suicide (Ostry et al. 2007). A systematic review conducted by Fassberg et al. found that, at least in industrialized countries, limited social connectedness is associated with suicidal ideation, suicidal attempt, and suicide in later life (Fässberg et al. 2012). Moreover, researchers on soldiers have shown that unit cohesion can buffer against the deleterious effects of stress, the development of post-traumatic stress disorder and other psychiatric symptoms, and potentially the occurrence of SB (Nock et al. 2013). Then, a case–control study involving 371 depressed inpatients found that religious affiliated subjects were less likely to have history of suicide attempt and current suicidal ideation, despite comparable severity of depression, number of adverse life events, and

severity of hopelessness (Dervic et al. 2004). Interestingly, the authors found weaker family ties in religiously unaffiliated subjects, which is consistent with previous reports about less dense social networks among atheists (Pescosolido and Georgianna 1989). Notably, being affiliated to a religion may also promote social link feeling, belonging to a community. Besides, lesbian, gay, and bisexual (LGB) individuals are at higher risk of SB than non-LGB individuals (Arnarsson et al. 2015; Blosnich and Bossarte 2012), especially in rural and remote areas (Morandini et al. 2015), which have been linked to perceived social exclusion (i.e., stigma and discrimination) (Michaels et al. 2015). In the same perspective, studies have reported that belonging to an ethnic minority increases the risk of SB in areas where there are in low density, whereas the suicide risk is decreased in minority more dense areas (Termorshuizen et al. 2015; Neeleman and Wessely 1999). Thus, primary prevention programs designed to enhance social connections as well as a sense of community could potentially decrease suicide risk. Finally, interventions based on social contact have shown effectiveness in suicide prevention, nearly halving the number of repeat episodes in 12 months thanks to postcard sending to patients at intervals after discharge for an episode of deliberate self-poisoning (Carter et al. 2005) and reducing the proportion of people who reattempt suicide over 1 year after one telephone recontact (Vaiva et al. 2006). In addition to recent environmental events triggering SB, former life events are involved in suicidal vulnerability. Indeed, a reliable association has been found between a history of childhood adversities (e.g., childhood sexual and physical abuse, household dysfunction) and subsequent SB (Brodsky and Stanley 2008; Joiner et al. 2007). These traumatic early life events may lead to the feeling of social non-desirability.

Stressors are known to induce hypothalamic-pituitary-adrenal axis (HPA) activation, resulting in an alteration of cytokine levels (Felger and Lotrich 2013). In fact, although cortisol inhibits cytokine secretion during acute stress (Ruud et al. 2013), inflammatory cytokines also modulate HPA-axis function in a complex manner: activating the CRH-ACTH-cortisol cascade and downregulating glucocorticoid receptors (Grs) (Pace et al. 2009a). There is evidence for decreased GR expression in hippocampus of suicide persons having a past history of abuse (Labonte et al. 2012; McGowan et al. 2009) and in the prefrontal cortex and amygdala of suicide adolescents (Pandey et al. 2013; Pérez-Ortiz et al. 2013). Thus, inflammation may induce a functional glucocorticoid insufficiency (Oquendo et al. 2014), related to disturbed feedback inhibition by endogenous corticoids related to a blunted responsiveness of the negative feedback loop to glucocorticoids (Holsboer 2000), as measured by the dexamethasone suppression test (DST) (Raison et al. 2009). In this perspective, long-term oral glucocorticoid therapy increases the risk of depression and SB (Fardet et al. 2012), both during treatment and withdrawal (Felger and Lotrich 2013). Thus, adults who experienced childhood trauma exhibit HPA-axis dysregulation leading to a systemic proinflammatory state (Tyrka et al. 2013). Inflammatory marker alterations could be relevant biomarkers for mediating health consequences associated with childhood adversities (Danese and McEwen 2012). Recently (Coelho et al. 2014) a correlation between history of childhood maltreatment and increased CRP, fibrinogen, and proinflammatory cytokines levels was

reported. Childhood maltreatment might induce physiological responses enduring long after the initial threat has stopped. Convincing evidence did correlate childhood stress-induced immune dysregulation with suicidal morbidity and mortality (Dich et al. 2015). Childhood maltreatment might trigger low chronic inflammation inducing a feed-forward cycle when subjects become exposed to stressors. Interestingly, a meta-analysis on trauma exposure as a risk factor for inflammation reported moderate-to-large correlations between proinflammatory markers (IL-1β, IL-6, and TNF-α, CRP) and trauma exposure across a range of sample types and diagnoses (Tursich et al. 2014). A National Child Development Study in Great Britain involving 7,462 participants showed that socially isolated children (between 7 and 11 years) had higher levels of C-reactive protein in midlife (Lacey et al. 2014). Then, Caspi's study (Caspi et al. 2006) found that socially isolated children have heightened risk of cardiovascular diseases in adulthood. Finally, in a community sample of 132 healthy older adults including 58 dementia family caregivers and 74 non-caregivers, Kiecolt-Glaser et al. (2011) found that childhood adversity was associated with both shorter telomeres and heightened serum IL-6 and TNF-alpha levels after controlling for age, caregiving status, gender, BMI, exercise, and sleep. Moreover, childhood abuse and caregiving status were significantly and independently associated with higher levels of depressive symptoms. These findings provide further evidence of the lifelong impact of childhood adversities on adult health, possibly through inflammation.

As previously mentioned, altered social link has been associated to SB. Interestingly, evidence support that inflammation could be a major mediator in this relation. In fact, individuals with vs. without larger social networks have lower IL-6 and CRP than those with smaller social networks (Ford et al. 2006). Among older adult, married men have lower CRP levels than those unmarried (Sbarra 2009). Notably, the effect size of marriage on CRP is comparable to that of other traditional cardiovascular risk factors such as smoking, hypertension, and obesity (Sbarra 2009). Furthermore, in a genome-wide DNA microarray study comparing socially isolated individuals with those reporting less social isolation, genes overexpressed involved proinflammatory response elements and gene underexpressed by socially isolated individuals involved anti-inflammatory response elements (Cole et al. 2007). Then, lower social support has been involved in decreased leukocyte traffic regulation by cortisol (Cole 2008), higher CRP levels during pregnancy (Coussons-Read et al. 2007), and overexpression of proinflammatory transcription factor Nf-kB in ovarian tumors (Lutgendorf et al. 2009). As opposite, satisfying relationship with others has been related to lower IL-6 levels in older women (Friedman et al. 2005) and in ovarian cancer patients (Costanzo et al. 2005). To follow on, interpersonal stress has been involved in larger lipopolysaccharide (LPS)-stimulated IL-6 production in adolescents (Miller et al. 2009) and in adults suffering from rheumatoid arthritis (Davis et al. 2008) and higher CRP plasma levels in adolescents (Fuligni et al. 2009). Interestingly, inflammatory response to interpersonal conflicts has also been experimentally studied. Indeed, hostile behavior during marital conflict has been associated with enhanced norepinephrine production (Kiecolt-Glaser and Newton 2001) and increased IL-6 (Kiecolt-Glaser et al. 2005). Thus, it has been suggested that low

frequency of positive partner exchanges (i.e., low partner support) or a high frequency of negative partner exchanges (i.e., high partner strain) could lead to elevated IL-6 (Whisman and Sbarra 2012); excessive inflammation could also increase risk for other diseases through processes such as glucocorticoid sensitivity (Kiecolt-Glaser et al. 2010). Noteworthy, shame – a socially exclusion emotion – has been associated to elevations in proinflammatory cytokine activity, in a dose-response way (Dickerson et al. 2004). Then, trait shame has been associated with inflammatory activity and glucocorticoid sensitivity (Rohleder et al. 2008). The Trier Social Stress Test (TSST) – the gold standard and most commonly employed paradigm in biopsychological stress research – induces increased proinflammatory cytokines and hyperactivity of the anterior cingulate cortex and anterior insula (Frisch et al. 2015), both regions involved in suicidal vulnerability (Ding et al. 2015). Finally, given that convincing data support the link between feelings of social isolation and inflammation, Eisenberger et al. (2010) have demonstrated that this link could be bidirectional. In fact, this famous team has found that in addition to endotoxin (vs. placebo) leading to significant increases in depressed mood, it also led to significant increases in feelings of social disconnection. Moreover, increases in social disconnection mediated the relationship between inflammatory activity and depressed mood, such that controlling for these social psychological changes eliminated the relationship between exposure to inflammatory challenge and depressed mood.

10.7 Inflammation and Suicide-Related Phenotypes

The démonstration of the role of inflammation in SB regardless of related psychiatric disorders does not rule out the possibility that some specific features of depressive states might also be involved, for instance, sleep disturbance role in inflammation (Bryant et al. 2004; Kodaka et al. 2014; Motivala et al. 2005; Suarez 2008; Opp et al. 2007) and increased risk of SB (Kodaka et al. 2014). Sleep deprivation results in increased circulating levels of IL-6, TNF-alpha, and CRP vs. undisturbed sleep (Felger and Lotrich 2013; Meier-Ewert et al. 2004; Vgontzas et al. 1999, 2004).

Treatment-resistant depression has been strongly associated with SB (Greden 2001). Nonresponders to antidepressants have higher concentrations of circulating cytokines and acute-phase proteins than responders (Lanquillon et al. 2000). Two recent studies used inflammatory biomarkers to stratify depressed patients to personalize their treatment. The first (Raison et al. 2013) reported that infliximab (TNF antagonist) alleviated depressive symptoms in patients with treatment-resistant depression vs. placebo, only in patients with high CRP levels (>5 mg/L). The GENDEP study (Uher et al. 2014) reported that CRP levels at baseline differentially predicted treatment outcome with two antidepressants (nortriptyline and escitalopram). Treatment could in fact be adjusted according to inflammatory status and that treatment-resistant patients might be good candidates for novel antidepressant therapies targeting cytokines and inflammatory signaling pathways.

Suicidal vulnerability involves several personality traits, associated with inflammatory markers: impulsive aggression, hostility and anger (Perroud et al. 2011),

hopelessness and pessimism (Oquendo et al. 2004), neuroticism, and harm avoidance (Perroud et al. 2013). The relationship between these personality traits and inflammation was the object of animal and human studies suggesting that behavioral traits related to hostile, angry, and aggressive dispositions were associated with elevated inflammatory markers, such as IL-6 and CRP. Self-assessed anger and aggressive dispositions were greater in patients treated by cytokine immunotherapy (Kraus et al. 2003). Plasma CRP and IL-6 levels were significantly higher in participants with intermittent explosive disorder vs. psychiatric or normal controls (Coccaro et al. 2014). A life history of suicide attempts was associated with a significant difference for higher IL-6 levels and aggression scores, the latter mediating the relationship between life history of suicide attempts and IL-6 levels. Among other SB, those exhibiting high aggression levels had a higher risk of developing inflammatory disease.

Studies in healthy subjects reported associations between cytokine concentrations and pessimism, hopelessness, neuroticism, or harm avoidance (Henningsson et al. 2008; Mitchell et al. 2013; O'Donovan et al. 2009; Roy et al. 2010; Sutin et al. 2010; Turiano et al. 2013). The link between personality dimensions and innate immune response deserves to be further investigated.

10.8 Conclusion and Further Perspectives

There is a growing body of evidence showing innate inflammation-related CNS abnormalities including glial pathology, elevated cytokines levels, cyclooxygenase activation, glutamate dysregulation, S100B levels, oxidative stress, and BBB dysfunction in SB (Felger and Lotrich 2013; Haroon et al. 2012).

Before proposing a coherent model explaining the role of neuroinflammation in SB, further studies are needed to focus on the well-characterized suicidal behaviors and their intermediate pathways. However, we can propose a comprehensive model suggesting how inflammation could contribute to the pathophysiology of suicidal behavior (Courtet et al. 2015a). Suicidal behavior occurs from interaction between suicidal vulnerability and stressors. Considering suicidal vulnerability, childhood maltreatment leads to a systemic inflammatory state, promoting HPA-axis dysregulation (Tyrka et al. 2013). Additionally, the available epidemiological and clinical studies strongly point to a link between sleep loss or disturbances and suicidality (i.e., suicidal ideation, suicide attempts, or completed suicide) (Norra et al. 2011). Interestingly, sleep loss induces an inflammation response characterized by increased in cytokine serum level and C-reactive protein (Mullington et al. 2009). Finally, suicidal patients have been reported to have increased *T. gondii* infection (Okusaga and Postolache 2012), promoting low chronic inflammatory state. This leads to indoleamine-2,3-dioxygenase (IDO) activation, which produces kynurenine from tryptophan (Hsu et al. 2014). Then, microglial activation (i.e., the 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 an increased activation in glutamatergic pathway which also contributes to neuronal apoptosis (Leonard 2000). Besides, enhanced metabolism of tryptophan results in depleted serotonin levels, involved in 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 (Müller and Schwarz 2007). Furthermore, stressors – psychiatric diseases and adverse life events (social isolation and rejection) – act on suicidal vulnerability to induce suicidal behavior, through an activation of inflammatory response (Tursich et al. 2014).

Because circulating proinflammatory cytokines may affect mood states via functional alteration of limbic brain circuits, brain imaging studies should investigate both neural and inflammatory responses to social stressors. Cytokines could be involved in some cognitive changes involving verbal memory, cognitive speed, and executive functions, previously associated with SB. Neuropsychological studies need to take into account inflammatory markers. Patients presenting with suicidal vulnerability might respond to social rejection in terms of inflammatory activity and psychological pain, a process potentially triggered by adverse social experiences and having activated a sensitized pathway. It is essential to study biological aspects of social ties in SB.

We need to test neuropharmacological strategies targeting the immune system to treat neuropsychiatric disorders like SB and develop better biomarkers to measure the relative status of the immune response (Haroon et al. 2012). One should not overlook the potential impact of new psychotherapies on inflammation and suicide. Mindfulness seems to decrease inflammatory responses to a psychosocial laboratory stressor (Pace et al. 2009b). Interestingly, mindfulness-based interventions have shown significant decreases in interleukin (IL)-6 levels in women with histories of interpersonal trauma (Gallegos et al. 2015), as well as reductions in proinflammatory gene expression and inflammatory signaling in premenopausal women diagnosed with breast cancer (Bower et al. 2015). Then, a day of intensive practice of mindfulness meditation has shown decreased expression of proinflammatory genes (RIPK2 and COX2) in meditators compared with controls (Kaliman et al. 2014). Notably, lower levels of RIPK2 predicted better cortisol recovery in the TSST. Finally, an 8-week mindfulness-based stress reduction (MBSR) program (compared to a wait-list control group) has shown a reduction in loneliness and a tendency to reduce C-reactive protein (Creswell et al. 2012). These mechanisms should be investigated when evaluating acceptance and commitment therapies for treating patients suffering from suicidal behavior disorder (Ducasse et al. 2014).

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A Social Neuroscience Perspective on Suicidal Behavior

11

Anthony J. Gifuni and Fabrice Jollant

These, then, are my last words to you: Be not afraid of life. Believe that life is worth living, and your belief will help create the fact. -William James, Is Life worth Living?, 1904

Abstract

Suicidal behavior is social in nature in many cases. Understanding the mechanisms underlying the development of the suicidal crisis and the occurrence of suicidal acts will benefit from using the tools of social neuroscience. In this chapter, we will briefly review some results. First, suicidal acts have been associated with deficient biochemical systems, notably the serotonergic system and the stress system, both being strongly implicated in social interactions. Second, several neurocognitive deficits have been recently showed including impaired decision-making, reduced cognitive control, and deficient memory. These deficits have been related to a dysfunctional network of brain regions including the orbitofrontal cortex and the dorsolateral prefrontal cortex. In an integrated view, we propose that one basic alteration increasing the risk of suicidal acts is a deficient valuation process. More generally, suicidal behavior may reflect a breach in social homeostasis.

Suicidal behavior is social in nature in many, if not all, cases. Durkheim (1897) in his famous book *Le suicide* highlighted this fact. However, he presented suicide as

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the consequence of the degree of integration of individuals in society and the degree of regulation by society on individuals. More recently, emphasis has been put on the individuals themselves, notably the variations in individual characteristics that may explain the increased risk of suicidal acts in stressful situations.

Even if "society" is not seen as sufficient to explain suicide, many factors plead for a social perspective of these complex acts. First, precipitants of social crisis are by large, interpersonal conflicts or issues questioning the place of the individual in society (e.g., unemployment, legal issues) (Foster 2011). Second, one major early environmental factor increasing the later risk of suicide is childhood sexual abuse, with its negative interpersonal consequences (Brezo et al. 2007; Fergusson et al. 2000). Third, many suicidal acts are clearly a cry for help exposing others to the individual's difficulties in solving a given situation (Brown et al. 2002). Fourth, personality disorders and traits, i.e., long-term tendencies towards inadequate relationships with others and oneself, are major vulnerability factors of suicidal acts (Dumais et al. 2005; Pietrefesa and Evans). Also, attempters tend to have a restricted social network (Szanto et al. 2012). Finally, suicide is a uniquely human behavior, therefore affecting one of few animal species showing highly developed social interactions and rules (Wilson 2012).

As a consequence, understanding suicide will benefit from integrating the tools and approaches developed by what is now usually referred as "social neuroscience." Social neuroscience is a conceptual framework emerging at the juncture of cognitive neuroscience and social psychology; it delineates the biological underpinning of social interactions, from perception to action (Cacioppo et al. 2014). In this chapter, we will summarize the main findings from biochemical to neurocognitive studies of suicidal behavior in the perspective of social neuroscience.

11.1 Deficient Biochemical Systems

11.1.1 Serotonin

Abnormalities of the serotonergic system have been robustly associated with suicidal risk. An early finding showed that lower levels of the main serotonin metabolite, 5-HIAA, in the cerebrospinal fluid were predictive of suicidal gestures in a population of depressed patients (Asberg et al. 1976; Mann et al. 2006). Several *postmortem* brain analyses in suicide completers as well as *in vivo* findings in suicide attempters have subsequently corroborated the role of a dysfunctional serotonergic system in suicidal behaviors (Mann 2003; Arango et al. 2002; Audenaert et al. 2001; Leyton et al. 2006).

The role of serotonin extends to many behaviors that require adaptation to the environment, notably the social environment. Alterations in the serotonergic system can influence parental attachment and caregiving, social play, aggressiveness, cooperation, and sexual behaviors (Kiser et al. 2012). Patients with impaired impulse control and violent behavior have similar deficiency in the serotonin system (Coccaro 1989; Davidson et al. 2000). Thus, reduced serotonergic activity

increases vulnerability to suicide through several pathways, including decreased inhibitory control on behavior (Turecki 2005). Moreover, genetic variations of the serotonin transporter (5-HTT) alter the perception of social cues (Canli and Lesch 2007). During a facial emotion-reading task, subjects with the short version of 5-HTT activated the amygdala significantly more than the controls (Hariri et al. 2002). Moreover, the same 5-HTT-linked polymorphic region short variant is associated with neuroticism (Lesch et al. 1996; Greenberg et al. 2000), a personality trait characterized by experiencing negative feelings and an identified risk factor for suicide (Bluml et al. 2013). Furthermore, mounting evidence suggests that social factors associated with suicide influence the serotonergic system. For example, depressed patients reporting childhood abuse seemed to have lower levels of 5-HTT than nonabused patients across the brain (Miller et al. 2009). Similarly in nonhuman primates, maternal deprivation causes reduced 5-HIAA levels in the cerebrospinal fluid (Shannon et al. 2005), a trait which remains stable throughout life (Higley et al. 1992). In sum, alterations in serotonergic activity, which result both from long-term genetic and early environmental influences, lead to deficits in different aspects of social cognition that can mediate an increased suicidal risk.

11.1.2 Stress Systems

Several anomalies have been found in the stress-response system of suicidal patients, including the noradrenergic system and the hypothalamic-pituitary-adrenal (HPA) axis (Mann 2003; Galfalvy et al. 2009). Notably, evidence suggests that the HPA axis is overactive in suicidal patients, with nonsuppression of the cortisol response by dexamethasone in depressed patients being associated with a fourfold increase in the risk of future suicide (Mann et al. 2006). Dysregulation of the HPA axis also seems to be an important moderator in the risk of suicide in victims of childhood abuse (McGowan et al. 2009).

The relationship between the stress-response and suicidal behaviors remains understudied at the social cognition level. Aversive social experiences such as rejection, humiliation, and loss of a love one are among the most stressful psychological events that can occur in one's life. These social events are known to trigger "suicidal crisis." Besides, social support, which is a protective factor against stress (Lepore et al. 1993; Turner-Cobb et al. 2000), constitutes a protective factor against suicide as well (Kleiman and Liu 2013; Kleiman and Riskind 2013). Not surprisingly, most preventive clinical interventions will promote help-seeking behaviors and try to mobilize social support around the suicidal patient. At a neurocognitive level, stress alters many cognitive functions, especially in vulnerable individuals (see below). Suicidal thoughts might be conceptualized as a maladaptive way to regulate excessive and overwhelming social stress, in the context of social isolation. More research is needed to clarify the role of the stress-response system, its reciprocal relationship with the surrounding social environment, and its role in the emergence of suicidal thoughts and acts.

11.2 Neurocognitive Deficits in Suicide Attempters

11.2.1 Impaired Decision-Making

Decision-making is the cognitive process by which an individual selects a course of action among a set of alternative possibilities. Human capacity for decision has evolved to make decision under variable and uncertain conditions, integrating both memory of past experiences and current internal and external stimuli (Fellows 2004). Decision-making is a crucial cognitive ability for survival and adaptation. Decision-making in complex situations involves cortical areas such as the prefrontal cortex and subcortical structures such as the ventral striatum and the amygdala (Lawrence et al. 2009). The serotonergic input to prefrontal regions also modulates decision-making (Rogers 2011) and influences impulse control (Van Praag 1991; New et al. 2002). Decision-making abilities are closely related to interpersonal capacities and emotional intelligence (Bar-On et al. 2003). Finally, decision-making is closely influenced by stress. An example of this link is found in abstinent drug addicts, in whom social stress uncovers "hidden" impaired decision-making (Zhang et al. 2011).

Several studies have reported impaired decision-making in suicide attempters, from adolescents to elderly, after accounting for psychiatric comorbidity (Jollant et al. 2005; Clark et al. 2011). Most of these studies have used the Iowa Gambling Task, an experimental paradigm intended to simulate real-life decision-making processes (Bechara et al. 1994), or the Cambridge Gamble Task. A recent meta-analysis confirmed lower decision-making performance in suicide attempters in comparison to patient controls with a moderate effect size (Richard-Devantoy et al. 2014a). Rather than being a fluctuating state, impaired decision-making seems to be a susceptibility trait persisting beyond the acute depressive state, as it has been found in patients in remission from depression (Jollant et al. 2005).

One study in suicide attempters (Jollant et al. 2007b) reported a correlation between disadvantageous decision-making and interpersonal conflicts, suggesting that impaired decision-making and its related biological basis may also be linked to inadequate interpersonal relationships. Impaired decision-making may therefore account for the choice of a suicidal act in an unbearable situation but, beforehand, promote the occurrence of social difficulties that are known triggers of suicidal acts.

The mechanisms underlying impaired decision-making in suicide attempters have yet to be clarified, but a partial explanation could reside in an altered brain response to external rewards and punishments and impaired risk encoding. Several studies suggest that many suicidal patients possess increased sensitivity to negative feedback (Dombrovski et al. 2010), make nearsighted decisions (Dombrovski et al. 2011), disproportionately anticipate negative outcomes (Dombrovski et al. 2013), and more generally show a deficient risk encoding (Jollant et al. 2010). Neuroimaging studies in suicidal patients have shown that these deficits are associated with functional anomalies in the basal ganglia (Dombrovski et al. 2011), ventromedial prefrontal cortex (Dombrovski et al. 2013), and orbitofrontal cortex (Jollant et al. 2010).

In terms of causal factors, genetic factors related to the serotonergic system have been found to modulate decision-making (Jollant et al. 2007a). A study (Guillaume et al. 2013) showed that childhood abuse is also associated with impaired adult decision-making and interacts with genetic polymorphisms linked to the HPA axis to modulate decision-making. Preliminary data from our group suggests that impaired decision-making is also found in first-degree relatives of suicide completers with no personal history of suicidal act, suggesting heritable features. Disadvantageous decision-making in adult suicide attempters may therefore results from an impaired development under genetic and early environmental influences (Turecki et al. 2012).

In sum, studies of the neuropsychological deficits of suicide attempters and their neurobiological correlates suggest that the decision to commit suicide is far from being a free choice. Rather, it is the result of a pathological neurocognitive process.

11.2.2 Deficient Cognitive Control

Cognitive control appears to be deficient in patients at risk of suicidal behaviors (Richard-Devantoy et al. 2012), a result recently confirmed by a meta-analysis (Richard-Devantoy et al. 2014a). Cognitive control is defined as the ability to prevent irrelevant stimuli to be used by working memory or to suppress no longer relevant stimuli that interfere with the task at hand (Miyake et al. 2000). For instance, the Stroop interference effect was found to be significantly higher in depressed suicide attempters compared to depressed non-attempters (Keilp et al. 2008). Additionally, greater interference was found on a Stroop task in suicide attempters when suicide-related words were used as distractors (Becker et al. 1999). This attentional bias for suicide-related words was predictive of future suicidal behavior in a 6-month longitudinal study (Cha et al. 2010). The effect seemed relatively specific, because an attentional bias for negatively valenced words did not have any predictive value on suicidal behaviors. These data support the notion that suicide-specific attentional biases contribute to the cognitive vulnerability to suicidal behaviors.

Attentional bias towards suicidal ideas might lead to an obsessive fixation on suicide and interfere with efficient problem-solving. Moreover, deficit in cognitive control impairs the regulation of emotions, thoughts, and actions (Joormann and Gotlib 2008). In the context of a suicidal crisis, suicidal acts might be facilitated by protracted negative ruminations, excessive intrusive thoughts, and sustained negative affect, which cannot be tempered by the limited cognitive inhibition capacities.

Dysfunction of the dorsolateral cortex, a region previously associated with suicidal behaviors (Jollant et al. 2011), might underlie the deficits of cognitive inhibition in suicidal patients. Here again, a deficient serotonergic system may explain alterations in cognitive inhibition (Roiser et al. 2007). The serotonergic system modulates activity of the medial and dorsolateral prefrontal cortices in suicide

attempters, activities that were correlated with suicidal intent and impulsivity, and subsequently lethality (Oquendo et al. 2003).

11.2.3 Memory Deficits

A recent systematic review and meta-analysis examined if memory deficits were a component of the neuropsychological vulnerability to suicide (Richard-Devantoy et al. 2014b). Autobiographical memory was significantly less specific in suicide attempters compared to patient controls. Furthermore, long-term memory and working memory were also altered in suicide attempters. In contrast, short-term memory was not found to be different between suicide attempters and patient controls, suggesting that any deficit in this domain pertained to the affective comorbidity. Specific autobiographical memory is thought to rely on a reciprocal relationship with the "working self," which is constituted of active personal goals and self-images (Conway and Pleydell-Pearce 2000). In suicidal patients, repeatedly thwarted personal goals combined with a constrained negative self-image might thus contribute to memory impairment, in a "defensive way" to prevent the painful experience of retrieval. Literature suggests that deficits in autobiographical memory impede social problem-solving skills (Beaman et al. 2007), which necessitates the use of past experiences.

The neural abnormalities explaining mnesic deficit in suicidal patients might be located in the hippocampus, although this has not been formally assessed. The literature suggests that several biochemical alterations can be found in the hippocampus of suicide completers (Labonte et al. 2013). More research is needed in this specific domain.

11.2.4 Impaired Responses to Negative Social Cues

In suicide attempters compared to affective controls, the perception of prototypical angry faces elicits an increased activation of the right orbitofrontal cortex and a decreased activation in the right superior prefrontal cortex (Jollant et al. 2008). Similarly, adolescents with past suicide attempts display functional neural alterations in response to angry faces compared to affective controls (Pan et al. 2013). Thus, suicide attempters seem to exhibit particularly high sensitivity responding to negative socioemotional cues, particularly angry facial expression. This emotion conveys signals of threat for the individual and forewarns an individual of the possibility of violent retribution (Öhman 2008). The ability to react adequately to angry faces is critical to regulate normal socioemotional functioning.

Preliminary data from a study in female euthymic patients suggest reduced response to a social exclusion paradigm in the left insula, superior temporal gyrus, and precuneus in attempters vs. patient controls (Olié et al. in prep). These findings suggest a downregulation of these regions involved in pain processing, self-awareness, and social processing. This could explain the reported higher tolerance

to pain in suicide attempters (Smith et al. 2010) and their tendency to commit more errors in social recognition (Szanto et al. 2012).

Finally, a study in elderly people using the Ultimatum Game, in which participants accept or refuse an offer on the basis of its level of unfairness, showed that high-lethality attempters tended to reject all unfair offers whatever the degree of unfairness (Szanto et al. 2014). These patients therefore seem to be particularly sensitive to unfairness and lack the necessary balance to evaluate the potential benefits of accepting some unfair offers, therefore leading to rigid decision-making.

11.3 An Integrative Understanding: Impaired Valuation and Homeostatic Processes in Suicidal Behavior

We proposed that deficits in valuation processes may be a key contributor to suicidal vulnerability (Jollant et al. 2011). This may underlie the inability to encode reward and risk (leading to risky decision-making), the response to some social stimuli, and more generally, the difficulty in fine-tuning the perception and the response in relation to the environment, notably the social environment. Additional processes, including memory and cognitive control deficits would add to the persistently induced painful state, the tendency for ruminative thinking, the inability to find alternative solutions based on past experience, and the higher risk of acting out.

A general hypothesis (Jollant and Courtet 2010) may be that suicidal behavior is the extreme outcome of the loss of social homeostasis, i.e., the internal regulation of social interactions, from the perception to the responses (cognitive, emotional, behavioral) brought about by the social environment. Breach in homeostasis signaled by psychological pain would lead to the ultimate choice of a suicidal act, either to alleviate an unbearable suffering by death or, in the case of nonfatal suicidal acts with low intent, recover balance.

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Psychological and Social Pain

12

E. Olié

Abstract

Suicidal behaviors are defined as a unique clinical entity, based on a stress-vulnerability model. Psychological pain, defined as a lasting unsustainable feeling resulting from an appraisal of an inability or deficiency of the self, is one of the most often mentioned reasons for suicide. Several authors have reported higher psychological pain in suicidal patients. Moreover, suicidal vulnerability influences psychological pain perception through neuropsychological impairments and neuroanatomical dysfunctions. Thus, suicidal individuals are in a state of intense focus on the pain and associated negative emotions. Interpersonal difficulties lead to social pain, a component of psychological pain. In addition, such difficulties are associated to impaired decision-making and trigger suicidal act. Thus, considering psychological/social pain at core of suicidal behavior may help to identify new biomarkers, to improve the understanding of pathophysiology of suicidal process, and to develop new therapeutic strategies.

Most likely, we all experience psychological pain at some point in our lives, for example, due to a pervasive illness, due to interpersonal conflicts such as breakup of a romantic relationship, or due to perceived social exclusion. Becoming unbearable for some of our patients, psychological pain is the most often mentioned reason for suicide (Chavez-Hernandez et al. 2009).

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12.1 Psychological Pain and Suicide

12.1.1 Definition

A major problem is the lack of agreement about distinctive features, conceptualization, and operational definition of psychological pain. In the literature, terms such as mental pain, psychic pain, psychological pain, emptiness, psychache, internal perturbation, and psychological quality of life have been used to refer to the same construct (review in Tossani 2013). Meerwijk et al. (Meerwijk and Weiss 2013) identified common characteristics to better define psychological pain: a lasting unpleasant unsustainable feeling, resulting from an appraisal of an inability or deficiency of the self (inability to protect yourself from shame or harm, an inability to achieve that what is of vital importance to you, or a deficiency in love, support, or affiliation among other things).

12.1.2 Association with Suicidal Ideation and Behaviors

Suicide notes often report "life is too hard to bear." Bancroft et al. (1979) interviewed 128 suicide attempters about the reasons for taking overdoses: 52 % of patients expressed a desire to get relief from a terrible psychological state, and 42 % wished to escape from the situation. Chavez-Hernandez et al. (2009) reported that the main trigger for suicidal act given by the patients was the existence of interpersonal difficulties in terms of environmental factors and the presence of an intolerable psychological pain in terms of individual psychological factors. Suicidal acts should thus be considered as the expression of an attempt to escape from this psychological suffering.

As proposed by Shneidman (1998), psychological pain can be considered at the core of suicidal process, ranging from suicidal ideation to suicide. It is important to highlight that psychological pain, hopelessness, and depression are associated but independent dimensions. Berlim et al. (2003) have reported that poor quality of life in psychological domain, an indirect measure of psychological pain, was strongly associated with suicidality (presence of suicidal ideation or suicide attempt) even after controlling for the level of depression and hopelessness. Van Heeringen et al. (2010) have shown a positive correlation between intensity of psychological pain, hopelessness, and suicidal ideation in depressed patients. However, intensity of psychological pain was not correlated with depression level. An association between psychological pain and suicidal ideation has also been reported in the general population (DeLisle and Holden 2004; DeLisle 2009).

Considering suicidal behaviors, among a sample of students (Holden et al. 2001), in a sample of 97 homeless men (Patterson and Holden 2012) and in 136 inmates (Mills et al. 2005) and in psychiatric patients, the intensity of psychological pain is associated with history of suicide attempt. Indeed higher perception of psychological pain is associated with history and number of suicide attempt in depressed patients (Mee et al. 2011; Olie et al. 2009). Finally, assessment of suicidal risk by

the clinician is associated with level of psychological pain reported by patients (Pompili et al. 2008). Several authors have shown that the association between psychological pain and suicide attempts was more robust than the association between depression or hopelessness and suicide attempt (DeLisle 2009; Pereira 2010). Finally, Li et al. (2014) have identified the role of psychological pain in the risk of suicide using a three-dimensional psychological pain model (pain arousal, painful feelings, pain avoidance). They have shown that increased levels of pain avoidance during a major depressive episode may be a dominant component of the motivation for suicide.

But can psychological pain a strong predictor of suicidal risk? Several studies have reported that the psychological pain significantly predicted suicidal thoughts or suicidal act, after controlling for levels of depression and hopelessness (DeLisle and Holden 2004). Troister et al. (Troister 2009; Troister et al. 2013; Troister and Holden 2012) have reported baseline, and at 2-year follow-up, psychological pain was the only contributor to the statistical prediction of suicide ideation in high-risk students. When examining change over time, change in psychological pain was the only factor that added significant unique variance to the prediction of change in suicide ideation (Troister and Holden 2013). Levi et al. (2008) have investigated the association between the intensity of psychological pain and lethality of suicidal act. Thirty-five subjects who made medically serious suicide attempts were compared with 67 medically not serious suicide attempters and 71 healthy controls. Psychological pain was a predictor of suicidal act for 48 % of the variance, but not for seriousness of suicidal act.

12.1.3 Role of Psychological Pain in Suicidal Mind

At a Cognitive Level

Shneidman claimed that psychological pain is at the core of suicidal process by identifying six steps in the suicidal process:

1. Existence of social stressors, feelings of rejection
2. Influence of vulnerability factors including genetic factors
3. Perception of stressors as negative and painful
4. Emergence of intolerable psychological pain
5. Death becoming a mean to get relief from pain
6. Psychological pain over tolerance threshold

According to the Shneidman theory, unbearable psychological pain is a condition preceding the suicidal act. Thus, suicidal act appears as an attempt to escape or to relieve intolerable suffering. Suicidal ideation may be considered as a coping mechanism. Some subjects are able to tolerate high levels of psychological pain by saying that if it becomes unbearable, suicide is an alternative of their suffering. Indeed Baumeister (1990) postulated that suicide is a way to escape from self and the surrounding world. Recently, Caceda et al. (2014) have studied the pattern of

choice with the monetary choice questionnaire in 62 depressed patients divided into three groups (patients having attempted suicide within 72 h, patients with and without suicidal thoughts) and 20 healthy controls. Suicide attempters and suicidal patients had higher level of psychological pain and were more likely to make choices associated with short-term rewards (vs. long-term rewards) than non-suicidal patients and controls. When repeating this measure a week later, the level of psychological pain and the number of impulsive choices were decreased, both dimensions being positively associated. It suggests that psychological pain affects the ability to make choices and impairs the ability of subjects to prefer long-term rewards (survival) rather than immediate outcomes (pain relief).

Orbach et al. (2003) have constructed a scale measuring tolerance psychological pain. Only Soumani et al. (2011) used this scale to determine the contribution of tolerance of psychological pain to suicidal risk. Psychological pain may be part of suicidal process by two nonexclusive ways: the suicidal act could occur when intensity of the pain increases and/or when ability to tolerate pain decreases. This theory assumes that level of psychological pain is stable but only level of tolerance to pain fluctuates.

Shneidman also hypothesized that suicidal individual is in a state of intense focus on the pain and associated negative emotions. Consistent with the inability of the subject to project and make delayed rewarded choices, psychological pain is associated with mental constriction that in line with the "cry of pain" model of Williams and Pollock. In this model (summarized in van Heeringen 2001), suicidal individuals are hypersensitive to signals of loss, defeat, and rejection. Using the emotional Stroop, suicidal individuals significantly take more time to name color of words related to suicide than neutral words compared to control groups (Becker et al. 1999). It suggests an attentional bias among suicide attempters. Becker et al. (1999) have also shown a significant correlation between attentional bias score (reading time for words related to suicide minus reading time for neutral words) and severity of suicidal ideation after adjusting for depression, anxiety, and hopelessness. Following this step, the suicide would have a greater tendency to feel trapped because of problem-solving difficulties. Problem-solving is measured using tests assessing the ability of a subject to generate time-limited maximum reasonable solutions to a problem. Suicidal individuals significantly generate fewer alternatives than controls. Faced with a negative life event, it would be more difficult to consider positive solutions for suicidal individuals.

Thus, several cognitive deficits of selective attention, autobiographical memory, and verbal fluency lead a subject to be more sensitive to environmental events, not to find solutions (leading to the feeling of no escape), and inability to consider positive events (leading to hopelessness). These cognitive aspects therefore represent internal elements of suicidal vulnerability.

At a Neuroanatomical Level

Only two functional neuroimaging studies have specifically tried to identify brain regions associated with psychological pain in suicidal vulnerability during depressive episode (Reisch et al. 2010; van Heeringen et al. 2010). In the first study conducted by

Van Heeringen et al. (2010), psychological pain, suicidal ideation, hopelessness, and regional cerebral blood flow as measured with single-photon emission computed tomography were assessed in 39 depressed individuals. When compared with patients with low levels of psychological pain, those with high levels of psychological pain showed relatively increased perfusion in the right dorsolateral prefrontal cortex, occipital cortex, and inferior frontal gyrus and left inferior temporal gyrus. These regions are involved in emotional regulation. In the second study conducted by Reisch et al. (2010), the authors used fMRI during presentation of autobiographical scripts extracted from personal narratives reactivating patients' memories of a recent episode of attempted suicide. Brain activation was measured during three recalled conditions: psychological pain, suicide action, and neutral activity. Recall of suicidal episodes, i.e., mental pain plus suicide action, compared to neutral activity, was associated with deactivation in the prefrontal cortex. Recall of suicide action, however, compared to mental pain, was associated with increased activity in the medial prefrontal cortex, the anterior cingulate cortex, and the hippocampus. This result is consistent with the hypothesis that the suicidal act is goal oriented, probably aiming at reducing psychological pain. Finally, Meerwijk et al. (2013) recently proposed a review of the literature of 18 studies in order to better define the neuroanatomical bases of psychological pain. The studies most frequently found hyperactivation of middle regions, such as thalamus, cingulate cortex, basal ganglia, and cerebellum. They also reported the involvement of prefrontal cortex (including ventrolateral, ventromedial, and orbitofrontal parts), but the way of activation results was more difficult to interpret, probably due to the heterogeneity of tasks used.

12.2 Social Pain and Suicide

12.2.1 Definition

Social pain may be considered as a variant or a component of psychological pain, emerging from the frustration of needs of belonging, self-esteem, and sense of existence. Social pain may be defined as the unpleasant experience that is associated with actual or potential damage to one's sense of social connection or social value (owing to social rejection, exclusion, negative social evaluation, or loss) (Eisenberger 2012).

12.2.2 Association with Suicidal Ideation and Behaviors

At the individual level, the transition to the suicidal act is usually precipitated by psychosocial stress. Nearly all suicide victims have experienced at least one or more adverse life events within the last year (mostly last few months). 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 interpersonal events, forensic events, unemployment, and loss events is independent of mental disorder (Foster

2011). All these factors are related to social features and threat social status of the individual. Indeed, such events decrease the potential for social investment defined as the ratio between the social value of an individual to the others and its social burden on others (Allen and Badcock 2003). When this ratio reaches a point where social value and social burden are approaching equivalence, the individual is in danger of social exclusion and becomes hypersensitive to signals of rejection. Durkheim theorized (1897) that suicide occurs when there is an imbalance of social forces, distinguishing (1) "egoistic suicide" when an individual is excluded or insufficiently integrated and has weak social ties and (2) "altruistic suicide" when an individual is willing to sacrifice his/her own life for the benefit of the group to which it belongs.

Other theories to understand suicidal behaviors suggest that the desire to die can arise from disruption of interpersonal relationships. The interpersonal-psychological theory of suicidal behavior (Joiner et al. 2005) holds that an individual will die by suicide if he/she has both the desire for suicide and capability to act on that desire. According to the theory, suicidal desire results from the convergence of two interpersonal states: perceived burdensomeness (increased perception of the "burden" that the subject represents) and thwarted belongingness (a reduced perception of belonging). Thwarted belongingness and perceived burdensomeness are associated with suicidal ideation and behavior (Joiner 2002; Joiner et al. 2009; Van Orden et al. 2008). However, desire alone is not sufficient to result in death by suicide—a third component must be present: the acquired capability for suicide, which develops from repeated exposure and habituation to painful and provocative events.

12.2.3 Role of Social Pain in Suicidal Mind

Pain serves to draw attention to important events that have a negative effect on human desires and aspirations (Thornhill 1989), in order to promote adaptive behaviors. When excluded or threatened with exclusion, a given subject adapts his/her behavior to encourage a return to baseline, i.e., inclusion (Williams 2007). But if he/she is repeatedly excluded, he/she develops susceptibility to perceive rejection even outside such situations. When the social investment ratio is low, the subject becomes hypersensitive to negative social cues. Of note, subjects with chronic feelings of loneliness are more likely to experience negative emotions (anger, anxiety) and pessimism. In addition, excluded subjects may present dysfunctional behaviors such as aggression and anger (Buckley et al. 2004), which are strongly associated to suicidal vulnerability. They also may develop self-injurious behaviors (Williams 2007). When experimentally excluded, individuals develop deficiency of self-regulatory behavior, associated with deficit of executive performances (Baumeister et al. 2002). They also perceive others as more hostile toward them (DeWall et al. 2009). Interestingly, interpersonal difficulties are negatively correlated with decision-making (Jollant et al. 2007). Suicide attempters are characterized by impaired decision-making. Thus, social exclusion inducing social pain affects the individual's ability to regulate itself by inhibiting the motivational resources to avoid impulsive/aggressive behaviors and promote long-term benefits.

Conclusion

To summarize, psychological pain is central in suicidal process as (1) an immediate consequence of psychosocial stressors and (2) a factor influencing vulnerability favoring its perception and increasing susceptibility to certain social events based partially on neuroanatomical bases.

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Biochemical Markers

13

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Abstract

Suicide is a complicated phenomenon related with the interaction of several neurobiological changes and psychosocial factors. The previous postmortem and clinical studies have explored neurobiological changes associated with suicide behavior. These suggest that decreased serotonin function and increased hypothalamic–pituitary–adrenal (HPA) axis are associated with suicide behavior. Serotonin dysfunction in individuals with suicidal behavior has been observed as decreased 5-hydroxyindoleacetic acid (5-HIAA) level in the cerebrospinal fluid, blunted prolactin response to fenfluramine challenge studies, and increased number of platelet serotonin 2A receptors. HPA axis dysfunction in those with suicidal behavior has been shown as increased cortisol level and non-suppression cortisol response to the dexamethasone suppression test. In addition, the reduction of cholesterol and BDNF levels in suicide has been observed, and they can be measured in blood, serum, or plasma. It is still a challenge to the field to find both promising and easily assessable neurobiological predictors of suicidal behavior.

13.1 Introduction

Most suicides occur in the context of psychiatric disorders, most commonly major depressive disorder (Lonnqvist et al. 1995). However, most psychiatric patients or depressive patients never attempt or complete suicide, which suggests that the

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predisposition of suicidal behavior can be independent of psychiatric disorders (Mann 2002).

The previous studies have examined potential biological markers or predictors of suicide and suicidal behavior in the context of mood disorders, especially major depression. Although work in this area has been inconclusive, dysfunctions of the serotonin system and hypothalamic–pituitary–adrenal (HPA) axis have been reported to be strongly associated with suicide, especially in individuals with mood disorders (Lee and Kim 2011; Mann et al. 2006). Additionally, other neurotransmitters, neurotrophic factors, and lipid metabolites have been reported to be associated with suicidal behavior (Ernst et al. 2009).

13.2 Serotonin

The serotonin is abundant and produced in the central nervous system (CNS) as well as the peripheral system including the gastrointestinal and vascular system (Cote et al. 2004; Gershon and Tack 2007). The serotonin has the various functions such as platelet aggregation, cardiovascular homeostasis, intestinal motility, and neurotransmission. The serotonin as a neurotransmitter has been widely investigated in studies of psychiatric disorder including major depression and suicidal behavior.

The serotonin in CNS is produced in a group of serotonergic neurons of the dorsal raphe nucleus (Lesch et al. 2012). These serotonergic neurons project into all regions of the brain, including the cerebral cortex, cerebellum, amygdala, and hippocampus that contain serotonin receptors (5-HTR). Various 5-HTR subtypes are distributed widely throughout the brain. The serotonergic transmission is known to mediate a variety of functions such as cognitive control and emotion regulation including mood, anxiety, impulsivity, and aggression. Serotonin is synthesized from the hydroxylation of tryptophan by the enzymes tryptophan hydroxylase (TPH). The TPH is one of the rate-limiting factors in the serotonin synthesis, and it has two isoforms, TPH1 and TPH2. The presynaptic neuron releases serotonin into the synaptic cleft, and the serotonin binds to receptors on the postsynaptic neuron. And then the serotonin is metabolized into 5-hydroxyindoleacetic acid (5-HIAA) by the enzymes monoamine oxidase and aldehyde dehydrogenase. The serotonin transporters (SERT) in the presynaptic neuron reuptake serotonin from the synaptic cleft.

13.2.1 The Postmortem Studies of Serotonin System

The postmortem studies in the brain of suicide victims have reported inconsistent results about the serotonin system. However, the major findings have suggested that serotonin dysfunction or deficient serotonin neurotransmission in the brains is associated with suicide behavior.

The number and density of serotonin neurons in the brainstem dorsal raphe nucleus was reported to be higher in suicide victims than controls (Underwood et al.

1999). Immunoautoradiography studies using TPH immunoreactivity have reported that the amount of TPH enzyme in the dorsal raphe nucleus is higher in depressed suicide victims (Boldrini et al. 2005) and in depressed suicide victims with alcohol dependence (Bonkale et al. 2006) when compared to controls. The increased of TPH2 expression in depressed suicide victim is found in the dorsal raphe nucleus (Bonkale et al. 2006).

The SERT binding in the postmortem brain of suicide victims has been reported to be decreased in various brain regions, particularly the frontal cortex and hippocampus of depressed suicide victims (Purselle and Nemeroff 2003). The study using quantitative autoradiography in the relative larger sample ($n = 159$) found that the SERT binding in subjects with a history of major depression was reduced throughout the prefrontal cortex (Mann et al. 2000). Moreover, it was reported that the SERT binding was lower in the ventral prefrontal cortex of suicides in comparison to non-suicides (Mann et al. 2000).

There have been several studies of 5-HT_{2A} receptors in the postmortem brain of suicide victims using radiolabeled ligand-binding techniques or determining a protein and mRNA expression (Pandey and Dwivedi 2010). Some studies using radiolabeled ligand binding have reported no difference in the binding of 5-HT_{2A} receptors in the prefrontal cortex of victims of suicide when compared to controls (Arranz et al. 1994; Stockmeier et al. 1997). Others have found the increase of 5-HT_{2A} receptor binding in the prefrontal cortex of suicidal individuals in comparison with non-suicidal individuals (Arango et al. 1990; Arora and Meltzer 1989b). The discrepancy in those findings could be related to the differences in a kind and specificity of radioligands used for labeling 5-HT_{2A} receptor. Moreover, the postmortem studies examining the mRNA or protein expression of 5-HT_{2A} receptors in the brains of suicide victims have observed a significant increase in protein or mRNA expression in the 5-HT_{2A} receptors in the prefrontal cortex of suicide victims compared with control subjects (Escriba et al. 2004; Pandey et al. 2002; Shelton et al. 2009).

The 5-HT_{1A} receptor, which is known to be an autoreceptor, has been studied in the postmortem brain of suicide victims. However, those studies have reported inconsistent findings. One study with agonist radioligand binding to 5-HT_{1A} autoreceptor in the dorsal raphe nucleus reported lower the volume and density of neuron with 5-HT_{1A} receptor binding in depressed suicide victims (Arango et al. 2001). However, other study detected that the agonist binding to 5-HT_{1A} autoreceptor was increased significantly in the dorsal raphe nucleus of depressed suicide victims as compared with control subjects (Stockmeier et al. 1998). Another study examining agonist and antagonist binding to 5-HT_{1A} receptor found that antagonist binding, not agonist binding, to 5-HT_{1A} receptor was significantly decreased in the frontal cortex of depressed suicide victims (Stockmeier et al. 2009).

Taken together, the postmortem studies of depressed suicide victim indicate increased activity of TPH in the dorsal raphe nucleus and decreased activity of serotonin transporter and increased activity of postsynaptic 5-HT_{2A} receptors in the frontal cortex. These findings could be compensatory consequences of serotonin dysfunction or deficient serotonin neurotransmission in the brains of suicide behavior. Such a reduction in serotonin system among individuals who had committed

suicide is known to be localized in restricted region of the prefrontal cortex such as the ventral prefrontal cortex, whereas a similar reduction among individuals with major depressive disorder could appear throughout the prefrontal cortex.

13.2.2 In Vivo Neuroimaging Studies of Suicidal Behavior

The neuroimaging studies of suicide attempters show similar findings to the post-mortem results (van Heeringen et al. 2011). Some studies scanned with high-resolution brain single-photon emission tomography (SPET) using a highly selective ligand to 5-HT_{2A} receptor have shown a decrease of the 5-HT_{2A} receptor biding in the frontal cortex of subjects with recently attempted suicide (Audenaert et al. 2001; van Heeringen et al. 2003). This finding indicates that a decrease in the number or binding affinity of 5-HT_{2A} receptor is associated with suicide attempt. Other SPECT studies measuring whole brain binding of the serotonin transporter (SERT) have reported no significant difference in the SERT binding between suicide attempters and control subjects (Lindstrom et al. 2004; Ryding et al. 2006). However, a low activity of SERT is found to be associated with impulsivity in suicide attempters (Lindstrom et al. 2004; Ryding et al. 2006).

A study using positron emission tomography (PET) scanning with measuring relative regional cerebral uptake of ^{18}F-fluorodeoxyglucose in subjects with major depression observed that high-lethality suicide attempters had lower regional cerebral uptake in ventral, medial, and lateral prefrontal cortex than low-lethality attempters (Oquendo et al. 2003). This difference between high- and low-lethality suicide attempters was more pronounced after fenfluramine administration. Moreover, it was found that lower activity of ventromedial prefrontal cortex was associated with higher lethality of suicide attempts. Another PET study with 11-C-methyl-tryptophan, an analogue of tryptophan, showed that high-lethality suicide attempters had decreased uptake in orbital and ventromedial prefrontal cortex compared to healthy controls (Leyton et al. 2006).

13.2.3 Serotonin Metabolite, 5-Hydroxyindoleacetic Acid, in the Cerebrospinal Fluid

Asberg et al. (1976) examined the level of 5-HIAA in the cerebrospinal fluid (CSF) in 68 patients with major depression. They found a bimodal distribution of CSF 5-HIAA such as low and high 5-HIAA mode based on 15 ng/ml of CSF 5-HIAA levels in depressed patients. Moreover, depressed patients with a history of suicide attempts were found significantly more often in the group with low 5-HIAA mode than in the group with high mode. Several subsequent studies indicate that low CSF 5-HIAA level is associated with suicidal behavior (Asberg 1997; Banki et al. 1984), though some investigators have failed to find a relationship between suicidal behavior and low CSF 5-HIAA levels. Some follow-up studies for 1 year or 2 years after attempted suicide suggested that the number of patients who completed suicide

during the follow-up period was significantly higher in patients with low CSF 5-HIAA levels (Asberg et al. 1976; Nordstrom et al. 1994; Samuelsson et al. 2006; Traskman et al. 1981). Other studies showed that low CSF 5-HIAA levels were associated with high lethality or violent attempt in patients with mood disorder (Sher et al. 2006, 2007).

One early meta-analysis reviewing 27 prospective and retrospective reports on CSF level of neurotransmitter metabolites suggested that individuals who attempt suicide, particularly those using violent methods, had lower CSF 5-HIAA levels in comparison with psychiatric controls (Lester 1995). It was also reported that among suicide attempter, those with lower CSF 5-HIAA level had tendency to make subsequent suicidal actions. Other meta-analyses of prospective studies of CSF 5-HIAA and dexamethasone suppression test (DST) in mood disorders estimated the odds ratio for the prediction of suicide completion (Mann et al. 2006). It suggested that patients with low levels of CSF 5-HIAA had about 4.5-fold greater risk of subsequent suicide in mood disorder. The CSF 5-HIAA could be a predictor of future suicide attempts and completions, as findings associating CSF 5-HIAA levels with suicidal behavior have been relatively consistent. However, getting the sample from the CSF is an invasive method, which is a limitation to apply CSF 5-HIAA easy for the clinical assessment.

13.2.4 Serotonin in Blood and Platelet

Several studies have determined the serotonin level in blood and platelets. Some studies showed lower serotonin level in the blood or platelets of suicidal patients compared with normal controls (Kovacic et al. 2008; Rao et al. 1998). Other studies observed that serotonin level in platelets was significantly lower in suicidal patients who had attempted suicide compared with non-suicidal patients among patients with major depression, but did not differ from those in healthy controls (Mann et al. 1992; Roggenbach et al. 2007).

Among several subtypes of serotonin receptors, only the 5-HT_{2A} receptor is present in peripheral sources including platelets. And then, the activity of the 5-HT_{2A} receptor binding in platelets has been explored in the studies in psychiatric disorders. The previous studies showed that the maximum number of binding sites (B_{max}) or density of 5-HT_{2A} receptors in platelets was significantly higher in depressed patients compared with normal control subjects (Arora and Meltzer 1989a; Biegon et al. 1987; Hrdina et al. 1995). Some studies reported that depressed patients with a recent history of suicide attempts or suicidal ideation had significantly higher binding density of platelets 5-HT_{2A} receptors than non-suicidal depressed patients and normal controls (Lauterbach et al. 2006; Pandey et al. 1990). Other subsequent studies examined the binding of platelets 5-HT_{2A} receptors in patients with major depression, bipolar disorder, schizophrenia, and schizoaffective disorder (Pandey et al. 1995; Rao et al. 1998). They also found that the density of platelets 5-HT_{2A} receptors was significantly increased in all suicidal patients, independent of diagnosis, compared with non-suicidal patients and normal control subjects. This finding

of upregulated platelet 5-HT_{2A} receptor binding related with suicide behavior is similar as the findings from the postmortem and neuroimaging studies about 5-HT_{2A} receptors in the brain. However, studies about serotonin reuptake function in platelets using imipramine binding did not show consistent findings between platelet SERT activity and suicidal behavior (Muller-Oerlinghausen et al. 2004). Some studies and reviews have indicated that platelet serotonergic parameters could be inadequate peripheral markers of suicidal behavior due to the unstable methods of measuring them (Lauterbach et al. 2006; Muller-Oerlinghausen et al. 2004; Roggenbach et al. 2007).

13.2.5 Neuroendocrine Challenge Test

The fenfluramine challenge test is a kind of neuroendocrine challenge tests to explore the function of serotonin in the brain. Fenfluramine is known to be as a highly selective serotonin releaser and reuptake inhibitor (Quattrone et al. 1983). And serotonin is one of the stimulating factors to prolactin release from pituitary gland. Since then, the assay of blood concentration after oral administration of fenfluramine or prolactin response to fenfluramine challenge has been used to indirectly assess central serotonin function. Decreased prolactin response to fenfluramine challenge tests can be indicative of a reduction in serotonin activity.

Previous studies have tried proving a deficiency of serotonin function associated with suicidal behavior using the fenfluramine challenge test. Many studies observed that significantly more blunted prolactin responses to fenfluramine challenge tests in depressed patients with a history of attempted suicide than in patients without such a history and in healthy controls (Cleare et al. 1996; Correa et al. 2000; Duval et al. 2001; Keilp et al. 2010; Malone et al. 1996; Mann et al. 1995; O'Keane and Dinan 1991). And prolactin response to fenfluramine was reported to be significantly lower among patients with a history of a high-lethality suicide attempt (Malone et al. 1996). Such a response to fenfluramine was observed in patients with a history of suicide attempts in studies including subjects with personality disorder or schizophrenia (Correa et al. 2002; Soloff et al. 2003). These findings have proposed that a blunted prolactin response to fenfluramine is associated with patients with a history of suicide attempts or past suicidal behavior. However, there was the negative report between prolactin response to fenfluramine and suicide behavior (Prochazka et al. 2000). Also, some investigators have presented complicated issues that prolactin response to fenfluramine could not reflect acute changes of clinical state including acute risk of suicide behavior or that cortisol could reduce prolactin response to fenfluramine (Keilp et al. 2010; Mitchell and Smythe 1992).

Several clinical studies have measured blood concentrations of cortisol as well as prolactin after the fenfluramine challenge. Serotonin can stimulate the hypothalamus and pituitary which then release adrenocorticotropic hormone (ACTH) and growth hormone beyond prolactin. ACTH can stimulate the adrenal gland to secrete cortisol. Therefore, this method of the fenfluramine challenge test could be expected to reflect both the central serotonin function and the interaction between serotonin

and HPA axis. A few studies have reported that cortisol response to fenfluramine challenge is more attenuated in depressed patients with a history of suicide attempt when compared with those without such a history (Cleare et al. 1996; Duval et al. 2001). However, there is yet a lack of the cumulated data about cortical response itself to the fenfluramine challenge and relationship between such a method and suicide behavior.

13.3 Norepinephrine

Brain norepinephrine (NE) is produced primarily by neurons in the locus coeruleus (Kvetnansky et al. 2009). NE is synthesized from the precursor tyrosine. A rate-limiting step in the synthesis of NE is an initial hydroxylation of tyrosine by tyrosine hydroxylase. In the brain, NE acts through α_1-, α_2-, β_1-, or β_2-adrenergic receptors. NE release is regulated by presynaptic adrenergic receptors. Presynaptic α_2-receptor as autoreceptor inhibits NE release, while presynaptic β_2-receptor facilitates its release. The action of NE at the synaptic cleft is terminated mainly through reuptake of NE by the NE transporter. NE is repackaged into vesicles in the neuron or degraded by monoamine oxidase (MAO). The main one of various NE metabolites in the brain is 3-methoxy-4-hydroxyphenylethylene glycol (MHPG).

Several studies have focused on how abnormalities of noradrenergic function could be involved in the pathophysiology of suicide. The postmortem studies have explored the enzyme tyrosine hydroxylase or the adrenergic receptors in the brain of suicide victims. The other clinical studies have determined the levels of NE or its metabolite, MHPG, in the urine or CSF of suicidal patients.

13.3.1 The Postmortem Studies of Norepinephrine System

The postmortem studies of tyrosine hydroxylase in the locus coeruleus showed controversial results in suicide victim. Some studies observed an increased level of tyrosine hydroxylase in the locus coeruleus of suicidal victim in comparison of those in controls (Ordway 1997; Ordway et al. 1994). Other studies examining the number of tyrosine hydroxylase immunoreactive neurons in depressed patients with mood disorders and normal controls showed no difference between the suicidal patients and controls (Baumann et al. 1999; Gos et al. 2008). However, an increase of tyrosine hydroxylase immunoreactive neurons was observed in suicidal patients compared with those in non-suicidal patients (Baumann et al. 1999). Moreover, violent suicide victims revealed an elevated number of tyrosine hydroxylase immunoreactive neurons compared with nonviolent suicide victims (Gos et al. 2008). On the contrary to these findings, there were a few reports of a decrease in tyrosine hydroxylase immunoreactivity in the locus coeruleus of suicide victim (Arango et al. 1996; Biegon and Fieldust 1992; Underwood et al. 2004).

Several studies of α- and β-adrenergic receptors in suicidal victims also found inconsistent results. The majority of postmortem studies exploring the binding of

α_2-adrenergic receptors found a significant increase in the binding capacity and number of α_2 -receptors in the hippocampus and frontal cortex of suicide victims compared with matched control subjects (Callado et al. 1998; Garcia-Sevilla et al. 1999; Gonzalez et al. 1994; Meana et al. 1992; Meana and Garcia-Sevilla 1987). These findings were observed in suicide victim diagnosed both with major depression and other psychiatric disorders. The mRNA expression of α_2-adrenergic receptors was reported to be elevated in the prefrontal cortex of suicide victims in comparison to controls (Escriba et al. 2004). However, one study reported that α_2-adrenergic receptors binding in the postmortem brain were decreased in alcoholic suicide victims compared with control subjects (Underwood et al. 2004).

There were several studies exploring β-adrenergic receptor binding of the postmortem brain in suicide victim. Some showed an increase in β-adrenergic receptor binding in the frontal and temporal cortex of suicide victims compared with control subjects (Arango et al. 1990; Mann et al. 1986). Others found a decreased number of β-adrenergic receptor in the frontal and temporal cortex of suicide victims (De Paermentier et al. 1990, 1992).

Some investigators have reviewed and concluded that the level of tyrosine hydroxylase and the binding of α_2- and β-adrenergic receptors are increased in the postmortem brain of suicide victims (Ordway 1997; Pandey and Dwivedi 2007), although the associated findings seemed to be controversial.

13.3.2 Norepinephrine in CSF of Clinical Studies

As mentioned above, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) is a main metabolite of brain NE. The level of MHPG was measured in blood, urine, or CSF in psychiatric researches.

A few previous studies observed decreased MHPG level in urine or plasma in subjects with violent suicidal behavior or current suicide attempt (Garvey et al. 1994; van Heeringen et al. 2000).

Several studies have examined CSF MHPG as an indicator of brain noradrenergic activity. The most studies with a cross-sectional approach have shown negative findings between CSF MHPG and suicidal behavior in various diagnosis groups (Lester 1995; Placidi et al. 2001; Roy et al. 1985; Sher et al. 2003, 2007). Some studies conducting follow-up surveys of a further suicide attempt or completion in suicide attempters after index admission for a suicide attempt suggested no differences in baseline CSF MHPG between those who did or did not further suicide behavior during follow-up period (Engstrom et al. 1999; Nordstrom et al. 1994; Sunnqvist et al. 2008). However, one follow-up study reported that completed suicides among suicide attempters had CSF MHPG levels above the median (Träskman-Bendz et al. 1992).

Moreover, other prospective studies conducted evaluated a further suicide behavior in patients with mood disorder who underwent CSF MHPG after their admission for treatments of mood disorder. They have found that lower CSF MHPG might be

associated with future suicide risk or suicide prediction and that lower CSF MHPG might be related with more lethality of future suicide attempts (Galfalvy et al. 2009; Jokinen et al. 2010; Sher et al. 2006).

The above clinical studies of noradrenergic functioning and suicide behavior showed negative or controversial findings. A few studies indicated that a reduced noradrenergic functioning might be associated with suicide attempt or future suicide.

13.4 Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis is the major biological system that was involved in the stress response. The paraventricular nucleus of the hypothalamus releases corticotropin-releasing factor (CRF), and CRF stimulates the pituitary to release ACTH. ACTH causes the production of glucocorticoids (cortisol in human) from the adrenal glands. Glucocorticoids regulate the HPA axis or their own secretion through a negative feedback mechanism. That is, glucocorticoids bind to glucocorticoid receptors in the pituitary and the hypothalamus, which inhibits the release of CRF and ACTH (Owens and Nemeroff 1991). Cortisol acts on mineralocorticoid receptor and glucocorticoid receptor. The mineralocorticoid receptor is known to be a high-affinity receptor, and it is predominantly occupied under basal conditions and has a role to maintain HPA axis tone. The glucocorticoid receptor is bound during the stress state and plays a role in turning off the HPA axis (Reul and de Kloet 1985).

Stress and depression are major risk factors for suicide. The stress model of depression states that chronic stress may lead to long-term activation of the HPA axis, which may result in reductions in the volume or impairments to the function of the hippocampus (Duman et al. 1997). Such a hyperactivity of the HPA axis in stress and depression has shown up in research findings including increased cortisol level, increased cortisol response to ACTH, and impaired negative feedback mechanism.

Many studies have suggested that a hyperactivity of the HPA axis is associated with suicide behavior. However, there are contrast findings which have observed a hypoactivity of the HPA axis in suicide behavior (Pompili et al. 2010b).

13.4.1 Hyperactivity of the HPA Axis and the Dexamethasone Suppression Test

Studies of postmortem brain in suicide victim have shown increased CRF levels in the CSF and in some regions of the brain, decreased number of CRF receptors or CRF binding sites in the frontal cortex, and altered mRNA expression of glucocorticoid receptor in the hippocampus of subjects who committed suicide (Arato et al. 1989; Lopez et al. 1992; McGowan et al. 2009; Merali et al. 2004, 2006; Nemeroff et al. 1988).

The dexamethasone suppression test (DST) is one of the useful assessments of HPA axis activity. During normal activity of the HPA axis, the administration of dexamethasone, an exogenous synthetic glucocorticoid hormone, leads to negative feedback in the HPA axis. That is, the administration of dexamethasone inhibits the release of ACTH from the hypothalamus, which causes suppression of the secretion of cortisol from the adrenal gland. Therefore, a positive result on the DST test is a decrease of cortisol levels examined in blood after the dexamethasone challenge.

A consistent association has been reported between non-suppression of cortisol in the DST and suicide behavior, suggesting an increase of the HPA axis activity in suicide.

The previous cross-sectional studies of patients with mood disorder have shown that the frequency of non-suppression on the DST test is higher in patients with suicide attempt than those without suicide attempt and that the frequency of suicide attempters is higher in the DST non-suppressors than the DST suppressors (Jokinen and Nordstrom 2008, 2009; Kunugi et al. 2004). Moreover, the prospective or follow-up studies have suggested that cortisol non-suppression of the DST test serves as a predictor of future suicidal behavior. Some follow-up studies of patients with mood disorder have found that the DST non-suppressors were more likely to have completed suicide than the DST suppressors and that suicidal events of attempted or committed suicide are more frequent in the DST non-suppressors (Jokinen et al. 2009; Yerevanian et al. 2004). The non-suppression of the DST test was observed to be more associated with committed suicide after over 1 year than within 1 year during the follow-up period (Jokinen et al. 2009). A 15-year follow-up study of patients with major depressive disorder or schizoaffective disorder, depressed type, reported that patients presenting DST non-suppression had a roughly 14-fold higher risk of suicide, when compared to those presenting DST suppression (Coryell and Schlesser 2001). The other study followed 106 depressed patients with an index suicide attempt up and revealed that a lower threshold of 3.3 microg/dl of cortisol level for the DST non-suppression predicted 17 of 25 suicides (sensitivity of 68 %) compared with 15 of 25 suicides (sensitivity 60 %) with a conventional threshold of 5 microg/dl of cortisol level at 4:00 p.m. following dexamethasone at 11:00 p.m. (Jokinen et al. 2008). One meta-analysis showed the odds ratio of the DST non-suppression was 4.65 for future completed suicide among patients with mood disorders (Mann et al. 2006). However, other long-term follow-up studies with the larger samples of patients with mood disorder found no significant difference in suicide risk between the suppressors and non-suppressors of the DST test among total subjects (Black et al. 2002; Coryell et al. 2006; Jokinen et al. 2007). Furthermore, these studies suggested that the DST test could be a useful predictor of future suicidal risk only among patients with mood disorders who had attempted suicide when entering these studies, not among the whole patients (Coryell et al. 2006; Jokinen et al. 2007).

Taken together, the cortisol non-suppression of the DST test is associated with suicide behavior or future suicide risk. Specially, the DST test might be a use predictor for future suicide risk within suicide attempter with mood disorder. However, some investigators have proposed the need for different thresholds for the DST

non-suppression, cortisol levels after the dexamethasone challenge at 11:00 p.m. according to gender or age for the DST test, to become a more useful predictor for future suicide risk or yield higher sensitivity (Jokinen et al. 2008; Jokinen and Nordstrom 2008).

13.4.2 Hypoactivity of the HPA Axis

Several studies observed findings of HPA axis hypoactivity in recurrent and chronic depressive disorders (Ehnvall et al. 2004; Oldehinkel et al. 2001; Watson et al. 2002).

Some studies observed decreased CSF CRF level in patients who had made previous suicide attempts (Traskman-Bendz et al. 1992; Westrin et al. 2001). One retrospective study of 310 depressed patients demonstrated that suicidal behavior including past and recent suicide attempts and suicidal ideation was associated with a lower cortisol response in the DST test and that patients with a recent suicide attempt had lowest hormone level (Pfennig et al. 2005). One study followed up attempted suicides and non-suicidal controls for 12 years and examined salivary cortisol level at follow-up (Lindqvist et al. 2008). It found that repeated suicide attempts among females were associated with low salivary cortisol level.

These findings indicated an association between hypoactivity of HPA axis and suicidal behavior, which might be interpreted as the following: that suicide might result from long-lasting and severe psychiatric illness which could have exhausted the HPA axis in turn.

13.5 Brain-Derived Neurotrophic Factor (BDNF)

Neurotrophins play the roles in neuronal development, survival, and plasticity (Huang and Reichardt 2001). In particular, the role of neurotrophins in the adult brain is important because they participate in neurogenesis and maintenance of neuronal functions and structural integrity.

Brain-derived neurotrophic factor (BDNF) is one of the neurotrophins. BDNF is synthesized as a precursor protein, prepro-BDNF, that is cleaved into pro-BDNF, which then is further cleaved into mature BDNF (Lessmann et al. 2003). Pro-BDNF and mature BDNF bind to different receptors and activate different intracellular signaling pathways (Numakawa et al. 2010). Immature neurotrophins including pro-BDNF bind the pan-neurotrophin receptor ($p75^{NTR}$). Pro-BDNF signals through the $p75^{NTR}$ receptor is known to be involved in apoptosis (Meldolesi et al. 2000). Mature BDNF produces its physiological effects by binding to the tropomyosin receptor kinase B (TrkB) receptors (Barbacid 1994; Middlemas et al. 1991). The TrkB receptors include two isoforms such as the full-length form and truncated form. The main actions of BDNF are mediated via full-length TrkB receptor. BDNF binding the truncated TrkB receptor acts as a negative modulator of BDNF signaling (Eide et al. 1996).

Many animal and clinical studies provide that modulation in the expression and activity of BDNF could be involved in behavior phenomena and biological processes related with stress and depression (Castren et al. 2007). Animal studies with stress paradigms propose that chronic stress increases glucocorticoids, which decreases the expression of BDNF or production of mature BDNF in the frontal cortex and hippocampus (Dwivedi et al. 2006). The neurotrophin hypothesis of depression suggests that depression is associated with a decrease of BDNF expression and that antidepressants induce an increase of BDNF expression, which then recovers depression (Castren et al. 2007).

13.5.1 The Postmortem Studies of BDNF

Some postmortem studies have reported that mRNA expression and protein levels of BDNF are significantly reduced in the brains of suicide victim regardless of their previous psychiatric diagnosis (Dwivedi et al. 2003; Karege et al. 2005; Pandey et al. 2008). Such a reduction of BDNF expression and protein levels is observed especially in the prefrontal cortex and hippocampus. One study found that protein levels of BDNF in suicide victims who were taking antidepressant drugs were not different from those in non-suicide controls (Karege et al. 2005).

In addition, the expression of full-length TrkB receptor has been shown to be decreased significantly in the prefrontal cortex and hippocampus of suicide victims, when compared with non-suicide controls in postmortem studies (Dwivedi et al. 2003; Pandey et al. 2008). The other postmortem study found decreased phosphorylation of TrkB receptors and increased expression ratios of $p75^{NTR}$ to Trk receptors in the prefrontal cortex and hippocampus of suicide victims (Dwivedi et al. 2009).

Taken together, a decreased expression of BDNF, decreased expression or activation of TrkB, and increased expression of p75NTR in the prefrontal cortex and hippocampus of suicide victims could be evidence of BDNF dysfunction or altered neuronal plasticity in the brain of individuals experiencing suicidal behavior and completion.

13.5.2 The Clinical Studies of BDNF

Animal studies have proposed that that BDNF can cross the blood–brain barrier in both directions and that there may be parallel correlations in the blood and brain levels of BDNF (Karege et al. 2002; Pan et al. 1998). Circulating BDNF is stored mainly in platelet, and it has been measured in whole blood, serum, and plasma in clinical studies.

It has been shown that BDNF levels in serum, plasma, or platelet are reduced in patients with major depressive disorder, compared with those in healthy controls (Autry and Monteggia 2012). Some studies reported that serum or platelet BDNF levels in depressed patients with suicide attempt did not differ from those in

depressed subjects without suicide attempt, but those were significantly lower than in healthy controls (Deveci et al. 2007; Lee and Kim 2009).

However, other studies, examining plasma BDNF levels in patients with major depression that both had and not had an attempted suicide, found that plasma BDNF levels were significantly lower in all the depressed patients than in normal controls (Kim et al. 2007; Lee et al. 2007). Moreover, plasma BDNF levels were shown to be significantly lower in suicidal patients than in non-suicidal patients with major depression controls (Kim et al. 2007; Lee et al. 2007). Another study examined BDNF levels in plasma directly sampled from the internal jugular vein and the brachial artery and determined the venoarterial BDNF plasma concentration gradient (Dawood et al. 2007). The venoarterial BDNF concentration gradient was shown to be reduced significantly among patients at medium to high suicide risk, as compared to those at low risk. Additionally, this gradient was observed to be negatively correlated with suicide risk among untreated patients with depression. Such a decrease of BDNF level in serum or plasma in depressed patients who attempted suicide from the clinical studies is consistent with the findings of reduced BDNF expression or protein level in suicidal from the postmortem studies.

13.6 Cholesterol

Previous clinical trials of cholesterol-lowering drugs and meta-analytic studies reported an increase in violence-related deaths, including suicides, accidents, and homicides in individuals taking cholesterol-lowering medications (Frick et al. 1987; Muldoon et al. 1990). However, the other meta-analysis revealed that statin drugs of cholesterol-lowering drugs did not rise non-illness mortality, whereas non-statin drugs were associated with a modest increase in deaths due to suicide and violence (Muldoon et al. 2001). These findings aroused interest in relation between lower cholesterol level and suicide behavior.

Several clinical studies with psychiatric subjects with various psychiatric diagnoses have revealed that serum cholesterol level was significantly lower in suicide attempters than in psychiatric non-attempters and healthy controls (Diaz-Sastre et al. 2007; Kim et al. 2002; Kunugi et al. 1997; Lee and Kim 2003; Vuksan-Cusa et al. 2009). Also, plasma cholesterol level was reported to be associated with the risk of acute suicidality (Papassotiropoulos et al. 1999). Some studies showed that serum cholesterol level was significantly lower in patients with violent suicidal attempt than those with nonviolent attempt and that low serum cholesterol might be associated with violent suicidal attempt, but not in nonviolent attempt (Alvarez et al. 2000; Vevera et al. 2003). One study of patients with major depression has reported that significant differences in serum cholesterol levels are between suicide patients and non-suicide depressed patients and between violent suicide patients and nonviolent suicide patients (Kim and Myint 2004). And it suggest two cutoff points of serum cholesterol levels to detect a suicide attempt in patients with major depression: 180 mg/dl, which may serve as a point for high sensitivity (82 %) of

possible risk of suicide, and 150 mg/dl, a point with a high specificity (72 %) of probable risk of suicide. In addition, studies with relative large samples have reported that the proportion of suicide attempters is significantly higher in the lowest cholesterol level quartile than that in the highest quartile (Ellison and Morrison 2001; Olie et al. 2011). One follow-up study also has shown that individuals in the lowest quartile of serum cholesterol level have over six times the risk of committing suicide compared with those in the highest quartile (Ellison and Morrison 2001). These findings suggest that low serum cholesterol level is associated with an increased risk of suicide. These findings can be explained as followings. First, low cholesterol levels have been related to decreased serotonin activity (Heron et al. 1980; Ringo et al. 1994). Second, reduced cholesterol in peripheral blood could decrease cholesterol levels in the brain, which could lead to reduced synaptic plasticity and brain dysfunction associated with impaired neurobehavioral consequences (Mauch et al. 2001; Pfrieger 2003).

However, there have been negative findings between serum cholesterol and suicidal behavior. Some studies including patient with major depressive disorder or patients with mood disorder reported no significant association between serum cholesterol and suicide attempt (Baek et al. 2014; Pompili et al. 2010a). The other study of lifetime suicide attempts in patients with bipolar disorder found no significant differences between patients with and without lifetime suicide attempts in serum cholesterol (D'Ambrosio et al. 2012). Another study of medication-free suicide attempters reported that serum cholesterol did not differ between violent and nonviolent suicide attempters or between suicide completers and survivors (Asellus et al. 2010). There was the study with a relative large sample that failed to determine a positive association between serum cholesterol and suicide attempt (de Leon et al. 2011).

Conclusion

Suicide is a complicated phenomenon which results from the interaction of several different factors including neurobiological changes and psychosocial factors. Postmortem and clinical studies suggest that decreased serotonin function and increased HPA axis are associated with suicide behavior. Serotonin dysfunction in individuals with suicidal behavior has been observed as decreased CSF 5-HIAA level, blunted prolactin response to fenfluramine challenge studies, and increased number of platelet 5-HT_{2A} receptors. HPA axis dysfunction in those with suicidal behavior has been shown as increased cortisol level and nonsuppression cortisol response to the dexamethasone suppression test. Serotonergic abnormalities may be associated with trait-related factors such as the impulsive–aggressive behavior in suicide and suicidal behavior. Abnormalities of HPA function may be associated with state-related factors or stress response in suicide. The reduction of cholesterol and BDNF levels in suicide is related to brain dysfunctions in subjects with suicidal behaviors. Cholesterol and BDNF levels can be measured in blood, serum, or plasma.

It is still a challenge to the field to find both promising and easily assessable neurobiological predictors of suicidal behavior.

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Translational Research in Suicide: Is It Possible to Study Suicide in Animal Models?

14

Stefano Comai and Gabriella Gobbi

Abstract

Suicide constitutes a serious medical and social problem. There are several risk factors for suicide including history of mental disorders, alcohol and substance abuse, impulsive or aggressive tendencies, family history of suicide, family history of child maltreatment, previous suicide attempts, feelings of hopelessness, cultural and religious beliefs, and physical illness, in particular chronic pain. Up to date, there are no animal models of suicide mainly because there is no instance of suicide among animals. Indeed suicide occurs almost exclusively in humans giving the link to two important aspects of the human being: (1) the self-consciousness and (2) the psychological suffering. However, in experimental animals we can model several of the main risk factors for suicidal behavior. In this chapter we will thus describe the main animal paradigms of mood disorders, aggression, impulsivity, and drug abuse/dependence. Moreover, we examine the *in-vivo* electrophysiology technique which allows the study of the neural activity of the different neurotransmitters implicated in suicide. The combination of behavioral pharmacology and electrophysiology is currently a gold standard for the investigation of the neurobiology of mental illness and has allowed answering clinically relevant questions and developing novel and efficacious treatments in psychiatry. This approach may thus have great potential also in the field of suicide allowing to increasing our understanding of the neurobiological basis of suicide. However, to develop novel pharmacological strategies to prevent suicide attempts, more translational research in humans is needed to understand the link between depression, impulsivity, self-consciousness, and psychological suffering.

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14.1 Introduction: Is It Possible to Study Suicide in Animal Models?

Suicide constitutes a serious medical and social problem. Current evidence suggests that suicide is associated with psychosocial, neurobiological, and genetic factors. Ninety-three percent of suicides are related to mental diseases and mental disorders, namely, major depression, borderline personality disorder, and substance abuse (Lesage et al. 1994), but 2–8 % of suicides occur in the absence of any mental disorder (Henriksson et al. 1993). However, this last percentage of people could be represented by patients with an underlying psychiatric process that the psychological autopsy method, as commonly carried out, failed to detect (Ernst et al. 2004). Risk factors for suicide include history of mental disorders such as unipolar and bipolar depression, history of alcohol and substance abuse, impulsive or aggressive tendencies, family history of suicide, family history of child maltreatment, previous suicide attempts, feelings of hopelessness, cultural and religious beliefs (e.g., belief that suicide is noble resolution of a personal dilemma), local epidemics of suicide, isolation, a feeling of being cut off from other people, barriers to accessing mental health treatment, loss (relational, social, work, or financial), and physical illness, in particular chronic pain (Borges et al. 2000; Harris and Barraclough 1997; Mann et al. 1999; World Health Organization 2014). However, impulsivity and aggression does not characterize all suicide attempters. In the last years, translational research approaches are dominating the field of psychiatry, in the attempt to foster the multidirectional integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving public health (Rubio et al. 2010). Several animal models have been thus proposed to better study the pathophysiology of psychiatric disorders and to try to accelerate treatment and cure for these invalidating diseases.

As reviewed in this chapter, animal models of depression reproducing the pathophysiology, evolution, and treatment of the disease are now available. Similarly, models of alcohol and substance abuse, hopelessness, impulsivity, and aggression have been developed and validated.

It is still largely debated whether or not there is any instance of suicide among animals and if animal models of suicide do exist (Preti 2011). There are several examples of self-destructive animal behavior that may indicate that animals have the capacity to perform an act similar to human suicide. These examples include pets that after experiencing separation from or the death of their owners sometimes starve to death near their owner's grave, cows throwing themselves off a cliff near the small village of Lauterbrunnen in the Alps, and the Newfoundland dog that repeatedly attempted suicide until it succeeded (Preti 2011). Parasites are organisms that either lives on or in a host from which they acquire biological necessities. The host suicide hypothesis is based on the fact that some parasites may engage the host in "suicidal" behaviors. The first convincing evidence of this hypothesis is the pea aphid (*Acyrthosiphon pisum*) that after being parasitized by the braconid wasp *Aphidius ervi* in a habitat, where alternative escape responses result in substantial differences in mortality risk, exhibits apparent suicidal behavior in response to both aphid alarm pheromone and approaching predators (McAllister and Roitberg 1987).

Especially after the Walt Disney documentary "White Wilderness," there is a belief that lemmings commit mass suicide running over cliffs or into the sea, but this phenomenon is likely the result of dispersal mechanisms when population density rise, rather than a voluntary and self-inflicted act.

Collectively, the examples above reported are mostly anecdotal and have not been confirmed to be animal models of suicide or self-aggression. Basically, suicide occurs almost exclusively in humans. Indeed, it is linked to the presence of two important aspects of the human being: (1) the self-consciousness and (2) the psychological suffering (Shneidman 1993).

1. Suicide implies an extreme choice, being the ultimate expression of acting on its own destiny. This kind of decision belongs to the self-consciousness of human being and cannot be simply linked to mechanistic causes (Bonino 2008). Suicide very often is an intentional conscious act. "Before you do it, you have to picture it, think about it, test it out in your mind and articulate it linguistically" (Hustvedt 2013). It requires reflective self-consciousness and active projective imagination in which the self sees himself dead; even in suicide in which the impulsivity component is high, the self-consciousness is present. The self experiences unbearable suffering and then can form a cognitive argument to kill (modified after Hustvedt (2013)). In support of this theory, suicide is quite rare in children and preadolescents (Shaffer and Fisher 1981), since suicide cannot occur before a child has developed the capacity to conceive of himself/herself as an other in time and the self-consciousness shaped by early attachment (Hustvedt 2013).
2. The common stimulus in suicide is an intolerable psychological pain, evoking negative emotions such as shame, guilt, anger, fear, and deep sadness. This psychological pain, also called "psychache," is so intense that only death can relieve this (Shneidman 1993). This kind of psychological pain is almost impossible to find and measure in the animal kingdom and rarely brings to death in animals.

These two aspects of human suicide are definitely absent in animals for the limited development of the cerebral cortex and the consequent diverse capacity for processing complex information (Cryan and Holmes 2005). In experimental animals, it is only possible to reproduce/model several of the main risk factors for suicidal behavior including mood disorders, aggression, impulsivity, and drug abuse/dependence.

In this chapter we will therefore present those animal paradigms that allow the study of specific traits associated with suicide in humans such as depression, impulsivity, aggressive behavior, and substance abuse disorders. By examining the different traits of suicidability, it is then possible to build and integrate neurobiological framework that very likely mirrors the human condition. Moreover, several pharmacological options may be tested and developed. It is important to note that this approach has been used for several years in other psychiatric diseases such as depression and has yielded a big advancement in the understanding of the neurobiology and pharmacological treatment of these diseases (Bambico et al. 2009).

Several independent investigations have underlined an association of lower serotonergic function and suicidal behavior (Mann et al. 2001). Even though less studied, impairments in other neurotransmitter systems (noradrenaline, dopamine, glutamate, and GABA) have been also related to the neurobiology of suicide (Carballo et al. 2008; Pandey 2013). Therefore, in this chapter we will also illustrate the electrophysiology technique, in particular the *in-vivo* single unit extracellular recording, which allows the study in rodents of the neural activity of the different neurotransmitters (Dominguez-Lopez et al. 2012). Remarkably, the combination of behavioral pharmacology and electrophysiology is currently a gold standard for the investigation of the neurobiology of mental illness and has allowed answering clinically relevant questions in psychiatry. If applied to the study of suicide, it may provide novel important insights for the understanding of this social, neurobiological, and medical challenge.

14.2 Animal Paradigms for the Study of Depression

The majority of the animal models of depression have been developed in rats and/or mice with the aim to test the possible antidepressant properties of novel compounds. However, following specific protocols, it is possible to induce in rodents some symptoms/traits that closely resemble the human condition. As example, in humans, stress plays an important role in the etiology of depressive disorders, and the exposure of rodents to chronic unpredictable mild stressors mimics this conditions and similarly yields to a state-like anhedonia (measured as a reduction in the preference for sucrose), enhanced behavioral despair in the forced swim test (FST), and impairment in sexual behavior (Willner et al. 1992). Nonetheless, as often occurs in the human disease, this animal paradigm produces a significant impairment in the monoaminergic neurotransmissions, in the hypothalamic-pituitary-adrenal (HPA) axis, and in the hippocampal neurogenesis (Willner et al. 1992).

Here, we will briefly describe those animal paradigms of depression that has been largely validated and are endowed with a remarkable degree of predictive validity.

14.2.1 The Forced Swim Test (FST)

The FST, also known as the behavioral despair or Porsolt swim test (Porsolt et al. 1978), is a well-characterized paradigm to analyze depression-like behavior in rodents and is the first stage test for antidepressant activity. The test is based on the propensity of the animal to increasingly assume passive behaviors when exposed to an inescapable water-filled pool. This propensity is measured as increased immobility and decreased swimming that correspond to learned behavioral despair.

This test is based on the evidence that acute and/or chronic treatment with antidepressants significantly reduces the behavioral despair (decreased immobility), whereas environmental, pharmacological, or genetic manipulations increasing the immobility have a depressogenic effect.

14.2.2 The Tail Suspension Test (TST)

In the TST, mice are suspended by their tails for six minutes during which they alternate between periods of activity and immobility (escape-related behaviors). Similarly to the FST, this inescapable and aversive situation reflects a behavioral despair, and the acute and/or chronic treatment with antidepressants reduces the tail suspension-induced immobility. Cryan et al. (2005) have extensively reviewed the validity and pros and cons of this test.

14.2.3 The Chronic Unpredictable Stress (CUS)

CUS (Willner et al. 1992), also known as chronic mild stress, involves the chronic sequential application of a variety of extremely mild and unpredictable stressors to rodents. CUS protocols may slightly vary between labs, but they all lead rodents to develop a depressive-like behavior such as increased anhedonic behavior (a core symptom of depression) and increased immobility in the FST and impairments in the monoaminergic neurotransmissions and in the HPA axis. Importantly, these consequences can be prevented or reversed by chronic treatment with antidepressants. This paradigm is considered to have higher face validity compared to the other animal models of depression here presented (Willner et al. 1992).

14.2.4 The Learned Helplessness (LH)

LH is a well-known behavioral paradigm originally developed by Seligman and Maier (1967) in dogs and subsequently extended to rodents (Seligman and Beagley 1975). Unpredictable, inescapable foot shock exposure of animals induces response deficits in a subsequent escape-learning task. The technique for LH is based on an operant behavior apparatus in which the animal can escape the shock during the test session by pressing a lever. Administration of antidepressants but not anxiolytics, neuroleptics, or stimulants prior to inescapable shock exposure prevents the shock-induced shuttle-box learning deficit typically observed. The main limitations of LH are that it requires very strong stressors to induce the behavioral phenotypes, which may raise ethical problems, and that it is more difficult than other paradigms to replicate between laboratories.

14.2.5 The Novelty-Suppressed Feeding Test (NSF)

The NSF ethologically measures anxiety-related behavior (Dulawa and Hen 2005). In this paradigm, rodents are food deprived generally for 24 h and then placed in a novel environment (open field box) in which some food pellets are placed in the center of the arena. The animal experiences conflict between the desire to approach and feed and the anxiety-induced avoidance of the novel environment. The latency

to feed in the new environment is used as an index of anxiety-like behavior, and while acute and chronic treatments with putative anxiolytics reduce this latency, feeding latency in the familiar home cage environment does not differ between drug-treated and control animals. Importantly, it is now well demonstrated that chronic but not acute treatment with antidepressants also decreases the latency to feed in the novel environment thus giving to this paradigm high predictive and construct validity for antidepressant response in humans (Dulawa and Hen 2005).

14.2.6 Sucrose Preference Test

Rodents are presented in their home cage with two bottles, one containing water and the other one a sweet sucrose solution. The sucrose solution is highly palatable and typically preferred over water. Rodents are given access to the two bottles and the preference for each is measured. A reduction in sucrose preference has been used as an indicator of anhedonia that is associated with depression-like behavior (Willner 2005). The reduction in sucrose preference is reversed by chronic but not acute treatment with antidepressants and is not changed by drugs that are ineffective as antidepressants (Santarelli et al. 2003). On the contrary, external conditions and/or manipulations such as stress which may lead to depression in susceptible individuals decrease sucrose preference.

14.3 Animal Models for the Study of Aggressive Behavior

Aggressive behavior is a highly adaptive behavior present in almost all animals. Several studies have identified a strong association between aggression and suicide (Conner et al. 2009; Romanov et al. 1994), and it has also been proposed a common neurobiological mechanism between suicide and other forms of aggressive behavior (Mann and Currier 2007). However, the relation between aggression and the severity of the suicidal attempt is variable. As per suicide, the first issue when studying aggression is related to its definition (Comai et al. 2012). One general classification distinguishes between offensive and defensive aggression even though a more detailed classification into predatory, intermale, territorial, maternal irritable, fear-induced, and instrumental aggression has been proposed. Numerous animal paradigms have been developed for the study of the neurobiology of aggression as well as for the screening of anti-aggressive compounds. The two most common paradigms used nowadays in preclinical research are the resident–intruder and maternal aggression tests. Other models such as the shock-elicited aggression and the predatory aggression paradigms are now rarely employed mainly because of ethical reasons.

14.3.1 Resident–Intruder Paradigm

In this test one male rodent (the intruder) is introduced into the home cage of another male rodent (the resident) and then allowed to interact for a certain period of time.

The resident will attack the unfamiliar intruder, and the number of attack bites to the intruder and the attack latency (the time between the introduction of the intruder and the first attack) are recorded as measures of aggressive behavior. An interesting aspect of this test is that it allows the study not only of offensive behavior in the resident but also of defensive behavior in the intruder. Defensive behavior is generally manifested by flight, crouching, upright defensive postures, emission of ultrasounds, and submissive postures. Anti-aggressive drugs induce a selective inhibition of attack behavior during resident–intruder encounters (Miczek 1979).

14.3.2 Maternal Aggression Paradigm

The maternal aggression paradigm (Olivier and Mos 1986) is based on the fact that a lactating female will exhibit offensive behaviors toward a wide variety of intruders, usually a male. Similarly to the resident–intruder paradigm, latency to first attack, number of attacks, and total duration of attacks are evaluated as an index of maternal aggression. From a neuropharmacological point of view, although the type of aggressive behavior examined with this paradigm is different than that of the resident–intruder in males, the effects of anti-aggressive or pro-aggressive drugs are basically the same.

14.3.3 Predatory Aggression

In this paradigm (Tulogdi et al. 2015), a prey species such as a mouse for rats or an insect for mice is introduced in the home cage containing the resident that consequently attacks and tries to kill the intruder. Since it seems that predatory aggression is very different from other forms of aggression, this model is currently employed only for research directly focused on killing.

14.4 Animal Models for the Study of Impulsivity

Impulsivity has not yet a unanimous definition, but it is usually considered as behavior without adequate thought, the tendency to act with less forethought than do most individuals of equal ability and knowledge, or a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions. Importantly, impulsive behavior is not always maladaptive since there are occasions when it is advantageous to respond rapidly. Several studies have shown a strong relationship between high levels of impulsivity and a higher likelihood of suicide attempts or suicidal ideation, especially when high levels of impulsivity are present in patients with mental or substance abuse/dependence disorders. Indeed, impulsivity is regarded as one of the few psychological characteristics in guidelines for conducting suicide assessments and determining its level of risk (Bryan and Rudd 2006). For this reason, the study of impulsivity in laboratory animals provides useful insights into the neurobiology of suicide.

A range of behavioral tests measuring the ability to stop or withhold a prepotent response (the go/no-go and stop-signal reaction time tasks) or to delay a gratification have been developed to evaluate impulsivity.

14.4.1 Stop-Signal Task (SST)

The SST is a powerful paradigm to study the aspect of impulsivity linked to the ability to inhibit a response once it has been initiated. In this test, the rodent is required to inhibit an ongoing movement following a stop signal (Eagle and Robbins 2003). The stop-signal reaction time, which measures the speed of the inhibitory processes derived from the SST, is retarded in several psychiatric disorders characterized by impulsive behavior (Lipszyc and Schachar 2010).

14.4.2 The Five-Choice Serial Reaction Time Task (5CSRTT)

5CSRTT was designed to study attention and motor impulsivity in rodents (Carli et al. 1983). In this paradigm, the rodent has to learn to respond to brief flashes of light presented pseudorandomly in one of the five openings, by poking its nose inside the correct hole in order to obtain a food reward. Three parameters are evaluated: (1) percentage of correct responses, (2) anticipatory responses (an index of impulsive behavior), and (3) perseverative responses (an index of compulsive behavior).

14.4.3 Delay Discounting of Reward

This paradigm measures explicit choice behavior when accounting for differential outcomes between response alternatives. Using a specific experimental protocol (for details see Mar and Robbins (2007)), rodents are trained to choose between a small immediate reward and a larger, delayed reward. The response to the immediate small reward provides an index of impulsivity.

14.5 Animal Models for the Study of Drug Abuse/Dependence

Substance abuse and addiction have been often used interchangeably even though dependence can be also a normal body response to a substance. Substance abuse/dependence has been strongly associated to increased risk of suicide and suicide attempts, and when in comorbidity with other mental disorders, this risk is even higher (Borges et al. 2000). Similarly to humans, animals voluntarily self-administer drugs. The drug self-administration model thus represents the most face-relevant paradigm to study substance abuse/dependence and can be used to test the response to basically all the substances that with different mechanism may lead to addiction.

In the field of alcohol addiction, three specific animal models have been developed: the alcohol reinstatement model, the long-term model of alcohol self-administration with repeated alcohol deprivation phases, and the point-of-no-return model (for details see Spanagel (2003).

14.5.1 Intravenous Self-Administration (SA) Paradigm

SA (Emmett-Oglesby et al. 1993) is a useful method for the study of drug-taking behavior in animals such as rodents and monkeys. The animal is implanted with a chronic indwelling intravenous catheter, and according to the performance of the animal on an operant response, typically a lever pressing but sometimes a nose poking, the drug is auto-administered. In the experimental chamber, there are two levers (one whose depression results in the delivery of a drug and the other whose depression does nothing or release vehicle solution) and two cue lights used for programming various experimental contingencies. The activity on these levers is used to measure drug administration, its potential abuse/dependence properties, and its short- and long-term effects. Remarkably, the behavior of the animal in this test is highly sensitive to manipulations of specific environmental, genetic, and pharmacological variables whose contribution on the neurobiological process of addiction can be therefore examined.

14.5.2 Electrophysiology

Electrophysiology is a technique that allows the understanding and the study of the electrical functioning of neurons in the central nervous system. Notably, it provides information on mental function and dysfunction and on the mechanism of action of neuroactive drugs (Dominguez-Lopez et al. 2012; Bambico et al. 2009). To date, a myriad of electrophysiological methods have been developed to study nervous system function in both *in-vitro* and *in-vivo* conditions. In this chapter, we will briefly describe in vivo single unit extracellular recording technique. This technique allows us evaluating the neuronal activity after brain insult (i.e. stress, maternal separation) or after the injection of a putative drug (i.e antidepressants) in a selected brain region. Theoretically, any site within the brain can be reached. The advantage of *in-vivo* compared to *in-vitro* electrophysiology is the study of neurons in their intact milieu with its normal complement of inputs and outputs.

The dorsal raphe nucleus (DRN) is the largest locus of serotonin (5-HT) producing neurons in the brain (Descarries et al. 1982). The characterization of 5-HT neurotransmission in the DRN has been a working model that has allowed gaining an important understanding of the pathophysiology and treatment of mental diseases (Dominguez-Lopez et al. 2012). 5-HT is very likely one of the most involved neurotransmitter in suicide and depression; a lower 5-HT firing activity is linked to a depressive state in animal models (Dominguez et al., 2012); and in humans; therefore, the investigation of DRN 5-HT neuronal activity provides pivotal neurobiological and pharmacological information for the study of this still unknown behavior.

Briefly, the rodent is anesthetized and then placed in a stereotaxic frame. After the exposure of the skull, a hole is drilled through the skull in a position determined by reference to the stereotaxic atlas of the brain for mice or rats. A single-barreled glass microelectrode filled with 2 M NaCl and a colorant for later histological verification is lowered into the DRN using a micropositioner until a firing cell having the electrophysiological characteristics of 5-HT neurons is reached. When adjacent to but outside the neuron, current fields generated by action potentials in that cell are detected by the microelectrode as small voltage deflections. The electrophysiological characteristics of 5-HT neurons are (1) slow (0.1–4 Hz) and prominently regular firing rate (coefficient of variation from 0.12 to 0.87) and (2) broad biphasic (positive–negative) or triphasic waveforms (0.8–3.5 ms; 1.4 ms first positive and negative deflections) (Bambico et al. 2010).

Conclusions

Even though to reproduce suicide in animals is very likely impossible for all the reasons discussed in this chapter, the study of the different neurotransmitter systems by using electrophysiology paired with behavioral testing related to the most important risk factors of suicide in humans is a promising platform to investigate the neurobiological basis of suicide and, most important, to examine and develop novel pharmacological strategies to prevent suicide attempts. Despite more than a century of research, we know a lot about the biology of single neurons and synapses and how they can control behavior, but still a lot remain to discover about their patterns of connection and the brain as a whole system. Consequently, our understanding of how the brain generates complex thoughts, emotions, and behaviors such as suicide still remains enigmatic in human beings. However, thanks to the fast development of novel tools and instrumental techniques, the mapping of the whole brain activity is under active investigations, and new important knowledge is soon expected. As example, the recent development of brain imaging and optogenetic techniques has provided a new way to establish and examine the relationships between brain activity and behavior in physiological and pathological conditions. As a consequence, their application in the context of the animal paradigms here described may shed new light into the neurobiology and thus our understanding of suicide. However, more research needs to be done in human subjects to understand the neurobiological basis connecting psychological suffering, impulsivity and deliberate decision to end own life. In particular, the development of research in the field of self-consciousness and the connections between negative emotions (pain, sadness, despair, worthlessness, helplessness) and self-awareness will allow us to better understand the mechanism inducing to suicide in the human being.

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Part III

Neo-Durkheimian View: From Society to Groups at Risk

Effect of Economic Crises on Suicide Rates

15

Marta Miret and Pilar López-García

Abstract

Economic crises can cause adverse health effects, such as an increase in the prevalence of mental disorders and suicide rates. Nevertheless, these effects might vary across countries. While some countries successfully decouple economic crises from adverse mental health outcomes, in others the suicide rates increase due to economic crises. The differential impact of the economic crises on suicide may depend on some of the policies taken to tackle the financial downturn. Some of the mechanisms that underlay the association between suicide and economic crisis are increased unemployment, job insecurity, decreased earnings, personal debt and sudden bankruptcy. Several measures can be taken in order to prevent or decrease the negative effects of economic downturns on suicide, such as reducing the barriers to accessing health care, improving the quality of treatment of mental disorders with special attention to depression, raising the price of spirits, providing support to tackle financial problems, investing in labour market programmes and encouraging social support.

The question of whether economic crises increase the incidence of suicide cannot definitely be answered with a yes or no. Suicide is a complex phenomenon and it has a wide spectrum of risk factors. Periods of economic recession are tough times that may impact differently on individuals and societies. Individual factors such as

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vulnerability and resilience may modulate the impact of economic crises on mental health. Besides, at the country level, different policies adopted to combat the financial crisis may have a different impact on the global health of the society (Arie 2013). As a result, the suicide studies that focus on economic crisis provide different results (Luo et al. 2011).

15.1 Suicide and Economic Cycles: A Look Back to History

At the end of the nineteenth century Émile Durkheim (1897), already pointed out the importance that the economic factors had on suicide and stated that serious readjustments in the social order, either due to sudden growth or an unexpected catastrophe, make individuals more inclined to self-destruction. Data from the United States supported this hypothesis by showing that suicide rates vary directly as the rate of change of the economic situation, independently of the direction of the change (Pierce 1967). Other studies show that economic growth can be followed by a decrease in suicide rates, but if economic growth is not accompanied by adequate infrastructures for mental health services, suicide rates might trend up (Blasco-Fontecilla et al. 2012). Therefore, the health policies and the investment in health seem to be better predictors of suicidal behaviour than the economic situation of the country.

A correlation between business depressions and suicides was already found at the beginning of the twentieth century in the United Kingdom, France, the United States and also later in Taiwan. Li (1971) postulated that this association might be explained by the fact that during periods of economic hardship, people suffer a loss of status and suicide might be a way to escape from it. During the years of the Great Depression, there was a significant increase in the proportion of suicide deaths in the United States, rising from 18.1 suicides per 100,000 population in 1929 to 21.6 per 100,000 population in 1932 (Stuckler et al. 2012). The economic crisis that started in the former Soviet Union in the early 1990s had devastating consequences on population health, with a reduction in life expectancy and a dramatic increase in mortality (Stuckler and Basu 2013). In Asia, there was also an increase in the suicide rates during the Southeast Asian crisis that took place in the years 1997 and 1998; Japan, Korea and Hong Kong had an increment in the number of suicides during that period (Chang et al. 2009).

15.2 Differential Impact of the 2008 Financial Recession on Suicide across Countries

As shown in Fig. 15.1, there is evidence that the global financial crisis that started in 2008 is causing adverse health effects, such as an increase in the prevalence of mental disorders and suicide rates (Karanikolos et al. 2013; Wahlbeck and McDaid 2012). Nevertheless, these effects might vary across countries. The World Health

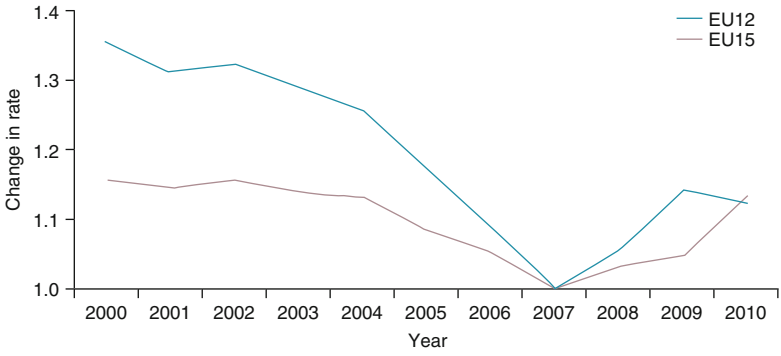

Fig. 15.1 Suicide rates before and after 2007 in the 12 post-2004 (EU12) and 15 pre-2004 (EU15) countries of the European Union (Reprinted from *The Lancet*, 383(9918):748–53, Copyright (2013), with permission from Elsevier (Karanikolos et al. 2013))

Organization (2014) has reported that the global age-standardized suicide rate has fallen to 26 % (23 % in men and 32 % in women) during the 12-year period from 2000 to 2012. Although the reasons for these changes are unknown, it might be associated to the improvement in global health care over that decade (World Health Organization 2014). But this global analysis masks country-specific changes in suicide rates. Among the 172 member states with populations of over 300,000, the 2000–2012 change in age-standardized suicide rates ranged from a decline of 69 % in Maldives to an increase of 270 % in Cyprus (World Health Organization 2014).

In the United States, the suicide rates have increased during the recent economic recession (Reeves et al. 2012). In Europe, the negative impact on health of the economic crisis differs among countries. Iceland's population health improved during the recession years, and in Finland and Sweden, the suicide rate declined during times of economic crisis (Stuckler et al. 2009). On the other hand, in Greece, the most affected country by the economic recession in Europe, there was a sharp rise, with suicides rising by more than 60 % since 2007 (Kentikelenis et al. 2011), despite being the country with the lowest suicide rate in Europe before the recession (Economou et al. 2013; Kentikelenis et al. 2014). In the United Kingdom, the rate of suicides before the economic crisis, from 2000 to 2007, was declining by 57 suicides per year (95 % confidence interval 56–58) in men. In contrast, there was a rise in the number of suicides during the crisis, with 846 more suicides among men than would have been expected if the trend found in the first part of the decade had continued in the period 2008–2010 (Barr et al. 2012). The evidence available for Spain shows mixed results. Although some studies have reported an association between the 2008 financial crisis and a relative increase in suicides (Lopez Bernal et al. 2013), other studies have not identified a strong suicide effect directly linked to the 2008 financial recession (Ayuso-Mateos et al. 2013; Salvador-Carulla and Roca 2013; Fountoulakis et al.

2014). A study comparing the prevalence of suicidal ideation and attempts in Spain during the economic crisis (in 2011–2012) with the prevalence 10 years before, a moment of economic prosperity, found that the prevalence was similar (Miret et al. 2014).

Despite the available evidence that the economic recession is a risk factor for suicide (Luo et al. 2011), the differences across countries cannot be completely explained yet. One possible explanation of the different impact that the crisis had in different countries is related to the policies adopted to respond to the economic downturn. Countries with fiscal austerity policies leading to cuts in public spending in health-care and welfare services might have increases in suicide rates and impairments in health (Arie 2013). This might explain why countries like Iceland and Finland did not suffer an increase in suicide rates, since they did not reduce their health budgets (Arie 2013).

15.3 Is the Impact of Economic Crises on Suicide the Same for Everyone?

There are some inequalities within each country regarding the risk of suicide associated with the economic downturn. The changes in health coverage and the austerity measures imposed on the health-care services in some countries mean that the effects might be higher in the weakest and most vulnerable members of society (Karanikolos et al. 2013). Evans-Lacko et al. (2013) analysing 27 European countries found that following the onset of the 2008 economic recession, the gap in unemployment rates between individuals with and without mental health problems significantly widened, showing that the economic downturn had a greater impact on people with mental health problems.

15.4 How Can Economic Crises Affect Suicide Rates?

Several mechanisms might underlay the association between suicide and economic crises. One of the most devastating consequences of the economic crises is the increase in unemployment. Although being unemployed can be less stigmatizing when the situation is shared by many others in the country, the poor prospects of finding a new job and the limited access to social services and medical treatment due to the austerity measures that might be implemented can make losing the job particularly harmful in times of economic crisis (Norstrom and Gronqvist 2015). Individual or family unemployment increases the risk of major depression (Legido-Quigley et al. 2013). Furthermore, observational and prospective studies also show that unemployed people are at a higher risk of suicide (Agerbo 2005; Dooley et al. 1994; Gunnell et al. 2004). The association between the increases in suicide after the crisis and the increases in unemployment particularly occurs in men (Chang et al. 2013) and in countries where the unemployment level before the crisis was relatively low (Hawton and Haw 2013; Chang et al. 2013). Male

suicide increases are significantly associated with each percentage point rise in male unemployment, by 0.94 % (95 % CI: 0.51, 1.36) (Kentikelenis et al. 2014). Long-term unemployment is associated with a greater risk of both suicide and attempted suicide than being unemployed for shorter periods (Haw et al. 2014). As stated above, vulnerable populations, such as patients with mental disorders, are more prompt to lose their jobs during economic crises (Evans-Lacko et al. 2013). However, in people with no record of serious mental illness, unemployment is still associated with about a 70 % greater suicide risk (Agerbo 2005). Although increased unemployment has led to higher suicide rates in some countries (Reeves et al. 2012; Barr et al. 2012), this has not been proved to be the case in other countries, such as Portugal (Ayuso-Mateos et al. 2013) and the Baltic states (Stankunas et al. 2013). In the United States, the rise in unemployment during the recession is associated with a 3.8 % increase in the suicide rate (Reeves et al. 2012). There is a need for longer observation to ascertain the association between suicide rates and unemployment across countries.

Job loss is not the only stress during economic crises. Other factors that have been linked to an increase of suicide are job insecurity and decreased earnings (Jenkins et al. 2008; Reeves et al. 2012). Job insecurity has been associated with 33 % more risk of having a common mental disorder (Stansfeld and Candy 2006). Sudden bankruptcy has also been found to be a risk factor for suicide (Haw et al. 2014), whereas in Hong Kong it was found that 24 % of all suicides in 2002 concerned people in debt (Yip et al. 2007).

Losing a job, home foreclosure and financial problems lead to an increase in the risk of suicide through comorbidity with other risk factors such as depression, anxiety and increased alcohol consumption (Hawton and Haw 2013), conditions that are associated with a higher risk of suicide. This relationship may be mediated by individual vulnerability and resilience factors, which could explain why some individuals are at a higher risk, while others seem more resilient to economic shocks (Kentikelenis and Papanicolas 2012).

15.5 Can the Effects of Economic Crises on Suicide Be Prevented?

Several measures can be taken in order to prevent or reduce the negative effects that economic downturns might have on suicide. As previously stated, the differential impact of the economic crises on suicide risk may depend on some of the policies taken to tackle the financial downturn. The fact that some societies have successfully decoupled economic crises from adverse mental health outcomes raises hope to eliminate the association of economic shocks and suicidality (Reeves et al. 2014). Although Kentikelenis et al. (2014) pointed out that the important issue is not the magnitude of the cut in health-care spending per se but its effect on health-care access and quality. Societies in which there is a protection on the access to health-care and welfare services are less likely to have health consequences, whereas in countries without comprehensive health-care provision, people most in need of

mental health services may be less inclined to access them because of the costs involved. Countries that have implemented policies that shift costs from the state to the patient are now facing the fact that more people do not have access to the medicines or procedures they need because they cannot afford them (Arie 2013). Conversely, a more universal health coverage should ameliorate the health consequences of the economic crises. Reducing the barriers to accessing health care is essential. Timely and effective access to health care is crucial to reduce the risk of suicide (World Health Organization 2014). Investing in primary care services for the early detection and treatment of common mental disorders and the assessment and management of patients presenting with suicidal behaviour is also a key measure (Haw et al. 2014).

Not augmenting the costs of antidepressants, keeping accessibility to them, rationalizing their use and improving the quality of treatment of depression can be cost-effective measures to reduce the incidence of suicide during crisis periods (Miret et al. 2014). Another cost-effective policy is to raise the price of spirits, since it reduces the harm done by heavy drinking (Anderson et al. 2009; Karanikolos et al. 2013; Wahlbeck and McDaid 2012; World Health Organization. Regional Office for Europe 2011).

Support to tackle financial problems is also a key area. Policy actions to prevent people from becoming over-indebted, as well as to make it easier for them to pay off their debts, can help people who are suffering from the stress of excessive debt (Wahlbeck and McDaid 2012; World Health Organization. Regional Office for Europe 2011). A generous unemployment protection might weaken the detrimental impact on suicide of the increasing unemployment during times of crisis (Norstrom and Gronqvist 2015). Investments in active labour market programmes have been shown to be effective (Stuckler et al. 2009). Since unemployed individuals are at a higher risk, policies should support them and their families. Higher levels of social capital can enhance resilience among vulnerable groups, buffering the impacts of the economic crisis on mental health (Reeves et al. 2015). Therefore, encouragement of social support can also have a protective effect (Haw et al. 2014).

15.6 Concluding Thoughts

Economic recessions, as they relate to cases of individual adversity through job or financial loss, can be associated with individual suicide risk (World Health Organization 2014). Nevertheless, increases in suicide are not inevitable during recessions. Although the correlation between recessions and suicide has been repeatedly reported, there is evidence that some societies have successfully overcome the adverse mental health outcomes of the economic crises. It is essential to identify the factors that lead to an increase in mental health problems and suicide risk during periods of financial hardship in order to adopt policies that protect individuals from the harm of recessions. The long-term effects of the recessions may last into the period of economic recovery. It is important that governments consider how to reduce the fatal consequences of economic recessions and of policy decisions on tackling such crises (Hawton and Haw 2013).

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Key Features of Suicidal Behavior in Mental Disorders

16

Emilie Olié, David Travers, and Jorge Lopez-Castroman

16.1 Bipolar Disorder

16.1.1 Context

Up to 50 % of patients suffering from bipolar disorder will attempt suicide during their life; 15–30 % will commit suicide. The risk of suicide is up to 20–30 times greater among bipolar patients than among the general population.

16.1.2 Specific Risk Factors

- History: personal and familial history of suicide attempt and personal history of childhood abuse
- Female gender
- Personality traits: hopelessness and cyclothymic/depressive temperament
- Features of acute mood episode: severity of depressive symptoms and presence of psychotic/atypical/mixed characteristics
- Evolution of bipolar disorder: young age at illness onset, first years of evolution, first depressive episode, onset and end of acute mood episode, transition periods,

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rapid cycling, predominant depressive polarity, and depressive polarity of first illness episode
- Comorbidities: substance use disorder, anxiety disorder, cluster B personality disorder, and eating disorder

16.1.3 Assessment

It is important to detect bipolar disorder in order to reduce the duration of untreated illness. Scales such as Mood Disorder Questionnaire could be used.

16.1.4 Specific Management

- To reduce risk of mood transition and induction of mixed characteristics of episode, antidepressant monotherapy should be avoided.
- Use of antiepileptic drugs reduces suicide attempt rates both relative to patients not receiving any psychotropic medication and relative to their pretreatment levels.
- Long-term lithium treatment has been associated with reduced risk of suicide and suicide attempts: the overall risk of suicides and attempts is around five times less among lithium-treated subjects than among those not treated with lithium. Lithium treatment discontinuation, particularly if abrupt, leads to suicidal behavior.
- Acceptance and commitment therapy and dialectical behavior therapy seem to be promising to reduce suicidal risk in bipolar disorder.

16.2 Major Depressive Disorder

16.2.1 Context

Up to 70 % of suicide attempters are depressed at the time of the gesture. In total, 15 % of patients suffering from depression will commit suicide. The standardized mortality ratios for suicide among depressed individuals compared to the general population are 21 for males and 27 for females.

16.2.2 Specific Risk Factors

- History: personal and familial history of suicide attempt and personal history of childhood abuse
- Male, younger age, and elderly
- Personality traits: hopelessness and impulsivity
- Features of acute mood episode: anhedonia, insomnia, anxiety, panic attacks, and severity of depressive symptoms
- Evolution of unipolar disorder: first years of evolution
- Comorbidities: anxiety disorders, substance misuse, and somatic diseases

16.2.3 Assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) may be used for assessment of suicidal ideation and behavior.

16.2.4 Specific Management

- Antidepressants decrease risk of completed suicide in depressed patients and suicidality in elderly. It is admitted that the risk posed by untreated depression has always been far greater than the very small risk associated with antidepressant treatment. But antidepressant use is still debated since the black-box warning of the Food and Drug Administration (FDA) in young people.
- Data from several studies indicate marked reductions of suicidal behavior and mortality during add-on long-term treatment with lithium salts.
- Intravenous ketamine, a widely used anesthetic agent, produces rapid reductions in suicidal ideation in treatment-resistant unipolar patients. However further studies are warranted to test ketamine's antisuicidal effects in higher-risk samples.
- An acute decrease of suicidal ideations following electroconvulsive therapy and repetitive transcranial magnetic stimulation has been reported in depressed patients.
- Existing evidence supports the efficacy of cognitive behavioral therapy in preventing suicidal behavior. Some other psychological treatments, such as acceptance and commitment therapy or positive psychology, are promising, but the supporting evidence remains insufficient.

16.3 Eating Disorders

16.3.1 Context

Suicide attempts occur in approximately 3–20 % of patients with anorexia nervosa and in 25–35 % of patients with bulimia nervosa.

The risk of suicide among patients suffering from eating disorder is very elevated, up to 30 times greater than that for the general population. Restrictive anorexia in particular is strongly associated with completed suicide. Anorexia purging type and bulimia nervosa are associated with suicide attempts rather than completed suicide.

16.3.2 Specific Risk Factors

- Being adult
- Severity of disorder
- Social burden of eating disorder
- Comorbidities: depressive episode, bipolar disorder, and substance use disorder
- For attempted suicide: purging symptomatology, use of laxative, self-induced vomiting, and period of switching to the bingeing/purging subtype of anorexia nervosa
- For completed suicide: being anorectic

16.3.3 Assessment

There is no specific scale for assessment of suicidal risk in eating disorders.

16.3.4 Specific Management

- Treatment of psychiatric comorbidities, especially substance abuse and depression, reduces suicidal risk.
- Hospitalization is justified if patients are at high suicidal risk and during transition periods.
- Dialectical behavior therapy seems to reduce suicidal behavior in patients suffering from purging behaviors.

16.4 Attention-Deficit and Hyperactivity Disorder

16.4.1 Context

In epidemiological studies, attention-deficit and hyperactivity disorder (ADHD) has been associated with an increased risk of suicidal behaviors compared to the general population. This association seems to be mediated by comorbid psychiatric disorders and moderated by the type of ADHD (inattention vs. hyperactivity). ADHD patients have increased risks of attempted (OR = 3.62) and completed suicide (OR = 5.91), even after adjusting for comorbid psychiatric disorders.

16.4.2 Specific Risk Factors

- Risk factors may have a different effect depending on gender: emotional and behavioral problems in males and depressive episodes in females increase the risk for suicidal behaviors.
- Comorbidities: antisocial personality disorder, borderline personality disorder, or bipolar disorder.
- Risk of attempted suicide among first-degree relatives (parents or full siblings of probands with ADHD): OR = 2.42 for parents and OR = 2.28 for siblings.
- Personality traits: impulsivity, impaired response inhibition, and poor emotion regulation.
- Characteristics of ADHD: severity of childhood hyperactivity, number of conduct disorder symptoms, hyperactive or combined ADHD subtype, and persistent symptomatology.

16.4.3 Assessment

The detection of adult ADHD is essential to evaluate the risk of suicidal behaviors, especially in comorbid conditions. The adult ADHD self-report scale (ASRS) can be used as a screening instrument in adults. The most used instrument for the diagnosis of ADHD in childhood is the Wender Utah Rating Scale (WURS).

16.4.4 Specific Management (Treatment Controversies)

- Security warnings have been raised in the USA and Canada to monitor closely the risk of suicidal ideation and attempts among children treated with atomoxetine. Suicidal tendencies are a contraindication for the prescription of methylphenidate in the EU.
- However, the effects of ADHD treatments on suicidal behavior remain unclear. A large recent register-based study confirms their association at a population level, but ADHD treatment reduced suicide-related events in within patient comparisons.

16.5 Borderline Personality Disorder

16.5.1 Context

Most patients with a borderline personality disorder will attempt suicide (60–70 %), but only a smaller fraction will die by suicide (5–10 %). They present a chronic suicidality, which is listed as a diagnostic criterion, and an average of 3.3 attempts during their lifetime.

16.5.2 Specific Risk Factors

- History: personal and familial history of suicide attempt and substance use disorders and personal history of childhood abuse (particularly sexual abuse).
- For attempted suicide: early onset, number of hospitalizations and previous attempts, depression, interpersonal triggers, poor social adjustment, chronic feelings of emptiness, impulsivity, and hostility.
- For completed suicide: male gender, impulsivity, hostility, comorbid cluster B disorders and substance use disorders, age over 30 years, and untreated cases.
- Affective instability and psychotic symptomatology might protect borderline patients from suicide completion.

- Early phases and follow-up in mental health services are associated with multiple threats and attempts but low lethal outcomes. Failed treatments and multiple previous attempts seem to predict more lethal future attempts.
- Comorbidities: major depression, antisocial personality disorder, anxiety disorder, substance use disorders, bipolar disorder, and eating disorders.

16.5.3 Assessment

Nonspecific questionnaires can be used to measure the frequency, intent, and medical severity of suicide attempts and self-harm in this population. The Linehan Suicide Risk Assessment and Management Protocol has been validated in samples of borderline patients.

16.5.4 Specific Management

- Psychotherapy is the recommended treatment option, with a focus on managing suicidal urges, reducing reinforcements, and preserving adherence to treatment programs.
- Pharmacotherapy is mostly viewed as an adjunctive component for comorbid axis I disorders and in periods of crisis. Behavioral dyscontrol can be treated with selective serotonin-reuptake inhibitors, mood stabilizers, and low-dose neuroleptics.
- Dialectical behavioral therapy is effective for reducing suicide attempts.
- Less intensive psychotherapies and brief crisis intervention may also reduce suicidal behaviors in this population.
- "No harm" contracts in the context of a therapeutic alliance and brief or partial hospitalization in periods of crisis should be considered.

16.6 Substance Use Disorders

16.6.1 Context

Seventeen to 45 % of patients seeking treatment for substance dependence report a history of suicide attempts, often multiple. Slightly smaller rates have been reported in community samples. Suicide is also a leading cause of death among substance users, independently of the substance, the only exception being cannabis. For instance, patients with alcohol dependence are ten times more likely to make a fatal suicide attempt than the general population, and 5–10 % of intravenous drug users complete suicide. Moreover, substance use seems to act as a trigger for suicidal behaviors.

16.6.2 Specific Risk Factors

- History: personal history of childhood abuse (physical, sexual, but also emotional) and neglect, family history of suicidal behavior, and history of unsuccessful treatment
- For suicide attempt: young age and female gender
- Demographic: poor social support (unemployment, marginalization) and disrupted family background, not being in couple
- Personality traits: impulsivity, hostility, and a history of aggression
- Evolution of the disorder: early onset (<18 years of age), intravenous use of stimulants, use of multiple substances, longer duration of illness, having experienced an overdose, and higher levels of dependence
- Comorbidities: major depressive disorder (antidepressant treatment), bipolar disorder, antisocial and borderline personality disorder, anxiety disorders, attention-deficit and hyperactivity disorder, and eating disorders

16.6.3 Assessment

Written policies for standardized assessment of suicidal risk among substance users are needed in all care centers dealing with substance use disorders. Every staff should also participate in regular (annual) training for risk assessment.

16.6.4 Specific Management

- The treatment plan should focus concomitantly on both addictive behavior and comorbid psychiatric disorders (dual diagnosis).
- Especially consider clinical management of impulsivity and hostility.
- Integrate motivational interviews and facilitate withdrawal in structured care programs.

  Preventive measures such as favoring social bonding, educational programs, or a reduction of available substances among adolescents.

16.7 Dementia

16.7.1 Context

Frequency of completed suicide highly increases with age, unlike frequency of suicide attempts, which decreases. Most of the general risk factors pile up in elderly people, from psychosocial to somatic or psychiatric ones. Considering dementia, its direct relationship with suicide remains unclear.

Caregivers are also concerned by suicidal risk for themselves.

16.7.2 Specific Risk Factors

- History: adjustment period following diagnosis.
- Type of dementia: semantic dementia.
- Features of dementia: global severity, lower age of onset, delusion, agitation/aggression, anxiety.
- Comorbidities: depression and anxiety occurring frequently during dementia could be the main factors leading to suicidal behaviors.
- Other: suicidal risk of the caregivers is increased.

16.7.3 Assessment

- Behavioral and psychological symptoms of dementia have to be regularly assessed: using Neuropsychiatric Inventory (NPI, Cummings), a hetero-questionnaire assessing 12 dimensions from delusion to appetite and eating change.
- Specific depression assessment tools can be used:
  - Geriatric depression scale (GDS, Brink and Lesavage). A 4- or 15-item scale for rapid or detailed screening of depression in elderly people.
  - Cornell Scale for Depression in Dementia (CSDD, Alexopoulos). Two semi-structured interviews with the informant and the patient, the final rating of the 19 items representing the rater's clinical impression.

16.7.4 Specific Management

- Pay attention to suicidal ideation in every stage and type of dementia, particularly at the time of diagnosis and during early stages of the illness.
- Develop psychological support and care support for patients.
- Screen and treat depression, which has to be specifically considered as a comorbid entity but not as a physiological feature or evolution of dementia.
- Assess and treat anxiety as soon as possible.
- Screen and assess dementia in elderly suicide attempters, regardless of a depression diagnosis.
- Consider psychological support for caregivers of dementia patients, especially patients with suicidal ideation.

16.8 Schizophrenia

16.8.1 Context

Regardless the cause, schizophrenic patients are highly at risk of premature death compared to general population and other psychiatric disorders. Death by suicide

represents the most frequent cause of death (10–15 %). Lifetime risk for suicide in schizophrenia is about 5 %. From 20 to 40 % of patients will attempt suicide at least once.

16.8.2 Specific Risk Factors

- Gender: compared to general population, males are more likely to attempt suicide, and women are more likely to die by suicide.
- Course of the illness: early age at onset, young age, and poor adherence to treatment.
- Features of schizophrenia:
  - Subtypes: schizoaffective and paranoid schizophrenia.
  - Clinical features: presence of hallucinations, suspicion, good insight (pay specific attention to insight recovery), and impulsivity/violence.

16.8.3 Assessment

- Consider specific scales to assess suicidal risk: Schizophrenia Suicide Risk Scale (SSRS, Taiminen).
- Assess quality of insight with scales considering multidimensional and dynamic features of insight: Scale to Assess Unawareness of Mental Disorder (SUMD, Amador).
- Assess depressive symptomatology using specific depression scales, in order to distinguish negative symptoms from depression symptoms: Calgary Depression Scale for Schizophrenia (CDSS, Addington and Addington).

16.8.4 Specific Management

- Consider personal history of suicidal behaviors, violent behaviors, and dimensions of impulsivity.
- Considering medications, second-generation antipsychotics, especially clozapine (specific indication for suicide risk in some but not all countries), should be preferred.
- Screen depression and its specific features (i.e., hopelessness and guilty ideas of reference), particularly during insight recovery after acute phases of the illness.

16.9 Anxiety Disorders

16.9.1 Context

Even though the question remains partially unclear because of the frequent and multiple comorbidities in anxiety disorders, suicide rates are higher compared to

general population in every anxiety disorder but obsessive-compulsive disorder (OCD). An approximate threefold increase of suicidal risk in patients suffering from anxiety disorders should be considered.

In panic disorders (PD), prevalence of suicide attempts is as high as in depression, i.e., 7 %. In post-traumatic stress disorder (PTSD), risk of suicide attempts increases by four, and risk of completed suicide increases by seven. In OCD, median rates of suicidal ideation and suicide attempts reach, respectively, 30.5 % and 13.4 %.

16.9.2 Specific Risk Factors

- Anxiety disorders (all):
  - Symptoms intensity.
  - Avoidant coping strategies (indirectly, through disability, social isolation).
- PTSD:
  - Re-experiencing and avoidance symptom clusters of PTSD.
- OCD:
  - Severity of OCD symptoms, mainly obsession symptoms.
  - Comorbid axis I diagnoses, severity of depressive, and anxiety symptoms.
- Comorbidities:
  - Mood disorders (depression, bipolar disorder).
  - Substance abuse (linked to the "auto-medication" of the anxiety disorder).

16.9.3 Assessment

Scales for the screening of anxiety disorders (Beck Anxiety Inventory, General Anxiety Disorder-7) should be used. Suicidal risk should be systematically assessed.

16.9.4 Specific Management

- Anxiety disorders (all): cognitive behavioral therapy (CBT) on the illness and on the avoidant coping strategies should be considered.
- Comorbidities have to be systematically checked, especially depression, other anxiety disorders, and alcohol abuse.

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How to Deal with Personality in Suicidal Behavior?

17

Jorge Lopez-Castroman and Hilario Blasco-Fontecilla

Abstract

There is a large variability in the personality of suicide attempters, but many personality traits and disorders have been consistently associated with suicidal behavior. In clinical settings, psychiatrists and psychologists must often face high-risk patients with marked personality traits, but they seldom investigate personality features to plan the subsequent treatment. This limitation is due to the difficulty of a reliable assessment of personality, the frequent comorbidity with other mental disorders (including other Axis II disorders), and the lack of know-how to apply this information into targeted interventions. However, researchers are progressively carving the features of personality that interact with each other and with other risk factors, such as life events, to amplify the risk of a suicidal act. In this chapter we will review recent findings and outline the options for intervention that are being opened.

17.1 Introduction

The personality is the enduring pattern of thoughts and behaviors that distinguish human beings from each other. For about 9–15 % of the population in developed countries (Lenzenweger et al. 2007), personality becomes problematic because it deviates markedly from the cultural background, being pervasive and inflexible from adolescence or early adulthood, and leading to significant impairments or distress. These are the criteria of a personality disorder (PD) according to the current version

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of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Some PDs are significantly associated with suicidal ideation, attempted and completed suicide, and high levels in some personality traits are recurrently found in samples of suicidal patients. Indeed, PDs are extremely frequent in clinical samples of psychiatric patients and even more among those becoming suicidal. About one-third of completed suicides according to autopsy studies and three in four suicide attempters could be diagnosed with a PD (Pompili et al. 2004). Considering the personality of patients at risk of suicidal behavior (SB) is important since: (i) PDs are frequently comorbid with other Axis I or Axis II disorders, (ii) the presence of a PD complicates prognosis and treatment response, and (iii) personality traits should inform any assessment of suicidal risk to control for their effect on other risk factors. Inversely, the role of personality is largely mediated by other factors, including comorbid psychopathology but also lifetime interpersonal difficulties or adverse life events (Schneider et al. 2008).

To date, research on risk factors of SB has mainly focused on Axis I mental disorders and sociodemographic features, and only some authors have focused on personality. However, personality features, along with other three dimensions, namely, psychopathology, life events, and suicidal staging, are critical to any model of SB aiming to attain an accurate risk representation (Courtet et al. 2011). For instance, personality features are clearly associated with the risk of repeating a suicide attempt. In a systematic review of the literature, personality traits such as anger/impulsivity, affect dysregulation, or compulsivity/anxiousness, as well as having a PD, were associated with the repetition of suicide attempts (Mendez-Bustos et al. 2013). Of note, although personality is a key element to understand SB, suicide attempters themselves cannot be easily clustered into "personality" groups. The results of studies of clustering are unclear but suggest two main subtypes of personality among attempters: (i) an internalizing subtype, characterized by general negative affect, and (ii) an emotionally dysregulated subtype, close to borderline PD (BPD; (Lopez-Castroman et al. 2015)). These subtypes have also been described as introverted/negativistic/avoidant/dependent/neurotic on the one hand and impulsive/hostile/antisocial on the other hand (Turecki 2005). However, personality features do not seem to differentiate the lethality or severity of suicide attempts in cluster analysis (Lopez-Castroman et al. 2015), which is in keeping with previous research (Blasco-Fontecilla et al. 2009a).

17.2 What Personality Traits and Personality Disorders Should We Look for in Patients at Risk of Suicidal Behavior?

The PDs most frequently associated with SB are situated in the so-called DSM-IV[1] cluster B (emotional/erratic), which includes antisocial, borderline, histrionic, and narcissistic PDs. These PDs account for the bulk of suicide risk among individuals with significant personality pathology (Ansell et al. 2015). However, the personality traits that increase the risk for suicidal acts are not exclusive of this cluster.

[1] The DSM-5 does not use anymore clusters of PD, but most clinicians continue using DSM-IV PD clustering system.

17.2.1 Borderline Personality Disorder (BPD)

Recurrent SB is one of the diagnostic criteria of BPD. Although as many as 46–92 % of BPD patients attempt suicide during their lifetime, completed suicide is relatively rare (3–10 %) (Soloff and Chiappetta 2012a). Sixty percent report multiple suicide attempts (Zanarini et al. 2008), and indeed the repetition of suicide attempts, compared to single attempters, is associated with this diagnosis (Forman 2004). Despite their bad reputation, there is evidence of a positive evolution for many BPD patients in the long term (Shea et al. 2002; Tracie Shea et al. 2009; Zanarini et al. 2010), underlining the importance of supportive and preventive interventions in the period of high suicidal risk of SB. In fact, suicidal acts in BPD may help to regulate the emotional response when the individual is confronted to high psychic pain (Paris 2004). However, BPD patients that commit suicide seem to be less prone to psychiatric treatment. A meta-analysis of the literature showed that higher rates of suicide in BPD are associated with short-term rather than long-term follow-up (Pompili et al. 2005).

Developmental models suggest an interaction between life events, particularly early trauma, with the evolution into the symptomatic disorder of BPD and SBs (Hayashi et al. 2015). In a study with 120 BPD patients, those who died by suicide ($n=70$) were compared with the rest of the sample (McGirr et al. 2007). BPD suicides had higher levels of Axis I and II comorbidity, novelty seeking, impulsivity, and hostility than survivors, as well as less suicide attempts and psychiatric hospitalizations. The interaction of impulsive and aggressive features and the comorbidity with other cluster B disorders (especially antisocial PD, which is found in 92.5 % of suicides), as well as lower harm avoidance, predicted a fatal outcome in this sample. Another study, the Collaborative Longitudinal Personality Disorders Study, followed 431 participants for 10 years while considering the severity and dimensionality of the PDs. According to their results, paranoid, antisocial, borderline, histrionic, and dependent PDs emerged as independent risk factors for ever attempting suicide, but only the severity of BPD was retained in the multivariate model (Ansell et al. 2015). In other words, the common variance underlying multiple PDs that leads to SB may be best reflected by the diagnosis of BPD. Despite these advances, the accurate identification of the more "risky" BPD patients continues to be a challenge in clinical settings.

17.2.2 Antisocial Personality and Antisocial Personality Disorder (ASPD)

Antisocial patients behave in an irresponsible, impulsive, abusive, and guiltless manner. Having an ASPD predicts comorbid addictive, psychiatric, and medical problems, as well as high rates of SB, homicides, and accidents. The literature on personality-related suicide risk has mainly been focused on BPD. Accordingly, literature on ASPD and suicide is relatively scarce (Blasco-Fontecilla et al. 2007). The rate of suicide attempts in individuals diagnosed with ASPD range from 11 % to 42 % (Blasco-Fontecilla et al. 2007; Zaheer et al. 2008), but up to 72 % of patients

with ASPD might attempt suicide (Garvey and Spoden 1980). Suicide attempts in ASPD individuals are usually considered nonserious, with no real intention to die, in order to manipulate others or to act out their frustration, and secondary to interpersonal loss or problems (Garvey and Spoden 1980; Frances et al. 1986). This lack of seriousness may suggest that they have no real intention of killing themselves and that they use suicide attempts to have a secondary gain (e.g., hospital admission) (Pompili et al. 2004). In a military hospital setting, antisocial patients used SB as an alternative channel to alleviating distress (Sayar et al. 2001).

The high rates of suicide attempts among ASPD individuals contrast to the rates of completed suicides (Blasco-Fontecilla et al. 2007). Suicide rates reported among patients with ASPD vary considerably as most studies use no operationalized criteria (Bronisch 2007), but most studies report rates around 5 % (Miles 1977; Zaheer et al. 2008), which is lower than the 8 % found in BPD in long-term follow-up studies (Bronisch 2007). Frances et al. (1986) hypothesized that the 5 % rate of suicide found in subjects with ASPD could be explained by the presence of a concurrent affective disorder, substance abuse, or other PD (Frances et al. 1986). Therefore, the traditional assumption derived from Cleckley and other classical authors that antisocial individuals could be so self-centered to actually try to kill themselves could be inconsistent with current findings (Lambert 2003).

In any case, ASPD individuals are typically quite refractory to medical treatment but show moderation with advancing age and positive life events, such as marriage or employment, which facilitate socialization (Black 2015). On the contrary, and independently of comorbid Axis I disorders, negative life events (particularly the death of the partner) seem to precede suicidal acts in this population (Blasco-Fontecilla et al. 2010). Serotonergic dysfunctions are found both in antisocial populations and patients at risk of SB. Interestingly, epigenetic mechanisms may explain the downregulation of serotonergic genes in antisocial offenders (Checknita et al. 2015). Of note, adolescent ASPD has been associated with all the stages of the suicidal process (ideation, attempts, and suicide), and inversely SB among adolescents is very frequently associated with antisocial behaviors according to the results of epidemiological studies (Marttunen et al. 1994). Furthermore, parents with antisocial personality transmit the risk of SBs to their offspring (Santana et al. 2015).

17.2.3 Histrionism and Histrionic Personality Disorder (HPD)

Histrionism is characterized by an enduring pattern of attention-seeking behavior and extreme emotionality. The concept of HPD arose from the clinical observation of common personality traits among women displaying conversion symptoms. Although it is usually associated to female gender, no gender differences were observed in an epidemiological study in the USA (Grant et al. 2004).

There is little knowledge about the link between SB and HPD. In a geriatric sample of 109 patients, histrionism showed negative correlations with suicidal ideation in the regression analyses (Segal et al. 2012). However, suicide attempts are frequent in people with HPD or histrionic personality traits, either as a way of

emotional blackmail to the ones who take care of them or to attract attention from people (Rubio Larrosa 2004). Moreover, hysterical personality traits have been associated with suicide attempts in both women and men (Pretorius et al. 1994). Although some suicide attempts by HPD individuals take place in "a mood, albeit short-lived, of genuine despair," usually it is clear from the circumstances that suicide attempts are made to coerce someone else into behaving in a way similar to the patient's liking (Kendell 1983). Indeed, most suicide attempts are precipitated by disturbed relationships with close relatives or sexual partners. Due to their demanding, egocentric behavior and their dependence needs, their interpersonal relationships are characteristically stormy and fragile (Kendell 1983). Thus, it is not surprising that in a recent study with 150 psychiatric inpatients who had engaged in some kind of SB, HPD was a specific risk factor for suicide gestures but not for suicide attempts (García-Nieto et al. 2014). In other words, it is possible that some of the suicide attempts by HPD individuals could be better classified as suicide gestures.

As for completed suicide, HPD seems to be associated with a lower risk at least compared to other cluster B PDs. However, even if histrionic individuals tend to mature with time, some fail to obtain attention, becoming increasingly lonely, depressed, or addicted, which could eventually lead to a fatal outcome (Kendell 1983). Interestingly, one study has found that comorbidity with HPD among BPD patients predicts less lethal suicide attempts (Soloff and Chiappetta 2012a).

17.2.4 Narcissism and Narcissistic Personality Disorder (NPD)

NPD is characterized by lack of empathy for others, extreme grandiosity, and extreme self-involvement, among others (Blasco-Fontecilla et al. 2007). Few studies have investigated the SB of narcissistic patients (Pompili et al. 2004). Kernberg (1993) suggested that NPD or narcissistic personality traits could make an individual vulnerable to SB (Kernberg 1993). This vulnerability could be related to a fragile self-esteem (Perry 1989), which they try to raise through suicidal acts (Ronningstam and Maltsberger 1998). Thus, when we compared suicide attempters in Madrid with different cluster B diagnoses, those with NPD had higher expected lethality, but not higher impulsivity, than those without. Inversely, attempters with ASPD, BDP, or HPD were more impulsive, but did not report more expected lethality, than those without (Blasco-Fontecilla et al. 2009b). Depressed geriatric patients with narcissistic personality (either disorder or traits) scored higher in suicide risk than non-narcissistic controls in another study (Heisel et al. 2007).

As for suicide, they are more likely to commit suicide than patients without NPD or narcissistic traits, particularly if BPD was also present, according to a 15-year follow-up study of 550 patients in New York (Stone 1989). In a postmortem study with 43 consecutive suicides among Israeli males aged 18–21 years during compulsory military service, the most common Axis II diagnoses were schizoid PD (37.2 %) and NPD (23.3 %) (Apter et al. 1993). In any case, according to the psychological autopsy method, it is an infrequent diagnosis in suicides (Links et al. 2003).

In conclusion, narcissistic traits should be carefully considered when evaluating patients at risk of SB, as patients with these traits may be particularly at risk of making fatal attempts. Individuals who have suffered a "narcissistic injury" might react with rage and envision suicide as a means for retaliating or regaining control and plan more carefully their acts (Blasco-Fontecilla et al. 2009b). Of note, a recent study has shown that a single question could provide good results to evaluate narcissism (Konrath et al. 2014).

17.2.5 Impulsive Aggression

Impulsive aggression has been proposed as an endophenotype of risk for SBs related to reactive aggression. A combination of high impulsivity and high aggression is frequent among suicide attempters (Gvion and Apter 2011), but the components of this construct seem to have different effects on the suicidal acts. Although impulsivity is clearly related with making more suicide attempts, its role in the severity of the attempts is less clear (Soloff et al. 2005). The impulsivity of the attempt does not correlate well with the impulsivity of the attempter, and some authors argue that impulsivity as a trait facilitate the exposition to adverse experiences through the lifetime that eventually lead to SB (Anestis et al. 2014). In fact, aggressiveness has shown to be a better predictor of SB than impulsivity or hostility among depressed patients (Keilp et al. 2006). However, as previously stated, there is a well-documented association between impulsive personality traits and lifetime aggression in suicidal subjects (Rujescu and Giegling 2012), and the interaction of both components contributes to suicide completion, at least in BPD (McGirr et al. 2007). The familial transmission of SB appears also to be mediated by impulsive aggression and hostility traits. Indeed, completing a vicious circle, early life adversities (suicidal acts or childhood abuse in the family) are frequently present in the history of suicidal patients with high impulsive aggression levels (Lopez-Castroman et al. 2014). Of note, a gender effect should be considered for personality traits, such as impulsive aggression, with regard to SB. In a case-control study of individuals with major depressive disorder, Dalca et al. (2013) have recently shown that male completers, but not females, were characterized by impulsive aggression compared to controls (Dalca et al. 2013). According to their results, only non-impulsive aggression was part of the suicidal diathesis in females.

17.2.6 Hostility, Anger, and Other Personality Traits

Hostility and anger are common traits of patients with cluster B disorders, and both are positively related to suicidal ideation, plans, and attempts in adolescents and adults (Ortigo et al. 2009; Zhang et al. 2012). Among prisoners, anger and hostility scores differentiate also those who had attempted suicide (Roy et al. 2014). Furthermore, hostility was found to be higher in depressed attempters with siblings concordant for SBs (Brent et al. 2003).

Apart from the abovementioned, many personality features have been related to SB. For instance, irritability, low self-esteem, problematic coping strategies, inability to support stable interpersonal relationships, external locus of control, despair, intense feelings of fault and/or of shame following minimal mistakes, cognitive rigid style, and perfectionism (Blasco-Fontecilla et al. 2007). Within the Five-Factor model, two personality dimensions have been associated with SB: low extraversion and high neuroticism (Ortigo et al. 2009). In a recent study, low positive affect, as well as high aggression, predicted subsequent suicide attempts (during a 6-month follow-up) in adolescent attempters better than any Axis I or II disorder (Yen et al. 2012). Indeed, the authors suggest that affective and behavioral dysregulation, a component of many psychiatric diagnoses, could mediate the risk of new attempts in this high-risk population. Schizotypic personality has also been associated with lifetime suicide attempts. One study suggests that the degree of schizotypy could be associated with the risk of lifetime suicide attempt in patients with schizophrenia (Teraishi et al. 2014).

Finally, it is important to bear in mind the stability of personality traits. Personality traits associated with SB, or "suicidal" traits, show some instability during the lifetime according to long-term follow-up studies. For instance, in the case of BPD, patients have a tendency to be revictimized and re-experiment traumatic situations, but in the long run they acquire better coping skills and see their impulsivity, together with the risk of SBs, decrease (Zanarini et al. 2010). It should be noted that the instability of PDs might in part be due to the limited validity of current diagnostic systems. First, the diagnosis of a PD is made with a heterogeneous combination of persisting traits and transversal symptoms that may disappear with the evolution of the disorder. Secondly, the severity of PDs might not be accurately reflected by current classifications (López-Castromán et al. 2012).

17.3 Comorbidity with Axis I Disorders

The comorbidity with an Axis I disorder is probably the most important risk factor for suicide among individuals with PDs. This comorbidity characterizes also an important subgroup of suicide attempters who are at particularly high risk of repeated SB (Cheng 1995; Foster et al. 1999; Hawton et al. 2003). Comorbidity of Axis I and Axis II disorders is reported in 14 % (Vijayakumar and Rajkumar 1999) to 58 % of all suicide victims (Cheng et al. 1997). Personality traits modify suicide risk differently depending on the underlying Axis I disorder (Schneider et al. 2008). Having a depression and being substance dependent are themselves suicide risk factors. But when they are comorbid with a PD, the risk of suicide goes beyond the simple sum of relative risks (Schneider et al. 2008). This may be particularly true for PDs in clusters B and C. For instance, the comorbidity of BPD and depression increased the number and seriousness of suicide attempts in a sample of inpatients (Soloff et al. 2000). A large population-based survey in Mexico describes multiplicative effects of depressed mood and antisocial problems with regard to death thoughts, suicidal plans, and attempts (Roth et al. 2011). According with a case-control study including

104 depressed males that had completed suicide and 74 living depressed male controls, completers had higher levels of comorbidity with substance use disorders and cluster B PDs, particularly ASPD and BPD (Dumais et al. 2005). The use of substances in BPD impairs the judgment of the patients and enhances the risk for impulsive attempts, which may explain why BPD with substance use disorders show worse suicide-related outcomes (Anestis et al. 2012).

17.4 Can We Reduce the Suicidal Risk Associated to Personality Disorders or Traits?

We can currently respond positively to this question, although individuals who suffer from PDs are still extremely difficult to treat for various reasons. Firstly, often patients are inobservant and demand treatment only when in stressful circumstances that render their coping abilities completely insufficient. Secondly, treatment of PDs typically involves a prolonged and intensive treatment with involvement of several forms of support. Thirdly, patients with PDs are frequently exposed to life events that trigger the suicidal crises (Yen et al. 2005). Finally, despite the increasing number of therapeutic options, both in psychopharmacology and psychotherapy, there is a paucity of specific treatments for the suicidality of PDs.

Thus, risk reduction in PDs needs to enhance the therapeutic alliance to avoid dropouts and provide a constant, regular, and long-term reference. The triggering effect of oncoming adversities can be anticipated and prevented when working closely with the patients. In this vein, Brodsky et al. (2006) found that the first suicide attempt in depressed BPD patients is commonly an interpersonal crisis (Brodsky et al. 2006). Besides, mental health professionals can focus on specific traits known to carry more risk. For instance, treating aggressive tendencies may reduce the risk for SB through integrative therapies (Zhang et al. 2012). But the first step in treatment is a good assessment. A complete psychiatric evaluation, after assessing for suicide risk and identifying the stage of the suicidal process (ideas, plan, or attempt), should investigate personality traits that are relevant for subsequent treatment. In the case of BPD patients, comorbid antisocial or schizotypal features may heighten suicide risk (Zaheer et al. 2008). Subsequent treatment should combine effective pharmacotherapy to treat comorbid Axis I disorders and relevant symptoms, such as depressed mood and affective lability, and psychotherapy. At the same time, supportive treatment in the context of a suicidal crisis should include all the interventions known to prevent suicide attempts such as 24 h crisis care, follow-up continuity in the days following the suicidal crisis, control of potential suicide means, treatment of comorbid substance use disorders, a policy on how to respond to noncompliant patients, or assertive outreach programs (While et al. 2012).

17.4.1 Psychotherapy

The usual treatment for PDs involves long-term psychotherapy with an experienced therapist. A recent meta-analysis of 19 randomized controlled trials in adolescents

has shown that suicidality (including suicide attempts and non-suicidal self-harm) during follow-up was reduced among adolescents receiving psychological or social interventions compared to controls. Dialectical behavioral therapy (DBT), followed by cognitive behavioral therapy (CBT), and mentalization-based therapy (MBT) showed the largest effect size (Ougrin et al. 2015). However, when suicide attempts and non-suicidal self-harm were studied separately, these interventions showed no difference with treatment as usual.

DBT is adapted to the features of BPD while focused on reducing self-harm behaviors (Linehan et al. 2012). However, DBT comprises multiple interventions, from individual therapy, to skills training, telephone coaching, and a consultation team. A recent study has found that all of these components actually play a role in the prevention of suicide attempts (Linehan et al. 2015). Interestingly, the decrease in suicide attempts and increase in anger control that is seen in BPD patients who receive DBT is fully mediated by the skills learned in the therapy (Neacsiu et al. 2010). Moreover, a DBT-based program for relatives of BPD patients, which provided general knowledge about SB and training for interpersonal skills, showed some promise of improving the family-patient relationship (Rajalin et al. 2009). However, ASPD is a risk factor for premature termination of DBT (Kröger et al. 2014).

Other structured treatments, such as transference-focused psychotherapy, have proved their utility in the reduction of suicidality compared to supportive therapies (Clarkin et al. 2007). Recently, acceptance and commitment therapy (ACT), an intervention designed to increase psychological flexibility, has been found useful to reduce psychic pain, depression scores, and suicidal ideation in a small sample of suicide attempters, many of which had a BPD (Ducasse et al. 2014). Of note, a recent review has compared the results of trials investigating the effectiveness of diverse types of psychotherapy to reduce SBs among BPD patients. The authors suggest that a more intense or long was not necessarily associated with a greater reduction of suicidal acts (Davidson and Tran 2014).

An interesting study examined through psychological autopsy the suicide victims that were receiving individual psychotherapy 3 months prior to their death. The authors found that nine out of 16 cases fulfilled criteria for a personality disorder, and they were frequently comorbid with a mood disorder (Pallaskorpi et al. 2005). Of note, those 16 patients were the only suicide completers receiving regular psychotherapy among 1,397 suicides from the Finnish national registry (1.1 % of the sample).

17.4.2 Pharmacotherapy

Psychotropic drugs are commonly used to treat some of the personality features that are associated with SB in clinical settings worldwide, such as impulsivity, anger, or mood shifts. The symptomatic relief provided by antidepressants, neuroleptics, or mood stabilizers appears to reduce the risk of suicidal acts for some patients. Kolla et al. (2008) have reviewed the psychopharmacological interventions for the

management of SB in BPD (Kolla et al. 2008). However, the evidence for the use of psychotropic medication to specifically reduce SBs among patients with PDs is still inconclusive (Saunders and Hawton 2009). The known or potential antisuicidal effect of some medications (especially lithium and clozapine) deserves the development of future trials.

17.4.3 Hospitalization vs. Ambulatory Treatment

Beyond the preventive and supportive strategies that have been developed for acutely suicidal patients, chronically suicidal patients, such as BPD patients, need long-term interventions in ambulatory settings. Some authors advise against hospitalizing BPD patients in the management of self-harm because there is no evidence that it may prevent completion and it may paradoxically induce the patients to use self-harm behaviors help to become chronic (Paris 2004), but in case of acute suicidal crises inpatient treatment may be needed to prevent fatal outcomes (Oldham 2006).

Importantly, the targets of treatment should change over time. A recent study with 90 BPD patients has shown how acute stressors (depression) predict suicide attempts only during a year, while poor psychosocial functioning has long-term effects on suicide risk (Soloff and Chiappetta 2012b). Moreover, the authors underline the importance of rehabilitation treatments to prevent the poor psychosocial outcomes among these patients. We should also keep in mind that personality plays a larger role in the SB of young patients. Compared with older patients, Axis II comorbidity has been repeatedly associated with completed suicides among the young (Turecki 2005). In other words, the treatment of personality disorders should be particularly intensive for young people at risk.

Conclusion

PDs and personality traits have a well-documented effect on suicide risk. Cluster B disorders, such as BPD, are among the mental disorders more intensely associated with suicidal outcomes, especially when comorbid with major depression. There is increasing evidence supporting an endophenotype of impulsive aggression that would mediate the relationship between cluster B disorders and SB (Turecki 2005). This knowledge is progressively being translated into effective interventions (DBT, MBT, ACT), some of them being personality specific. Among the needs, further studies should investigate the specific effect of less common PDs (in clusters A and C) while considering the extensive comorbidity of these entities and their dimensionality (Ansell et al. 2015). However, any intervention with "risky" personalities, very often coming to the emergency room only after a suicide attempt, should cultivate their observance and commitment with potential treatments.

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How Japan Reduced Suicides: A Law That Changed Society – The Japanese Model

18

Yasuyuki Shimizu

18.1 Current Situation Regarding Suicide in Japan

Let me begin with some facts regarding suicide in Japan. Figure 18.1 shows the number of suicides in Japan from 1978 to 2014. As you can see, during the 1978–1997 period the number of suicides each year averaged approximately 25,000. However, this number rose dramatically from 24,391 in 1997 to 32,863 in 1998. The Japanese suicide rate per 100,000 also jumped from 19.3 to 26.0. As a result, Japan had one of the highest suicide rates in the world (Fig. 18.2).

The number of suicides per year continued to exceed 30,000 for 14 consecutive years up to 2012. In total, 453,040 people – more than the total population of the city of Nagasaki – committed suicide in Japan during these 14 years. However, from 2010 onwards, the number of suicides per year has been on the decline for 5 consecutive years, and has now returned to pre-1998 levels.

In order to understand the background to the incidence of suicide in Japan, we need to focus on three key points.

The first point to consider is the reason for the sudden increase in the number of suicides that occurred in 1998. There are some important demographic features regarding age groups and occupations that are related to this increase. We need to examine a breakdown of this data in more detail.

The second point to consider is the reason why the number of suicides did not decrease for 14 years. I would like to discuss what was happening during this period in terms of suicide prevention, focusing especially on the establishment of the Basic Act for Suicide Prevention in 2006 and how this brought about drastic changes in Japanese suicide prevention.

The third point to consider is the reason for the decline in the number of suicides, starting from 2010. This decline did not happen automatically. The establishment of

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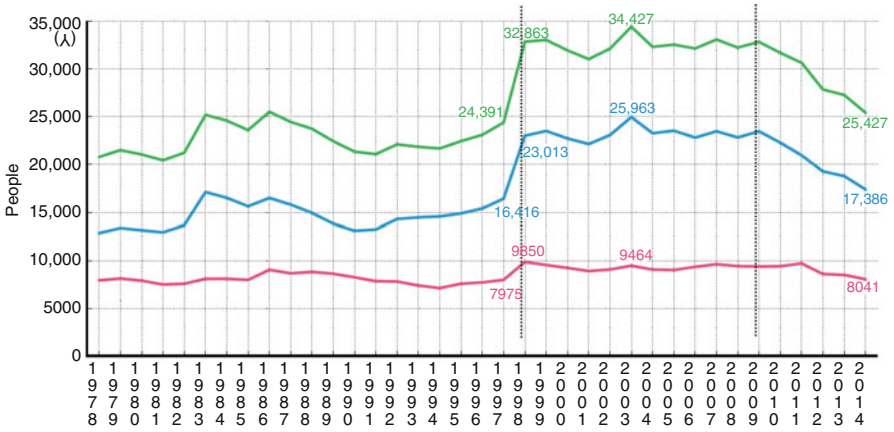


Fig. 18.1 Number of suicides per year in Japan (Source: National Police Agency, "Suicide statistics," prepared by the Cabinet Office)

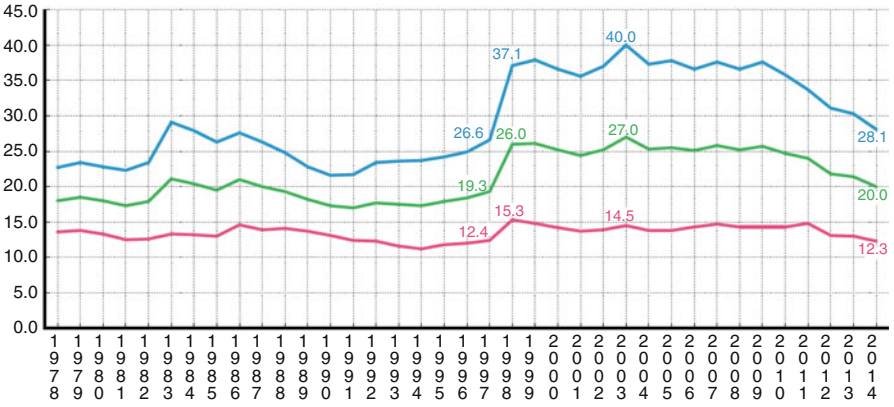


Fig. 18.2 Suicide rate per 100,000 in Japan (Source: National Police Agency, "Suicide statistics," prepared by the Cabinet Office)

the Basic Act for Suicide Prevention brought about five significant changes to the framework used for suicide prevention, and I would now like to discuss these further.

18.2 Sudden Increase in 1998

As I have outlined above, the number of suicides per year, as well as the suicide rate, both rose dramatically in 1998. The increase in the suicide rate was found in all age groups, but was particularly marked among middle-aged men. Figure 18.3 shows a comparison of the suicide rate per age group across different decades. It is obvious that the suicide rate for males aged 40–60 years increased dramatically from 1990 to 2000.

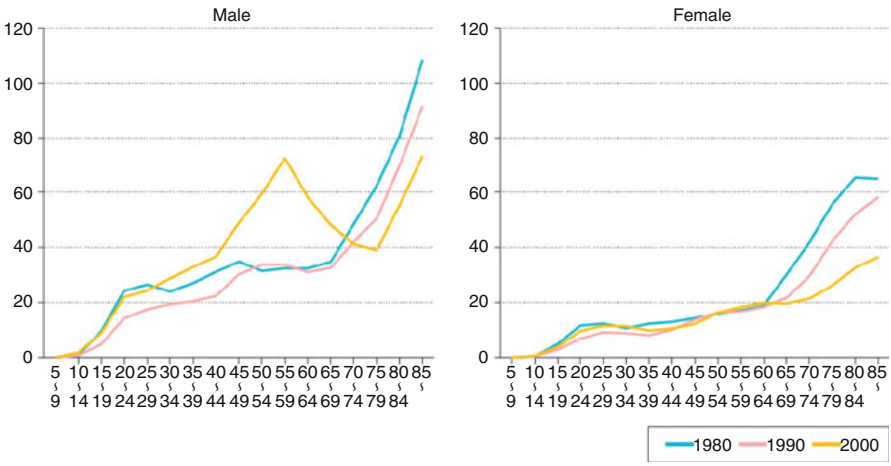


Fig. 18.3 Changes in suicide rate per age group

From 1997 to 1998, the number of suicides in the 40–60 male group increased by 44.6 % from 8,763 to 12,669. This represents 49.6 % of the total increase shown across all ages. We can also demonstrate a link between suicide rates and types of occupation over that same time period. The number of self-employed and family business owners increased by 43.8 % from 3,028 to 4,355, and the number of employees and office workers increased by 39.6 % from 6,212 to 8,673. When we look at a breakdown of the causes and factors contributing to suicide rates, we can see that "work-related issues" increased by 52.6 % from 1,230 to 1,877, while "economic and livelihood issues" increased by 70.4 % from 3,556 to 6,058.

The main reason for these increases in 1998 is thought to have been the country's socioeconomic problems. Actually, this can also be inferred from the timing of the increase. Thus, the number of suicides rose in March 1998. March is the end of the fiscal year in Japan, and several Japanese major banks and financial institutions went bankrupt in the fall of the previous year.

That was the biggest economic collapse ever experienced by modern Japan. Many local businesses also failed and the unemployment rate increased significantly. Many middle-aged men who were the breadwinners for their families lost their jobs. They were deprived not only of their source of income but also their identity and pride as hard-working Japanese businessmen. In Japan, there is a close correlation between the suicide rate and the unemployment rate, as you can see in Fig. 18.4.

18.3 No Decrease for 14 Years

Despite the presence of commonly recognized risk factors, talking about suicide has largely remained a social taboo in Japan. It has long been considered a personal problem and was not widely or publicly discussed. This created a vicious spiral of suicides with no-one willing to talk about them. Misunderstandings regarding

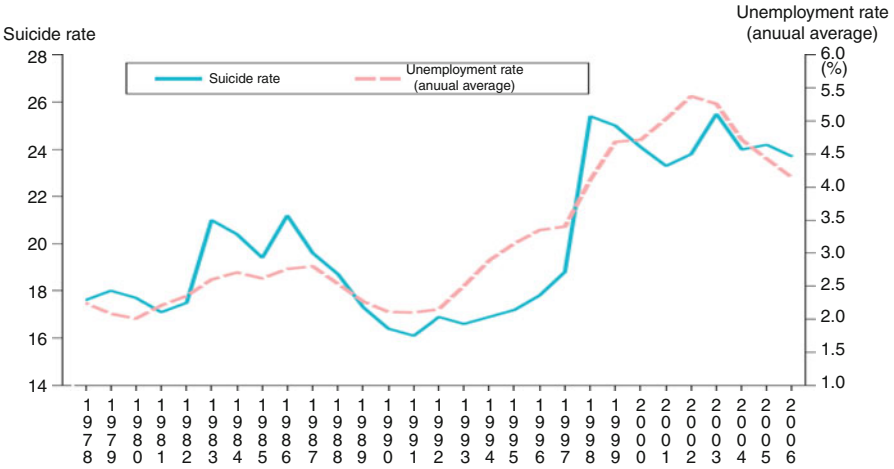


Fig. 18.4 Correlation between suicide rate and unemployment rate

suicide were not addressed and awareness of suicide-related issues was not shared. Thus, no countermeasures were taken and the number of suicides stayed over 30,000 for many years.

In 2000, the situation began to change when children who had lost their parents to suicide began to break the taboo by speaking out in the media about their experiences. I was working as a TV producer for NHK, the Japan Broadcasting Corporation, and I became involved in making documentaries about these bereaved children. I realized that suicides also affect the ones who are left behind, and that there were almost no suicide prevention activities undertaken by the national government and the local governments. About 100 people were committing suicide every single day, but suicide was still regarded as a very personal problem.

As a journalist, I felt that this stigma associated with suicide was the biggest impediment to promoting suicide prevention, so I tried to apply pressure to the government by broadcasting TV programs on suicide-related issues. In 2002, the Ministry of Health, Labour and Welfare held an "expert roundtable on suicide prevention measures." The ensuing report stated that a suicide prevention policy must not only address mental health issues effectively but must also include a multifaceted examination of psychological, social, cultural and economic factors. It seemed that countermeasures would now be taken at long last. However, this report was treated simply as a series of recommendations from experts, and it was not fully reflected in any actual policies. The disappointment felt by the bereaved children and myself was immeasurable.

After continuing to provide coverage of the children affected by suicide, the notes left by people who committed suicide and suicide prevention initiatives, I decided that the effectiveness of Japanese suicide prevention was limited due to the lack of a group dedicated to promoting such initiatives. So, in the spring of 2004 I quit NHK and, in order to help organize further suicide prevention initiatives, I established NGO LIFELINK in fall that same year and took up a position as its representative.

From the beginning, we aimed to get the Basic Act for Suicide Prevention accepted into law. There were two reasons for this. One was to make suicide prevention a government priority – the Basic Act could then form the basis for national and local governments to directly engage in suicide prevention. Another was to help resolve the debate over whether suicide is a private problem or a social problem. Usually a law is created in order to tackle a specific social problem after it has been recognized, but we approached the problem from the opposite direction. We felt that if we could enact a law for suicide prevention, then that would provide strong support for suicide to be recognized as a social problem rather than a purely private one.

So, in May 2005, LIFELINK collaborated with a member of parliament and planned and held the first ever symposium on the theme of suicide prevention within parliament building itself. At this forum, LIFELINK and other NGOs submitted urgent proposals for a comprehensive system of suicide prevention. The Minister of Health, Labour and Welfare, who attended the forum, vowed on behalf of the government to tackle the issue of suicide. This was widely reported by the media who had been gathered together for the forum.

Subsequently, a bipartisan parliamentary group was formed in May 2006 to support the formation of a suicide prevention policy. At the same time, we also organized a petition for suicide prevention legislation – collecting 100,000 signatures in less than 2 months (even though the original goal was only 30,000) and thereby contributing to the creation of the Basic Act for Suicide Prevention. The Basic Act for Suicide Prevention was eventually signed into law in June 2006, finally accomplishing our goal of having suicide in Japan formally accepted as a legitimate social issue.

18.4 Decline from 2010 Onwards

The Basic Act for Suicide Prevention consists of 21 articles (listed at the end of this chapter). The key points can be summarized as follows:

Article 1 states its purpose. "The purpose of this law is to prevent suicide and enhance support for the relatives, etc., of suicide victims by comprehensively promoting suicide prevention measures, and thereby contribute to the creation of a society in which everyone can live healthy, meaningful lives."

In other words, the purpose of the Basic Act is not only to just support individuals but also to change society so that no one feels forced to commit suicide and anyone can choose to live their life to the full.

Article 2 states basic philosophy of the act. "Suicide countermeasures must be implemented not just from the perspective of mental health, but also in a way that is in line with the realities of suicide – based on the fact that suicide has various complex causes and contexts."

The introduction of the Basic Act for Suicide Prevention brought about five significant changes in the framework used for suicide prevention.

First, detailed local suicide statistics are now increasingly made publicly available. In the past, only nationwide suicide statistics were published, once a year, with a 6-month lag time in the results.

Since 2010, however, individual municipalities have reported monthly data on suicides with a lag time of only 1 month. The awareness shown by the heads of municipalities and those individuals in charge of suicide countermeasures has thus markedly improved.

In the past, while municipalities recognized the necessity of introducing suicide prevention programs, they did not have any way to determine their intrinsic effect on actual suicide rates. Their attempts could be compared to shooting an arrow in the dark. However, they have now begun to adopt practical measures reflecting the actual conditions regarding suicide in their local communities.

Second, pioneering efforts have been carried out throughout Japan in the field of modeling. For example, Adachi Ward in Tokyo has developed an urban model of suicide prevention, while Arakawa Ward in Tokyo has developed a supportive program for the survivors of suicide attempts – based on cooperation between the healthcare sector and the local community. Metropolitan Tokyo also holds comprehensive consultation sessions for those suffering mental health- and life-related problems, and hosts a multidisciplinary seminar.

Because suicide rates in urban areas are lower than those in rural areas, the introduction of effective preventive measures has been slower in cities. Recently, however, a series of pioneering efforts involving modeling have been established and reliable examples of suicide prevention programs that can easily be followed in practice have been presented.

Third, municipalities have learned from the models and examples that other municipalities have developed. Moreover, the network that supports the nationwide expansion of these models and examples has now grown – enabling a national platform for suicide prevention measures to be established.

At present, 300 municipalities belong to the Municipality Committee for Creating a Society Without Suicide that was established in 2011. Currently, 80 organizations also belong to the Nationwide Private Network for Suicide Prevention that was established in 2010.

These two networks work very closely with people at high risk of committing suicide and who are in need of appropriate support, and promote mutual cooperation by holding joint training seminars.

Fourth, the importance of the timely introduction of preventive measures has increasingly been recognized. Because an upward trend in suicides in Japan has, historically, been observed every March, in 2010 the Japanese government designated March as Suicide Prevention Enhancement Month. Frequent consultation meetings and educational events are held in March throughout Japan.

The administrative sectors that had once stigmatized suicide have also begun to change their attitude and have now started to play an active role in promoting local suicide prevention programs. In April 2010, following on from Suicide Prevention Enhancement Month, the number of suicides decreased by 16 % compared with the same month in the previous year. This was the maximum rate of decrease ever recorded.

Fifth, the necessary financial sources to support these initiatives have now been assured. In 2009, the Japanese government set up a Fund for the Urgent

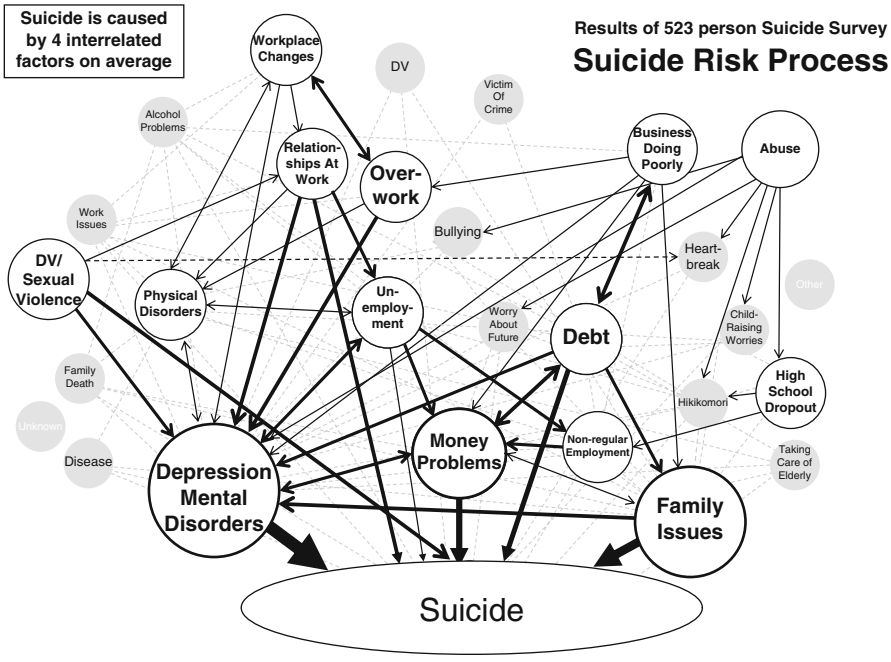
Enhancement of Local Suicide Prevention and distributed funding to all prefectures. Each prefecture then distributed the funds to each municipality. In this way, local governments under financial pressure can now receive a subsidy from the Japanese government in order to introduce the necessary measures.

As a result of a combination of all these five factors, a range of social measures designed to prevent suicide have been introduced over recent years. During Suicide Prevention Enhancement Month, in particular, the sectors in charge promote various programs by following pioneering, locally based models. Using the funds provided, they are then able to introduce measures that correspond to the actual conditions regarding suicide in their local communities.

18.5 Findings That Support Prevention

To complement the five changes made to the framework for suicide prevention, as described above, we also conducted a survey from 2007 to 2013 to help promote the understanding of suicide and suicide prevention activities.

In cooperation with 523 survivors of suicide, we conducted a survey to clarify actual conditions relating to suicide and developed the following diagram entitled "Suicide Risk Processes." This chart schematically illustrates the processes that drive people to commit suicide. Suicide victims are in a complex state of mind because they are, on average, subjected to four different but interrelated suicide risk factors.



For example, unemployment can bring about hardship and significant levels of debt. These factors are often involved in the development of depression, which can then lead to suicide. High school dropouts often have difficulty finding stable employment and can experience more hardship in life than others. These factors can drive them into debt and cause domestic problems which can also lead to suicide. In another example, a woman who had been subjected to abuse in childhood got married but suffered from a psychiatric disorder as a result of her husband's violence. She then got divorced and experienced further hardship in life – leading to her suicide. As demonstrated by these examples, multiple factors are generally linked together to bring about the decision to commit suicide.

18.6 Activities at the Local Level

The major changes highlighted by the framework on suicide prevention and the survey described above have had a very big impact on the local governments involved.

For example, Tokyo's Adachi Ward has been engaged in a comprehensive suicide prevention program since 2009. In 2014, this program contributed to a reduction in the number of suicide victims by 40 individuals, or as much as 20 % compared with the previous year, even though the number of suicides increased by 6 % in the Tokyo metropolitan area as a whole. The percentage reduction achieved by Adachi Ward was the largest of all 23 wards.

Similarly in Akita Prefecture, which has been playing a leading role in promoting the suicide prevention program, the number of suicides decreased by as much as 40 % in 2014, compared to the peak year, as a result of the implementation of long-term comprehensive measures. About 10 years ago, in the former Matsunoyama Town, Niigata Prefecture, the suicide rate (which had been nine times as high as the nationwide average) was successfully reduced to less than one quarter of the national average.

These municipalities differ in population and age composition, but they took similar approaches to promote their suicide prevention programs.

First, they conducted a local suicide assessment to identify the group of individuals at most risk of committing suicide. As I mentioned earlier, the Japanese government began releasing the suicide statistics of local governments in 2010 so that we can now access this data over the Internet. They analyzed the statistics and identified the demographics of the dominant at-risk group, focusing on occupation, age and gender in each region. This process identified a high suicide rate among unemployed individuals and males in their 30s in Adachi Ward, and among elderly females in the former Matsunoyama Town.

Second, the organizations concerned promoted cooperation and provided the high-risk groups clearly identified by the assessment process with comprehensive support. Because the problems that unemployed individuals frequently face were already known, in order to improve confounding problems such as

unemployment, hardship in life, significant debt and depression, lawyers, health nurses, employment agencies and welfare offices all took part in a cooperative approach – holding comprehensive consultation meetings in order to provide these at-risk individuals with support. The problems that elderly females often face include feelings of loss and lack of any meaningful role, poor relationships with family members, and depression. To ameliorate these problems, local clinics, psychiatrists and health centers took a collaborative approach, promoting the early detection and treatment of depression and providing educational programs for family members.

Third, these municipalities did not stigmatize suicide but actively promoted educational activities in the community. In Adachi Ward, display panels for suicide prevention were exhibited in all ward libraries, and community buses displayed posters providing information on the consultation meetings. Ward newsletters featuring suicide prevention were also distributed to all households. In Akita Prefecture, the private, public and academic sectors all made concerted efforts to promote the suicide prevention movement – including a street campaign at the prefectural level.

Many individuals who display a strong desire to die also have a strong desire to live and may decide to do so as long as the necessary support can be obtained. People may choose life if the number of factors that promote this choice can be increased as much as possible – while at the same time eliminating those factors that promote the choice of death to the greatest extent possible. Suicide prevention is one such effort providing comprehensive support for the choice of life. All organizations involved should carefully consider the needs of the high-risk group and take a collaborative approach to prevention. In this manner, more people will decide to live and the number of suicides in the community will decrease.

Local data on suicides should be thoroughly analyzed and practical measures reflecting the actual conditions in each region should be promoted in a comprehensive manner. Therefore, switching from government-led programs that focus on education to municipality-led programs that focus on practical operations should be further accelerated.

Suicide is the result of a serious aggravation of various social problems. More than 70 individuals commit suicide every day in Japan. In this situation, controlling the infinite spread of the grief cycle that results from suicide helps us create a society in which everybody can live a comfortable life or at least a society in which everybody can share in the comfort of living.

18.7 Cf. The Basic Act for Suicide Prevention

Chapter I: General Provisions (Articles 1–10)
Chapter II: Basic Policies (Articles 11–19)
Chapter III: Suicide Countermeasures Council (Articles 20–21)
Supplementary Provisions

18.7.1 Chapter I: General Provisions

(Purpose)

Article 1.

In light of the fact that the number of deaths by suicide has remained at a high level in Japan in recent years, this law sets forth a basic philosophy regarding suicide countermeasures; clarifies the responsibilities of the national government, local public entities, and others; and stipulates foundational matters for suicide countermeasures.

The purpose of this law is to prevent suicide and enhance support for the relatives, etc., of suicide victims by comprehensively promoting suicide measures and thereby contribute to the creation of a society in which everyone can live healthy, meaningful lives.

(Basic Philosophy)

Article 2.

1. Suicide countermeasures must be implemented as a society-wide effort based on the fact that suicide should be viewed not only as the problem of the individual but as something influenced by various social factors.
2. Suicide countermeasures must be implemented not just from the perspective of mental health but also in a way that is in line with the realities of suicide, based on the fact that suicide has various complex factors and contexts.
3. Suicide countermeasures must be implemented as effective policies tailored to the stages of suicide prevention, the response to the risk of suicide, and the post-event response for both those who commit suicide and those who survive a suicide attempt.
4. Suicide countermeasures must be implemented through close coordination between the national government, local public entities, medical institutions, business owners, schools, private-sector entities that conduct suicide prevention activities, and other related parties.

(Responsibilities of the National Government)

Article 3.

The national government shall be responsible for comprehensively formulating and implementing suicide countermeasures in accordance with the basic philosophy stated in the preceding article (referred to in the next section).

(Responsibilities of Local Public Entities)

Article 4.

Local public entities shall be responsible for formulating and implementing policies regarding suicide countermeasures, in cooperation with the national government, in light of the situation in the region in question, and in accordance with the Basic Philosophy.

(Responsibilities of Business Owners)

Article 5.

Business owners shall cooperate in the suicide countermeasures that the national government and local public entities implement and shall endeavor to implement measures necessary to maintain the mental health of the workers they employ.

(Responsibilities of Members of the Public)

Article 6.

Members of the public shall endeavor to deepen their awareness and understanding of the importance of suicide countermeasures.

(Consideration of Personal Honor and Peace in Life)

Article 7.

The implementation of suicide countermeasures must be conducted with full consideration given to the personal honor and peace in life of those who commit suicide, those who survive suicide attempts, and their relatives, etc., and must not unduly violate such personal feelings and values.

(Fundamental Policy Principles)

Article 8.

The government must set forth the fundamental principles for basic, comprehensive suicide countermeasures as guidelines for suicide countermeasures that the government should promote.

(Legislative Measures, etc.)

Article 9.

The government must implement the necessary legislative and fiscal measures, as well as other measures, in order to achieve the purpose of this law.

(Annual Report)

Article 10.

Every year, the government must submit to the National Diet a written report that gives an overview of suicide in Japan and the implementation status of the government's suicide countermeasures.

18.7.2 Chapter II: Basic Policies

(Promotion of Surveys and Research, etc.)

Article 11.

1. The national government and local public entities shall, in connection with suicide prevention, promote surveys and research and collect, organize, analyze and provide information.
2. The national government shall develop a framework to contribute to the effective and efficient implementation of the measures described in the preceding paragraph.

(Promotion of Public Understanding)

Article 12.

The national government and local public entities shall implement the necessary policies to improve public understanding regarding suicide prevention, etc., through educational and PR activities.

(Securing Human Resources etc.)

Article 13.

The national government and local public entities shall implement the policies necessary to secure and train human resources regarding suicide prevention, etc., and to improve the quality of those human resources.

(Development of a Framework Related to Mental Health Promotion)

Article 14.

The national government and local public entities shall implement the policies necessary to develop a framework for the promotion of mental health in professional occupations, schools, regions, etc.

(Development of a Framework for Medical Treatment Provision)

Article 15.

The national government and local public entities shall implement the necessary policies so that the medical care for those who are at risk of suicide due to impediments to the maintenance of their mental health is provided in a prompt and appropriate way, including developing an environment that makes it easy for those with mental disorders to receive medical care from doctors with an academic background in mental health (referred to in the remainder of this article as "psychiatrists"); ensuring the proper coordination between the psychiatrists and the medical doctors who provide medical care for physical injury or disease in the early stages of such medical care; and ensuring the proper coordination between the psychiatrists and the medical doctors who provide emergency medical care.

(Development, etc., of the Framework to Prevent Suicide)

Article 16.

The national government and local public entities shall implement the policies necessary to develop and improve the framework used for the early detection of those at high risk of suicide and the provision of an appropriate response to prevent the occurrence of suicide, including consultations.

(Support for Suicide Attempt Survivors)

Article 17.

The national government and local public entities shall implement the policies necessary to provide appropriate support to those who survive suicide attempts so that they do not attempt suicide again.

(Support for the Relatives, etc., of Suicide Victims)

Article 18.

The national government and local public entities shall implement the policies necessary to provide appropriate support for the relatives, etc., of suicide victims and survivors of suicide attempts in order to alleviate the effects of any serious psychological impacts on them resulting from suicide or suicide attempts.

(Support for Activities by Private-Sector Entities)
Article 19.

The national government and local public entities shall implement the policies necessary to support the activities of private-sector entities in order to prevent suicide.

18.7.3 Chapter III: Suicide Countermeasures Council

(Council Establishment and Affairs under its Jurisdiction)
Article 20.

1. The Suicide Countermeasures Council (hereinafter referred to as the "Council") shall be established in the Cabinet Office as a special organ.
2. The Council shall administer the following affairs:

   (a) Preparation of the draft of the Fundamental Policy Principles provided in Article 8
   (b) Coordination of the relevant administrative organs necessary for the implementation of suicide countermeasures
   (c) Deliberation on key matters related to suicide countermeasures and promotion of the implementation of suicide countermeasures

(Organization, etc.)
Article 21.

1. The Council shall be composed of a chairperson and members.
2. The chairperson shall be the Chief Cabinet Secretary.
3. The members shall be those persons designated by the Prime Minister from among the Ministers of State (other than the Chief Cabinet Secretary).
4. The Council shall have a secretary.
5. The Prime Minister shall appoint the secretary from among the employees of the relevant administrative organs.
6. The secretary shall support the chairperson and the members regarding the affairs under the jurisdiction of the Council.
7. In addition to the matters stipulated in each of the preceding paragraphs, required matters related to the organization and operation of the Council shall be provided by Cabinet Order.

18.7.4 Supplementary Provisions

(Effective Date)
Article 1.

This law shall come into force as from the date specified by a Cabinet Order within a period not exceeding six (6) months from the day of promulgation.

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Preventing suicide: a global imperative (World Health Organization, 2009)
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White paper on suicide prevention in Japan (Cabinet Office)

The Challenge to Survive in Jail

19

Marco Sarchiapone, Marianna D'Aulerio, and Miriam Iosue

Abstract

Prisoners are one of the groups at higher risk of suicide, with higher suicide rates than in the general population. Inmate suicide afflicts all the countries in the world, and this requires the development of effective suicide prevention programs. In fact, even if it isn't possible to determine if and when the suicidal behavior will occur, it is possible to prevent it, addressing specific risk factors, such as psychiatric disorders and impulsive personality traits, as well as several other factors specifically associated to imprisonment and its consequences. Among the studies proposed and realized in this field, those which demonstrated the effectiveness of some suicidal prevention programs in prison are the comprehensive multifactored interventions, based on staff training and screening.

Also the phases after release are at high risk of suicide. For this reason, it's indispensable that the prevention programs are not limited to the period of detention, but extended even after the release of the inmates.

19.1 Introduction

More than 10.1 million of people live behind bars worldwide, mostly as pretrial detainees/remand prisoners or as sentenced prisoners. The higher rate is in the US, with 2.29 million; followed by China, with 1.65 million; and Russia, with 0.81 million (ICPS – International Centre for Prison Studies 2010).

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And behind bars, suicide is one of the leading causes of prisoners' death (Larney et al. 2012). Even if the real number of suicides in jails is controversial, it's estimated that the suicide rate in jail is three to eight times higher than the rate reported for the general population (Fazel et al. 2011).

Since prisoners are one of the groups at higher risk of suicide, effective suicide prevention programs targeting this population are needed.

Several programs, developed in these years, have been focused on identification of risk factors among inmates, among which sociodemographic characteristics, psychiatric disorders, personality disorders, some personal traits (impulsive/aggressive behaviors), history of childhood trauma, stressful life events and biological aspects, and of how these factors cross some specific prison conditions, such as loss of freedom, restrictions, and loss of contact with own family and with friends (Sarchiapone, in press; World Health Organization 2007).

19.2 Sociodemographic Characteristics of Prisoners with Suicidal Behavior

Gender As in the general population, also among offenders, the suicide rates are higher for men than for women (Mumola 2005), both in prison and after release (Kariminia et al. 2007). These data were confirmed by Fazel et al. (2011). In their study, conducted on 12 countries, they found that on 861 suicides in prison, 810 were men.

Age The average age of suicide among inmates is lower than in the general population (Liebling 2002). However, the rates of suicidal behaviors tend to increase with the age of the inmate (Mumola 2005). Indeed, Liebling (2002) found that the inmates aged 18–24 years have the lower probability to commit suicide, while this rate steadily increases for those aged 25–34 and 35–44 years.

Ethnicity In offender's group, the differences across ethnicity are more evident for the suicidal behaviors (Mumola 2005). Several researches reported higher rate of suicidal behaviors among white prisoners (Haycock 1989). Mumola found that the death rate of White jail inmates was 86 % higher than that of Black inmates and over twice as high as the rate for Hispanic inmates (Mumola 2005). Confirming these data, Pratt et al. (2010) found that offenders with non-white ethnicity and a history of previous imprisonment reported lower risk of suicide.

Marital Status Several researches showed an increased risk of suicidal behavior among inmates who are single. Analyzing the characteristics of 133 prisoners died by suicide in the Canadian Federal Penitentiary Service, Gree et al. (1993) found that more than 70 % of these prisoners were single or separated/divorced. The same results were found by Hayes (1989) that in a sample of 339 jail suicides found that only 30.1 % were married or living under a common-law relationship. The remaining victims were single, separated, divorced, and widowed. In case of attempted suicide among offenders, it's possible to identify the same significant association between risk of suicide and to be unmarried (Carli et al. 2011).

19.3 Psychiatric Diseases

The prevalence of mental illness is disproportionately represented within the inmates. It is estimated that half of them have a mental illness, compared to 11 % of the general population (Zhang et al. 2010). In particular, suicidal behaviors in prisoners are significantly associated with higher rates of psychosis, personality disorder, depression (Rivlin et al. 2013; Woodward et al. 2000), and history of alcohol (Fazel et al. 2008) and/or drug use (Cuomo et al. 2008). Furthermore, the presence of schizophrenia and personality disorders, especially antisocial disorder, increases the risk of suicide among offenders (Joukamaa 1995; Richard-Devantoy et al. 2009).

19.4 Psychopathological Traits (Impulsivity and Aggression)

Verona et al. (2001), analyzing the relationship between suicide risk, psychopathology, and antisocial personality in 313 male inmates, found that the impulsive antisocial deviance and suicidal behavior are affiliated expressions of a common dispositional vulnerability. Similar data were found by Rivlin et al. (2013) and Sarchiapone et al. (2009) who showed that offenders, compared to controls, had higher levels of impulsivity and exhibited aggression in prison and hostility and significantly lower self-esteem. Also Carli et al. (2010) explored the associations between impulsivity, aggression, and suicidal behaviors in a sample of 1,265 Italian male prisoners, reporting higher levels of impulsivity in offenders with suicidal behavior.

19.5 Biological Aspects

Several studies analyzed the association between serotonergic system in suicide among offenders. In a sample of violent offenders with a history of severe suicide attempts with following hospitalization, the levels of cerebrospinal fluid 5-hydroxyindoleacetic acid, the main metabolite of serotonin, and 3-methoxy-4-hydroxyphenylglycol (metabolite of norepinephrine degradation) concentrations were lower compared to subjects without a history of suicide attempts (Virkkunen et al. 1989). Other studies focused their attention to the association between low serum cholesterol concentrations that were linked to violent and aggressive behavior (Golomb et al. 2000; Hillbrand et al. 1995; Kaplan et al. 1991).

19.6 Childhood Trauma

The rates of suicide attempts and completed suicide seem to be higher among offenders who experienced childhood trauma, especially emotional or physical abuse, or emotional neglect (Mandelli et al. 2011; Rivlin et al. 2013; Roy and Janal 2006). In particular, research shows significant associations between different types of childhood trauma, near-lethal self-harm, family history of suicide, and high levels of depression, aggression, impulsivity, and hostility and low levels of self-esteem and social support (Mandelli et al. 2011; Marzano et al. 2011).

19.7 Suicidal Risk Factors Associated with Detention

Beyond the risk factors just listed, there are many other risk factors for suicide related to the permanence in prison, which may act as precipitating factors. Being imprisoned can be considered a serious stressful life event since it deprives the person of important resources. Often, the incarceration causes the loss of family and social support, the loss of control over life, and the loss of privacy. The incarceration is also accompanied by the fear of the unknown, the fear of physical or sexual violence, the uncertainty about the future, the embarrassment and guilt over the offence, and the fear or stress related to poor environmental conditions (Correctional Services Canada 1994; Gupta and Girdhar 2004). All the perceived stress in prison and the resulting physical and emotional breakdown tends to increase over time. For these reasons, the rate of suicidal behaviors seems to be intensified by the length of stay (Gupta and Girdhar 2004).

19.8 Suicide Prevention Programs for Inmates

Suicidal behavior among inmates is a serious public health problem, and its prevention and control are indispensable. However, the planning of effective prevention program is not simple.

For this reason, the World Health Organization formed the International Task Force focused on Prevention of Suicide in Prison. In its document "Preventing suicide in jails and prisons" (2007), the key components of an effective suicide prevention program are outlined: training, screening, observation, communication, modification of the physical environment, and mental health treatment. The application of these measures turned out effective, producing a reduction over 50 % of correctional suicide rates (Hanson, 2010).

The importance of these key elements for suicide prevention programs in jail has been confirmed by the systematic review conducted by Barker et al. (2014). The authors found that the most effective programs for suicide prevention in jail are the multifactored programs, especially those focused on risk factors. The multifactored programs may include screening and assessment of inmates, improving the staff training, monitoring and providing psychological treatment, avoiding the isolation, and ensuring the constant observation for inmates with suicide risk.

The assessment of prisoner must be implemented as soon as possible, since most of inmate suicides occur within the first days of confinement (Towl 2008). The majority of inmates are not diagnosed as depressed; however, as described before, the imprisonment may produce a shock for the individuals: the shame, the fear, and the loss of liberty and contact with own family, associated with the presence of predisposing risk factors, may consequently increase the risk of suicide. For this reason, it's necessary to identify the new inmates who are likely to become suicidal, in order to implement the recommendations for general suicidal behavior treatment (Hayes 2012). Signals of suicidal risk could be presence of suicidal thoughts or plans and/or previous suicide attempts; feelings of hopelessness, shame, guilt, and fear; emotional withdrawal, isolation, and crying; poor appetite; sleeplessness or

agitation; history of psychiatric care and/or signs of psychiatric disorders, such as depression, psychosis, anxiety, and/or aggression; history of substance abuse; current use of psychotropic medication; and poor support from the family (Jail Bulletin 1999; Sarchiapone, in press).

The screening should preferably be conducted by trained professionals, preferably a psychologist or psychiatrist with expertise in the field of suicide prevention (Sarchiapone, in press).

An adequate screening to identify suicide risk, associated with higher staff awareness and expertise, allows to reduce the risk of suicide in prisons. The staff training is an essential component of any suicide prevention program. Training is important not only for psychologist or psychiatrist but also for all the other staff members that have regular contact with inmates. Inadequate awareness and competences of the staff concerning the suicide risk assessment and management may produce the inability to understand what is the real suicidal risk of an inmate, with consequent wrong decisions about its management (Hayes 2012).

Conclusions

Inmates represent a group at high risk of suicide. Suicide among prisoners afflicts all the countries in the world, and this requires the development of effective suicide prevention programs.

Suicidal behavior is a complex and multidimensional phenomenon, and for this reason, it is not possible to determine if and when it will occur. However, suicide behavior can be prevented addressing specific risk factors, such as psychiatric disorders and impulsive personality traits, as well as several other factors specifically associated to imprisonment and its consequences.

Recent researches demonstrated the effectiveness of some suicidal prevention programs in prison, especially those implementing comprehensive multifactored interventions, based on staff training and screening (Barker et al. 2014).

Finally, since several studies reported a high risk of suicide even after the release (Pratt et al. 2010; Putkonen et al. 2003), these prevention programs should not be limited to the period of detention, but they should be extended even after the release of the inmates.

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Racism and Discrimination, Killers?

20

Mohammed Taleb and Aicha Dahdouh

Abstract

Discrimination consists in distinguishing or treating differently (mostly worse) someone or a group relatively to the rest of the community or against another person on various factors such as race, colour, sex, ethnic origin, language, religion, opinion politics, etc. It violates the fundamental principles of human rights and produces inequality.

Racial and ethnic discrimination is a common and widespread form of unequal treatment of individuals. It is now proved that it creates physical health problems. It is also recognised as a risk factor for mental disorders. Research conceptualised these results and considers discrimination as an important factor of social stress. It could be a predictive factor of a history of attempted suicide and is associated with a greater likelihood of suicide attempt and suicide.

We need many more studies on the links between discrimination, mental disorders and suicide and understand the mechanisms involved.

20.1 Introduction

Suicide is a complex and multifactorial behaviour directly related to the social environment. Several models establish a relationship between biological, cognitive and psychological vulnerability; environmental stressors; and suicide. Mental disorders

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are a recognised risk factor, but many people suffering from mental illness do not express suicidal thoughts and do not commit any suicide attempt. Other societal and individual factors must be taken into account. Among them, one must highlight the importance of social relationships. They may be the cause of stress, as well as psychological and adaptation issues. It is then necessary to understand the different links between these stress-generating social situations and mental health and why specific social contexts can be powerful stressors.

Suicidal behaviours can be influenced by interpersonal relationships and broader social contexts. Among these social situations, racism and discrimination along with their psychological effects can represent potential risk factors. They are considered as stressors that can exceed the resources of adaptation for an individual and lead him to have a negative self-image and the feeling of a lack or the absence of social support (Farrelly et al. 2015).

Racism is a form of discrimination that stems from the belief that groups should be treated differently according to phenotypic difference (Chakraborty and McKenzie 2002). In general, discrimination means depriving an individual of the enjoyment of his political, civic, economic, social and cultural rights and freedoms. Discrimination opposes a fundamental principle of human rights, the equality of rights between individuals. Most national constitutions contain provisions against discrimination. The Universal Declaration of Human Rights stipulates in its first article: "All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood". In Europe, the European Convention on Human Rights declares in article 14: "The enjoyment of the rights and freedoms set forth in this Convention shall be secured without discrimination on any ground such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status".

Most national constitutions and legislation in democratic countries reflect these fundamental human rights principles. Discrimination violates these principles and produces inequality. It can also aggravate pre-existing inequality to the extent that the person who is in a situation of inferiority can be subject of stigma and discrimination (disability, illness). Discrimination also has an impact on society as a whole and tends to reinforce prejudice and racist attitudes.

20.2 Different Forms of Discrimination

There are several definitions of discrimination, but most of them take up a number of commonalities, which consider that discrimination is based on factors such as race, colour of skin, sex, ethnicity, language, religion, political opinion, etc. Discriminatory phenomena may apply simultaneously to several factors including the ethnic or social origin, gender and sexual orientation of a person. Article 2 of the Universal Declaration of Human Rights details one of the consequences of the principle contained in article 1: the prohibition of all discriminations. "Everyone is entitled to all the rights and freedoms set forth in this Declaration, without

distinction of any kind, such as race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status". Article 7 gives concrete form to this equality. The law must be equal for all, but it must also protect against behaviours that could threaten this equality; this is the absolute prohibition of discrimination: "All are equal before the law and are entitled without any discrimination to equal protection of the law. All are entitled to equal protection against any discrimination in violation of this Declaration and against any incitement to such discrimination".

It is difficult to establish an exhaustive list of situations fulfilling the criteria of discrimination. In France, for example, article 225-1 of the penal code defines a list of criteria which constitute discrimination: "Constitutes discrimination any distinction made between natural persons because of their origin, sex, marital status, pregnancy, physical appearance, surname, place of residence, state of health, disability, genetic characteristics, manners, sexual identity or orientation, age, political opinion, trade union activities, membership or non-membership, real or supposed, to a determined ethnic group, nation, race or religion".

The experience of discrimination results from exposure to these prejudices and stereotypes. Discriminations based on skin colour or origins are the most recognised. They often take place in a wider social context of stigma and hostility to ethnic minorities. Skin colour plays a decisive role in racism. In this chapter we will focus on only developing discriminations based on ethnic origin or the colour of the skin and that are in connection with widespread beliefs or prejudices. It is understood that all discriminations, whatever their origins, share common consequences such as rejection, exclusion and inequality.

Discrimination based on ethnic origin can be direct. They are characterised by the deliberate will to discriminate against a person because of his ethnicity or his skin colour. Indirect discriminations place the members of a minority in disadvantage compared to the other. Their effects are noticeable relatively to statistical data. The difference between direct and indirect discrimination is not a difference in nature. It reflects the degree of complexity of the links between perception of an individual and his belonging to an ethnic group. When direct discrimination requires an individual assessment to highlight a difference in treatment linked to an intention. When it is indirect, it falls under an overall assessment.

20.3 Perceived Discrimination

In general, the concept of discrimination does not necessarily imply the highlighting of an underlying or hidden intent, and in some situations, the discriminatory nature of the acts does not appear not in foreground.

Beyond the objective or alleged reality of discrimination, we prefer to use the notion of perceived discrimination. This concept covers the subjective perception of discriminatory treatment. It ignores the only objective reality of a different and discriminatory treatment, but it takes into account the experience characterised by the feeling in an individual of an unjust and unfair attitude towards him. The

demonstration of the intention to discriminate is not required in the evaluation and analysis of the psychological consequences. What seems essential is the experience of people who perceive or deem certain behaviour towards them or their group membership as being discrimination (Taylor et al. 1994). Often observed reluctance to characterise certain attitudes as racist stems from the very large adversarial dimension of the term. The racist term indeed represents a real sentence and can give rise to a general moral disapproval. The situation of discrimination can then appear as an object whose reality is both negotiable and the source of different interpretations and even of conflicts.

The perception of discrimination is directly linked to people membership of minority social groups usually subject to negative prejudices and discrimination. It causes stress, feelings of frustration or threat to self-image. In this case, repeated exposure to social adversity in individuals belonging to these groups can cause cognitive and emotional biases that predispose the formation of symptoms (Morgan et al. 2010). Social failure and stigma can lead to anxiety and ideas of persecution by increasing anticipation of a threat (Selten and Cantor-Graae 2005). The experience of racism creates a shape of memory in discriminated people who will feed their general fear of ethnic discrimination and take them to consider a given situation as racist. Repeated past experiences of discriminatory attitudes give the discriminated person the ability to significantly account for these situations. This sensitivity is often regarded as a cognitive bias through which interpersonal relationships are interpreted. For people who suffer racism, discrimination can represent a frequent situation in their social life. It contributes to the shaping of the way they perceive their social environment, as well as the meaning and the interpretation they give to this negative social context. The more an individual feels treated unfairly, the more he may develop feelings of exclusion and psychological distress. People who perceive discriminatory situations against them are more likely to stress symptoms or depressive symptoms. In the case of collective discrimination, victims will be more likely to contribute to movements to restore equity.

An important challenge is the assessment and measurement of perceived discrimination, which is particularly difficult when this is a subjective perception or even the interpretation of a given situation (Krieger 1999). There is no consensus in literature for the optimal measures to capture exposure to discrimination (Williams et al. 2003). This can be complicated because of its possible confusion or association with paranoid ideas (Sharpley et al. 2001).

20.4 Discrimination, a Factor of Bad Physical and Mental Health

Social inequalities related to ethnic origins have led to a large number of studies on racism as a potential determinant of health inequalities (Williams et al. 2003). These inequalities arise largely from inequalities in income, access to education, employment, healthcare and social support networks. These are unfavourable situations to which ethnic minorities are more exposed.

Discrimination is associated with several indicators of a worse physical and mental health (Krieger 1999). Literature data suggests potential pathways linking perceived discrimination and negative health outcomes (Pascoe and Smart 2009; Dolezsar et al. 2014). It is related to several types of physical health problems, such as hypertension, feeling of bad health and breast cancer. It is also a potential risk factor for diseases such as obesity, high blood pressure and usage of substances. It also has harmful effects on mental health in the form of troubles as depression, psychological distress and anxiety (Williams et al. 2003).

Several data suggest that environmental stress is an important determinant of bad mental health. This issue has been an important development in psychiatry in recent years. We saw the appearance of studies on the effects of racism and ethnic discrimination. Research mainly conceptualised discrimination as a factor of stress and suggests that the disparities in mental health between social groups can be partly attributed to experiences of discrimination and stigma. The experience of daily and repeated acts of discrimination may constitute a factor of chronic stress, while more overtly racist acts are regarded as acute stress that overlaps with chronic stress (Chakraborty and McKenzie 2002). Many studies have reported a link between discrimination and psychological distress (Williams et al. 2003; Tobler et al. 2013; Hwang and Goto 2008). Perceived discrimination is then considered as a psychological mechanism that makes the connection between social stress and risk in mental health among ethnic minorities (Gilvarry et al. 1999; Veling et al. 2007; Karlsen and Nazroo 2002).

In Europe, the research on mental disorders within immigrant populations showed that among the factors associated with the mental health of immigrants, cultural and social marginalisation and ethnic discrimination were found (Bernal 2003). Several psychiatrists described frequent symptoms in most of the immigrants, which they referred as the "Chronic and Multiple Stress Syndrome". Immigrants affected by this syndrome present depressive symptomatology with atypical characteristics, where depressive symptoms are mixed with anxious, somatoform and dissociative symptoms. The psychiatrist team proposed that the "Chronic and Multiple Stress Syndrome" should constitute an autonomous category situated between adjustment disorders and post-traumatic stress disorder (Carta et al. 2005).

Generations of children of migrants from ethnic minorities may develop psychological disorders related to the socio-economic difficulties and integration they incur. A greater frequency of depressive symptoms and use of substances is found among them (Peña et al. 2008). They have an increased risk of psychological distress (Kosidou et al. 2012). It is also established that the relative risk for psychotic disorders is more than doubled among ethnic minorities issued from migrations (Cantor-Graae and Selten 2005). This risk persists among the second generation (Bourque et al. 2011) and even among the third generation (Amad et al. 2013).

20.5 Discrimination and Suicide

It is worth noting the scarcity of data on links between discrimination and suicidal behaviours. The few studies on the subject are too weak samples or are too methodologically different to be able to draw general conclusions.

The stress associated with perceived discrimination was considered a predictive factor of a history of attempted suicide and associated with a greater likelihood of suicide attempt (Gomez et al. 2011). It is part of the confirmed risk factors of suicidal ideation (Cheng et al. 2010). Higher levels of perceived discrimination were associated with higher lifetime risk for suicidal ideation and attempts (Perez-Rodriguez et al. 2014). A form of vulnerability to suicide linked with perceived ethnic discrimination was highlighted among subgroups of Americans (Walker et al. 2014).

High rates of suicide and attempted suicide among migrants in the countries of European Union are reported and have been linked to their high rates of depression (Lindert et al. 2008; Gilliver et al. 2014). The second generation of migrants may be at greater risk of suicide than their first-generation parents (Hjern and Allebeck 2002). In the United Kingdom, rates of suicide for young immigrants from the Indian subcontinent are higher than those of their peers in their countries of origin (Patel and Gaw 1996). Family disputes are considered as precipitating factors, but we can also think that integration difficulties associated with stigma and marginalisation can contribute to these high rates. High rates of unemployment among migrants and their children are often linked with phenomena of discrimination in access to employment and indirectly lead to suicide. In the Netherlands, while the rate of unemployment among migrants was nearly three times more important than for aboriginal people in 1994, the rate of suicide among children of immigrants was considerably higher during this period than for national population (De Jong 1994).

Membership of a minority group increases the risk of mental disorder (van Os et al. 2010). The hypothesis of ethnic density proposes that the rate of suicide among migrant groups varies inversely with the relative size of these groups at the local level. In other words, the risk of suicide is higher in areas where migrants are fewer and lower in areas where they are proportionally more present. Neeleman et al. reported that attendance at emergencies for suicide attempts by Afro-Caribbean and South Asian patients was linked to the ethnic density of the population (Neeleman et al. 2001). Minority suicide rates are higher in areas where minority groups are smaller. This effect is ethnic specific (Neeleman and Wessely 1999). Social stress linked to situations of social discrimination and marginalisation is at the origin of mental disorders. This has already been mentioned for psychotic disorders within certain ethnic minorities (Selten and Cantor-Graae 2005; Cantor-Graae and Selten 2005).

We can think that these same factors also contribute to the increased risk of suicide among these same populations. Social marginalisation and insertion issues can influence the relationship between immigration and poor mental health. Unemployment, precariousness of resources and insertion, academic, professional and social failure are factors to be taken into account (Bursztein Lipsicas and Henrik Mäkinen 2010; Clarke et al. 2008). In the theoretical perspective of Durkheim, work is a powerful vector of social integration. A poor professional integration creates the risk of a low social integration. In the beginning of the 1990s where unemployment rates were high in Europe, particularly among populations with foreign origins, higher rates of suicide were found among children of migrants (De Jong 1994). Some people subject to prolonged discrimination may arrive at a social withdrawal.

It is a sentiment that takes the form of a feeling of emptiness and boredom in individuals but also a deep disinterest for usual activities. The poor self-esteem is an important sign, the subject describing himself in negative terms. This low self-esteem is often supplemented by an exaggerated or even pathological guiltiness. Moreover, the prediction of other negative events and treatment and the perception of an absence or deficiency of social support networks may lead individuals to feelings of despair and suicidal tendencies.

20.6 Hypotheses

There are recent models that give an important role to the effects of social stress and the feeling of perceived discrimination (Morgan et al. 2010; Wager and Gianaros 2014). These models, which put in the foreground the effects of experiences of social adversity and chronic social stress among ethnic minorities, are strengthened by the existence of socially relevant indices such as the colour of the skin or the belonging to an ethnic minority (Selten and Cantor-Graae 2005; Morgan et al. 2008).

Research on the involved neural mechanisms tends to demonstrate the sensitivity of the brain to social stress. These results support the hypothesis that negative experiences modify the ability of the brain to regulate social stress especially when they are early (Krabbendam et al. 2014). The feelings of perceived discrimination, internalised stigma and exclusion are powerful social stressors (Wager and Gianaros 2014). Neuroimaging studies attempt to highlight the neural processes involved in this type of social stress and explore the links between epidemiology data on the effects of social marginalisation and the involvement of specific neural circuits and brain areas. Ethnic minority individuals had significantly higher perceived chronic stress levels as well as increased activation and increased functional connectivity of the perigenual anterior cingulate cortex, a part of the ventromedial prefrontal cortex implicated in the generation and regulation of social threat and other emotional states. Ethnic minority individuals had significant correlations between perceived group discrimination and activation in the perigenual anterior cingulate cortex and ventral striatum and mediation of the relationship between perceived discrimination and the perigenual anterior cingulate cortex-dorsal anterior cingulate cortex connectivity by chronic stress (Akdeniz et al. 2014). These results suggest the existence of a link between a demographic variable that is the status of belonging to an ethnic minority and an increase of the biological sensitivity to social threat and stress.

A variety of animal models has been developed to study the consequences and the mechanisms that underlie the various forms of social stress. Negative experiences can cause psychological or physiological changes that can be attributed to a final common pathway of cognitive bias and/or alteration of dopaminergic neurotransmission (Collip et al. 2008). A model commonly used to explore the effects of chronic hostility or aggressiveness is the social defeat model where animals are exposed repeatedly to larger and more aggressive individuals (Selten and Cantor-Graae 2005; Cochrane 1987). Social adversity, urbanity, marginalisation and negative ethnic identification constitute among ethnic minorities

significant sources of chronic stress that occurs particularly during social interactions. These situations could chronically contribute to social defeat experience. The effects of the position of minority may be mediated by chronic social adversity and discrimination, leading to social marginalisation or a state of social defeat, the translation of a chronic experience of a position of inferiority and social exclusion (Collip et al. 2008).

Another path of reflection comes from sociology. In its work on poverty, the French sociologist S. Paugam has developed the concept of social disqualification, which, according to him, corresponds to a weakening or rupture of the links between the individual and society leading to a loss of social recognition (Paugam 2009). The deterioration of employment and the weakening of social bonds generate situations of vulnerability and cause phenomena of exclusion and stigmatisation. The excluded person is disqualified and its social status is deteriorating. The disqualification led to the discrediting of those who do not participate in economic life. They acquire a specific social status, inferior and devalued, profoundly marking their identity. Our hypothesis is that social disqualification in the meaning of S. Paugam is a situation comparable to that of members of ethnic minorities experiencing racism and discrimination. Their position is socially devalued and disqualified with a risk of stigmatisation.

Conclusion

Suicide represents a complex behaviour resulting from interactions between several psychological, social, environmental, genetic and neurobiological factors. Social factors such as the experiences of ethnic discrimination, marginalisation and exclusion are increasingly recognised as factors of mental disorder risk. It is very likely that they play an important role in suicidal behaviours as demonstrated by the few data at our disposal. The question that arises is whether it is possible to integrate these different aspects within unified and integrative models that simultaneously take into account biological, neuropsychological and social aspects. New approaches, ranging from animal studies to the modelling attempts, and methods of evaluation of the concept of perceived discrimination, will contribute to the understanding of the complexity of suicidal behaviour. We see here the whole point of the development of interdisciplinary approaches across the field of social neuroscience.

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Why It Is Important to Talk About Religion

21

Olfa Mandhouj and Philippe Huguelet

Abstract

Religion and spirituality may influence the attitudes and beliefs people have toward experience of distress and illness, how it may be a means for coping with mental health problems, and how it may enhance psychiatric patients sense of social belonging and integration. Also religion may be part of people's explanatory model of their life's experiences, may ameliorate the relationship with mental health professionals, and may enhance the trust and access to mental health services. Spiritual beliefs and values are part of the patient's cultural background, and their consideration in mental health may help to pursue the important aim of offering culturally sensitive prevention/intervention strategies. In the particular situation of patients at risk for suicide, religion may be specifically involved, as it tackles moral issues and personal views about what may happen after death. Religions generally forbid suicide. Also, there is some evidence that religion may provide support and a way for coping with difficulties leading to suicide. This gives some evidence that psychiatrists should broach this topic when treating patients concerned by suicide drives. It is thus expected that professionals in mental health should perform an in-depth diagnostic assessment of the spirituality of their patients.

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21.1 Introduction

The relation between religion and suicide began to be studied by the French sociologist Emile Durkheim (1897) who illustrated the protective effect of religion among Catholics. Since Durkheim, most researches looking at the relationship between religiosity and suicidal behaviors found an inverse association between these two parameters.

Epidemiologic, sociologic, and clinical studies showed that spirituality and religion (SR) are associated with a lower risk of suicide attempts (Bostwick and Rummans 2007). Multiple aspects of relatedness and social aspects of religious observance appear to be associated with reduced depression and suicidality in faith adherents (Bostwick and Rummans 2007). A review on this issue found that 84 % of studies showed lower prevalence of suicidal behavior among people who were more religiously involved (Koenig et al. 2001). Koenig (2009) found that 57 out of 68 studies about SR and suicide showed that suicide rate was lower among people having a high religiousness. Concerning the mechanisms involved, SR may to some extent prevent suicide because most religions forbid it. Also, religions can give a meaning for life and bring hope, i.e., a factor associated with a lower suicidal risk. Finally religious involvement may prevent suicide by the fact that religious persons often feel sustained by the social support brought by his/her community and/or religious leaders.

Beyond theory and epidemiology, how may religion help? SR is a complex aspect of human culture often neglected in comprehensive biopsychosocial models of psychopathology. Yet, religious commitment to a few core lifesaving beliefs may protect against suicide, and religion may provide a positive force that counteracts suicidal ideation in the face of depression, hopelessness, and stressful events. Surveys among psychiatric patients found that religious affiliation, religious beliefs, and moral objections were often reported as preventing patients from attempting suicide (Dervic et al. 2004). In this perspective, psychologists of religion (e.g., Pargament) have developed the concept of religious coping. Pargament and Brant (1998) suggested that religious coping potentially serves several purposes: spiritual (meaning, purpose, hope), self-development, resolve (self-efficacy), sharing (closeness, connectedness to a community), and restrain (help in keeping emotion and behavior under control). Religious coping may be adaptive or not. Tepper et al. (2001) showed that 80 % of patients with persistent mental illness used religious beliefs or activities to cope with daily difficulties or frustrations, particularly those who were experiencing more severe symptoms. Also SR has been identified as an important coping resource that allows overcoming stressful events (Pargament et al. 2000).

Clinicians often avoid – or forget – to speak about SR with their patients, even with patients featuring suicidal risk. This may be due to a lack of knowledge, leading clinicians to think being incompetent to address this issue, to a lack of time, to a fear to impose one's point of view, or to a lack of interest or a negative vision of religion (Swinton 2001; Mohr et al. 2007; Neeleman and Persaud 1995). Psychiatrists are also reported to be less religious than the general population (Neeleman and King 1993; Galanter et al. 1991). Hence, it appears that clinicians involved with patients with mental disorders avoid considering it (Huguelet et al. 2006). This

avoidance leads to some concern when considering patients willing to die, as spiritual assessment may allow clinicians to figure out patients' meaning in life, purpose in life, their desire to stay alive, and the quality of their social support. Also, their worldview gives them a representation of what is beyond death, i.e., a representation likely to play a role when considering suicide. Overall all these aspects lead to recommend performing an SR assessment of patients with psychiatric conditions, particularly with those at risk for suicide.

21.2 Suicide and Religion: A Historical Perspective

In most known religions of the world, suicide is condemned, especially in the three monotheistic religions: Judaism, Christianity, and Islam. However, the strength of this condemnation has varied over time and within the religions themselves. Among the early Christians, martyrdom was a means to prove love and fidelity to God. It was only in the fourth century A.D, with Saint Augustine, that the official Catholic Church disapproval toward suicide began to spread. In 1943, the Pope condemned the "grave sin of suicide" (Pescosolido and Georgianna 1989). To note, concerning the attitudes toward suicide among Christians, Catholics may be less tolerant than non-Catholics. Bagley and Ramsay (1989) saw that members of conservative protestant groups and Catholics featured more negative attitude toward suicide than did members of less conservative domination or Jews. People who do not belong to any religion are more accepting of suicide.

In the nineteenth century, sociologist Emile Durkheim found suicide rates to be higher in the Protestant cantons of Switzerland as compared with the Catholic ones. He argued that stronger social cohesion and social integration among Catholics may have resulted in lower suicide rates in those communities. Indeed, Catholics are required to interact with others frequently when going to mass, obtaining sacraments, and confessing. Hence, they may have benefited from a strong supportive social network at that time.

Durkheim's views have been confirmed by most research since then (Koenig et al. 2001). Yet Stark et al. (1983) have strongly criticized Durkheim for ignoring theological explanations for the differential suicide rates of Catholics and Protestants and his claim that the effects of religion on suicide are for the most a reflection of social integration.

In Judaism, suicide is often viewed as a greater crime than homicide. In Durkheim's theorization, Judaism also offered a protective effect against suicide, even stronger than Catholicism, because of its capacity to integrate individuals by means of communal ties and strong prohibitions for suicide.

Islam has also a quite condemnatory attitude toward killing, whether against oneself or another person. Suicide is a crime under Islamic law; suicide attempts may lead to prosecution and to a denied access to heaven. Suicide is also considered as a shameful act within families and may be subsequently concealed (Khan and Reza 2000). Still, while Islam condemns on one hand, forgiveness also exists on the other, as suicide victims are often seen as mentally ill (Simpson and Conklin 1988).

In contrast, in Asia, Brahiminism, Buddhism, and Shinto institutionalize suicide sometimes. Hinduism and Buddhism teach transmigration of souls. Hindu philosophies of Karma and reincarnation mean that life does not end with death and that death leads to rebirth. These believe may facilitate the idea that putting an end to one's life is not the final step (Bolz 2002).

In Spoerri et al. (2010) and colleagues led a longitudinal study to examine the influence of religious affiliation on the risk of suicide in Switzerland, where assisted suicide is legal if the motive is not selfish. The censuses on the whole population were linked to the mortality records. The authors found a protective effect of religious affiliation among Catholics compared to Protestants (suicide rates per 100,000 inhabitants were 19.7 in Catholics, 28.5 in Protestants, and 39.0 in those with no affiliation). The protective effect of religion was also stronger in older than in younger people, stronger in women than in men, and particularly strong for assisted suicides. Authors confirmed Durkheim's finding and related this finding to the fact that Catholics are more integrated than Protestants and Protestants more integrated than people with no religious affiliation. Hence, suicide rates would be expected to be highest in people with no religious affiliation and lowest in Catholics. Rates of suicide were lowest among married individuals and people living with others, this finding also suggesting the importance of social integration.

Dervic et al. (2004) found that those with religious affiliations featured significantly fewer deaths by suicide than those without such affiliation. The religiously affiliated were more likely to find suicide morally repugnant, to be married, to have children, and to be entangled in networks of family relationships. In contrast, suicide attempters were more likely to be alone and cut off from social networks that spiritual institutions provide and intimate connections that spouses, offspring, and extended families generally afford.

From a cross-cultural study on religion and suicidal attempts, Kok (1988) referred to the cultural and religious differences among Chinese, Malays, and Indians to explain the rate of female suicide attempts in Singapore. He reported that Indian females featured the highest rate, that being at least partially explained by the rigidly defined role expectations for the Indian women and by the lack of explicit forbiddance of suicide in Hinduism.

21.3 Religion Involvement and Suicide

Religious involvement, as measured by frequency of religious attendance, frequency of prayer, and degree of religious salience, is negatively associated with suicide, suicide behavior, suicidal ideation, and tolerant attitudes toward suicide across a variety of samples across many nations (Koenig et al. 2001). Actually a variety of mechanisms may explain why religious involvement might deter suicide. The most important mechanisms are encouraging beliefs in an afterlife and in a loving God, conveying purpose and self-esteem, providing role models for coping with stress and crisis, and offering resources for reframing life's struggles and difficulties.

The greatest protective effect of religion on suicide is reported to be present in subjects who have relatives and friends of the same religion (Clarke et al. 2003). Nisbet et al. (2000) showed that visiting or talking with friends or relatives did not reduce the likelihood of suicide, but frequent participation in religious activities did. These findings suggest that something more specifically intrinsic to religious practice might be responsible for decreasing suicide risk.

Pescosolido and Georgianna (1989) showed that either religious or other network ties have both integrative and regulative aspects and act therefore as important sources of social and emotional support. They highlighted that the influence of religion on suicide may be modeled within certain social and geographical contexts. Indeed, the relationship between religion and suicide has been altered by three sociohistorical trends: secularization, ecumenicalism, and evangelical revival. The impact of religion and spirituality changes in different cultural and sociopolitical contexts and during historical periods.

Aside from these hypotheses concerning the relations between religion and suicide, S/R may influence suicidal risk through other indirect psychological mechanisms. Suicidal behaviors are related to aggressive and impulsive traits, and anger predicts future suicidal behavior especially among adolescent boys (Goldney et al. 1997). Religiosity has been reported to be associated with lower hostility, less anger, and less aggressiveness. Therefore, religious affiliation may affect suicidal behavior by lowering aggression levels and through moral objections to suicide. Thus, supporting religious beliefs considered as useful by patients for coping with stress (e.g., by reducing anger) could be a useful tool in a therapeutic process that targets suicide prevention (Dervic et al. 2004; Koenig et al. 2001).

21.3.1 Meaning in Life

Spirituality incorporates a sense of meaning and purpose that may or may not be aligned with formal religious belief or practice (Hill and Pargament 2003). Wong and Prem (1998b) point out that it is a common viewpoint that questions about meaning and purpose are too subjective and philosophical to be answered scientifically. They suggest that promotion of personal meaning may be effective in addressing social problems, such as drug addiction, alcoholism, and suicide. Wong and Prem proposed a culturally appropriate meaning-centered counseling, a hybrid between existential-humanistic psychology and cognitive-behavioral therapy. Lester (1998) offers a different perspective in regard to the role of meaning in suicidal behavior stating that, for some suicidal individuals, suicide is a search for spirituality, for God, for a meaning of life, and for a rebirth.

Aside from the "meaning" in a religious perspective, personal meaning has been a core concept for several phenomenological philosophers and existential scholars. The most notable and influential is Viktor Frankl, a psychiatrist survivor of a Nazi concentration camp in Germany. Frankl (1963) suggested that the primary motivating factor of mental health is the human quest for meaning and purpose, which belongs to the *noetic* dimension of human beings. This concept was so important to

him that he developed a therapeutic approach – *logotherapy* – which focuses on meaning in life. Human survival depends on finding and preserving meaning and on filling the "existential vacuum," "a feeling of aimlessness and emptiness" (Frankl 1963). Man is characterized by his reaching out for meaning and purpose in life. The lack of meaning, in Frankl's view, is experienced by the individual as a sense of complete emptiness and an absence of purpose for continuing to live. Suicide, then, may seem a viable solution to relieve this distressing state of being. A similar concept is affirmed by Marsella (1999) and Tacey (2005). The former asserts that those who have no meaning attached to life do not continue to live. Marsella (1999) states the centrality of meaning along life's journey, the absence of which causes despair, alienation, and suicide. Marsella declares: "It seems to me that many discomforts, disorders, and diseases of our time are related to an absence of meaning-seeking and meaning-making" (1999, p. 49). Camus (Le mythe de Sisyphe, 1985) underscores that the "only" serious question is whether life is worth living or whether one would be better off committing suicide. His answer was that suicide was a form of self-defeat.

Individuals who experience a deeper and broader sense of meaning and purpose enjoy greater life satisfaction, higher levels of psychological and physical well-being, and positive mental health (Reker 1994), whereas, in Petersen and Roy's opinion (1985), people whose lives lack meaning and purpose experience feeling of emptiness or a lack of direction and have difficulty making sense out of their existence and question the significance of being who or what they are. A seldom-posed but important question is not why depressed patients want to commit suicide, but why they want to live. Existentialists such as Camus postulate that human being should make something of the emptiness of human existence and create something meaningful in its place (Van Deurzen 2010).

21.3.2 Religion, Suicide, and Clinicians

Swinton (2001) affirms that while spirituality remains a peripheral issue for many mental health professionals, it is in fact of central importance to many people who are struggling with the pain and confusion of mental health problem. He argues that spirituality can be studied in a scientific way and asks for the development of complementary methodologies and ways of exploring the spiritual dimension that can dig into the hidden depths of human emotion and experience and reveal aspects and perspectives that are unavailable to other ways of doing research.

He lists reasons explaining why mental health professionals are wary and skeptical about spirituality: in addition to the aforementioned factors, the impact of psychoanalysis and other therapeutic theories may play a role.

Baetz et al. (2002) interviewed psychiatrists who were all members of the Christian Medical and Dental Society, 80 % of them declared that they often or always inquired about their patient's religious beliefs. Two thirds of them felt they were able to integrate spiritual issues into their practices if they chose to do so. Physicians who had strong religious beliefs are more likely to discuss about

religiosity with their patients. However, only one third felt that they should ask their patients about faith-healing experiences. Koenig and collaborator's showed that mental health professionals rarely make referrals to clergy or other religious leaders. Huguelet et al. (2006) showed that spiritual assessment was rarely performed by psychiatrists, who were most of the time not aware of the religious background of their patients, hence not knowing whether it may help or not. Later they taught to clinicians how to perform a spiritual assessment and evaluated its effect over 4 months in a randomized protocol (Huguelet et al. 2011). This assessment brought about important clinical issues in patients.

21.4 Clinical Implications

We've tried to underscore how religion and spirituality may influence the attitudes and beliefs people have toward experience of distress and illness, how it may be a means for coping with mental health problems, and how it may enhance psychiatric patients sense of social belonging and integration. Also religion may be part of people's explanatory model of their life's experiences, may ameliorate the relationship with mental health professionals, and may enhance the trust and access to mental health services. Spiritual beliefs and values are part of the patient's cultural background, and their consideration in mental health may help to pursue the important aim of offering culturally sensitive prevention/intervention strategies. In the particular situation of patients at risk for suicide, religion may be specifically involved, as it tackles moral issues and personal views about what may happen after death.

Suicide is a major issue around the world. Religions generally forbid suicide. Also, there is some evidence that religion may provide support and a way for coping with difficulties leading to suicide. This gives some evidence that psychiatrists should broach this topic when treating patients concerned by suicide drives. It is thus expected that professionals in mental health should perform an in-depth diagnostic assessment of the spirituality the patient is "imbued with" in order to address this aspect when treating their patients.

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Part IV

Treatments of Suicidal Behaviour (and Related Traits)

Surveillance Is a Powerful Tool to Prevent Suicidal Acts

22

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Abstract

Is it usefull to keeping under surveillance a suicidal crisis whenever a subject met after a suicide attempt? We advocate an ethic of worriness, keeping the concern of the other, bringing connectedness, etc. But is it effective to keep watch on a suicidal crisis? Several devices have been imagined and tested, although none alone shows a decrease of suicidal behaviors in the general population. Hence, we developped the idea of a simple algorithm (ALGOS) that could combine the qualities of some of the proposed features: a crisis card issued to first attempters, phone call to 15 days for the suicide repeaters, sending a few postcards to uncontactable subjects or diagnosed at risk during the phone call, etc. The ALGOS device is being tested in 23 metropolitan France's centers, and for now, more than 1000 patients are included in a randomized clinical trial comparing the algorithm effect to a control group of suicide attempters treated as usual (i.e., referred to the general practitioner). This kind of device would be inexpensive to implement and easily generalizable in a territory, can thus bring an important innovation in public health.

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Since 2000, significant progresses have been made in the field of suicide prevention. In France, these advances predominate in two directions:

1. On one hand, an improvement in taking account of the suicidal risk in clinical population, i.e., in groups of subjects with some psychopathological disorders, is worth noting. The decrease of suicidal conduct is mostly the result of screening and earlier recognition of the underlying condition; unfortunately, the diagnosis of illnesses like schizophrenia or bipolar mood disorder is usually delayed (1 year and almost 8 years, respectively).
2. On the other hand, an unprecedented effort in training the first-line responders generates increased awareness and more frequent screening for suicidal behaviors in certain at-risk groups: in-school adolescents, inmates, people bereaved by suicide or with professional burnout, etc.

Thus, in France, the number of death by suicide decreased from 12,000 in 1999 to 10,314 deaths in 2011 (CépiDC INSERM). A stabilization, or at least a slight decrease in suicide mortality, can be observed in every western country (Bertolote and De Leo 2012; Isacsson 2000).

Nevertheless, suicidal behaviors are rather multifactorial phenomena. Therefore, it is always difficult to define clear-cut strategies when facing a suicide attempt, essentially in general population. Thus, all health-care plans specifically designed toward suicide attempters have failed to show their efficiency in reducing suicidal reattempting or even mortality by suicide (Reulbach and Bleich 2008).

The positive endeavors can be divided into two families: the intensive intervention programs and the surveillance programs.

An English study reports first intensive intervention operation. It aimed to determine the effect of nursing intervention at the patient's residence (Guthrie et al. 2001). Four sessions (50 min a week) of problem-solving-oriented interpersonal psychodynamic therapy were carried out at the patient's home in the first month following the suicidal act. Of 587 suicide attempters addressed to the emergency room (ER), 233 were eligible and 119 accepted the study and were therefore randomized. Evaluations took place at 1 month (89/119, i.e., 25 % were lost) and at 6 months (95/119, 20 % lost). At month 6, suicidal intentionality as measured by the Beck's scale and suicidal reattempting were greatly reduced (7.9 versus 12.8; $p=0.005$ and 9 % versus 28 %; $p=0.009$, respectively). There was no difference in the use of health services.

A second study assessed a series of brief psychotherapeutic intervention (BPI). This program was proposed by the team from Brest in France and evaluated the efficiency of a protocol of brief psychotherapy administered within 1 month after the release from the emergencies (five interviews: J1, J4-J8, J15-J28) on reattempting suicide at 1 year (Walter and Genest 2004). The therapists were experienced or in-training psychiatrists and trained to the BPI and were those who had initially met the patients. The studied population included all suicide attempters (age range: 15–34 years), consecutively admitted during 12–24 h in a psychiatric emergency unit, with no ongoing psychiatric follow-up and who were not requiring hospital

care in the course of their suicidal act. At 12 months, 19 patients (18.6 %) have reattempted, 11 (20 %) in the control cohort and 8 (16 %) in the BPI ($p=0.45$) cohort. Among the subjects younger than 20 years old, no reattempt was found in the BPI cohort (0/21) versus 11 in the control cohort (11/22) ($p=0.03$); there was no significant difference for patients older than 20 (7/22 versus 8/18; $p=0.76$).

These two trials have great strength but also weakness: their strength is the efficiency they demonstrate on the number of re-attempters in the short and medium term; their weakness is the institutional heaviness of implementation and deployment of such programs and thus their financial burden. In a concern of public health and health-care organization, it is difficult to imagine their quick and easy generalization in a wide area.

The other positive trials have in common that they challenge classical intervention plan, offering instead a "keeping in touch" model ("*rester en contact*" in French), a surveillance device, which does not invade the daily life of the suicide attempter, which is suitable with simultaneous support cares when these are appropriate, but which delivers tools or reliable and effective answers to the suicidal crisis. These "case management" or "surveillance" works led Jerome Motto to the neologism of "connectedness," to symbolize this "feeling of keeping in touch" (Motto and Bostrom 2001). In France, terms like "*Clinique du souci*" (Worry clinic) or as proposed by the Swiss philosopher Pierre Cornu, "*Ethique de l'inquiétude*" (ethics of anxiety), are used. Keeping contact with the patient seems to be as much effective as it is active and should not exclusively be left up to the patient; it has to be regular, customized, and considered a long-term project (Du Roscoat and Beck 2013).

Each one of these surveillance programs is of sharp interest with certain categories of suicide attempters, when considering exclusively very simple criteria such as sex and the number of previous attempts. As they are financially lighter and easily and widely generalizable, these devices also stand out from intensive intervention programs.

Here are the details of this proposed surveillance:

22.1 Phone Recontacting of the Suicide Attempters

A first work was proposed by our team and was carried out in France in the region Nord-Pas-de-Calais in 13 of the 16 emergency rooms in the area (Vaiva et al. 2006). Suicide attempters were recontacted by phone, on behalf of the emergency department which had received them in the wake of the suicidal act, by a trained psychologist or psychiatrist. This phone call occurred at 1 or 3 months after the discharge from the emergency department. Supportive therapy pondering with the patient whether the elements of the release compromise were still relevant to the current situation was used. Crisis intervention could be implemented by phone, whose main goal was to define or adjust the recourse to the then necessary care. If a risk of suicidal situation was detected, a face-to-face interview was organized within 24 h with the emergency room psychiatrist that had initially received the patient. This action of surveillance adds to the previously agreed care plan as setup in the ER.

Population concerned. The trial has been proposed for 6 months (during working days and hours) to subjects surviving an SA by drug intoxication and who currently do not meet any criteria for somatic or psychiatric hospitalization. Eight hundred forty-two were eligible and 605 subjects who agreed with the study were randomized. Monitoring spanned on 14 months. Nine percent were lost to follow up.

Results. One-third of the volunteer subjects to an effective recontacting could not be reached three attempts. In addition, on the 150 suicidal reattempts numbered during the follow-up, 48 occurred before the end of the first month of the trial, before the first attempt of a possible phone call. Thus, the statistical analysis in intention to treat between the three groups (month 1 recontact, month 1 recontact, and no recontact) was negative with $p = 0.25$. However, when considering only the subjects actually recontacted (per protocol analysis), the systematic call at 1 month proved to be very effective, reducing by a half the number of recidivism in the year (12 % versus 21.6 % in the control group). Another point of significance, is that in this recontacted group at 1 month, 12 of the 13 subjects detected with a risk of suicidal attempt during the phone call actually went to the quickly organized interview with the emergency psychiatrist.

The post-hoc subgroup analyses showed the same effect whatever the gender.

However, in the subgroup of the 300 first-suicide-attempter subjects, no effect of the recontact call was found (even though the number of re-attempters in this group was much lower). In addition, we found that 80 % of reattempts occurred within the first 6 months; the 20 % remaining might correspond to recidivism of suicidal crisis, rather than the extension of the index crisis.

Finally, the proposal of recontact phone call was very well accepted and perceived among this population of suicidal attempters leaving the ER; a qualitative analysis of the subjective experience of the program has been conducted on 400 of the 605 subjects, showing the impact perceived by the target population and the lack of major undesirable effects reported by the subjects (no reactivation of suicidal ideation in relation to the call or the prospect of being called); on the contrary, control subjects often complained about delays before being recontacted (at the 13th month for the final evaluation) (Gruat et al. 2010).

Synthesis This study showed the positive effect of a phone recontact for the subjects recontacted at the end of the first month after a suicide attempt. We noted the relevance of focusing on the first 6 months, rather than the whole year. The "telephone recontact effect" was not relevant for the first-suicide-attempters. Several points remained unresolved:

- What should be proposed to subjects not reachable by phone?
- What should be proposed to those denying the needed care or monitoring?
- In the study, of 1/3 of reattempts occurring before the end of the first month, it would be critical to anticipate the phone call, between the 15th and the 21st day after the SA.

Since this work of 2006, two foreign studies should be reported: OR = 0.64; 95 % CI 0.34–1.26.

- A work in Spanish Catalonia involved 991 suicide attempters, called by telephone at several times during the 12 months following the SA (1 week, 1 month, 3 months, 6 months, and 1 year). Telephone recalls were related to a decrease in the number of re-attempters: (a) in comparison with the year preceding the study (intervention 6 % (16/296) versus baseline 14 % (39/285) difference 8 %, 95 % CI: 2–12 %) and (b) in comparison with the population of a control territory (intervention 6 % (16/296) versus control (31/218) difference 8 %, 95 % CI: 13–2 %) (Cebria et al. 2013).
- The very nice work led by the WHO (SUPRE-MISS study) in five developing countries (China, Iran, India, Sri Lanka, Brazil) and concerning 1867 suicidal subjects, who were all given a 1-h intervention of psychoeducation before the release from the ER, and completed with a nine phone recontact intervention during the following 18 months. The results showed a very interesting effectiveness on suicide mortality (0.2 % versus 2.2 % at 18 months), with no effect suicide reattempts (Bertolote et al. 2010).

22.2 Delivering a "Resource Card" (*Crisis Card*)

This program has been proposed by the English team in Bristol and is of high interest for first-suicide-attempters. It seems to complete the previous media.

In this procedure, every suicide attempter, after the setting up of the usual treatment depending on the initial assessment (advice, appointment, or psychiatric hospitalization), was given a "resource card" with the phone number of a junior doctor available 24/7 within the 6 months after the attempt. The evaluation at 6 months showed a beneficial effect on the recidivism rate of the first-suicide-attempters (OR = 0.64; 95 % CI 0.34–1.26), when compared to a control group (Evans et al. 1999, 2005). A second work has tested the effect of the systematic delivery of such a "resource card" at 12 months: of 827 patients, 167 (20.2 %) had recurred, 90 (21.6 %) in the group that had received the card and 77 (18.8 %) in the control group (OR = 1.19; 95 % CI 0.85–1.67). There was no difference between those groups regarding the time of relapse. The subgroup analysis confirmed the principal analysis: in the first-suicide-attempter subgroup, 30 (13.6 %) have recurred in the intervention group and 31 (15 %) in the control group (OR = 0.89; 95 % CI 0.52–1.32); in the "previous suicide attempts" subgroup, 60 (30.9 %) have recurred in the intervention group and 45 (22.5 %) in the control group (OR = 1.54; 95 % CI 0.98–2.42). Thus, the beneficial effect observed at 6 months seems to be lost in the six following months. It is worth noting that the 70 patients who called the psychiatrist within 6 months had very high rates of recidivism (OR = 4.91; 95 % CI 2.83–8.50). Thus, these 6 % of patients who

called the number "pointed themselves out" as at risk of suicidal attempt; in the future, a specific intervention can be implemented for these subjects, in order to amplify the effect of the "crisis card."

Synthesis From this work, we should keep in mind the following points:

- Delivering a "resource card" to the first-suicide-attempters may prove itself useful, beneficial, and pragmatic during the first 6-month period post-SA (half of the suicide attempters are first-suicide-attempters and they reattempt twice fewer than the suicidal recidivists).
- The 6 % of subjects calling the given number seem to "point themselves out" as a high suicidal recidivism risk subgroup and then could justify both a proactive "to go to" intervention and care.

22.3 Sending Mails ("Short Letters" According to Motto)

The pioneer of these case management plans is undoubtedly Jerome Motto, which has proposed a strategy of postal recontact and has followed his device for 15 years (Motto and Bostrom 2001). A short letter was sent to the patient by a person who has met him during his hospital stay When possible, this mail was personalized (e.g., by using an anecdote related to his hospitalization) and sent with a non-stamped answering envelope; a total of 24 letters were sent to patients, at month 1 (M1), M2, M3, M4, M6, M8, M10, and M12, then every 3 months over a period of 5 years. The letter tried to avoid suggesting that any information or action would be desired from the patient. The stated aim was that the patient realized that a person remains concerned by him (his life) and maintains positive feelings toward him; it explains the neologism proposed by the author: "connectedness."

In this study, the mail sending concerned 3005 patients who were hospitalized for depression or suicidal crisis from 1969 to 1974, in nine inpatient facilities in San Francisco. The idea was to try keeping in touch with reluctant subjects or subjects refusing the plan of care set at the hospital: 30 days after release from the hospital, patients were asked on the phone about their agreement to the defined care; nonobservant subjects were then randomized into two parallel groups with sending ($n = 389$) or not the mail ($N = 454$). The follow-up lasted 15 years and the main criterion of study was the impact on the subsequent mortality. As for results, this study showed contrasted results at 5 and 15 years. At 5 years, a significant decrease in deaths from suicide acts was observed in the group of inobservant subjects who were recontacted (15/389 versus 21/454), but the difference disappeared at 15 years (25/389 suicide acts versus 26/454). As long as the sending of mail was scheduled, the effect was maintained; as soon as the device stopped at 5 years, the effect was fading.

Synthesis From this work, we should keep in mind the following points:

- The target population is composed by inobservant subjects with a plan of care defined during hospitalization.
- In this very poorly accessible population, this procedure seems to reduce the mortality by suicide at a short and medium term and is financially inexpensive.

22.4 Sending Postcards

Close to Motto's idea, an Australian work published in 2005 (EDGE project) has tested a procedure of scheduled and systematic sending of postcards during the year following the suicidal act (Carter et al. 2005). The message was the same for each patient: "we met some time ago… do not hesitate to give us news on occasion…" The postcards were sent in months 1, 2, 3, 4, 6, 8, 10, and 12 after discharge.

Assessment covered all subjects surviving to a self-poisoning SA and hospitalized a few days in a "toxicology" unit (ER). The test has been proposed for 1 year to a complete series of consecutive 922 subjects who were over 16 years old; 772 subjects agreed to the study and were randomized in two parallel groups. The initial follow-up was 12 months, lately completed with a 1-year extension (Carter et al. 2007).

Results. This work did not show a decrease in the number of suicide re-attempters (15.1 % versus 17.3 % at 1 year, 21.2 % versus 22.8 % at 2 years). However, the authors noted a lower number of reattempts in the recontacted-suicide-attempter group (risk ratio 0.55 at 1 year, risk ratio 0.49 at 2 years) among those who reattempted during the follow-up period. Post-hoc analysis showed a significant effect in women (risk ratio = 0.49), in contrast to the men's one (risk ratio = 0.97).

This device has been replicated in a lighter form by Beautrais's team in New Zealand: a randomized controlled trial involving 327 people, who were at least 16 years old and who showed up consecutively at the ER for a suicide attempt, regardless of the method used. The intervention consisted in sending four 'postcards' to the patients, at 2 weeks, and then at 1, 3, and 6 months (Beautrais et al. 2008). Patients assigned to the control group didn't receive any postcards. All subjects simultaneously received standard treatment. The number of recorded reattempts was significantly lower in the intervention group (31/153, 20.3 %) than in the control group (88/174, 50.6 %). It is worth underlining that the number of subjects repeating the act in both groups, particularly in the control group, was very high.

We could report a recent and extensive replication study, in Iran, with a sending rate of eight cards on 12 months, in collaboration with Greg Carter, about 2300 suicide attempters and showing a slight decrease in suicide reattempts (3 % versus 5.1 %). This difference involved only women and patients with previous suicide attempt (Hassanian-Moghaddam et al. 2011).

Synthesis From these studies, we should keep in mind the following points:

- The target population would rather be women, following a brief hospitalization after SA.
- With less sending, on a shorter period and with non-customized letters, the device seems to be financially inexpensive and less heavy.
- But it only shows a slight effect in terms of number of reattempting subjects, which limits its interest.

22.4.1 Text Messaging

Text messages provide several characteristics of existing monitoring strategy for suicide attempt repeaters. The feasibility and acceptability of this device was explored in a pilot study (Berrouiguet et al. 2014). Messages were personalized as recommended by Motto, reaching patient earlier than with a letter. Care services clearly identify as the senders of the messages, as it would have been done in a letter. In line with the contact strategy by, call-back numbers proposed were available 24 h per day and 7 days per week (Evans et al. 1999, 2005). In comparison to the contact strategies by letter, access to the service was made easier as the patient simply had to press the call button on his/her telephone to contact us upon receiving the text message. Furthermore, sending a message with such is ten times cheaper than sending a postcard or a letter. This monitoring system does not require an action of a clinician to be sent. All messages are written and scheduled before discharge and automatically sent over the monitoring period. Despite the variation in suicidal behavior and standards of care across the areas (De Leo et al. 2013), the worldwide diffusion of mobile phone could offer new perspectives in suicide reattempt prevention. Text messaging intervention for suicide prevention could be easily implemented in mobile or web-based applications. As text messages provide several characteristics of interventions that showed a significant reduction in the number of SA repeaters, assessment of its efficacy on reducing suicide reattempt in SA population is currently assessed (Berrouiguet et al. 2014).

22.4.2 Toward a Surveillance Algorithm

Thus, some of us have discussed the possibility of building a kind of surveillance algorithm in the shape of a follow-up decisional tree (Vaiva et al. 2011). The ALGOS algorithm takes the following form over the 6 months after the SA:

1. For the first-suicide-attempters → "resource card"
   (a) In case of a call to the "resource center" and detection of an at risk for suicide situation → need for a proactive intervention or a consultation at the emergencies within 24 h

2. For re-attempters → "phone call between the 10th and the 21st day"
   (a) In case of a suicidal risk situation → need for a proactive intervention or consultation at the emergencies within 24 h
   (b) If not reachable or turning down medical support → "postcards" according to Carter

The general practitioner and more generally the patient's health-care contact are informed with an interview report as soon as the patient enters the procedure and after each one of the phone recontacts.

The ALGOS device is being tested in 23 metropolitan France's centers, and for now, more than 1000 patients are included in a randomized clinical trial comparing the algorithm effect to a control group of suicide attempters treated as usual (i.e., referred to the general practitioner). The preliminary results are much in favor of the algorithm, both in "intention to treat" and in the "per protocol" analysis (Vaiva et al. 2013).

22.4.3 Three Striking Points

1. The effect in reducing the mortality by suicide at 6 months, 12 months, and 18 months
2. The identification of a new at-risk subgroup, detected through the phone call at the third week
3. The potential interest in sending MMS instead of postcards

Simultaneously with the ALGOS, a sociological and qualitative study is led by an IReSP (*Institut de Recherche en Santé Publique*)-independent team: the EQUATION study. All the contributors involved in the surveillance process are contacted: patients, of course, but also general practitioners, psychiatrists and psychotherapists, ER staff, and "recontacters." Preliminary results show a patient's sense of belonging and a display of interest from the doctors. Nevertheless, this interactive time with family doctors deserves to be better worked, maintained, and put in use.

Today, the ALGOS program demonstrates the efficiency of a combination of several surveillance systems. It points out how possible it is to reshape our health-care system toward a centralized coordination of this surveillance. Such a system, in turn, may work as a vector and a source of continuous improvement for the "remain linked" processes.

22.4.4 Perspectives

The next step would be the deployment of a pilot experiment on one or more given territories, in "real-life" condition, while taking care of learning the lessons from the literature and qualitative sociological studies. Its framework might be:

- The principle of a surveillance algorithm of suicide attempters, centralized on a territory and tightened with a small task force team dedicated to the coordination of suicide prevention; this team would ensure and make the link with human intervention means.
- Deployment on a given area after delivering an advertisement campaign to the public and professionals concerned by suicide issues.
- Including as many general practitioners (GP) as possible.
- To depend on preexisting networks. Many countries indeed have emergency medical service already qualified in the telephone regulation, the measurement of the emergency degree of a situation, and decision making over the phone. It becomes thus legitimate to raise the question to establish these surveillance programs within these hospital services.
- Improving information given to the various health partners of the suicide attempters and their significant others, throughout the monitoring process.
- With more customized intervention means, compared with tested intervention programs in scientific literature: being able to multiply phone contacts if necessary, creating a mobile and rapid reaction force dedicated to local emergency interventions in case of detected crisis, etc.

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Preventing Suicidality Through Online Tools: The SUPREME Project

23

Vladimir Carli

Abstract

Suicide Prevention by Internet and Media-Based Mental Health Promotion (SUPREME) is a mental health promotion programme, which comprises a multi-language, culturally adapted, highly interactive website accessible to the general public that is particularly aimed at adolescents. The website offered users access to interactive services such as a real-time chat communication and a discussion forum moderated by mental health professionals, as well as written information addressing various mental health problems. The written content aimed to raise knowledge and awareness about mental health and suicide, to combat stigma and to stimulate helping and help-seeking behaviours. The effectiveness of the intervention website was tested in a randomised, single-blind, minimal treatment-controlled, parallel, multi-centre trial. A statistically significant decline in nearly all mental health-related outcomes, such as depression, anxiety and stress, suicidal thoughts and ideation was observed. The decline was continuously shown after the second and third wave of data collection. However, the interaction effects between study arms did not reach statistical significance.

Internet-based interventions have, if properly executed, great potential of making mental health-promoting activities and services more salient, available and affordable to people regardless of socio-economic status. As indicated by the data collected in SUPREME, the vast majority of European adolescents spend considerable time on the Internet every day. This provides an opportunity to offer mental health promotion even to those individuals who are unlikely to speak about their problems intimately with a professional or others.

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23.1 Introduction

Globally every year there are nearly 800,000 deaths due to suicide – roughly one every 40 s (Bertolote et al. 2009; World Health Organization 2014) and approximately 63,000 of these suicides are committed by Europeans within the 27 EU member states (Eurostat: EUROSTAT 2009). This makes suicide one of the leading causes of death worldwide and the second leading cause of death amongst people aged below 25 (World Health Organization 2014). Mental ill health is the main underlying cause of these unnecessary deaths, making it one of the biggest public health problems in Europe (Wasserman and Wasserman 2009).

Mental health promotion is a central aspect of reducing overall suicide rates and mental ill health, but the impact of different approaches to such promotion is likely to depend very much on how interventions are implemented and disseminated, and not only what content information and/or other types of help it offers. The Internet has since long been used to reach out to large populations. In June of 2015 there were 3.3 billion Internet users worldwide (Internet World Stats). In a random sample of over 3,000 American adults, 58 % of the Internet users reported searching for health-related information for themselves (Atkinson et al. 2009). If this figure is representative of the rest of the globe, there are around 1.9 billion Internet users that search for health-related information. It is becoming easier and more cost-effective to spread information online, and the Internet is also becoming increasingly available through TV, tablets, smartphones and even watches. Several suicide preventive and mental health promoting websites have been launched and evaluated with encouraging results (Gilat and Shahar 2009; Mishara and Kanderkhof 2013). However, in order to assess whether a web-based intervention has practical significance for public health, it might not be enough to assess whether that intervention has statistical significance in terms of effectiveness in an experimental setting, as even an intervention with a high statistical effect size will be of little practical use if those who need it cannot find it.

Since there is good reason to believe that the Internet and other media sources can be used as effective tools for disseminating suicide-preventive interventions and improving their mental health, the question on how to best use these tools should be considered an important one. Answering this question should involve assessing the effects of the intervention content, as well as identifying ways to promote the public's use of it.

23.2 The SUPREME Project

Suicide Prevention by Internet and Media-Based Mental Health Promotion (SUPREME) is a mental health promotion programme, which comprises a multi-language, culturally adapted, highly interactive website accessible to the general public that is particularly aimed at adolescents. The general objective of the programme is to enhance and improve the mental health and well-being of European

adolescents through an Internet-based mental health promotion and suicide-preventive intervention. The project started in 2011 and had a duration of 3 years. The National Centre for Suicide Research and Prevention of Mental Ill-Health (NASP) at Karolinska Institutet is the leading centre. Associated partners are based in Italy, England, Spain, Lithuania, Estonia and Hungary. The project was co-funded by the Health Programme of the European Commission.

The contents of the web-based intervention developed in SUPREME project were based on scientific evidence gathered from literature reviews and other systematically collected expert recommendations. Information from focus groups interviews was used to aid in the design and structure of the website. The intervention comprised a highly interactive website targeted at adolescents and young adults in the age group 14–24. The website offered users access to interactive services such as a real-time chat communication and a discussion forum moderated by mental health professionals, as well as written information addressing various mental health problems. The written content aimed to raise knowledge and awareness about mental health and suicide, to combat stigma and to stimulate helping and help-seeking behaviours. The effectiveness of the intervention website was tested in a randomised, single-blind, minimal treatment-controlled, parallel, multi-centre trial conducted in all SUPREME consortium member countries. The study was approved by local ethics committees in all participating countries and was registered in ISRCTN Current Controlled Trials (trial registration number: ISRCTN65120704). Pupils, 14–18 years old, were recruited from public schools in each country, resulting in a total sample of 2286 consenting participants. Schools were randomised into a full intervention or to a control condition. The full intervention participants were given unrestricted access to the online intervention, in combination with a minimal intervention comprising a leaflet with contact information to mental healthcare facilities and resources (such as helplines) accessible to the public from the participants' area of residence. Control subjects only received the minimal intervention. It was optional for participants in the intervention condition to visit and use the intervention website. Subjects participated in three waves of data collection that took place during school-based sessions carried out at baseline, 2 and 4 months follow-up. Demographic data, Internet habits, risk and help-seeking behaviours, mental health indicators (depression, anxiety and stress), suicidal thoughts and behaviours were collected by means of an extensive evaluation questionnaire.

23.3 Ethical Issues

For ethical reasons – mainly to ensure the possibility of identifying suicidal pupils by means of the evaluation questionnaire – study participation was not anonymous. Instead, participant's identities were encrypted using randomly assigned participant IDs. A specific procedure was used to evaluate and immediately assist participants with high risk of suicide. Emergency cases were identified by means of two specific items in the evaluation questionnaire. Pupils were considered emergency cases if

they responded "Yes, during the past 2 weeks" to the item "Have you tried to take your own life?" and/or if they responded above the cut-off on a 1–7 Likert scale (ranging from "Never" to "Always") to the question "During the past two weeks, have you reached the point where you seriously considered taking your life or perhaps made plans how you would go about doing it?"

Adolescents have been included in the study only if consent was obtained from their parents and assent from the pupils themselves. Ethical permission for the project was obtained in each participating country by the respective Research Ethics Committees.

23.4 Content of the Online Intervention

23.4.1 Focus Groups

The design and content of the intervention website were based on anonymous focus group interviews made with two groups of adolescents who were given a brief description of the SUPREME project. The purpose of the interviews was to understand which online platforms the adolescents used and how the intervention website could be promoted to reach the largest number of young people. The first group consisted of nine healthy pupils recruited from a Swedish school, the second a group of nine inpatients from a psychiatric clinic in Hungary. The mean age in both groups was 17. The low number of participants allowed for an open discussion. A semi-structured interview protocol with open-ended questions was used for all interviews.

The general outline and content of the intervention website was generally the same from both groups. Professional and factual content was favoured. Frequently asked questions (FAQ) and forum modules were also agreed upon. Both groups preferred some contact with a mental health professional, either through a designated hotline or an "instant chat". Both groups independently agreed that the search items they were most interested in looking at online were common stress symptoms, eating disorders, anxiety and common ailments such as physical pain, headaches and depression. Both groups agreed that some of their friends had been "low" or depressed. They agreed that the website ought to have a serious and professional tone and layout, without being "childish", "dumbed down" or patronising. The information presented should be simple and understandable, yet objective and factual. A marked difference between the two groups was that the adolescents from the psychiatric clinic wanted to read real-life accounts and interviews with young people who were suffering from mental ill health (and especially those that have recovered). They felt that it would help combat stigma surrounding the topic and would benefit people looking for support and advice. The second focus group of "healthy" students randomly selected in the general population favoured more factual and objective information. The choice of terminology was also an important issue: the

adolescents did not like the wording “mental ill health”, “illness”, “disease” or “committing suicide”, perceiving these terms as too serious and stigmatised. They preferred “stress”, “worry” or “problems”. The adolescents from the psychiatric unit, but not the healthy group, also thought that it was preferable to have the text edited by teenagers before it was launched.

Adolescents generally disliked websites where they had to register their personal details especially when researching health-related information. Google was the most commonly used search engine by all participants in the focus groups. Facebook and “email host” advertisements were acknowledged by both groups as influencing which sites they visited. The students felt that although teachers organised groups to discuss student stress, they did not really understand the pressures students were under. A website that was not patronising but showed some empathy for their situation was therefore preferred. If a teacher were to recommend a website, the impact that this would have on them would depend on which teacher was recommending it and whether or not he/she had bothered to look at it first.

23.4.2 Overall Structure of the Website

The website contains both static and interactive components. Different components of the website are attempts to change unhealthy behaviours, increase mental health knowledge and changing attitudes/stigma associated with mental ill health and suicide. Other components aim to reduce mental ill health and suicidality by encouraging users to employ coping strategies, offering real-time online consultations from mental health professionals and a discussion forum. The website contents have been translated and adapted to each country/culture and online usage. The website was publicly open, but visitors were required to create an anonymous user account in order to access its interactive modules.

23.4.3 Information Articles

Different mental health problems (depression, anxiety, eating disorders, substance misuse, Internet addiction and violent behaviours/bullying) are addressed in information articles specifically created for the intervention website. The terminology and language in these articles were carefully adapted according to the recommendations from the focus group interviews (e.g. “sadness” instead of “depression”). In these articles, the nature of the “condition” is first explained in terms of possible (biological, psychological, behavioural, etc.) causes and symptoms. Secondly, prevention techniques and self-help advice are given where appropriate and possible treatments that local healthcare services can offer are described. Contact information to such services is compiled in a separate section of the website.

23.4.4 Mental Health Awareness Module

The website also includes a second section of static information, which is based on the contents of the Youth Aware of Mental health (YAM) Programme designed to promote knowledge of mental health, healthy lifestyles and behaviours amongst adolescents. The YAM programme was developed by researchers the National Centre for Suicide Research and Prevention of Mental Ill-Health (NASP), Karolinska Institutet, Sweden, and from Columbia University, New York. YAM was found to be effective in reducing incident suicide attempts and severe suicidal ideation in a large multi-centre randomised controlled trial (RCT) (Wasserman et al. 2015). The module covers six specific topics concerning: (1) awareness of mental health, (2) self-help advice, (3) stress and crisis, (4) depression and suicidal thoughts, (5) helping a troubled friend and (6) getting advice – who to contact with telephone numbers and email addresses to local healthcare facilities (Wasserman et al. 2012). The booklet thus contains information both similar and complementary to the aforementioned articles, also including information and advice on sleeping and eating disorders, loneliness, communicating feelings, bullying, difficulties in school, exercise and substance misuse.

23.4.5 Mental Health Monitor Module (Self-Assessment)

In the so-called "self-assessment" module on the website, users may choose to fill out a short questionnaire related to their mental health. The questionnaire is based on the WHO-5 Well-Being Index Scale (World Health Organization), in which five statements that indicate general well-being are rated on a scale from 0 to 5 as to how much it applies to oneself. After completing the questionnaire, score-relevant information is immediately displayed to the user, describing the results and making suggestions for action when necessary.

23.4.6 Chat Module

The web-based chat module is the most interactive module on the intervention website. It provides an opportunity for users to establish a direct text-based communication with a mental health professional associated with the respective SUPREME centre. The primary purpose of the chat is to act as an anonymous hotline for young people who are in need of help but may also be used for more general questions. The chat module is available for about 2–4 h a day, Monday to Friday in the afternoon and evening, when adolescents are more likely to have privacy and access to a computer. Each chat session must be booked in advance through a dedicated online booking system.

23.4.7 Idea-Box with Professional Feedback

This platform is aimed at involving young people in mental health promotion. Users can submit ideas they have regarding mental health promotion projects or actions,

e.g. how to improve the healthcare in their schools. These ideas are reviewed by the centre which then provides feedback and assists these active adolescents in bringing their ideas to life if possible. Anonymity is optional and other users are able to post comments to each other's ideas.

23.4.8 Mental Health Forum

This online discussion forum is aimed at generating discussions about mental health, sharing experiences, feelings, advice and learning from professionals. The forum is moderated by mental health professionals who also participate in discussions when asked or when necessary.

23.4.9 Reasons for Living Module

The purpose of this module is twofold. One is for users to post a brief message with a "reason for living" (any source of happiness, interest, enjoyment, etc.) that is displayed to everyone on the front page of the website. The module is also designed to disseminate the intervention website and to increase its salience on the Internet. After submitting a "reason for living", the user is rewarded a virtual "SUPREME book badge" which is sent to their email. The badge is the website's logo picture with an embedded link to it and, when clicked, redirects to the intervention website. The badge can be attached to emails, personal websites, blogs and social networking sites, testifying that the owner of the badge supports mental health promotion.

23.5 Main Results of the SUPREME Project

23.5.1 Cross-Sectional Findings

Mental health problems were more frequent among females (all measures had p-values < 0.001); the prevalence of severe to extremely severe depression, anxiety and stress was 12 %, 15 % and 9 %, respectively, compared to 5 %, 8 % and 3 % in males. About 4–5 % of the adolescents reported that they, within the past 2 weeks before baseline, consistently had felt that life was not worth living and 1 % of males and 2 % of females had seriously considered a suicide attempt. 3 % of males and 10 % of female respondents reported that they had committed a suicide attempt at one point in their lives. 90% of the subjects used the Internet on a daily basis. Most frequent activities were as follows: social networking, communication and school work. Females reported being involved in these activities more than males ($p < 0.001$). Interestingly, performing targeted searches (e.g. on Google) was particularly associated with depression, anxiety and stress in both males and females (r's ranging between 0.10 and 0.18, p-values < 0.01). A positive correlation between the intensity of Internet use and scores on depression,

anxiety, stress and suicidal thoughts/ideation was found ($r = 0.08$, 0.09, 0.07, 0.12, respectively, for males and 0.2, 0.11, 0.14, 0.13 for females). Participants who reported more negative outcomes (e.g. sleep loss, moodiness) of the Internet activities that they commonly engage in had also a significantly higher average score on depression (males: $r = 0.28$; females: $r = 0.36$), anxiety (males: $r = 0.28$; females: $r = 0.32$), stress (males: $r = 0.27$; females: $r = 0.37$) and suicidal thoughts (males: $r = 0.09$; females: $r = 0.22$).

23.5.2 Longitudinal Findings

A statistically significant decline in nearly all mental health-related outcomes, such as depression, anxiety and stress, suicidal thoughts and ideation was observed in the total sample (all p-values < 0.01 or < 0.001). The decline was continuously shown after the second and third wave of data collection. This positive trend was generally stronger amongst participants in the intervention arm compared to controls; however, the interaction effects between study arms did not reach statistical significance. It is possible that this is attributable to the observed, unexpectedly strong, effect of the minimal intervention performed in all study arms.

23.6 Impact and Recommendations

Internet-based interventions have, if properly executed, great potential of making mental health-promoting activities and services more salient, available and affordable to people regardless of socio-economic status. As indicated by the data collected in this project, the vast majority of European adolescents spend considerable time on the Internet every day. This provides an opportunity to offer mental health promotion even to those individuals who are unlikely to speak about their problems intimately with a professional or others. Keeping the intervention website online is one way of ceasing that opportunity. Further, the project outcomes indicate that this method indeed has a positive effect, and this knowledge is essential to encourage stakeholders and economic and political decision-makers to implement and evaluate similar services in the future.

The main recommendations arising from the implementation of the SUPREME project are detailed in the guidelines for Internet- and media-based mental health promotion (reference to link for download) and can be summarised as follows:

- It is suggested that mental health professionals collaborate with the media and other intermediaries, so the media (owners and journalists) strictly observe the media guidelines agreed by their professional organisations. One of the most important factors that appear to influence the usefulness of guidelines is media participation in their development.
- A mental health promotion website for young people from different backgrounds, gender and sexual orientation should involve adolescents in all stages of the website development, from concept to dissemination.

- An online mental health service for young people should present information through both inactive and interactive formats and should use online tools that are popular amongst adolescents.
- It may be useful for an online youth mental health service to provide help and support to users around the clock. Any interactive service, however, should be actively moderated to ensure safety of users. A balance between available resources and availability of the system should be sought.
- Online youth mental health and suicide prevention services should create a strong presence on online websites that are popular young people. Promotion should especially occur on websites that are popular amongst females and males, respectively. For young females, marketing may occur on social networking sites. Young men are more easily targeted at popular gaming, entertainment and social community websites.
- The website needs to be evaluated on a regular basis to continually improve its effectiveness and remain evidence based.

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Antidepressants and Suicide Risk: A Challenge

24

Maurizio Pompili, Gloria Giordano, and Dorian A. Lamis

Abstract

The topic of whether antidepressant drugs increase or decrease the risk of various aspects of "suicidality" is still controversial, especially among patients with a mood disorder diagnosis. Recent data has shown a possible increase in risk of suicidal behavior among children and adolescents treated with selective serotonin reuptake inhibitors (SSRIs). In 2004, the Food and Drug Administration (FDA) established that antidepressant drugs should display a black box on their label, with warning information about the elevated risk of suicidal behavior in individuals aged 18–24 years. Research on the relationship between pharmacotherapy and suicidal behavior was virtually nonexistent until a decade ago. Since then, several studies have demonstrated that antidepressants reduce suicide risk among psychiatric patients, whereas others have found an increase in suicide risk during antidepressant treatment. Close monitoring is critical, and prudent follow-up care should be provided for patients prescribed with antidepressants.

24.1 Introduction

Current research in suicidology points to a broader view of suicide, rather than confining it to a given diagnosis or mood disorder as commonly reported (Turecki et al. 2012). Even when dealing with a pharmacological approach to suicide prevention, the clinician should first deal with how to manage the pain and negative emotions – shame, guilt, abandonment, ennui, dysphoria, hopelessness, and inanition – what Shneidman

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(1993) calls psychache. Viewing suicidal impulses (thoughts and actions) phenomenologically can provide a proper view of suicide risk in a unique individual (Pompili 2010). Although literature considers that many cases of suicide (81–95 %) in the general population involve psychiatric illnesses, with mood disorders contributing to nearly half of suicide deaths (Roy 2000), there are however several of more variables involved when considering the precipitation of suicide. Nevertheless, risk factors for suicide include the presence of a major mood disorder with hopelessness, in particular when co-occurring with alcohol or substance abuse (APA 2003; Roy 2000; Tondo et al. 2003). Risk is especially high among youth, impulsive-aggressive individuals, and older (≥65) unmarried men (APA 2003). It has been well established that the risk of suicide death is higher among men than women (20.6 % versus 5.5 %), confirming the greater lethality of suicide methods in men (Drapeau and McIntosh 2014). Suicide rates are also very high among patients with anxiety disorders (Harris and Barraclough 1998; Khan et al. 2002). Suicidal behavior may often be associated with severe anxiety; however, it is unclear whether or not antianxiety medications reduce suicidal risk among these patients (Khan et al. 2002). The risk of dying by suicide among patients with bipolar disorder is nearly 10 % (Baldessarini et al. 2004), and this rate seems to remain high even with the introduction of several new pharmacological treatments. More than one-third of suicide attempts occur within the first year of illness onset, whereas more than half occur within the first 5 years of illness. Approximately 75 % of the severe and unsolved morbidity among bipolar patients is due to depression (Baldessarini et al. 2004; Post et al. 2003). This may explain the widespread use of antidepressants (ADs) in patients with bipolar disorder, although researchers (e.g., Akiskal et al. 2005; Maj et al. 2006) have reported that the use of ADs might increase suicidal risk in some patients with dysphoric-mixed-agitated or psychotic states.

The use of ADs has increased considerably since the introduction of selective serotonin reuptake inhibitors (SSRIs) in the 1990s, mainly due to better recognition, treatment, and prescribing with regard to depression. Moreover, although lethal overdoses of SSRIs are rare, the role of ADs in terms of decreasing rates of suicide and benefits in patients with a high suicidal risk remains unclear. Research regarding the effects of treatments on suicidal risk has garnered increased interest in recent years; however, evidence that most modern psychiatric treatments reduce long-term suicide risk is limited (APA 2003; Oquendo et al. 2005).

In order to examine the literature on suicide risk during AD treatment, we conducted a careful MEDLINE, Excerpta Medica, PsycLIT and PsycINFO, and Index Medicus search to identify articles and book chapters focused on this issue, selecting only English articles published from 1960 to 2014 which addressed ADs and suicide risk.

24.2 Suicide Risk and Antidepressant Treatment

An important research question of interest is whether or not ADs should be prescribed to patients with a high suicide risk. In particular, it is important to understand the role played by SSRIs in the potential worsening of suicidal thoughts in

vulnerable patients (Moller et al. 2008). It is still controversial whether AD drugs increase or decrease the risk of various aspects of suicidality, especially among patients with a mood disorder diagnosis (Baldessarini et al. 2006).

In a systematic review, Fergusson et al. (2005) compared randomized controlled trials (RCTs) using SSRIs and RCTs employing placebo or additional active treatments. The researchers found that participants exposed to SSRIs had almost twice the odds of fatal and nonfatal suicidal acts. There was no increase in risk when only suicide deaths were included. In another systematic review, Gunnell et al. (2005) compared studies in which adults with depression and other clinical conditions were treated with SSRIs or placebo. The authors found that there was only weak evidence of nonfatal self-harm and no increase in the risk of death by suicide. In a meta-analysis conducted by Stone et al. (2009), 372 randomized placebo-controlled trials of ADs have been examined, including a total of 100,000 patients. The authors observed that the risk of suicidal behavior was strongly related to age. Specifically, the use of ADs increased suicidal risk in young patients (age 25 or younger), while it reduced it among elderly subjects (aged 65 or older). The suicide risk of individuals aged between 25 and 64 years was not influenced, although it showed a reduction when suicidal ideation and behavior were considered together.

Many data are obtained from large cohort studies of depressed patients in general clinical practice or health maintenance organization data sources with large case-control comparison groups differing in exposure to various ADs. Seventeen reports (Angst et al. 2005; Barak and Aizenberg 2006; Bauer et al. 2006; Didham et al. 2005; Jick et al. 1995, 2004; Juurlink et al. 2006; Leon et al. 1999; Martinez et al. 2005; Olfson et al. 2006; Oquendo et al. 2002; Simon et al. 2006; Sondergard et al. 2006a, b; Tiihonen et al. 2006; Warshaw and Keller 1996; Yerevanian et al. 2004) included over one million depressed patients. These studies found no definitive results. Eleven studies were designed to compare the suicide risk of patients using SSRIs with respect to other drugs or placebo. Nine of these 11 studies did not demonstrate an increased risk of suicide associated with AD treatment. Among the remaining six studies, four demonstrated a decrease or no difference in suicidal risk with AD drugs. Olfson et al. (2006) and Sondergard et al. (2006a) found a small increase in suicide risk among adolescents using SSRIs, whereas Juurlink et al. (2006) found a larger increase in suicidality among elderly patients in AD treatment. Tiihonen et al. (2006) demonstrated that AD treatment contributed to a decrease in suicide deaths but an increase in attempts. Reeves and Ladner (2010) found that an increase in suicide risk in AD treatment is an uncommon but legitimate occurrence.

There have been numerous RCTs that have examined the effects of many new ADs compared to older standard drugs and placebo (Acharya et al. 2006; Baldessarini et al. 2006; Fergusson et al. 2005; Gunnell et al. 2005; Hammad et al. 2006a; Khan et al. 2000, 2003; Laughren and Levin 2006; Storosum et al. 2001; Tollefson et al. 1994). The majority of these studies showed only negligible differences in the rates of suicidal acts among patients treated with SSRIs, other ADs, and placebo, although the higher suicidal risk was associated with AD use. Only Fergusson et al. (2005) found a higher rate of suicidal acts during SSRI treatment. In 2007, a FDA review

examined all of the results from 386 RCTs evaluating the use of new AD drugs in a total sample of 112,875 patients with major depressive disorder and other psychiatric illnesses. The most identified aspect of suicidal behavior was suicidal ideation. The suicide death (0.013 %) and attempt (0.198 %) rates were very low and may be due to the brief exposure time to drugs (only 2 months). The suicide rate among adult patients with a diagnosis of major depressive disorder exposed to AD drugs for 8 weeks was 77/100,000/year, which is approximately six times above the general population (13/100,000/year) (WHO 2010). Analogous RCTs (Acharya et al. 2006; Khan et al. 2000, 2003) reported a suicide rate of 862/100,000/year. Stratifying by age group, the results showed that the suicide risk, largely "suicidal ideation," increased among younger patients treated with SSRIs versus placebo, whereas AD drugs seemed to be protective among elderly individuals.

The association between AD drugs and suicide rates differs among various countries. For example, Barbui et al. (1999) investigated the changes in AD consumption in Italy from 1988 to 1994, exploring whether the introduction of SSRIs may be connected to a reduction in suicide rates. The authors found that in the period in which prescriptions for SSRIs increased, male suicide rates increased from 9.8 to 10.2 per 100,000 inhabitants, whereas female suicide rates declined from 3.9 to 3.2 per 100,000 inhabitants. They deduced that, in Italy, there was not an important modification of suicide rates after the introduction of SSRIs. In Sweden, Carlsten and colleagues (2001) examined suicide rates in two different periods, from 1977 to 1979 and from 1995 to 1997. They found that, in concurrence with an increase prescribing of ADs (especially in the 1993–1996 period), suicide rates decreased by 30.9 % among men and by 34.0 % among women, during both census periods. The statistically significant reduction in suicidal behavior in Sweden may be only partially explained by the introduction of SSRIs, because the declining suicide trend started years before these drugs were introduced.

Isacsson (2000) showed a parallel decreasing suicide rate of 19 % with an increase in AD prescriptions in Norway, Sweden, Denmark, and Finland. In Hungary, Rihmer and colleagues (2000, 2001, 2003) demonstrated a decrease in suicide rates from 45.9 per 100,000 inhabitants in 1984 to 32.1 per 100,000 inhabitants in 1998. In the same period, there was an important implementation of the Hungarian sanitary system and AD drug prescriptions, especially SSRIs, which increased fivefold from 1984 to 1998. During the same period, there was also an increase in unemployment, alcoholism, and divorce rates. The authors suggested that several various factors contribute to suicidality, and thus, the direct association between AD use and reduced suicide rates cannot be easily demonstrated.

Grunebaum et al. (2004) found that, from 1985 to 1999 in the United States, there was an association between the increased use of non-tricyclic ADs and the decreased national suicide rates. However, some scholars (e.g., Levi et al. 2003) suggest that the suicide rates in the United States were already declining before 1985, especially among women. Gibbons et al. (2005) showed that, in the United States, the use of new generation of ADs (non-SSRIs, e.g., nefazodone, venlafaxine, mirtazapine, bupropion) was related to a decrease in national suicide rates. Moreover, in the United Kingdom, Davis et al. (2010) demonstrated that it is possible to

prescribe venlafaxine to patients with a high suicide risk only if an adequate follow-up is realized. Morgan and colleagues (2004) found that the increased use of ADs in England was accompanied by a decrease in suicide rates. In Austria, Kasper et al. (2010) showed that mirtazapine was correlated with a lower risk of suicide compared to placebo. Hall et al. (2003) demonstrated that in Australia, between 1991 and 2000, the number of suicides decreased in elderly men and women, whereas suicide deaths increased among young men. AD prescriptions were higher for women than men in all age groups and increased for both genders, especially among elderly individuals. The authors confirmed a significant correlation between increased consumption of ADs and decreased rates of suicide among women, but not among men, although within both genders, the groups with the largest decline in suicide rates were among those most exposed to ADs. In Israel, use of SSRIs increased 2.6-fold between 1998 and 2002, and Barak et al. (2006) demonstrated a significant decrease in suicide rates only among elderly men.

Unfortunately, the aforementioned studies were not without limitations. The data failed to support the expected reduction in suicide rates during all AD treatments, suggesting that the risk of suicide attempts and deaths may be greater during treatment with some AD drugs. However, although several studies found a large decrease in ratings of suicidal ideation among depressed patients treated with ADs compared to placebo, these RCTs showed subjective results, often incidental and based on post hoc assessment of individual items on standard depression symptom rating scales (e.g., Montgomery-Asberg item 10 and Hamilton item 3). It should also be noted that the relatively short duration of follow-up in many RCTs for acute depression fails to adequately examine the long-term side effects, including suicidal behavior.

Moreover, data from several studies are compromised by the biased risk of morbidity or indication. Typically, pharmacological treatment is more likely to be provided to more severely ill patients with high suicide risk, and, often, the clinicians select the drug with the lowest risk of toxic effects in case of overdose (SSRIs versus tricyclic ADs). Finally, the non-randomized clinically selected treatment in many studies may alter the associations between an increased suicide risk and AD treatment. Close monitoring is critical, and prudent follow-up care should be provided for patients prescribed with antidepressants.

24.3 Children and Adolescents

Several results from pediatric trials on paroxetine have suggested that AD drugs may increase the risk of suicidal ideation and attempts among children and adolescents. The FDA evaluated all of these data and presented them to a joint meeting of two FDA advisory committees in 2004 (Hammad et al. 2006b). It was demonstrated that the treatment with ADs, compared to placebo, contributed to a relative increase in suicidal ideation of 1.95 (95 % confidence interval 1.28–2.98). Accordingly, the FDA established that ADs should display a black box on their label, with warning information about the increasing risk of suicidal behavior in individuals aged

18–24 years (Barbui et al. 2008; FDA 2004; Leon 2007). The warning was extended in 2007 to ADs prescribed to adults aged 25 and under. Laughren and Levin (2006) observed that the RCTs included by the FDA were not designed to determine lethal suicidality, given that they included various outcomes such as suicidal thoughts, preparatory acts, and suicide attempts as well as suicide deaths. In fact, among all suicidal events that were examined, less than 30 % were serious suicide attempts or deaths. In addition, in many of the studies, suicidality was self-reported, rather than observed by others. It is possible to speculate that AD drugs, especially among younger patients, may enhance communication about suicidality and promote open thoughts and behaviors.

Among the authors that supported the decision of the FDA to include the black warning box on the label of ADs, Schneeweiss and colleagues (2010) conducted a 9-year cohort study on 20,906 children that started an AD treatment. The authors found that 266 children attempted suicide and 3 died by suicide, with no significant variation in the rates when comparing different SSRIs. In the same year, the authors conducted another important cohort study on 287,543 adults aged 18 years and older that used ADs. Results demonstrated that most suicidal events occurred in the first 6 months after starting the treatment, and there were no clinical differences in suicide risk among various ADs.

Regulatory authorities had approved worldwide warnings about the use of ADs in children and adolescents. The European Medicines Agency (EMEA) had decided that SSRIs and selective norepinephrine reuptake inhibitors (SNRIs) should not be prescribed to children and adolescents under 18 years old. The Committee on Safety of Medicines in the United Kingdom (MHRA 2004) had confirmed the uncertain safety of ADs in pediatric populations, especially of SSRIs, such as paroxetine, citalopram, sertraline, venlafaxine, escitalopram, and mirtazapine. In 2009, Barbui et al. demonstrated that the use of SSRIs increased the risk of attempted suicide and suicide death among adolescents, while it decreased it among adults. It seemed that the use of SSRIs appeared to have a protective effect in people aged 65 years or more. It was also demonstrated that SSRI treatment had an important protective effect against depression in all subjects.

In their simultaneous studies, Olfson et al. (2006) and Tiihonen et al. (2006) showed that paroxetine and venlafaxine were significantly associated with a higher risk of suicide among adolescents. It is important to note that it is difficult for observational studies to adjust for baseline differences, which often biases results. Furthermore, SSRI treatment is reserved for the most severe cases among adolescents, so it may be possible that the high suicide rate in these individuals may be due to the higher severity of psychiatric disorder. In contrast, SSRIs are often prescribed among adults for every level of depression severity, so the confounding factors may be less important.

In a recent study, Lu et al. (2014) assessed changes in outcomes after the FDA warnings in 2004. The study cohorts included adolescents (around 1.1 million), young adults (around 1.4 million), and adults (around 5 million). The authors demonstrated that trends in AD use and poisonings changed abruptly following the warnings. In the second year after the warnings, relative changes in AD use

were −31.0 % (95 % confidence interval −33.0 to −29.0 %) among adolescents, −24.3 % (−25.4 to −23.2 %) among young adults, and −14.5 % (−16.0 to −12.9 %) among adults. These reflected absolute reductions of 696, 1216, and 1621 dispensings per 100,000 people among adolescents, young adults, and adults, respectively. Simultaneously, there were significant, relative increases in psychotropic drug poisonings in adolescents (21.7 %, 95 % confidence interval 4.9–38.5 %) and young adults (33.7 %, 26.9–40.4 %), but not among adults (5.2 %, −6.5 to 16.9 %). These reflected absolute increases of 2 and 4 poisonings per 100,000 adolescents and young adults, respectively (approximately 77 additional poisonings in our cohort of 2.5 million young people). Suicide deaths did not change for any age group. The authors concluded that "safety warnings about ADs and widespread media coverage decreased AD use, and there were simultaneous increases in suicide attempts among young people. It is essential to monitor and reduce possible unintended consequences of FDA warnings and media reporting."

Barber et al. (2014) argued against the theories proposed by Lu and colleagues, citing the various limitations in their study. The authors suggested that the measure that Lu et al. used as a proxy of suicide attempts (i.e., poisonings by psychotropic medications) was faulty and that, after the FDA warnings, more direct measures of attempts and deaths showed no increase in the overall balance.

In 2009, Bailly found that, compared to placebo, SSRIs are effective in the treatment of pediatric cases of affective disorder and not related to an increase in suicidal ideation and behavior. On the contrary, according to the author, SSRIs are also associated with a significant decrease in suicide rates among children and adolescents, possibly for their efficacy, the compliance of patients, and the low toxicity in overdose.

Recently, Cooper and colleagues (2014) conducted a retrospective cohort study that included 36,842 children from 6 to 18 years who recently initiated with fluoxetine, sertraline, paroxetine, citalopram, escitalopram, or venlafaxine. The results showed that 419 subjects had a suicide attempt and 4 patients died by suicide. The adjusted rate of suicide attempts did not differ significantly among users of SSRI and SNRI ADs compared to users of fluoxetine. Patients treated with multiple ADs concomitantly had an increased risk of suicide attempt. The authors concluded that they were not able to find evidence of increased risk for SSRI or SNRI ADs compared to fluoxetine for new users of ADs in their sample. Moreover, this study was not designed to identify risk of suicide attempts for AD users compared to nonusers.

The possible association among AD treatment and suicidal behavior among children and adolescents still remains unclear. The increase in suicide risk among young people, compared to adults, is weak but consistent in many studies, although epidemiological studies do not show a relationship between AD treatment and the suicide death rate (Masi et al. 2010). Further research is needed to better understand the long-term efficacy and safety of ADs among children and adolescents and when ADs are prescribed; close monitoring for the possibility of increased suicide risk is suggested for these patients.

24.4 Management of Suicide Risk during Antidepressant Treatment

It is still unclear why ADs may have no effect on suicidal risk or, otherwise, increase it. It has been suggested that ADs may have limitations of clinical effectiveness in some individuals, especially younger patients, or some aspects of depressive symptoms may be particularly pertinent to suicidal risk. It is also possible that ADs may present both beneficial and adverse effects, with a null impact on suicide. Finally, it must be considered that several available studies have many limitations. Matthews and Fava (2000) suggested that there is a particular and delicate period during pharmacological treatment with ADs, characterized by the relatively earlier energizing effects of ADs and the contemporary persistent anhedonic features of depression. This phase may present an increased suicide risk. Regarding the adverse effects of ADs, it has been suggested that some individuals, especially younger patients, experienced an "activation syndrome," contributing to an increase in suicidal acts. There are several clinical observations that confirmed the newly emerging aggressive and suicidal behaviors among patients treated with ADs. It is not yet understood if these reactions may be more frequent with SSRIs or tricyclic antidepressants. Many researchers have shown that AD treatment is associated, in some cases, with overstimulation, restlessness similar to akathisia, agitation, insomnia, severe anxiety, mixed-dysphoric bipolar states, and psychosis (Baldessarini and Willmuth 1968; Healy and Whitaker 2003; Teicher et al. 1993). Pompili et al. (2005) have proposed a host of warning signs to consider for emerging suicidality during an AD treatment:

- Previous suicide attempts
- Suspected bipolarity
- Recurrent depression
- Suspected psychotic disorder
- Juvenile depression
- Agitation, akathisia, and anxiety
- Insomnia
- Dysphoria
- Anger and aggression
- Mixed states
- Worsening of depression and hopelessness
- Social isolation
- New somatic symptoms
- Abuse of alcohol
- Access to firearms or drugs
- Inadequate clinical supervision and follow-up

These responses, often emerging early during AD treatment, require a close clinical follow-up in order to effectively assess suicide risk. When risk is high, treatment should be properly modified, changing AD medications; decreasing or

suspending ADs; adding sedatives, antipsychotics, or mood stabilizers; considering lithium in compliant patients; and supplying additional individual support. The clinician should also express explicit concern for patient's growing discomfort and despair, enlist the help of a family member to monitor the patient and dispense drugs, monitor for access to lethal means, and emphasize the availability for extra routine visits or calls and also in emergency.

Conclusions

Several studies have demonstrated that ADs reduce suicide risk among psychiatric patients, whereas others have found an increase in suicide risk during ADs treatment. According to many studies, younger patients may show an increase in suicide risk when treated with ADs. More research is needed in order to better understand the role of ADs in suicide ideation, attempts, and deaths and to provide patients with better clinical care.

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Lithium: The Key Antisuicide Agent

25

Clinical Evidence and Potential Mechanisms

Frank Bellivier and Sebastien Guillaume

Abstract

Since the early 1970s, extensive clinical evidence supports that lithium is effective in reducing the risk of both attempted and completed suicide in patients suffering from mood disorders. This effect appears to be independent of its mood stabilizer efficiency. This antisuicidal effect is specific to lithium compared with other medications. Despite its clinical effectiveness, the mechanisms by which lithium exerts antisuicidal effects are poorly understood. Several pathways and endophenotypes involved in suicide vulnerability might be improved by a long-term treatment by lithium. This might include a reduction of inflammatory cascade, a restoration of abnormal circadian rhythms, or an action on neuropsychological trait such as decision-making or impulsivity.

Lithium was the first pharmacological agent that was proven to be effective as a mood stabilizer in the treatment of bipolar disorder. Lithium is a prototypical mood stabilizer as it has robust efficacy in the treatment and prevention of both depressive and manic phases of bipolar disorder. Lithium is also prescribed as an adjunct medication for treatment-resistant depression patients. In addition to these therapeutic

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uses, since the early 1970s, there is increasing evidence suggesting lithium efficacy to reduce the risk of suicide. We will first review these available evidences and discuss through which mechanisms and mediating factors lithium exerts its antisuicidal effects.

25.1 Lithium and Suicide: Epidemiological and Clinical Evidences

Lithium, as a natural trace element, is eluded from rock and soil and accumulates in groundwater. These natural doses are significantly lower than those used in therapeutic treatment, but several studies have considered the effect on these natural doses on lithium on suicidal behavior. The first ecological study on the association of lithium in drinking water and suicide rates came from Texas, USA. This study was based on aggregated data from 27 counties grouped into low-, medium-, and high-lithium counties and statistically tested to explore relationships between lithium and crime, suicide, within each of the three groups. Authors found that the incidence rates of suicide, homicide, and rape were significantly higher in counties whose drinking water supplies contain little or no lithium than in counties with water lithium levels ranging from 70 to 170 I~g/L (Schrauzer and Shrestha 1990). Concerning suicidal behavior, these results have been confirmed in nine consecutive studies from six different countries all over the world (see Vita et al. 2015 for review). These results remained significant after sensitivity analyses and adjustment for socioeconomic factors.

Besides these studies suggesting that higher level of lithium may be associated with reduced risk of suicide in general population, extensive clinical evidence supports that lithium is effective in reducing the risk of both attempted and completed suicide in patients suffering from mood disorders. Thus, Cipriani et al. (2013) performed a meta-analysis including more than 6600 patients suffering from major affective disorders. It indicates that lithium drastically reduces the number of suicides (odds ratio 0.13, 95 % confidence interval 0.03–0.66) in comparison with placebo. The more lithium prescription is extended, the more antisuicide effect is marked. In acute phases, antisuicide effect seems weak, but a prescription on long term (more than 18 months) would reduce by 80 % suicidal events and would decrease the lethality in case of acting out. The number needed to treat to prevent an act of suicide is 22.6 (Baldessarini et al. 2006; Baldessarini and Tondo 2008). In addition, discontinuation of lithium treatment appears to be associated with a recurrence of suicidal behavior (Müller-Oerlinghausen et al. 1992; Bocchetta et al. 1998; Oquendo et al. 2011). However, the optimal lithium dosage is still a matter of debate. A randomized placebo-controlled study showed favorable effects of low-dose lithium supplementation (0.4 mg daily) on mood, in a small sample of former drug users Schrauzer and de Vroey (1994). This is in accordance with epidemiological evidence previously discussed. Conversely, a randomized controlled study comparing suicidality on an add-on study among people with a major depressive disorder suggests the need of a lithium level above 0.5 meq/l to decrease suicidal ideation (Khan et al. 2011). Indeed, lithium may be also effective as an adjunctive treatment at least in mood disorders (Lauterbach et al. 2008). Data in personality disorders are less convincing (Rombold et al. 2014). This antisuicidal

effect is specific to lithium compared with other medications such as carbamazepine (Cipriani et al. 2013), valproic acid (Oquendo et al. 2011), or antidepressant (Toffol et al. 2015).

There is evidence that the antisuicidal effect of lithium is specific and does not result from improvement of the underlying mood disorder. Indeed, patients who have an antisuicidal response do not necessarily have a mood stabilization (Ahrens and Müller-Oerlinghausen 2001). Moreover, the decrease in suicidal ideation seems to precede the eventual improvement in mood (Khan et al. 2011).

25.2 Lithium as a Key Antisuicidal Agent: What Potential Mechanisms Are Underlying?

25.2.1 Lithium, Inflammation, and Suicidal Behaviors

Several lines of evidence demonstrate that stress increases inflammation and inflammation is associated with suicide-related phenotypes such as impulsivity, hostility/aggression, and depression (for review, see Beurel and Jope 2014). Whether specific inflammatory molecules mediate the different behavioral outcomes remains unknown and no specific "suicide inflammatory blood profile" has been identified so far. Differential effects of inflammatory markers on specific brain regions, neural circuits, and gene expression through epigenetic modifications are also likely to account for the different stress-induced phenotypes. One possible mechanism of the inflammatory cascade is that stress activates GSK3. This hypothesis may also explain part of the antisuicidal effect of lithium through the inhibition of GSK3 beta.

Several lines of evidence demonstrate that stress increases inflammation and inflammation is associated with suicidal behavior. Increased levels of interleukin-6 (in the blood or CSF) are one of most replicated finding in patients who attempted suicide (Nässberger and Träskman-Bendz 1993; Kim et al. 2008; Janelidze et al. 2011; Lindqvist et al. 2009, 2011). Other association studies identified IL-2, IL-6, IL-8, TNF-α, and VEGF (for review, see Serafini et al. 2013). Postmortem brain studies of suicide victims provided consistent results (Steiner et al. 2008; Tonelli et al. 2008; Pandey et al. 2012, 2014). Also consistent with this hypothesis are the observation of cytokine treatment (mainly interferon) inducing suicidal ideation and suicidal behavior (Fragoso et al. 2010) and the results of "inflammation" candidate gene studies in samples of patients with suicidal behaviors (Galfalvy et al. 2013). Finally, it has been suggested that the indoleamine-2,3-dioxygenase (IDO)-kynurenine pathway could be associated specifically with suicide attempt risk (Sublette et al. 2011).

Inflammation is also associated with suicide-related phenotypes such as impulsivity, hostility/aggression, and depression. In humans, aggressive traits are well correlated with increased immuno-inflammatory markers. Indeed, increased inflammation has been demonstrated in several suicide-related traits such as hostility/aggression (Zalcman and Siegel 2006) with several cytokines possibly implicated, including TNF, C-reactive protein, or IL-6 (Coccaro et al. 2014). Preliminary results in animal studies also indicate an association between aggression and inflammation (Patel et al. 2010; Bierbrauer et al. 2006). The well-established action of lithium

treatment on hostility/aggressive behavior has been linked to its antisuicidal properties (Müller-Oerlinghausen and Lewitzka 2010; Kovacsics and Gould 2010). Suicidal behaviors are also strongly linked to impulsive behavior and preliminary studies indicated an association between impulsivity and immuno-inflammatory activation (Sutin et al. 2012). Lithium efficacy on impulsive behavior is well established in humans (Hollander et al. 2005) and in rodents (Halcomb et al. 2013), but the link between the inflammation reduction induced by lithium and its anti-impulsive properties deserves further investigations.

Depression is another important suicide-related behavior and inflammation is associated with depression in blood studies and postmortem brain studies (for review, see Dantzer et al. 2008; Miller et al. 2009). Although lithium is not primarily used as an antidepressant, it has antidepressant properties in some depressive states in humans as well as in depression-like paradigms in rodents.

Evidences suggesting that activated GSK3 may contribute to suicidal behaviors through immuno-inflammatory activation have recently been reviewed by Beurel and Jope (2014): GSK3 is activated by stress, leading to increased inflammation that is associated with suicide-related behaviors (aggressive, impulsive, and depression). They also reviewed studies showing that lithium and other GSK3 inhibitors reduce inflammation. These data raised the hypothesis that the lithium antisuicidal effect could be mediated by the reduction of inflammation induced by GSK3 inhibition, leading to the idea that GSK3 is a possible target for suicidal behavior.

25.2.2 Lithium, Circadian Rhythms, and Suicidal Behaviors

Several lines of evidence suggest links between abnormal sleep or circadian rhythm variations and suicidal behaviors. First, suicide mortality is influenced by the seasons (Kevan 1980; Kim et al. 2015). Light is also associated with suicidal behavior and violent subtypes of suicide attempt (Maes et al. 1994; Maldonado and Kraus 1991; Preti and Miotto 1998). Disrupted circadian rhythms and difficulties to adapt to rhythm changes have also been associated with vulnerability to suicidal behaviors (Rockwell et al. 1978). In bipolar patients, abnormal sleep patterns (hypersomnia, insomnia, nightmares) have been also associated with suicide risk (Ağargün et al. 1997; Fawcett et al. 1990).

Several lines of evidence indicate that lithium may work in part via a chronobiological mechanism (McClung 2007). Lithium has phase-delaying properties because it lengthens the circadian period in a variety of organisms, including humans (Geoffroy et al. 2014; Abe et al. 2000). In addition, lithium enhances the amplitude of PER2 protein cycling in the central and peripheral circadian clockwork (Li et al. 2012). We already mentioned that chronic lithium treatment reverses the manic-like phenotype of transgenic mice carrying a mutation in the *Clock* gene (Roybal et al. 2007). Pharmacogenetic studies of lithium also indicate that variations in circadian genes may influence lithium response. In particular, *GSK3beta* and *NR1D1* genes have been recently associated to lithium response (McCarthy et al. 2011). Low doses of lithium carbonate reduce melatonin secretion in response to light in healthy volunteers, suggesting that lithium also acts on the melatonergic system (Hallam

et al. 2005). To which extent these results can be extrapolated to lithium mechanism of action in suicide prevention deserves further studies.

25.2.3 Lithium, Neuropsychological Processes, and Suicidal Behaviors

Several lines of evidence suggest that lithium might enhance impaired decision-making. First, decision-making impairment has been found to be independently associated with both suicidal behavior and bipolar disorders (Jollant et al. 2007). We also recently found that sample of patient treated with lithium had better decision-making performances than groups receiving valproic acid or antipsychotics. Moreover, lithium dose was significant and independent predictors of IGT net score (Adida et al. 2015). Also, differences in IGT performance are seen in individuals with neuropsychiatric disorders characterized by problems in impulse control and emotional regulation, and in cognitive impulsivity tasks, an impulsive choice reflects decision-making processes. Finally, decision-making relies on the prefrontal cortex (Jollant et al. 2010). In a PET study, lithium was found to modify metabolism of the orbitofrontal cortex and dorsolateral frontal cortex in bipolar patients with pathological gambling (Hollander et al. 2008). Most of the structural neuroimaging studies demonstrated increased brain volumes after lithium administration, in particular dorsolateral prefrontal cortical volumes in healthy individuals (Monkul et al. 2007). Benedetti et al. (2011) have reported that bipolar suicide attempters showed reduced gray matter volumes in several brain areas involved in decision-making (dorsolateral prefrontal cortex, orbitofrontal cortex). Long-term lithium treatment was associated with increased gray matter volumes in these areas where suicide was associated with decreased gray matter. In summary, even if these available evidences are preliminary, the antisuicidal effect may be supported by an effect on the neuropsychological endophenotypes, such as altered decision-making through a reduction of impulsivity and an enhancement of functionality of prefrontal regions.

In a recent study in euthymic bipolar patients evaluated in FondaMental network, we found that subjects who did a highly lethal suicide attempt had better verbal learning (Olié et al. 2015). This intriguing result is to be compared with those of a meta-analysis on the cognitive effects of lithium, who found impaired verbal learning skills during lithium treatment (Wingo et al. 2009). Thus, it also raises the hypothesis that lithium altering this cognitive function associated with serious suicide attempts could allow a reduction in suicidal lethality.

25.2.4 Lithium, Genetic Vulnerability Factors, and Suicidal Behaviors

Only few studies have investigated specifically the association between candidate gene polymorphism and lithium efficacy on suicidal behaviors. Serum spermidine/spermine N1-acetyltransferase 1 (SAT1) level has been shown to predict suicidal

behavior and SAT1 gene transcription is modulated by lithium (Le-Niculescu et al. 2013; Squassina et al. 2013). We previously showed that there is a strong rationale for the implication of abnormal circadian rhythms and the vulnerability to suicidal behaviors. Recent data indicate that genetic variations in CLOCK, IMPA2, INPP1, and GSK3β genes are associated with suicidal behavior (Benedetti et al. 2015; Jimenez et al. 2013). Through which pathway and in interaction with which circadian genes lithium modulated suicidal risk remain open questions.

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Antipsychotics

26

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Abstract

Suicide is a fatal outcome that frequently occurs in people suffering from schizophrenia and other psychoses. Lifetime rate of suicide in patients with schizophrenia has been reported to be around 10 %. Suicidal risk in schizophrenia is mainly related to affective symptoms, previous suicidal attempts, number of psychiatric admissions, younger age at onset, substance misuse or dependence, closeness to illness onset, male sex, and period during or following psychiatric discharge. Except for clozapine, no antipsychotic treatment has been established to be useful in reducing suicidality in patients with schizophrenia, being the only drug whose potential anti-suicidal properties have been officially recognized by the FDA in the USA. However, in light of recent data, the anti-suicidal effect of antipsychotics could be extended to other second-generation antipsychotics (mainly olanzapine and risperidone). The anti-suicidal effect of antipsychotics in non-psychotic patients needs to be further demonstrated. Timely and appropriate use of antipsychotic agents, bearing in mind adverse events, might contribute to a net positive effect on suicidality in psychotic and perhaps even in non-psychotic patients.

26.1 Introduction

Suicide is a tragic outcome that frequently occurs in people suffering from schizophrenia and other psychoses. The lifetime rate of suicide in schizophrenia has historically been reported as 10 % (Caldwell and Gottesman 1990; Chapman et al. 2015; Gonzalez-Rodriguez et al. 2014). Another measure indicates 0.24 for

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completed and 0.74 for attempted suicides per 100 person-years of exposure (Fleischhacker et al. 2014). Around 2 % died by suicide within 5 years of their initial diagnosis (Fazel et al. 2014).

Previous data indicate that suicidal risk in schizophrenia is mainly related to affective symptoms, history of a suicidal attempt, and number of psychiatric admissions. Other risk factors that have been identified are younger age, closeness to illness onset, older age at illness onset, male sex, substance abuse, and period during or following psychiatric discharge (Fleischhacker et al. 2014; Popovic et al. 2014; Randall et al. 2014). In first-episode psychosis, variables associated with an increased risk of Deliberate Self Harm (DSH) were younger age at onset, younger age at first treatment, depressed mood, substance use, and duration of untreated psychosis (Challis et al. 2013).

26.2 Association Between Antipsychotics and Suicide

Do antipsychotics in any way influence suicidal behaviour? The question has no easy answer. The magnitude of suicidal risk is hard to establish because of the sporadic nature of the event. In addition, methodological problems make it difficult to compare data and draw clear conclusions about if or when antipsychotic drugs have a net effect on suicide in schizophrenia.

The use of any antipsychotic, compared with nonuse, has been associated with both lower global mortality (Tiihonen et al. 2006, 2011) and lower suicidal mortality (Haukka et al. 2008; Johnson et al. 1983) in people with schizophrenia. Furthermore, earlier treatment of first-episode psychosis may reduce suicidal mortality in early psychosis (Challis et al. 2013). However, other studies with antipsychotic medications have shown increased (Hussar 1962) or unchanged (Planansky and Johnston 1971; Cohen et al. 1964; Kasckow et al. 2011) rates of suicide in schizophrenia. Based on this discrepancy, some authors suggest that the literature on the effects of antipsychotics (both first-generation antipsychotics, or FGAs, and second-generation antipsychotics, or SGAs) is inconsistent in determining whether these agents are helpful with the suicidal patient (Mamo 2007; Khan et al. 2001).

Conversely, it could be that antipsychotics do not help to prevent suicidal behaviour because suicidality may be a partially independent domain that is related to patient characteristics other than psychosis such as personality or substance abuse (Hearon et al. 2015; Zeng et al. 2015) or symptom dimensions such as agitated-aggressive syndrome (Huber et al. 2014), which are present before starting antipsychotic therapy. In fact, some studies indicate that classifying patients with schizophrenia on the basis of antipsychotic treatment response does not differentiate them with regard to suicidality (Modestin et al. 2005). Furthermore, even the presence of command auditory hallucinations for suicide did not directly predict suicide attempts (Wilkinson and Bacon 1984; Harkavy-Friedman et al. 2003). Some authors postulate a predominant environmental (shared or individual) role to account for variability in suicidal attempts. Individual environmental and shared familial

(e.g. parent-child interactions) experiences are likely to contribute substantially to the aetiology of suicidal attempts in psychosis (Zalsman et al. 2008). This view substantiates the null effect that antipsychotic drugs have on suicide in some of the studies reviewed.

26.3 Anti-suicidal Mechanism of Action of Antipsychotics

Even for promising pharmacological treatments, the neurobiological mechanism that confers protection against suicide remains essentially unknown, especially at the level of neural system function (Minzenberg et al. 2014). We review the hypotheses on suicidal behaviour closely related to psychosis.

Suicidal risk seems directly related to prefrontal cortex-based circuit dysfunction during goal representation in major mental illness with significant suicidal rates. Among those with suicidal ideation, the overt expression of suicidal behaviour may stem from impairments in premotor cortex support of action-planning as an expression of control (Minzenberg et al. 2014). In this case, any antipsychotic that would improve frontal function would have anti-suicidal effect.

Many studies and meta-analyses have shown a link between suicidal behaviour and low lipid levels, especially cholesterol, and some studies have also suggested such a relationship with schizophrenia. A recent study of 148 (69 males, 79 females) schizophrenia patients with a mean age of 32 ± 10 years, all recently admitted for acute exacerbation of their mental illness, suggests that, similar to depressed patients, low total and LDL cholesterol, triglycerides, and total lipids can be state-dependent risk factors for suicidal behaviour (Ainiyet and Rybakowski 2014).

Factors other than direct pharmacological effects could be involved in suicide. Nonadherence to antipsychotics can increase the risk of suicidal attempts. A four-fold increased risk was found for attempting suicide among patients on drug holiday (RR adjusted for age and gender 4.2, 95 % CI: 1.7–10.1) compared to patients not on drug holiday (Herings and Erkens 2003).

Clozapine has several pharmacological and non-pharmacological singularities. From a neurobiological point of view, the anti-suicidal effect of clozapine can be mediated by an increased central availability of norepinephrine and dopamine, along with a normalization of central 5-HT activity, especially in the prefrontal cortex, through downregulation of central 5-HT2A and increased availability of central 5-HT (Van Oekelen et al. 2003; Spivak et al. 1998). The effect of antipsychotics such as clozapine on lipids can also mediate an anti-suicidal effect. Several other factors can influence the superiority of clozapine, such an indirect effect through a direct antidepressant action, improved cognitive function and insight, diminished negative symptoms, reduced substance abuse, and improved compliance. These effects may converge to lessen feelings of hopelessness and increase its converse, optimism (Meltzer 2002). The treatment of anxiety/agitation, impulsivity, and aggression is crucial for suicidal prevention in psychosis. In this regard, clozapine also has an advantage over other antipsychotics as a specific anti-hostility agent (Citrome et al. 2001).

Non-pharmacological effects from weekly contact with patients for white blood cell monitoring have also been put forward as one explanation (Meltzer 1999). Additionally, there is also the possibility of a strictly psychological benefit from clozapine in the domain of suicidality in that patients may adopt an attitude that life and death are "out of my hands now" in response to "playing Russian roulette" with the potentially fatal complication of agranulocytosis (Aguilar and Siris 2007).

26.4 Evidence of Anti-suicidal Action of Antipsychotics

26.4.1 No Association

Data that deny the association of antipsychotics and suicidality are poor and weak. Some studies indicate that classifying patients with schizophrenia based on antipsychotic treatment response does not differentiate them with regard to suicidality (Modestin et al. 2005). Two studies find no differences in suicidal behaviour with antipsychotics and the placebo anti-suicidal effect in schizophrenia (Khan et al. 2001; Storosum et al. 2003). Both of them have methodological limitations because they were specifically designed to demonstrate that increased risk of suicide or attempted suicide in the placebo group should not be an argument against conducting placebo-controlled trials in schizophrenia. All of these trials are limited by having a brief duration. In addition, patients with a high risk of suicidal behaviour were excluded. Even with clozapine, some data fail to support the hypothesis that this treatment is significantly associated with fewer deaths due to suicide (Sernyak et al. 2001; Modai et al. 2000), but methodological weaknesses of the studies force us to interpret this with caution. The available evidence for the impact of psychotropics on suicidal risk in patients with bipolar disorder is largely methodologically flawed and, except for a few instances, clinically not useful at this point (Yerevanian and Choi 2013).

26.4.2 Antipsychotics Increase Suicidal Rates

The majority of patients with psychosis receive antipsychotics and a relatively high number of them commit suicide. It seems pertinent to ask whether there may be a positive relationship between these two facts (Modestin and Boker 1992). Comparison of data on the pre- and post-antipsychotic ages shows increased suicidal rates after the introduction of antipsychotics. Although deinstitutionalization is probably the single most important factor in determining suicide, pharmacotherapy appears to contribute to this risk (Healy et al. 2006). A retrospective study reviewing records of 405 veterans with bipolar disorder followed for a mean of 3 years found that treatment of bipolar patients with antipsychotics was associated with an increase in nonlethal suicidal behaviour and, for this reason, it

recommended careful monitoring for suicidal behaviour when antipsychotics are used in bipolar patients (Yerevanian et al. 2007). Another retrospective study reviewing the lifetime records of 133 treatment-refractory patients with bipolar disorder showed that neuroleptic-exposed and nonexposed bipolar patients were differentiated by increased suicidality in the neuroleptic-treated group (Brotman et al. 2000).

Antipsychotics can increase suicidality through side effects that cause indirect pro-suicidal neurological and consecutive psychological impact. Parkinsonism, dystonia, akathisia, and, less consistently, tardive dyskinesia are linked to suicidal behaviour (Cheng et al. 2013; Seemuller et al. 2012; Sandyk et al. 1991; Yassa and Jones 1985). Although it has been reported that antipsychotics, mainly FGA, can provoke "akinetic depression" (Van Putten and May 1978), the effect of akinesia is not clear because this state attenuates all kinds of behaviours (Siris 2001).

Dopamine synapses are involved in brain "reward" pathways. Therefore dopamine blockade by antipsychotics could lead to anhedonia and perhaps depression. Indeed, a state of dysphoria is commonly described by neuroleptic-treated patients (Awad 1993; Hogan and Awad 1983; Krakowski et al. 1997). These mental states can increase the risk of suicide (Hogan and Awad 1983; De Alarcon and Carney 1969). Despite the amount of positive data, not all studies find this association and there are views against pharmacogenic depression because depressive symptoms are frequently present before the initiation of antipsychotic treatment (Siris 2001) and both FGAs and SGAs have been found to have antidepressant properties (Di Fiorino et al. 2014; Keck et al. 2000).

No clear dose-effect relationship with suicidal behaviour has been found for antipsychotic medications. One study finds no association (Gaertner et al. 2002). Two studies find a positive relationship between suicide and antipsychotic doses, one of them with lower doses (Taiminen and Kujari 1994) and the other with higher doses (Cheng et al. 1990). These findings may also be explained by the fact that antipsychotic effects follow an inverted "U" curve in which very low doses would be ineffective and higher doses might also be associated with higher suicidal rates through side effects (Palmer et al. 1999). However the most likely hypothesis is that antipsychotic doses in the suicidal group were more a consequence of differences in symptom profile than a direct causal relationship to suicides per se.

Regarding long-acting injectable antipsychotics, a systematic review has found that they have safety profiles consistent with their oral parent formulations, but there are warning signs since the leading cause of death among patients enrolled in risperidone-LAI studies was suicide (Gentile 2013).

Probably, the best thing is to say that suicidal-promoting effects of antipsychotics cannot be postulated on the basis of the available data; however, they also cannot be fully ruled out in individual cases (Modestin and Boker 1992). Some data support a complex and idiosyncratic antipsychotic effect, so dynamic interactions between the state of the dopamine receptor and the pharmacological properties of antipsychotics may be responsible for individual variability in dysphoric responses (Awad and Voruganti 2005).

26.4.3 Antipsychotics Decrease Suicidal Rates

FGA

Some studies suggest at least a modest overall beneficial effect of first-generation antipsychotics on suicidality (Palmer et al. 1999). A Finnish nationwide, register-based, 5-year follow-up study of all patients presenting with first-episode schizophrenia between 1998 and 2003 found that FGAs, particularly chlorprothixene, were associated with decreased suicidal mortality (Kiviniemi et al. 2013). Another retrospective study from Finland examining psychological autopsies in suicidal victims who had schizophrenia found that most patients who died by suicide either were receiving inadequate antipsychotic medication, were noncompliant, or did not respond to adequate typical antipsychotic medication (Heila et al. 1999). A prospective case-control study (Johnson et al. 1983) found more self-injurious behaviours in patients after discontinuation of depot FGA at 18 months compared with patients who were maintained on the medication.

SGA

On the other hand, robust data exist suggesting SGAs, mainly clozapine, have a preventive effect on suicidal attempts and completed suicide in schizophrenia (Wilkinson and Bacon 1984; Palmer et al. 1999; Ernst and Goldberg 2004). In a retrospective case-control study assessing all records of admissions for schizophrenia or schizoaffective disorder (ICD-10) between January 1998 and December 2002 and examining the effect of risperidone and olanzapine on suicidality, the authors found that both of drugs provided protection from suicidality (Barak et al. 2004) and yielded an odds ratio of 3.54 (95 % CI 2.4, 5.3).

A Swedish case-control study defining as case patients with a first clinical discharge diagnosis of schizophrenia or schizoaffective disorder in Stockholm County between 1984 and 2000 ($n=4000$), who died by suicide within 5 years of discharge, found a lower suicidal risk for patients who had been prescribed second-generation antipsychotics, probably related to a pharmacological effect of these drugs (Reutfors et al. 2013). The data do not show any differences in impact on suicide of the different SGAs. A US study of suicidal attempts and death by suicide in patients ages ≥18 enrolled continuously for ≥3 months in their health plans before receiving their first-ever antipsychotic (November 2002–December 2005) found no differences in suicidal impact among aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone (Ulcickas Yood et al. 2010).

Comparison of SGAs Versus FGAs

Pharmacodynamic differences involve a higher number of side effects in FGA (Leucht et al. 2009) and those side effects are potentially significant risk factors for suicide. Newer antipsychotic agents that have a lower incidence of extrapyramidal side effects could offer greater safety in this population (Palmer et al. 1999). SGAs also seem to have a greater positive impact on quality of life than FGA (Ritsner et al. 2004; Awad and Voruganti 2013, 2004), and poorer quality of life has been recognized as a risk factor for suicidal behaviour (Min et al. 2015). However, data

on quality of life are not conclusive. It has been found that switching from SGAs to FGAs for clinical reasons did not result in any deterioration in quality of life or symptoms in patients with schizophrenia (Jones et al. 2006). Lower suicidal rates also may be related to differences in adherence or to differences in other patient characteristics associated with lower suicidal risk (Reutfors et al. 2013).

Are there real clinical differences in suicidal effects between FGAs and SGAs? There have been no prospective, randomized, controlled studies comparing the effect of first- and second-generation antipsychotic drugs on suicidal behaviour, and the differences in the impact of different antipsychotics on suicidal rates vary across studies. One small retrospective study suggested that patients attempting suicide were more likely to be taking first-generation antipsychotic medication, while non-attempters were more likely to be taking second-generation antipsychotic agents (Altamura et al. 2003). In a larger study, all patients with a first clinical discharge diagnosis of schizophrenia or schizoaffective disorder in Stockholm County between 1984 and 2000 ($n=4000$) who died by suicide within 5 years of diagnosis were defined as cases ($n=84$; 54 % male) and individually matched controls were identified from the same population. Lower suicidal risk was found in patients who had been prescribed a second-generation antipsychotic (clozapine, olanzapine, risperidone, or ziprasidone; 12 cases and 20 controls): OR 0.29 (95 % CI: 0.09–0.97) (Reutfors et al. 2013). To review the effects of quetiapine in comparison with typical antipsychotics in the treatment of schizophrenia and schizophrenia-like psychosis, a study was performed in the Cochrane Schizophrenia Group Trials Register (March 2010), and references of all identified studies were examined. No significant difference was found between the two groups in suicidal attempts or suicide (Suttajit et al. 2013).

Therefore, although most of the studies indicate the newer antipsychotics have a favourable influence on aspects of patient-reported outcomes, for the moment, such a conclusion can only be considered a trend due to the many design and methodological limitations of many of these studies (Awad and Voruganti 2013).

Clozapine

Clozapine has been commonly associated with a substantially lower risk of suicide than any other antipsychotic drug, although the mode of action for this effect is unknown (Meltzer 1999; Warnez and Alessi-Severini 2014). The literature review conducted in light of the Schizophrenia Patient Outcomes Research Team psychopharmacological treatment recommendations and other guidelines suggests using clozapine in people with schizophrenia who exhibit marked and persistent suicidal thoughts and behaviours (Buchanan et al. 2010).

A nationwide register used to compare cause-specific mortality in patients versus the total population between 1996 and 2006 in Finland (Tiihonen et al. 2009) found that the use of clozapine was associated with a substantially lower risk of suicide than was any other drug. The study has several methodological weaknesses (De Hert et al. 2010), but on the other hand, the data seem all the more valuable since clozapine is used only in the most severely ill patients who are resistant to other drugs and have the highest risk of suicide (Meltzer et al. 2003). Another Finnish

register-based 5-year follow-up study of all patients presenting with first-episode schizophrenia between 1998 and 2003 (Kiviniemi et al. 2013) also shows that clozapine is associated with lower suicidal risk. The same conclusion had been reached when comparing rates of various causes of death in clozapine users and linked data from a national registry of clozapine recipients to the National Death Index and Social Security Administration Death Master File in the USA (Walker et al. 1997).

In a retrospective study in which prior episodes of suicidality were assessed in a total of 237 antipsychotic-responsive and 184 antipsychotic-resistant patients with schizophrenia or schizoaffective disorder, data show that the overall morbidity and mortality of patients with resistant schizophrenia are lower with clozapine therapy than with typical antipsychotic drugs because of less suicidality (Meltzer and Okayli 1995). Clozapine also appears to be superior to FGAs with respect to suicidal attempts in a comparison of 30 antipsychotic-resistant chronic schizophrenia patients, maintained on clozapine for 1 year versus 30 chronic schizophrenia patients maintained on classical antipsychotic agents for the same period of time (Spivak et al. 1998). A study using a mirror-image retrospective design with hospitalized patients found odds ratios of 11.6 (95 % CI = 3.4–39.9) and 12.3 (95 % CI = 1.6–97.5) for suicidal and serious suicidal behaviour, respectively, in favour of the clozapine period in comparison with the pre-clozapine period. The authors also found that, in patients who discontinued clozapine, the rate of suicidal behaviour increased to the baseline rate and that the anti-suicidal effect of clozapine possibly disappears at doses that are too low (Modestin et al. 2005).

There is evidence of the superiority of clozapine over other atypical antipsychotics. A multicentre, open-label, randomized, international, 2-year study comparing the risk for suicidal behaviour (suicidal attempts or completions, or hospitalization to prevent suicides) in patients treated with clozapine versus olanzapine, conducted in 980 patients with schizophrenia or schizoaffective disorder, found that use of clozapine in this population should lead to a significant reduction in suicidal behaviour (Meltzer et al. 2003). This study also demonstrated that the severity of accompanying parkinsonian symptoms accounted for most of the suicidal behaviour (Potkin et al. 2003). Another comparative study designed to measure health care outcomes over a 1-year period after antipsychotic therapy initiated between 1997 and 2002 also concludes that clozapine decreased suicidal attempts compared to olanzapine (Thomas et al. 2015).

Not all data confirm the anti-suicidal effect of clozapine. Some authors consider the favourable data inconclusive, and they suggest the need for positive research with the highest level of evidence (Hennen and Baldessarini 2005).

The singularities of clozapine, such as safety restrictions, can have caused a selection bias in the different studies, whereby patients in the best health and with the lowest risk of death would have been more likely to receive this drug, thus biasing the results (Meltzer et al. 2003). A 4-year study of all patients who initiated treatment with clozapine while hospitalized within the Department of Veterans Affairs (VA) system ($N = 1415$), matched with a schizophrenia control group ($N = 2830$), finds a lower mortality ratio in patients exposed to clozapine. However the authors explain the lower rate of death as due to fewer physical disorders in the

clozapine group since they did not find significant differences in rates of suicide or accidental death (Sernyak et al. 2001). This investigation, however, did not match the comparison group on variables related to risk of suicide and follow-up. Furthermore, one-third of the sample received clozapine for <6 months, even though the follow-up period was 5–6 years (Kasckow et al. 2011). Lower mortality from physical problems also occurs in the Finish cohort (Tiihonen et al. 2009), although in this case a decrease in mortality by suicide was also detected.

Clozapine may be a little more efficacious than other FGAs and SGAs, but further trials are required to confirm this finding. Clozapine differs more clearly in adverse effects from other second-generation antipsychotics and the side-effect profile could be key in the selection of treatment depending on the clinical situation and patient preferences. Data on other important outcomes such as cognitive functioning, quality of life, death, or service use are currently largely missing, making further large and well-designed trials necessary (Asenjo Lobos et al. 2010).

26.5 Anti-suicidal Effect of Antipsychotics in Non-schizophrenic Patients

Clozapine has been associated with an important decrease in suicidality, with only a minimal improvement in mood, in a severely and persistently ill bipolar woman (Vangala et al. 1999). In a study on bipolar or schizoaffective treatment-resistant patients who were randomized to clozapine add-on treatment or treatment as usual (no clozapine), the results showed a significant improvement in the clozapine group (Suppes et al. 1999). In a naturalistic study on schizoaffective disorder or bipolar disorder with psychotic features, clozapine at flexible dosages over a 24-month period appeared to be effective in controlling suicidality (Ciapparelli et al. 2000). Again in this area, clozapine seems to show anti-suicidal superiority, although there is also evidence of positive effects of other antipsychotics.

A pilot study with a small sample size suggests that risperidone is beneficial as an augmenting treatment in major depressive disorder (MDD) patients who have developed high-risk suicidal ideation during a depressive episode, especially in the acute phase of severe depressive symptoms (Modestin et al. 2005; Reeves et al. 2008). Low-dose risperidone has also been shown to be effective as augmentation of antidepressants in another small study in depression (Viner et al. 2003). Data pooled from two aripiprazole augmentation studies to assess the impact of adjunctive aripiprazole versus adjunctive placebo treatment on suicidality in patients with MDD demonstrated that adjunctive aripiprazole treatment in patients with depression with a history of inadequate response to antidepressant medication is associated with a decreased rate of suicidality in a group of subjects not at significant risk (Weisler et al. 2011).

Several antipsychotics have also shown a beneficial effect on borderline personality disorder (BPD) in studies involving the effect of depot fluphenazine (Battaglia et al. 1999), flupenthixol (Montgomery and Montgomery 1982), or low-dose clozapine (Benedetti et al. 1998). In non-suicidal self-injury (NSSI) BPD, only one

randomized control trial has evaluated the efficacy of medication for reducing NSSI specifically, demonstrating that, among adults with BPD, more participants abstained from NSSI during treatment with aripiprazole and at the 18-month follow-up, compared with those receiving a placebo (Nickel et al. 2006).

Despite the above data, we are not completely convinced of the anti-suicidal effect of antipsychotics in non-psychotic patients with suicidal risk. A comparison of pharmacotherapy in suicidal victims with a control group matched for age, gender, and diagnosis at the time of hospital discharge showed that antipsychotics (classical and atypical) were more frequently used in suicidal victims with affective psychosis (Gaertner et al. 2002). A positive association has also been seen between suicidal ideation, adjusted for symptoms of depression and anxiety, and antipsychotic medication in different diagnostic groups (schizophrenia, other psychosis, and no psychosis). Individuals receiving antipsychotic medication show more suicidal ideation regardless of diagnostic group and antipsychotic type. In the non-psychotic group, higher antipsychotic doses were associated with more suicidal ideation, even when adjusted for symptoms of depression and anxiety ($p < 0.05$). These results suggest that suicidal ideation should be taken into account when prescribing antipsychotic medication, especially for off-label use (Rissanen et al. 2012).

Conclusion

Except for clozapine, no antipsychotic treatment has been established to be useful in reducing suicidality. It is the only drug with a reduction of suicidal risk in psychosis as an official indication in the USA. However, in light of recent data, this anti-suicidal effect could be extended to other SGAs. Timely and appropriate use of these antipsychotic agents, bearing in mind adverse events, might contribute to a net positive effect on suicidality in psychotic and perhaps even in non-psychotic patients.

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Psychological Interventions in Suicide

27

Raffaella Calati

Abstract

Psychological treatments targeting suicidal behavior disorder (SBD) have been evaluated here in their efficacy through different diagnoses. In particular, transference-focused psychotherapy (TFP), mentalization-based treatment (MBT), interpersonal psychotherapy (IPT), dialectical behavior therapy (DBT), schema-focused therapy (SFT), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR), acceptance and commitment therapy (ACT), and cognitive behavior therapy (CBT) were the main structured treatments considered here in association with their impact on SBD. Some of them showed higher efficacy in suicide (DBT and MBT). Moreover, some treatments have been primarily studied in a specific diagnosis: TFP, MBT, DBT, and SFT in borderline personality disorder and IPT and CBT in depression. Concerning new treatments, promising preliminary results have been reported (SFT, MBCT, MBSR, and ACT) as well. Summarizing, consistent reduction in suicidal and self-destructive phenomena through psychotherapeutic treatments has been found throughout methodologically heterogeneous trials, in particular focused on DBT and MBT. In conclusion, two movies by the Italian documentarist/director Alina Marazzi have been illustrated in their connection with SBD.

Abbreviations

ACT	Acceptance and commitment therapy
BD	Bipolar disorder
BPD	Borderline personality disorder

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CBT	Cognitive behavior therapy
DBT	Dialectical behavior therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMS	Early maladaptive schema
IPT	Interpersonal psychotherapy
MBCT	Mindfulness-based cognitive therapy
MBSR	Mindfulness-based stress reduction
MBT	Mentalization-based treatment
MDD	Major depressive disorder
NSSI	Non-suicidal self-injury
RCT	Randomized controlled trial
SBD	Suicidal behavior disorder
SFT	Schema-focused therapy
SPI	Safety planning intervention
TAU	Treatment as usual
TFP	Transference-focused psychotherapy

27.1 Introduction

Un'ora sola ti vorrei
Io che non so scordarti mai
Per dirti ancor nei baci miei
Che cosa sei per me

Un'ora sola ti vorrei
Per dirti quello che non sai
Ed in quest'ora donerei
la vita mia per te

Io non vedo il mondo
Quando penso a te
Vedo gli occhi tuoi nei miei
Ma se non mi vuoi
Non è niente sai
La vita mia per me

Un'ora sola ti vorrei
Io che non so scordarti mai
Per dirti ancor nei baci miei
Che cosa sei per me.[1] Bertini and Marchetti (1938)

[1] Literal translation: I'd wish you just for one hour/I am not able to forget you/To tell you again in my kisses/What you are for me. I'd wish you just for one hour/To tell you what you don't know/And during this hour I'd give/My life for you. I can't see the world/When I think of you/I see your eyes in mine/But if you don't want me/My life, you know/Doesn't mean anything to me. I'd wish you just for one hour/I am not able to forget you/To tell you again in my kisses/What you are for me.

The inclusion of suicidal behavior disorder (SBD) in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association 2013) highlights the need to deepen its knowledge and to identify new strategies that could be more effective for SBD prevention and treatment across different diagnoses. Psychiatric disorders related to suicidal thoughts and behaviors are mainly borderline personality disorder (BPD), major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, anxiety disorders (post-traumatic stress, panic, and social anxiety disorders), and anorexia nervosa.

Generally, the clinical management of SBD patients requires a careful consideration of therapist interventions, with the focus on three main principles in the context of shared responsibilities for patient safety: the alliance between the patient and the clinician, the enhancement of curiosity about suicidal thoughts, and the enhancement of experience, expression, and understanding of intense emotions (Fowler 2013). These three principles should be developed in a collaborative relationship with the therapist in order to decrease the patient isolation in case of intense and overwhelming emotions.

Beyond broad clinical treatment principles, structured psychotherapy treatments have been found to be significantly beneficial for patients with suicidal thoughts and behaviors, obviously together with higher level of care, such as hospitalization and intense inpatient or outpatient treatments in acute phases. In particular, specific interventions targeting suicidality, including both short- and long-term treatments, have been found to be effective.

The primary aim of this chapter is to give to the reader an as much as possible complete overview of the main available psychological interventions that, to some extent, have been found to be effective in the treatment of SBD. So my aim was not to perform a systematic review of the literature but to include the most significant (e.g., published in high-impact factor journals) and recent studies only. The secondary aim of this work is to critically evaluate the spread survey of findings, trying to suggest ways of integrating the overall results. Since the literature state of the art is quite scattered, this chapter might represent a starting summarizing point and a way to give some recommendations for future studies.

27.2 Methods

A literature web search was performed to identify studies focusing on psychological interventions in SBD. PubMed database was used to search articles published until August 2015 using the word combinations "psychological interventions" or "psychotherapy" or words specifically indicating psychotherapeutic models (e.g., "transference-focused psychotherapy") and "suicide." Only papers in English language were included. The reference lists of the identified studies and reviews were checked for further relevant articles as well. Concerning the primary aim of this chapter, studies were included if (1) they focused on psychological interventions in SBD; (2) they focused on psychiatric patients; (3) they considered adolescents, adults, or elderly patients; and (4) they examined every kind of psychological

interventions. Studies were excluded if (1) they did not consider suicidal behavior or self-harm as an outcome and (2) they were focused on treatments different from structured psychological ones (e.g., clinical management, implementation of emergency call centers, programs in schools, information campaigns). Further studies have been included if interesting for the secondary aim of this chapter.

Since this is not a systematic review of the literature, the most significant and recent studies have been included only. When a recent review on a specific topic was published, I referred to that one, without reporting each single previous study.

27.3 Transference-Focused Psychotherapy

The transference-focused psychotherapy (TFP) is a psychodynamic object relations approach introduced by Clarkin et al. (1999) and Kernberg et al. (2008). TFP's primary focus is the dominant affects that emerge in the relationship between patient and therapist. This therapeutic approach is prominent in the treatment of BPD considered as a level of psychic functioning, an organization, and not a clinical syndrome like in DSM. Moreover, TFP is described in its specificity for the treatment of characterologically based suicidal and parasuicidal tendencies in the context of the patient's personality disorder (Kernberg 2001). Kernberg focused on the self-destructiveness of these patients, which could lead to suicidal behavior, differentiating them from patients affected by depression (Kernberg 2014): in personality disorder patients, the suicidal behavior could represent an unconscious triumph on the treatment, while in depression it is expression of guilt. This should be repeatedly underlined with these patients and with their families as well. Another point is the unconscious identification with a sadistic object and its interpretation during treatment and not only the focus on the patient as a victim of trauma. More generally, the therapist should deal with the negative affects in the countertransference relation. The therapist should be able to recognize antitherapeutic defense mechanisms as repression, turning against himself, reaction formation, projection, distortion, and denial of countertransference hate that might increase the danger of suicide (Maltsberger and Buie 1974).

After a preliminary uncontrolled trial on TFP supporting its positive impact on suicidal behavior (Clarkin et al. 2001), the same team of research compared three treatments for BPD: TFP, dialectical behavior therapy (DBT), and dynamic supportive treatment (Clarkin et al. 2007); both TFP and DBT were significantly associated with improvement in suicidality. The efficacy of TFP treatment in the reduction of suicidality has been reported as well when comparing it with treatment by experienced community psychotherapists (Doering et al. 2010).

27.4 Mentalization-Based Treatment

The mentalization-based treatment (MBT) (Bateman and Fonagy 2004, 2006) is a psychodynamic treatment rooted in attachment and cognitive theory. Mentalization is a deeply social construct, the process by which a subject has a sense of identity

and is able to make sense of the other person in terms of subjective states and mental processes and consequently to have good relationships (Bateman and Fonagy 2010). The word mentalization derives from the Ecole Psychosomatique de Paris (Leslie 1987), and it was used for the first time by Fonagy in relation to mental disorders (Fonagy 1989). This concept is different from the one of introspection since it consists in an unconscious implicit automatic awareness instead of a conscious one. Deficits of this mentalization capacity can be found in most mental disorders, including suicidal behavior, which implies the tendency to misinterpret other peoples' motivations. This misinterpretation is hypothesized to be due to the lack of a mirroring response of the caregiver, which might contribute, together with other factors, to the inactivation of the mentalization capacity in the child.

MBT is focused on strengthening patients' capacity to understand their own and others' mental states. Since it requires limited training, with moderate levels of supervision, it represents a cost-effective treatment for suicidal behavior. MBT efficacy on suicidal and self-destructive phenomena has been investigated in BPD patients. Patients randomly assigned to 18-month MBT showed a consistent reduction in suicide attempts, severe incidents of self-harm, and hospitalization in comparison with structured clinical treatment (Bateman and Fonagy 2009). Self-harm improved more slowly with MBT than with structured clinical treatment, although with a final more remarkable reduction. Interestingly, even 5 years after discharge, 18-month MBT showed clinical and statistical superiority to treatment as usual (TAU) on suicidality (Bateman and Fonagy 2008). Also when specifically considering self-harm in adolescent population, MBT was found to be more effective than TAU (Rossouw and Fonagy 2012).

In a Norwegian study, a naturalistic longitudinal comparison of treatment effects for BPD patients before (patients were admitted to a psychodynamic treatment program) and after transition to MBT has been performed (Kvarstein et al. 2015). A decrease in suicidal/self-harming acts and hospital admissions has been reported during both treatments. However, considering further outcomes (symptom distress, interpersonal problems, and global functioning), MBT seemed to be more effective than psychodynamic treatment. A positive impact on both suicide attempts and self-harm acts has been also reported in the Netherlands (Bales et al. 2012).

Summarizing, MBT has been found to be effective on suicide and self-harm mainly in BPD. Since mentalization disturbances are involved in psychotic disorders (Brent et al. 2014; Brent 2009), further studies specifically investigating the impact on suicide in these (and further) disorders are needed.

27.5 Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) has been developed in the New Haven-Boston Collaborative Depression Research Project by Klerman and Weissman (Klerman et al. 1974; Weissman et al. 1979), being inspired by Sullivan's psychodynamic interpersonal theory (Sullivan 1953). IPT focuses on identifying and helping to solve interpersonal difficulties which cause or exacerbate psychological distress.

In particular, addressed problems fall into four categories: interpersonal disputes or conflicts, role transitions, grief, and interpersonal deficits.

IPT has been specifically evaluated concerning suicide: patients who had deliberately poisoned themselves and had received IPT reported a higher reduction in suicidal ideation at 6-month follow-up compared with those of the TAU control group (Guthrie et al. 2001). More recently, IPT appeared to be a safe treatment for unipolar depressive patients with past suicide attempts (Rucci et al. 2011).

IPT efficacy has been also evaluated in different populations in relation to suicide. In depressed adolescents with suicidal risk, it has been found to be effective in comparison with TAU in reducing suicidal ideation, hopelessness, and severity of depression and anxiety (Tang et al. 2009). Furthermore, IPT has been adapted for elderly individuals (over 60 years) at risk for suicide (current suicide ideation, death ideation, and/or recent self-injury) in a Canadian uncontrolled pre- to posttreatment psychotherapy trial (Heisel et al. 2014). After 16 IPT sessions, patients were found to report decreased suicide ideation, death ideation, and depressive symptom severity and increased perceived meaning in life, social adjustment, perceived social support, and other psychological well-being variables.

27.6 Psychodynamic Psychotherapy

Since we know little about the therapeutic process and mechanisms of change associated with recovering from suicidal behaviors, Canadian Perry's team focused on it in the context of a long-term psychodynamic psychotherapy trial (Perry et al. 2013). In general a consistent reduction of suicidal behaviors has been reported. Patients with suicidal ideation used to stay in treatment longer and with a higher rate of sessions than those without suicidal ideation. So, suicidal ideation was not only an indicator of both symptom severity and treatment duration but also of the possibility of improvement and recovery. Moreover, suicidal patients reported higher rates of negative reactions to treatment, reflecting their higher level of expression of negative affects. The improvement was linked to the capability for patients to express these negative affects in the therapeutic dialogue. In fact it is relevant that the mobilization of negative affects was found to be related with symptom improvement. Concerning therapeutic alliance, suicidal ideation has been found to be associated with higher rate of difficulties in the early participation and in the exploration of topics. However, these difficulties diminished during the first 6 months of follow-up. Hence, negative affects toward the therapist (e.g., negative countertransference) are not necessarily problematic, but an instrument to be used in the direction of recovery. Consequently, it is possible to conclude that the expression of negative affects in the treatment of suicidal patients is strictly linked to the recovery process and that the therapists should actively inquire these affects and/or address defenses inhibiting them (e.g., repression).

The effectiveness of combined treatment (medication plus psychodynamic psychotherapy) versus only psychodynamic psychotherapy on both suicidality and impulsivity has been evaluated in inpatients with severe personality disorder (Vaslamatzis et al. 2014): predictably combined treatment was more effective in suicidality.

27.7 Dialectical Behavior Therapy

DBT is a treatment for suicidal behavior and BPD (Linehan and Wilks 2015; Linehan 1993a, b). Furthermore, preliminary evidence that DBT could be efficacious in BPD-related disorders as PTSD (Harned et al. 2012), binge eating disorder and bulimia nervosa (Chen et al. 2008), and substance abuse disorders (van den Bosch et al. 2005) has been reported as well.

BPD has been seen as a primary dysfunction of the emotion regulation system. BPD patients attempted suicide since it appears to them to be a behavioral solution to intolerably painful emotions. Three essential strategies of a DBT session have been recognized: structuring the content of the session, core strategies of problem-solving and validation, and dialectical strategies and worldview (Bedics et al. 2013).

The effectiveness of DBT in reducing suicidal behavior has been extensively studied. It has been firstly reported by Linehan et al. (1991), with decreased suicide behaviors, less medically severe ones, and fewer inpatient psychiatric days, in comparison with TAU (Linehan et al. 1993). Moreover, 1 year of DBT has been compared to community treatment by experts (Linehan et al. 2006). DBT was associated with better outcomes. In particular, subjects receiving DBT were half as likely to attempt suicide, required lower rates of hospitalization for suicide ideation, and reported lower medical risk across both suicide attempts and self-injurious acts considered together. Furthermore, higher reduction of self-mutilating and self-damaging impulsive behaviors compared with TAU, in particular among patients with a history of frequent self-mutilation, has been detected (Verheul et al. 2003). It should be underlined that results are mostly referred to women. Interestingly, it has been specifically assessed if the effectiveness of DBT could be attributed to general factors associated with psychotherapy, and DBT appeared to have a unique efficacy in reducing suicide attempts (Linehan et al. 2006). Recently M. Linehan and colleagues evaluated the importance of the skills training component of DBT in a randomized trial and reported that interventions including DBT skills training were more effective than DBT without it for reducing suicide attempts and non-suicidal self-injury (NSSI) episodes (Linehan et al. 2015). In a Canadian 2-year prospective naturalistic follow-up study, BPD patients were randomly allocated to 1 year of either DBT or general psychiatric management. Both treatments showed similar and statistically significant improvements on suicidal and NSSI behaviors 2 years after discharge (McMain et al. 2012). Similar results have been previously reported by the same team of research after 1 year of treatment (McMain et al. 2009). The persistence of DBT efficacy after 2 years of follow-up has been reported as well (Kleindienst et al. 2008). Furthermore, in adolescents with self-harming/previous suicide attempt, DBT seemed to be an effective intervention to reduce self-harm, suicidal ideation, depression, and NSSI behavior (Mehlum et al. 2014; Fleischhaker et al. 2011) (for reviews on DBT on adolescents, see MacPherson et al. (2013) and Klein and Miller (2011)).

Considering the advantages of the group approach in terms of cost-effectiveness over individual treatment, a first attempt in showing that DBT in an outpatient group

setting can be effective in reducing psychiatric complaints has been performed with positive preliminary findings (Gutteling et al. 2012).

Summarizing, a consistent number of studies confirmed the efficacy of DBT in the treatment of suicidal behavior, and new highly cost-effective strategies might be further implemented.

27.8 Schema-Focused Therapy

Schema-focused therapy (SFT) is among the third-wave cognitive therapies together with mindfulness-based approaches and acceptance and commitment therapy (ACT). SFT combines elements of cognitive behavioral, attachment, object relations, and emotion-focused models (Young 1994). The construct of early maladaptive schema (EMS) corresponds to an early-developed pervasive emotional and cognitive pattern regarding the self and the relationships with others that is dysfunctional. There are four main EMSs that are the focus of SFT (Boulougouris et al. 2013): child modes, maladaptive coping modes, maladaptive parent modes, and a healthy adult mode.

SFT has been found to be effective in BPD (Nadort et al. 2009). Specifically concerning suicidal behavior, the relationship between SFT for suicide prevention and neurobiological models has been deepened (Boulougouris et al. 2013). In fact, authors underlined the existing link between the serotonergic system and temperamental traits and dysfunctional attitudes of suicidal patients, and they focused on the correlation between some of these temperamental traits and EMSs.

In a multicenter randomized trial, the effectiveness of SFT has been compared to the one of TFP in BPD patients (Giesen-Bloo et al. 2006). SFT group improved more than TFP one with respect to suicidal behavior. However, as suggested by the authors, it is possible to hypothesize that MBT and DBT are most efficacious for BPD patients with suicidal behavior, whereas TFP and SFT are mostly meaningful for the wide range of BPD patients.

Unfortunately, only a few studies considered SFT efficacy on suicide. For example, in a study supporting the efficacy of group SFT for BPD, all the included patients had a history of suicide attempts and self-injury in the previous 2-year period (Farrell et al. 2009), but outcome measures did not include suicidal behaviors.

27.9 Mindfulness-Based Approaches

The word mindfulness refers to a particular way of paying attention to the present moment consisting in a receptive and nonjudgmental attitude (Kabat-Zinn 1994). Mindfulness-based approaches are becoming broadly used for suicidal behavior patients (Williams et al. 2006; Williams and Swales 2004). In particular, mindfulness-based cognitive therapy (MBCT) effects on two aspects of mode of processing have been evaluated in suicidal depressed patients: patients having received MBCT

displayed differences in meta-awareness and specificity of memory compared with those having received TAU (Hargus et al. 2010). Furthermore, a preliminary study examined MBCT effects on thought suppression and depression in individuals with past depression and suicidality, reporting evidence that MBCT may reduce self-reported attempts to suppress thoughts in the previous week (Hepburn et al. 2009). Moreover, MBCT was found to decrease suicidal ideation in patients with residual depressive symptoms, and this effect seemed to be partially mediated by patients' enhanced capacity to distance themselves from worrying thoughts (Forkmann et al. 2014). Finally, significant reductions in suicidal ideation, anxiety, and depression were observed after mindfulness-based stress reduction (MBSR) training in veterans (Serpa et al. 2014).

Further studies are required to evaluate both MBCT and MBSR impact on suicide.

27.10 Acceptance and Commitment Therapy

ACT is a "third-wave" cognitive therapy that could be considered as consistent with mindfulness conceptualizations as well. It is an effective putative psychotherapeutic approach among new prevention and treatment strategies in SBD (Hayes et al. 2006). Indeed, it has been found to be efficient for the treatment of several psychiatric disorders – most of them associated with an increased suicidal risk – such as BPD, MDD, eating disorders, obsessive compulsive disorder, generalized anxiety disorder, psychosis, and substance use disorders. Interestingly, two case reports have suggested the ACT role in the prevention of suicidal reattempt at 1 year (Luoma and Villatte 2012). Moreover, in a recent pilot study, ACT was found to decrease suicidal ideation in patients with current SBD (Ducasse et al. 2014). Consequently, ACT seems to represent a promising adjunctive treatment for high-suicidal-risk patients.

27.11 Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is the best known structured form of psychotherapy. It is based on Beck's cognitive theory (Beck 1976). Two main mechanisms, poor problem-solving skills and a certain cognitive style characterized by overgeneralization, distortion, and lack of positive expectations, have been identified in suicidal patients (Schneider 2012). The behavioral modification includes the acquisition of skills for stress reduction and learning problem-solving. The cognitive modification encompasses modification of negative core beliefs (hopelessness), thought-stopping, examining options and alternatives, externalizing inner voices, and reattribution. In particular, hopelessness is viewed as one of the strongest contributing factors to suicidal ideation, and a large part of the treatment intends to restore hope.

It has been suggested that suicide risk linked to severe mental illness might be reduced by the improvement of the access to psychological/psychosocial

interventions, remarkably CBT (Foster 2013). Moreover, in an extremely interesting 7- to 19-year follow-up study, to have responded to CBT for anxiety during childhood conferred benefits later in life, in particular less chance to report both lifetime and current suicidal ideation in comparison to CBT nonresponders (Wolk et al. 2015).

Concerning depression, CBT has been so far considered as a first-line treatment both for adults (Jayasekara et al. 2014; Jakobsen et al. 2011; Sudak 2012) and adolescents (Nardi et al. 2013; De Silva et al. 2013). CBT is the most extensively studied psychological treatment in MDD, and, to our knowledge, this is one of the few psychological treatments that could have been analyzed through meta-analytic methodology (Jakobsen et al. 2011; Dubicka et al. 2010). In particular, randomized trials comparing CBT effects versus no intervention in MDD have been meta-analyzed. CBT effects on suicidality are far to be clear since only a few trials reported suicidal ideation, suicide attempts, and suicide deaths. Moreover, in adolescent depression no evidence of a significant benefit of combined treatment over antidepressants has been reported for suicidality (Dubicka et al. 2010). Consequently, despite the high number of CBT studies, further research is required on MDD and the other psychiatric disorders. Concerning BPD, evidence of efficacy on symptomatology is not robust (Stoffers et al. 2012), and suicide outcome should be more deeply investigated as well.

27.12 Comparison among Different Treatments across Different Diagnoses

Recent reviews have been published on the efficacy of psychotherapies in BPD (Lana and Fernandez-San Martin 2013; Paris 2010; Zanarini 2009; Rafaeli 2009; Stone 2006). Concerning BPD suicidality, DBT seemed to be one of the most efficacious treatments. For a clinical comparative description by four master clinicians of, respectively, TFP, MBT, DBT, and good psychiatric treatment in BPD, see Hopwood et al. (2014). The impact of less versus more intensive psychotherapies in reducing suicidal behavior and depression in BPD suicidal patients was examined assessing six trials focused on CBT, MBT, and DBT (Davidson and Tran 2014). Both different length therapies were found to significantly decrease suicidal behaviors. Two follow-up studies showed that this reduction is maintained over time. So, it has been suggested that all the treatments, which have several similarities, could be shortened to make them more accessible. An intriguing program for individuals diagnosed with personality disorders is the Chrysalis Community Day Treatment Program, which integrates aspects of three therapies: TFP, MBT, and DBT, with preliminary promising outcomes such as decreases in self-injurious behavior, suicide attempts, and psychiatric hospitalizations at a 1-year follow-up (Rivera and Darke 2012).

In a recent review of interventions for co-occurring BPD and substance use disorder, ten studies have been included (Lee et al. 2015): four studies examined DBT, three studies examined dynamic deconstructive psychotherapy (DDP), a treatment specifically tailored for BPD patients with co-occurring substance use disorders (see Gregory and Remen (2008)), and three studies examined dual-focused

SFT. Both DBT and DDP demonstrated reductions in suicidal/self-harm behaviors and substance use and improved treatment retention.

Concerning MDD treatment, previous randomized controlled trials (RCTs) and meta-analyses supported the efficacy of CBT, IPT, behavioral activation therapy, problem-solving therapy, supportive counseling, and possibly psychodynamic therapy (Weitz et al. 2014). Concerning suicidal ideation there is limited evidence to whether or not psychotherapy for MDD represents the best course of action. However, a consistent reduction in hopelessness has been reported. Internet-based CBT and IPT need further investigation. In particular IPT seems to be efficacious in different populations like adolescents and elderly. However, in a recent meta-analysis, sensitivity analyses revealed no differences between different types of psychological treatments (e.g., CBT, IPT) (van Zoonen et al. 2014). Third-wave cognitive therapy may be more effective than MBT for depressive symptomatology (Jakobsen et al. 2014; Jakobsen 2014).

Concerning BD, both psychosocial suicide crisis interventions and longer-term psychosocial treatments have been evaluated in their efficacy to reduce suicide risk (Chesin and Stanley 2013). Very short suicide prevention interventions include contacts, psychoeducation on warning signs, and CBT strategies. Regarding contacts, letters/messages sent on a regular schedule seemed to be efficacious in reducing suicide rates and further subsequent self-harm even after 2 years of follow-up; however, this kind of contact may work for specific subgroups of patients only. Moreover, short interventions providing educations on risk factors, coping skills, and treatment motivation enhancement seemed to be effective. The same could be said for the means restriction education, a short intervention for the parents of children and adolescents at suicide risk. The new Safety Planning Intervention (SPI) has been evaluated as well with promising preliminary results on its efficacy. It consists of a written, personalized safety plan for the reference of the patients in future suicidal crisis, given to patients after a single session. It has six steps: a detailed assessment of warning signs of the suicidal crisis, internal coping skills, social contacts that may distract from suicidal thoughts and urges, family members that may offer help, professional and agency contacts, and means restriction. Summarizing, short interventions seemed to be efficacious but showing better outcomes in the shorter term. Concerning longer interventions, the DBT obtained the largest evidence of efficacy. However, a validated psychosocial intervention targeting suicidality in BD patients should be developed.

Interestingly, a systematic review has been performed on suicide and self-harm through different diagnoses in young people (between 6 and 25 years) (De Silva et al. 2013). Promising interventions that need further investigation were school-based prevention programs with a skills training component, individual CBT, IPT, and attachment-based family therapy.

27.13 A Meta-analysis

A lack of consensus on the effectiveness of psychological interventions in suicidal behavior has been reported in meta-analyses as well. In a first one, the efficacy of a wide range of therapies – CBT, DBT, and problem-solving approaches – has been

reported in reducing suicidal behavior when it was considered as an extremely wide outcome variable, comprising different indicators (such as suicidal attempts, behaviors, plans, thoughts together with hopelessness and satisfaction with life measures) (Tarrier et al. 2008). On the contrary, psychosocial interventions following self-harm seemed not to have a marked effect on the likelihood of subsequent suicide death (Crawford et al. 2007).

A further recent interesting meta-analysis has been published on adolescents to evaluate the efficacy of therapeutic interventions (psychological, social, and pharmacological) in reducing any self-harm (suicide attempts, non-suicidal self-injury (NSSI), and/or self-harm with ambiguous intent) (nineteen included studies) and suicide attempts separately considered (eight included studies) (Ougrin et al. 2015). Evidence of efficacy was reported for the global category of self-harm, with high between-study heterogeneity, but not for suicide attempts.

Consequently, we performed a meta-analysis of RCTs assessing efficacy of psychological interventions in reducing suicidal attempts and NSSI (submitted). We included RCTs comparing psychotherapy interventions versus TAU in preventing suicidal attempts/NSSI across a wide range of psychiatric diagnoses. In the 32 included RCTs, 4114 patients were randomly assigned to receive psychotherapy ($n = 2106$) or TAU ($n = 2008$). Patients who received psychotherapy were less likely to attempt suicide during follow-up. Moreover, in sensitivity analyses the efficacy of psychotherapy on suicide attempts was found in particular in adults, BPD diagnosis, both previous suicidal patients and non-previous suicidal ones, both short- and long-term therapies, and MBT. No evidence of efficacy has been found in NSSI behaviors, with the exception of MBT; however, this subanalysis was underpowered to lead to firm conclusions. Hence, psychotherapy seems to be effective in the prevention of suicide attempts. However, evidence of between-study heterogeneity and publication bias slightly tempers enthusiasm and optimism led by results.

27.14 Discussion

The primary aim of this work was to provide an as much as possible complete overview of all the psychological interventions available that, to some extent, have been found to be effective in the treatment of SBD. To the best of our knowledge, current research suggests that there are several effective treatments for SBD. This might mean that they contain generic common elements which are responsible for their positive outcome. As suggested by Bateman and Fonagy, a specific focus using a coherent theoretical model is likely to improve outcomes (Bateman and Fonagy 2009). DBT in particular showed high efficacy in suicide even if the corresponding higher rate of studies performed on suicide outcome, in comparison with the ones on different treatments, should be taken into account in the evaluation of this conclusion. Interestingly, in our meta-analysis MBT was the only efficacious treatment for the prevention of both suicide attempts and NSSI, even if the fact that only two studies on MBT have been included represents a limitation of these findings.

Concerning the relation between adherence to therapy and its efficacy, even if the hypothesis that greater adherence to therapy is indicative of its efficacy has been broadly sustained, the reported great variability renders possible another hypothesis: considering the fact that therapists are obviously not blind to the treatment, it could be hypothesized that therapists trained in new therapies could tend to be more enthusiastic and to cope with difficulties with higher liveliness in comparison to those applying standard or unstructured treatments (Lana and Fernandez-San Martin 2013; National Collaborating Centre for Mental Health 2009). Therefore, in future studies, a higher consideration of the therapy specificity should be paid.

Several setting features extensively variable throughout the studies could have represented extremely relevant factors of heterogeneity.

(i) The trials' design: the case of naturalistic studies versus randomized controlled ones; the focus on extremely different outcomes, such as suicidal ideation, suicide attempt, NSSI, self-harm, and suicidal events (Posner et al. 2007); the lack of the focus on suicidal behavior, but the focus on a broader symptomatology until psychotherapeutic process (examination of session transcripts) – the majority of the included studies were not performed with the primary outcome of suicidal behavior; the lack of a deep consideration of a differentiation between suicide prevention studies and studies focused on patients after a suicide attempt; different population samples (adults, adolescents, elderly); individual versus group therapies; the inclusion/exclusion selection criteria of SBD patients; the focus on extremely different diagnoses (e.g., BPD versus MDD); and the unpowered sample size of the studies.
(ii) The therapist factor: the duration of the therapists' training and supervision, the mean year of his/her post-training experience, and the therapists' specific training on the treatment of SBD.
(iii) The treatment factor: a systematic therapy versus a nonsystematic one; the mean duration of psychotherapeutic treatment (short- versus long-term therapies) and the number of weekly sessions; the duration of the follow-up; the use of specific therapy manuals and/or supervision groups; the concomitant use of psychotropic drugs (pharmacological classes and dosages), concurrently or sequentially and the concomitant use of further therapeutic treatments (self-help groups, family or couples therapy, psychoeducational groups); and treatments specifically focused to target SBD or not.

When cost-effectiveness of treatments for BPD has been evaluated, most evidence has been found for DBT. CBT and SFT have been found to be cost-saving as well, with scarce evidence for other interventions (Brettschneider et al. 2014). Moreover, when cost-effectiveness of SFT versus TFP in treating BPD has been assessed, the SFT was found to be less costly and more effective than TFP for recovery (van Asselt et al. 2008). Summarizing, the economic evidence is not sufficient to draw robust conclusions for all treatments, with the exception of DBT and SFT. Consequently, further studies concerning the cost-effectiveness of treatments throughout different diagnoses and specifically focusing on suicidal behavior as an effect measure are necessary.

27.14.1 Limitations

Specific limitations of this literature review and conclusions could be linked to the previously listed limitations of the included studies. In particular, the variability observed in outcome variables could have modulated differences in the results on treatment efficacy. Furthermore, the multiple hypotheses of the majority of studies, not all clearly focused on a primary outcome, and the unpowered samples could have biased the findings. Limitations linked to bias of study selection and conclusions should be acknowledged as well: articles not written in English, not included here, could offer a consistent increase on the knowledge on psychotherapeutic treatments; moreover, not all treatments could have been included here but the most extensively studied only; finally, considering my psychoanalytic background, psychodynamic concepts might be better deepened and discussed.

27.14.2 Conclusions

Consistent reduction in suicidal and self-destructive phenomena through psychotherapeutic treatments has been found throughout methodologically heterogeneous trials, in particular focused on DBT and MBT. Hence, current research suggests that there are several effective treatments for SBD. This might mean that they contain generic common elements which are responsible for their positive outcome.

27.15 Alina

I would like to conclude this chapter on psychotherapeutic treatments in suicide with the story of Alina Marazzi, an Italian courageous woman who lost her suicidal mother when she was 7 years old. With her work as a documentarist/director, she guides us through her private way to deal with grief and mourning. She firstly realized a documentary entitled "For One More Hour with You" ("Un'ora sola ti vorrei") (Marazzi 2002) entirely focused on her mother, Luisa (Liseli) Marazzi Hoepli, born in 1938. She was the granddaughter of Ulrico Hoepli (Tuttwil, Switzerland 1847 – Milan 1935), who, in 1870, had left Switzerland for Milan where he founded the publishing house which today still carries his name. The documentary is Alina's attempt to collect the pieces of her mother's life, who died in 1972 at 33. It is not possible to convey here the emotional patchwork of melodies (the film's title is the one of an old Italian love song), home movies, and recordings that Alina selected for this documentary to recreate pictures of her mother. However, the pages of Liseli's personal diaries allow putting together and describing her entire life in its different periods: the adolescence, the love, the children, and the depression. Some parts could be reported here to try to approach her. "I'd always slept comfortably in a sort of illusion of serenity where problems didn't exist but even then it was as if I already knew that I would never

really manage to fit into the world." This sounds so visionary. Liseli suffered from postpartum depression, and she extensively referred to this thematic of need and worry in front of the relation with the other: "The first face we look at when we enter into the world is our mother face. It's the one we know and remember best"; "Dear mummy, thank you for everything you did for me. I didn't do anything for my children, in fact I have made them suffer cruelly. I hope I can make up for it soon"; "Mummy dearest, it seems ages since we last wrote. I miss you more and more." You would probably say: "You've got Martino, Alina, and Antonio." "Yes, you are right, but it's different. I have so many responsibilities now and this makes me feel so alone"; "I have a terrible urge to talk these days and to be listened too as well. But then they say I am boring and I am worried about a sort of stupid things." Alina explains presenting the film that this documentary is a gift to her mother, and to all children and parents, and I think it could be of interest for professionals of mental health as well that have to deal with the everyday care of the other.

With her last movie "All About You" ("Tutto parla di te") (Marazzi 2012), Alina does a further step toward the elaboration of her mother's loss, focusing on maternity and postpartum depression. This is the story of a mirrorlike relationship between two women, Pauline, a woman in her 60s, and Emma, a young mother in deep crisis since she does not know how to face motherhood. A relationship of complicity develops between them. The climax is reached and represented in a scene in which Emma is going to abandon her child in the street during a walk. In this moment she is totally disconnected from the world outside and off-scene a ringing phone shakes her and the viewer. It is Pauline calling Emma's house. As she could hear the ringing, Emma goes back to her child, and later she will be able to discover a meaningful sense of self in her new identity as a mother, so full of complexity and dramatic features. So, the meaning suggested by the phone call is the power of being kept in the mind of the other, not being left alone, and this is the final – simple but in the meantime delicate and important – message of Marazzi's work. Hence, the director, on the contrary of her dramatic personal experience, is able to trace a difference and to provide a lively epilogue resulting from the experience of interpersonal relation.

I conclude with the last words by Liseli: "What should I do? How can I fill this void and face with, and keep it from swelling me and pushing me to such despair that I might do the most insane things? It's a question therapy hasn't found an answer to yet and I wonder what it will answer, if ever. So, I am still hoping that one day the answer will arrive and that I will find peace and serenity, not the wasteland of love and feelings."

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Advocacy Organisations

28

Károly Oriold

Abstract

According to Hungarian surveys, family members and relatives of persons who committed suicide are in substantial risk (26-fold) of also committing suicide, in comparison to members of the control group. Unfortunately there is no institutionalised help available in Hungary for suicidal families, neither in workplaces, to colleagues of the deceased, nor to officials dealing with the cases, like ambulance staff, police officers who may be confronted with suicide incidents regularly and may themselves turn to be at risk of "repetition". Non-profit organisations and foundations like the "At Home in Soul" (Hungarian name: Lélekben Otthon) regard as its prime task to support members of suicidal families, survivals (those left behind). One form of support is the dissemination of information leaflets to concerned families, police departments and ambulance centres, compiled by psychiatrists, psychologists and based on foreign good practice and experience. We have trained volunteers, who are able to provide support in the mourning process that shows differences from "normal" deaths. Guidelines are being elaborated to members of the media concerning ways of communicating suicide incidents, with a view to avoiding repetition. The support of our volunteers is now also requested in workplaces, former colleagues of the suicide victims.

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28.1 In Daily Practice: The Foundation's Help-Line

Budapest, 21st July 2014. 11 a.m.

The helpline phone rings. Elderly woman's voice:

Is that the foundation of "At Home in Soul?"	Yes, you are in the right place. This phone number was recommended to me by a friend; I am Mrs XY and would like to request your help. My son died half a year ago
Are you requesting the help of our volunteer?	Yes, they said there is someone I can talk to at your foundation, talk to someone who can help
I see, let me ask you how old are you?	I'm 61
And how old was your son?	He was 35
Did he have a family?	Yes, he left behind a one-and-half-year-old little boy (her voice choked)
I wait a few moments. All right, if we can call you back on the number displayed on my phone, then one of our volunteers will call you back today	Yes, I look forward to the call
(We hang up the phone, almost at the same time)	

The names of three volunteers come to my mind, who may be suitable to meet with her. Robert does not answer my call. Klára is next; she picks up the phone. Hello! Are you in town? Yes. A lady is asking for the support of a volunteer. Do you want to help? Are you ready for a meeting with her? All right, I will meet her gladly. Mrs XY is 61 years old, and her son died 6 months ago and left behind an 18-month-old child. A few minutes later, I get a callback from Klára. We agreed on an appointment; we are meeting tomorrow before noon, in the office of the foundation. (The location is quiet, such meetings can take place undisturbed.)

The meeting takes place on the next day.

During the summer months, we always receive more calls. Persons seeking our help are usually family members, siblings, next of kin, the father or mother, rarely the husbands. From among men, it is the fathers who have more difficulty to overcome their loss. During the autumn months, help of our volunteers is requested by colleagues of the deceased. Another busy period for our volunteers is around Christmas time.

So far we have trained about 50 volunteers. The training period is 6 months. We begin with theoretical training, lectures, case studies and numerous situation practices, evaluated by the other volunteers, who also offer their advice. Interviews are performed prior to the selection of the volunteers; we explore their background to find out why they wish to become volunteers. There are regular supervisions during their activity.

Who are our volunteers? There is also a psychologist among them, a paediatrician, teacher, lawyer, shop assistant, pensioner, factory worker, priests of the Reform and Catholic Church and also a film director. They are excellent people, helpful and

open. Our volunteers have the opportunity to meet (maximum on three occasions) with persons who received our leaflet. (Investigating police officers working around the country would hand over to relatives our leaflet in suicide incidents; in other instances, it is handed over by ambulance staff.) The helpline brochure is also available on our website, and we also have online enquirers. We operate a special helpline for those in need of our support (+36 20 464 8005, www.lelekbenotthon.hu).

A single meeting is sufficient in most of the cases, and on rare occasions, a second one may be requested, and so far there was no call for a third one. The form of the help available is explained during the first occasion.

Our leaflet is distributed to clients in the following ways:

The ambulance staff is the first to arrive to a death case, later followed by the police. In some cases, it can take hours before all the officials arrive to the site. There is emotional benefit to both the ambulance staff and police officers to be able to offer some comfort to family members, through our leaflets. At times they are only at arm's length from the deceased person, sometimes with children present. Handing over the leaflet is accompanied by the following words of comfort: We know that you are in difficulty now, but please keep this leaflet, because you may find it useful later on. Please read it later.

28.2 Our Present Situation, Working Circumstances

For the past decades, Hungary ranks very high in comparative suicide statistics figures. Many officials are embarrassed about this circumstance, the fact that society can provide poor living conditions and that we are unable to save the life of over 2,000 fellowmen. There are no national prevention programmes in place; the forms of the attempts show great variation. Instances of self-hanging and poisoning show declining numbers by the year, but the number of fatalities on railway lines is showing a marked increase (by 30–40 % just in the past 2 years, according to figures of the Hungarian Railways). In yearly average, over six fatal suicides are reported daily in Hungary, but this figure is much higher in the summer months, lower in winter and spring. Suicide is a very complex issue; it can be likened to the complexity of our thinking. There are some aspects that we need to clarify also in the effort to improve our working methods and to set the limits in our daily activity. We have to take into consideration that Hungarian population is both forgiving and admissive about suicide. At the same time, it is less admissive about illnesses and the ill; therefore, ill persons are reluctant to share the fact that they are vulnerable or "weak". Levels of social trust are still very low (study by Kopp and Strabsky 1988), and the environment of distrust is bad for our vulnerable fellow countrymen who are in need of help. They are fearful of both the social stigma and of not receiving effective support. The question arises whether a person with mental disorders will come forward to request professional help. According to a related study by Almási et al 2008), there was higher incidence of suicides among persons receiving some form of psychiatric treatment in the

control group. According to the principles adopted by staff of our foundation, persons receiving psychiatric treatment of therapy are less at suicidal risk than those untreated. Persons under medical care are in "good hands" in our opinion. Thus, the purpose of our foundation is to "guide" our high-risk clients into psychiatric or psychotherapy care.

28.3 What Are the Social Problems We Are Faced with?

Suicide is a social "taboo" in Hungary. It is part of the taboo that surrounds the topic of violence. It is part of our daily life but less spoken about. It is a question of limits, both in social and in medical terms. It is hard to decide where the boundaries are. However, it would be very important to clarify this point because the suicidal person is ill (medical study by Kalmár et al. (2010)), but the path leading to the fatal decision is dotted very much by social issues (e.g. mental health, trust, hope, expectations about the future, levels of social differences, admissive social approach to self-destruction and addictions, etc.).

We have to face the fact that the Hungarian population is both admissive and forgiving regarding suicidal activity. At the same time, it is less admissive about illnesses and the ill person; therefore, many ill persons will refuse to accept professional opinion about a mental disorder, and many will refuse to take steps for their recovery.

28.4 Theoretical Principles of the Foundation

What are the theoretical principles we are basing our activity on?

Primarily, why do we need to decrease the number of suicide incidents? Many of my fellow countrymen may think that in order to improve Hungary's bad rating in world statistics. In my view, this issue needs reconsideration. It is my conviction that if we are governed by aspects of pride, we end up in failure. When our staff is faced with acts of suicide, the main purpose is to help the other person, and we do not think about statistics. The sentiments of pain and shock are so overwhelming that we focus only on providing some form of comfort.

I personally have been active in suicide prevention in the past 13 years. I have met with a number of parents who lost their only child, born to parents past 40 years of age. These parents had no other chance (past 50) to have another child, like in the case of younger parents in similar conditions. From among the many mourning parents I have met, there were none who did have to take antidepressants or had suicidal thoughts themselves, during the crisis period. In some periods of the grievance, often the task remains just "survival" and management of the crisis situation. Our volunteers are often helping mourning persons by mitigating their strict disposal against themselves (self-accusation, why am I so weak unlike the others, it should not hurt so much, my husband and children expect that I should be over this grievance, but I'm unable…).

I have met with a number of adults whose father or mother committed suicide when they were children. The question was present in them also: If I wasn't enough reason for him/her to stay alive, then maybe I'm worthless and maybe suicide is also my fate?

The cost of each suicide incident in countries of the EU is estimated at EUR 5 million. We are seeing and experiencing these costs. Nevertheless there are no prevention campaigns in Hungary, and no state-run crisis intervention, specialising on suicide cases.

Our foundation offers support primarily to family members "left behind", but help is also offered on a wider scale, in a complex form. We are involved not only in supporting our clients but making efforts to educate and influence the public mind in the long term, by publishing and distributing to the press and media updated information on the topic.

When offering our support to clients, we have to stand to the following theoretical principles: Clarkin et al. 2010).

- The period of mourning in the wake of a suicide incident differs from normal grievance. The sense of guilt is much higher and this may turn into anger at times. If the sense of guilt is persistent, the accompanying anger can make the mourner turn against himself/herself. In this psychological stalemate in Hungary, we often see the denial and suppression of suicide.
- Suppression and denial are very often marked mechanism of self-defence. In such cases, there are openly articulated sentences such as the following: Of course he committed suicide because he was incurable with cancer. Of course he committed suicide for he had a lot of debts. It is understandable that he committed it because this is the way he wanted to help his family. In such cases (e.g. like the latter sentence), the psychological pressure on those left behind is even greater, often pathological processes are triggered. Another possible and frequent solution is the denial of the suicide incident, when the client behaves as if the relative was lost not as a consequence of the suicide.
- Some mourners are reluctant to face the reality, do not notice human flaws and weaknesses that may reveal the deceased person's drug or alcohol abuse, or his refusal to take the prescribed medicines, for failing to seek help when needed. The mourner fails to see the responsibility of the suicidal relative that may shed light on his flaws. This is part of a pathological suicide mourning process that differs from the average. It offers an opportunity for our volunteers to guide the mourners towards the reality and channel them towards a "normal" mourning process.
- Seeing a suicidal death can be so shocking at the beginning that many family members may display signs of passivity and lethargy (they are almost speechless, unable to get out of bed). We need to notice that in these instances, another relative may come forward, showing strength and ability in crisis management, who takes on a heavy burden and "steps over" his own mourning process. Consequently, the evolving interpersonal relationships within the family may become so pathological, which in turn may lead to unconscious symbiotic attachment to the other which may be very difficult to break with, in a later stage.

- When discussing the high number of suicide incidents in Hungary, there are obvious abnormal factors (like untreated depression, genetics aspect, learned or copied problem-solving methods, addictions). A significant number (5–9 %) of Hungarian male suicide incidents can be traced back to alcoholism. For example, a divorced 45–55-year-old alcoholic man commits suicide after a drunken night spent "celebrating" his unhappy birthday, usually in June, July or August Monday early morning. This high prevalence calls for a reasonable explanation.
- We also need to mention the "mirror neuron" system, although it may be widely discussed in other chapters of this study. Mirror neurons in the premotor cortex and in Broca's area of the human brain are activated both when I engage in specific instrumental actions and when I observe someone else engage in those actions. Also specific overlapping neural areas (shared representation), in parts of the frontal and parietal cortices, are activated under the following conditions: (1) when I engage in an intentional action, (2) when I observe some other person engage in that action, (3) when I imagine myself or another person engage in that action, and (4) when I prepare to imitate another person's action (Gallagher and Zahavi 2008). It is my conviction that the high number of suicide cases in Hungary can be explained through this system. The simple fact that a particular suicide incident is narrated and shared in family circles, or among friends or in workplace, may become a "pattern". In case family members witness the tragic event, then they may become part of a community's problem-solving system. People may hear the "story" of Mr. XYZ who went up to the attic on the fatal day and took with him the rope, tied it onto the beam, pulled it over his head and hanged himself. Merely the sharing of these thoughts (about the attic, the beam and the rope so familiar to the listeners) makes listeners become involved in the tragic event and activates the mirror neuron system.

Irresponsible media reporting about the venue and method of suicide incidents (with detailed photo coverage even of the victim on the front page) and its wide discussion may serve as a "pattern" also for others, to members of even larger communities, or national scale, in their own problem-solving method. Thus, we can safely say that suicide is contagious in this respect.

We must keep in mind that a suicide incident is always a movement, an act, leaving no space for words. The mirror neuron system promotes the movement activation, particularly during alcohol consumption, when neuronal impediment functions become inactive. The work performed by our volunteers gives rise to hope of success that by sharing experience and narratives of successful coping, thoughts of self-destruction are pushed into background, into a symbolic field.

In my view, there are two main factors to successful suicide prevention. One of them is the chance to build contacts and the other is the ability and process of symbolising. The contact can be likened to an open hand: e.g. the available helpline number and the e-mail address. The symbolising ability is demonstrated during our work and contact with the client.

28.5 The Beginnings

The foundation's website (www.lelekbenotthon.hu (At Home in Soul.hu)) was set up in November 2011 with the purpose of discussing mental health issues. A separate column on suicide matters was included from the start. We began by translating into Hungarian the guidelines of the WHO on suicide prevention and distributed copies (to family doctors, to prison authorities, to police departments, the media and others). We placed information on our website about setting up self-help groups for relatives. We were pleased to see that most of the enquiries on our website came from teachers and police officers. However, from among media representatives, there are almost no enquiries regarding reporting guidelines, setting down principles of proper news coverage and respecting human dignity of our fellow human beings.

The website offers the possibility of anonymous entries, or after registration using a nickname for posting comments. In March 2004, we found an unusual comment in the suicide column: "I will commit suicide on 11.09.2004". We were of course alarmed to read it. In the following days, many of our readers offered support to the 17-year-old girl who posted the message. She was asked to "talk about it" online, and it turned out to be a classic case of "cry for help". Both her parents and her school were contacted; hopefully she is safe and sound now.

28.6 The Foundation's Activity, Goals and Tasks Ahead

The activity of our foundation is very much limited. As a first step, we had to clarify what issues we can take on and those we cannot, and of course the circle of our future clients. In our efforts of suicide prevention, two distinct groups were set up. The first group, including our volunteers, is working in the "frontline", comprised of psychiatrists, family doctors, firemen, police officers, psychotherapists and psychologists. They meet face-to-face with persons in crisis; perhaps for this reason they are in high-risk category themselves (with reference to the mirror neuron model above). Persons working in the second line include media representatives, decision-makers who can influence the public mind, politicians, teachers and individuals who are able to notice warning signs of suicide and can prevent it.

Our task is to offer comfort to persons in crisis, to help our clients in their time of grief, ease their feelings of remorse and suppression and recommend for them to seek professional (psychiatry) help if necessary. We also try to take care of them and keep them safe as possible.

28.7 The Extent of Our Volunteers' Responsibility

Emphasis on the limits to the work of our volunteers is an important element in their training programme. Their role is limited in time and space. They cannot perform any activities for the person seeking their help (e.g. reporting or administration of

the incident to authorities, matters of inheritance or even posting a letter). They cannot meet the client on more than three occasions; their main task is to ease and keep the mourning period on "normal" tracks. In summary, by listening carefully, by placing the traumatic experience into a narrative and if necessary to suggest to the client to seek professional help and assist him to do so, the volunteer's task is performed.

We have prepared two kinds of information leaflets for dissemination. One of them was compiled with help from managers of the main crisis centre in Budapest, Mr Márk Bérdi and Dr. Simon Szilágyi. The leaflet is intended for our compatriots who have suicidal thoughts or even plans. We are fortunate to be able to measure the number of visitors to the suicide column of our website (including the time spent reading our leaflet). During the summer months, we have 15–20 visitors per day, who usually spend about 8–10 min reading our leaflet. We are encouraged by these online data.

Our other leaflet, as mentioned, has been disseminated to relatives of the deceased for the past 3 years, by police officers and ambulance staff on duty. A reprint was sent to police authorities on two occasions. This information leaflet explains that suicide was committed, a tragic event ("the skies fell"), and the family was left behind, thus losing a loved one. Part of this practical leaflet was translated from Swedish into Hungarian; it also includes a list of the main crisis helplines available in Hungary and an Internet link that details the related administrative tasks to be performed.

Another important activity of our foundation is to promote the psychiatry and psychotherapy in our country. We try to increase the confidence towards these institutes.

28.8 Experiences

During the past 2 years, we have offered help to about 35 clients in crisis. Can this be regarded as much or too little? Compared to local suicide statistical figures, this is a considerable number, but in absolute measure, it is but few. However, the leaflet on our website intended for persons with suicide thoughts has been read by thousands.

We are not in a position to decide how successful we are.

On the 10th of September each year, on the eve of the World Day for Suicide Prevention, we organise a major press event and ceremony during which we present an award (a diploma) to a person who had saved most lives in the given year. The first person we have awarded was Mr. József Balázs, colonel of the Fire Arms, who managed to bring down from the top of high-rise buildings and bridges countless of suicidal persons and managed to get help for persons "trapped" in their own home. The second person we awarded was Ms Éva Brandisz, who helped to save many lives over the years as a volunteer, answering calls on our helpline. She stopped this activity; in this case, she has given up her anonymity. This year we are planning to present the award to an organisation that offers computer and Internet training

programmes for the elderly. After the theoretical training, practical tasks are handed over by the manager to young volunteers. The use of the Internet mitigates the isolation of the ageing population and gives them hope and confidence while connecting them with family and friends.

The important message conveyed by our annual award ceremonies and also through our activity is that suicide is not "written in our stars", but there is hope and help available at times of difficulty. Suicide is preventable by uniting our forces in the atmosphere of trust and confidence.

The author is certified also in method-specific arts therapy, in psychological group analytics.

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Part V

A Need for Personalized Suicidology

Childhood Maltreatment

29

Nader Perroud

Abstract

Childhood maltreatment increases the risk of suicide regardless of the comorbid psychiatric disorder encountered. This increase in the risk of suicide might also be the indirect consequence of the greater severity of comorbid psychiatric disorders or the result of the impact of child abuse on intermediary dimensions such as emotion regulation and impulsivity. It is therefore important to research a history of maltreatment in childhood when treating a patient because it not only provides information on the suicide risk but also on the therapeutic direction to take. A worse response to treatment in abused subjects is indeed expected compared to non-abused ones, and the care, whether pharmacological or psychotherapeutic, may be more complicated. In the neurobiological point of view, several recent studies have shown that epigenetics plays a crucial role in mediating the impact of childhood adversities on adulthood psychopathology. These studies have highlighted quantitative (more epigenetic changes) as well as qualitative epigenetic changes in subjects reporting childhood maltreatments. Further researches are needed to better define whether these epigenetic changes may be useful, in a clinical point of view, as possible biomarkers for suicide and/or for treatment response.

29.1 Introduction

Childhood maltreatments, because of their high frequency and because of the long-lasting impact they have on the development and psychological outcomes of children, are a major public health issue. In Europe and North America, it is estimated

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that 30 % of the general population suffers, to one or another, from abuse and/or neglect in childhood, and over 10 % have been sexually abused (Afifi et al. 2011). Despite this alarming situation, the problem of child maltreatment is too often overlooked by politicians and health actors. It is therefore the duty of every caregiver to find and prevent such acts (Levitan et al. 2003).

29.2 Definition

Childhood maltreatment is defined as all forms of physical and emotional ill-treatment, sexual abuse, neglect, and exploitation that results in actual or potential harm to the child's health, development, or dignity. Traditionally, two types of maltreatments are recognized: active and passive. In its active form it includes sexual abuse, ranging from fondling to anal, vaginal, and oral penetrations; emotional abuse, including humiliation, verbal aggression against a child, direct or indirect involvement in domestic violence, and manipulation of the child by the environment; and physical abuse including all forms of bodily harm other than sex. In its passive form, childhood maltreatment includes emotional neglect or failure, for example, not to give the child the emotional necessary support, not to respond to his distress, and not to help him in his school careers, and physical neglect which includes among others the failure to meet the child's basic needs (food, clothing, physical, etc.).

If studies show that girls are more often victims of sexual abuse, boys suffer more from physical abuse. This finding could, according to some authors, account for a different expression of the psychopathology in adulthood (Bateman and Fonagy 2010a, b): girls developing borderline personality traits, whereas boys developing more antisocial personality traits. In the Western countries, childhood maltreatment is essentially preformed by a member or close relative of the family: men (father, grandfather, godfather, or neighbor) committing most often sexual violence and women (mothers usually) other forms of violence.

29.3 The Link with Suicidal Behaviors

29.3.1 The Direct Link with Suicidal Behaviors

The large majority of studies (cross-sectional and longitudinal) revealed that childhood maltreatment, of any type, increases the risk of suicide attempts and ideation in adolescence and adulthood. This effect appears relatively robust as it remains significant when controlling for several covariates including demographic ones such as age, gender, education, IQ, and family socioeconomic status, for instance (Miller et al. 2013). Moreover it also appears that this relationship is partly independent of comorbid psychiatric disorders (Miller et al. 2013). Interestingly, although, in multivariate models, particular emphasis should be given to emotional and sexual abuses as they seem to remain significantly associated to suicide when all types of childhood maltreatments are entered into the

models with emotional abuse having the strongest effects (Miller et al. 2013). This clearly needs to be investigated further, as, according to some theory, the emotional component of maltreatment might be the core phenomenon linking abuses to adulthood psychopathologies (Bateman and Fonagy 2004, 2010b). Finally, the risk of suicide attempts increases with greater severity of abuses/neglects with an additive effect of these maltreatments (Zoroglu et al. 2003). For instance, Fergusson et al. (1996) found that the relative risk of suicide attempt in adolescents was greater when they report sexual abuses involving contact (i.e., touching, intercourse) with the perpetrator compared to adolescents who reported noncontact sexual abuse (i.e., verbal sexual harassment) or no sexual abuse history. One very interesting study found that the risk of suicide attempt correlated with the degree of relatedness between the victim and the perpetrator, namely, the closer was the victim to his/her abuser, the higher was the risk of suicide (Brezo et al. 2008). This again strengthens the hypothesis that what matters in terms of increasing the risk of adulthood psychopathology (including suicidal behavior) is the emotional component of it; when a subject is not able to receive the support from his/her caregiver because the latter is the perpetrator of the abuse, this weakens the construction of the self and identity leading to emotional dysregulation and consecutively to suicidal behaviors. This hypothesis has been well studied in borderline personality disorder and should clearly deserve more emphasis in relation to suicidal behaviors.

29.3.2 The Indirect Link with Suicidal Behaviors

Apart from increasing the risk of suicide attempts and ideation independently of psychiatric disorders, childhood maltreatments might also act indirectly by increasing the risk of other psychiatric disorders, the latter being then a trigger for the emergence of suicidal behavior in the stress-diathesis model. Early adverse life events and especially abuses in childhood increase the risk of suffering from psychiatric diseases strongly associated with suicidal behaviors such as bipolar disorder, borderline personality disorder, major depressive disorders, anxiety disorders, substance dependence, psychotic disorders, and posttraumatic stress disorder (Scott et al. 2010). For instance, 40–60 % of subjects suffering from bipolar disorder report having experienced severe physical or sexual abuse during childhood (Goldberg and Garno 2005). In one study of 118 patients with a first manic episode, 80 % had suffered from stressful life events in childhood, and 24.9 % had experienced severe physical or sexual abuse (Conus et al. 2010). In this perspective, childhood maltreatment or early adversity accounts for about 30–70 % of the population attributable risk fraction of psychiatric disorders (Teicher and Samson 2013). This observation is stronger if the heritability component of the disorder is low. The attributable risk is indeed lower for bipolar disorder or schizophrenia than for depression or borderline personality disorder. Concerning the risk of suicide, exposure to adverse experiences in childhood accounts for 67 % of the population attributable risk fraction for suicide attempts (Teicher and Samson 2013). Childhood maltreatment therefore plays a significant role in increasing the risk of suicide in a person.

Early traumas not only promote the emergence of psychiatric disorders but are also associated with greater severity of these: early age at onset, poor response to treatment, more frequent hospitalizations, poorer premorbid functioning, poorer cognitive performance, and, for bipolar disorder and depressive disorder, more psychotic symptoms and more and longer mood episodes (Bifulco et al. 2002; Leverich et al. 2002; Garno et al. 2005). So if we consider suicidal behavior as a marker of severity of psychiatric disorders, it is natural to think that the adverse events experienced in childhood promote their appearance in adolescence or adulthood.

Child abuses might moreover promote the expression of intermediary dimensions such as impulsivity or poor anger control possibly by the impact they have on the serotoninergic systems (Braquehais et al. 2010; Maniglio 2011). This dysfunction of the serotoninergic system and its related increases in impulsivity and aggressiveness may secondarily promote suicidal behavior (Maniglio 2011). This is supported by several data suggesting that suicidal patients have low levels of serotonin metabolites (Asberg et al. 1976).

29.4 The Neurobiology of Child Maltreatments

People who experienced maltreatments in childhood have different specific biological changes compared to people who did not experience such events, independently of the coexisting psychiatric disorder. Several studies have consistently shown reduced size of the hippocampus and a smaller number of neurons in this structure in maltreated subjects or in those having lived stressful life events in childhood than non-abused subjects (Vythilingam et al. 2002; Woon et al. 2010). This structure is actively involved in cognitive functions and in our ability to regulate emotions and could be responsible for the greater vulnerability of abused subjects to develop psychiatric disorders including suicidal behavior. The amygdala, another region which plays a crucial role in our response to certain emotions, is also associated with childhood maltreatment. Indeed overactivity of this structure in response to faces showing emotions was observed in people with a history of trauma in childhood (van Harmelen et al. 2013). The anterior cingulate cortex, the orbitofrontal cortex, and the dorsolateral prefrontal cortex are also sensitive to childhood maltreatments in the sense of a reduction in their activity (Cohen et al. 2006). Finally, the serotonergic system seems particularly vulnerable in the sense of depletion of serotonin stocks by repeated stress (Matsumoto et al. 2005).

It also appears that there are key periods when these brain regions are more sensitive to the impact of the environment than others and that maltreatment suffered at the age of 3 years would not have the same effect on the brain development than an abuse suffered at the age of 11 years (Lupien et al. 2009).

Child abuse could therefore disrupt the development of brain regions necessary for regulating emotions and other functions such as impulsivity or decision making. The dysfunction of these regions, the prefrontal cortex and amygdala in particular, has also been observed in people with suicidal behavior (Jollant et al. 2011).

29.4.1 The Stress Response System and Epigenetics

The hypothalamo-pituitary-adrenal (HPA) axis is the main system of stress response and is activated when one is faced with an environmental stressor. Many studies, both in humans and in animals, have shown that childhood maltreatments have a long-lasting impact on this axis mainly in the sense of hyperactivity (McGowan and Szyf 2010). Some authors have suggested that the excess glucocorticoids resulting from this hyperactivity of the HPA axis could account for the neuroanatomical abnormalities observed in victims of child abuse. Indeed glucocorticoids have a neurotoxic effect well demonstrated in animal studies, and it is probably the same in humans (De Bellis et al. 1999). Genetic studies have shown that genes playing a key role in the regulation of this axis significantly interacted with child abuse to increase suicide risk (Ben-Efraim et al. 2011). Animal studies have successfully demonstrated that early stress permanently alters the HPA axis and that these changes are associated with long-lasting abnormal behaviors in animals in the sense of more reactivity to stress (Heim and Nemeroff 2001). More recently, researchers have been able to correlate these permanent changes of the HPA axis to changes in the regulation of gene expression, commonly called epigenetic mechanisms. Both in humans and in animals, child maltreatment has been associated with increased methylation of the gene coding for the glucocorticoid receptor (*NR3C1*) (McGowan et al. 2009; Perroud et al. 2011). This increased methylation of the *NR3C1* gene is associated with less expression of the glucocorticoid receptor and consecutively with an overactivity of the HPA axis. The resulting excess of glucocorticoids, by their neurotoxicity, will disrupt brain development which will favor the development of psychiatric disorders in adulthood including suicidal behavior (Perroud et al. 2011).

Although *NR3C1* has clearly been the most studied gene in terms of epigenetics, several other genes involved in the regulation of the HPA axis were also found to be changed in relation to early life adverse events such as the gene coding for arginine vasopressin (*AVP*) or the one encoding a protein regulating the binding of glucocorticoids on their receptor (*FKPB5*) (Klengel et al. 2013; Murgatroyd and Spengler 2014). Finally other genes involved in the brain development such as *BDNF* (for brain-derived neurotrophic factor) have also been linked to child abuse and/or psychiatric disorders. This gene is of particular interest as it plays a major role in brain plasticity and neuronal migration and differentiation especially during brain development. Animal and human studies found hypermethylation of this gene in relation to psychosocial stress (Tsankova et al. 2006; Roth et al. 2011; Perroud et al. 2013). More interesting is the fact that a specialized type of psychotherapeutic treatment for borderline personality disorder, a disorder strongly associated with suicidal behaviors, was found to be associated with demethylation of methylated regions in the *BDNF* gene (Perroud et al. 2013).

Very recently whole-genome analyses have been launched and revealed epigenetic changes not only qualitatively but also quantitatively in connection with childhood maltreatment. Indeed these studies have found a general reprogramming of DNA methylation in connection with environmental stresses (Perroud et al. 2013;

Prados et al. 2015). This suggests that the candidate gene approach is certainly far too restrictive and does not take account of the complexity of systems affected by early life adversities.

Although usually not directly considered in the so-called epigenetic mechanisms, microRNAs (miRNAs) deserve some considerations. miRNAs are small noncoding RNAs, with a length ranging from 21 to 23 nucleotides, regulating protein synthesis through the inactivation or degradation of the RNA messengers. They therefore play a key role in gene expression as well as other epigenetic factors and could therefore be important players in mediating environmental effects on humans (Sato et al. 2011). In addition, miRNAs are differentially expressed at different developmental stages, so they are of great interest in understanding the impact of early stress on brain development and thus on the psychiatric outcome of subjects exposed to such stress (Dwivedi 2014). In this perspective, a recent study has been able to demonstrate, in mice, that early stress alters the expression of many miRNAs resulting in behavioral and metabolic problems in adulthood but also in the offspring of these mice (Gapp et al. 2014).

29.5 Childhood Maltreatment in Clinical Setting

Childhood maltreatment thus has an important impact on brain development and thus on the coping mechanisms of the individual to face the world. Brain lesions in people having endured child abuses account for the greater difficulty in regulating emotions, the tendency to be impulsive, and impaired decision making. This certainly accounts for the increased suicide risk among abused subjects. Because child maltreatment accounts for a large variance of the attributable risk in suicidal behaviors, it might be possible to consider such conduct as an epiphenomenon of these traumas. Considering this, it seems crucial for any clinician to ascertain the existence of childhood maltreatment in the history of a patient, because the risk of suicide, independently of other variables, is certainly not the same for abused and non-abused subjects.

Assuming that the expression of psychiatric disorders is not the same in abused and non-abused subjects, some authors have proposed considering subjects who suffered from child maltreatment as a distinct clinical subgroup (Teicher and Samson 2013). People abused as children have a more severe "phenotype": early age of onset of the disease, poorer response to treatment, greater vulnerability to suicidal behavior and nonspecific laboratory abnormalities such as specific brain changes, changes in gene expression, disruption of stress regulation systems, reduction of telomeres, and reduced life expectancy (Teicher and Samson 2013). Teicher et al. (Teicher and Samson 2013) have suggested that the subtype "abused" could be thought of as a phenotypic specialization (a "phenocopy") whose main feature would be the result of environmental experience or an "ecophenotype". These authors and others also assume that childhood maltreatments and not the ones occurring later in life of an individual are responsible of the increased risk in developing psychiatric disorders and hence suicide in adulthood. Bateman and Fonagy

(2004, 2010a), in their treatise on mentalization and borderline personality disorder, hypothesized, on the basis of many neurobiological studies, that the mother-child interaction or more generally the caregiver-child interaction is crucial for the proper development of personality. Any disruption of this relationship, already at a very early stage, would be associated with a weakening of identity construction leading to a weakening of the defenses of the subject enabling the emergence of a psychiatric condition. Child abuse is therefore thought to be a nonspecific enhancer of biological vulnerability for a given psychiatric pathology. Bateman and Fonagy assume that failure to mentalize directly arises from this inability of the environment to teach the child's emotions. This lack of mentalizing is the core etiological factor of borderline personality disorder and therefore of suicidal behaviors in this disorder (Bateman and Fonagy 2004, 2010b). As mentioned above, for these authors as well as others, emotional abuse, and not other forms of abuse, is thought to be the main determining factor of in the development of psychiatric disorder in adulthood (De Bellis et al. 1999), sexual and physical abuses having an impact mainly because of their emotional component. In summary this is not the fact of having been sexually abused as a child that matters (in terms of making an individual more vulnerable for the development of a psychiatric disorder), but the fact that this abuse is not recognized by relatives or even worse perpetrated by them.

Many studies have shown that maltreated people respond less well to treatment regardless of the psychiatric disorder (Teicher and Samson 2013). It is therefore important to be aware of the existence of a child abuse or neglect in the childhood of a patient, as the care of an abused person is expected to be more difficult than a non-abused one! Interestingly, it seems that abused subjects may preferentially respond to non-pharmacological treatments. In a study of depressed subjects who suffered or not from child abuse, it was found that cognitive behavioral therapy (CBT) was superior to nefazodone in abused subjects, non-abused ones responding better to nefazodone (Nemeroff et al. 2003). If these results were to be confirmed, specific psychotherapeutic approaches for people who experienced child abuse could be useful. These approaches should focus on emotion regulation and impulsivity as these dimensions are disturbed by childhood maltreatments and promote suicidal behaviors. Although not specifically targeting suicidal behaviors, psychotherapeutic approaches for people with borderline personality disorder, such as mentalization-based treatment (MBT) or dialectical behavior therapy (DBT), reduce suicidal behavior in this population and may represent an alternative for the treatment of suicidal patients who have experienced abuse in their childhood (Bateman and Fonagy 2004; Harned et al. 2010). These approaches indeed focus on emotion regulation and impulsivity in order, among other things, to reduce the risk of suicide. They have in common to consider childhood maltreatment as an aggravating factor of current conditions, and they encourage clinicians to investigate the existence of traumas in childhood. But, and importantly, they also insist that, once the information has been collected, clinicians should avoid talking about these maltreatments during therapy. Insisting or using childhood traumas to understand what is happening during a session would only worsen the clinical situation (mainly by increased arousal and emotional distress not allowing the patient to participate fully

to the session) and is therefore prohibited. In a recent meta-analysis of suicide attempts and self-harm in adolescents, Ougrin et al. found DBT and MBT to be effective in reducing these behaviors, but there is still a need for independent replication, and this should be a research priority in the search of targeted interventions to prevent suicide (Ougrin et al. 2015).

Conclusions

Current research suggests that child abuse increases the risk of suicide. However, it remains unclear whether this increased risk is an indirect effect of a more severe psychiatric disorder, an effect on intermediate dimensions such as emotion regulation and impulsivity or if there is an independent effect. Clearly research in the field is just beginning and cannot clearly answer this question. However, from a clinical point of view, it is important to be aware of the existence of a trauma in a patient because it influences the expression of this disorder not only by increasing the suicide risk but also by modifying the treatment response. Although clinicians should investigate whether a patient suffered from child maltreatment as this would help targeting the treatment, it is not recommended to use this information latter in the psychotherapeutic sessions with the patient, as it will only worsen the clinical condition. It is important to focus on the current problem and help the patient find a solution to his/her desire to die if the risk of suicidal behavior is the object of the treatment.

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Family Risk Factors for Suicidal Behavior: Opportunities for Early Identification and Intervention

30

David A. Brent

Abstract

In this chapter, the most common and potent familial risk and protective factors for suicidal behavior will be reviewed, namely, family history of psychiatric disorder and suicidal behavior and exposure to family adversity, such as bereavement, divorce, or maltreatment. We then will discuss strategies for identification of families and youth at risk and extant and proposed preventive interventions that could attenuate the risk for youth suicidal behavior.

The following schematic (Fig. 30.1) provides a developmental framework for understanding familial risk and protective factors as targets for screening, prevention, and early intervention. Individuals are at risk for suicide and suicide attempts due to family history of suicidal behavior, psychiatric disorders, and impulsive aggression that increase the likelihood that the child will inherit these conditions, which increased offspring's risk of suicidal behavior. In addition, family history increases the likelihood of perinatal complications, and of family adversity, both of which also increase the likelihood of child risk factors and of suicidal behavior. We first review the relationship of each of these categories of risk to suicidal outcome and then, using this developmental framework, discuss evidence-based preventive and treatment interventions that target these risk factors to decrease the risk of suicidal behavior or one of its precursors.

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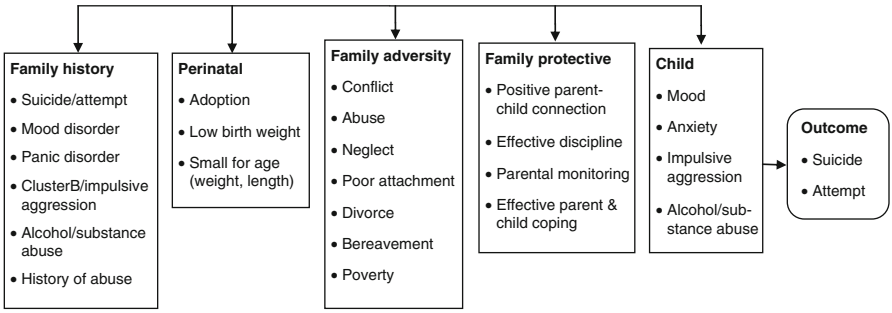

Fig. 30.1 Family-environmental factors leading to suicidal behavior

30.1 Family History

30.1.1 Family History of Suicidal Behavior

Parental and sibling suicide and suicidal behavior increases the risk for suicidal behavior two- to sixfold (Brent and Melhem 2008; Geulayov et al. 2012). The clinical phenotype that is familially transmitted includes both suicide attempts and suicide, since relatives of suicide victims have higher rates of suicide attempts, and vice versa (Brent and Melhem 2008; Geulayov et al. 2012). Although non-suicidal self-injury (NSSI) has been shown to be a risk factor for attempted suicide (Cox et al. 2012), a family history of suicidal behavior is not related to risk for NSSI, nor is a family history of NSSI is related to suicidal behavior (Cox et al. 2012; Geulayov et al. 2014). Familial aggregation of suicidal behavior persists even after controlling for the transmission of psychiatric disorder (Brent and Melhem 2008; Qin et al. 2002). Genetic mechanisms are supported by adoption studies that show a higher rate of suicide in the biological relatives of suicide victims but no increase in the adoptive relatives, and twin studies that show higher concordance for suicidal behavior in monozygotic twins vs. dizygotic twins (Brent and Melhem 2008). In a nested case-control study of 14,440 patients hospitalized for a suicide attempt and 144,400 controls, the attributable risk for a suicide attempt conferred by familial suicidal behavior and familial psychiatric disorder was 8 % and 13 %, respectively (Mittendorfer-Rutz et al. 2012). Twin studies show that the unique heritability, above and beyond that of psychiatric disorder for suicide attempt, is 17 % and of the broader phenotype of ideation and attempt, 30–55 % (Brent and Melhem 2008).

The mechanism of transmission of suicidal behavior from parent to child, particularly in earlier onset suicidal behavior, appears to be in part explained by the transmission of impulsive aggression, defined as a tendency to response with hostility or aggression to provocation or frustration (Brent and Melhem 2008). In a 5.6-year longitudinal study of 701 offspring of mood-disordered parents, around half of whom had a history of a suicide attempt, parental suicide attempt conveyed a 4.7-fold increased risk for offspring attempt, even controlling for offspring previous

attempt and mood disorder (Brent et al. 2014). Parental suicidal behavior was also transmitted via offspring mood disorder, and indirectly by impulsive aggression, which in turn increased the risk for mood disorder.

30.1.2 Parental History of Psychiatric Disorder

In a World Health Organization survey of 55,299 respondents, every type of parental disorder was associated with offspring suicidal ideation (Gureje et al. 2011). Parental depression and generalized anxiety disorder were related to the onset and growth of suicidal ideation, and parental antisocial personality, generalized anxiety, and panic disorders were related to attempts in those with ideation, and the number of parental disorders was also related to the risk for attempt in dose-response manner (Gureje et al. 2011). Although these analyses controlled for offspring disorder, the parental disorders associated with a transition from ideation to attempt are very similar to offspring disorders of impulse and distress (e.g., antisocial and panic disorders) associated with such a transition (Nock et al. 2009).

There is an increased risk for suicidal behavior in the offspring of parents who are psychiatrically hospitalized, with the greatest effects within the first 2 years of the hospitalization and during adolescence (Mittendorfer-Rutz et al. 2012; Stenager and Qin 2008). Offspring of biological parents who had attempted suicide were more likely to attempt suicide themselves if their adoptive mother had been hospitalized for a psychiatric disorder (Wilcox et al. 2012). In young suicide attempters, persistent parental psychiatric disorder increases the risk of reattempt (Jakobsen et al. 2011). Maternal depression has been shown to interfere with efficacious treatments for child and adolescent anxiety and depression (Brent et al. 1998; Southam-Gerow et al. 2001), and conversely, treatment of maternal depression improves child functioning and symptoms of externalizing (Pilowsky et al. 2008) and internalizing (Swartz et al. 2008) symptoms.

30.1.3 Perinatal Factors

Adoptees are at least twice as likely to attempt suicide as non-adoptees, with the highest risk for international adoptees (von Borczyskowski et al. 2006). In a nested case-control study of 1047 suicides and 10,752 suicide attempters matched to 10 controls, low birth weight, short length, and being small for gestational age increased the risk for suicide attempt (Niederkrotenthaler et al. 2012).

30.2 Family Adversity

30.2.1 Socioeconomic Adversity

Multiple changes in residence are associated with suicide attempt and suicide, in a dose-response manner, even controlling for parental loss and parental and personal

psychiatric history (Qin et al. 2009). Experiencing socioeconomic adversity is related to an increased risk for attempts (Fergusson et al. 2000; Agerbo et al. 2002). The effects of neighborhood poverty may be mediated by exposure to more negative life events (Dupere et al. 2009).

30.2.2 Parent-Child Relationship

A poor parent-child relationship is predictive of ideation and suicide attempts in young adolescents (Fergusson et al. 2000). Conversely, a positive relationship with at least one parent is protective against suicidal ideation and behavior (Samm et al. 2010).

30.2.3 Family Constellation

Living in a family without the presence of both biological parents, as well as marital disruption, is associated with an increased risk for suicide attempt and suicide (Fergusson et al. 2000; Agerbo et al. 2002), although the effect may be attenuated after controlling for parental psychiatric disorder (Afifi et al. 2009). Young age of parenthood is associated with an increased risk for suicide and attempt (Niederkrotenthaler et al. 2012).

30.2.4 Abuse

Children whose parents have a history of sexual abuse are much more likely to attempt suicide, with the effects additive to parental history of suicide attempt (Melhem et al. 2007). Abuse, particularly sexual abuse, greatly increases the risk for an attempt, even after controlling for the risk for mental disorder. Sexual abuse may explain 19 % of the population attributable risk for suicide attempt in youth (Fergusson et al. 2000; Enns et al. 2006; Molnar et al. 2001). Parental history of suicidal behavior and mood disorder are related to offspring abuse, impulsive aggression, earlier onset of mood disorder, and suicide attempt (Mann et al. 2005).

30.2.5 Bereavement

Parental death by suicide, accidental death, or sudden natural death is associated with higher rates of mood disorder and substance abuse in the deceased and surviving biological parent and greater exposure to negative life events, discord, and abuse (Melhem et al. 2008). In a study of 26,096 individuals bereaved by parental suicide, and 32,395 bereaved by parental unintentional injury, the rate of hospitalization for suicide attempt was higher in both groups than in non-bereaved controls, with the highest risk and earliest onset in those bereaved by suicide (Kuramoto et al. 2013). In a registry study of 44,397 offspring of parental suicide and 41,467 parents with

accidental death, and 3,807,867 non-bereaved controls, bereavement by suicide was associated with an increased risk for suicide and suicide attempt (Wilcox et al. 2010). Parental bereavement by suicide, relative to bereavement by accident or sudden natural death, is associated with a higher risk of depression, alcohol and substance abuse, and blunted cortisol response to a social stressor in offspring (Brent et al. 2009; Hamdan et al. 2013; Dietz et al. 2013).

30.2.6 Offspring Factors

Suicidal ideation is related to mood and anxiety disorders, but the transition from ideation to attempt is associated with disorders of distress (e.g., panic disorder) and of impulsivity (e.g., antisocial disorder, substance abuse) (Nock et al. 2009). Impulsive aggression increases the risk for mood disorder and suicidal behavior (Brent et al. 2014).

30.3 Implications for Early Detection and Intervention

In this section, we provide some examples of intervention programs that have been shown to have an impact on at least one of the risk factors for suicidal behavior.

30.3.1 Parental Suicidal Behavior and Psychiatric Disorder

If a younger person is suicidal, it is important to assess parents, as parental disorder such as depression can lead to recurrence of suicidal behavior (Jakobsen et al. 2011) and treatment nonresponse (Brent et al. 1998; Garber et al. 2009). Treatment of parental disorder can also result in symptomatic improvement for offspring (Pilowsky et al. 2008; Swartz et al. 2008). Conversely, if a parent is hospitalized for suicidal behavior, the children should be assessed to determine whether they are manifesting risk factors for suicidal behavior.

There are preventive interventions for parents with mood disorder that have been shown to reduce the incidence of offspring depressive disorder (Garber et al. 2009). A family-based cognitive intervention for the offspring of depressed parents may be especially robust with respect to outcome, regardless of parental mood status, and had effects on both internalizing and externalizing symptoms (Compas et al. 2011).

30.3.2 Perinatal Factors

Adopting parents should be aware that adoptees are at higher risk for suicidal behavior and be mindful to seek evaluation for children with symptoms and functional impairment. Adequate prenatal care may help to prevent or reverse inadequate intrauterine growth.

30.3.3 Abuse

The Nurse Family Partnership (NFP), which involves around 20 visits from a nurse to mother when the child is between 0 and 2 years of age, reduces crime and substance abuse and improves employment in both mothers and children (Kitzman et al. 2010). In one study of NFP, the incidence of child abuse was reduced (Selph et al. 2013). While the incidence of suicidal behavior as a result of participation in the NFP has not been reported, the NFP does result in reduced premature mortality among youth and mothers (Olds et al. 2014). A primary-care-based intervention, Safe Environment for Every Kid (SEEK), which consists of a screen for maltreatment risk by the pediatrician followed by a referral to a social worker for high-risk families, results in fewer child welfare reports and decreases harsh parenting, compared to usual care (Selph et al. 2013). The Triple P program is a stepped intervention that ranges from a brief educational parent intervention to intensive family treatment. In a randomized clinical trial, with the county as the unit of analysis, Triple P reduced the incidence of child welfare reports, emergency room visits for maltreatment, and child removal from families for maltreatment (Prinz et al. 2009). In families where child abuse has already taken place, the combination of self-motivation and Parent-Child Interaction Therapy (PCIT) resulted in fewer child welfare reports than comparison conditions (Chaffin et al. 2011).

30.3.4 Socioeconomic Adversity

In a natural experiment, a casino was opened on an American Indian reservation in North Carolina and provided employment and income supplements to members of the tribe. In children of families who moved from below to above the poverty line, there was a decline in child externalizing symptoms, with benefits sustained in these youth into adulthood (Costello et al. 2003, 2010).

30.3.5 Divorce and Bereavement

Prevention scientists developed a 12-session parallel group session for children and parents undergoing divorce, the New Beginnings Program (NBP), with a similar intervention for bereaved parents and children, the Family Bereavement Program (FBP). These interventions focus on promoting positive, engaged parenting, with appropriate discipline and parental monitoring, and adaptive coping for youth. While samples are too small to detect effects on suicidal behavior, 15-year follow-up of the divorce sample demonstrated that the NBP improved parent mental health and child school performance and lowered the risk of child internalizing and externalizing disorders, with the effects mediated by more positive and effective parenting and improvement in child coping (Wolchik et al. 2013; Sandler et al. 2011). Similarly, after the 6-year follow-up, FBP resulted in decreased parental symptomatology,

decreased youth symptoms of complicated grief, internalizing, and externalizing disorder, improved self-esteem, and higher morning basal salivary cortisol, with similar meditational patterns to NBP (Ayers et al. 2013; Luecken et al. 2014).

30.3.6 Family Conflict and Promotion of Protective Factors

There are some universal and indicated preventive interventions to promote effective and better decision-making with regard to substance use among adolescents that have demonstrated decreases in rates of delinquency and alcohol and drug use, such as the Promoting Drug-Free Years (Mason et al. 2003). Another effective intervention is the Family Check-Up, a stepped, universal intervention that provides feedback on observed family interactions and education about positive parenting, with several levels of more intensive intervention for those with more problematic family interaction (Van Ryzin et al. 2012). The Communities That Care (CTC) program is a "meta-prevention" intervention, in which communities are engaged in an assessment of youth risk and protective profiles and a planning process to decide which evidence-based prevention programs to implement or enhance. In community-level randomized trials, CTC resulted in strong, enduring effects on delinquency and alcohol and drug abuse in high school students, compared to usual management (Hawkins et al. 2014).

30.3.7 Child Factors

A common profile for suicide in youth is the combination of conduct disorder, alcohol or drug abuse, and depression, particularly in males (Shaffer et al. 1996). Longitudinal studies show that impulsive aggression is a precursor to depression and suicide attempt (Brent et al. 2014). Therefore, interventions to target impulsive aggression can prevent the progression to mood disorders and suicidal behavior (Kosterman et al. 2009).

The Good Behavior Game (GBG) is a universal classroom-based intervention implemented by teachers to teach first graders skills in problem-solving and self-regulation. Randomized trials show enduring program effects into young adulthood, with higher employment rates and lower levels of criminality, alcohol and substance use, externalizing and internalizing symptoms, and suicidal ideation and, in one of the two trials, lower rates of suicide attempts (Embry 2002; Wilcox et al. 2008).

Familias Unidas is a family intervention for delinquent Latino youth that emphasizes the above-noted elements of effective parenting. Latino youth with externalizing problems treated with Familias Unidas, relative to comparison treatments, reduced criminal involvement, drug and alcohol use, and depressive symptoms, with the effects mediated through improvements in parent-child communication (Perrino et al. 2014).

30.4 Summary and Conclusion

Parental suicidal behavior, mood, panic, and antisocial disorders can increase the risk of suicidal behavior in offspring. Family adversity, e.g., maltreatment, parent-child discord, residential instability, and negative life events such as parental bereavement or divorce, also contributes to suicidal risk in offspring. The clinician should consider family context in order to identify and intervene with family risk factors, which in turn attenuate the risk for suicidal behavior in offspring. Specific strategies include being aware of psychiatric disorder in the parents and screening for maltreatment and maladaptive parenting. There are effective interventions to decrease the incidence of maltreatment. Others can improve parenting in order to buffer parents and children from the effects of bereavement and divorce and decrease the risk of substance abuse, delinquency, and internalizing disorders.

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The Gender Matters

31

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Abstract

While there is converging evidence suggesting gender differences in the rates of suicidal behaviors, substantially less is known about the mechanisms underlying these differences. What follows is a review of the evidence supporting gender differences in suicidal behaviors, including epidemiology, age trends, methods, risk and protective factors, treatment, and the effects of sexual orientation and culture.

Although some of the gender differences in suicidal behaviors may be partially explained by environmental and behavioral factors, there is very little data on the role of sex differences in neurobiological risk factors. Surprisingly, the role of sexual hormones and sex differences in brain development on the risk for suicidal behaviors remains largely unexplored.

31.1 Epidemiology of Suicide: Focus on Gender and Age

Gender differences in both suicide attempts and suicide have been documented for many years (Pitman et al. 2012). With few exceptions, this gender gap has been reported globally (WHO, 2014). Females tend to have higher rates of suicide attempts than males at a 3:1 ratio (Baca-Garcia et al. 2010; Kessler et al. 1999; General 2012), while males have higher rates of suicide at a 4:1 ratio compared to females in most countries (WHO suicide rates).

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For example, in the United States, in 2012, a total of 286,367 females attempted suicide compared to 197,229 males (CDC 2014). However, males complete 79 % of all suicides in the United States (CDC 2012). In 2011, there were 31,003 suicides by males compared to 8515 suicides by females.

The rates of suicide decrease with age in both females and males. Suicide is the second leading cause of death in both genders from ages 15–24 and then proceeds to drop down the list with age (CDC 2012).

In females, the highest rate of suicide occurs between ages 45 and 54. It is notable that after age 54, suicide drops off of the ten leading causes of death in females but remains a leading cause of death for males until age 64. Indeed, suicide rates for men are highest among those aged 75 and older. Thus, men in midlife and older men have been consistently identified as high-risk groups with particularly high rates of suicide that need to be targeted by prevention programs (General 2012).

31.1.1 Explaining the Gender Gap in Suicide

There are several theories that aim to explain the evident gender gap that is seen in both suicide attempts and suicides; they include choice and access to lethal methods as well as views of these behaviors as either masculine or feminine.

A higher proportion of males (84 %) use violent methods, more likely to result in death, as compared to females (54 %) (McGirr et al. 2006). The three most common methods that have been observed in completed suicides in both genders are firearms, hanging, and drug poisoning in the United States. US women are 73 % less likely to use firearms – a particularly lethal method – as a means of committing suicide than men (Kposowa and McElvain 2006). Hanging is the most common method of suicide used by young men in Europe and Australasia; pesticide poisoning is the leading method used by young men in India, and charcoal-burning is rising as a leading cause of suicide by young men in Taiwan and Hong Kong (Pitman et al. 2012). The trend in method choice appears to be constant through the life span as adolescent males are also more likely than females to use means of suicide that are more irreversible and this is due to the fact that females tended to overdose (Brent et al. 1999).

Another reason why method is an important consideration is because it may affect whether the incident is considered a suicide attempt or not. For example, women use less immediately lethal means of suicide which can at times be misconstrued or not identified as a suicide, i.e., self-poisoning versus shooting self in head (Canetto and Sakinofsky 1998). Furthermore, the "rescuability" of a suicide attempt will affect the ratio of completed suicides versus attempts regardless of intent. For example, a woman who poisons herself with complete intent does not result in immediate death, providing the possibility of survival if helped in time. This chance of survival is not true for more immediate methods that are usually used by males (Canetto and Sakinofsky 1998). In males, guns and explosives are used four times more than either hanging or self-poisoning.

Supporting this theory, firearms significantly outnumber the other methods used by males; self-poisoning is the method of choice in females and results in a lower rate of death.

The definition of a "suicide attempt" is also an important factor in these studies as Nock and Kessler (2006) found that almost half of the participants studied that reported suicide attempt stated they had no intent to die. Intent is always a significant factor when addressing suicide risk and is independent from a physician's perceived lethality of a suicide attempt.

Females and males who attempt suicide appear to have equal intent in wanting to kill themselves (Canetto and Sakinofsky 1998). Thus, it appears that the gender gap in suicide completions may be explained by method choice better than by intent (Denning et al. 2000). The level of intent seems to be constant across the life span. Indeed, when looking at adolescent males and females, there was no difference in suicidal intent (Brent et al. 1999). Nock and Kessler (2006) also found that the level of intent to die seems to be persistent in those with repeated self-injurious acts as 70.8 % of them reported the same level of intent for their first and most recent acts. However, adult males who perform self-injurious acts may be more likely to report an intent to die (Nock and Kessler 2006).

Men and women also may differ in factors that increase risk for future suicidal acts (Oquendo et al. 2007). In a depressed population, a history of suicide attempts is a significant risk factor for both genders; however, it is more significant in females as it increased the risk of future suicidal acts sixfold versus a threefold increase in males (Oquendo et al. 2007). Moreover, although major depression is a known risk factor for suicidal acts in both men and women, the annual rates of suicide relative to the annual rates of major depression were higher among men compared to women. This may be interpreted as depression having a larger impact on suicidal risk among men or as evidence for factors that protect women against suicide in major depression (Oquendo et al. 2001).

Other factors such as socioeconomic cycles may have a different impact on risk for suicide in men and women due to the different rates of employment and different cultural roles for each gender (Blasco-Fontecilla et al. 2012). For example, in many cultures, men are expected to be the main breadwinner for the household. Pitman et al. (2012) analyzed suicide patterns in 44 countries. They observed that, though the absolute number of suicides is about the same in high-income versus low-income countries, suicides make up a higher proportion of the total deaths in young men from higher-income countries.

Gender-specific views of suicide attempts versus completed suicides may also be an important factor. Studies have suggested that suicide attempts are seen as feminine which can lead to two different hypotheses: males may underreport these acts for fear of being seen as less masculine or the effect may be protective in that men will avoid performing those behaviors so as to not be seen as effeminate (Canetto and Sakinofsky 1998).

Interestingly, completed suicide is seen as a masculine act, so that males may ensure that the act is something that they will not survive because by surviving it, it would become a feminine act.

31.1.2 Sexual Orientation, Gender, and Suicidality

Lesbian, gay, bisexual, and transgender (LGBT) populations have been recently identified as a high-risk group for suicidal behaviors. In a meta-analysis including data from over 200,000 individuals, lesbian, gay, and bisexual individuals had a two- to fourfold excess in risk for suicide attempts compared to the non-LGBT population (King et al. 2008). The increase in suicide risk was larger among men compared to women.

Same-sex sexual orientation is associated with increased risk of suicide attempts in adolescent females and males, even after controlling for risk factors common to all adolescents (Russell and Joyner 2001; Marshall et al. 2011). Remafedi et al. (1998) found a significant association with increased suicidal intent and attempts among bisexual or homosexual males. More than a sevenfold increase in odds of attempting suicide was seen in that population. Intriguingly, this association is not as strong in bisexual or homosexual females.

The increased risk of suicidal thoughts and behavior in adolescent males with same-sex sexual orientation appears to be more pronounced in adolescence (Russell and Toomey 2012). It has been suggested that female adolescents generally experience less pressure in regard to gender and sexuality; however, Marshall et al. (2011) found that gender did not significantly affect the association between sexual orientation and adolescent depression or suicidality.

Of note, men who grew up being thought of as more feminine are more likely to engage in nonfatal suicidal behavior. Specifically, gay and bisexual male youth that are seen as more feminine tend to have a history of nonfatal suicidal behavior (Russell and Joyner 2001).

31.2 Gender Differences in the Neurobiology of Suicide

Although abnormalities in several biological systems including the serotonergic and dopaminergic systems, the hypothalamic-pituitary-adrenal (HPA) axis, the polyamine stress response system, neurotrophins, immune factors, and receptor-linked signaling mechanisms have been linked to increased risk for suicide (Pandey 2013; Turecki 2014), there is very limited data on gender differences in the neurobiology of suicide.

This may be caused in part by a lack of reporting of any gender-specific results by the authors but also because of the inclusion of samples of only men or women in some studies. Several recent reviews (Pandey 2013; Turecki 2014) outline the current knowledge regarding the neurobiology of suicide and acknowledge gender differences among attempters and suicide victims in behavioral features, symptoms, and comorbidity. However, no specific gender discrepancies in the neurobiology are noted with the exception of cytokine abnormalities (Pandey 2013). Specifically, in the prefrontal cortex of female suicide victims, there was increased mRNA expression of IL-3 and IL-4, whereas male victims demonstrated increased IL-13 expression (Tonelli et al. 2008). This is a gap in knowledge that warrants further investigation.

What follows is a brief review of the few reported sex differences in biological risk factors for suicidal behaviors.

31.2.1 Gender-Specific Genetic Risk Factors

Despite converging evidence from twin, adoption, and family studies supporting a genetic component for suicide risk, few studies have investigated gender differences in the genetic underpinnings of a vulnerability to suicide. Candidate gene studies have identified several genes with gender-specific effects on suicidal behaviors, including the serotonin transporter (5-HTT), monoamine oxidase A (MAO-A), catechol-O-methyltransferase (COMT), and cholecystokinin genes (Fiori et al. 2011).

MAO-A is a particularly interesting candidate because of its location on the X chromosome. Males are hemizygous for all genes located on the X chromosome and only carry one copy of this gene, which may be an important source of potential sex-specific variability (Fiori et al. 2011).

Fiori et al. (2011) recently identified nine haplotype windows and several individual markers in the X chromosome that were associated with suicide. Moreover, six genes within the regions identified were found to be differentially expressed in the brains of an independent sample of suicide completers compared to non-suicidal controls.

31.2.2 Sex Differences in Brain Imaging and Postmortem Studies

Several lines of evidence support sex effects in brain biomarkers related to suicide risk. For example, several studies using in vivo brain imaging and postmortem techniques have found sex differences in the serotonin system, which modulates key traits related to suicide, such as aggression (Parsey et al. 2002; Boldrini et al. 2008; Soloff et al. 2010). However, sex differences in brain biomarkers related to suicidal behaviors as the main outcome measures remain mostly unexplored.

31.2.3 Sexual Hormones and Suicide

It has been postulated that the gender differences in rates of suicidal behaviors may arise as a result of differences in the concentration and activity of sex hormones in men and women.

This speculation is bolstered by differing rates of psychiatric illness in women versus men across the life cycle, particularly during periods of hormonal change. Depression rates diverge between boys and girls after puberty, whereas they are similar in children and the elderly (Accortt et al. 2008; Sprock and Yoder 1997; Wolk and Weissman 1995). Maturation of the hypothalamic-pituitary-gonadal axis may contribute to elevated incidence of depression in adolescent girls (Accortt et al. 2008; Angold and Costello 2006).

Proposed mechanisms of female sex hormone modulation of depression include estradiol-mediated gene expression of the serotonin 2A receptor and serotonin transporter (SERT) in the dorsal raphe nucleus, hence increasing receptor and transporter density in the forebrain (Accortt et al. 2008, Fink et al. 1998; Sumner et al. 1999). Estrogen has also been linked to dendrite and synapse formations early in the menstrual cycle (Accortt et al. 2008; Tanapat et al. 1999), with dendritic pruning at lower estrogen levels (Genazzani et al. 2002). As such, the neuroendocrine etiology of premenstrual dysphoric disorder (PMDD) and depression in menopause may be attributable to changes in estrogen levels and downregulation of neurogenesis (Accortt et al. 2008; Genazzani et al. 2002).

Despite fluctuations in estrogen having been linked to premenstrual symptoms and PMDD, no definitive links between menstrual phase and completed suicides exist (Mendez-Bustos et al. 2013; Saunders and Hawton 2006). However, the rates of suicidal ideation and attempts are increased in women during periods of low estrogen including the late luteal and follicular phases and menopause (Mendez-Bustos et al. 2013; Saunders and Hawton 2006; Baca-Garcia et al. 2003, 2004).

The postmenopausal hypogonadal milieu of elevated follicle-stimulating hormone (FSH) and decreased androgens has been linked to lower sex drive, lower energy, and depressive symptoms, although no data on hormonal modulation of postmenopausal suicidality specifically exists (Soares and Zitek 2008; Soules et al. 2001; Arlt 2006; Freedman 2002).

With elevated levels of estrogen and progesterone during pregnancy, the precipitous drop in circulating sex hormones may play a role in the development of postpartum psychiatric disorders (Soares and Zitek 2008). Studies on postpartum psychiatric illness have not established a clear contribution of sex hormones, although there is heightened risk for depressive symptoms among at-risk women with a history of postpartum depression (Block et al. 2000).

Several papers have explored the relationship between testosterone and suicidality; however, findings have not been consistent across studies (Sher 2013; Tripodianakis et al. 2007; Markianos et al. 2009; Sher et al. 2012; Brower et al. 1989; Perez-Rodriguez et al. 2011; Butterfield et al. 2005). For example, researchers have questioned whether men's multifold higher concentration of testosterone compared to women may confer a higher risk for completed suicide. Testosterone is produced by male testes and female ovaries, with small concentrations arising from the adrenals (Sher 2013).

Prior studies have implicated testosterone as a contributor to aggression, with several showing elevated testosterone levels in the cerebrospinal fluid (CSF) and saliva of violent individuals (Sher 2013, 2012; Ehrenkranz et al. 1974; Mattsson et al. 1980; Soler et al. 2000). Testosterone supplementation has also been linked with increased likelihood of aggression in response to threat (Sher 2013; Su et al. 1993; Pope et al. 2000; Pope and Katz 1994).

It is reasonable to deduce that since testosterone promotes increased aggression, which is itself a predictor of suicide (Sher 2013; Sher et al. 2014), testosterone may also increase the risk for suicidal behavior. However, contradicting this theory, plasma testosterone levels among violent suicide attempters have been found to be

lower than those in nonviolent attempts and accident victims (Sher et al. 2014; Tripodianakis et al. 2007; Markianos et al. 2009).

Of note, other studies controlling for confounding factors such as age and circadian variation in testosterone levels have not found associations between testosterone and suicide (Perez-Rodriguez et al. 2011).

Intriguingly, testosterone has been associated with other psychiatric symptoms that may affect the risk for suicidal behaviors. For example, the emergence of mania has been documented with testosterone supplementation, and depressive symptoms have emerged upon testosterone withdrawal (Sher 2013; Pope and Katz 1994, 1988; Ebinger et al. 2009; Zarrouf et al. 2009). Lower testosterone levels in men are correlated with symptoms of depression, impaired cognition, and dementia of the Alzheimer's type (Sher 2013, 2012; Chu et al. 2010; Thilers et al. 2006; Barett-Conner et al. 1999; Seidman and Walsh 1999). In fact, testosterone may serve to combat depression as evidenced by rodent studies (Sher 2013; Frye and Walf 2009; Carrier and Kabbaj 2012a, b) and may exert a neuroprotective effect as demonstrated via cognitive functioning tests and prospective studies on the risk of Alzheimer's (Chu et al. 2010; Thilers et al. 2006).

There is conflicting data on the correlation of high levels of testosterone with mood in men versus women with bipolar disorder. In bipolar patients of both sexes, studies have positively correlated testosterone levels with number of manic episodes and suicide attempts (Mathews et al. 2013; Sher et al. 2012). However, a study among only women with bipolar disorder demonstrated positive correlation between testosterone and depressive episodes and suicide attempts (Sher et al. 2012). This further complicates the analysis of the relationship between testosterone and suicide.

Low cholesterol and triglyceride levels have been reported among suicide attempters, prompting questions about the role of cholesterol as a precursor of testosterone, estrogen, and cortisol and subsequent risk of suicide (Mathews et al. 2013; Lalovic et al. 2004; Ringo et al. 1994; Mauch et al. 2001). Gender differences have been reported in some of these studies, with stronger evidence for an association between cholesterol levels and suicide attempts among men (Diaz-Sastre et al. 2007; Perez-Rodriguez et al. 2008a).

31.2.4 Pregnancy and Suicide

While some studies that pregnancy and having young children suicide risk (Mendos Bustos et al. 2013; Hawton and Harris 2008; Qin et al. 2000), others suggest that among postpartum women, there is increased risk for psychiatric disorders and subsequent deleterious behaviors including suicide and infanticide (Pinheiro et al. 2012; Kelly and Sharma 2010).

Up to one quarter of pregnant and postpartum women may experience a depressive or anxiety disorder (Mendos Bustos et al. 2013; Andersson et al. 2003; Melville et al. 2010; da Silva et al. 2012; Reck et al. 2008). Such illnesses confer a higher risk of suicide, particularly within the two first months of the postpartum period (Mendos Bustos et al. 2013; Frautschi et al. 1994; Gissler et al. 1996).

The increased risk for psychiatric illness in the postpartum period may be related at least in part to precipitous drops in estrogen and progesterone levels as described in the previous sections (Accortt et al. 2008; Winstead and Sanchez 2005).

Regardless of the hormonal relationship between postpartum periods and psychiatric episodes, psychosocial risk factors for perinatal psychopathology include low socioeconomic status, being unmarried, and possessing a lower level of education (Soares and Zitek 2008; Field et al. 2006; Bennett et al. 2004). These risk factors should be assessed in screening for suicide risk among pregnant women.

Supporting the role of psychosocial stressors in suicide risk, low levels of brain-derived neurotrophic factor (BDNF) were found in postpartum women with three or more stressful life events during pregnancy; in the same sample, low BDNF levels were associated with a high risk for suicide (Pinheiro et al. 2012).

31.3 Psychopathology, Gender, and Suicide

Lesage et al. (1994) found that 88 % of young men who completed suicide had an axis 1 disorder compared to 37.3 % of a control group. In Kessler et al.'s (2005) analysis of suicide trends in the United States, 89–88 % of those that had attempted suicide met criteria for at least one DSM disorder; depression ranking highest among them. Similarly, in a large meta-analysis of 27 psychological autopsy studies including 3275 suicides, Arsenault-Lapierre et al. (2004) reported that 87.3 % had been diagnosed with a mental disorder prior to their death.

In a prospective follow-up study after first contact with mental health services, the absolute risk of lifetime suicide was highest in men with bipolar disorder and in women with schizophrenia. In all mental disorders, a concurrent unipolar affective disorder doubled the overall incidence of suicide (Nordentoft 2011).

It has been consistently found that females who die by suicide are more likely than males to have an affective disorder (Arsenault-Lapierre et al. 2004). Males are more likely than females to have substance use dependence, and they are more likely to have been intoxicated with alcohol at the time of suicide (Brent 1995; Canetto and Sakinofsky 1998). This is consistent with the well-replicated finding that men have higher rates of externalizing disorders, while women have higher rates of internalizing disorders (Eaton et al. 2012).

However, McGirr et al. (2006) found that the few females who did meet criteria for current or lifetime alcohol abuse were less likely than males to have a comorbid depression. The mood disorders seen in males with completed suicide are more likely to be secondary to substance use (Brent 1995; Lesage et al. 1994).

In males, alcohol use may be viewed as an alternative to suicide attempts, which is more acceptable, as alcohol and substance use is seen as a masculine act (Canetto and Sakinofsky 1998). Alcohol dependence and abuse increase suicide risk by 20-fold in females but only by fourfold among males compared to the general population. A possible interpretation is that women who go against the norm by drinking heavily may have further psychological factors that increase their suicide risk.

Eating disorders are of particular interest when discussing gender differences in suicide risk as they are more commonly seen in females. Both anorexia nervosa and bulimia nervosa have higher rates of suicide than general population (Preti et al. 2011; Harris and Barraclough 1997). Anorexia nervosa in particular has significantly higher rates. Currently, there is not enough suicide data for binge eating disorder to know if an increased risk is associated with the disorder.

The incidence of anorexia nervosa is 19 females per 100,000 per year but only 2 males per 100,000 per year, and for bulimia nervosa, it is 29 females and only 1 male per 100,000 per year (Fairburn and Harrison 2003). More suicidal ideation is seen in adolescents that scored higher on eating disorder inventories in both females and males. However, more females scored positively in eating disorder inventories, which would explain why more suicidal ideation is seen in females with eating disorders (Miotto et al. 2003). In anorexia nervosa, those with a longer duration of illness had a stronger association with suicidality. Furthermore, subjects that had attempted suicide also tended to have failed more therapeutic approaches than non-attempters (Favaro and Santonastaso 1997).

An early onset of psychiatric illness seems to confer a particularly high risk for suicidal behaviors later in life. When looking at a population of child and adolescent psychiatric patients, the overall suicide risk was about five times that of the general population (Harris and Barraclough 1997). Interestingly, when comparing females and males in this population, females have an increased risk –2.8 times that of males- (Harris and Barraclough 1997). Males that die by suicide were found to have childhood-onset psychiatric disorders more often than females (Arsenault-Lapierre et al. 2004).

31.3.1 Personality Disorders and Suicide

There is very little data regarding the relationship between personality disorders and suicide. The few studies that have investigated this topic have found a large effect of personality disorders on risk for suicidal behaviors, although the specific personality disorders that confer the highest risk differ across studies. Fulfilling diagnostic criteria for any personality disorder increases suicide risk by 2.9, and if it is a cluster B disorder, the suicide risk is increased 8.5-fold (Brent 1995).

In a direct comparison between two populations of suicide attempters and completers, respectively, Giner et al. (2013) found that those who had died by suicide were 20 times more likely to be diagnosed with narcissistic personality disorder compared to suicide attempters. Conversely, borderline and avoidant personality disorders were the most common personality disorders among suicide attempters in both sexes. In a case-control study of young men by Lesage et al. (1994), an axis II disorder was found in more than half of the subjects who died by suicide as compared to a quarter of the subjects in the control group. In this population, antisocial personality and borderline personality disorder were the most prevalent. Younger female attempters with severe personality disorders are at higher risk for repeated suicide attempts than men (Blasco-Fontecilla et al. 2009).

Suicide rates in cohorts with borderline personality disorder are generally higher than in the general population (Pompili et al. 2005). Pompili also found that the number of suicides appears to be higher in short follow-up periods of subjects with borderline personality disorder, which may suggest that suicide risk is higher during the first phase of the illness rather than once it is a chronic condition. In a depressed population, borderline personality disorder increased risk of future suicidal acts in both genders (Oquendo et al. 2007).

It appears that among patients with borderline personality disorder, there is no difference in rates for suicidal behaviors between males and females. However, earlier reports suggested that borderline personality disorder was much more common in females, which is why it may seem that female borderline patients are at higher risk for suicide (Kullgren 1988). Of note, the female to male ratio of borderline personality disorder has previously been over estimated as over 3:1 in the DSM-IV (APA 1994) and the DSM5 (APA 2013). More recent data using validated instruments has found no differences in the lifetime prevalence of BPD in men and women (Grant et al. 2008).

31.4 The Role of Culture and Ethnicity and Gender

One important issue that is not well understood is the relationship between culture/ethnicity, gender, and suicidal behaviors. There is very little research data, and most studies suggest that the relationship between culture/ethnicity, gender, and suicidal behavior is likely complex, may be specific for each ethnic group and for each country, and may change over time (Hunt et al. 2003; Baca-Garcia et al. 2011, 2010; Perez-Rodriguez et al. 2014, 2008b).

It is not clear whether risk factors and high-risk groups for suicidal behaviors among the general population also apply to specific ethnic groups (Perez-Rodriguez et al. 2008b; Pitman et al. 2012; Willis et al. 2003).

The high heterogeneity within some ethnic groups – e.g., in terms of culture, geography, acculturation, migration patterns, socioeconomic status, among other factors – poses a significant challenge for studying the relationship between ethnicity and suicidal behaviors (Perez-Rodriguez et al. 2008b). Moreover, some of the ethnic populations are relatively small (less than 5 % of the general population), and suicide-related outcomes are too rare to allow for uncovering statistically significant differences in epidemiological surveys in the general population (Perez-Rodriguez et al. 2008b; Kessler et al. 2005; Baca-Garcia et al. 2011).

The available evidence to date suggests that despite the existence of some specific risk factors such as acculturation or family cultural conflict, specific ethnic groups share many of the risk factors and gender differences in rates of suicidal behaviors found in the general population, with some exceptions described below (Perez-Rodriguez et al. 2008b).

For example, contradicting the consistent finding of higher rates of suicide attempts among women compared to men across age groups in most countries and ethnic groups, Native American men – but not women – aged 45–64 years were

identified as a high-risk group for suicide attempts in the United States (Baca-Garcia et al. 2010). While in most developed countries suicide rates are higher among men than women, women in China have higher rates of suicide compared to men (Hawton and van Heeringen 2009).

Of note, within a specific gender and age group (e.g., young men, young women, etc.), ethnic origin and indigenous group predict suicide risk, such that the rates of suicide among young men and women differ widely across different ethnic and geographical subgroups (Pitman et al. 2012; Hawton and van Heeringen 2009; Baca-Garcia et al. 2010). For example, in the United States, suicide rates are much higher among American Indian/Alaska Native young men than among young men overall (General 2012).

31.5 Stressful Life Events and Gender

The stress-diathesis model posits that, given a neurobiologically mediated vulnerability for acting on suicidal urges, stressors such as life events or episodes of psychiatric disorders – such as a major depressive episode – determine the timing of suicidal acts (Mann et al. 1999).

Given this theoretical interest in stressful life events as possible triggers for suicidal behaviors, there is surprisingly little prospective research on the relationship between stressful life events and suicidal behaviors and even less data on its relationship with gender (Oquendo et al. 2014). In a recent prospective study, female gender conferred a higher risk for future suicidal behaviors (including both suicide attempts and suicides) even after controlling for life events and major depressive episodes (Oquendo et al. 2014).

Women suffer higher rates of several types of stressful life events, such as domestic violence or physical and/or sexual abuse, which are linked to increased risk of suicidal ideation and attempts (Molnar et al. 2001a, b; Wunderlich et al. 2001).

Although some researchers conclude that stressful life events such as childhood abuse equally increase risk for suicidal behavior in both women and men, others have found sex differences in risk for suicidal behaviors based on life event history (Afifi et al. 2008; Spokas et al. 2009). For example, although women were more likely to endorse a history of childhood sexual abuse, men reporting childhood sexual abuse experienced more hopelessness and suicide ideation and were more likely to have attempted suicide multiple times (Spokas et al. 2009). Similarly, a history of childhood abuse had a higher impact on the risk for suicidal ideation and attempts among men compared to women (Afifi et al. 2008).

31.6 Treatment and Gender

The differences in access to mental health services and treatment in females and males may account for some of the gender gap in suicide rates. For example, compared to men, women have higher rates of treatment for depression, which is

associated with increased risk for suicide. Thus, by treating their depression, suicidal ideation and behavior is likely decreased, which may partly explain why woman have lower rates of suicide (Moscicki 1994).

However, Canetto and Sakinofsky (1998) remarked that if women's depression had been adequately treated as the previous study suggests, then not only suicide rates, but also nonfatal suicidal behavior rates should be lower, but they are not.

On average, women show more favorable attitudes toward seeking help for psychological problems than men. Internationally, studies have shown that young men below the age of 45 are less likely to seek help for depression (Pitman et al. 2012). A study by Mackenzie et al. (2006) suggests that the underutilization of mental health services by men may be due to their negative attitudes related to psychological openness. Lesage et al. (1994) noted that fewer than 30 % of young men who die by suicide have been in contact with psychiatric services within the past year. In a university student population where there is universal access to free short-term psychotherapy and basic health services, females still used services more than males, despite the availability of the services (Eisenberg et al. 2007).

Studies have also shown that diagnostic biases exist among physicians, in that physicians are more likely to report being aware of depressive symptoms among women than among men. And they are also more likely to be aware of or act to address mental health issues in female compared to male patients (Borowsky et al. 2000). This may be partly explained by the finding that women are able to give better histories than men and may report suicidal ideation history more accurately than men, so men may have just as many suicidal thoughts or attempts as women, but they do not report them (Moscicki 1994). One reason could be the previously discussed view of suicidal thoughts as feminine. According to this theory, self-report studies can accurately identify those women with a history of suicidal behavior but likely underestimate the number of men with history of suicidality, which could explain the high documented rates of nonfatal suicidal behavior in women (Moscicki 1994).

31.7 Protective Factors and Gender

Most studies investigating variables associated with suicidal behaviors have focused on risk factors, which are those that increase risk for suicidal behaviors. Conversely, only a small number of studies have examined protective factors, which decrease the risk for suicidal behaviors. The study of protective factors is important since they can be the focus of preventive interventions to decrease suicidal behavior (Oquendo et al. 2005).

In studies that compare populations with and without suicidal behaviors, respectively, protective factors are usually the opposite of risk factors for suicidal behaviors (Baca-Garcia et al. 2008). Protective factors generally promote resilience and healthy coping against suicidal behavior even in the face of risk factors.

The Practice Guideline for the Assessment and Treatment of Suicidal Behaviors published by the American Psychiatric Association (2003) lists ten protective factors against suicidal behaviors: children in the home (except among those with postpartum psychosis or mood disorder), sense of responsibility to family, pregnancy, religiosity, life satisfaction, reality testing ability, positive coping skills, positive problem-solving skills, positive social support, and positive therapeutic relationship (Baca-Garcia et al. 2008).

The construct of Reasons for Living – measured with the Reasons for Living Inventory, RFLI (Linehan et al. 1983) – was developed to assess protective factors for suicidal behaviors. It is based on a cognitive-behavioral theory of suicidal behavior that suggests that individuals who do not act on their suicidal urges have different beliefs, expectations, and adaptive ways of thinking than those who yield to suicidal urges and attempt suicide. The RFLI (Linehan et al. 1983) measures six factors: survival and coping beliefs, responsibility to family, child-related concerns, fear of suicide, fear of social disapproval, and moral objections to suicide. It has consistently been reported that individuals who attempt suicide have significantly lower total scores on the RFLI than those who do not (Oquendo et al. 2005; Lizardi et al. 2007).

While many protective factors against suicide are common to men and women, there are some sex differences in the rates and effects of several protective factors. Indeed, women and men score differently across subscales of the RFLI, suggesting that there may be significant sex differences in the levels of adaptive characteristics against suicide. For example, Ellis and Lamis (2007) found that women scored higher than men on the survival and coping beliefs, responsibility to family, child-related concerns, and fear of suicide subscales of the RFLI.

Some protective factors seem to have a stronger effect in one of the sexes. For example, having children has a protective effect against suicidal behaviors particularly among women (Hoyer and Lund 1993; Qin and Mortensen 2003). Conversely, being married seems to be protective against suicide particularly among men (Luoma and Pearson 2002).

Pregnancy and the perinatal period also seem to be protective against suicidal behaviors for women in the general population. However, risk for suicidal behaviors may be increased in pregnancy and the perinatal period for specific groups such as teenagers, women with a history of depression or suicide attempts, and those hospitalized with perinatal psychiatric disorders (Baca-Garcia et al. 2008).

Conclusions

While there is consistent evidence suggesting gender differences in the rates of suicidal behaviors, substantially less is known about the mechanisms underlying these differences. Although some of the gender differences in suicidality may be partially explained by environmental and behavioral factors, there is very little data on the role of sex differences in neurobiological factors. Surprisingly, the role of sexual hormones and sex differences in brain development on the risk for suicidal behaviors remains largely unexplored.

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A Need for Personalised Suicidology: Pharmacoepidemiology

32

Marie Tournier

Abstract

A principal issue in pharmacoepidemiology is to estimate the impact of drugs on suicide risk in view of numerous methodological limitations. Owing to methodological concerns or differences, the findings of studies are often conflicting so it is difficult to draw conclusions about the suicide risk associated with drugs. An additional challenge in personalised suicidology is to identify characteristics of patients whose risk of suicide is increased when they are exposed to specific drugs. In this review, we investigate the impact of drugs on suicide risk in specific populations and the characteristics associated with an increased risk for the various therapeutic classes on the basis of the available data. Suicidal behaviours are linked to at least 58 different approved prescription drugs. The main mentioned classes are antidepressants, anticonvulsants and smoking cessation drugs. Antidepressants, anticonvulsants and sedative medications have been associated with suicidal behaviour in specific contexts. However, these associations remain to be proven and their mechanisms elucidated.

Suicidology aims at understanding the mechanisms of suicide, improving its predictability and thus its prevention. Pharmacoepidemiology examines the use of drugs, its patterns and its impact in real-life settings. A principal issue in pharmacoepidemiology is to estimate the impact of drugs on suicide risk in view of numerous methodological limitations such as prescription channelling and confounding by

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indication. It may be assessed globally in the general population or specifically either by therapeutic classes/products or in specific populations. Owing to methodological concerns or differences, the findings of studies are often conflicting so it is difficult to draw conclusions about the suicide risk associated with drugs. An additional challenge in personalised suicidology is to identify characteristics of patients whose risk of suicide is increased when they are exposed to specific drugs. Indeed, some drugs may prevent suicide in some patients while increase its risk in others. Thus, including all patients in studies may lead to incorrectly finding no significant relationship or to under-/overestimating the risk. In addition, studying all products together may lead to incorrect conclusions. In this review, we investigate the impact of drugs on suicide risk in specific populations and the characteristics associated with an increased risk for the various therapeutic classes on the basis of the available data.

32.1 Suicidal Behaviour as an Adverse Event of Drugs

Suicidal behaviours are linked to at least 58 different approved prescription drugs that have boxed warnings, warnings or precautions on the package inserts (Moore et al. 2011). The list includes varenicline, 23 antidepressant drugs, 17 anticonvulsants and drugs for asthma, viral illness, malaria prevention and acne. Class warnings for anticonvulsants and antidepressant drugs are based on US Food and Drug Administration (FDA) meta-analyses of clinical trials and have been extended to similar drugs. Most other warnings are based on adverse event reports.

Between 1998 and 2011 in the UK, many drugs were subject to spontaneous reports of suicidal behaviours as possible adverse events: 58 drugs were linked to 10 or more reports of non-fatal suicidal behaviour and 33 to 5 or more reports of suicide (Thomas et al. 2014). Selective serotonin reuptake inhibitors (SSRIs), venlafaxine, varenicline and the antipsychotic medicine clozapine, were in the top five medicines with the most frequent reports of fatal or non-fatal suicidal behaviour. Whereas most of the top ten drugs with reports of depressive disorders are treatments for non-nervous system indications, psychotropic drugs were mainly involved in reports of suicidal behaviour. These include antidepressants but also antipsychotics (25 % of suicide reports and 15 % of reports of non-fatal suicidal behaviour) and anticonvulsants (15 % of reports of non-fatal suicidal behaviour). Other drug classes are also implicated: smoking cessation drugs (10 % of reports of non-fatal suicidal behaviour and 5 % of suicide reports), weight loss medicines and antimalarials (5 % of reports of suicide). Spontaneous reports raise signals and cannot be used to determine causality between drugs and adverse drug reactions. Other study designs should therefore be used to confirm such associations (Gibbons and Mann 2011).

32.2 Antidepressants

Since 2002, the FDA issued warnings about a possible association between exposure to antidepressants and the occurrence of suicidal behaviours on the basis of findings from randomised controlled trials. Since then, many studies have been

conducted using various designs and in various types of population, leading to conflicting results (Isacsson and Rich 2014).

First, as individual drug characteristics such as neurotransmitter selectivity and elimination half-life can differentially influence the neurobiological processes of suicide, some studies have compared various antidepressant products or classes for the risk of suicidal behaviour. An example is a recent propensity score-matched cohort study of incident users of antidepressant agents that assessed the risk of deliberate self-harm in depressed patients aged 10–64 years who initiated use of SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) (Miller et al. 2014a). Similar rates of deliberate self-harm were found in depressed patients who initiated treatment with either an SSRI or an SNRI. Indeed, most studies finding differences across products concluded in a prescription channelling that was leading to the selection of some of them in patients with a high suicidal risk. Moreover, risk of suicide has been associated with starting an antidepressant and with an antidepressant dose change (Valenstein et al. 2009; Wasserman et al. 2012; Hawton et al. 2013). This may be biased by confounding by indication. Indeed, a large observational cohort study (the National Institute of Mental Health Collaborative Depression Study (CDS)) found that patients with affective disorders were more likely to start an antidepressant treatment when they were more severely ill, whereas the risk of suicidal behaviour was globally reduced when they were treated by antidepressants (Leon et al. 2012). The propensity model included several demographic and clinical variables: gender, study site, education, marital status, social class, depression, age, prior suicide attempt, severity of affective symptoms and the trajectory of symptom severity. Another propensity score-matched cohort study conducted in depressed patients aged 10–64 years suggested that a high starting dose of the antidepressant increased the risk of deliberate self-harm in children and young adults, but not in adults aged 25 years and over (Miller et al. 2014b). The authors recommended not initiating pharmacotherapy at high therapeutic doses and monitoring all patients starting antidepressants, especially young ones, for several months.

Other studies focused on the characteristics of treated patients. In a key meta-analysis of clinical trials, antidepressants increased the suicidal risk in youths until 24 years of age, had no impact in adults and decreased the risk in people aged 65 years and over (Stone et al. 2009). The population likely to present with suicidal ideation/behaviour when exposed to antidepressants might therefore be the youngest patients. Some guidelines recommend limiting their use in youth (Wasserman et al. 2012; Ayuso-Mateos et al. 2012). Recent studies specifically investigated this age group. A Cochrane meta-analysis compiled randomised controlled trials, crossover trials and cluster trials comparing a newer generation antidepressant with a placebo in depressed youths aged 6–18 years (Hetrick et al. 2012). It found an increased risk of suicidal behaviour/ideation for those on antidepressants compared with a placebo, without any class effect. The authors found that trials excluded young people at high risk of suicide and with many comorbid conditions and that the participants were likely to be less unwell than those seen in clinical practice. In their opinion, the indication for antidepressants in youth depended on depression severity, and the threshold of severity for treatment with antidepressant medication should be raised. A retrospective cohort study assessed various products in this

population and compared the risk for medically treated suicide attempts and completed suicide with sertraline, paroxetine, citalopram, escitalopram and venlafaxine to the risk with fluoxetine, the currently recommended antidepressant for depression in youth (Cooper et al. 2014). Participants were children aged 6–18 years who were new antidepressant users. The adjusted rate of suicide attempts did not differ significantly among current users of SSRI and SNRI antidepressants compared with current users of fluoxetine. In analyses stratified by gender, older age, absence of a suicide attempt before initiating antidepressants and data from the most recent years of the study period, there was also no evidence of increased risk for any of the study drugs compared to fluoxetine. The sole increase in risk was found in users of multiple antidepressants concomitantly, which may reflect an increased severity of depression rather than a drug effect.

Some studies focused on the possible mechanisms for such an association. A randomised controlled trial comparing fluoxetine and venlafaxine with placebo assessed the mediating effect of changes in depressive symptoms (Gibbons et al. 2012). Both drugs decreased suicidal thoughts and behaviour in adult and geriatric patients. This protective effect was mediated by decreases in depressive symptoms with treatment. No significant effects of treatment on suicidal thoughts and behaviour were found in youths, although depression responded to treatment. No evidence of increased suicide risk was observed in youths receiving active medication. The increase in risk might only be the consequence of the absence of protective effects. Moreover, the risk of suicidal behaviour in depressed patients treated with antidepressants may be linked to inefficacy, i.e. during the time to action or in case of non-response, or to adverse events of antidepressants (Wasserman et al. 2012).

A recent study used marginal structural models (MSM) to examine the risk of suicidal behaviour in depressed children aged 5–17 years and treated with antidepressants in two large observational US medical claims databases (Gibbons et al. 2015). The fundamental idea of MSM is that there are two dynamic models, one for the treatment selection process and the other for the dynamic effect of treatment on the outcome of interest. Whereas a significantly increased risk of suicidal behaviour was observed during antidepressant treatment episodes, MSM showed that the majority of this association and its statistical significance were produced by treatment selection effects in which the dynamic characteristics of patients and prior treatment influenced the likelihood of both future treatment and suicidal behaviour. Results were quite similar when the analysis was restricted to SSRIs. Thus, the major part of the association between suicidal behaviour and exposure to antidepressants may be due to confounding bias by indication.

For some authors, the main explanation for the existence of an association between antidepressant exposure and suicidal behaviour, mainly in youth, is the depression-worsening potential of antidepressant monotherapy in sub-threshold and mixed bipolar depressed patients falsely diagnosed as suffering from unipolar major depression (Rihmer and Gonda 2013). Another mechanism underlying such an association may be rapid cycling that is both related to suicidal risk and to a causal role for the use of antidepressants (Carvalho et al. 2014). Furthermore, antidepressants are not effective in bipolar depression (Yerevanian and Choi 2013). Therefore,

patients with an unrecognised bipolar vulnerability may be the population at risk of suicidal behaviour when exposed to antidepressants. Antidepressant-induced suicidality might even be an external validator and an endophenotype of bipolar disorder (Yerevanian and Choi 2013). Some predictors of treatment-emergent suicidality might include agitation, anger, insomnia, prolonged dysphoria and mixed states, which might be different from the general suicide risk factors in patients with bipolar disorder.

32.3 Anticonvulsants

In 2008, the FDA issued a warning about an increased risk of suicidal ideation and behaviour in people treated with anticonvulsant drugs. This resulted from a meta-analysis of multisite randomised placebo-controlled trials of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate and zonisamide). A task force of the International League Against Epilepsy (ILAE) has highlighted the limitations of this meta-analysis (Mula et al. 2013). First, the FDA's warning concerned all anticonvulsants, whereas only two were significantly associated with this risk, topiramate and lamotrigine. Second, the addition of three studies on lamotrigine resulted in the loss of statistical significance for this drug. Third, most studies did not adjust for past suicidal behaviours, whereas prescribing practices might be influenced by suicidal history, since some drugs may have positive effects on mood and others a negative one (i.e. prescription channelling bias).

Results are contradictory among studies with regard to the association between suicidal behaviour and anticonvulsants. One explanation could be differences across products, as found in older subjects aged 65 years and over (Pugh et al. 2012). Gabapentin, phenytoin, lamotrigine, levetiracetam, topiramate and valproate were significantly associated with suicidal behaviours after adjustment for propensity to receive anticonvulsants, i.e. psychiatric history, epilepsy, chronic pain conditions including migraine and dementia. Similar results were found in patients with and without mental health comorbidities. In the expert consensus statement developed by ILAE, some anticonvulsants were associated with the occurrence of depression (barbiturates, tiagabine, topiramate, vigabatrin, zonisamide), psychosis (ethosuximide, levetiracetam, phenytoin, topiramate, vigabatrin, zonisamide) or emotional liability (felbamate, lamotrigine, levetiracetam) (Mula et al. 2013). Some other anticonvulsants seem to have positive psychotropic properties, such as carbamazepine. Indeed, in the CDS, a large observational cohort study that included the three anticonvulsants approved by the FDA for bipolar disorder (carbamazepine, lamotrigine and valproate), participants with bipolar disorder were more likely to receive one of them when they were more severely ill, while there was no evidence of elevation in risk of suicidal behaviour among subjects while receiving them (Leon et al. 2012). The propensity model included several demographic and clinical variables: gender, study site, education, marital status, social class, age, prior suicide attempt, antipsychotic use, severity of mania, severity of hypomania and cumulative affective

morbidity. For the ILAE task force, psychiatric adverse events are more likely in patients at risk of developing psychiatric disorders, because of either a past psychiatric history or a family psychiatric history. Hence, personal and family psychiatric history should help in choosing the anticonvulsant drug.

One study tried to identify patients at increased risk of suicidal behaviours with anticonvulsant drugs (carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate and zonisamide) in a large clinical database, the Health Improvement Network (THIN) database (Arana et al. 2010). The frequency of suicidal behaviours (suicides and attempts) was assessed in current users, past users and non-users of anticonvulsants, excluding patients with a family history of suicide and a personal history of suicide attempt. In this study, the underlying illness was more strongly associated with suicidal behaviours than was the use or non-use of anticonvulsant drugs. Hence, no significant increase in the risk of suicidal behaviours was observed among current users of anticonvulsant drugs as compared with non-users in the subgroups of patients with epilepsy alone, of patients with bipolar disorder alone or of patients with epilepsy and depression. Among patients with depression alone, the use of antiepileptic drugs was significantly associated with a slightly increased risk of suicidal behaviours. Similarly, the current use of antiepileptic drugs in patients without epilepsy, depression or bipolar disorder was associated with an increased risk of suicide-related events. Overall, the risk of suicidal behaviours was increased among patients who received anticonvulsant drugs for indications other than epilepsy or bipolar disorder, i.e. off-label indications. In patients with depression, the increased risk may result from a causal role of anticonvulsant drugs, although the use of such drugs in these patients may be a marker of severe and/or refractory depression. In the FDA meta-analysis in 2008, the findings were converse and the increase in suicidal behaviours was significant in patients treated for epilepsy but not in those treated for psychiatric illnesses or other conditions such as migraine and neuropathic pain (Mula et al. 2013). Finally, in a case-control study that was carried on in patients 66 years and over using data from the Veterans Health Administration, the most important predictive factor of suicide was a diagnosis of affective disorder (depression, anxiety, post-traumatic stress disorder) prior to initiation of anticonvulsant treatment (VanCott et al. 2010). Most individuals received gabapentin (76.8 % of the sample) and others phenytoin, phenobarbital/primidone, valproate, carbamazepine, levetiracetam or lamotrigine. No difference was found between the drugs in this study. The dominant role of treated condition was supported by the investigation of the temporal relationship between a new anticonvulsant treatment and suicidal behaviours in a cohort of subjects aged 65 years and older (Pugh et al. 2013). The frequency of suicidal behaviour was highest the month prior to anticonvulsant initiation after adjusting for potential confounders, and it gradually diminished over time after treatment initiation.

All in all, some studies suggest that some but not all anticonvulsant drugs are significantly associated with suicidal behaviours independently from psychiatric conditions (Pugh et al. 2012), others that the underlying disorder is more strongly associated with suicidal behaviours than the use of anticonvulsants (VanCott et al.

2010; Pugh et al. 2013) and others that only some patients treated for specific conditions are likely to present with suicidal behaviours when exposed to anticonvulsants (Mula et al. 2013; Arana et al. 2010). Suicidal behaviours in individuals treated with anticonvulsants may be multifactorial, including disease type and severity, anticonvulsant type and dose, treatment duration and coexisting psychiatric conditions (Mula et al. 2013; VanCott et al. 2010; Mula and Sander 2013). A striking example of this complexity is the association between epilepsy and suicidal behaviours, implying biological, constitutional and psychosocial variables (Mula et al. 2013; Mula and Sander 2013). Risk factors involve peri-ictal mood symptoms, postictal suicidal ideation, inter-ictal dysphoric disorder, a personal or family history of psychiatric disorders, the underlying brain pathology and the psychotropic effect of anticonvulsants. A subgroup of people with epilepsy might be at risk of developing treatment-emergent psychiatric adverse effects of anticonvulsants independently of the specific mechanism of action of the drug (Mula et al. 2013). A Danish case-control study showed that the rate ratio of suicide in people with epilepsy was two compared with those without epilepsy, after excluding people with psychiatric disease and adjusting for various factors (Christensen et al. 2007). In this context, the choice of the anticonvulsant treatment may be important. Clinicians need to pay attention not only to seizure patterns but also to a number of different parameters, not least the mental state of the patient (Mula et al. 2013). A rapid titration of the drug in people with refractory epilepsy, a past history of depression and a limbic system dysfunction were major determinants for the occurrence of suicidal behaviours (Mula et al. 2013). There might be a genetic and biological substrate related to the underlying brain condition on which the psychotropic properties of anticonvulsants may have their deleterious effects. Such a biological substrate may be linked to epilepsy, as such effects are less frequent in people with primary psychiatric disorders where anticonvulsants appear to be commonly and successfully used.

32.4 Smoking Cessation Treatment

The FDA has required boxed warnings for physicians and a mandatory medication guide for patients regarding depressed mood and suicidal behaviour for two pharmacological treatments, varenicline and bupropion. However, there is some evidence for an increased risk in smoking or smoking cessation independent of treatment. One study compared varenicline, bupropion for smoking cessation and nicotine replacement products using the FDA's Adverse Event Reporting System (AERS) database (Moore et al. 2011). The outcome was the ratio of reported suicide/self-injury or depression cases for each drug compared to all other serious events for that drug. Bupropion showed some additional excess reported risk when used for smoking cessation compared to the nicotine products, and varenicline had a markedly higher reported risk than any of the comparators. The disproportionality persisted after excluding reports indicating concomitant therapy with any of 58 drugs with suicidal behaviour warnings or precautions in the prescribing information. For the authors, varenicline is unsuitable for first-line use in smoking

cessation. However, a recent study conducted in the Clinical Practice Research Datalink, a large primary care database, did not find any evidence of an increased risk in suicidal behaviour in patients prescribed with varenicline or bupropion compared with those prescribed with nicotine replacement therapy (Thomas et al. 2013). In addition, these drugs were not associated with an increased risk of treated depression. This study used three methods to minimise confounding by indication. Using a different method, another study reanalysed placebo-controlled, randomised trials of varenicline without finding any increase in the risk of suicidal behaviour, depression or aggression/agitation in individuals with and without a recent history of a psychiatric disorder (Gibbons and Mann 2013). In all, the association that was previously noticed might be linked to notoriety bias, and patients with psychiatric disorders might not be more exposed to suicidal adverse events.

32.5 Other Drugs

The association between suicidal behaviour and antipsychotics is partly unknown. Antipsychotics seem less protective against suicide than mood stabilisers in bipolar disorder (Ahearn et al. 2013). In schizophrenia, they are expected to prevent suicidal behaviour, particularly clozapine and maybe olanzapine, or to have no impact (Ringback Weitoft et al. 2014). Some studies, particularly meta-analyses of clinical trials, found an elevated risk of suicidal ideation in children and adolescents receiving drugs for attention deficit hyperactivity disorder (ADHD) (atomoxetine, methylphenidate). However, a recent cohort study found no evidence of an increased rate of suicidal behaviour associated with their use (Chen et al. 2014). At the population level, they seemed to be associated with an increased rate of concomitant suicide-related events, but a reduced within-patient rate of suicidal behaviour was seen among stimulant users during treatment periods compared with non-treatment periods, irrespective of whether the drug was a stimulant or non-stimulant. In fact, the results suggested that ADHD drug treatment is associated with a reduction in concomitant suicide-related events and that the positive association previously observed might be linked to a confounding by indication bias through the severity of ADHD.

Finally, very few studies have assessed the impact of anxiolytics and/or hypnotics on the risk of suicidal behaviour. However, most found an increase in this risk in specific populations: patients treated for substance use disorders (Darke et al. 2004; Maloney et al. 2007; Wines et al. 2004), patients with schizophrenia (Tiihonen et al. 2012), suicide victims aged 65 years and over (Carlsten and Waern 2009) and treatment-resistant, depressed adolescents (Brent et al. 2009). Few studies have been conducted in patients with mood disorders. The authors of a literature review suggested that using sedative/hypnotics as an early adjunct to antidepressant treatment of anxious or depressed patients might produce depressant and/or disinhibitory effects in a small proportion of people, without clear evidence that their brief use early in depression increases suicide risk (Youssef and Rich 2008). Finally, in a study that compared the treatment of inpatients who had or had not made a suicide attempt just before their admission, it was not possible

to rule out that antidepressants or benzodiazepines might induce, worsen or precipitate suicidal behaviour in some patients, especially in those affected by mood disorders with depressive or mixed features (Raja et al. 2009). The authors concluded that the potential risks of prescribing sedative/hypnotics for depressed patients who may be suicidal are serious.

Conclusion

Antidepressants, anticonvulsants and sedative medications might be associated with suicidal behaviour. Suicidal behaviour might occur when starting an antidepressant and with higher starting doses, particularly in children and adolescents, a fact that might be linked to a bipolar susceptibility. In addition, suicidal behaviour when exposed to anticonvulsants has been linked to disease type and severity, anticonvulsant type and dose, treatment duration and coexisting psychiatric conditions. However, these associations remain to be proven and their mechanisms elucidated.

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Pharmacogenetic Studies of Suicide: Potential Relevance of Main Polymorphic CYPs and ABCB1

33

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Abstract

The present review focuses on existing information about studies of polymorphic genes mostly involved in the pharmacokinetics of widely clinically prescribed drugs for the treatment of suicide that have been related to suicide and suicidal behaviors. It also presents an overview of studies that found associations of other genes (e.g., *BDNF*, *NTRK2*, *CREB1*, *ADRA2A*, *GRIA3*, *GRIK2*, *GDA*, *IL28RA*, *FKBP5*, *PAPLN*) with emergence or worsening of suicidal ideation during treatment with antidepressants.

The most studied pharmacokinetics-related genetic polymorphisms have been *CYP2D6* and recently *CYP2C19* and *ABCB1*. An increased frequency of *CYP2D6* ultrarapid metabolizers has been described in forensic suicide samples, eating disordered patients with a lifetime history of suicidal behavior, depressive inpatients with high suicide risk, and attempters from the general population with high scores on the *Beck Suicide Intent Scale – objective circumstances section*. Furthermore, the latter suicide phenotype was associated in another population of attempters with a high CYP2D6-CYP2C19 combined metabolic capacity, particularly in those without a family history of suicidal behavior. Recently, the *ABCB1* has been found in relation to violent methods of attempted and completed suicide.

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Results are in agreement with FDA drug labels information about the need to implement CYP2D6 and CYP219 for safety and efficacy purposes before prescribing many antidepressants, as well as CYP2D6 for many antipsychotics and CYP2C19 for some anxiolytics. Moreover, the PharmGKB database shows the highest level of evidence for several antidepressant drugs metabolized by CYP2D6 and/or CYP2C19. Thus, available quantitative and qualitative data about CYP2D6 and CYP2C19 suggest that they might be potentially relevant pharmacokinetics-related biomarkers for suicide. Although their role in the metabolism of neuroactive endobiotics related to suicide remains to be clarified.

33.1 Pharmacogenetics of Suicide: Concepts and Mechanisms

Pharmacogenetics studies the influence of inherited genetic variation on drug response by determining the association of genetic polymorphisms with drug absorption, distribution, metabolism, and elimination, as well as drug receptor target effects (Weber 1997; Goldstein et al. 2003). In simpler words, it studies heritable variation to interindividual variation in drug response.

The terms pharmacogenetics and *pharmacogenomics* are often used interchangeably, but these terms are also distinguished and used depending on context. Although both terms relate to drug response based on genetic influences, pharmacogenetics focuses more on single drug-gene interactions, whereas pharmacogenomics seems to imply the study of many genes including entire genomes and the study of mRNA or protein levels too (Goldstein et al. 2003).

Pharmacogenetics and pharmacogenomics are part of a field called personalized medicine, which is aimed at using this information to guide therapy by tailoring treatments to each patient in every way possible. Personalized medicine then requires that the patients' clinical evaluations to be fully informed by what is known about the pharmacogenetic variants that may influence drug response.

Pharmacogenetics of suicide. Pharmacogenetics and personalized medicine are expected to be helpful in clinical decision making for suicide if they are proved able to identify, a priori, which individuals exposed to antidepressant (or other psychotropic) drugs are most likely to suffer adverse drug reactions (ADRs) or lack of response to such drugs that were previously related to increases in suicidal ideation, suicidal behavior, and/or death by suicide (Brent et al. 2010b).

The relationship between genes involved in the drug pharmacokinetics and/or pharmacodynamics (pharmacogenes) and suicide can be potentially due to different mechanisms. For example, while on the one hand, the very same *drug could act as an etiological factor for the suicidal event*, as it has been shown in clinical trials for SSRIs in young individuals, which is largely debated (Stone et al. 2009). However, there does not appear to be clinical trials directly exploring drug safety for suicide, since available information is mostly based on indirect analyses of suicidal events as ADRs during clinical trials on antidepressant or other drugs (Goldstein et al.

2003). On the other, the pharmacogenes could explain, at least partially, suicidal events in relation to the *lack of efficacy for a standardized drug treatment* in an individual vulnerable to suicide.

In keeping with this fact, there appears to be a need of studies exploring genes involved in the pharmacokinetics and pharmacodynamics of drug treatment and suicidal events. Such studies should include analyses of drug plasma levels and drug response in order to determine whether there is a causal relation between the targeted genetic polymorphisms and the specific phenotype of suicide. To the best of our knowledge, there are no studies simultaneously examining the interrelationship between genes and drug exposure, response across specific suicidal events up to date.

Therefore, the present review will focus on existing information about studies of highly polymorphic genes mostly involved in the metabolism (cytochrome P450) and transport (*ABCB1*) of widely clinically prescribed drugs for the treatment of suicide that have been related to suicide and suicide attempts. The available information derives mainly from a few studies of clinical populations with individuals who have survived one or various suicide attempts classified according to low or high degree of severity (suicide attempters) and of forensic samples with individuals who have died by suicide or by natural causes.

The present review is structured as follows. Section 33.2 summarizes the studies that have analyzed relevant polymorphic pharmacogenes in relation to phenotypes of suicidal behavior. In addition, it also gives an overview of those studies exploring associations between pharmacodynamic genes and suicidal events, which are practically all related to emergence or increases in suicidal ideation, during antidepressant treatment. Section 33.3 describes the characteristics of the main polymorphic studied pharmacogenes (*CYPs* and *ABCB1*) found in association with suicidal behaviors. Section 33.4 describes the pharmacogenetics of drugs used for the treatment of suicidal events, where a regulatory perspective is given analyzing the genetic biomarkers included in their Food and Drug Administration (FDA) drug labels.

Section 33.5 discusses existing data, supporting the two most likely hypotheses to explain why pharmacogenes might influence suicidal behaviors, which may be either due to their role in endogenous physiological processes or in drug metabolism and transport. It also finally discusses the future outlook of the pharmacogenetics of suicide.

33.2 Studies on Pharmacogenetics of Suicide

33.2.1 Genetic Polymorphisms Related to Pharmacokinetics

Table 33.1 summarizes studies analyzing the potential association of pharmacokinetic-relevant genes related to interindividual variability in drug plasma concentration with specific phenotypes of suicidal behavior. So far, studies have been mostly performed in European individuals from Sweden, Spain, France, and

Table 33.1 Studies of pharmacokinetics-related genes and suicide

Study	Country	Aim	Population	Genes/alleles	Clinical phenotypes	Conclusion
Zackrisson et al. (2010)	Sweden	Study the genetic profile of individuals with regard to the presence of *CYP2D6* and *CYP2C19* genes	Cases of fatal intoxication (242), suicide (intoxication excluded) (262), and natural death (212)	***CYP2D6****: *1, *1xN, *2, *2xN, *3, *4, *4xN, *5, *6* ***CYP2C19****: *1, *2, *3, *4, *17*	Suicide	Among those who died of suicide (suicide cases), there was a higher number carrying more than two active *CYP2D6* genes (corresponding to the phenotype of ultrarapid metabolizer) as compared with those who died of natural causes (natural-death cases)
Peñas-Lledó et al. (2011)	Spain	Analyze the relationship between *CYP2D6* genetic polymorphism and lifetime suicidal behavior in eating disorder patients	267 patients with eating disorders	***CYP2D6***: *2, *3, *4, *5, *6, *7, wtxN*	Lifetime suicide attempts	*CYP2D6* UMs among eating disorders have a greater risk of engaging in suicidal behavior, which adds more evidence to previous findings about the relationship between UMs and suicide in the general population
Stingl and Viviani (2011)	Germany	Analyze whether *CYP2D6* gene duplication also plays a role in suicidality in depressed patients	285 inpatients experiencing a depressive episode of either the unipolar or bipolar variety	***CYP2D6***: *3, *4, *5, *6, *9, *10, *35, wtxN*	Risk of suicidality (Mini International Neuropsychiatric Interview (M.I.N.I.))	In *CYP2D6* UMs subjects, the risk of a high suicidality score was elevated as compared to those with other genotypes

Peñas-Lledó et al. (2012)	Spain	Analyze the relationship between the severity of the suicidal intent and *CYP2D6* number of active genes among survivors	342 survivors of a suicide attempt	***CYP2D6****: *3, *4, *5, *6, *10, *17, wtxN*	Severity of suicidal intent (<percentile 75 in the Beck Suicide intent subscale of Objective Circumstances)	High severity of the suicide intent among survivors is related to higher number of *CYP2D6* active genes
Höfer et al. (2013)	European: Austria, Israel, Belgium, France, Italy	Investigate the role of genetic polymorphisms of the cytochrome P450 genes on suicide risk and/or a personal history of suicide attempts	243 major depressive disorder patients	***CYP1A2****: *1A, *1F, *1C, *1J, *1K* ***CYP2C9****: *2, *3* ***CYP2C19****: *2, *17* ***CYP2D6****: *3, *4, *5, *6, *9, *19, wtxN*	Suicide risk and personal history of suicide attempts	No association between the metabolic profiles of *CYP1A2*, *CYP2C9*, *CYP2C19* and *CYP2D6* genes and clinical phenotypes. However, patients were missclassified genotypically and phenotypes were confusing (Discussed in Peñas-Lledó et al. 2013)
Peñas-Lledó et al. (2014)	France	Examine whether a high CYP2D6-CYP2C19 metabolic capacity combination increases the likelihood of suicidal intent severity in a large study cohort	587 survivors of a suicide attempt	***CYP2D6****: *3, *4, *4xN, *5, *6, *10, wtxN* ***CYP2C19****: *2, *17*	Severity of suicidal intent (<percentile 75 in the Beck Suicide intent subscale of Objective Circumstances)	A high CYP2D6-CYP2C19 metabolic capacity increases these verity of the suicide intent, which appears to be especially relevant among those without a family history of suicide

(continued)

Table 33.1 (continued)

Study	Country	Aim	Population	Genes/alleles	Clinical phenotypes	Conclusion
Boiso Moreno et al. (2013)	Sweden	Examine the impact of the *ABCB1* polymorphisms 1199G>A, 1236C>T, 2677G>T/A, and 3435C>T in deaths by suicide using violent methods	998 consecutive Swedish forensic autopsies	***ABCB1****:* 1199G>A, 1236C>T, 2677G>T/A, 3435C>T	Suicide and violent suicide	The allele *T* in three *ABCB1* polymorphisms was associated with an increased risk for completed suicides using violent methods
Peñas-Lledó et al. (2015)	France	Examine whether these *ABCB1* SNPs were associated with the use of violent suicide methods among survivors of a suicide attempt	578 survivors of a suicide attempt	***ABCB1****:* 1236C>T, 2677G>T/A, 3435C>T	Violent suicide attempt	*ABCB1* haplotype (1236TT-2677TT-3435TT) increased the risk of violent suicide attempts, in particular in first suicide attempters

Germany. Different types of samples have been studied ranging from forensic autopsies (716 and 998 in Sweden, Zackrisson et al. 2010; Boiso-Moreno et al. 2013), to those collected in the frame of prospective studies of suicide attempters (342 from Spain, Peñas-Lledó et al. 2012; 587 from France, Peñas-Lledó et al. 2014, 2015). Other target populations have been of psychiatric patients with eating disorders (267 from Spain, Peñas-Lledó et al. 2011) or depressive episodes (285 from Germany, Stingl and Viviani 2011; 243 from a multicenter European study, Höffer et al. 2013), where history or current risk of suicide attempts was analyzed. Up to date, a total of 2,984 patients have been studied: 1,260 had completed suicide, 929 had survived one or more suicide attempts, and a subset of the remaining presented suicidal events in the context of psychiatric disorders (528 depressive patients and 267 eating disorders).

Among the several genes involved in the metabolism of antidepressants and/or other psychotropic drugs, so far *CYP2D6*, *CYP2C19*, *CYP2C9*, and *CYP1A2* have been studied in relation to suicide. Additionally, the relevant drug transporter *ABCB1* has been also analyzed recently (Table 33.1).

Of all, as it can be observed in Table 33.1 (Studies of Pharmacokinetic-Related Genes and Suicide), *CYP2D6* has been the most extensively studied, since it is very clinically relevant given that it is highly polymorphic and is involved in the metabolism of many widely used antidepressant drugs (e.g., fluoxetine, amitriptyline, paroxetine, fluvoxamine, venlafaxine, mirtazapine, citalopram) and other like antipsychotics or opioids and presents high degree of polymorphism (LLerena et al. 2014). Thus, it may influence functional variability in various psychotropic drug responses. The first study exploring the relations between *CYP2D6* and death by suicide expected to find individuals intoxicated by drugs metabolized by this enzyme due to lack or poor enzyme activity but instead found an increased frequency of individuals with duplication/multiplication of the active *CYP2D6* gene, who are considered ultrarapid metabolizers (UMs) related to fast enzyme activity (Zackrisson et al. 2010). Later, *CYP2D6* UMs were also found to be more frequent among young eating disorder patients with a lifetime history of suicidal behavior (Peñas Lledó et al. 2011), among depressive inpatients with high suicide risk (Stingl and Viviani 2011), and among attempters from the general population with scores of 75th percentile or above on the "objective circumstances subscale" of the Beck Suicide Intent Scale related to planning (Peñas-Lledó et al. 2012). Furthermore, when looking at CYP2D6 activity in combination with another polymorphic enzyme, CYP2C19, also involved in the metabolism of widely used antidepressant and anxiolytic drugs (e.g., citalopram, sertraline, diazepam), the frequency of suicide attempters with a high CYP2D6-CYP2C19 combined metabolic capacity was also shown to increase the likelihood of a highly planned suicide attempt, in particular, in individuals without a family history of suicidal behavior (Peñas-Lledó et al. 2014). Recently, the *ABCB1*, involved also in the transport of antidepressants at the blood-brain barrier (e.g., citalopram, venlafaxine, paroxetine, and amitriptyline), has been found in relation to the use of violent suicide method in completed suicide (Boisso-Moreno et al. 2013) and survivors of an attempt (Peñas-Lledó et al. 2015).

In short, the most studied pharmacokinetics-related genetic polymorphisms have been *CYP2D6*, *CYP2C19*, and also *CYP2C9*, *CYP1A2*, and *ABCB1*, which will be reviewed later (Sect. 33.3). The clinical outcomes evaluated were mostly completed suicide and suicide attempts, which were classified in different phenotypes.

33.2.2 Genetic Polymorphisms Related to Pharmacodynamics

Besides the abovementioned genetic polymorphisms involved in drug metabolism and transport, other pharmacogenetic studies have been developed. Many other candidate gene variants mostly involved in the pharmacodynamic mechanisms of some antidepressants have been analyzed. Considering that this review focuses on genetic polymorphisms affecting drug pharmacokinetics, an overview of those studies is presented. The majority of these studies address the potential influence of these candidate genes on the phenotype of emergence or worsening of suicidal ideation during antidepressant treatment in the context of major depression regardless the response to such drugs (reviewed by Brent et al. 2010b).

For example, Perroud et al. (2009) found that some *BDNF* and *NTRK2* polymorphisms out of 123 polymorphisms in nine candidate genes were associated with emergence or worsening of suicidal ideation in a population of adults with unipolar depression taking escitalopram or nortriptyline. Suicidal ideation was also associated with another SNP in the alpha (2A)-adrenergic receptor gene (*ADRA2A*, rs11195419) only among men under nortriptyline treatment. However, Laje et al. (2007) did not find these genes in association with emergence of suicidal ideation in patients from the STAR*D clinical trial under treatment with SSRIs, but found that the glutamate receptor genes, glutamate receptor, ionotropic, kainite 2 (*GRIK2* rs2518224 CC genotype), and glutamate receptor, ionotropic, and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate 3 (*GRIA3* rs4825476 G allele) were related. Additionally, it was observed that these two risk alleles were unrelated to a past history of suicide attempt, past suicidal ideation or suicidal ideation at baseline prior to treatment. *GRIK2* and *GRIA3* genetic polymorphisms were also found in association with emergence of suicidal ideation, in depressed inpatients treated with a wide variety of antidepressants by Menke et al. (2008) but the former with different SNPs (rs2852618, rs954765, and rs2782900) and the latter with a different allele (rs4825476 A). Curiously, there were three suicide victims during the study and all of them carried all these risk alleles.

Perlis et al. (2007) found *CREB1* SNPs (rs7569963 and rs4675690) associated with emergence or increases in suicidal ideation within the first month of treatment, but only in males from all STAR*D participants that were treated with citalopram. There was no relationship between these polymorphisms and either suicidal ideation at intake, or a past history of a suicide attempt.

Brent et al. (2010a) found that genotypes of *FKBP5* (rs1360780 TT and rs3800373 GG) associated with induction of the greatest reduction in the sensitivity of the glucocorticoid receptor were associated with suicidal events including both

emergence and worsening of suicidal ideation or suicidal attempt. This study despite was also unrelated to drug response and was developed among treatment-resistant unipolar depression adolescents that had not responded to an adequate trial with an SSRI after 12 weeks and were switched to another SSRI (paroxetine, citalopram, or fluoxetine) or venlafaxine. These genotypes were not associated with current suicidal ideation or history of a past attempt.

Perroud et al. (2011) also found three polymorphisms in three genes of the nine candidate genes studied. The *FKBP5* SNP as the strongest genetic predictor (rs1360780), followed by the 2677T allele in the *ABCB1* associated with increasing suicidal ideation during antidepressant treatment in major depressive outpatients, also regardless the type of the drug. However, they also found that the SNP within the 5-*HTR1B* (rs130058) demonstrated a differential association with increasing suicidal ideation depending on antidepressant type.

33.2.3 Other Pharmacogenetic Biomarkers of Suicide

Other recent studies have moved from pharmacogenetics into pharmacogenomics. For example, Laje et al. (2009) developed the first genome-wide association study (GWAS) and found that the proteoglycan-like sulfated glycoprotein papilin gene (*PAPLN* rs11628713 C allele) and the interleukin receptor gene (*IL28RA* rs10903034) were related to suicidal ideation. Perroud et al. (2012) also found other variants; specifically one in a gene-encoding guanine deaminase (*GDA*, rs11143230) was related to increasing suicidal ideation during escitalopram and nortriptyline treatment.

Finally, other peripheral *gene expression biomarkers* of response to citalopram in patients with major depression have been proposed such as a downregulation of SMA- and MAD-related protein 7 and sialic acid-binding immunoglobulin-like lectin, pseudogene 3 prior to drug treatment (Mamdani et al. 2014) and upregulation of interferon regulatory factor 7 by citalopram treatment (Mamdani et al. 2011).

In sum, some of the genetic polymorphisms related to drug pharmacodynamics studied mainly in relation to onset or increases in suicidal ideation were those also involved in the neurotrophic and synaptic plasticity systems (*BDNF*, *NTRK2*, and *CREB1*), noradrenergic system (*ADRA2A*), glutamatergic system (*GRIA3*, *GRIK2* and *GDA*), inflammatory and hypothalamic-pituitary-adrenal (HPA) axis systems (*IL28RA* and *FKBP5*), and other in different brain functions (e.g., *PAPLN*).

33.3 Pharmacokinetic Genes Analyzed in Relation to Suicidal Behavior

As shown in Table 33.1, the pharmacokinetic-related genes most analyzed in pharmacogenetic studies of suicide attempt or suicide are so far *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, and *ABCB1*, which are reviewed below. A summary of their main characteristics is given to justify their potential implication in suicide.

33.3.1 CYP2D6

***CYP2D6* genetic polymorphism** The *CYP2D6* gene is polymorphic, with over 100 allelic variants described to date. Among these variants, *CYP2D6*3*, **4*, **5*, or **6* are related to lack of protein activity or synthesis; *CYP2D6*10*, **17*, **29* or **41* are associated with reduced enzyme activity and the duplication/multiplication of active alleles (*CYP2D6*1xN*, **2xN*) with increased activity (reviewed in LLerena et al. 2014). Subjects who have null enzyme activity are denominated poor metabolizers (PMs), whereas individuals with increased activity are called UMs.

CYP2D6 drug and endogenous substrates The CYP2D6 enzyme is mainly expressed in the liver and has been implicated in the metabolism of around 25 % of the drugs commonly used in clinical practice. Typical substrates for CYP2D6 are largely lipophilic bases and include most antidepressants, antipsychotics, and opioids and some antiarrhythmics, antiemetics, beta-adrenoceptor antagonists (beta-blockers), and opioids (reviewed in LLerena et al. 2009, 2014). In addition, CYP2D6 has been found in neurons in numerous human brain areas and plays a role in the metabolism of endogenous compounds (5-methoxytryptamine, anandamide, progesterone, and tyramine and in generation of serotonin and dopamine from trace amines) (reviewed in Peñas-Lledó and LLerena 2014; Stingl et al. 2013; Ingelman-Sundberg et al. 2014). Consistently, although there are contradictory results, CYP2D6 has been related to personality and cognitive functions as well as to vulnerability to psychopathology (LLerena et al. 1993; Peñas-Lledó et al. 2010).

Clinically, the functional PM and UM phenotypes are particularly relevant because they may present increased susceptibility to adverse drug reactions, or lack of response to treatment with CYP2D6 substrates (reviewed in LLerena et al. 2014).

33.3.2 CYP2C19

***CYP2C19* genetic polymorphism** The *CYP2C19* gene is polymorphic with over 30 allelic variants described to date, ranging from null to increased enzymatic activity (reviewed in Fricke-Galindo et al. 2015). Individuals carrying two inactive *CYP2C19* alleles (i.e., *CYP2C19*2*, **3*) have been classified as PMs, and those carrying two increased activity alleles (**17*) or the **17* in confluence with an active variant as UMs.

CYP2C19 drugs and endogenous substrates CYP2C19 is also involved in the metabolism of psychoactive drugs used for the relief of anxious and depressive symptoms such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and benzodiazepines. However, it does not seem to be involved in the metabolism of antipsychotic drugs (LLerena et al. 1993; reviewed in Peñas Lledó et al. 2014). CYP2C19 expression has been recently shown in the human fetal brain, where it also participates in the metabolism of endogenous steroids and cannabinoid-like

compounds (reviewed in Ingelman-Sundberg et al. 2014), although most evidence is in vitro. It has been also related to alterations in brain development and affective behavior in a transgenic mouse model carrying the human CYP2C19 (reviewed in Ingelman-Sundberg et al. 2014) and in PMs with protection against depressive symptoms (Sim et al. 2010).

Clinically, individuals considered as CYP2C19 PMs or UMs have also shown variation in the response to drugs metabolized by this enzyme (reviewed in Fricke-Galindo et al. 2015).

33.3.3 CYP2C9

***CYP2C9* genetic polymorphism** Currently, more than 60 *CYP2C9* variants have been described. Of them, *CYP2C9* alleles related to a null hydroxylation capacity are, for example, *CYP2C9*6*, **15*, **25*, and **35*, although, most of the variants described so far are associated with enzyme capacity (e.g., *CYP2C9*2*, **3*, **5*, **11*) (reviewed in Céspedes-Garro et al. 2015). Recently, the *CYP2C9* IVS8-109T allele is being investigated with regard to its potential to increase the enzyme activity (Dorado et al. 2014).

CYP2C9 drugs and endogenous substrates CYP2C9 is one of the major cytochrome P450 enzymes, and it is responsible for the phase I metabolism of several commonly used drugs such as oral anticoagulants, nonsteroidal anti-inflammatory drugs, hypoglycemic agents, and antiepileptic drugs, some of them with narrow therapeutic index (reviewed in Céspedes-Garro et al. 2015). This enzyme has been related to the metabolism of endogenous substrates like steroids, retinoids, arachidonic acid, and melatonin (Zhou et al. 2009), which are involved in several processes such as circadian rhythms, mood, reproduction, aging, etc., and arachidonic acid, which has been related to depression. Interestingly, a higher frequency of *CYP2C9*3* allele was found among patients diagnosed with major depression when compared to schizophrenic patients and healthy volunteers (LLerena et al. 2003).

Clinically, individuals with null enzyme activity, carriers of two null alleles or the reduced allele *CYP2C9*3*, who are identified as PMs may present adverse drug reactions when taking these substrates.

33.3.4 CYP1A2

***CYP1A2* genetic polymorphism** *CYP1A2* variant alleles do not appear to cause any important alteration in gene expression or enzyme activity. It is highlighted that the *CYP1A2*1F* allele has been shown to influence the gene inducibility as well as to increase the metabolism of caffeine in vivo after smoking (Djordjevic et al. 2008). Additionally, a rare variant has been found in African populations (*CYP1A2*1K*)

(Aklillu et al. 2003), which has been related to decreased CYP1A2 expression and caffeine metabolism.

CYP1A2 drugs and endogenous substrates There are over 100 drugs metabolized by CYP1A2 to a moderate extent such as such as the psychotropic drugs clozapine, olanzapine, duloxetine, caffeine, etc., to a minor extent (10–30 %) such as paracetamol, lidocaine, and imipramine. The enzyme seems also to be involved in the metabolism of endogenous substrates such as melatonin, bilirubin, uroporphyrinogen, estrone and estradiol, and arachidonic acid (Zhou et al. 2009).

Clinically, there are reports of decreases in the plasma levels of several antipsychotics including clozapine in relation to *CYP1A2*1F* (e.g., Ivanova et al. 2015).

33.3.5 ABCB1

ABCB1 gene encodes for the transporter P glycoprotein (P-gp).

P-gp drugs and endogenous substrates P-gp is relevant for the transport of clinically useful drugs (i.e., amitriptyline, carbamazepine, chlorpromazine, clopidogrel, cimetidine, citalopram, digoxin, diltiazem, lamotrigine, lansoprazole, levofloxacin, losartan, morphine, omeprazole, phenytoin, propanolol, ranitidine, rifampicin, ritonavir, saquinavir, simvastatin, verapamil) and xenobiotics but also of endogenous substances (lipids, steroids, peptides, bilirubin, glucocorticoids) across the blood-brain barrier. It protects against the entrance of toxic substances in the CNS and favors their elimination transporting them into the gut, urine, bile, etc. (Hodges et al. 2011). Therefore, given the role of P-gp in the exogenous and endogenous metabolism, it has the potential to influence both drug treatment response and behavior, which may support its implication in suicidal behavior (Boiso-Moreno et al. 2013; Peñas-Lledó et al. 2015).

Clinically, several common coding variants in *ABCB1* have been studied for their potential influence on P-gp expression, function, and disease risk. Genetic associations with molecular or clinical phenotypes have largely been inconsistent, and replication studies are needed (Hodges et al. 2011).

33.4 Pharmacogenetics of the Drug Treatment for Suicide, Regulatory Impact, and Clinical Relevance

The goal of any pharmacologic treatment for suicide may be acute relief of suicidal symptoms and its prevention, which is not only limited to individuals who have already shown suicidality but also include those who may end up developing suicidal events. Antidepressants, anxiolytics, second-generation antipsychotics, and mood-stabilizing agents are widely used to manage the suicidal patient and treat any

mental health problem (reviewed by the American Psychiatric Association Practice Guidelines for Suicidal Behaviors).

33.4.1 Drug Treatment

Antidepressants The strong association between depressive disorders and suicide supports the use of antidepressants. During the last decades, suicide rates have significantly fallen across some populations coinciding with the increasing clinical use of SSRIs and newer antidepressants (Tondo et al. 2003; Carlsten et al. 2001; Joyce 2001; Ohberg et al. 1998; Isacsson et al. 1999; Berecz et al. 2005). However, at the patient level, the antidepressant medication should be administered in adequate doses to be efficacious and safe. Indeed, safety prescribing practices usually start with low doses with further increases in case of nonresponse. While this practice might be very helpful for individuals with null enzyme activity for the substrate administered, it can be very risky for those with increased enzyme activity. In support of this, CYP2D6 UM status has been related to lack of response to antidepressant drugs (Rau et al. 2004; Kawanishi et al. 2004) and also to early dropout from monotherapy antidepressant treatment with the MAOI amitriptyline or the SSRI fluoxetine (Peñas Lledó et al. 2013) in depressive patients.

Antipsychotics Clozapine is used to prevent suicide in patients with schizophrenia since it has been shown to reduce suicide attempt rates (Meltzer and Okayli 1995; Reid et al. 1998; Sernyak et al. 2001). Subjects with genetic vulnerability may have increased risk of clozapine severe adverse effects. Moreover, CYP2D6 PMs and UMs may have an increased risk of adverse effects and lack of benefit under standard doses, respectively, when taking other antipsychotics metabolized by this enzyme such as risperidone, olanzapine, and aripiprazole, which are used to reduce suicide risk in agitated patients (Meltzer et al. 2003).

Anxiolytics Suicide risk may be also associated with severe symptoms of psychic anxiety, panic, and insomnia (Fawcett et al. 1990). Although benzodiazepine treatment may reduce them, it remains to be known if anxiolytics might be less effective for those individuals under treatment with CYP2C19 substrates who are UMs.

33.4.2 Pharmacogenetics of Suicide in Drug Labeling

FDA labels of the drugs used to treat suicide were reviewed in order to evaluate the relevance of pharmacogenetic biomarkers. A total of 36 drugs (N05A, N05B, N05C, N06A WHO ATC groups), 11 antipsychotics, 8 anxiolytics and hypnotics, and 17 antidepressants were reviewed. Seven genetic biomarkers have been found in their drug labels: *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP2B6*, *CYP2D6*, *CYP3A4*, and *ABCB1*. The most relevant biomarker is CYP2D6 included in many antidepressants and antipsychotics (http://www.fda.gov).

Most *antidepressant* labels include CYP2D6 (imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, fluoxetine, citalopram, escitalopram, paroxetine fluvoxamine, venlafaxine, duloxetine, and vortioxetine), and, some of them, CYP2C19 (imipramine, clomipramine, citalopram, escitalopram, sertraline), CYP1A2 (imipramine, clomipramine, and duloxetine), or *ABCB1* (sertraline).

Among *antipsychotic drugs*, CYP2D6 is also the most relevant pharmacokinetic biomarker (fluphenazine, haloperidol, pimozide, loxapine, clozapine, risperidone, aripiprazole, paliperidone, lurasidone). CYP1A2 is involved in the metabolism of loxapine, clozapine, and olanzapine. However, CYP2C9 and CYP2C19 do not seem to be relevant for the metabolism of this group.

There are just a few genetic biomarkers for *anxiolytics and hypnotic* drugs, since only *CYP2C19* (diazepam, clobazam) and *CYP1A2* (zolpidem) are included.

In other words, CYP2D6 and CYP219 are involved in the metabolism of many antidepressants. Furthermore, while CYP2D6 appears also relevant for antipsychotics, CYP2C19 does not, but instead is relevant for some anxiolytics. Other CYPs such as CYP1A2 and CYP2C9, and CYP2B6, are involved in a much fewer number of drugs. Finally, the CYP3A4, that participates in the metabolism of many drugs, is described up-to-date as presenting a low degree of polymorphism, suggesting less influence on drug response and safety.

33.4.3 Clinical Relevance

The PharmGKB database (https://www.pharmgkb.org) was reviewed to determine the biomarkers with the highest level of evidence (1A). Evidence 1A is given for those annotations of a variant-drug combination in a CPIC (Clinical Guidelines) or medical society-endorsed pharmacogenetic guidelines, or for those implemented at the PGNR site (US Network of Pharmacogenetics) or another major healthcare system.

It is of note that among all psychotropic drugs studied, only *CYP2D6* (imipramine, clomipramine, trimipramine, amitriptyline, and nortriptyline) and *CYP2C19* (amitriptyline, citalopram, escitalopram, and sertraline) have evidence level 1A.

In the light of present data, both *CYP2D6* and *CYP2C19* genetic polymorphisms are recommended to be determined in individuals taking such antidepressants to prevent suicide since they may affect drug response and safety.

33.5 Concluding Remarks

33.5.1 Pharmacogenetic Drug-Metabolizing Enzymes and Suicidal Attempts

Up to date, main pharmacokinetics-related genes found in association with suicidal events have been *CYP2D6* and recently *CYP2C19* and *ABCB1*. The first most likely explanation for these relationships is therapeutic failure in patients taking drugs

mainly metabolized by these polymorphic enzymes. A second explanation is the implication of these enzymes in the endogenous metabolism of neuroactive compounds like amines, steroids, and cannabinoids, of potential relevance for the suicidal behavior. In sum, the effect of pharmacokinetics-related genes on suicidal behavior can be partially due to drug therapeutic failure during treatment with related substrates and/or to differences in the CNS regulation related to the suicidal phenotype.

In agreement with these hypotheses, most drugs used for treating individuals with risk of suicide are metabolized by CYP2D6 and CYP2C19, which have the highest level of evidence (PharmGKB), and are also known to participate in the metabolism of CNS endogenous substrates (reviewed in Peñas Lledó et al. 2010; Peñas-Lledó and LLerena 2014). Then, the evaluation of the combined influence of these polymorphic genes could be used as a strategy to prevent suicidal behavior. Consistently, the results of the first and only study showed that a high CYP2D6-CYP2C19 metabolic capacity was related to increased severity of the suicidal behavior in survivors of a suicide attempt (Peñas-Lledó et al. 2014).

On the one hand, this finding could be indirectly supported by the evidence about the role of both CYP2D6 and CYP2C19 in the metabolism of endogenous neuroactive substances like steroids and endocannabinoids known to influence behavior and psychopathology. In keeping with that, variability in CYP2D6 has been related to differences in personality traits, neurocognitive functions, and mental health problems (Peñas-Lledó et al. 2010). With regard to the latter, previous studies have reported positive relationships between the number of *CYP2D6* active genes and suicide completion (Zackrisson et al. 2010), lifetime history of suicide attempts (Peñas-Lledó et al. 2011), suicide risk (Stingl and Viviani 2011), and the severity of the objective circumstances mostly related to the preparation of the suicide attempt (Peñas-Lledó et al. 2012). Similarly, CYP2C19 has been recently shown to be expressed in the human fetal brain and to explain differences in the brain development and affective behavior of transgenic mice carrying the human CYP2C19 (Persson et al. 2014). Consistently, variability of *CYP2C19* in humans has been related to depressive symptoms (Sim et al. 2010). On the other hand, CYP2D6 and CYP2C19 are involved in the metabolism of many psychotropic drugs such as most antidepressants, which may lead to variability in drug response during treatment with these substrates. For example, individuals carrying more than two *CYP2D6* active genes have shown poor response to antidepressant drugs or early dropout from monotherapy treatment with antidepressant substrates (Peñas-Lledó et al. 2013).

33.5.2 Future Outlook

In the future, all pharmacokinetics- and pharmacodynamics-related genes for a given drug must be studied simultaneously. Up to date, study designs are limited to associations; however, hypotheses about the relation of pharmacokinetic related genes need to include evaluation of drug plasma concentration in order to explore

the potential cause-effect relationship. The definition of the suicidal phenotypes should be also improved in particular of those that poses a major lethality risk.

Pharmacogenetics might be clinically useful for psychiatric problems such as suicide, because an association between genotype and drug response might be of direct use. For example, in using genetic predictors to avoid rare ADRs or to select which of several alternative drugs have the highest efficacy. Therefore, the final goal is identifying pharmacogenetic variants, which through diagnostic testing can rapidly increase the efficacy of existing drug therapies, and therefore prevent suicide attempts or death by suicide.

Pharmacogenetics may work for those with a family or personal history of suicide attempts who are prescribed a drug treatment to prevent new attempts. However, one of the main problems of the pharmacogenetics of suicide comes represented by those *without history of suicide attempts*, since many deaths by suicide are in first attempters (Isometsa and Lonnqvist 1998). It seems to be that genes such as *ABCB1* are related to use of violent suicide methods, which are highly lethal, in first attempters (Peñas-Lledó et al. 2015); therefore, this problem would require a primary prevention program in all those taking *ABCB1* substrates and who carry the haplotype which increases the risk of developing suicide gestures.

Even more difficult is to prevent suicide in individuals with *no personal history of suicide together with no family history of suicide*. Considering that the increased combined activity of CYP2D6 and CYP2C19 has been related to the performance of a severe suicide attempt implicating premeditation and precautions to avoid rescue or discovery (Peñas-Lledó et al. 2014), all individuals under treatment with substrates metabolized by these polymorphic enzymes should be genotyped for preventive purposes. Then, a global pharmacogenetic preventive program for suicide may consider genotyping individuals under treatment with substrates of these polymorphic enzymes even if they have no family and/or personal history of suicide.

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https://www.pharmgkb.org/

Monitoring, Evaluation, and Referral of Patients with Suicide Risk Upon Hospital Admission

34

Lucas Giner, Christopher W. Root, and Philippe Courtet

Abstract

Monitoring patients for suicide risk is a vital aspect of both initial and long-term psychiatric care for patients with suicidal behavior. A prior suicide attempt is the biggest risk factor for completed suicide, and the period immediately following a suicide attempt requires a high level of vigilance on the part of the care providers. Ongoing long-term monitoring for suicide risk is also crucial, because the risk of suicide can persist well beyond the acute phase of care. In this chapter, we discuss the importance of monitoring patients for suicide risk. We outline a number of well-known risk factors for suicidal behavior and discuss standardized instruments that are effective at predicting a high risk of suicidal behavior. We also detail our unit's specific experience in dealing with suicidal patients and describe out strategies for inpatient and outpatient care as well as methods for ensuring continuity of care between these distinct phases.

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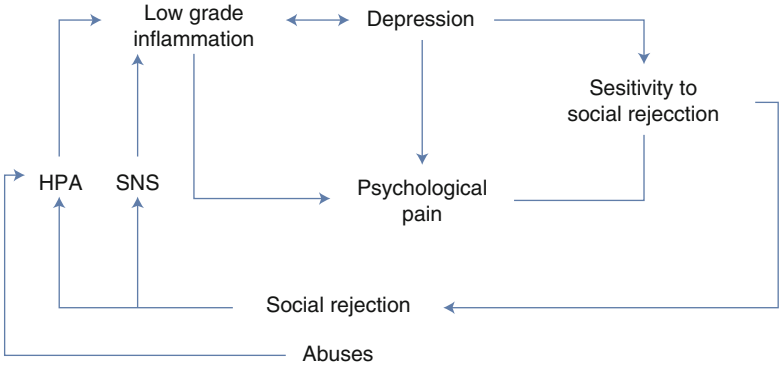
34.1 Introduction

Suicide is known to be a significant problem in the world of public health that is challenging to address. We know that previous suicide attempts are the principal risk factor for both completed suicides and for additional suicide attempts. Prospective studies have shown that roughly 10 % of subjects with a prior suicide attempt die by suicide (Osvath et al. 2003), and half of these deaths occur within 2 years of the attempt (Suokas et al. 2001). It is estimated that there are between 10 and 20 suicide attempts for every completed suicide, and a portion of these attempts will not be discovered in any type of health assessment. Therefore, the identification of these individuals and their treatment is a priority in the global prevention of suicide. The conceptualization of suicidal behavior is changing, thanks to research being conducted at present. The latest edition of the DSM (American Psychiatric Association 2013) lists suicidal behavior as a clinical situation that requires further study, but the results of ongoing research may lead to classification as a disorder in the future. According to the proposed criteria for suicidal behavior as a disorder, it can be classified as active (the first year after the attempt) or in remission (between 1 and 2 years after the attempt).

Suicidal behavior in response to the patient's social situation is not a new concept. What is new is approaching this behavior from a biological perspective. We know that social inclusion or rejection influences one's physical health, psychological health, and their physiological responses (Eisenberger and Cole 2012; Meyer-Lindenberg and Tost 2012). It has been proposed that this influence is due in part to an inflammatory response regulated by the central nervous system. This central control is partially regulated by the hypothalamic-pituitary-adrenal axis (HPA). The interactions of these structures can result in the transcription of proinflammatory cytokines such as IL-1B, IL6, and TNF. This inflammatory response is also mediated in the sympathetic nervous system by epinephrine and norepinephrine (Eisenberger and Cole 2012). Another aspect of the inflammatory response is the activation of the anterior cingulate cortex, which serves as a signal to peripheral proinflammatory cytokines and is thought to modulate the stress response via the HPA. Subjects with suicidal behavior have been found to have hyperactive anterior cingulate cortices, and childhood sexual and/or sexual abuse has been shown to lead to alterations in the HPA and in the receptors related to the inflammatory response (Lopez-Castroman et al. 2012; McGowan et al. 2009). These changes have been linked to an increase in the risk of suicide as an adult. A recent study has shown evidence of a low-grade inflammatory response in subjects with suicide attempts and completed suicides (Courtet et al. 2015). Therefore, we can surmise that social exclusion can provoke an inflammatory response, which, over time, will increase one's sensitivity to rejection and lead to a higher risk of suicidal behavior. It is also worth noting that the regions activated by social rejection (both in healthy subjects and subjects with prior suicidal behavior) are related to the zones of psychological pain studied in subjects with depressive disorders. This psychological pain could be the expression of the low-grade inflammation in the presence of a significant social exclusion in an individual who is already hypersensitive and

predisposed to a certain response. We propose that patients with a vulnerability to suicide enter into a vicious circle of heightened sensitivity to social rejection and increasing psychological pain.



SNS: Sympathetic nervous system
HPA: Hypothalamic-pituitary-adrenal axis

Shneidman proposed that suicidal behavior represented an attempt to alleviate psychological pain (Shneidman 1993). This idea is a recurring theme in suicide notes (Valente 1994). Currently, psychological pain is conceptualized as a long-standing and maintained unpleasant sensation, which leads to a negative evaluation of self (Meerwijk et al. 2014). It also appears that psychological pain and somatic pain share the same neural pathways. Some studies have shown that those with prior suicide attempts have a diminished pain threshold, independent of any depressive disorder. Our group conducted a study of the use of analgesics (both opioid and non-opioid) in a cohort of 857 subjects greater than 65 years of age with no history of dementia over the course of 3 years. Among the subjects, 41 had a history of suicide attempts, 410 had a history of depression without suicide attempts, and 406 had no history of either depression or suicide attempts and served as the control group. Our results indicated a higher consumption of opioid analgesics among the subjects with suicide attempts compared to those with depression only and those in the control group. On the other hand, consumption of non-opioid analgesics was higher in the control group and the depression group compared with the group with a history of suicide attempts (Olie et al. 2013). In another study (Olie et al. 2010), the sensation of psychological pain in subjects with depression was evaluated with a visual analog scale. The responses of those with suicide attempts were compared to the response of those who had never attempted suicide. The rating of the psychological pain was noted to be greater among those who had previously attempted suicide. Furthermore, a higher rating of psychological pain was linked to a greater intensity and frequency of suicidal ideation.

34.2 Our Experience in a Specific Hospital Unit

The relation we have identified between psychological pain and the risk of suicide is the basis of the intervention we are proposing for the prompt identification of subjects with a high risk of suicide. Our principal objective is the maximum reduction of the psychological pain that has brought the patient to the verge of attempting or planning a suicide. This is the primary goal of our Department of Psychiatric Emergency and Acute Care at the Montpellier University Hospital in which we attend patients with suicide attempts or serious suicidal ideation. In our experience, demonstrating to the patient a comprehension of their suffering and the intent to alleviate it during their hospitalization creates an alliance between the providers and the patient, even in those cases with significant circumstances outside of the realm of clinical help.

In our unit, we have designed a therapeutic plan that consists of roughly 1 week's treatment in an open psychiatric unit. During this week, the following occur:

1. Complete evaluation of the patient and his or her environment

   The length of stay allows a detailed evaluation of various aspects the patient and his or her environment to occur over the course of several days. We utilize standardized assessment instruments that focus on variables related to the risk of suicide. We also recognize that these evaluations are underutilized in hospital inpatient units and even psychiatric emergency departments. Collecting the data that these instruments require allows us to undertake a far more thorough evaluation, which is beneficial from both a clinical and a medicolegal perspective. Understanding the facts of an individual case from multiple distinct points of view helps us to offer personalized assistance to the patient and their family. On the one hand, we can help them identify high-risk situations in order to prevent repeat attempts, on the other hand, we are able to help the family members better manage the impact of a loved one's suicidal behavior. For these reasons, the family should participate in the loved one's treatment as much as is practical. The family should be involved in the process of psychoeducation, so that they can recognize high-risk situations and know how to respond and ask for help. Furthermore, the family plays a fundamental role in the initial formation of the therapeutic alliance.
2. Reduction of psychological pain through sedation-relaxation

   This is one of the principal objectives at intake. To be able to meet our objectives, we utilize treatments to address the symptoms associated with risk for suicidal behavior. The symptoms include, but are not limited to: restlessness, agitation, insomnia, emotional instability or lability, anger, irritability, aggression, and anxiety (Rudd 2008). The initial therapeutic goal is to utilize sedative treatment in order to curb escalating psychological pain. The combination of pharmacological agents utilized is obviously very case dependent, but typical agents include benzodiazepines, neuroleptics, antiepileptics, and others. These interventions require intensive monitoring by the nursing staff, due to the active risk of suicide and the potential adverse effects of the medicines administered.

3. Choice of treatments in the acute phase

   In this phase, in addition to the medications administered to reduce the psychological pain through sedation and relaxation, it is also appropriate to initiate therapy with the medications for underlying diagnosis so that they may be continued through discharge.

   For some time, numerous articles have highlighted the effects of ketamine on suicidal ideation and depressive symptoms in these situations. The results indicate a potent effect on suicidal ideation in depressed patients from the first administration of the drug, even within the first hour (Ballard et al. 2014; Diazgranados et al. 2010). Results as robust and remarkable as these offer new ways to approach and manage suicide risk in the urgent setting. The mechanism by which ketamine affects suicidal ideation is still not well understood. It is possible however that ketamine acts not only as an antidepressant but also that it alleviates psychological pain through anti-inflammatory effects along the glutamate pathway (Ballard et al. 2014; Loix et al. 2011).
4. Psychological intervention in crisis

   In addition to psychopharmacological treatments to palliate the sensation of psychological pain, it is essential that the psychotherapeutic approach have the same goal. In our unit, we apply acceptance and compromise therapy (ACT), a form of contextual therapy or third-generation behavioral therapy (Hayes et al. 2006). To summarize this technique drastically, the objectives are to develop the ability to effectively manage negative thoughts and feelings that impede us from being effective in life without avoiding them or succumbing to them. The technique also requires the individual to identify and keep in mind the things that give meaning to his or her existence. The therapy combines concepts of mindfulness, acceptance, behavioral change, and compromise.

At our unit, we conducted a naturalistic study to determine how the reduction in the intensity of suicidal ideation is related to the acquisition of habit of acceptance as opposed to relief of depressive symptoms. The results suggest that ACT can be effective at addressing multiple dimensions of suicide risk like psychological pain and cognitive rigidity and not just the patient's affective state (Ducasse et al. 2014). At present, we are conducting a randomized controlled trial to confirm that these results are as promising as they seem.

5. Team meeting for diagnostic consensus and orientation of maintenance therapy

   Outlining the diagnosis of a person with suicide risk is fundamental to his or her successful treatment. The initial steps of diagnosis should be accomplished during the inpatient week with the assistance of the family. Once the diagnosis is established, the choice of treatment is the next step toward the prevention of suicidal behavior. The most prevalent diagnoses associated with attempts at suicide are depressive disorders and anxiety disorder (Giner et al. 2014); therefore, antidepressants play a role in the majority of the treatment plans for these patients. On the one, epidemiologic studies have shown a link between widespread prescription of antidepressants and a decrease in

completed suicides in different countries (Nakagawa et al. 2007; Grunebaum et al. 2004). However, it is also well known that there is an increase in the risk of suicidal behavior in the first weeks of treatment with antidepressants. A recent study showed that this risk of suicidal behavior is greater in subjects under the age of 25 (Termorshuizen et al. 2015). In light of this, though antidepressants are key to the treatment of depressive disorders, caution and vigilance are paramount in the initial phase of treatment. With the idea of identifying risk factors related to repeat suicide attempts, we conducted a naturalistic study of 4357 patients during the first 6 weeks of their treatment with antidepressants (Courtet et al. 2014a). In the first 6 weeks, 1.7 % of patients had a new suicide attempt. The risk factors that were independently associated with an increase in risk for new attempts were: worsening depressive symptoms, change of antidepressant, absence of response to treatment in general, and the presence of treatment-resistant depression. Other associated factors were an increase in feelings of hopelessness, prior suicide attempts, and alcoholism. In another study, it was observed that those patients who are started on selective serotonin reuptake inhibitors (SSRIs) at a dose above that which was recommended presented with twice the risk of an increase in suicidal ideation (Courtet et al. 2014b). These findings correspond to those previously published by Miller et al. (2014), in which they found that the risk of suicidal ideation also increased at the start of treatment with SSRIs independent of the severity of the depressive disorder. One might assume that more severe depressive symptoms would justify starting treatment at higher initial doses. Though the recommendation for SSRIs is to start at small doses and increase them gradually (Brent and Gibbons 2014), it is estimated that one third of patients receiving antidepressant therapy are started at doses above the recommended levels.

In addition to antidepressants, certain molecules have been shown to be especially useful in the treatment of suicidal behavior. Lithium has been shown to have an antisuicidal effect in the treatment of bipolar disorder (Cipriani et al. 2013). However, lithium's utility is not limited to only bipolar disorder; numerous studies have suggested that lithium has a similar antisuicidal effect in other patient populations, independent of its mood-stabilizing effect (Cipriani et al. 2013).

Among the endophenotypes of subjects with greater vulnerability to suicide, one will find impulsivity and aggression, early onset of major depressive disorder, neurocognitive dysfunction (including decision-making ability), and overproduction of cortisol in response to social stress (Mann et al. 2009; Courtet et al. 2005; Jollant et al. 2005). Recently, we have written about the positive influence of lithium therapy on the decision-making abilities of patients with euthymic bipolar disorder (Adida et al. 2015). This may indicate that the antisuicidal effect of lithium is due to a regulation of decision-making processes. These results require further confirmation in randomized controlled trials.

34.3 Aspects Related to Short-Term Follow-Up

After the inpatient period, ambulatory follow-up is strongly recommended. The transition from the inpatient to outpatient setting can occur in various forms that favor continuity of care so that patients do not miss treatment or skip prior appointments. A transitional period of intermediate care between inpatient and outpatient can occur during which the inpatient physician continues to have follow-up appointments with the patient after discharge from the unit. In all patients determined to have a risk of suicide, especially in the period immediately following discharge, it is important to differentiate the factors associated with suicidal ideation and those associated with actually attempting suicide. A global study in which 9282 subjects were interviewed indicated that adverse life events and associated depressive symptoms lead to suicidal ideation, while anxiety disorders, substance abuse, psychiatric comorbidities, and impulsive characteristics lead to suicide attempts (Nock et al. 2010). In a now classic study conducted by Fawcett (Fawcett et al. 1990), the presence of anxiety disorders, insomnia, and anhedonia as well as alcohol consumption and a diagnosis of bipolar were determined to be risk factors for suicide in the short term in subjects with depressive disorders. In a study in which we analyzed the risk factors for repeated suicide attempts in a group of 1349 Spanish and French patients with prior suicide attempts, we found that anxiety disorder was the only diagnosis that was linked to repeated suicide attempts (Lopez-Castroman et al. 2011). Therefore, it makes sense to pay special attentions to the presence of or changes in the symptoms of anxiety that the patient is experiencing during the immediate follow-up period.

However, the follow-up period is not only for the evaluation of symptoms, it should include ongoing evaluation for the risk of suicide. It is understandable that once the patient is out of the acute phase of his or her suicidal crisis, less attention is paid to the patient's "suicidal state." During follow-up, more clinical effort is focused on the treatment of the underlying pathology. However, as was mentioned earlier, current classification guidelines suggest that suicidal behavior may be considered as a mental disorder in and of itself (American Psychiatric Association 2013). Once the imminent risk of suicide is no longer the patient's principal clinical problem, it can easily be overlooked. This is due in part to the fact that we lack a means of classifying suicide risk independent of another underlying diagnosis. In these cases, the underlying diagnosis becomes the focus of all of the clinical efforts, and it may cloud the recognition of problems related to suicidal behavior.

Additionally, the specific event of the suicide attempt can become muddled in among the patient's other diagnoses.

For these reasons, we recommend that ongoing evaluation for the risk of suicide utilizing standardized instruments be a part of the follow-up for all patients with psychiatric illness and those with a history of suicidal behavior in particular. One such instrument is the Columbia-Suicide Severity Rating Scale (C-SRSS), which is recommended by the US Food and Drug Administration. This scale and its self-administered online version have been demonstrated to be an effective predictor of

suicide attempts in the following year across distinct populations and diagnoses (Greist et al. 2014).

In addition to psychiatric care, the physical health of the patients cannot be forgotten during follow-up. Numerous studies have shown that psychiatric patients generally have poorer health than others during follow-up care (van Hasselt et al. 2013). Studies of patients with schizophrenia and bipolar disorder have yielded similar findings (von Hausswolff-Juhlin et al. 2009; Young and Grunze 2013). Patients with depression have been shown to have a propensity for cardiovascular issues (Bradley and Rumsfeld 2015). Within the area of our concern, patients with a history of suicidal behavior have an increased risk of premature death from various disease pathologies. Bergen and his colleagues (2012) analyzed a cohort of 30,950 subjects with documented suicide attempts over the course of 6 years. They observed that during the study period, 6.1 % of the cohort died. They found the risk of natural death for those who had attempted suicide to be between 2 and 7.5 times higher than the general population. Those who had attempted suicide had an average of approximately 25 years of potential life lost. The most common health problems encountered in the study population were cardiovascular and digestive in nature.

34.4 Immediate Follow-Up at Present and in the Near Future

We know that there is a percentage of subjects that will be inconsistent in their follow-up treatment, or abandon it completely. They will do this in spite of being identified as at risk and being given adequate treatment in the appropriate setting in accordance with current recommendations. In order to approach this problem, we need to understand that the factors that are associated with an increased risk of suicide also present an obstacle to the provision of quality follow-up care. The risk factors for suicidal behavior that also serve as obstacles to follow-up care include: impulsivity, hostility, altered decision-making processes, emotional instability, hypersensitivity to social rejection, and a diminished perception of social support. Data shows that 60 % of subjects that have attempted suicide do not have more than 1 week of follow-up care, 43 % of suicides occur in the month following hospital discharge, and 47 % occur prior to the first follow-up appointment (Hunt et al. 2009; Lizardi and Stanley 2010; Courtet et al. 2011). It is possible that the psychiatric care in these cases could have been more proactive and taken the initiative in follow-up. It has been years since studies first indicated a decreased rate of repeat suicide attempts when the patient receives some form of contact from the service that attended them initially, and the success of this intervention has been replicated in multiple randomized controlled trials (Motto and Bostrom 2001; Carter et al. 2005; Vaiva et al. 2006; Cebria et al. 2013). The contact was made either by mail or telephone. The message indicated a concern with the patient's well-being and invited them to reconnect if they desired. It is clear that feeling more cared for will lead one to feel more socially connected. We need to reflect on the discrepancies between the level of organizational support that we typically offer to our patients and the care that suicidal patients truly need.

Today, this discrepancy can be reduced through the use of new technologies, which are easy to use and highly accessible. It is not surprising to see increasing reports of novel methods for follow-up including the use of mobile device-based applications designed to monitor the risk of suicide in patients with a predetermined level of risk.

In our service, we have developed a protocol for follow-up after discharge with the objective of maintaining the benefit of the brief hospitalization in our unit, decreasing the period during which the patient is not monitored and reducing the impact of the shift from the inpatient to the outpatient setting. Our protocol is initiated within the first week of discharge and lasts for 2 weeks. In the first 2 weeks, there will be four face-to-face contacts (either with a physician or a nurse), and after the initial 2 weeks, there will be ongoing phone contact, with or without in-person appointments as needed. Additionally, home visits may be utilized in cases where there does not appear to be improvement. The objective of this protocol is to ensure continuity of care during the first 3 months following the suicidal crisis before referring the patient to ambulatory psychiatric care or primary care. At the same time, the nursing staff is actively coordinating between the various resources available to the patient to assure that comprehensive care is always available.

In certain regions of France, they are implementing intensive monitoring protocols for the period between hospitalization and outpatient follow-up. The contact with the patient is based on an algorithm, which takes different patient types into account (Vaiva et al. 2011). In this process, all patients who have attempted suicide are contacted, and if the patient is determined to again be at risk for suicide, a referral to the psychiatric emergency department is made with the intent of resolving it. In cases in which there is a repeat attempt, the patient is contacted between 10 and 21 days after discharge. If the patient cannot be reached or is noncompliant, then the patient is sent a postcard. In these cases, a referral to the psychiatric emergency department is also organized in case a suicidal crisis is discovered. At present, they are also conducting a 2-year, multicenter, randomized controlled trial to determine the effectiveness of text messages (SMS) for the prevention of repeat suicide attempts in patients discharged from the hospital after a suicide attempt.

In our hospital, we are conducting an ecological study utilizing electronic surveys administered in the patient's actual environment over the course of 1 week. The study population is divided into four groups: healthy controls, subjects with a history of euthymic depression, subjects with prior suicide attempts, and subjects recently discharged following inpatient treatment for a suicide attempt (Husky et al. 2014). The study had very high rates of participation and completion of multiple surveys. At first, there were doubts raised with respect to the possible negative influence of the methodology and possible intrusion into the life of the subjects given the limited experience that exists in this regard. Nonetheless, the data obtained indicated that neither negative thinking nor suicidal ideation increased during the duration of the study, which indicated the absence of any iatrogenic effects. This indicates that studies of this sort may be utilized further in the future without the risk of negatively influencing the patients.

Conclusions

In conclusion, we would like to reiterate that there are studies that have shown us the path we should be taking. In spite of the difficulties encountered in preventing suicidal behavior, we know that there are certain unequivocal warning signs. We know that a suicide attempt is the most significant risk factor for a completed suicide, and this is why primary, secondary, and tertiary prevention are all so important. Our recommendations for prevention include the implementation of the "Patient Safety First" campaign that is utilized in the United Kingdom. The plan consists of efforts to reduce the access to means of suicide in hospital, promote continuity of care, and avoid the abandonment of follow-up in these patients by promoting strict adherence. Finally, we cannot understate the importance of awareness training for mental health professionals through recertification requirements and continuing education.

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