UNDERSTANDING THE COMPLEX PHENOMENON OF SUICIDE: FROM RESEARCH TO CLINICAL PRACTICE

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UNDERSTANDING THE COMPLEX PHENOMENON OF SUICIDE: FROM RESEARCH TO CLINICAL PRACTICE

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Suicide is undoubtedly a worldwide major challenge for the public health. It is estimated that more than 150,000 persons in Europe die as a result of suicide every year and in several European countries suicide represents the principal cause of death among young people aged 14–25 years. It is true that suicide is a complex (and yet not fully understood) phenomenon and may be determined by the interaction between various factors, such as neurobiology, personal and familiar history, stressful events, sociocultural environment, etc. The suicide is always a plague for the population at risk and one of the most disgraceful events for a human being. Moreover, it implies a lot of pain often shared by the relatives and persons who are close to suicide subjects. Furthermore, it has been widely demonstrated that the loss of a subject due to suicide may be one of the most distressing events that may occur in mental health professionals resulting in several negative consequences, such as burnout, development of psychiatric symptoms and lower quality of life and work productivity. All considered, it is clear that the suicide prevention is a worldwide priority and every effort should be made in order to improve the early recognition of imminent suicide, manage suicidal subjects, and strengthen suicide prevention strategies. In our opinion, the first step of prevention is the improvement of knowledge in the field: this was the aim of this present special issue on Frontiers in Psychiatry. In this special issue, several papers have contributed to the suicide knowledge from several viewpoints and we hope that this will contribute to improve and disseminate knowledge on this topic.

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Editorial: Understanding the Complex Phenomenon of Suicide: From Research to Clinical Practice

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Editorial on the Research Topic

Understanding the Complex Phenomenon of Suicide: From Research to Clinical Practice

Suicide is undoubtedly a worldwide major challenge for the public health. It is estimated that more than 150,000 persons in Europe die as a result of suicide every year and in several European countries suicide represents the principal cause of death among young people aged 14–25 years (1). Moreover, it has been reported that the standardized death rate for intentional self-harm in the European Union is higher in the elderly (≥65 years) and over than for younger people (2, 3). The highest suicide rates in the world (21–35/100,000) have been found in the countries of Eastern Europe where the numbers of deaths due to suicide may be considered as an emergency (4, 5). Moreover, in a recent study, Olfson et al. (6) have reported that also suicide attempts in USA increased significantly from 0.62 to 0.79% among the adult population aged 21 years and older, based on representative community samples recruited from 2004 to 2005 and 2012 to 2013.

It is true that suicide is a complex (and yet not fully understood) phenomenon and may be determined by the interaction between various factors, such as neurobiology, personal and familiar history, stressful events, sociocultural environment, etc. (7). In fact, suicide results from many multifaceted social and cultural factors and is more likely to happen during periods of socioeconomic, family, and individual crisis situations (e.g., death of a loved one, loss of employment, etc.) (8). However, suicide remains an important problem that violently hits the world public health and suicide prevention should be always a priority even in those nations where suicide rates are lower. In fact, it is necessary to underline that several strategies aimed to reduce suicide when implemented are often effective and, for governments and health economics, quite inexpensive when compared to the direct and indirect costs of lives' loss (9, 10).

The suicide is always a plague for the population at risk and one of the most disgraceful events for a human being. Moreover, it implies a lot of pain often shared by the relatives and persons who are close to suicide subjects (11, 12). Furthermore, it has been widely demonstrated that the loss of a subject due to suicide may be one of the most distressing events that may occur in mental health professionals resulting in several negative consequences, such as burnout, development of psychiatric symptoms (anxiety and depression), and lower quality of life and work productivity (13–15). In addition, the loss of a patient by suicide may have for the physicians and mental health professionals' medico-legal consequences that may increase the burden (16, 17).

It is important to underline that the majority of suicides typically occurs in the context of a psychiatric disorder and/or as a consequence of severe medical diseases (18–20). Thus, all people who work in the context of public and mental health must know the most important literature about suicide and be informed of risk factors and warning signs of it (21). Mental health is supposed to be at a greater risk of suicide, as individuals with mental disorders (mostly mood disorders) are an extremely vulnerable population (22–24). It is important to remark that many subjects with (but also without)

psychiatric disorders often try to seek help before attempting or completing suicide (25, 26). This "crying for help" may be often covert and psychiatrist must be trained to early recognize the warning signs of an imminent suicide (27). It is remarkable that the topic of suicide is often forgotten or neglected in psychiatric residency and training and merely limited to consider it a simple epiphenomenon of a psychiatric disorder (28). We firmly believe that the introduction of "Suicidology" as a teaching subject in all universities and psychiatry schools should be warranted in order to provide an adequate training on this topic to all who will deal with medical and psychiatric illnesses.

Moreover, the global distressing actual conditions due to economic crisis may contribute further to increase suicidal ideation and/or behaviors. In 1897, the French suicidologist Emile Durkheim, in his well-known book "Le Suicide. Étude de Sociologie," examined the relationship between industrial and financial crises and suicide rate. Several studies have recently evaluated the relationships between suicide and economic crisis but this association is often unclear and may be mediated by the development of psychiatric disorders or other factors (29–31).

From these data, it is clear that suicide prevention is a worldwide priority and every effort should be made in order to improve early recognition of imminent suicide, manage suicidal subjects, and strengthen suicide prevention strategies. In our opinion, the first step of prevention is the improvement of knowledge in the field: this was the aim of this present special issue on Frontiers in Psychiatry. In the special issue, several papers have contributed to the suicide knowledge from several viewpoints.

From an historical perspective López-Muñoz and Cuerda-Galindo reviewed suicide in inmates in Nazis and Soviet concentration camps and showed that the incidence of suicide in Nazi camps could be up to 30 times higher than the general population and was also much higher than in Soviet special camps even if data interpretation is very controversial.

From a psychopathological point of view, several contributions were remarkable. Hilario Blasco-Fontecilla et al. suggested that both non-suicidal self-injury and suicidal behavior can be conceptualized as addictions and if some individual's self-harming behaviors are so conceptualized, treatment approaches could be taken this into account and tailored to this addiction. Verrocchio et al. conducted a systematic review analyzing the relationship between mental pain and suicide and found that mental pain was a core clinical factor for understanding suicide, both in the context of mood disorders and independently from depression. Falgares et al. evaluated a sample of 340 high-school students to evaluate whether self-criticism and dependency mediate the relationship between insecure attachment styles and suicidality. They found that both self-criticism and dependency were significant mediators in the relationship between attachment anxiety and suicidality, whereas only self-criticism mediated the relationship between attachment avoidance and suicidality. De Berardis et al. reviewed the role of alexithymia in triggering suicidal ideation and behavior in psychiatric patients. They underlined the importance of alexithymia screening in everyday clinical practice, as well as the evaluation of clinical correlates of alexithymic traits that should be integral parts of all disease management programs and, especially, of suicide prevention plans and interventions.

From a neural perspective, Deshpande et al. tried to understand the neural substrates underlying the gender differences in the rate of fatal suicidal behavior keeping in mind the Interpersonal–Psychological Theory of Suicide. They conclude that suicidal desire generally leads to fatal/decisive action in males, while, in females, it manifests as depression, ideation, and generally non-fatal actions and this has different neural basis. The importance of these finding was remarked by Professor Gonda's commentary on the Deshpande's paper.

From a social psychiatry perspective, the paper of Carpiniello and Pinna focused on the complex relationships that may exist between suicidal behavior and stigmatizing attitudes. They pointed out a reciprocal relationship between stigma and suicide: suicide may cause stigmatizing attitudes, but stigma toward mental disorders may be a risk factor for suicidality. Therefore, we must fight a battle against stigma to sustain self-esteem, reduce isolation, and empower those suffering from perceived or internalized stigma.

From an epidemiological point of view, two papers were of particular interest. Ventriglio et al. reviewed the available data on relationships between that first episode of psychosis (FEP) and the suicide risk. They concluded that patient with FEB may be at risk of suicide and the most relevant risk factors for suicide in FEP were associated with age of onset of psychotic symptoms, duration of untreated psychosis, some demographic characteristics, psychopathology, trauma, and insight. Orsolini et al. aimed at providing a focused review about epidemiological data, risk and protective factors, and an overview about the main clinical correlates associated with the suicidal behavior during the pregnancy and postpartum period. Despite a common belief that pregnancy and postpartum period may be at lower risk of suicide, they found that suicide still remains one of the most common leading causes of maternal death during the 1 year following delivery. The screening during the perinatal period (particularly during pregnancy) represents an essential clinical tool for identifying women at higher risk of perinatal suicidality.

From a clinical perspective, Morales et al. tried to gain a deeper understanding of the state of suicide risk by determining the combination of variables that distinguishes between groups with and without suicide risk, evaluating 707 patients consulting for mental health issues in three health centers in Greater Santiago, Chile. They individuated the interactions among a group of variables associated with suicidal ideation and behavior and, using these variables, it was possible to generate four decision trees that can distinguish between groups with and without suicidal behavior. Gramaglia et al. aimed to compare the severity of depressive symptoms in depressed inpatients admitted after an attempted suicide and those admitted for any other reason and to assess the severity of suicide attempts and the management of suicidal risk in clinical settings. They found no correlations among psychiatric diagnosis, psychiatric and physical comorbidity, severity of depressive symptoms, and suicidal behavior. On the other hand, antidepressant therapy was found to protect against suicide attempts. Schneider et al. used the Traumatic Brain Injury (TBI)-4, a four-question screener used to identify those with a probable lifetime history of TBI, administered to 1,097 Veterans at the time of mental health intake, to determine

whether a positive screen on the TBI-4 was associated with increased risk for suicide attempt within 1-year post screening. They found that Veterans with a positive TBI screen at mental health intake had a higher proportion of suicide behavior reports in Veteran electronic medical records than those who screened negative for TBI.

From a psychosomatic perspective Conti et al. carried out a systematic review analyzing the relationship between Diabetes Mellitus (DM) and suicide by providing a qualitative data synthesis of the studies. DM was found to be significantly associated with a marked increase in suicidal behaviors and suicidal ideation, especially in patients with depressive symptoms. Authors remark that health-care professionals need to be aware of the higher suicidal risk in some patient subgroups based on the clinical characteristics of DM.

Concerning the "hot" topic of suicide prevention, Klimes-Dougan et al. evaluated how the suicide prevention public service announcements may impact help-seeking attitudes. They conclude that "The Message Makes a Difference." In fact,

the results of the study provided some optimism that carefully crafted billboard messages may favorably influence help-seeking attitudes of participants.

In conclusion, in this special issue, we tried to improve the knowledge on suicide from several different perspectives. The number of published papers demonstrated a great worldwide attention to the topic. Today, the suicide is a major concern and we firmly believe that improving knowledge may also improve prevention strategies. This is our hope, and every subject at risk of suicide deserves all efforts that we can put in place, as clinicians and as human beings.

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Suicide in Inmates in Nazis and Soviet Concentration Camps: Historical Overview and Critique

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Living conditions in concentration camps were harsh and often inhumane, leading many prisoners to commit suicide. We have reviewed this topic in Nazi concentration camps (KL), Soviet special camps, and gulags, providing some preliminary data for our research. Data show that the incidence of suicide in Nazi KL could be up to 30 times higher than the general population and was also much higher than in Soviet special camps (maybe due to more favorable conditions for prisoners and the abolishment of death penalty), while available data on Soviet gulags are contradictory. However, data interpretation is very controversial, because, for example, the Nazi KL authorities used to cover-up the murder victims as suicides. Most of the suicides were committed in the first years of imprisonment, and the method of suicide most commonly used was hanging, although other methods included cutting blood vessels, poisoning, contact with electrified wire, or starvation. It is possible to differentiate two behaviors when committing suicide; impulsive behavior (contact with electrified barbed wire fences) or premeditated suicide (hanging up or through poison). In Soviet special camps, possible motives for suicides could include feelings of guilt for crimes committed, fear of punishment, and a misguided understanding of honor on the eve of criminal trials. Self-destructive behaviors, such as self-mutilation in gulag camps or prisoners who let themselves die, have been widely reported. Committing suicide in concentration camps was a common practice, although precise data may be impossible to obtain.

Keywords: suicide, concentration camps, Nazi, Soviets, history of psychiatry

INTRODUCTION

Suicides under extraordinary or extreme conditions, such as prisons, war conflicts, or concentration camps, have been studied previously (1–6). Specific studies, including imprisonment (7, 8), deportation (9), exclusion, and torture (10, 11), show a higher rate of suicide in these groups. Suicide in ghettos or transit camps before extermination, as Theresienstadt (12, 13), Nazi concentration camps (*Konzentrationslager*; KL) (14, 15), and Soviet gulags (16) has also been studied.

Prisoners are generally more likely to commit suicide than other people. Suicide rates in prisoners are estimated to be 55–107/100,000 (3, 17, 18). Rates of suicides in prisons in Austria and Switzerland are reported to be between 1.4 and 14 times higher than in the general population (19). More detailed

records for Germany between 2003 and 2010 suggest that suicide rates for men serving a prison sentence are about three times higher. (20).

In prewar Berlin, it has been pointed out that suicides were significantly more common in Jewish citizens than in the general population, and timing was often closely associated with antisemitic persecution (21, 22). Comprehensive data are not available, but in 1942, those who were persecuted after being classified as Jewish according to Nazi race laws were 26 times more likely to commit suicide (rate: 1,480/100,000) than the non-Jewish. Suicides were highly correlated with deportation from Berlin to ghettos and camps in Eastern Europe (23).

Suicidality has been described in Lodtz ghetto: some authors calculated a suicide rate of 85 per 100,000 in 1942 (24). The methods of suicide were recorded as follows: suicide by jumping represented 38%, poisoning 27%, and hanging 17% (21). Other authors reported just a few cases per thousand per year. They explained the relatively low number of suicides by the exhaustion and apathy of inhabitants or because of the strong will to survive, as well as a strong desire to resist the occupiers (13).

The topic of suicides in the Nazi KL has been studied more widely in memoirs than in medical or historical literature (25–27), but those studies based on original documents are scarce. These studies report that the incidence of suicide in Nazi KL was 10–30 times higher than for the general public (28) and was also much higher than in the Soviet special camps, possibly because the prisoners' living conditions were also much harder (slave labor, medical experiments, etc.), while available data on the Soviet gulags are scarce and contradictory (16, 29).

NAZI CONCENTRATION CAMPS

The main purpose of Nazi KL existence was to eliminate the Nazi Government's enemies. In Nazi KL history, two periods must be differentiated, the prewar period from 1933 to 1939 and the war period from October 1939 to the end of war in 1945 (15). During the first phase, before the outbreak of the war, legal officials investigated dubious cases of death in the KL (most of all, in Dachau), including alleged suicides, but the SS (*Schutzstaffel*) authorities covered up the murder victims as suicides (21). Nazi leaders considered that the judiciary was inadequate for the implementation of the Third Reich's racial and political agenda (30, 31). In the second phase, SS courts were in charge of investigating all deaths of camp inmates, including suicides, with complete independence from the judiciary (32, 33). The central Inspection of Concentration Camps (IKL) administered all KL in Germany and was located at Oranienburg from 1938. IKL controlled imprisoner's life conditions, forced labor, punishment, and medical experiments (34, 35).

Epidemiologic Data

Some authors have reported suicides in Nazi KL based on psychiatric interviews with the former prisoners. They described suicide as more frequent in those inmates who suffered the cruelest abuse, suffering from infectious diseases, forced to participate in medical experiments, during periods of mass extermination, and generally in autumn and winter (36).

Some authors argue that suicides were extremely high in Nazi KL based on witness testimonies (2, 15, 37–40). In contrast, others suggest that suicides were not so common and argue that in survivor's memories, under extreme conditions, exists an increase in the self-preservation instinct (27, 41–43). Other authors have estimated that suicides amounted to 25,000–100,000 per year based on testimonies (38). Compared to actual national suicide rates (60 per 100,000 per year), these rates are significantly high (24). Our group, in a preliminary report, has identified 222 cases of suicide in Sachsenhausen KL (44). But no precise data exist from which the suicide rate in KL can be calculated.

There are several problems that make difficult a correct approach to this analysis (a) in the Nazi KL, mostly after 1940, suicides frequently passed unnoticed because death was so common, and only suicides committed by a well-known inmate or by a terrible method were noticed (27); (b) suicide ratios may vary significantly depending on the period studied; suicide levels must have been raised because the camp populations increased in 1937–1938, with the numerous criminals and Jews imprisonment. Baganz (45) suggests that suicide levels in Sachsenhausen camp rose from 7 per month in 1937 to 33 per month in 1938; (c) the SS covered up the murder victims as suicides, which make the counting and interpretation of such suicides very problematic (15). In some cases of famous inmates, they preferred to cover-up the murder to avoid one scandal; and (d) finally, in most cases, data are incomplete mainly because Nazis destroyed documents when leaving the camps at the end of the war.

Profile of Suicidal Inmate

In Nazi KL, men and women of different age, race, nationality, profession, and social strata committed suicide. Some authors assess that suicides were most often committed by Jewish prisoners due to the fact that they were the largest group. But the Jewish group was extraordinarily inhomogeneous, composed of individuals from various social strata, cultures, and language groups (46). There are frequent reports of suicides committed by Jewish population in Germany, mostly after the Nazi Party came to power and Nuremberg rules were approved (47–49). In other smaller groups, such as communists or Jehovah's, witnesses' cohesion was higher (50) and maybe the suicide rate was lower, but it depends on KL and year. Our preliminary report confirms a higher rate of suicides in Sachsenhausen KL among Protestant and Catholic population than in Jews (44). Suicides were overwhelmingly committed by male, reflecting the fact that the majority of KL prisoners were men.

Moment of Suicidal Act

Inmates, especially in their first period of imprisonment, are often desperate about their lack of freedom and the strict rules (51, 52). In Nazi time, suicides committed during transportation to the KL are reported (53). Oral testimonies report that the majority of suicides were committed in the first years of camp existence (22, 54). Maybe, this fact is related to the special repression during the first years. Political prisoners are reported to commit suicide in order to avoid betraying bearers of secrets

under torture (15, 55), and in the first years of existence of camps they committed suicide encouraged by SS authorities (39). In large KL (such as Auschwitz), it has been described that Jewish prisoners frequently committed suicide when they were selected for the *Sonderkommandos* (task force) or for extermination (42).

Manners of Suicide

The methods to commit suicide in Nazi KL were varied, although these methods are related to the internal structure of the camps. For example, the camp authorities confiscated all knives and razor blades to avoid committing suicides by cutting blood vessels (56). For Theresienstadt ghetto, data from archival sources are available: until 1943, out of 430 people, 285 people had committed suicide by poisoning (barbital, Veronal®), 65 by cutting blood veins, 45 by jumping, and 35 by hanging (12), showing the differences in the methods of suicide in one KL and in one ghetto where more options were available.

The most frequent method to commit suicide in KL was hanging. In the early months of the Third Reich, camp guards often encouraged prisoners to kill themselves, even bringing them rope with which to do it. Suicide by hanging took place in isolated places, committed during night hours, when vigilance was lower, and there were many objects with which the inmates could commit suicide by hanging, such as belts, scarfs, or others, so giving prisoners rope with which to hang themselves was an act of mental torture.

Suicide through poisoning was very rare and used by prisoners who were members of the camp resistance movement and who had access to poisons or chemical substances. Some prisoners committed suicide by different poisons: iodine, cyanide, arsenic, strychnine, or even by swallowing cement (36). Other prisoners deliberately ventured across the SS guard lines to get shot. This method is reported in most of the camps (36, 57). Different authors have also reported that the contact with electrified barbed wire fences surrounding the camp was the most frequent form of suicide (58). However, these inmates killed on the fences or shot by guards would be classified as "killed in an escape attempt" instead of suicide.

Some authors (43, 58, 59) argue that some prisoners had chosen forms of suicide, which were not recognized as suicide, like "muslims." The typical behavior of the so-called Muselmann (pl. *Muselmänner*) has been interpreted as a consequence of starvation but can be a bio–psycho–social process with an organic brain syndrome with apathy and affective disorders (60–62). There have been suggestions that "muslims" were inmates who have given up the will to live and thus could be regarded as concealed or passive suicides.

There are also descriptions of cases of mass suicide; it is reported that some soviet prisoners flung themselves onto the electric wires when they did not receive any food and water for days (27).

In most of cases, medical doctors in the camps falsified the primary cause of death, including suicide, on the prisoner's death certificate. Sometimes, suicides were photographed by staff in various camps, as Auschwitz and Dachau (2, 59), but the meaning of this procedure is unknown.

Aspects Related to Motivation and Suicidal Behavior

In Nazi KL, the desire to die in prisoners who committed suicide was deep, and they did not treat suicide as an act of demonstration as they did not want to gain the attention of others (63). Suicide was perceived by some as the last way of escape from unbearable conditions. For some prisoners, suicide was an opportunity to exercise free will and control, and the option of suicide was perceived as a human act of self-assertion (64). During the war phase of the existence of KL, the proximity of death erased borders between life and death to such an extent that it was not necessary to commit suicide (39).

Some authors (65, 66) distinguish three phases in the reactions of KL prisoners (a) initial shock with acute depersonalization; (b) complete exhaustion; and (c) despair just before the camp arrival. Affective life was reduced to a minimum, and the individual's interests were limited to their immediate and most physical needs. The second phase is the adaptation as apathy state, as a self-protecting mechanism. There was also a pronounced irritability from a chronic lack of sleep and apathy because the prisoners were suffering from malnutrition. The third phase consists in a kind of depersonalization, regressive behavior, denial, isolation of affect, and discharge of aggression through alternative channels such as dreams (58, 61, 67).

We can differentiate two forms of behaviors when committing suicide in Nazi KL (a) impulsive behavior, such as crossing SS guard lines to get shot or touching the electrified barbed wire fences and (b) premeditated suicide, by hanging up or poisoning. These methods require more reflexion, looking for isolated places or poison to have. In case that we would consider self-starvation ("muslims") as a suicide method, we could include it in this point.

Finally, it is noteworthy that some protective factors have been described (5, 68), such as desire to survive, familial responsibilities, children, fear of suicide or social censure, moral, or religious values. In Nazi KL, individual annulation and depersonalization eliminated most of these protective factors. Other factors such familial separation, suspicion of death of relatives, physical suffering, illness, hopelessness or extermination certainty extermination could eliminate capacity to survive (69).

SOVIET SPECIAL CAMPS

In May 1945, the Soviet secret service, the NKVD (*Naródniy komissariat vnútrennij del*), created special camps (70) in former KL located in Soviet-occupied territories. These camps did not have the same function as in the Nazi period; they were neither labor nor extermination camps. Nevertheless, living conditions were harsh and inmates were completely isolated from the outside world (71). In these camps, there was hunger and cold, most of the barracks were overfilled, and insufficient hygiene, sanitation, and nutrition lead to illness and epidemics (72). Nazi functionaries, including those responsible for block and

cell units, members of SS, and Gestapo, and political prisoners sentenced by Soviet Military Tribunal were held in the camps, and others civilians were sent to these special camps without trial (73).

Data on suicides in Soviet special camps in Germany have not been published in the scientific literature, except the preliminary data provided by our group about Soviet Special Camp number 7, created in Sachsenhausen KL (74). The number of reported suicides in this camp under Soviet rule (1945–1950) was not significantly higher than in the general population (75) and much lower than the number reported when the camp was under Nazi rule. We calculated 2.8/10,000 suicides per year for the period from 1945 to 1950 against 11/10,000 suicides per year in the Nazi KL (74). This could be due to less atrocious conditions for prisoners, even when during the 5 years, 12,000 prisoners died from disease, hunger, and malnutrition. This can be explained by at least two reasons: first, it could be that not all suicides were reported as such by soviet camp authorities and second, it is reported that people with a major depressive disorder (and this could be the case of many German prisoners) do not have the motivation and energy required to commit suicide (14). In addition to this, finding the tools and opportunities to actively commit suicide in the Special Camps might not have been easy.

However, we want to emphasize that a high number of suicides committed by general population, Nazi leaders, and lower officials, occurred in Germany around the period of German surrender in 1945. During 1945, in the months around the end of the war, direct propaganda to the population exhorting to self-sacrifice and carrying cyanide capsules was quite common. Suicide levels reached their maximum in Berlin in April 1945 when no fewer than 3,881 people killed themselves (76).

The most commonly reported method for suicide in this Special Camp was hanging. Although it is not easy to establish, among the possible motivations for committing suicide, we can mention feelings of guilt for crimes committed, resignation or fear of punishment, and misguided understanding of the honor on the eve of criminal trials. Some authors reported suicidal tendencies in Nazi leaders (77), explaining that suicidal impulses were a result of the capture, trial, and condemnatory sentence (78), or alternatively, the Nazi regime's brutality led to homicidal tendencies and turned into self-destructive behavior under the conditions of detention.

SOVIET GULAG CAMPS

The gulag (*Glavnoie Upravlenie LAGerei*) was a Soviet system of concentration camps established just after the Russian Revolution that lasted into the early 1980s, with a period of maximum activity between the late 1930s and the early 1950s. According to Applebaum (16), between 1929 and 1953, roughly 18 million Soviet citizens passed through the Gulag camps. But, if other people are also considered, such as exiled and prisoners of war, the total number could be up to almost 29 million. Soviet gulag camps differed from the Special camps created in Germany not only in the kind of prisoners (mainly political opponents) but

also in the enforcement of the penalty of hard labor in order to support the industrialization of the Soviet Union (72).

Suicides in Soviet gulag camps have also been studied (29), although data on suicide rates in these camps are often widely conflicting. Mortality in Soviet gulag camps and labor colonies was 24.9% in 1942, 5.95% in 1945, and 0.95% in 1950 (29). It should be taken into account that infectious diseases, malnutrition, and hunger were the global challenges faced in the immediate postwar era. There are no official statistics available regarding the number of prisoners who attempted or completed suicide in gulags and some authors claim that suicides and mental illnesses were very rare (79, 80), while others report numerous accounts of suicide (16).

Maybe only active suicides were reported as such, but passive suicides were not. Self-destructive behaviors, such as self-mutilation in gulag camps or prisoners who let themselves die, have been widely reported. Self-mutilation was, in many cases, an attempt to save one's life by escaping slave labor, being sent to the hospital, or even released as invalid (16). On the other hand, as happened in Nazi KL, those groups of dying prisoners suffering from infectious diseases, starvation, and vitamin deficiency were called *dokbodyagi* by gulag inmates (81). Some authors have described this behavior as a form of passive suicide (27).

CONCLUSION

Suicides in KL are difficult to study because few documents are disposable, except data from interviews and testimonies. Moreover, there are a huge number of potential confounders in this topic: bias, because it is a self-report (recall bias), different religious, political and moral values, the setting (monitoring of the inmates, the kind and number of available tools), the time of imprisonment, etc. The topic of suicides in the Nazi KL has been studied more widely than in Soviet camps (Special camps and gulags), and there are marked differences between them, not only in the incidence rates (lower in the Soviet ones) but also in the possible motivation and suicidal behavior of suicidal inmates. The incidence of suicide in Nazi KL can be up to 10–30 times higher than for the general population. The main conclusions of topic analyzed are there are no specific profiles of suicidal group in the camps; the most frequent method to commit suicide was hanging; and the highest incidence of suicides occurs in the first years of imprisonment. Data on suicides during the Holocaust need to be analyzed in their fullness.

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FL-M and EC-G both contributed ideas to the writing of the present mini-review.

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frontiers
in Psychiatry

The Addictive Model of Self-Harming (Non-suicidal and Suicidal) Behavior

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Introduction: Behavioral addictions such as gambling, sun-tanning, shopping, Internet use, work, exercise, or even love and sex are frequent, and share many characteristics and common neurobiological and genetic underpinnings with substance addictions (i.e., tolerance, withdrawal, and relapse). Recent literature suggests that both non-suicidal self-injury (NSSI) and suicidal behavior (SB) can also be conceptualized as addictions. The major aim of this mini review is to review the literature and explore the neurobiological and psychological mechanisms underlying the addiction to self-harming behaviors.

Method: This is a narrative review. The authors performed literature searches in PubMed and Google for suicidal behavior, self-harming, addiction, and "major repeaters." Given the scarce literature on the topic, a subset of the most closely related studies was selected. The authors also focused on three empirical studies testing the hypothesis that major repeaters (individuals with ≥5 lifetime suicide attempts) represent a distinctive suicidal phenotype and are the individuals at risk of developing an addiction to SB.

Results: The authors reviewed the concept of behavioral addictions and major repeaters, current empirical evidence testing concerning whether or not NSSI and SB can be understood as "addictions," and the putative mechanisms underlying them.

Conclusion: Our review suggests that both NSSI and SB can be conceptualized as addictions. This is relevant because if some individual's self-harming behaviors are better conceptualized as an addiction, treatment approaches could be tailored to this addiction.

Keywords: suicidal behavior, non-suicidal self-injury, addiction, stress, opioid, dopamine

INTRODUCTION

Behavioral addictions can be defined "as a process whereby a behavior [...] is employed in a pattern characterized by loss of control and continuation despite significant negative consequences [...]" (1). They are frequent, and share many characteristics and common neurobiological and genetic underpinnings with substance addictions (i.e., tolerance, withdrawal, and relapse) (2). Behavioral addictions include activities such as gambling, sun-tanning, shopping, Internet use, work, exercise, or even love and sex (3–10). Recent literature suggests that both repetitive non-suicidal self-injury (NSSI) and suicidal behavior (SB) could also be understood as "addictive behaviors" in some individuals (11–16). If confirmed, this might change the way we currently treat repetitive self-harming

behaviors. For instance, in the same vein as alcoholics are treated with naltrexone, individuals characterized by repetitive self-harming behaviors could benefit from treatment regimens traditionally used for substance dependence. The present mini review is aimed at briefly examining the literature on this topic.

METHODS

Initially, the authors performed literature searches in PubMed for suicidal behavior, self-harming, addiction, and "major repeaters." Given that there was not a single reference, we expanded our search to Google. We found just one reference by Ken Tullis. Later on, we also included PubMed and Google searches on self-harming and addiction. Given the scarce literature on the topic, a subset of the studies most closely related to our aim was selected. The authors also focused on three empirical studies testing the hypothesis published in 2012 by Blasco-Fontecilla (see later) that major repeaters (individuals with ≥5 lifetime suicide attempts) represent a distinctive suicidal phenotype and are the individuals at risk of developing an addiction to SB.

RESULTS

Non-Suicidal Self-Injury as a Behavioral Addiction

There is substantive theoretical literature suggesting that NSSI can be understood as a behavioral addiction, but very few empirical studies testing this compelling hypothesis exist (16). For instance, Faye suggested that the emotional state preceding NSSI is similar to the aversive withdrawal symptoms experienced by drug users (17). Washburn et al. also reported that individuals displaying NSSI often have strong urges to self-injure (18). Furthermore, some authors have reported that endogenous opioids are reduced in individuals who engage in NSSI, but evidence contradicting this hypothesis is also found [see Victor et al. (16), for a review]. In 2002, Nixon et al. (15) explored whether NSSI could be explained under an addictive paradigm in adolescents displaying repetitive NSSI. They developed a self-report measure, adapted from the DSM-IV criteria for substance dependence, and reported that 81% endorsed more than five criteria. Victor et al. (16) stressed that, whereas both negative and positive reinforcement sustain substance use, "only negative reinforcement perpetuates NSSI." These authors were of the opinion that the repetition of NSSI was better explained by emotional processes than by addiction mechanisms.

Suicidal Behavior as a Behavioral Addiction

As for suicidal behavior, in 1998, Tullis proposed a theory of suicide addiction (19). He described individuals addicted to SB as having three characteristics: (1) childhood trauma, (2) mood disorders, and (3) multiple addictions. Until recently, the only study that empirically supported this hypothesis was a report of three cases (20). In 2012, we proposed that some suicide attempters (major repeaters, individuals with ≥5 lifetime suicide attempts) were indeed the individuals addicted to SB (14). The characterization

of major repeaters has been a neglected area of research (12). In a seminal paper, Kreitman and Casey studied over 3,000 parasuicides. They arbitrarily divided individuals into "first-evers" (those with no previous parasuicide), "minor repeaters" (those with a lifetime history of 2–4 parasuicides), and "major or grand repeaters" (those with ≥5 lifetime parasuicides) (21). They also warned that the variables associated with "minor repetition" were not necessarily the same related to "major repetition" (21). Major repeaters represent around 10% of all suicide attempters (21–23). They are heavy consumers of health resources, pose a challenge to clinicians (21), and are at higher risk of suicide completion (24, 25). Later on, we tried to empirically test our hypothesis in a series of different samples (11–14).

In a first study, we aimed at better characterizing major repeaters and testing whether they represent a distinctive suicidal phenotype; compared with 335 non-major repeaters (<5 suicide attempts), major repeaters ($n = 35$) were more likely to be female, diagnosed with anorexia nervosa or substance dependence, and to have higher levels of trait anger with lower expression of anger (12).

In a second study, we demonstrated that, compared to non-major repeaters ($n = 71$), major repeaters ($n = 11$, 13%) more frequently endorsed automatic positive reinforcement ("To feel something, because you felt numb or empty") as a way to explain their SB. In this study, all major repeaters and 93% of the remaining suicide attempters received at least one Axis I diagnosis, but there were no statistically significant differences between the groups. Borderline personality disorder was more frequently diagnosed among major repeaters. However, relieving emptiness (automatic positive reinforcement) was an important pathway, even more relevant than borderline personality disorder, to major repetition of suicide attempts in our study (11). This is important because, in contrast with the above-mentioned study suggesting that NSSI is perpetuated mainly through the removal of negative emotions (negative reinforcement) (16), our study suggests that major repetition of suicide attempts is perpetuated primarily through the generation of emotions (positive reinforcement; for instance, relieving emptiness, or raising the level of care or support from their relatives). Given that suicide attempts may replace self-mutilation, a type of NSSI, to regulate negative emotions in multiple-suicide attempters (26), it is possible that some major repeaters initially begin their "suicide career" with repetitive NSSI (negative reinforcement) and then replace it with repetitive SB (positive reinforcement).

In a third study, a cross-sectional study at Puerta de Hierro University Hospital (Madrid, Spain), we recruited 118 suicide attempters including 8 major repeaters (7%, all women) (13). We found that major repeaters "were more likely diagnosed with panic disorder without agoraphobia," borderline personality disorder, and a history of psychiatric inpatient admission than non-major repeaters. We explored whether or not major repeaters are addicted to SB by using seven criteria modified from the DSM-IV criteria for substance dependence: (1) tolerance, (2) withdrawal, (3) loss of control, (4) problems in quitting/cutting down, (5) much time spent using, (6) substantial reduction in activities, and (7) adverse physiological/physical consequences (13). Total dependence on SB was diagnosed if the individual had three or

more of the seven criteria in the last 12 months. In our study, 83% of major repeaters met criteria for total dependence on SB, which is pretty similar to the 81% of individuals displaying NSSI who endorsed more than five dependence criteria on NSSI (15). In this third study, we ran a backward stepwise logistic regression model to provide odds ratios between major repeater status and total dependence corrected by confounding variables (13). The model selected total dependence and age as the remaining significant variables in the last step. In other words, our study suggested that major repeaters were addicted to SB, and that our finding was probably not explained by the presence of borderline personality disorder (13).

Here, it is important to refer to Stanley and colleagues; they have suggested that suicide attempters with a history of self-mutilation are a unique sub-population who use self-mutilation to deal with psychological pain (27). Unfortunately, their study involved DSM-IV, cluster B personality patients, and therefore, their findings could not be generalized. In any case, multiple-suicide attempters may use self-mutilation as a way of self-regulating negative emotions in the short term (26). However, in the long term, self-mutilating behaviors increase negative affectivity and become another stressor. Suicide attempts might then replace self-mutilation to regulate negative emotions in multiple-suicide attempters (26). In an adolescent study, suicide attempters, relative to suicide ideators, were less likely to display anger after a suicidal act (28). **Figure 1** displays the putative transition from repetitive NSSI to repetitive SB and the mechanisms involved as suggested in the literature.

Putative Mechanisms of the Addictive Hypothesis of Self-Harming Behaviors

The addiction to self-harming behaviors can be explained either by *neurobiological* or *psychological mechanisms*. Regarding *neurobiological mechanisms*, if self-harming behaviors can be addictive in some instances, it is reasonable to think that a compromised functioning of the brain's motivational systems, including the mesocortical dopamine reward system and the endogenous opioid systems (29–31), and an overactivation of the stress system, are involved (29, 32). To the best of our knowledge, there are no studies directly relating the mesocortical reward system and self-harming behaviors. However, some authors have recently suggested that this system might be involved in the development of depression in a social defeat model of depression (30). Moreover, some authors demonstrated elevated endogenous opioid release

following stressful events. For instance, chronic stress in mice produces opioid dependence (33), and prolonged mutilating elevates met-enkephalins (34). Given the role of psychological pain in suicide (35), and the growing evidence linking self-mutilation in particular and NSSI in general with the stress and opioid systems (27, 36), it is reasonable to think that the relief of psychological pain is probably associated with endogenous opioid release in the central nervous system in major repeaters. This opioid release may ultimately produce tolerance and addiction in vulnerable subjects (14). Furthermore, both acute and chronic stress increase the risk of using drugs (31), and corticotropin-releasing factor (CRF) is involved in the vulnerability to drug withdrawal (37) and relapse (38). Indeed, gene polymorphisms of the CRF receptors have been related to exacerbated stress responses and vulnerability to develop drug addiction (39). Furthermore, patients displaying repetitive NSSI were more likely to display lower levels of adrenocorticotropic hormone (ACTH) measured in the morning or evening (40). In other words, the hypothalamic–pituitary–adrenal (HPA) stress system (CRH, ACTH) and opioid systems (beta-endorphins) are closely related (41). This is not surprising, given that ACTH and β-endorphins are derived from the same precursor, pro-opiomelanocortin (POMC) (42, 43). In sum, opioid and dopaminergic systems, and HPA axis, which interact in the forebrain (31, 32) and can be activated either by psychoactive drugs or by behaviors (44), are probably involved in the development of an addiction to self-harming behaviors (**Figure 2**).

As for *psychological mechanisms*, Beck's "sensitizing" hypothesis (45) and a cathartic effect (46) are probably involved in the addiction to self-harming behaviors. Beck (45) suggested that previous SB sensitizes suicidal thoughts and behaviors, such that they become more autonomous and easily precipitated. As self-harming episodes become more easily triggered by stressful life events, they also become more persistent and severe. Self-aggression ameliorates the emotional tension and painful emotions (i.e., emptiness) that precede SB (47–51). In a pilot fMRI study, the authors suggested that SB reduces mental pain (52). Beck's "sensitizing" hypothesis of SB has gained some empirical support (53, 54). Furthermore, even after prolonged "free" periods, there is the risk of relapse, often precipitated by similar life events, in a way similar to that of drug addiction (55). The cathartic effect might be explained by either mobilization of interpersonal support (i.e., medical attention, caring family) (48, 51) or emotional venting of an unbearable emotional or physical state (48, 50). Indeed, self-harming behaviors can be used as a signaling strategy within the "bargaining model" of depression; self-harming behaviors would be a way to impose costs to the social group where there is a conflict (56).

Therapeutic Implications

The addictive model of self-harming might have an important impact in the way we treat repetitive self-harming behaviors, and help in reducing the economic cost associated with them. The most evident targets for halting the development of an addiction to self-harming behaviors are the opioid and dopaminergic systems, and the HPA axis (37). In 1989, some advocated for clinical trials of opiate antagonists (i.e., naltrexone

FIGURE 1 | Putative transition from repetitive NSSI to repetitive SB and the mechanisms involved.
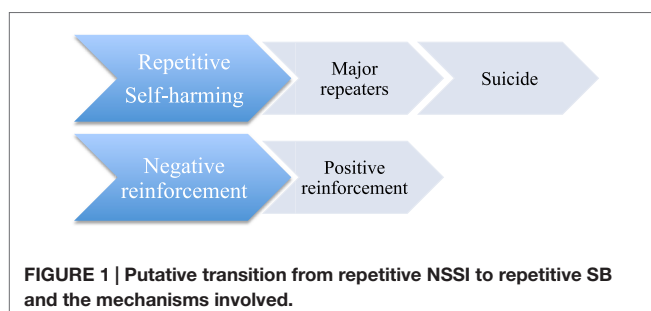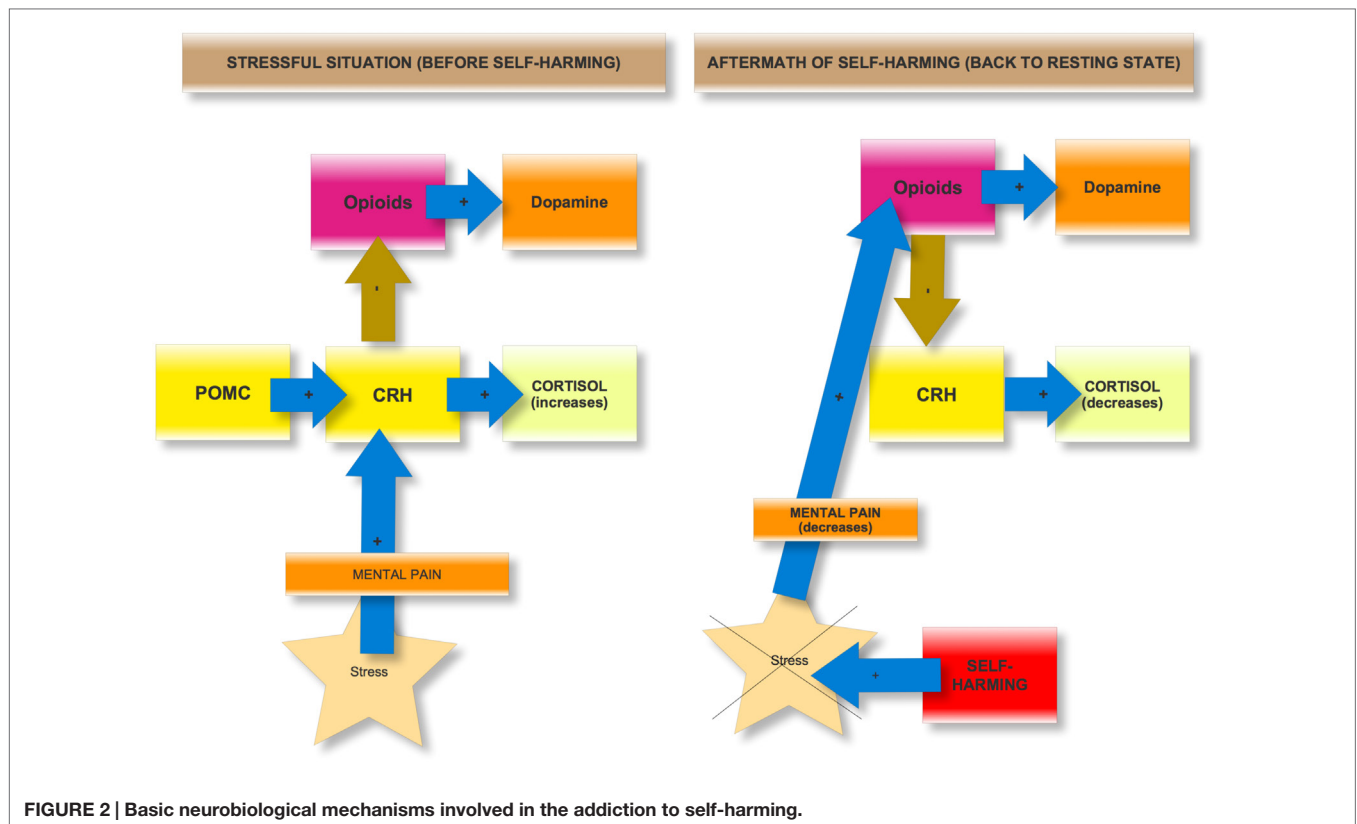
FIGURE 2 | Basic neurobiological mechanisms involved in the addiction to self-harming.

and buprenorphine) to treat NSSI (57). For instance, a recent yet unpublished controlled trial demonstrated that ultra-low-dose sublingual buprenorphine was effective in decreasing suicidal ideation (58). CRF receptor antagonists, particularly CRF1 antagonists (i.e., antalarmin), have also shown promising results for the treatment of drug abuse and addiction (39). CRF1 antagonists could have a lasting effect in blunting the elevated stress sensitivity in dependent individuals (39). As for the dopaminergic system, many animal models for self-injurious behavior share a compromised striatal dopamine system (59). Given that striatal dopamine receptors are coupled to L-type calcium channels, some have confirmed that calcium blockers, such as nifedipine, suppress self-injurious behavior in animal models (60).

Furthermore, any treatment alleviating psychological pain might also halt the development of the addiction to self-harming behaviors. For instance, lithium, known to have a specific "antisuicidal effect" (61), has an antinociceptive role probably mediated through the opioid system (62). In a still classic study, rats with brain lithium levels >0.5 mEq/L had a potentiation of endogenous enkephalin release (63). In another study, acute lithium enhanced "the morphine-induced analgesia in rats with or without chronic morphine treatment" (64). In any case, it is surprising that lithium's putative antinociceptive action has been very poorly studied in the clinical arena. Moreover, medications acting on glutamatergic transmission, such as gabapentin, lamotrigine, topiramate, acamprosate, memantine, modafinil, D-cycloserine, and N-acetylcysteine, "are also of potential utility in the treatment

of drug addiction, as well as various behavioral addictions such as pathological gambling" (65) and might also be useful in the treatment of addiction to self-harming behaviors.

Finally, new therapeutic pathways focused on treating either emptiness or psychological pain might also have a role in treating individuals addicted to self-harming behaviors. Regarding emptiness, some authors consider emptiness to be one of "the strongest precipitating factors in self-killing" (66). Quite surprisingly, as we have quoted before, there is little empirical research on the relationship between emptiness and SB (67). Some authors think that chronic feelings of emptiness are resistant to psychopharmacological agents (68). However, the cholinergic and serotonin systems might play a role in emptiness. For instance, some authors administered an acetylcholinesterase inhibitor – physostigmine – to individuals diagnosed with borderline personality disorder, other personality disorders, and healthy controls (69). Those individuals diagnosed with a personality disorder who displayed a depressive response to the physostigmine challenge were more likely to present a sense of emptiness. As we have previously suggested, drugs with anticholinergic activity, such as tricyclic or low potency antipsychotics, might prove useful in treating emptiness, among others (67). Regarding serotonin and emptiness, in 1998, Verkes and colleagues (70) discovered that patients meeting the criterion of "chronic feelings of emptiness and boredom" had the most elevated platelet serotonin in a sample of 144 consecutive recurrent suicide attempters. They suggested that some patients with borderline personality disorder, particularly when displaying

elevated emptiness, might have a different pre-synaptic re-uptake of serotonin. Accordingly, their response to drugs acting *via* serotonin might be different.

As for psychological (mental) pain, more than 90% of suicide attempters report it (11). Indeed, we have recently proposed that what really unifies SB is psychological pain (71). Given the increasing evidence that physical and psychological pain share common neural pathways (72, 73), why shouldn't we treat psychological pain using the same drugs that we use, for instance, for a headache? For the same reasons that we don't use opioids for a headache (i.e., tolerance, abstinence, dependence), we shouldn't use opioid agonists for individuals addicted to SB. However, non-steroidal anti-inflammatory drugs and acetaminophen could, *a priori*, be used. For instance, acetaminophen, taken during a 2-week period, reduced daily self-reported hurt feelings in comparison to a placebo (74, 75). Furthermore, there is increasing evidence that a single infusion of ketamine, an *N*-methyl-D-asparate antagonist, traditionally used as anesthetic, but also with analgesic properties, can lead to a rapid resolution of suicidal ideation in patients with treatment-resistant major depressive disorder (76). Moreover, we humans are a social species, and social peptides such as oxytocin, are involved in the development of different psychiatric disorders (77). Some self-harming behaviors are displayed in response to social problems and stressful life events, as previously stated. Given the critical role of oxytocin in bonding and stress, it is not surprising to find that low cerebrospinal fluid (CSF) oxytocin is related to high intent in suicide attempters (78). The use of an intranasal application of oxytocin might modify behavior. We might think that intranasal oxytocin could be used for some patients displaying self-harming behaviors in the aftermath of social problems; however, a recent editorial skeptically warned that "The wish to believe in the effectiveness of intranasal oxytocin appears to be widespread and needs to be guarded against with skepticism and rigor" (79). Finally, acceptance and commitment therapy has also proven effective in reducing psychological pain in suicide attempters (80), and therefore might be useful in halting the development of an addiction to self-harming behaviors.

CONCLUSION

Our review suggests that both NSSI and SB can be conceptualized as addictions. This is relevant because if some individual's self-harming behaviors are better conceptualized as an addiction, treatment approaches could be tailored to this addiction. The major limitation of the present review is that, given the space constraints, we could not expand our review to other interesting topics such as the putative role of impulsivity, a personality trait closely related to SB; impulsivity could be considered as the underpinning psychopathological substrate between mood, addiction, and self-injury behavior. Indeed, impulsivity has been proposed as the interface between mood and a number of addictive behaviors (81).

AUTHOR CONTRIBUTIONS

All authors: HB-F, RF-F, LC, LF, RP-B, and JL have made substantial contributions to the review, the drafting of the work, have approved the final version, and are accountable for all aspects of the work.

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Alexithymia and Suicide Risk in Psychiatric Disorders: A Mini-Review

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It is well known that alexithymic individuals may show significantly higher levels of anxiety, depression, and psychological suffering than non-alexithymics. There is an increasing evidence that alexithymia may be considered a risk factor for suicide, even simply increasing the risk of development of depressive symptoms or *per se*. Therefore, the purpose of this narrative mini-review was to elucidate a possible relationship between alexithymia and suicide risk. The majority of reviewed studies pointed out a relationship between alexithymia and an increased suicide risk. In several studies, this relationship was mediated by depressive symptoms. In conclusion, the importance of alexithymia screening in everyday clinical practice and the evaluation of clinical correlates of alexithymic traits should be integral parts of all disease management programs and, especially, of suicide prevention plans and interventions. However, limitations of studies are discussed and must be considered.

Keywords: alexithymia, suicide risk, psychiatric disorders, stress, prevention

INTRODUCTION

It has been demonstrated in several studies that often alexithymic individuals may show significantly higher levels of psychological distress than non-alexithymics and may develop "functional" somatic symptoms and psychiatric symptoms such as anxiety and depression (1–3).

Moreover, it has been suggested that alexithymic subjects may scarcely respond to both pharmacotherapy and psychotherapy. The characteristic attributes of alexithymic behavior are predominantly manifest in social interactions with high emotional significance (4). The affect-avoiding interpersonal pattern behavior showed by such subjects is often maladaptive and may elicit disorders and

conflicts in important relationships, lastly contributing the risk of development of psychiatric symptoms such as depression or anxiety, thus increasing the risk of suicide (5). Moreover, it has been demonstrated that alexithymia should be considered as a relative stable personality trait (6, 7), enhancing vulnerability to depressive symptoms (8, 9), and is generally associated with higher risk of death for several causes (accidents, injury, or violence) (10).

There is an increasing evidence that alexithymia may be considered a risk factor for suicide, even simply increasing the risk of development of depressive symptoms or *per se* (11). This evidence comes out from the results of several studies conducted on both general population and clinical samples of patients with psychiatric disorders or medical conditions.

Therefore, the aim of this narrative review was to elucidate the possible relationships between alexithymia and suicide risk, evaluating published studies on general population, suicide attempters, and subjects with psychiatric disorders [such as anxiety disorders, affective disorders, eating disorders (EDs), etc.]. Studies were identified searching the electronic databases such as MEDLINE, Embase, PsycINFO, and the Cochrane Library.

STUDIES ON RELATIONSHIPS BETWEEN ALEXITHYMIA AND SUICIDE RISK IN GENERAL POPULATION

So far, two main and relevant studies on general population (both conducted in Finland) have been done to evaluate the relationships between alexithymia and suicide risk.

First, a sample of 1,722 participants (735 men and 987 women) were evaluated (12). In particular, the study focused on the hopelessness, a widely recognized risk factor for suicide (13). Researchers found that a lower financial status, poor personal health, and reduced working ability independently associated with hopelessness. Interestingly, the probability of moderate or severe hopelessness was considerably increased in individuals with alexithymia and suicidal ideation. They concluded that life discontent, depressive symptoms, alexithymia, and suicidal ideation were the most powerful factors associated with moderate to severe hopelessness, but causal association was not possible to argue as this was a cross-sectional study.

The second study analyzed a huge sample of 1,563 subjects in the Kuopio Depression Study (14). Interestingly, this study proved that the most common self-report measure of alexithymia [the 20-item Toronto Alexithymia Scale (TAS-20)] showed a large overlap with a largely used self-report inventory for measuring the severity of depression, the Beck Depression Inventory. The associations of alexithymia with levels of suicidal ideation across time "…were no longer independent when adjusted for concomitant changes in the level of depressive symptoms…" (14), as reported by author themselves. Thus, the conclusion was that depressive symptoms were the mediators between alexithymia and psychiatric morbidity, hence including suicide ideation.

All considered, studies on general population support the hypothesis of a relationship between alexithymia and suicidal ideation mediated by depressive symptoms.

STUDIES ON RELATIONSHIPS BETWEEN ALEXITHYMIA AND SUICIDE RISK IN CLINICAL SAMPLES

Several studies on clinical samples of patients with psychiatric disorders have confirmed the hypothesis that alexithymia may increase the suicide risk, especially through the development of depressive symptoms.

Studies on Suicide Attempters

The studies on possible risk factors in suicide attempters are very interesting due to several reasons. In fact, subjects who had a previous suicide attempt are at risk to reattempt suicide (15, 16). Therefore, the evaluation of alexithymia in such subject may be of particular interest to include it as a putative risk factor.

Interestingly, three studies have been conducted in suicide attempters. First (17), 50 suicide attempters were evaluated within 24 h after hospital admission, and most of the attempters showed depressive symptoms with near half regarded as positive for alexithymia. However, alexithymia was not more prevalent in suicide attempters than in non-suicidal subjects with depressive symptoms. Depressive symptoms and alexithymia were considerably associated, but the authors found no significant correlation between alexithymic traits and lethality of the suicide attempt or suicidal intent (17). The authors concluded that alexithymia in suicide attempters was associated with depressive symptoms, but not intrinsically with suicidal behavior. Moreover, in a study conducted on 100 suicide attempters compared to 60 healthy controls, the sample of suicide attempters did not show significantly higher scores on the alexithymia rating scale than healthy subjects, and alexithymia was not found to be a predominant trait of personality among suicide attempters or a significant predictive factor of suicidal behavior (18).

More recently, in a Greek study (19), researchers evaluated the possible relationship between alexithymia (measured using the Shalling-Sifneos Personality Scale Revised), depression, and serum lipids in 50 non-violent suicide attempters and found a significant association between alexithymia and depression in those who attempted suicide, but only alexithymia was correlated with higher serum triglyceride levels.

Overall, no direct link was found between alexithymia and suicidality among suicide attempters, while there was a confirmation that measures of alexithymia were strongly related to measures of depression.

Studies on Patients with Psychiatric Disorders

The prevalence of alexithymia is quite high in subjects with psychiatric disorders (20). Therefore, the studies on relationships between alexithymia and suicide risk on clinical samples of patients with psychiatric disorders are very interesting as alexithymia may predispose to their development or worsen an existing one (8, 9, 21, 22).

Studies on Patients with Anxiety Disorders (ADs)

The presence of alexithymic traits in patients with ADs may be a risk factor of suicide, simply worsening the AD itself *per se*

or leading to the development of depressive symptoms or even a comorbid clinically relevant major depressive episode (MDE) (23–25).

Concerning obsessive–compulsive disorder (OCD), it has been found that alexithymia and depressive symptoms were significantly correlated in subjects with OCD (11). In a study on 86 patients with OCD, alexithymia was associated with higher suicide risk, especially in patient with poor or absent insight and with a greater disorder severity (26). In this study, the "Difficulty in Identifying Feelings" (DIF) dimension of TAS-20 was positively correlated with higher scores on the Scale for Suicide Ideation (SSI). The relationships between alexithymia and higher suicide risk were also confirmed in another study that pointed out that alexithymic patients showed higher suicidal ideation than non-alexithymic patients, and this was associated with lower high-density lipoprotein (HDL) cholesterol levels and with the DIF subscale of TAS-20, regardless of depressive symptoms (27). More recently, De Berardis et al. (28) further demonstrated that alexithymic OCD subjects showed higher disorder severity, poor or absent insight, and exaggerated responsibility, all associated with suicide ideation, regardless of depressive symptoms. Again, in this research, the DIF subscale of TAS-20 was associated with higher SSI scores. Moreover, alexithymia and perfectionism have been found to contribute to higher suicidality in 81 patients with OCD (29). It should be noted that in most studies on patients with OCD, the links between alexithymia and depression were evaluated by comparing a self-rating scale (TAS-20) with an observer-rated scale, the Montgomery Åsberg Depression Rating Scale (MADRS). This must be accounted as a potential source of bias. In fact, when used as a modified self-report questionnaire, it was found that the MADRS focused on core symptoms of depression and was less influenced by maladaptive personality traits, and, therefore, this bias may be more marked with the observer-rated version of the scale (30).

Also in subjects with panic disorder (PD), a significant relationship between alexithymia and increased suicidal ideation has been found linked by a serum lipid dysregulation (31). In particular, the presence of lower HDL and higher very low-density lipoprotein cholesterol levels and DIF subscale of TAS-20 were associated with higher suicide ideation in a sample of 72 outpatients with PD. This positive correlation between alexithymia and increased suicidal ideation was substantially confirmed also in patients with generalized anxiety disorder (32).

Only one study directly evaluated alexithymia and suicide risk in posttraumatic stress disorder (PTSD), even if a link between alexithymia and posttraumatic symptoms has been showed in several studies (20, 33–37). Kusevic et al. (38) evaluated 127 veterans from the 1991 to 1995 war in Croatia, and results of the study suggested that alexithymia can be considered as a risk factor for attempted suicide among war veterans with PTSD. However, in this study, no independent measure of depression was used, and this may have biased results.

Overall, studies on ADs support the notion of a relationship between alexithymia and suicide ideation, even if in the absence of clinically relevant depressive symptoms.

Studies on Patients with Affective Disorders

Despite the great number of studies that have evaluated the presence and clinical correlates of alexithymia in affective disorders (AD) such as major depression (MD) (39–42), surprisingly, relatively few studies have directly investigated its relationships with suicide risk. Alexithymia may be a risk factor of suicide in adolescent depression especially in the presence of maladaptive early schematas (43). Concerning adults, De Berardis et al. (41) evaluated 145 drug-naive adult outpatients with a DSM-IV diagnosis of MD and found that alexithymic patients showed higher scores on SSI, thus indicating a higher suicide risk. In a linear regression model, lower HDL levels, DIF, and "Difficulty in Describing Feelings" (DDF) dimensions of TAS-20 were associated with higher suicide risk.

Moreover, Loas et al. (24) evaluated a mixed sample of patients with both mood (2 with bipolar depression and 35 with unipolar depression) and ADs and pointed out that alexithymia and, particularly, DIF dimension of TAS-20 had strong relationships with suicidal ideations and low cholesterol levels, low HDL levels, or low triglycerides levels in patients with both mood or ADs.

Recently, Serafini et al. (44) recruited 281 euthymic participants of whom 62.3% had MD and 37.7% had bipolar disorder and showed that such subjects may suffer from significant difficulties in processing sensory input (measure with the adolescent/adult sensory profile), which have been significantly linked with higher depression, impulsivity, alexithymia, and hopelessness. Lower registration of sensory input referring to hyposensitivity and sensation avoiding referring to hypersensitivity significantly correlated with higher alexithymia and, in particular, with DIF and DDF dimensions of TAS-20, accounting for higher impulsivity and hopelessness (that may be risk factors of suicide).

Taken together, all studies on patients with AD pointed out a relationship between alexithymia and suicide ideation, even if there are, to date, too few studies to draw definite conclusions.

Studies on Other Psychiatric Disorders

Positive correlations between alexithymia and increased suicide risk have been found in other several psychiatric disorders. Somatoform disorder patients with lifetime suicide attempts might have greater difficulties in identifying and describing emotions and are prone to intensely feel and express anger (45). Moreover, in patients with conversion disorder (CD), alexithymia is higher in suicide attempters (46).

Several evidences point out that alexithymia may be a risk factor of suicide in EDs. For example, Carano et al. (47) demonstrated that individuals with binge eating disorder (BED) and alexithymia showed higher suicide ideation than non-alexithymics, especially in the presence of subclinical depressive symptoms. Alpaslan et al. (48) evaluated 381 female students in Turkey and found that disordered eating attitudes (DEAs) were a quite common phenomenon in female students and the occurrence of alexithymia was related with a higher suicide risk in such subjects. However, no studies have been conducted to evaluate the association between alexithymia and increased suicide ideation in patients with anorexia nervosa and bulimia.

Moreover, several studies have pointed out that alexithymia may be a risk factor for suicide and self-harm in individuals with substance use disorders (SUDs) (49–51).

To date, just one study evaluated relationships between alexithymia and suicide risk in subjects with schizophrenia, and study results showed that the occurrence of alexithymic traits in schizophrenia was associated with more prominent suicide ideation and more serious depressive symptoms, independently by the severity of positive and negative symptoms (52).

In conclusion, it seems that alexithymia may be a putative risk factor for suicide in patients with CD, BED, DEAs, SUD, and schizophrenia, but further prospective studies are needed to further confirm this association.

OTHER LIMITATIONS OF REVIEWED STUDIES

We have discussed some limitations of the reviewed studies above in the text. However, some other general limitations should be acknowledged.

The principal limitation of most studies on the relationships between alexithymia and suicide is that these are often cross-sectional and not prospective. Therefore, it may be difficult to interpret the identified associations and draw predictive conclusions.

Moreover, almost all reviewed studies employed the TAS-20, a self-report scale, to measure alexithymia. Even if the TAS-20 is a very useful tool in everyday "real-world" clinical practice to screen whether the subject is positive for alexithymia, it should be noted that findings based on self-report tools may be source of bias that in some cases may be poorly informative. Task-based studies should be preferred, but, to date, no task studies evaluating alexithymia were developed. However, future studies should employ the Toronto Structured Interview for Alexithymia (TSIA) (53), a reliable and valid structured interview for assessing the alexithymia construct, that can overcome the limitations of TAS-20 (54, 55).

Finally, the lack of control for adequate and comparable measures of depression and alexithymia or adequate statistical models of the interaction between depression and alexithymia (mixed models rather than ANCOVA) was a limitation of several reviewed studies, and this should be recognized.

CONCLUSION

Taken together, the almost all studies have pointed out a significant relationship between alexithymia and an increased suicide risk.

These findings may be explained in several ways. One is in accordance to the theory proposed by Freyberger of acute "secondary alexithymia" as a response to stressful conditions (56). The "acute secondary alexithymia" (56) can be defined as a transient, state-dependent experience that may occur as a consequence of subjective distress and can decline when an acute episode of illness has resolved (57). As the presence of alexithymia may worsen an existing psychiatric or medical disease, this worsening may be related to the development of suicidal ideation *per se* or through the development of depressive symptoms or even a comorbid clinically relevant MDE (4). However, even if alexithymia may be a state-dependent phenomenon (i.e., alexithymia may worsen during an acute disease episode, as described above), it should be considered a relatively stable personality trait that may be also present even before the onset of a psychiatric disorder or a medical disease (6, 7). Thus, research findings may be also in accordance with the "stress-alexithymia hypothesis" (58): alexithymia may be a chronic condition [maybe with an onset during infancy or early adolescence and often in consequence of childhood abuse or neglect (49, 59)] characterized by a pronounced inflammatory state with an impaired hypothalamic–pituitary–adrenal axis reactivity to even mild to moderate life stressors (60). Therefore, it should be deemed as a chronic state reaction as a response to stressful conditions that may always complicate a psychiatric disorder or a medical disease (61).

In conclusion, the importance of alexithymia screening in everyday clinical practice and the evaluation of clinical correlates of alexithymic traits should be integral parts of all disease management programs and, especially, of suicide prevention plans and interventions. The TAS-20 is a very useful tool in everyday "real world" clinical practice to screen subject positive or not for alexithymia, even if it is a self-report scale with all limitations of such instruments. However, if a subject is positive for alexithymia on TAS-20, a careful evaluation should be conducted (also completing the assessment of alexithymia with the TSIA, if possible) concerning the presence of depressive symptoms and suicidal ideation.

AUTHOR CONTRIBUTIONS

We state that (1) all authors have read the paper and approved the data and the conclusions presented therein; (2) each author believes that the paper represents honest work; and (3) all authors have contributed to the present paper with equal effort.

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Attachment Styles and Suicide-Related Behaviors in Adolescence: The Mediating Role of Self-Criticism and Dependency

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Insecure attachment and the personality dimensions of self-criticism and dependency have been proposed as risk factors for suicide in adolescents. The present study examines whether self-criticism and dependency mediate the relationship between insecure attachment styles and suicidality. A sample of 340 high-school students (73.2% females), ranging in age from 13 to 20 years (M = 16.47, SD = 1.52), completed the Depressive Experiences Questionnaire for Adolescents, the Depressive Experiences Questionnaire for Adolescents, the Attachment Style Questionnaire, and the Suicidal Behaviors Questionnaire-Revised. The results partially support the expected mediation effects. Self-criticism, but not dependency, mediates the link between insecure attachment (anxiety and avoidance) and suicide-related behaviors. Implications for suicide risk assessment and management are discussed.

Keywords: attachment, depressive experiences questionnaire for adolescents, personality, suicide, mediation effect

INTRODUCTION

Suicidal ideation and behavior among adolescents is an emerging global public health problem (1). According to the Italian National Institute of Statistics, Italy is among the European countries with the lowest levels of mortality by suicide, despite suicide being the second leading cause of death among men aged 15–29 years and the third leading cause of death among women of the same age range (2).

Among potential risk factors implicated for suicidal ideation (i.e., thoughts about engaging in behaviors that are intended to end one's life) and attempts (i.e., deliberately causing harm to oneself with at least some intent to die) in adolescents (3, 4), empirical research has focused on a range of factors, including drug and alcohol abuse, caregiver suicide attempts (5), previous suicide attempts, and experiences of childhood abuse and neglect (6). Other studies have examined school problems, such as bullying or academic failure (7, 8), as well as interpersonal (9) and familial difficulties including frequent criticism, poor communication, perceived lack of support (10, 11), peer rejection, and low social support from friends (12). Still other studies have examined intrapersonal markers of risk, including impulsivity, rumination, hopelessness, mental pain (13–16), hostility (17–19), and the presence of a chronic disease, particularly depression (20).

Moreover, theory and research both suggest that two important personality vulnerability factors, namely dependency and self-criticism [e.g., Ref. (21–23)] and early developmental vulnerabilities, in particular, insecure attachment [e.g., Ref. (10, 23, 24)] confer vulnerability for suicidality in adolescents. However, to our knowledge, the literature to date pertaining to dependency and self-criticism has not evaluated them as clinical factors linking the potential association between attachment and suicidality in adolescents. Thus, the present study aims to evaluate the association between attachment styles, personality vulnerability dimensions, and suicide-related behaviors during adolescence.

Specifically, in order to examine the relationship between attachment and suicide risk, we focused on the possible mediating effect of the personality traits of self-criticism and dependency according to Blatt's two-configurations model (21, 25).

The Associations between Blatt's Two-Configurations Model and Suicidality

According to Blatt's two-configurations model (26, 27), personality proceeds through a dialectical and continuing interaction between the issues of identity, autonomy, and achievement on the one hand, and interpersonal issues of relatedness, attachment, and intimacy, on the other (28). It has been proposed that this model may contribute to our understanding of vulnerability to suicide in adolescents and adults as it may elucidate specific patterns of risk (22, 29, 30), further, our knowledge of the etiology of suicidal behaviors, and improve our treatments for suicidal patients (31).

Mature personality can be considered a synergistic product of these two developmental configurations that extend throughout life: interpersonal relatedness, which involves developing the capacity for mature, intimate, reciprocal, and mutually satisfactory interpersonal relationships, and self-definition, which involves the development of a realistic, integrated, and differentiated identity or sense of self (32). Even in normal development, individuals usually place an emphasis on one dimension, creating two basic personality styles. For some, the emphasis is on interpersonal relatedness and is more focused on the desire for harmonious, supportive, and reciprocal relationships. For others, there is an emphasis on self-definition, which is more focused on individuation, achievements, and identity formation (21).

A disruption in this normal developmental dialectic process may result in a rigid, one-sided preoccupation with one of these two dimensions at the expense of the other. In particular, an overemphasis on issues of relatedness is the basis of a pathological personality style that Blatt labeled *dependent/anaclitic*. An overemphasis on issues of self-definition is the basis of a pathological personality style labeled *self-criticism* (33).

According to Blatt (34), high levels of dependency and/or self-criticism can confer vulnerability to two different forms of depression. Specifically, dependent individuals are characterized by preoccupations with issues of closeness, affiliation, and interpersonal connectedness; these individuals are especially sensitive to situations of separation and loss and tend to respond to such situations with feelings of helplessness and emptiness. In contrast, self-critical individuals are particularly concerned about experiences of shame and personal failure. Highly self-critical individuals tend to experience feelings of guilt and self-blame during instances of perceived failure and are particularly prone to depression in these contexts (35).

Research has systematically demonstrated that the pathological personality traits of dependency and self-criticism are related to depression, which is in turn linked with suicidality (22). It has also been proposed that dependent and self-critical individuals may display different types of suicidal behaviors, similar to the differences shown by these two personality types with regard to depression (36). Fehon et al. (13), for example, examined associations between dependency, self-criticism, impulsivity, and suicidal behavior in a sample of adolescent patients. Although they (13) found that suicide risk did not greatly differ between highly self-critical and highly dependent patients, dependent individuals appeared generally to engage in patterns of impulsive gestures and attempts, whereas self-critical individuals appeared less impulsive and more likely to plan acts of self-harm.

Fazaa and Page (36) found that more highly self-critical patients were more likely to have made a suicide attempt in response to a personal or professional failure, and that their intention in attempting suicide was to escape from the actual events–expectations discrepancy (37), and that their suicide attempts on the whole were rated as more lethal than more relatively dependent patients. Dependent suicide attempters were more likely to have made their attempt in response to an interpersonal stressor and indicated that their intention in attempting suicide was to communicate their feelings of distress to others.

Fazaa and Page (38), also, found that adult participants with higher levels of dependency showed higher rescue scores (i.e., using methods that made rescue more likely), compared to those scoring lower on dependency. In contrast, higher levels of self-criticism were associated with increased suicidal intent (i.e., greater wish to die), compared to those scoring lower on self-criticism. In an adult sample, Campos et al. (22) found that depressive symptoms mediated the association between self-critical perfectionism and suicidality. Highly self-critically perfectionistic individuals are vulnerable to intense depression, often accompanied by suicidal impulses, when confronted with stressful life events, and, in particular, events that disrupt self-definition and/or a sense of personal achievement.

Campos and Mesquita (20) tested a model of suicidality that included dependency, self-criticism, anger-temperament, depression, and anger-in (i.e., the expression of anger against the self) in a community of adolescents. Self-critical, dependent, and anger-in traits predicted depression, which in turn predicted suicidality directly and indirectly through anger-in. Similarly, Campos and Holden (39) showed that, even within a sample of depressed adults, elevated self-criticism is associated with a greater likelihood of suicidal behaviors.

Finally, Campos et al. (40) found that depression and social withdrawal mediated the relationship between both dependent and self-critical vulnerabilities and suicidality in a community sample of adolescents.

In summary, much theory and evidence in adolescents has linked the personality traits of self-criticism and dependency to suicidal ideations and behaviors, which suggests that they may be important etiological components of risk for suicide.

Attachment Dimensions As Risk Factors for Suicide among Adolescents

Maimon et al. (41) identified family attachment as a protective factor against adolescent suicide attempts. Similarly, evidence consistently indicates that disrupted parent–child interactions play a significant role in the development of a self-critical or dependent vulnerability to depression [see Ref. (32), for a review], which is in turn an important factor for suicide risk for adolescents (22, 42, 43).

Attachment theory argues that early experiences with caregivers are translated into internal working models that guide individuals' understanding of relationships across the lifespan (44, 45). Insecure attachment is relevant to adolescent suicidal behavior because it is associated with relationship dysfunction (46), which often precedes adolescent suicide attempts (47).

Indeed, Violato and Arato (48) showed that preoccupied and disorganized attachment was associated with suicidal behavior among adolescents in psychiatric treatment. Among undergraduates, a history of suicide ideation or attempts was associated with low attachment security, whereas preoccupied and dismissing attachments predicted suicidality.

Based on findings of Sheftall et al. (49), suicide attempters reported significantly higher greater attachment avoidance and anxiety. Attachment avoidance, but not anxiety, predicted suicide attempt status in a conditional logistic regression analysis that controlled for depressive symptoms and family alliance.

In contrast, however, Venta and Sharp (10) found no relation between attachment organization and suicidal thoughts and behavior. Instead, they confirmed the relation between internalizing disorders and a lifetime history of self-harm, suicide ideation during the past year, and lifetime suicide attempts, whereas externalizing disorders were associated with increased lifetime self-harm. They suggest that the link between attachment organization and suicidal thoughts and behavior may be mediated by other factors.

The Role of Self-Criticism and Dependency in the Link between Attachment Styles and Suicidality

Despite evidence that self-criticism, dependency, and attachment dimensions are distinguishable constructs (43), Blatt's two-configurations model and attachment theory both posit that personality functioning involves a balance between relatedness and self-definition expressed in low to moderate levels of attachment anxiety and avoidance typical of secure attachment (50). Maladaptive personality functioning, in contrast, typical of insecure attachment, results from an overemphasis of relatedness/attachment anxiety or self-definition/attachment avoidance or both (21).

Specifically, the attachment avoidance dimension, defined in terms of "discomfort with closeness and with discomfort depending on others" [(51), p. 87], is conceptually related to the self-definition dimension. Attachment anxiety, in contrast, defined in terms of "fear of rejection and abandonment" [(51), p. 91], is conceptually related to the relatedness dimension. Many studies have empirically confirmed these hypotheses. For example, Zuroff and Fitzpatrick (52) found an association between self-criticism and fearful-avoidant styles and between dependency and anxious attachment styles. Specifically, results in Zuroff and Fitzpatrick (52) as well as other showed that attachment anxiety was positively correlated with dependency while avoidance was positively related with self-criticism (51–55). Major features of attachment anxiety include the desire for interpersonal closeness and a fear of interpersonal rejection or abandonment (56). Therefore, these individuals may develop a dependent tendency in order to ensure others' availability and validation.

Conversely, research suggests that those with higher levels of attachment avoidance may be able to prevent psychopathological symptoms by avoiding dependence (52, 54). This also supports the theoretical perspective that those with higher levels of attachment avoidance have learned that others are untrustworthy. As a result, they have learned to rely on themselves instead of others in order to prevent hurt or disappointment. In sum, avoidantly attached individuals may actively avoid being dependent on others and, instead, strive for autonomy and independence, two values that are important to highly self-critical people. Moreover, avoidantly attached people have a negative working model of themselves or a poor sense of self-worth and often have a negative working model of others (57), which is similar to how self-critical individuals are often critical of both themselves and others (58).

To our knowledge, no studies have specifically investigated the mediating role of Blattian variables among attachment styles and suicidality, although some have focused on the influence of parenting on suicidality *via* self-criticism and dependency.

For example, Quinlan et al. (59) found that individual descriptions of both parents as less benevolent and more punitive correlated positively with self-criticism. The findings indicate that perceived dysfunctional early relationships with caregivers is associated with self-criticism as well as with depression and suicidal behavior.

Moreover, Campos et al. (22) examined whether self-criticism and depressive symptoms mediate the relationship between recollections of parental rejection and suicidality. Findings indicate that recollections of parental rejection are significantly associated with suicidality and depressive symptoms and that recollections of parental rejection are also indirectly associated with suicidality and depression through self-criticism. Moreover, the association between self-criticism and suicidality was mediated by depressive symptoms.

In sum, we expect the Blattian traits of self-criticism and dependency to mediate already well-known relationship between attachment and suicidality. Specifically, we expect self-criticism to mediate the link between both attachment anxiety and avoidance, and suicidality, whereas we expect dependency to mediate the link between attachment anxiety and suicidality. This study stands to provide relevant clinical information regarding the distinct motivations (particularly in terms of different vulnerability factors) that render individuals prone to suicidal crises.

MATERIALS AND METHODS

Participants

Four hundred three high school students from three schools in Palermo (Italy) were invited to participate: 41 did not accept and thus, 362 participated. Of these, 10 (2.76%) were eliminated because the questionnaires were not completed. Specifically, missing data for one or more variables were replaced with the mean of the scale where they did not exceed 20%. If in every questionnaire, missing data exceeded this cutoff, they were excluded from the analyses. The questionnaires were also excluded if there were univariate outliers ($N = 12$; z scores >3). There were no multivariate outliers (scores did not exceed the Kurtosis multivariate Mardia coefficient, equal to 80).

The final sample consisted of 340 participants (73.2% female; $M_{age} = 16.47$, SD = 1.52, range 13–20 years). All participants were Caucasian.

Measures

Depressive Experiences Questionnaire for Adolescents (DEQ-A)

The DEQ-A (60) is a 66-item self-report questionnaire, in which items are scored on a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). The original factor weighting coefficients were used in the present study (61). The DEQ-A scoring program yields three scales: dependency, self-criticism, and efficacy. In the present study, we considered only the DEQ self-criticism and dependency scales. In our sample, internal consistency was found to be moderate to good ($\alpha_{dep} = 0.61$; $\alpha_{sc} = 0.82$). The Italian version of the DEQ-A was developed using the back-translation method. This method achieves conceptual and cultural equivalence, as well as linguistic equivalence. First, a bilingual translator from the Department of Psychology translated the instructions and items of the original version into Italian. Next, the Italian version was back-translated into English by another bilingual translator from the Department of Humanistic Sciences. Finally, the original version was compared with the back-translated. The measure was reviewed by two Italian expert psychologists who had lived for at least 2 years in the United States. These experts contributed to the cultural adaptation of the questionnaire from American English into Italian. Where discrepancies occurred in the back-translations, the translators and the experts held discussions and worked cooperatively to make corrections to the Italian version. No items were eliminated or significantly adjusted during the translation process (62).

Attachment Style Questionnaire

The Italian version (63) of the Attachment Style Questionnaire [(ASQ); (64)] was used. It is a 40-item self-report scale containing five subscales that assess (a) adult secure attachment (*via* the confidence subscale), (b) insecure anxious attachment (*via* the Need for approval and the preoccupation with relationships subscales), and (c) insecure avoidant attachment (*via* the discomfort with closeness and relationships as secondary subscales). The factor structure has been reproduced among various community

and psychiatric samples (51). All items are rated on a 6-point Likert-type response format ranging from 1 (totally disagree) to 6 (totally agree). In the current study, the 10-item discomfort with closeness, the 8-item confidence in self and others, and the 8-item relationships as secondary subscales were used as indicator variables for the attachment avoidance latent factor, whereas the 7-item Need for approval and the 7-item preoccupation with relationships subscales were used as indicator variables for the attachment anxiety latent factor. The Cronbach alpha coefficients for the five subscales ranged from 0.62 for Confidence in Self and others to 0.76 for Need for approval.

Suicidal Behaviors Questionnaire-Revised (SBQ-R)

Suicidal behaviors were assessed by SBQ-R (65). The SBQ-R is a 4-item measure of lifetime suicide ideation and attempts ("Have you ever thought about or attempted to kill yourself?"), frequency of suicide ideation in the last year ("How often have you thought about killing yourself in the past year?"), threat of suicidal behavior ("Have you ever told someone that you were going to commit suicide, or that you might do it?"), and likelihood of future suicidal behavior ("How likely is it that you will attempt suicide someday?").

Respondents are asked to answer each question in terms of the frequency with which they engaged in the suicidal behavior, using a Likert-type scale. For example, respondents are asked to indicate their frequency of having suicidal ideations, ranging from 1 (never) to 5 (very often). Scores on the SBQ-R have been found to differentiate between suicidal and non-suicidal adults (65). In the present sample, internal reliability for the SBQ-R was 0.73. Higher scores on the SBQ-R are indicative of greater suicidal behaviors.

The Italian version of the SBQ-R was developed using the back-translation method following the process described above for the DEQ-A.

Procedure

Students were asked to participate in a research study as volunteers. During class time and in groups of 25–30, students received a brief explanation about the purpose of the study. They subsequently completed the questionnaires. All students were given the possibility to call the Department of Psychology for subsequent information about the research. Participants gave written informed consent. In the case of students under the age of 18, their parents also gave written informed consent. Three administration sessions were required to obtain the sample.

The research protocol was approved, according to the Declaration of Helsinki and its revisions (66), by the Institutional Review Board of the University of Palermo.

Statistical Analysis

We used structural equation modeling (SEM) (67) to test our hypotheses as these analyses can evaluate *a priori* models, suggest causal sequences, identify mediators, and elucidate direct and indirect paths. We examined the link between participants' attachment style and their current suicidal behaviors, as well as the mediating role of self-criticism and dependency in this association. This allowed us to evaluate the association between

attachment styles, self-criticism and dependency, and suicidal behaviors. SEM analyses were performed with the AMOS software [version 18.0; (68)] using maximum-likelihood estimation.

After verifying the univariate normality of the distributions using the Skewness and Kurtosis indices, the Kurtosis multivariate Mardia coefficient was used to test the multivariate normality between the variables (69). Then, we calculated the descriptive statistics for each variable, as well as bivariate correlations.

We examined the influence of all demographic variables. In particular, we explored the invariance across gender to determine whether gender might serve as a confounding variable related to the main analyses. A multiple-group analysis was conducted to check whether effects were equivalent across females and males (70).

Regarding SEM analyses, in addition to the overall χ^2 test of exact fit, as suggested by Browne and Cudeck (71) and Hu and Bentler (72), the following fit indices were used to evaluate the proposed models: comparative fit index; values of 0.95 or greater are desirable, the standardized root-mean-square residual; values of 0.08 or less are desirable, and the root-mean-square error of approximation; values of 0.08 or less are considered to be reasonable.

Finally, since AMOS only provides bootstrap estimates, SEs and confidence bounds for total indirect effects [e.g., the sum of all specific indirect effects; (73–75)], mediation analyses were conducted using the PROCESS macro designed for SPSS (76) to test specific indirect effects. This macro uses bootstrapped sampling to estimate the indirect mediation effect. In this analysis, 1,000 bootstrapped samples were drawn and bias corrected 95% bootstrap confidence intervals (CIs) were reported. CI that do not include 0 indicate a significant indirect effect of the independent variable on the dependent variable through the mediators (76). Standardized betas are reported.

RESULTS

Preliminary Analyses and Descriptive Statistics

We examined the influence of all demographic variables (age, education, school class, area of study, parental education and job, family income, and parental marital status) and found no significant relations with any study variables.

Gender analyses revealed significant mean level differences for all variables. Specifically, males scored higher in confidence ($p < 0.001$) and relationships as secondary ($p < 0.05$), whereas females scored higher in all the other variables ($p < 0.01$).

Then, we examined the invariance of the full model across genders to determine whether sex might moderate any of the paths in our model. Two models (a freely estimated model and a constrained model) were used to determine whether regression estimates varied significantly across genders. The freely estimated model was allowed to estimate regression paths and the structural covariances among factors without restriction, whereas, in the constrained model, factor loadings and the structural covariances among factors were constrained to be equal across the female and male groups. When the fits of the constrained and

the unconstrained models differ significantly, this suggests at least some paths differ significantly between groups. This constrained model did not yield a significantly different fit than the unconstrained model, $\Delta\chi^2$ (10, N = 340, p > 0.05) = 8.51. This suggests that, in our study, the relationships between attachment styles, Blattian variables, and suicidal behaviors were not moderated by gender; nonetheless, since we had found that gender was related to some variables at a mean level, subsequent mediation analyses were conducted controlling for gender.

The expected correlations among all variables were statistically significant ($p < 0.05$), with the exception of the correlation between dependency and self-criticism ($r = 0.03$, ns), confidence ($r = 0.02$, ns), discomfort with closeness ($r = -0.04$, ns), and suicidal behaviors ($r = -0.05$, ns). Finally, the association between relationships as secondary and preoccupation with relationships was not significant ($r = 0.01$, ns).

Table 1 presents the descriptive statistics and correlations between the study variables.

Blattian Variables As Mediators between Attachment Style and Suicidal Behaviors

Despite a significant chi-square [χ^2 (14) = 51.54, $p < 0.001$; χ^2/df = 3.68], fit indices [RMSEA = 0.09 (90% CI = 0.064; 0.116), CFI = 0.94, SRMR = 0.05], the model showed an acceptable fit (**Figure 1**).

Greater attachment anxiety predicted greater dependency ($\beta = 0.39$, $p < 0.001$) and self-criticism ($\beta = 0.67$, $p < 0.001$). Furthermore, greater self-criticism ($\beta = 0.22$, $p < 0.01$) predicted increased while greater dependency ($\beta = -0.14$, $p < 0.05$) predicted fewer suicidal behaviors. The indirect effects of attachment anxiety on suicidal behaviors through both self-criticism [*point estimate* = 0.15 (95% CI: 0.06, 0.25)] and dependency [*p.e.* = −0.05 (95% CI: −0.11, −0.01)] were significant.

Attachment avoidance predicted lower levels of dependency ($\beta = -0.17$, $p < 0.01$) and greater levels of self-criticism ($\beta = 0.71$, $p < 0.001$). Self-criticism was also significantly associated with increased suicidal behaviors ($\beta = 0.19$, $p < 0.05$) although dependency was not ($\beta = -0.05$, $p > 0.05$).

The indirect effect of attachment avoidance on suicidal behaviors through self-criticism was significant [*p.e.* = 0.13 (95% CI: 0.04, 0.23)], although the same indirect path *via* dependency was not [*p.e.* = 0.01 (95% CI: −0.01, 0.03)].

DISCUSSION

The present study examined whether self-criticism and dependency mediate the relationship between attachment anxiety and avoidance and suicidal risk among adolescents. The current results support the expected mediation effects. Overall, both self-criticism and dependency were significant mediators in the relationship between attachment anxiety and suicidality, whereas only self-criticism mediated the relationship between attachment avoidance and suicidality.

This result, taken together with previous theory and evidence [e.g., Ref. (22, 36, 77–79)] indicates that a self-critical personality style, characterized by substantial sensitivity to criticism by

TABLE 1 | Summary of intercorrelations, means, SDs, and alpha values for scores on the study variables.

Variables	1	2	3	4	5	6	7	8
1. Dependency								
2. Self-criticism	0.03							
3. Confidence	0.03	−0.42[a]						
4. Discomfort with closeness	−0.04	0.41[a]	−0.34[a]					
5. Relationships as secondary	−0.23[a]	0.24[a]	−0.17[a]	0.25[a]				
6. Need for approval	0.30[a]	0.51[a]	−0.37[a]	0.39[a]	0.24[a]			
7. Preoccupation with relationships	0.36[a]	0.50[a]	−0.23[a]	0.29[a]	0.01	0.54[a]		
8. Suicidal behaviors	−0.05	0.34[a]	−0.30[a]	0.20[a]	0.14[a]	0.27[a]	0.16[a]	
M	−0.60	−0.18	30.62	37.95	16.53	22.32	30.38	7.14
SD	0.77	1.09	5.59	7.41	5.86	6.94	7.12	2.47
α	0.61	0.82	0.62	0.66	0.72	0.76	0.72	0.73

[a]Correlation is significant at the 0.01 level (two-tailed).
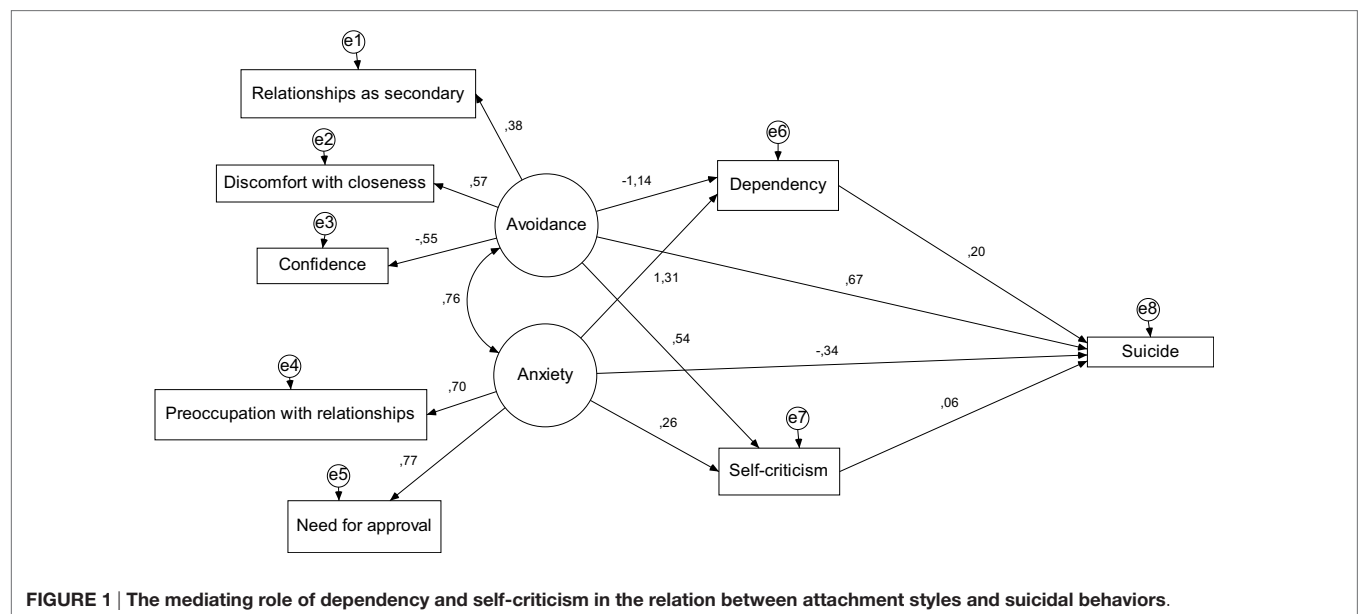
FIGURE 1 | The mediating role of dependency and self-criticism in the relation between attachment styles and suicidal behaviors.

others and to their own self-scrutiny and critical judgment (21), is a significant risk factor for engaging in suicidal ideation and behavior.

Specifically, results supported the prediction that self-criticism would mediate the link between both attachment anxiety and avoidance and suicidality, whereas, we found that dependency mediates the link between attachment anxiety and suicidality (52, 55). According to Cantanzaro and Wei (53), this finding can be explained by the following scenario: individuals with higher levels of attachment anxiety tend to develop a negative internal working model of the self (45, 80) and to automatically engage in self-criticism and harsh self-evaluation with the aim of reducing the likelihood of being criticized by others (81). A suicidal attempt could be explained as the outcome of the emotional breakdown, which is a consequence of the failure of this strategy, particularly when others show critical or harsh attitudes (20), from which the individual concludes they are fundamentally worthless and do not deserve to live.

Those with higher levels of attachment avoidance tend to develop a negative view of others and may develop beliefs

surrounding the need to be highly competent or nearly flawless at life tasks in order to maintain self-reliance rather than risk further rejection (58). Suicide could be a reaction to interpersonal rejection and/or to failing to reach these excessively high standards.

Regarding the association between attachment anxiety, dependency, and suicidality, results indicate a significant mediational negative effect for dependency, indicating that dependent people seem to be less at risk for suicide. The major features of attachment anxiety are the desire for interpersonal closeness and the fear of interpersonal rejection or abandonment (56), as well as a negative internal working model of the self. Therefore, these individuals may develop a dependent tendency in order to ensure others' availability and validation (52). Moreover, suicide would be the ultimate form of cutting close emotional ties, of which dependent individuals are quite afraid. This may explain why they use less lethal methods. That is, they do not want to die; rather, they want help from and to maintain close ties to others.

In line with hypotheses, regarding the association between attachment avoidance, dependency, and suicidality, results do not

indicate a mediational effect for dependency. There are multiple possible explanations for this lack of an effect.

First, this finding is consistent with literature showing an unclear role of interpersonal vulnerabilities (i.e., dependency) in suicidality (40). Second, according to previous research [e.g., Ref. (52)], attachment avoidance and dependency show a negative association. Those with higher levels of attachment avoidance, in order to protect themselves against anticipated rejection, are likely to develop a tendency of not relying on others who are likely perceived as unavailable. Third, dependency is a multifaceted construct that is more weakly related to negative outcomes compared to self-criticism and which has been used to describe a wide array of personality traits by investigators from different fields of inquiry (21, 82, 83). As such, specific facets of dependency may be differentially related to suicidality relative to others.

This study has a number of limitations. First, the exclusive use of self-report measures may have inflated effects due to shared method variance. Further, such measures are susceptible to response bias, despite all being validated against more robust, contextual, interview-based approaches. This study is also limited by the cross-sectional design. Longitudinal studies are needed to investigate whether the clinical variables studied are associated over time as well as the direction of the relationship between them. Third, a relatively brief assessment of attachment styles was used which gives a continuous score of attachment insecurity rather than categorical styles. Finally, a community sample was used in the present study. Although this approach carries many advantages for research into developmental psychopathology (84), it limits our ability to make clinical inferences. Findings should be replicated in other samples with other measures of attachment style.

AUTHOR CONTRIBUTIONS

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Mental Pain and Suicide: A Systematic Review of the Literature

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Background: Mental pain, defined as a subjective experience characterized by perception of strong negative feelings and changes in the self and its function, is no less real than other types of grief. Mental pain has been considered to be a distinct entity from depression. We have performed a systematic review analyzing the relationship between mental pain and suicide by providing a qualitative data synthesis of the studies.

Methods: We have conducted, in accordance with PRISMA guidelines, a systematic search for the literature in PubMed, Web Of Science, and Scopus. Search terms were "mental pain" "OR" "psychological pain" OR "psychache" combined with the Boolean "AND" operator with "suicid*." In addition, a manual search of the literature, only including the term "psychache," was performed on Google Scholar for further studies not yet identified.

Results: Initial search identified 1450 citations. A total of 42 research reports met the predefined inclusion criteria and were analyzed. Mental pain was found to be a significant predictive factor of suicide risk, even in the absence of a diagnosed mental disorder. Specifically, mental pain is a stronger factor of vulnerability of suicidal ideation than depression.

Conclusion: Mental pain is a core clinical factor for understanding suicide, both in the context of mood disorders and independently from depression. Health care professionals need to be aware of the higher suicidal risk in patients reporting mental pain. In this regard, psychological assessment should include a clinimetric evaluation of mental pain in order to further detect its contribution to suicidal tendency.

Keywords: mental pain, psychological pain, psychache, suicidal ideation, suicide attempt, suicidal behavior

INTRODUCTION

The World Health Organization estimated 804,000 suicide deaths occurred worldwide in 2012, representing an annual global age-standardized suicide rate of 11.4 per 100,000 population (15.0 for males and 8.0 for females). For every completed suicide, there are many more people who attempt suicide every year (1). The suicide is the consequence of a complex interaction of several variables, including psychological (i.e., personality traits, individual characteristics, emotional elements, and dysregulation), biological (i.e., genetics, medications, comorbid illness), and environmental factors (i.e., social support, demographics) (2). Despite each of risk factors proposed

having some power in the prediction of suicide, a significant body of data (3) emphasized the prominent association between mental pain or psychache and suicidal behavior. By following the literature, mental pain, psychache, and psychological pain are specific terms used to refer to the same construct (4). In this regard, we have used the specific expression reported by authors referring to pain originating from an individual psychological dimension. In the "cubic model" defined by Shneidman (5), psychache is defined as one of three essential dimensions, when individuals are considering suicide. The cubic model is the conceptualization of suicidal behavior. The two other dimensions are stress and perturbation. Psychache, as the central aspect of suicidal behavior, provides a theoretical definition of this construct as a general psychological pain reaching intolerable intensity that encompasses shame, guilt, humiliation, loneliness, fear, angst, and dread (6). That is, other psychological factors (e.g., depression) are relevant only to the extent in that they relate to psychache (7) that acts as a mediator of other risk factors. In other words, suicide would not occur without psychological pain (8). Orbach et al. (9) have described nine dimensions of mental pain: lack of control, irreversibility of pain, emotional flooding, estrangement, emotional flooding, confusion, social distancing, and emptiness. Buchwald (10) has considered the suicide as "a permanent solution to a temporary problem" resulting from an overwhelming angst of the subject (i.e., psychache). When taking into consideration the evidence that there are, on the one hand, depressed patients who did not die by suicide, and, on the other hand, not clinically depressed suicide attempters, several authors have proposed that there is a core risk factor for suicide, which has been conceptualized as psychache or psychological pain (11). In this regard, a recent research report from Soumani et al. (12) highlighted that this type of mental pain contributes significantly to suicide risk independent of depression.

The clinical link between psychological pain and suicide, as well as the concept of psychache as essential factor affecting suicidality, has been established with empirical research studies showing psychache's full mediation effects on the suicide risk (13). Furthermore, growing evidence has considered the suicide as a behavior motivated by the desire to escape from unbearable psychological pain (14–16). In a recent editorial, de Leon et al. (17) proposes that suicidal ideation, suicide attempts, and completed suicide may not be continuous phenomena and they can be influenced at different levels by the relative weight of psychosocial versus biological predictors. These authors argued that mental pain is the construct that unifies all suicide behavior even if how mental pain can be explained varies across suicide behavior levels. Studies on this issue are needed, by including also the evaluation of hopelessness that is an important factor for understanding the suicidal state of mind (18).

Despite the extensively reported data of the literature supporting the association between psychache and several dimensions of suicidality, such as suicide thoughts or ideation, suicide motivation and preparation, suicide attempt, and suicide act (19), to date, no systematic review study was fulfilled.

On this preliminary background, the aim of the current study is to provide a systematic review of original studies by focusing on the relationship (including associations or correlations, comparisons and differences, mediating roles, as well as contributions or predictions) between mental pain and the core suicidal clinical factors, namely ideation, attempt, and suicidal act.

MATERIALS AND METHODS

Information Sources and Searches

In line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20), a comprehensive electronic search strategy was used to identify peer-reviewed articles on the relationship between mental pain and suicide up to May 2016. The following keywords were used: "mental pain OR psychological pain OR psychache" AND "suicid*." After the initial search was performed, the studies were screened for eligibility; their relevance was assessed using at first their titles and abstracts, and finally the full review of papers. Searching and eligibility of target responses were carried out independently by two investigators; disagreements were resolved by consensus among these primary raters and a senior investigator. Electronic research-literature databases searched included PubMed, Web of Science, and Scopus. A manual search of the literature, only including the term "psychache," was also performed on Google Scholar for further studies not yet identified. In order to detect any missed articles during the literature search, reference lists of candidate articles were reviewed, yielding no additional articles. For each excluded study, we determined which elements of the electronic search were not addressed.

Eligibility Criteria

Papers were eligible for inclusion if they were original research reports in English language describing data on mental pain in relation to suicidal ideation, attempt, and behavior. We excluded peer-reviewed articles published prior to 1995, single case studies, reviews, meta-analyses, letters to the editor and commentaries, conference abstracts, books, and papers that were clearly irrelevant. Studies were discarded whether full text was not available. Results were not limited to chronological age of participants.

Analysis and Data Synthesis

Due to the heterogeneity of study design, measures, and features of the samples, it was not possible to combine the results into a meta-analysis. Consequently, results have been described reporting data through a systematic review. Studies were categorized based on the sample recruited for the study, by summarizing and comparing significant information for each study.

RESULTS

The search of PubMed, Scopus, Web of Science, and Google Scholar databases provided a total of 1450 citations. Based both on inclusion and exclusion criteria, a total of 42 original research studies were identified and selected for inclusion in the systematic review, as reported in the flowchart displayed in **Figure 1**.

FIGURE 1 | Flowchart of the systematic search.
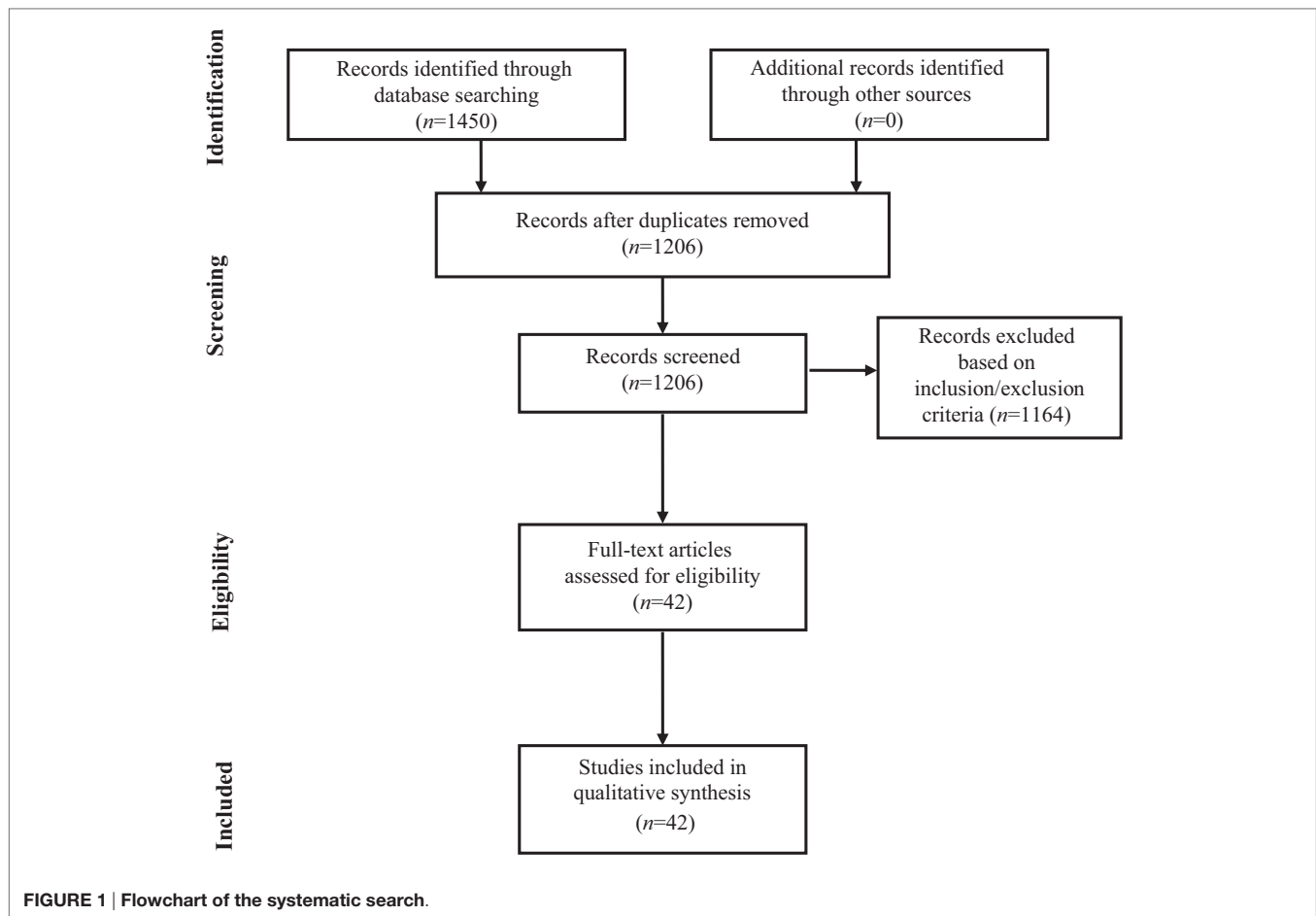
Mental Pain and Suicide in Samples with Mood Disorders

Several studies conducted with mood disorder patients have shown significant associations between mental pain and suicidality (see **Table 1** for a detailed description of reviewed studies). By focusing on a clinical sample consisting of patients with mood disorder (i.e., newly diagnosed depressed adult outpatients), Berlim et al. (21) reported a significant association between psychache and suicidality with a correlation identified as the highest in magnitude. These results were confirmed by Mee et al. (3), using a sample of 73 outpatients with major depression compared with 96 non-psychiatric controls. Xie et al. (16) have provided a further evidence supporting the relevance of psychological pain in the risk of suicide by demonstrating that outpatients with major depressive episodes and high levels of suicidal ideation showed anticipatory anhedonia and stronger pain avoidance matched to those with low levels of suicidal ideation and healthy controls.

High levels of psychache during a major depression may represent a condition of vulnerability for suicidal ideation and act. Olié et al. (22), by comparing 87 recent suicide attempters both with 61 patients with a past history of suicidal acts and 62 non-attempters patients, have found that higher current psychological pain was more frequent in recent and former suicide attempters

than in non-attempters. Moreover, the authors also showed that the severity of current psychological pain was significantly associated with the intensity [OR = 2.7 (95% CI: 1.5–4.9)] and frequency of suicidal ideation [OR = 3.0 (95% CI: 1.7–5.5)]. These data further confirm that a higher tendency to experience current mental pain during a major depression is a significant trait of vulnerability to suicidal behavior (i.e., ideation and acts), differentiating patients with a past or current history of suicide attempts from patients without any suicidal history. Caceda et al. (23), evaluating a sample of 62 depressed patients compared with a sample of 20 healthy controls, have highlighted that psychological pain predicted the presence of suicidal ideation in the overall sample by differentiating, using logistic regression analysis, between the suicide attempt and suicidal ideation groups. In a study with 111 outpatients with major depression, Huanhuan et al. (24), by using the stepwise regression analyses, were able to demonstrate that pain avoidance (i.e., the desire of escaping from unbearable psychological pain) was the only significant predictor of suicidal ideation at one's worst point and of suicidal acts.

In order to demonstrate the association between the degree of mental pain and changes in the cerebral blood flow in specific areas of the brain (i.e., right occipital cortex, left inferior temporal gyrus, right dorsolateral prefrontal cortex, and right

TABLE 1 | Studies on mental pain and suicide in samples with mood disorders.

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Berlim et al. (21)	Psychache and suicidality in adult mood disordered outpatients in Brazil	To assess the prediction that psychache (as derived by psychological quality of life) is associated with suicidality over and above depressive symptoms, hopelessness, interpersonal, and physical domains of quality of life	Sample size: 60 diagnosed depressed adult patients Mean age: 49.6 (SD 12.41) years Female: 83%	WHO-QOL psychological domain (6 items)	BDI suicidality item; MINI questions about suicidality
Caceda et al. (23)	Impulsive choice and psychological pain in acutely suicidal depressed patients	To examine the relationship of psychological pain and choice impulsivity with acute suicidal behavior	Sample size: 82 participants divided into four groups; G1, suicide attempters (20); G2, suicide ideators (22); G3, depressed controls (20); G4, healthy controls (20) Mean age: G1 = 36.4 (SD = 3.8) years, G2 = 43.1 (SD = 2.7) years, G3 = 46.2 (SD = 2.5) years, G4 = 39.3 (SD = 4.5) years Female: G1 = 60%, G2 = 50%, G3 = 65%, G4 = 50%	PAS	C-SSRS BDI
Huanhuan et al. (24)	Clarifying the role of psychological pain in the risks of suicidal ideation and suicidal acts among patients with major depressive episodes	To further investigate the role of psychological pain in suicidal ideation and suicidal acts among patients with major depressive episodes	Sample size: 111 depressed patients divided into two groups; G1, depressed patients with a history of suicide attempts (28); G2, depressed patients with no history of suicide attempts (83) Mean age: G1 = 28.93 (SD = 12.37), G2 = 33.99 (SD = 12.63) Female: G1 = 71%, G2 = 60%	TDPPS PAS	BSS Structured clinical interview assessing suicidal acts that include some degree of seriousness and/or lethality
Mee et al. (3)	Assessment of psychological pain in major depressive episodes	To evaluate, developing a brief measure of psychological pain, the role of psychological pain in suicide, and depression	Sample size: 168 participants divided into two groups; G1, major depressive episode patients (73); G2, non-psychiatric controls (95) Mean age: G1 males = 54.00 (SD = 12) and females = 46.00 (SD = 17); G2 males = 55.00 (SD = 17) and females = 45.00 (SD = 17) Female: G1 = 38%, G2 = 40%	MBPPAS	SBQ
Meerwijk and Weiss (26)	Does suicidal desire moderate the association between frontal delta power and psychological pain?	To investigate the moderating effect of recent suicidal desire on the association between resting-state neurophysiological parameters and psychological pain	Sample size: 35 adults with a history of depression, divided into two groups Mean age: 34.91 (SD = 11.60) Female: 77%	PAS OMMP	BSS
Ollié et al. (22)	Higher psychological pain during a major depressive episode may be a factor of vulnerability to suicidal ideation and act	To test the hypothesis that higher psychological pain during a major depressive episode may represent a trait of vulnerability to suicidal ideation and suicidal acts	Sample size: 210 patients divided into three groups; G1, recent suicide attempters (87); G2, former suicide attempters (61); G3, non-suicide attempters (62) Mean age: G1 = 40 (NA) years, G2 = 38 (NA) years, G3 = 38 (NA) years Female: G1 = 67%, G2 = 74%, G3 = 73%	Three items assessing intensity of psychological pain currently and during the last 15 days (including usual and maximum)	Two items measuring intensity of suicidal ideation and frequency of suicidal ideation
van Heeringen et al. (25)	The functional neuroanatomy of mental pain in depression	To evaluate neurofunctional aspects of mental pain related to suicidality	Sample size: 39 depressed patients divided into three groups; G1, 13 patients with low levels of mental pain; G2, 13 patients with medium levels of mental pain; G3, 13 patients with high levels of mental pain Mean age: G1 = 42.5 (SD = 15.0) years, G2 = 35.15 (SD = 12.9) years, G3 = 44.77 (SD = 15.3) years Female: G1 = 53.8%, G2 = 61.5%, G3 = 53.8%	OMMP	Item 9 of the BDI assessing occurrence and severity of suicidal ideation

(Continued)

TABLE 1 | Continued

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Xie et al. (16)	Anhedonia and pain avoidance in the suicidal mind: behavioral evidence for motivational manifestations of suicidal ideation in patients with major depressive disorder	To provide empirical evidence for the relationship between anhedonia, psychological pain (i.e., pain avoidance), and suicidal ideation	Sample size: 60 participants divided into three groups; G1, high suicide ideation participants (27 depressed patients); G2, low suicide ideation participants (13 depressed patients); G3 healthy control participants (20) Mean age: G1 = 14.07 (SD = 3.03), G2 = 13.77 (SD = 3.39), G3 = 14.75 (SD = 2.83) Female: G1 = 70.4%, G2 = 69.2%, G3 = 60.0%	TDPPS PAS	BSS

NA, Not Available; G1, Group 1; G2, Group 2; G3, Group 3; G4, Group 4. C-SSRS, Columbia Suicide Severity Rating Scale; BDI, Beck Depression Inventory; BSS, Beck Scale for Suicide Ideation; MBPPAS, Mee–Bunney Psychological Pain Assessment Scale; MINI, Mini International Neuropsychiatric Interview; OMMP, Orbach and Mikulincer Mental Pain Scale; PAS, Psychache Scale; SBQ, Suicidal Behavior Questionnaire; TDPPS, three-dimensional Psychological Pain Scale; TMPS, Tolerance for Mental Pain Scale; WHO-QOL, World Health Organization's Quality of Life Instrument.

inferior frontal gyrus, as well as left medulla at pontine levels) van Heeringen et al. (25), by performing functional neuroimaging in 39 depressed inpatients, showed that scores of mental pain on the Orbach & Mikulincer Mental Pain Scale (9) correlated significantly with the scores on the Beck Depression Inventory suicidality item. A recent study by Meerwijk and Weiss (26) evidenced that recent suicide desire moderates the relationship between psychache and resting-state neurophysiological parameters. Decreased low-frequency heart rate variability and EEG delta power were interpreted by authors as indicators of less effective emotion regulations, including increased rumination and an inability to reappraise the causes and consequences of psychological pain.

Mental Pain and Suicide in Different Clinical Samples

Studies conducted with different clinical groups (e.g., suicidal patients and/or psychiatric patients) showed significant associations between mental pain and suicide (27, 28) (**Table 2**). Orbach et al. (29) have found that suicidal patients scored showed significantly higher scores on mental pain rates than both psychiatric patients and control participants, with three specific mental pain factors (i.e., irreversibility, loss of control, and emptiness) having a unique contribution for the differentiation between suicidal and non-suicidal groups. These results, confirmed by Pompili et al. (30), have demonstrated that patients currently at risk for suicide showed significantly higher current psychache and higher worst-ever psychological pain.

A recent research (31) on motivations for suicide attempts in an inpatient adolescent sample reported psychache, hopelessness, and escape as the three most strongly endorsed motivations.

Levi et al. (32) have found higher levels of unbearable psychological pain among clinical sample (i.e., medically serious suicide attempt) compared to healthy controls. Furthermore, by conducting a hierarchical regression analysis, the authors have demonstrated that the presence of suicidal behavior was significantly predicted by mental pain accounting for 48% of the variance. In this study, mental pain was a predictor of suicidal behavior, whereas the interpersonal and communication difficulties, such as low self-disclosure ability, in addition to schizoid traits, alexithymia, and loneliness, were predictors of the lethality and seriousness of suicidal behavior. In a more recent research, Levi-Belz et al. (33) showed that suicide attempters obtained significantly higher scores on individual experience of mental pain than controls (i.e., both non-suicidal psychiatric patients and healthy participants). Communication difficulties and mental pain play an important role in medically serious suicide attempts, but the contribution of each is different. Results have showed that mental pain differentiates suicide attempters from psychiatric and healthy controls, and only communication difficulties distinguished medically serious suicide attempters from medically non-serious suicide attempters. In addition, the interaction between mental pain and communication difficulties accounting for 23% of the variance in suicide lethality, above and beyond the contribution of each component alone. These findings showed that the severity of the attempt depends on the individual's ability

TABLE 2 | Studies on mental pain and suicide in different clinical samples.

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Barak and Miron (27)	Writing characteristics of suicidal people on the internet: a psychological investigation of emerging social environments	To support, in Study 3, Shneidman's original argument that there are specific themes that characterized suicidal people, such as unbearable emotional pain (and cognitive constriction), focusing on the content of online writers' messages	Sample size: 64 online messages by 39 participants in the SAHAR suicidal support forum and by 24 participants in the sexual assault forum Mean age: NA Female: NA	Leenaars' (1996) thematic guide for predicting suicide	NA
Campos and Holden (39)	Testing models relating rejection, depression, interpersonal needs, and psychache to suicide risk in non-clinical individuals	To evaluate a model of suicide risk based on the contribution of four psychological variables, parental rejection, depression, interpersonal need, and psychache	Sample size: 203 non-clinical participants Mean age: 37.86 (SD = 11.68) Female: 51%	PAS	SBQ-R
Gould et al. (38)	An evaluation of crisis hotline outcomes part 2: suicidal callers	To determine, among other objectives, predictors (i.e., intent to die, psychological pain, hopelessness) of suicidality after the call to crisis services/hotlines	Sample size: 1085 suicidal callers Mean age: NA Female: 61%	Two items assessing psychological pain	Nine questions about suicidal thoughts, plans, and attempts
Gvion et al. (36)	A proposed model of the development of suicidal ideations	To develop a model of suicide ideation in psychiatric patients and the general population taking into account the role of mental pain domain, aggressive-impulsive domain, communication difficulties domain, and life events	Sample size: 196 participants divided into three groups; G1, suicide attempters (92 psychiatric patients); G2, non-attempters (47 psychiatric patients); G3 controls (57 healthy subjects) Mean age: G1 = 38.93 (SD = 13.56) years, G2 = 40.96 (SD = 14.07) years, G3 = 37.28 (SD = 12.34) Female: G1 = 35%, G2 = 30%, G3 = 46%	OMMP	Item 9 of the BDI LRS
Gvion et al. (2)	Aggression–impulsivity, mental pain, and communication difficulties in medically serious and medically non-serious suicide attempters	To evaluate, among other objectives, the role of mental pain, depression, and hopelessness in differentiating suicide attempters from non-attempters	Sample size: 196 participants divided into four groups; G1, medically serious suicide attempters (43); G2, medically non-serious suicide attempters (49); G3, psychiatric control group (47); G4, healthy control group (57) Mean age: G1 = 37.37 (SD = 13.31) years, G2 = 40.31 (SD = 13.76) years, G3 = 40.96 (SD = 14.07), G4 = 37.28 (SD = 12.34) Female: G1 = 40%, G2 = 31%, G3 = 30%, G4 = 46%	OMMP	LRS Objective Planning Subscale of the SIS
Horesh et al. (34)	Medically serious versus non-serious suicide attempts: relationships of lethality and intent to clinical and interpersonal characteristics	To investigate, among other objectives, the relationship between mental pain and subjective/objective suicide intent in both medically serious and medically non-serious attempters	Sample size: 102 participants divided into two groups; G1, patients after a medically serious suicide attempt (35); G2, patients after a medically non-serious suicide attempt (67) Mean age: G1 = 39.70 (SD = 15.30) years, G2 = 37.30 (SD = 14.00) years Female: G1 = 49%; G2 = 54%	OMMP	SIS LRS
Leenars et al. (28)	Suicide notes in alcoholism	To assess whether suicide notes of non-alcoholics differ from suicide notes of alcoholics in Leenars' dimensions of suicide, including unbearable pain	Sample size: 16 suicide notes of alcoholics and matched suicide notes of non-alcoholics Mean age: NA Female: NA	Suicide notes	Suicide notes
Levi et al. (32)	Mental pain and its communication in medically serious suicide attempts: an "impossible situation"	To test the hypothesis that mental pain is a general risk factor for suicidal behavior (and communication difficulties are a particular risk factor for medically serious suicidal behavior)	Sample size: 173 subjects divided into three groups; G1, patients after a medically serious suicide attempt (35); G2, patients after a medically non-serious suicide attempt (67); G3 healthy controls (71) Mean age: G1 = 39.70 (SD = 15.30) years; G2 = 37.30 (SD = 14.00) years; G3 = 36.50 (SD = 14.00) years Female: G1 = 49%; G2 = 54%; G3 = 48%	OMMP	LRS

(Continued)

TABLE 2 | Continued

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Levi-Belz et al. (35)	Attachment patterns in medically serious suicide attempts: the mediating role of self-disclosure and loneliness	To assess the contribution of attachment style to medical lethality of the suicidal attempt above and beyond mental pain (and the meditational role of communication difficulties in the relationship between attachment style and medically serious suicide attempt)	Sample size: 102 patients divided into two groups; G1, patients after a medically serious suicide attempt (35); G2, patients after a medically non-serious suicide attempt (67) Mean age: G1 = 39.70 (SD = 15.30) years, G2 = 37.30 (SD = 14.00) years Female: G1 = 49%, G2 = 54%	Mental pain is only indirectly evaluated with measures of depression, hopelessness and negative life events, BDI, BHS, and LES, respectively	LRS SIS
Levi-Belz et al. (33)	Mental pain, communication difficulties, and medically serious suicide attempts: a case-control study	To assess the role of mental pain and communication difficulties in medically serious suicide attempt	Sample size: 336 participants divided into four groups; G1, medically serious suicide attempters (78); G2, medically non-serious suicide attempters (116); G3, psychiatric control group (47); G4, healthy control group (95) Mean age: G1 = 38.5 (SD = 14.2) years, G2 = 38.5 (SD = 13.9) years, G3 = 40.9 (SD = 14.0) years, G4 = 38.5 (SD = 14.2) years Female: G1 = 44%, G2 = 44%, G3 = 70%, G4 = 45%	OMMP	LRS
Levinger and Holden (41)	Reliability and validation of the Hebrew Version of the Reasons for Attempting Suicide Questionnaire (RASQ-H) and its importance for mental pain	To evaluate, among other objectives, relationships of the RASQ-H with mental pain and the tolerance of mental pain	Sample size: 97 participants divided into three groups; G1, suicide attempter inpatients (42); G2, non-suicidal psychiatric inpatients (26); G3, non-clinical individuals (29) Mean age: 19.51 (SD = 3.30); data for single groups NA Female: 50% of the total sample; rates for single groups NA	OMMP TMPS	RASQ-H BSS MAST LSAS
Levinger et al. (40)	The importance of mental pain and physical dissociation in youth suicidality	To assess whether physical dissociation can make a unique contribution to suicidal risk above and beyond the contributions of mental pain and low tolerance for that mental pain	Sample size: 123 young adults divided into three groups; G1, suicidal patients (42); G2, non-suicidal inpatients (36); G3 non-clinical group (45) Mean age: G1 = 18.60 (SD = 3.3) years, G2 = 21.08 (SD = 2.73) years, G3 = 19.29 (SD = 3.07) years Female: G1 = 55%, G2 = 42%, G3 = 56%	OMMP TMPS	MAST BSS LSAS
May et al. (31)	Descriptive and psychometric properties of the Inventory of Motivations for Suicide Attempts (IMSA) in an inpatient adolescent sample	To investigate, among other objectives, the motivations (e.g., psychache, hopelessness, and escape) adolescents endorsed for their suicide attempts	Sample size: 52 adolescent psychiatric inpatients who attempted suicide Mean age: 14.8 (SD = 1.4) Female: 85%	Psychache scale of the IMSA	Interview assessing lifetime suicide attempts C-SSRS
Nahaliel et al. (11)	Mental pain as a mediator of suicidal tendency: a path analysis	To examine the mediating role of mental pain in the relationship between number of lifetime losses, self-destruction, and suicidal tendency	Sample size: 150 adults divided into three groups; G1, suicide attempt patients (50); G2, non-suicidal psychiatric patients (50); G3, healthy controls (50) Mean age: G1 = 43.26 (SD = 14.5) years, G2 = 43.86 (SD = 15.4) years, G3 = 40.40 (SD = 16.1) years Female: G1 = 70%, G2 = 70%, G3 = 68%	OMMP	MAST
Orbach et al. (29)	Mental pain and its relationship to suicidality and life meaning	To test, among other objectives, Shneidman's proposition – on the relationship between mental pain and suicide – by comparing the mental pain of suicidal and non-suicidal individuals	Sample size: 91 subjects divided into three groups; G1, suicide attempters patients (32); G2, non-suicide attempters patients (29); G3 control participants (30) Mean age: G1 = 32.43 (SD = 5.43) years, G2 = 34.28 (SD = 6.71) years, G3 = 31.62 (SD = 5.84) years Female: G1 = 56%, G2 = 62%, G3 = 53%	OMMP	MAST

(Continued)

TABLE 2 | Continued

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Pompili et al. (30)	Psychache and suicide: a preliminary investigation	To explore the usefulness of Shneidman's measure of psychache using a sample of psychiatric patients. one specific objective was to address the association between PPAS score and current suicidal risk and suicidal history	Sample size: 88 psychiatric patients Mean age: for males and females, 41.8 (SD = 14.0) years and 41.2 (SD = 14.1) years, respectively Female: 60%	PPAS	Section about suicidal risk of the MINI integrated with Clinician's opinion
Reisch et al. (15)	An fMRI study on mental pain and suicidal behavior	To investigate the neural correlates of script-driven recall of mental pain plus suicide action	Sample size: 10 individuals who had attempted suicide 1 to 4 weeks prior to the interview Mean age: 38.5 (SD = 13.1) years Female: 100%	OMMP Mental pain sequences from narrative interviews	Suicide action and suicide attempt sequences from narrative interviews
Trakhtenbrot et al. (37)	Predictive value of psychological characteristics and suicide history on medical lethality of suicide attempts: a follow-up study of hospitalized patients	To test, among other assumptions, the hypothesis that mental pain, depression, and hopelessness are positively related to follow-up suicide attempt	Sample size: 153 subjects divided into three groups; G1, patients hospitalized for a medically serious suicide attempt (53); G2, patients hospitalized for a medically non-serious suicide attempt (64); G3, psychiatric control group (36) Mean age: G1 = 37.60 (SD = 12.25) years; G2 = 37.74 (SD = 13.05) years; G3 = 40.27 (SD = 13.26) years Female: G1 = 59%; G2 = 61%; G3 = 69%	OMMP	Clinician assessment of suicide attempts, medical severity of the attempts, and medical severity of the follow-up attempt

NA, not available; G1, Group 1; G2, Group 2; G3, Group 3; G4, Group 4; S1, Study 1; S2, Study 2. C-SSRS Columbia Suicide Severity Rating Scale; BDI Beck Depression Inventory; BHS Beck Hopelessness Scale; BSS Beck Scale for Suicide Ideation; IMSA Inventory of Motivations for Suicide Attempts; LES Life Event Scale; LRS Lethality Rating Scale; LSAS Lethality of Suicide Attempt Scale; MAST Multi-Attitude Suicidal Tendencies Scale; MBPPAS Mee–Bunney Psychological Pain Assessment Scale; MINI, Mini International Neuropsychiatric Interview; OMMP Orbach and Mikulincer Mental Pain Scale; PAS Psychache Scale; PPAS Psychological Pain Assessment Scale; RASQ-H Hebrew Reasons for Attempting Suicide Questionnaire; SBQ-R Suicidal Behavior Questionnaire–Revised; SIS Suicide Intent Scale; TMPS Tolerance for Mental Pain Scale.

to communicate his or her distress to others. Gvion et al.(2), in a different sample (medically serious and medically non-serious suicide attempters), by performing a hierarchical regression analysis, demonstrated that mental pain factors only accounted for 3% of the variance and did not significantly predict suicide lethality. However, the interaction of mental pain and schizoid traits significantly predicted suicidal medical lethality after all other variables (i.e., aggression–impulsivity, and communication difficulties) had been entered. These findings suggest that the degree to which an individual can tolerate negative emotions (e.g., mental pain, violence, aggressive–impulsive tendencies, anger) may play an important role in the decision to attempt suicide.

In order to further study the lethality of the suicide intent, as dichotomously conceptualized in its subjective vs. objective components, Horesh et al. (34) have found that mental pain significantly contributed in the only prediction of the subjective intent having only a limited association with lethality of the suicidal attempt. By following another study on suicidal lethality, Levi-Belz et al. (35) have revealed that the attachment style significantly predicted (above and beyond the contribution of mental pain) the severity of the suicidal attempt. As regards the study of the suicide attempts, another research by Gvion et al. (36) provided a bidirectional model showing that hopelessness and depression mediated between mental pain and current suicidal ideation in suicide attempters. A recent follow-up study on psychiatric inpatients (37) demonstrated that mental pain did not predict a follow-up suicide attempt over time. Only hopelessness and depression were predictors of a follow-up attempt at suicide and the medical severity of the follow-up attempt.

The relationship between suicidal risk and mental pain was further evaluated in a study by Gould et al. (38) aimed at investigating the effectiveness of a telephone crisis services. Gould et al. (38) have found a significant reduction in suicide risk factors (i.e., plans, actions, and prior attempts) with diminishing levels of psychological pain from the beginning to the end of the call.

Other studies investigated the mediational role of mental pain. Nahaliel et al. (11) have showed that self-destruction causes both a direct effect on suicidal tendency, and an indirect effect mediated by the presence of mental pain. Subsequently, Campos and Holden (39) have revealed that psychache and interpersonal needs mediate the relationship between depression and suicide risk.

Mental pain seems to be a leading cause of suicide only when it is experienced as unbearable according to the cubic model of Shneidman (5). Recently, studies highlighted the clinical relevance of tolerance as a component of mental pain to explain its association with suicidality. In this regard, Levinger et al. (40), by using a multivariate analysis of covariance (i.e., MANCOVA), have demonstrated that suicidal respondents reported higher levels of mental pain, as well as a lower tolerance for such pain compared to non-suicidal group. Furthermore, when testing the hypothesis that mental pain and tolerance for this pain predict the suicidal risk, the authors confirmed that current mental pain was the strongest predictor of many aspects linked to suicidal behavior (i.e., self-reported suicidal ideation, suicide preparation, repulsion by life, and attraction to death). In addition, physical

dissociation can increase the likelihood of choosing a suicidal act rather than another form of coping with intense and intolerable mental pain. Levinger et al. (40) suggested that when mental pain becomes intolerable and persistent, blocking awareness of the body and its signals renders the body a lifeless object and an easier target to attack.

A previous study from Levinger and Holden (41), when examining the reliability and validity of the Hebrew Version of the Reasons for Attempting Suicide Questionnaire (RASQ-H), has found that the correlations between psychache and its tolerance with the Internal Perturbation-Based Reasons scale were significantly stronger than those with the Extrapunitive/Manipulative Motivations scale.

Finally, an fMRI study (15) aimed at investigating the neural correlates of suicide and its main risk factor (i.e., mental pain), has underlined a general deactivation in frontal cortical areas of suicide attempters (i.e., BA 46, 10, and 6), namely with a reduced activation in the left dorsolateral prefrontal cortex (BA 46), in the right anterior prefrontal cortex (BA 10), and the left medial prefrontal cortex (BA 6).

Mental Pain and Suicide in Samples of Students

Several studies, conducted with university students, have demonstrated associations between psychache and a history of suicidal ideation (42) and suicide attempts (43) as well as the role of psychological pain in the prediction of suicidal manifestations over and above depression, hopelessness (13, 44, 45), and self-destructive criterion (46). **Table 3** presents reviewed studies of this category. By confirming these results in a large Chinese students sample, You et al. (47) reported that psychache and life satisfaction were both significant predictors for suicidal ideation and suicide attempt. Specifically, psychache had stronger power in predicting suicidal ideation and suicide attempt than life satisfaction. However, for suicidal ideation, life satisfaction, regardless of psychache, has a significant predictive role. That is, psychache partially mediated the relationship between life satisfaction and suicidal ideation. These findings indicate that life satisfaction may relieve the psychache and, therefore, reduces the risk for suicidal ideation and suicide attempt.

Flamenbaum and Holden (7), using a structural equation model, determined that psychache fully mediated the relationship between perfectionism and suicidality.

When longitudinally evaluating the relationship between psychache and suicidality, Troister and Holden (48) have confirmed the specific contribution of psychological pain as a predictor of suicidal ideation by demonstrating that modification in psychache contributed unique variance predicting change in suicide ideation both at baseline and at 2-year follow-up. In line with their previous research studies, Troister et al. (19) have revealed that psychological pain was significantly associated with the total suicide ideation, motivation, and preparation, by further confirming the same results at 5-month follow-up. Furthermore, associations between psychache and total suicide ideation, motivation, and preparation remain statistically significant after controlling for depression and hopelessness. The last interesting result of this

study was that variation of the levels of psychological pain was significantly related to change in each of total suicide ideation. A recent paper (49) confirmed this evidence finding that 3-year changes in suicide motivation and preparation were significantly associated with changes in psychache but not to changes in depression or hopelessness. In the same article (49), a disclosure of the association between psychological pain, depressive symptoms, hopelessness, and suicidality was outlined. Results showed that depressive symptoms related to life-time suicidality through hopelessness and psychache. Hopelessness connected indirectly with life-time suicidality through psychache that related directly with life-time suicidality.

Mental Pain and Suicide in Samples of Special Populations

The relationship between mental pain and suicide was further addressed in special populations of prisoner, homeless, and soldiers (**Table 4**).

Two studies were founded in prisoner populations. Mills et al. (50) found a significant association between the score of the Psychache Scale and a history of prior suicide attempts. A study by Pereira et al. (51) confirmed the significant correlation between variables (with a large effect size), and it showed that psychache was the more significant statistical predictor of self-harming ideation and act than either depression and hopelessness.

Assessing the mental pain contribution to suicidality among homeless, a research study of Coohey et al. (52) showed that psychological pain was related to thoughts of suicide, by underlining that homeless with suicidal thoughts reported more psychological pain than homeless without suicidal thoughts. Furthermore, when considering each additional source of psychological pain, participants were 46% more likely to show suicidal thoughts supporting the authors' hypotheses that the number of sources of psychache explained suicidal thoughts above and beyond other important predictors. In line with these results, Patterson and Holden (53) further confirmed the Shneidman's theory of suicidality by indicating the associations between psychache and suicide factors (i.e., ideation, preparation, attempt history, as well as number of lifetime attempts) as having the higher correlation values than depression, hopelessness, and life meaning. Moreover, the authors (53) have also confirmed, by using multiple regression analyses, that psychological pain was the only significant factor predicting unique variance over and above the contribution by depression, hopelessness, and life meaning.

Meaningful results were recently reported by Shelef and Holden (54) testing a population of 168 soldiers. The major result comprises the evidence that emotional regulation of mental pain moderates the association between psychological pain and suicide ideation. In other terms, the authors (54) showed that mental pain was related to higher suicidal ideation only among soldiers who have difficulty to regulate mental pain.

DISCUSSION

Intense negative emotions, such as guilt, shame, and hopelessness may become a generalized experience of unbearable mental

TABLE 3 | Studies on mental pain and suicide in samples of students.

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Campos et al. (49)	Self-report depressive symptoms do not directly predict suicidality in non-clinical individuals: contributions toward a more psychosocial approach to suicide risk	To use a longitudinal design to test several hypotheses. Study 2 assessed the hypothesis that change in suicide ideation is associated with change in psychache after controlling for changes in depression and hopelessness. Study 3 tested the hypothesis that the combination of psychache and hopelessness fully mediated the relationship between depression and life-time suicidality, and that hopelessness related indirectly to life-time suicidality through psychache	Sample size: S2 90 undergraduate students having a history of suicidal ideation or suicide attempt; S3 280 university students Mean age: S2 = 18.31 (SD = 2.24); S3 = 19.73 (SD = 2.17) Female: S2 = 87%; S3 = 70%	PAS	BSS SBQ-R
DeLisle and Holden (44)	Differentiating between depression, hopelessness, and psychache in university undergraduates	To measure the overlap between depression, hopelessness, and psychache constructs in predicting suicide risk	Sample size: 587 undergraduate students Mean age: 18.72 years (SD = 2.49) Female: 78%	PAS	BSS RASQ
Flamenbaum and Holden (7)	Psychache as a mediator in the relationship between perfectionism and suicidality	To assess whether psychache mediates the relationship between perfectionism and suicide	Sample size: 264 university students Mean age: 18.91 (SD = 3.34) years Female: 75.8%	PAS	Five items assessing suicide history BSS RASQ
Holden et al. (46)	Development and preliminary validation of a scale of psychache	To assess psychometric properties of the Psychache Scale and its association with suicidal manifestations	Sample size: S1 = 294 university students; S2 = 211 university students Mean age: S1 = 19.1 (SD = 1.6); S1 = 19.4 (SD = 2.4) Female: S1 = 76%; S2 = 100%	PAS	RASQ SMQ
Leenars and Lester (43)	A note on Shneidman's Psychological Pain Assessment Scale	To explore validity and reliability of the PPAS as a correlate of suicidality	Sample size: 127 undergraduate students Mean age: 22.90 (SD = 6.40) years Female: 71%	PPAS	Questions about prior suicidal ideation, prior suicide attempts, and lethality of prior attempts
Lester (42)	Psychache, depression, and personality	To explore the correlation of psychache with a history of suicidal ideation and suicide attempts (and manic-depressive tendencies and temperament)	Sample size: 51 undergraduate students Mean age: 24.8 (SD = 7.1) years Female: 76%	PPAS	Questions assessing history of suicidal ideation, and history of suicide attempts
Troister et al. (19)	A 5-month longitudinal study of psychache and suicide ideation: replication in general and high-risk university students	To evaluate whether psychache and suicidality are associated, and whether this association continues when other suicide-relevant variables of depression and hopelessness are controlled statistically	Sample size: 945 university students into two groups; G1, 683 general sample of participants; G2, 262 high-risk university students Mean age: G1 = 18.23 (SD = NA) years; G2 = 18.17 (SD = NA) Female: G1 = 80%, G2 = 80%	PAS	Five questions asked about lifetime suicide attempts BSS
Troister and Holden (13)	Factorial differentiation among depression, hopelessness, and psychache in statistically predicting suicidality	To evaluate the unique contributions of psychache, depression, and hopelessness in the prediction of suicide ideation	Sample size: 2,974 university students Mean age: 18.31 (SD = 2.26) years Female: 71.8%	PAS	BSS

(Continued)

TABLE 3 | Continued

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Troister and Holden (48)	A two-year prospective study of psychache and its relationship to suicidality among high-risk undergraduates	To use a longitudinal design to investigate psychache contribution to suicidality in at-risk university students	Sample size: 41 at-risk university students Mean age: 17.95 (SD = 0.95) years Female: 83%	PAS	BSS
Troister et al. (45)	Comparing psychache, depression, and hopelessness in their associations with suicidality: a test of Shneidman's theory of suicide	To test Shneidman's theory of suicide by evaluating the contributions of psychache, depression, and hopelessness, to the statistical prediction of suicidality	Sample size: 1475 undergraduate students Mean age: (18.36, SD = 2.09) Female: 71%	PAS	Five questions asked about lifetime suicide attempts BSS
You et al. (47)	Effects of life satisfaction and psychache on risk for suicidal behavior: a cross-sectional study based on data from Chinese undergraduates	To investigate the predictive power of life satisfaction and psychache on risks for suicidal ideation and suicide attempt in Chinese university students	Sample size: 5988 college students Mean age: 19.94 (SD = 1.38) Female: 46%	PAS	Two questions assessing suicidal ideation Three questions assessing suicide attempt

NA, not available; S1, Study 1; S2, Study 2; S3, Study 3.
BSS, Beck Scale for Suicide Ideation; PAS, Psychache Scale; PPAS, Psychological Pain Assessment Scale; RASQ, Reasons for Attempting Suicide Questionnaire; SBQ-R, Suicide Behaviors Questionnaire-Revised; SMQ, Suicidal Manifestations Questionnaire.

pain, especially when there is no foreseeable change in the future. Consequently, individuals may seek to escape their "psychache" dying by suicide (8). Several theories, measurements, clinical risk assessments, and studies have been developed over the past decade in order to describe, assess, and confirm mental pain as a central key in suicide [e.g., Ref. (8, 46, 55)]. Mental pain has been shown in the literature as having a strong association with suicidality and it seems to be caused by the basic psychological needs of the individual (e.g., love, closeness, appreciation, and independence) not being sufficiently satisfied. By following a recent editorial from Tossani (4), it is highly significant from a clinical point of view to improve the study of the main implications linking mental pain to higher suicidal risk. That is, it is clinically important to assess psychological pain because it may be conceptualized as the core clinical factor that leads individuals to be vulnerable for suicidality. Therefore, when taking the potential clinical implications related to this relatively novel concept into account, to the very best of our knowledge, the present study is the first review manuscript aimed at systematically investigating the published original research reports evaluating the emerging clinical links between psychological pain and suicidal factors.

Associations between mental pain and suicidality were found in patients with mood disorders, in other clinical and non-clinical samples. High levels of mental pain may represent a condition of vulnerability to suicidal ideation, suicidal attempts, and suicide acts. When taking the clinical consequences of the research studies analyzing the relationship between psychache and suicide into consideration, the findings revealed the unique value of psychological pain in predicting suicidal behavior (i.e., ideation, attempts, and acts) when controlling for the effects of other variables (i.e., depression, hopelessness, aggression-impulsivity) potentially associated with suicidality (21). In other terms, the results indicate that levels of mental pain are associated with an increased risk of suicide, independently from the severity of depressive condition (25). Research findings confirmed that mental pain is much more than the sum of negative feelings and sensations, making it a uniquely intolerable experience (29). It may be accompanied by the belief that it is not possible to change and this may lead to the conclusion that the only solution is self-destruction (29). Recent studies have shown that mental pain alone will not lead to suicidal behavior, but will become critical when the person has no ability to regulate the emotional pain experienced. That is, if mental pain is controlled, the single effect of many factors would be largely attenuated or become insignificant. Recent studies have showed that mental pain alone did not significantly predict suicide lethality [e.g., Ref. (2, 32)]. When mental pain is associated with inability to communicate the stress, painful feelings remain unaddressed, help is not available, and more serious forms of suicidal behavior might ensue (32, 33). The lethality and seriousness of suicidal behavior were strongly predicted by the interaction of mental pain with other variables, such as interpersonal and communication difficulties (33), schizoid traits (2), alexithymia, and loneliness (32). These associations are very meaningful from a clinical point of view. The factor that plays an important role in the decision to attempt suicide consists of the degree to which an individual can tolerate own mental pain that in turn depends from own personal and social

TABLE 4 | Studies on mental pain and suicide in samples of special populations.

Study	Title	Aim	Sample information	Measure of mental pain	Measure of suicide
Coohey et al. (52)	Sources of psychological pain and suicidal thoughts among homeless adults	To assess the association between several sources of psychological pain (i.e., drug problems, family relationship problems, social problems, psychiatric problems, past emotional abuse, past physical abuse, and past sexual abuse) and suicidal thoughts	Sample size: 457 homeless adults Mean age: 38.7 years (SD = NA) Female: 62%	ASI questions on sources of psychological pain	ASI questions about current suicidal thoughts and past suicide attempts
Mills et al. (50)	An evaluation of the Psychache Scale on an offender population	To test the hypothesis that the Psychache Scale is more strongly related to suicide indicators than measures of either depression or hopelessness in an offender population	Sample size: 136 inmates of a medium security prison Mean age: 38.0 (SD = 11.0) years Female: 0%	PAS	DHS
Patterson et al. (53)	Psychache and suicide ideation among men who Are homeless: a test of Shneidman's model	To evaluate psychache as a stronger predictor of suicide among homeless	Sample size: 97 homeless Mean age: 46.58 (SD = 11.97) years Female: 0%	PAS	BSS Questions about history of a previous suicide attempt and the lifetime number of suicide attempts
Pereira et al. (51)	Testing Shneidman's model of suicidality in incarcerated offenders and in undergraduates	To evaluate psychache as a stronger predictor of suicide among offenders and undergraduates	Sample size: 233 participants divided into three groups; G1, incarcerated offenders (73); G2, male undergraduate students (80); G3, female undergraduate students (80) Mean age: G1 = 44.89 (SD = 9.94) years, G2 = 19.04 (SD = 1.62) years, G3 = 19.55 (SD = 1.63) years Female: G1 = 0%, G2 = 0%, G3 = 100%	PAS	DHS
Shelef et al. (54)	Emotional regulation of mental pain as moderator of suicidal ideation in military settings	To examine how mental pain and emotional regulation of mental pain contribute to suicide ideation. Additionally, it explores whether emotional regulation of mental pain moderates the relationship between mental pain and suicide ideation.	Sample size: 168 soldiers divided into three groups; G1, soldiers attempted suicide (58); G2, soldiers psychologically treated without a history of suicide attempt (58); G3 soldiers control group (50) Mean age: total sample 19.7 (SD = 1) years, data for single groups NA Female: total sample = 40.5%, G1 = 38.0%, G2 = 39.7%, G3 = 42.0%	OMMP TMPS	SSI

NA, not available; G1, Group 1; G2, Group 2; G3, Group 3.
ASI, Addiction Severity Index; BSS, Beck Scale for Suicide Ideation; DHS, Depression, Hopelessness and Suicide Screening Form; OMMP, Orbach and Mikulincer Mental Pain Scale; PAS, Psychache Scale; SSI, Scale for Suicide Ideation; TMPS, Tolerance for Mental Pain Scale.

resources. Literature highlighted that lack of individual resources, as expressed by an insecure attachment style (35) or an inability to disclose emotions and thoughts (2, 32, 33, 36) can amplify mental pain eliciting an intolerable experience that facilitates lethal suicidal actions. Some authors (40) suggested that when mental pain is experienced as unbearable and persistent, a reduced awareness of the body and its signals increases the likelihood to perceive it as an object as well as an easier target to attack.

Recent studies have examined the mediation role of mental pain, finding that this construct mediates both the relationship between self-destruction and suicidal tendency (11), and the association between depression and suicide risk (39).

Longitudinal studies confirmed the critical role of mental pain in student populations, demonstrating that changes in suicide motivation and preparation were significantly associated with changes in psychache (19, 52, 53). However, to further support these results, additional longitudinal studies with clinical samples are needed.

By supporting the evidence that psychological pain and its different dimensions (i.e., pain avoidance, emotional pain) play a central role in predicting suicide, the results of this review study could further underline the clinical relevance of psychache in prevention (i.e., early detection) as well as in treatment of suicide. In this regard, mental pain may represent, from a clinical point of view, an important therapeutic target, when considering that diminishing levels of psychache potentially

means to decrease the risk of suicidal acts (22). Therefore, by identifying psychological pain in order to evaluate the suicidal risk, psychache can be targeted during clinical interventions and considered amenable to treatment (45, 55). It is also suggested that suicide is a balanced consequence, depending on the presence of risk factors and the absence of protective factors against suicide. For example, if psychache is balanced by the presence of protective factors, such as life satisfaction, the unbearable mental pain can become acceptable and the individual would stay to live on (47). Further research into positive variables is needed.

In conclusion, several measures have been developed to assess mental pain (4) and these instruments can be easily included into risk assessment along with measures of depression and hopelessness, in order to improve the accuracy of suicide risk prediction.

According to recent developments on clinical psychometrics (56), clinimetrics provides significant possibilities for evaluating clinical variables, such as mental pain (4, 57).

Based on this background, it is highly meaningful to clinimetrically evaluate measurement aspects (i.e., construct validity) of the instruments in order to assess psychache in clinical setting.

AUTHOR CONTRIBUTIONS

All authors participated in the concept and writing of this manuscript. All authors approved the final version of the manuscript.

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A Neural Basis for the Acquired Capability for Suicide

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The high rate of fatal suicidal behavior (SB) in men is an urgent issue as highlighted in the public eye *via* news sources and media outlets. In this study, we have attempted to address this issue and understand the neural substrates underlying the gender differences in the rate of fatal SB. The Interpersonal–Psychological Theory of Suicide has proposed an explanation for the seemingly paradoxical relationship between gender and SB, i.e., greater non-fatal suicide attempts by women but higher number of deaths by suicide in men. This theory states that possessing suicidal desire (due to conditions such as depression) alone is not sufficient for a lethal suicide attempt. It is imperative for an individual to have the acquired capability for suicide (ACS) along with suicidal desire in order to die by suicide. Therefore, higher levels of ACS in men may explain why men are more likely to die by suicide than women, despite being less likely to experience suicidal ideation or depression. In this study, we used activation likelihood estimation meta-analysis to investigate a potential ACS network that involves neural substrates underlying emotional stoicism, sensation-seeking, pain tolerance, and fearlessness of death, along with a potential depression network that involves neural substrates that underlie clinical depression. Brain regions commonly found in ACS and depression networks for males and females were further used as seeds to obtain regions functionally and structurally connected to them. We found that the male-specific networks were more widespread and diverse than the female-specific ones. Also, while the former involved motor regions, such as the premotor cortex and cerebellum, the latter was dominated by limbic regions. This may support the fact that suicidal desire generally leads to fatal/decisive action in males, while, in females, it manifests as depression, ideation, and generally non-fatal actions. The proposed model is a first attempt to characterize the neural networks underlying gender differences in SB. Future studies should examine the proposed network to better characterize and refine this network using tasks specifically targeted toward constructs underlying ACS.

Keywords: suicide, depression, gender difference, functional magnetic resonance imaging, diffusion tensor imaging, meta-analysis, meta-analytic functional connectivity, structural connectivity

INTRODUCTION

Each year in the United States, over 40,000 individuals die by suicide (1). These figures do not include non-fatal suicide attempts, which are estimated to occur 25 times more frequently than fatal suicide attempts (1). One of the most well-established and, yet, paradoxical findings with regard to the epidemiology of suicidal behavior (SB) is that men are far more likely to die by suicide than women are (2), despite the fact that they are significantly less likely to experience depression [e.g., Ref. (3, 4)], suicidal ideation (5), and non-fatal suicide attempts (5). Although men tend to choose more lethal methods than women do (6, 7), a recent study has demonstrated that, even among those who choose the same method, men are more likely than women are to have a fatal outcome (8). Thus, method selection alone cannot explain the observed gender differences in fatal SB.

Neural Mechanisms of Suicide

The neural basis of SB has been explored using structural (9–11), functional (12, 13), and metabolic imaging (14, 15). However, research on this topic often does not provide a satisfactory explanation for the observed sex differences in both non-fatal and fatal SB.

One conclusion from the existing literature is that prefrontal hypoactivity (16), which is modulated by decreased serotonin binding in the prefrontal cortex (17), is implicated in SB. However, hypoactivity in the prefrontal cortex is associated with a range of psychopathology, including depression (18), post-traumatic stress disorder (19), and schizophrenia (20). Thus, the specificity of this risk factor for SB is unclear. Additionally, there is evidence that women have decreased serotonin binding in the prefrontal cortex compared to men [e.g., Ref. (21, 22)]. This pattern suggests that prefrontal hypoactivity may explain the elevated risk for non-lethal SB in women. However, this risk factor does not provide a satisfactory explanation for the elevated risk for lethal SB in men. It is not surprising that the identified neural substrates for SB are plausible explanations for female vulnerability, as, virtually, all of the existing research has focused on non-fatal SB. In a recent review of functional and structural brain studies of SB (17), 21 of the 22 articles included were comparisons between non-fatal suicide attempters and controls. Given the association between female gender and non-fatal suicide attempts, conclusions from these research studies are not particularly informative regarding neural substrates that may explain the association between male gender and fatal suicide attempts.

Research on the neural substrates of fatal SB is hampered by the difficulty of conducting research on individuals who die by suicide. Indeed, brain imaging research on suicide decedents is impossible unless premorbid imaging data are available, as was the case in the sole imaging study that has examined suicide decedents (23). To date, this difficulty has been addressed using non-fatal suicide attempts as a proxy for fatal SB. This is problematic, as this approach will not uncover neural activations that distinguish fatal versus non-fatal SB, which may explain the gender paradox in SB that was presented above.

As an alternative to using non-fatal suicide attempts as a proxy for fatal suicide attempts, some have proposed the investigation of endophenotypes for SB [i.e., discrete, measurable traits that

mediate the link between genetic risk and a particular form of pathology; Ref. (24)]. Given the heterogeneity of various forms of SB, the complex interplay between biological and environmental risk factors, and the difficulty in conducting research on fatal SB, focusing on endophenotypes may prove promising in elucidating biological risk factors for suicide. Several endophenotypes for suicide have been identified, to date [e.g., impulsive aggression, disadvantageous decision-making; Ref. (24)]. However, Courtet et al. (24) state the need for research that investigates gender differences in the neurobiology of SB, an aspect that has not been thoroughly investigated.

The Interpersonal–Psychological Theory of Suicide

Although Courtet et al. (24) propose some promising endophenotypes for suicide, the existing literature on this topic is atheoretical. The benefits of grounding empirical research in theory are numerous; in this particular case, we propose that using a comprehensive account of suicide as a theoretical framework would integrate what is already known while fostering novel predictions. One theory that appears promising in this regard is the interpersonal–psychological theory of suicide (IPTS) (25, 26). According to the IPTS, even individuals who experience intense suicidal desire will not die by suicide without the fearlessness about death and pain tolerance necessary to endure the act of making a lethal suicide attempt. Together, fearlessness about death and physical pain tolerance comprise a novel construct first introduced by Joiner (25), known as the acquired capability for suicide (ACS). According to the IPTS, suicidal desire stems from the simultaneous presence of thwarted belongingness (i.e., loneliness and lack of reciprocal care) and perceived burdensomeness (i.e., feeling like a liability on others and self-hatred). It is only when a desire for suicide simultaneously occurs with the ACS that a lethal suicide attempt is even possible. The IPTS offers the following explanation for gender differences in non-fatal and fatal SB: women are more likely to experience thwarted belongingness and/or perceived burdensomeness and men are more likely to acquire the capability for suicide – a proposition that has borne out in the behavioral literature [e.g., Ref. (27–30)]. Consequently, men who experience suicidal desire may be more likely to have a fatal outcome than women with similar levels of suicidal desire.

There are two main explanations for why men may have higher ACS than women do. First, according to the IPTS, the capability for lethal self-harm is acquired primarily through exposure to life experiences that are painful and provocative, which result in habituation to fear of death and/or physical pain. Many such experiences (e.g., combat exposure, impulsive/aggressive behaviors) are more common among men. Second, the IPTS allows for the possibility that various neurobiological and temperamental factors may make an individual more likely to acquire the capability for suicide over the course of his/her lifetime (26). A recent study (30) examined sensation-seeking and emotional stoicism as potential temperamental characteristics that explain the relationship between gender and both facets of ACS. Across two large, independent samples, sensation-seeking fully accounted for the relationship between gender and fearlessness about death, and

stoicism fully accounted for the relationship between gender and physical pain insensitivity. Thus, these temperamental characteristics may explain the observed gender differences in the ACS and, therefore, greater likelihood of death by suicide among men.

Witte et al.'s (30) findings, when viewed within the purview of IPTS, suggest a possible brain network that may explain the biological basis for the gender differences in lethal SB. We hypothesize that this network would involve neural substrates that underlie emotional stoicism, sensation-seeking, pain tolerance, and fearlessness about death, all of which may be considered endophenotypes for fatal suicide attempts. Our proposed brain network is based on a body of literature, suggesting that these constructs are interconnected. Numerous studies have demonstrated an association between male gender and both stoicism and sensation-seeking (31–35). Additionally, several studies have established the link between stoicism and pain tolerance [e.g., Ref. (30, 36–39)]. Likewise, sensation-seeking has been found to be an important correlate of ACS, as two studies have demonstrated associations between sensation-seeking and the ACS (30, 40). Given the overlapping theoretical constructs, the current study represents the first investigation of the neural substrates that may underlie gender differences in lethal SB.

As noted above, the existing research on the neural basis of SB is limited and is largely focused on factors that explain the increased risk for non-fatal SB seen in women, without providing an adequate explanation for the increased risk for death by suicide seen in men. By parsing out suicidal desire and capability for suicide, the IPTS offers a useful, theoretically driven framework, suggesting the possibility of separate neural substrates underlying the theoretical constructs. In this study, we hope to address the two aforementioned challenges in this area of research by distinguishing the neural substrates for ACS from neural substrates relevant to suicidal desire and attempting to explain the higher suicide mortality seen in men in terms of gender differences of underlying neural substrates. In order to do so, we conducted two separate activation likelihood estimation (ALE) meta-analyses. The first focused on our proposed ACS brain network by finding brain regions commonly activated by at least two of the four tenets of ACS: emotional stoicism, sensation-seeking, pain tolerance, and fearlessness of death. Our second meta-analysis focused on brain regions activated by clinical depression, since it is intricately linked to suicidal desire. The intersection of these two followed by meta-analytic connectivity modeling provided us with an ACS–depression network, which may underlie lethal suicide attempt and which is distinct in males and females. Further, we performed structural connectivity analysis using diffusion tensor imaging (DTI) for demonstrating that this ACS–depression network has different structural connectivity patterns in males and females. We show that the meta-analyses coupled with insights from DTI leads to testable hypotheses regarding the neural basis of IPTS and the ACS.

MATERIALS AND METHODS

Activation Likelihood Estimation

Activation likelihood estimation algorithm (41–43) was used to investigate brain regions mediating gender differences underlying ACS and depression. ALE is a widely used probabilistic approach for coordinate-based meta-analysis. Importantly, ALE accounts for the spatial uncertainties associated with different subjects and brain templates. Here, we present a brief overview of the general procedure involved while performing meta-analysis based on ALE. In the following section, we explain our specific analyses. In the ALE approach, every focus that was reported to be activated in an experiment yields an estimated 3D probability distribution with the center of distribution being at the focus. The ALE scores for each voxel are calculated by the union of activation probabilities for each voxel. The activation probability of a given focus at a voxel is calculated using a Gaussian probability function P.

$$P = \frac{e^{\frac{-d^2}{2\sigma^2}}}{(2\pi)^{0.5}\,\sigma}$$

where d is the Euclidean distance from center of voxel to particular foci, σ is the SD of the probability distribution. The σ values are calculated using the Euclidean distance between the same focus in different subjects. After obtaining the ALE scores of all voxels present in the brain, they are then compared with a null distribution. The null distribution is obtained by calculating ALE scores of voxels when there is no biological activity in the brain. By comparing the activation-related ALE score of voxels with the null distribution, a thresholded activation map can be generated (41–43).

Meta-analytic Connectivity Modeling: An ALE Meta-analysis

We searched the BrainMap database for papers coded with specific search criteria, described below, using the Sleuth search portal (44–46). The BrainMap database archives whole-brain coordinates from functional neuroimaging studies, using a rigorous coding scheme (46, 47). Coordinates of activation from contrasts meeting our criteria were then downloaded, and meta-analytic statistics were computed using GingerALE software (41–43) to determine regions of convergence among our search set using the ALE algorithm described in the previous section. Resultant ALE maps were thresholded with a minimum cluster size of 100 mm³ and a p-value of 0.05 and corrected for false positives using false discovery rate. Robinson et al. (48, 49) coined the term "meta-analytic connectivity modeling," which is based on the assumption that voxels that are statistically coactivated by a given condition across many different experiments must be functionally connected (48, 49). Here, we used this concept to find functional networks underlying ACS and depression in males and females. All searches had the basic criteria of including only activations for both ACS and depression and only normal subjects in the case of ACS whereas only depressed in the case of Depression. All searches were performed for males and females separately. In order to form a functional neural network for ACS, different ALE meta-analyses were performed using search criteria related to (i) emotion (i.e., all aforementioned search criteria plus "Experiments – Behavioral domain – Emotion – All subtypes" giving us, for males: 446 experiments, 2145 subjects and for

females: 355 experiments, 149 subjects, to be used for ALE meta-analyses); (ii) pain processing (i.e., all basic search criteria plus "Experiments – Behavioral domain – Perception – Somesthesis Pain," giving us, for males: 79 experiments, 372 subjects and for females: 34 experiments and 178 subjects, to be used for ALE meta-analyses); (iii) sensation-seeking (i.e., all basic search criteria and experiments with paradigm class as reward, given the intimate association between sensation-seeking and the brain's reward system, giving us, for males: 127 experiments and 621 subjects and for females: 35 experiments and 174 subjects, to be used for ALE meta-analyses); and (iv) fear (i.e., all basic search criteria in addition to "Experiments – Behavioral domain – Emotion – Fear," giving us, for males: 54 experiments and 318 subjects and for females: 32 experiments and 231 subjects, to be used for ALE meta-analyses). Each of these searches was run separately. The above search criteria are motivated by the four main constructs underlying IPTS as outlined in the Section "Introduction," i.e., emotional stoicism, sensation-seeking, pain tolerance, and fearlessness of death. It is noteworthy that using these exact terms in the Sleuth search would give very few or no relevant papers. Therefore, we searched for broader conceptualizations of these constructs. For example, we believe that the extent of activation in the fear-related regions might be an important factor modulating fearlessness of death, and hence, we used "Experiments – Behavioral domain – Emotion – Fear" as the search criterion. The ACS was proposed with two constructs, pain tolerance and fearlessness of death. However, a recent study (30) examined sensation-seeking and emotional stoicism as potential temperamental characteristics that explain the relationship between gender and both facets of ACS. Therefore, as the prevalence of at least two of the four constructs underlying IPTS might account for ACS, we deemed all voxels that were activated by two or more of the search conditions to represent the functional neural network in males and females separately for ACS (we will call this "ACS network").

In order to obtain the functional neural network for depression, ALE meta-analyses were performed using search criteria related to depression. Two Sleuth searches were performed, one for males and the second for females. Common search criteria used for both of the searches were subjects diagnosed with depression (Subjects – Diagnosis – Depression) and experiments showing only activations as results (Experiments – Activations only), giving us, for males: 31 experiments and 112 subjects and for females: 29 experiments and 149 subjects, to be used for ALE meta-analyses. Additional criterion used for the first search was only male subjects (Subjects – Gender – Males only) and the second search was for only female subjects (Subjects – Gender – Females only). The resultant ALE map from this search was interpreted as a representation of the functional neural network in males and females, separately underlying depression (we will call this "depression network"). **Figure 1** describes the steps involved in forming the ACS and depression networks.

Acquired capability for suicide and depression networks were examined to identify overlapping voxels, which may be indicative of common neural substrates underlying ACS and depression in males and females. These common voxels (we will call these "ACS–depression network seeds") were then used as ROIs in

a subsequent ALE-based meta-analysis, wherein these seed locations were used for obtaining voxels coactivated by them, and hence, by inference, functionally connected to them. Further, we investigated whether the functional network obtained by ACS–depression network seeds using meta-analytic connectivity modeling (we call this "ACS–depression network") were different in males and females.

Structural Connectivity Using Diffusion Tensor Imaging

To investigate the structural basis of the functional networks derived through meta-analysis, DTI techniques were used. White matter axonal tracts, from the ACS–depression network seed voxels identified previously, were calculated using diffusion-weighted data in order to determine the regions structurally connected to them. Diffusion-weighted data were acquired from 31 healthy individuals using Siemens 7T MAGNETOM scanner (26 right-handed, 12 males, 19 females, M ± SD = 21.13 ± 1.43). The study was approved by the Institutional review board at Auburn University and all human subjects provided informed consent. A high resolution DTI scan (40 slices, 2 mm³ isotropic voxels, TR/TE: 5200/94 ms, base/phase resolution 122/100%, GRAPPA acceleration factor of 3, $b = 0$ and 1000, 30 directions, 3 averages, collected in an interleaved fashion) was acquired. All diffusion-weighted images were skull-stripped using tools provided in FSL software (50) and manually checked to ensure accuracy. Probabilistic diffusion tractography was carried out as described previously (51–53), using a probability density function that was created at each voxel on the principal fiber direction. Connectivity probabilities were estimated between the seed voxels and target voxels (i.e., the rest of the brain) by repeatedly sampling connected pathways through the probability distribution function. The differences in the white matter pathways originating from ACS–depression network seeds in males and females were examined. **Figure 1** illustrates the entire analysis procedure.

RESULTS

The ACS and Depression Networks

The thresholded ALE maps obtained from conducting ALE meta-analysis on the aforementioned four tenets of ACS, emotional stoicism, sensation-seeking, pain tolerance, and fearlessness of death, were overlaid on the same anatomical image for males and females separately. The regions that were commonly activated by at least two of the four conditions were hypothesized to represent the ACS network for males as well as females (**Figure 2**). Similarly, regions constituting the functional network underlying depression, obtained from ALE-based meta-analysis performed for depression are shown in **Figure 3** for males and females. **Table 1** provides list of the major regions in the ACS network in males and females, separately showing regions of overlap as well as gender-specific activations. The regions that were common to the functional networks underlying depression in males and along with those that were specific to males or females are listed in **Table 2**. Note that ALE values are provided in **Table 2** and not

FIGURE 1 | A schematic illustration of the entire procedure involving ALE meta-analysis, meta-analytic functional connectivity modeling, and structural connectivity analysis.
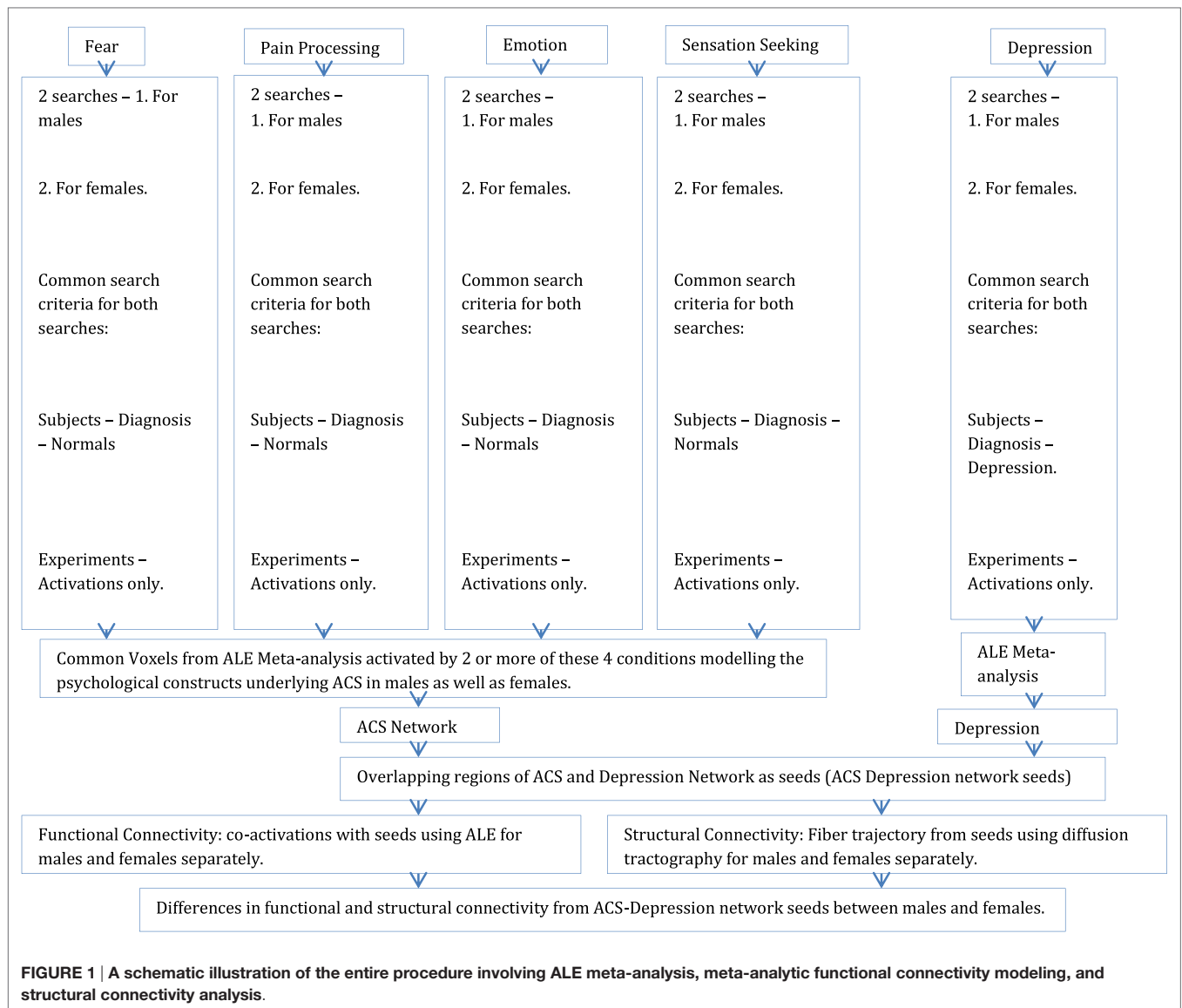
in **Table 1**, as the latter is an intersection map obtained from four different primary ALE analyses.

The Overlap between ACS and Depression Networks

The voxels identified in the ACS and depression networks in males and females from **Figures 2** and **3**, respectively, were overlaid on a single anatomical image as shown in **Figure 4**, to investigate common neural substrates underlying ACS and depression. The overlap between ACS and depression networks in males consisted of left precentral gyrus, bilateral putamen, left claustrum, bilateral caudate, right cingulate gyrus, right Insula, right middle frontal gyrus (also referred to as dorsolateral prefrontal cortex), and right thalamus. Likewise, the overlap between ACS and depression networks in females consisted of bilateral putamen, left lateral globus pallidus, and left insula. These activations in the males and females form the

ACS–depression network seeds, which were subsequently used in order to determine meta-analytic functional connectivity and DTI-based structural connectivity. As noted before, since the depression network was assumed to represent a network that may underlie suicidal desire, the overlap between ACS and Depression networks may form a basis for lethal SB. Putamen was commonly activated in ACS–depression Network in males as well as females. The ACS–depression network seeds organized by lobes and weighted centers of seeds that were obtained in males and females are enlisted in **Table 3**.

Functional and Structural Connectivity

We obtained voxels coactivated by the ACS–depression network seeds (**Figure 4**) separately in males and females, using ALE-based meta-analytic connectivity modeling. The corresponding results, shown in **Figures 5** and **6**, indicate that, even though the ACS–depression network in males and females underlie a
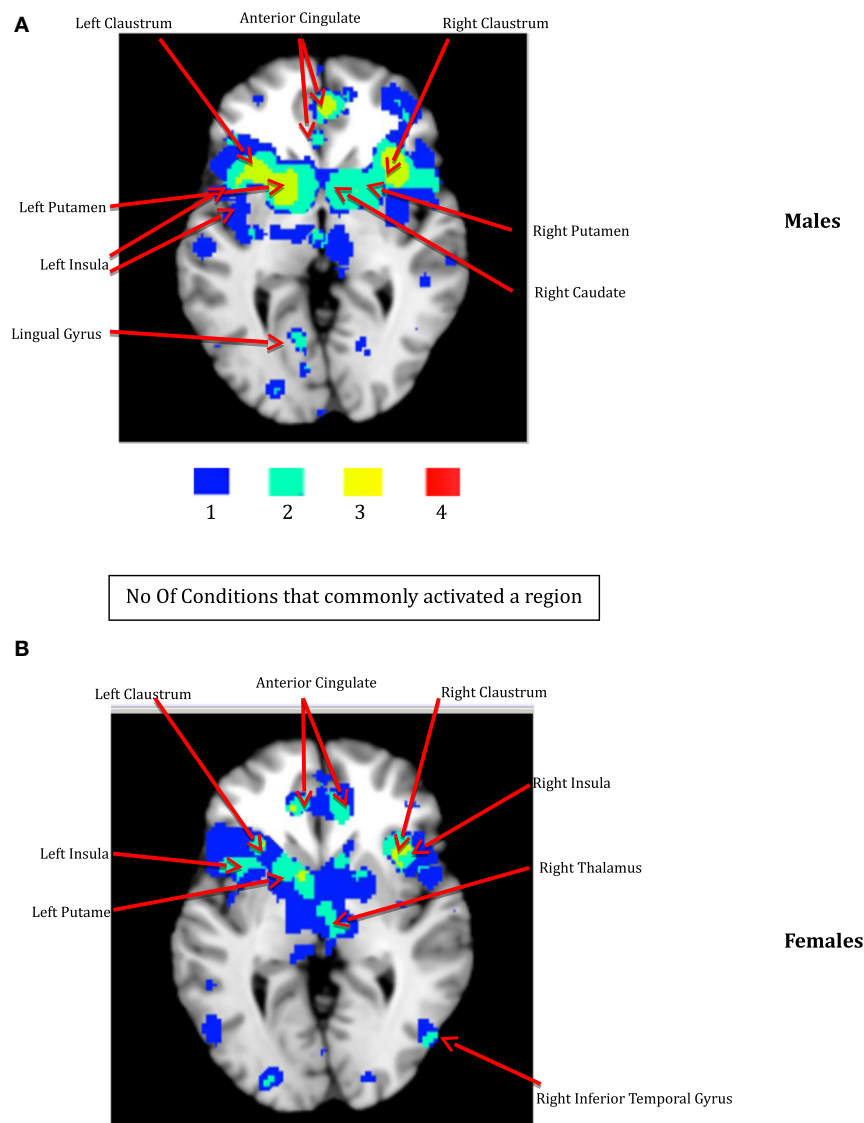
FIGURE 2 | The ACS network for males (A) and females (B). The color bar illustrates the color scheme used for depicting the regions that were commonly activated by just one, two, three, or four of the following conditions – emotion, pain processing, sensation-seeking, and fear. Voxels activated by any one of the above mentioned four conditions are shown in blue, by any two of the above conditions are shown in aquamarine, and by any three of the four conditions in yellow, respectively. Regions represented by aquamarine and yellow colors together form the ACS network.

common neurophysiological framework, there are both commonalities and differences in their underlying neural substrates. Major brain regions, which were commonly coactivated by the ACS–depression network seeds in males and females, are listed in **Table 4**, while gender-specific coactivations are listed in **Table 5**. This provides an exploratory model for differentiating the neural basis of lethal suicide attempts between males and females.

Further, we performed axonal fiber tractography using the ACS–depression network seeds to demonstrate the distinct structural connectivity likely involved in the ACS–depression network in males and females. The axonal trajectories derived

from the ACS–depression network seeds in males and females are shown in **Figure 7**. Further, a 3D rendering of the trajectories is shown in Videos S1 and S2 (corresponding to males and females) in Supplementary Material accompanying this paper, in order to give a better understanding of the projections from the seeds.

It can be observed from **Figures 4** and **7** and **Table 3** that ACS–depression network seeds in the left and right putamen are present in both males and females. Given the role of putamen in the hate circuit (54), it may mediate gender differences in lethal SB (more on this in the Section "Discussion"). In order to better understand and demonstrate the differences in structural connectivity between males and females involved in
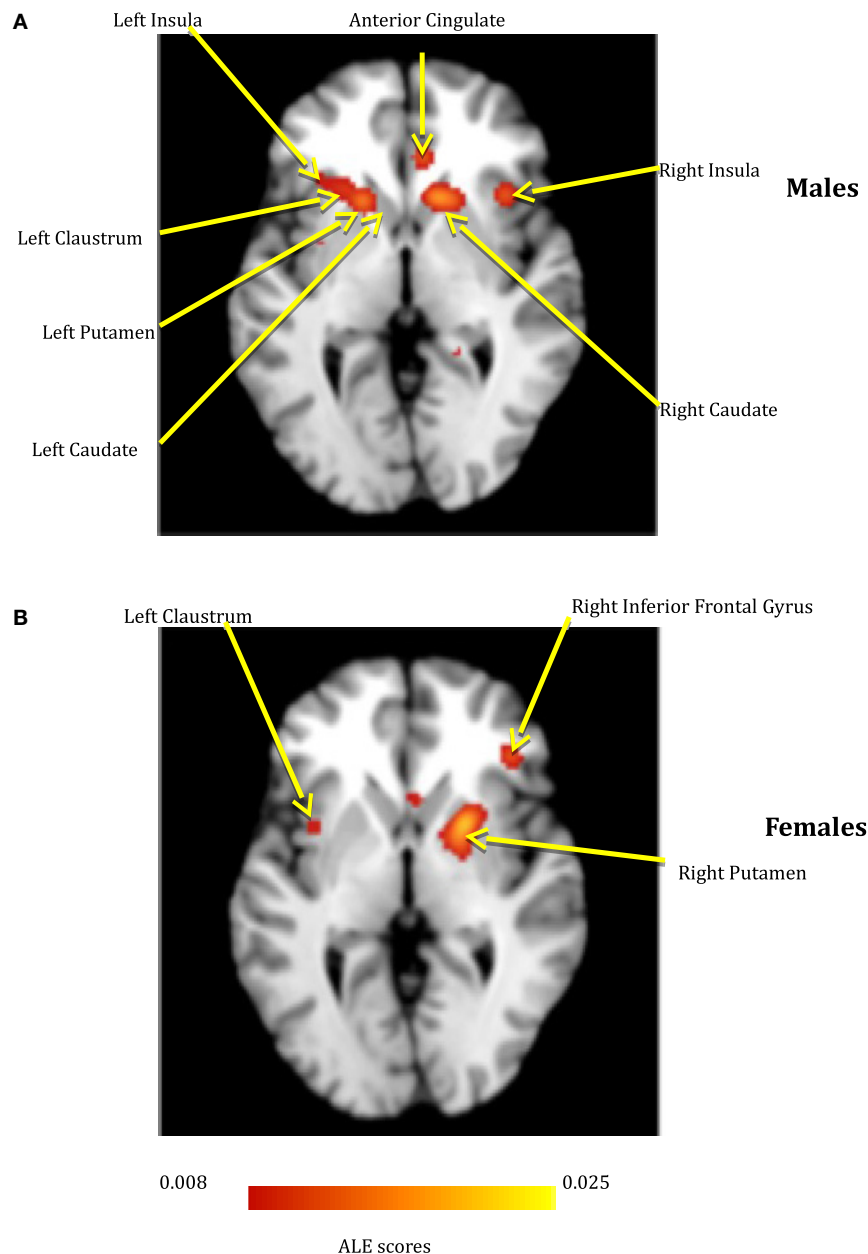
FIGURE 3 | The depression network for males (A) and females (B).

ACS–depression network, just the fiber trajectories from these seeds in both males and females were overlaid on the same anatomical image in **Figure 8**. The fiber trajectories from the left putamen seed in males, projected toward left insula, medial frontal gyrus, thalamus, and premotor cortex. Whereas in females, the fiber projections from left putamen did not travel farther while that from the right putamen seed projected to the anterior cingulate and thalamus. This qualitative depiction of structural connectivity demonstrates that the ACS–depression network in males might cover a vast expanse of cortical and sub-lobar brain regions, compared to females.

DISCUSSION

One of the most well-established findings with regard to SB is that men are far likelier to engage in fatal SB, whereas women are far likelier to engage in non-fatal SB. Most existing functional and structural studies of suicide are focused on non-fatal SB (17); as such, they do not necessarily provide information about neural substrates involved in fatal SB and, therefore, cannot explain the so-called gender paradox of suicide. The goal of this study was to address this limitation in the literature. Given the challenges inherent in studying the neural basis for fatal SB, we used the

TABLE 1 | Activation statistics in males and females corresponding to the ACS network.

Lobe	Region	BA	Males			Females		
			x	y	z	x	y	z
Convergent seeds								
Sub-lobar	Right caudate	Caudate body	8	10	4	8	12	6
	Right putamen (lentiform nucleus)		21	4	4	17	6	6
	Right claustrum		29	16	4	33	20	3
	Right insula		41	14	4	36	19	3
	Left putamen (lentiform nucleus)		−18	6	2	−25	−3	−9
	Left claustrum		−29	17	2	−30	12	6
	Left insula	13	−40	13	2	−36	11	6
	Right thalamus		8	2	4	3	−14	2
Male-specific network								
Sub-lobar	Left caudate	Caudate body	−9	11	2			
Frontal	Right precentral gyrus	44	48	12	4			
	Left precentral gyrus	6	−42	0	35			
	Right mid frontal gyrus	10, 9	35	41	13			
			40	17	25			
Posterior	Right cerebellum declive		33	−71	−17			
	Left cerebellum declive		−33	−63	−18			
Limbic	Right anterior cingulate	32	6	45	3			
	Right cingulate gyrus	23	5	−28	26			
Occipital	Right lingual gyrus	17	21	−87	8			
	Left lingual gyrus		11	−63	2			
Female-specific network								
Sub-lobar	Left lat glob pallidus (lentiform nucleus)					−19	−4	−9
	Amygdala					−20	−7	−13
	Right lat glob pallidus (lentiform nucleus)					18	1	−10
Limbic	Left cingulate gyrus	32, 24				−3	12	42
						−3	9	42
	Left anterior cingulate	32				−12	39	0
	Right anterior cingulate	24				7	37	4
Parietal	Left postcentral gyrus	40				−54	−27	20
Occipital	Right inf temporal gyrus	37				48	−69	2

BA, Brodmann area.

IPTS (25, 26) as a theoretical foundation for identifying potential endophenotypes of fatal SB. On the basis of prior research (30), we investigated several psychological constructs relevant to the ACS (i.e., emotional stoicism, sensation-seeking, pain tolerance, and fearlessness about death). Gender differences in neural networks that underlie these endophenotypes may eventually help to explain the gender paradox of SB. To accomplish our goal, we conducted an exploratory investigation of the neural mechanisms that are differentially activated by the psychological/psychiatric constructs in the ACS and depression in males and females. As noted before, since the depression network was assumed to represent a network that may underlie suicidal desire, the overlap between ACS and depression networks may form a basis for lethal SB. Here, we have demonstrated that meta-analysis and meta-analytic connectivity modeling can be used to develop neural models and testable hypotheses regarding the gender paradox of SB.

Our research has identified a preliminary network of regions commonly activated by two or more psychological constructs underlying the ACS in males and females separately. Given that most functional and effective connectivity models require the definition of *a priori* ROIs, identifying the neural nodes associated with ACS in a sensitive and robust fashion represents a key

advancement for future experimental studies that can examine gender differences in the neural connectivity of these networks. Second, we found that the regions corresponding to both the ACS and depression networks have significantly different foci in males and females, which implies potential for distinct functional and structural connectivity differences. The proportional contribution of each of the regions in the ACS and depression networks to the individual psychological constructs of the IPTS may provide a gender-specific, multidimensional imaging biomarker of SB. As such, this study provides a foundation for future studies examining the neural substrates of the ACS, allowing for integration of previous findings of higher male vulnerability for death by suicide and higher female vulnerability for non-fatal SB. Importantly, since the ACS is a multidimensional construct, identification of neural regions involved in each of the individual constructs provides the basis for their underlying biosignatures.

ACS Network

Several brain regions demonstrated consistent activation during imaging studies examining psychological constructs thought to be related to the IPTS dimensions. While no previous meta-analyses exist that combine all these constructs of the ACS, some studies have reported ALE analyses of individual constructs. For

TABLE 2 | Activation statistics in males and females corresponding to the Depression network.

Lobe	Region	BA	Males			Females			ALE	
			x	y	z	x	y	z		
Convergent regions										
Sub-lobar	Right putamen (lentiform nucleus)		28	−4	8	22	8	2	0.015	0.020
	Left putamen (lentiform nucleus)		−26	−2	8	−24	−4	10	0.014	0.024
						−22	−2	−6		0.012
						−26	10	6		0.009
	Left claustrum		−24	20	4	−28	8	−8	0.012	0.014
	Right insula	13	40	−18	16	44	−38	18	0.025	0.010
			38	18	4				0.015	
			38	4	10				0.008	
	Left insula	13	−50	−18	24	−36	6	4	0.012	0.010
	Right caudate	Caudate head	14	16	0	2	16	2	0.019	0.009
Limbic	Left cingulate gyrus	23	−6	−32	28	−8	−12	30	0.014	0.013
Female-specific network										
Frontal	Right inferior frontal gyrus	47				40	32	0		0.013
						18	20	−16		0.011
						18	30	−2		0.009
						24	30	−4		0.008
	Left mid frontal gyrus	9				−50	14	26		0.010
Limbic	Left anterior cingulate	32				−4	20	−8		0.012
	Left cingulate gyrus	23				−8	−12	30		0.013
	Right posterior cingulate	23				4	−28	22		0.024
	Right anterior cingulate	24, 32, 25				6	32	4		0.015
						2	26	−8		0.013
						2	2	−4		0.010
	Right cingulate gyrus	31, 24				12	−40	28		0.010
						12	8	26		0.014
	Right parahippocampal gyrus	35, 36				24	−20	−18		0.018
						28	−28	−10		0.014
	Left parahippocampal gyrus	28, 19				−20	−18	−14		0.013
						−24	−42	−2		0.010
Temporal	Left middle temporal gyrus	39				−44	−62	22		0.010
Anterior	Right cerebellum anterior lobe: dentate					12	−52	−22		0.009
Sub-lobar	Left lat glob pallidus (lentiform nucleus)					−20	−3	6		
Male-specific network										
Frontal	Left precentral gyrus	9, 6	−36	8	38				0.023	
			−37	5	35					
	Right precentral gyrus	6	38	2	34				0.011	
	Right mid frontal gyrus	46, 8, 9	42	28	18				0.014	
			28	12	38				0.013	
			39	18	23					
	Left inferior frontal gyrus	45	−32	24	4				0.010	
Parietal	Left supramarginal gyrus	40	−38	−44	34				0.020	
	Left inferior parietal lobule	40	−46	−42	28				0.017	
	Right inferior parietal lobule	40	42	−34	34				0.015	
Sub-lobar	Left caudate	Caudate head	−16	16	2				0.016	
	Right caudate	Caudate body	16	−18	26				0.011	
	Right claustrum		36	−4	−4				0.011	
	Right thalamus		4	−4	6				0.011	
Temporal	Left superior temporal gyrus	13	−36	−26	8				0.011	
Occipital	Right lingual gyrus	30	18	−42	0				0.009	
Limbic	Right cingulate gyrus	23	5	−28	28					

BA, Brodmann area.

example, a meta-analysis of gender differences in emotional processing has been reported earlier (55) and is consistent with what we found. There were no regions commonly activated by all four conditions. Fearlessness about death and pain tolerance were not correlated with one another in Witte et al. (30) and, thus, could be said to develop somewhat independently. Thus,
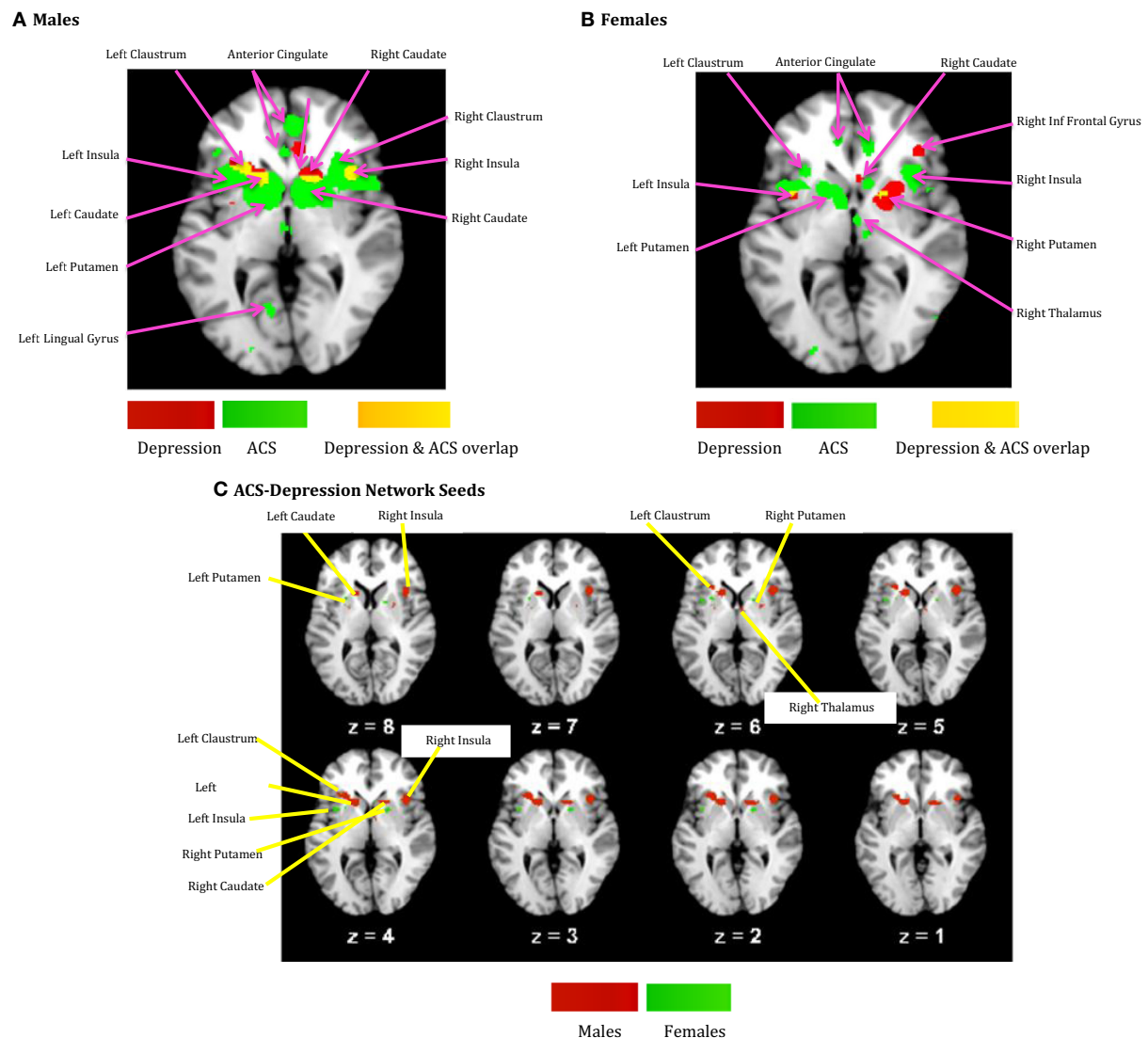
FIGURE 4 | (A) ACS and depression networks identified in males, both overlaid on same anatomical image. **(B)** ACS and depression networks identified in females, both overlaid on same anatomical image. **(C)** Voxels commonly found in the ACS and depression networks identified in males and females, overlaid on a single anatomical image. These form the ACS–depression network seeds.

it stands to reason that distinct neural areas might be associated with some of the constructs that contribute to acquired capability.

Our data demonstrate that males and females exhibited similar sub-lobar neural network consisting of bilateral putamen, bilateral claustrum, bilateral insula, right caudate, and right thalamus identified under two or more of the IPTS dimensions. This network of brain regions represents a sub-lobar nucleus of regions at the crossroads of emotion and cognitive processing, with functional contributions to both systems. Even so, there were notable differences in the functional network identified for males and females. The primary motor cortex and premotor cortex pertaining to bilateral precentral gyrus and right mid frontal gyrus (also referred to as dorsolateral prefrontal cortex)

along with regions in cerebellum were activated exclusively in males, whereas females exhibited activations restricted to limbic system regions, such as the amygdala and cingulate cortex, commonly known to be involved in emotion formation and processing (56). The utilization of motor areas in the ACS network in males may imply that, if the ACS network is activated in males, there are greater chances of them executing the action as intended, in contrast to females. The inclusion of emotionally reactive regions in the ACS network in females supports suicidal ideation but lack of motor regions engaged in the network might be the reason of females having lower chances of implementing a lethal attempt. Additionally, while males demonstrated bilateral caudate activation, females demonstrated right caudate utilization.

TABLE 3 | Seeds corresponding to ACS–depression network (Figure 4C).

Lobe	Region	BA	Males			Females		
			x	*y*	*z*	*x*	*y*	*z*
Convergent seeds								
Sub-lobar	Left putamen (lentiform nucleus)		−19	14	4	−26	9	7
	Right putamen (lentiform nucleus)		24	1	7	17	7	4
Female-specific seeds								
Sub-lobar	Left insula	13		−37	7		5	
	Left lat glob pallidus (lentiform nucleus)			−21	0		6	
Male-specific seeds								
Sub-lobar	Left claustrum			−27	21		4	
	Left caudate	Caudate body		−16	15		4	
	Right caudate	Caudate body		14	15		4	
	Right insula	13		37	18		5	
	Right thalamus			5	−2		6	
Frontal	Left precentral gyrus	6		−40	2		35	
	Right middle frontal gyrus	9		40	18		23	
Limbic	Right cingulate gyrus	23		4	−28		28	

Depression Network

Several meta-analysis studies have been previously conducted to investigate depression (57–59), and our results are in general agreement with them. However, to the best of our knowledge, ALE meta-analyses on gender differences in depression have not been reported before, and hence, this is a contribution of the present work. In our meta-analysis study, the depression network identified for both males and females consisted of bilateral putamen, left claustrum, bilateral insula, right caudate, and left cingulate gyrus. In spite of the commonly activated regions, depression also exclusively activated some regions specific to either males or females. For males, the caudate that has been known for its involvement in reward processing was identified not only in the right, but also the left hemisphere. For females, we identified the right inferior frontal gyrus, which has been notably linked to depression in several research studies and serves as a target for transcranial magnetic stimulation (60). Additionally, females demonstrated activations in numerous regions, such as anterior and posterior cingulate cortex, which have been implicated to be the neural substrates underlying the vulnerability to SB or suicidal ideation (61). This might explain females being at a higher risk of depression, suicidal ideation, and non-lethal SB, than males.

Neurofunctional Network Supporting Both ACS and Depression

Regions common to ACS and depression network were designated as ACS–depression seeds, separately in males and females. Using meta-analytic connectivity modeling, we obtained regions coactivated by these seeds in males and females, which we designate as the ACS–depression functional network. Although this network contained some regions that were common to both males and females, there were noteworthy differences in the regions activated in males and females. Such regions (**Table 5**)

were found to contain voxels common to both males and females but also had voxels that were exclusive to the male or female networks. This indicates some level of functional parcellation/differentiation in these brain regions. The notable amount of premotor, primary motor, and cerebellar regions engaged in the ACS–depression network in males might point toward the existence of a neural substrate supporting motor action. This could possibly result in higher probability of a fatal outcome in men on account of experiencing suicidal desire, compared to women. Males also engaged a larger ACS–depression functional network than women, which might be a factor responsible for higher lethal SB in men.

Structural Network for ACS–Depression

The putamen was the only brain region commonly present in the ACS–depression network seeds for males and females. Therefore, this may be a region of particular importance in understanding SB across men and women. This result is consistent with a recent meta-analytic finding that individuals with a history of SB had decreased volumes in the putamen compared to individuals with a history of psychiatric disorders (61). Upon investigation of the fiber trajectories from the putamen seeds in males and females, differential structural connectivity patterns were observed between males and females. The trajectories from the left putamen seed in males projected up to the premotor cortex, medial frontal gyrus, left insula, and thalamus. Premotor cortex (involved in motor planning), medial frontal gyrus [known to play a role in executive mechanisms (62)], and left insula have been previously shown to form a part of the hate circuit (54) that is engaged while experiencing hate toward an individual [notably, insula is also implicated in perception of the degree of real (63) as well as imaginary pain (64); this provides a possible link as to why it may be involved in the hate circuit], which may be relevant to self-hatred. Engaging a large portion of hate circuit and, more importantly, direct structural connections among

the regions in the hate circuit might strengthen the intent of suicide and its execution in males, especially given the involvement of the premotor cortex. While the projections from the left putamen in females were localized, males had projections from the right putamen seed extending up to the anterior cingulate and thalamus. The anterior cingulate has been implicated in a previous study (61) to be a neural substrate underlying suicidal ideation. This might be a reason for higher vulnerability of women for suicidal ideation and non-fatal attempts. The regions identified in the functional ACS–depression network and the structural connectivity of the ACS–depression seeds may be the key to understanding gender differences in the rates of fatal and non-fatal SB.

It is instructive to examine existing literature on postmortem studies from completed suicide with our findings. Furczyk et al. (65) have provided a comprehensive review of postmortem

studies in completed suicide. They show that genetics, neuro-transmitters, cell signaling, and markers of neural plasticity are altered in individuals who have committed suicide. They report alterations in the above metrics in some of the same regions that we have found. Specifically, (i) Table 1 in Furczyk et al. (65) lists all studies which have shown altered genetic expression and transcription in specific brain regions, notably the prefrontal cortex in postmortem studies, (ii) Table 2 in Furczyk et al. (65) lists all postmortem studies, which have shown alterations in various neurotransmitter systems, including serotonergic, noradrenergic, dopaminergic, glutamatergic, GAMA-ergic, and endocannabinoid systems. These systems comprises regions implicated in our study, notably the frontal cortex, putamen, amygdala, hippocampus, and other areas of the limbic system, (iii) Table 3 in Furczyk et al. (65) lists all postmortem studies, which have shown alterations in various cell signaling systems,
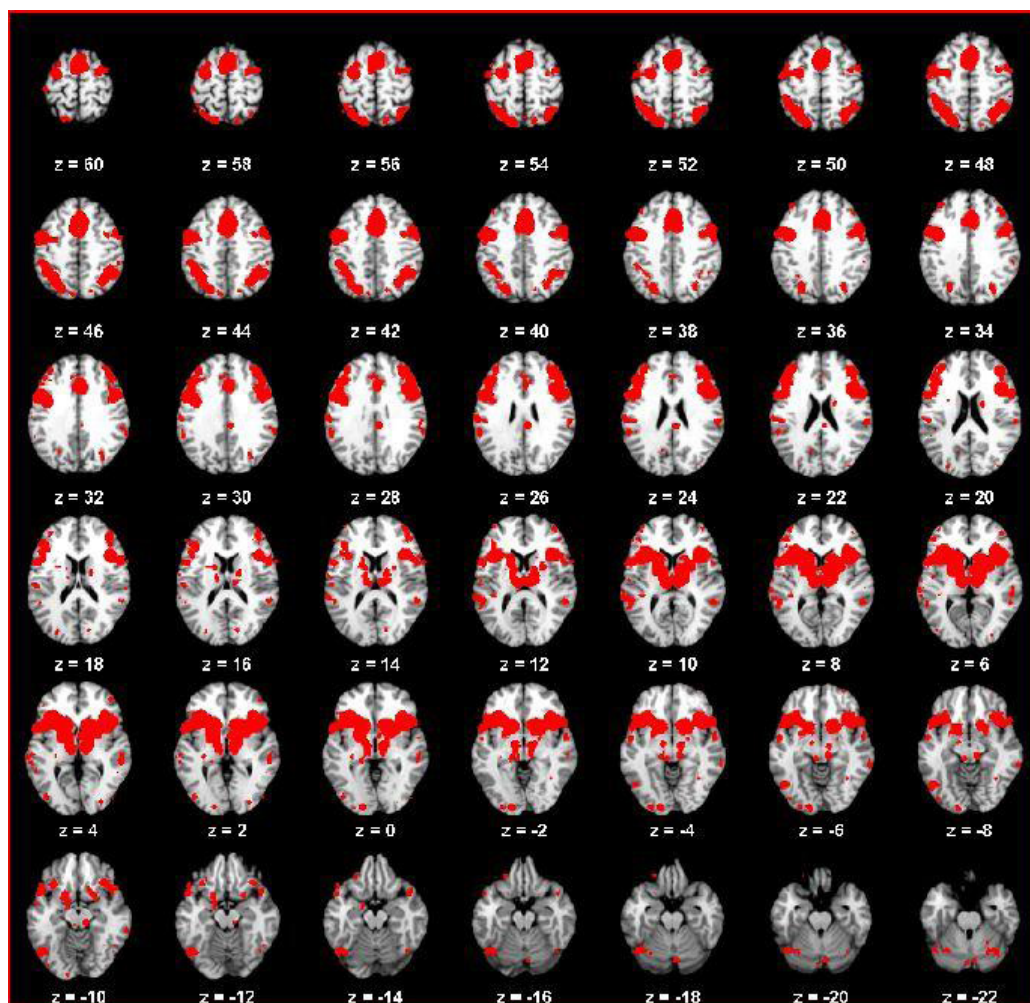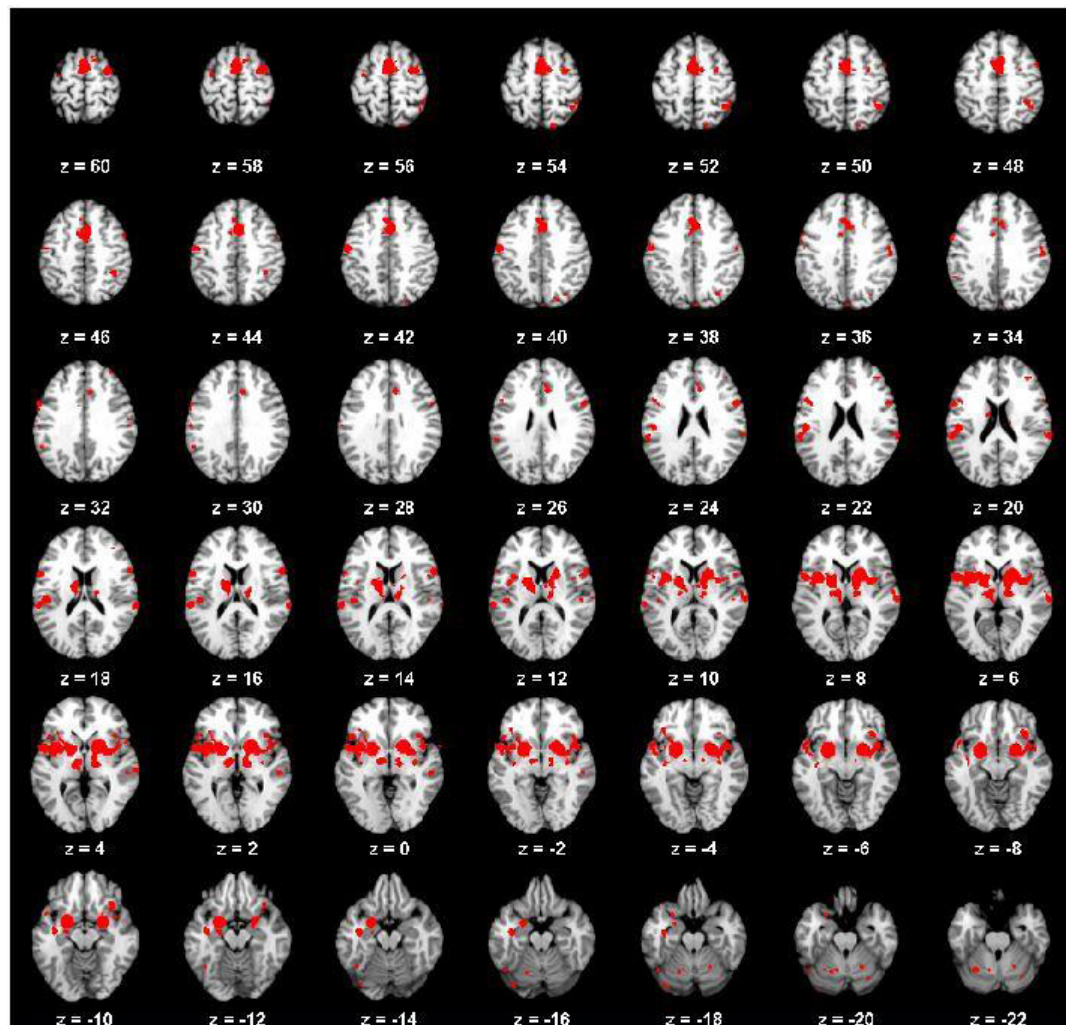

A Males

FIGURE 5 | Continued

FIGURE 5 | ACS–depression network in males (A) and females (B) obtained by finding voxels coactivated by the ACS–depression network seeds found in Figure 4.

including adenylate cyclase, phospholipase C, and cytokines with location specificity mainly in the prefrontal cortex and hippocampus, (iv) Table 4 in Furczyk et al. (65) lists all postmortem studies, which have shown changes in neural plasticity in suicide victims; changes in neurotrophic factors seems to be localized to the prefrontal cortex and hippocampus, while changes in polyamines seem to be global. While some of the studies cited by Furczyk et al. were carried out in only males or females, we could not find any reports where in sex differences have been investigated in postmortem studies.

The results of our study have important implications for the construct validity of ACS. The vast majority of research on ACS has utilized either self-report measures or assessments of physical pain tolerance; to our knowledge, this is the first investigation of neural substrates that may underlie ACS. By constructing a layout of the neural networks, research will also be enhanced as efforts are directed toward answering more complex questions about how neuronal networks contribute to SB.

Some limitations of the current study are noteworthy. First, and perhaps most importantly, we did not investigate SB as an outcome variable. Thus, future research is needed to demonstrate a link between the proposed ACS network and fatal suicide attempts as an outcome. Related to this point, we would like to emphasize that the proposed ACS network is not put forward as
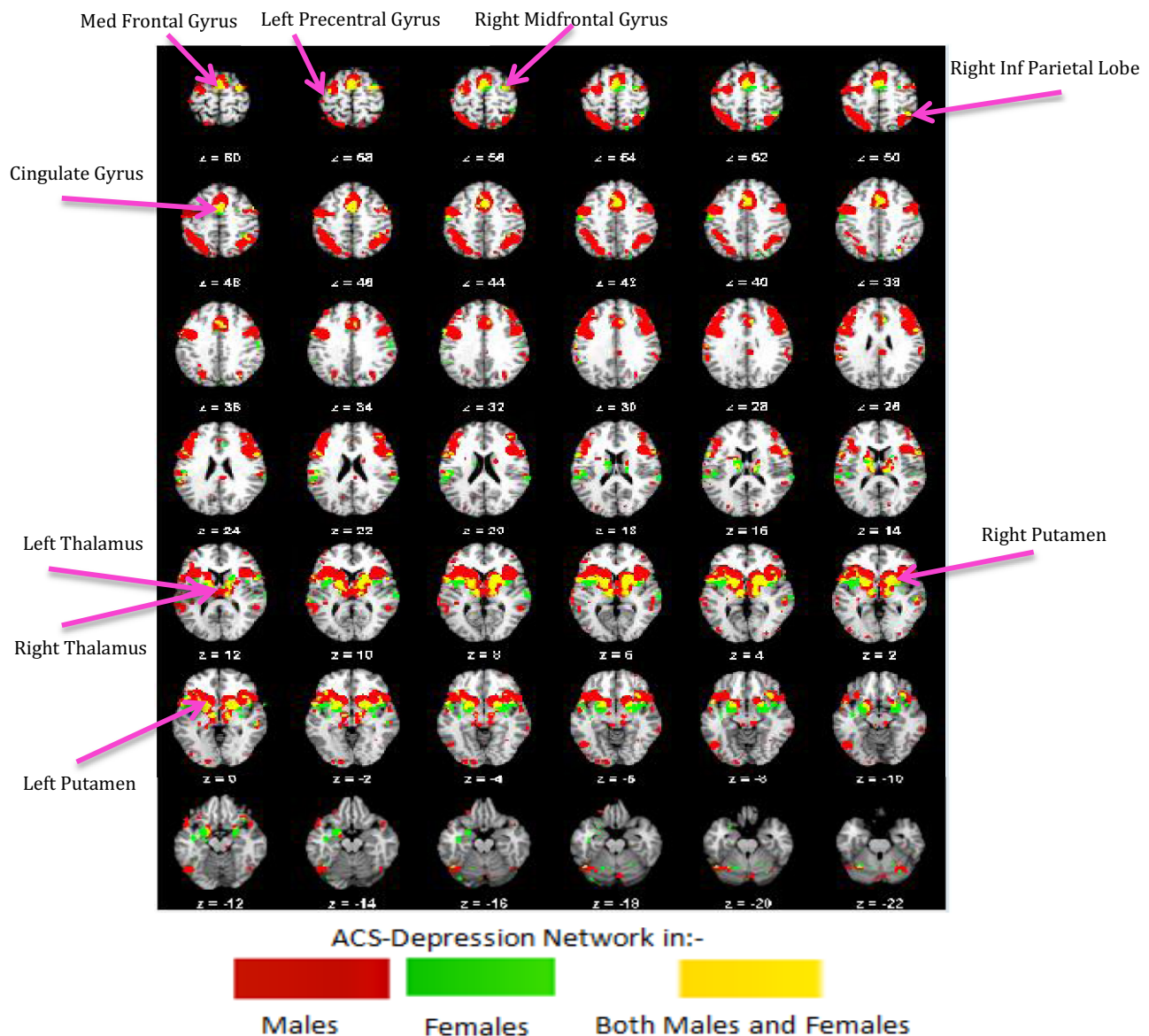
FIGURE 6 | **ACS–depression network, which was obtained separately in males and females, is overlaid on a single anatomical image**. Green represents the ACS–depression network in females, red in males, and yellow represents their overlap. Only regions of overlap are labeled in the figure while **Table 5** provides labels of regions, which were exclusively coactivated with ACS–depression network seeds only in males and females.

a neural substrate for suicide *per se*; rather, we are proposing that it underlies endophenotypes for suicide (i.e., emotional stoicism, sensation-seeking, pain tolerance, and fearlessness about death), which themselves may be endophenotypes for suicide. Given the complexity involved in SB, we are not proposing pure biological determinism, as we recognize the strong influence of environmental risk factors on SB. Second, there are few imaging studies investigating the specific constructs of ACS (i.e., emotional stoicism, sensation-seeking, pain tolerance, and fearlessness of death). Therefore, we performed meta-analyses on emotion, reward, pain, and fear, respectively (since they represent a

super-set of the original constructs of ACS), with the assumption that the voxels activated in more than two of the four conditions would be related to ACS. This illustrates one of the weaknesses of meta-analyses. Nevertheless, it is useful to make this assumption as an attempt to generate a hypothesis about the underlying neural substrates of ACS so that future experimental studies may perform experiments to confirm or deny the hypotheses generated by this initial attempt. Similarly, our definition of the ACS network is not ideal (i.e., >2 of the IPTS dimensions), and as the databases become larger, we may be able to refine this definition. Third, we did not investigate all components of the IPTS. Thus, although

TABLE 4 | Major regions that demonstrated meta-analytic functional connectivity to the ACS–depression seeds in both males and females.

Lobe	Region	BA	x	y	z
Sub-lobar	Left putamen (lentiform nucleus)		−19	4	4
	Left lat glob pallidus (lentiform nucleus)		−19	−3	4
	Left insula	13	−38	10	4
	Left thalamus		−10	−16	4
	Right putamen (lentiform nucleus)		23	5	4
	Right lat glob pallidus (lentiform nucleus)		18	0	4
	Right insula	13	42	8	4
	Right caudate	Caudate body	13	8	4
	Right thalamus		15	−15	4
	Right claustrum		31	24	−7
Frontal	Left precentral gyrus	44	−51	8	4
	Left med frontal gyrus	6, 32	−3	3	58
			−2	13	43
	Right med frontal gyrus	6, 32	4	5	58
			6	15	43
	Right midfrontal gyrus	6	28	−3	60
	Right inf frontal gyrus	44	54	11	15
Limbic	Right cingulate gyrus	32, 24	2	16	41
			2	14	45
	Left cingulate gyrus	32, 24	−2	23	41
			−3	10	38
Parietal	Right inf parietal lob	40	39	−46	50
Anterior	Left cerebellum culmen		−29	−60	−26

TABLE 5 | Male- and female-specific major regions exclusively coactivated with ACS–depression network seeds.

Lobe	Regions	BA
Male specific-regions		
Sub-lobar	Left claustrum	
	Left putamen (lentiform nucleus)	
	Left caudate	Caudate body
	Right thalamus	
	Right putamen (lentiform nucleus)	
	Right insula	13
	Right caudate	Caudate body
	Left thalamus	
	Left insula	13
	Right caudate	Caudate head
	Right claustrum	
Frontal	Left precentral gyrus	6
	Right mid frontal gyrus	9
	Left precentral gyrus	44
	Left mid frontal gyrus	6, 9, 46
	Left inf frontal gyrus	9, 45, 13
	Right inf frontal gyrus	9
	Right precentral gyrus	6, 9
	Right med frontal gyrus	6, 8
	Right sup frontal gyrus 6	
Limbic	Right cingulate gyrus	32, 24, 23
Parietal	Left inf parietal lob	40
	Left angular gyrus	39
	Left precuneus	7, 19, 39
	Left sup parietal lob	7
	Left supramarginal gyrus	40
	Right sup parietal lob	7
	Right precuneus	7
	Right inf parietal lob	40
Temporal	Left fusiform gyrus	37
	Left sup temporal gyrus	22
	Left mid temporal gyrus	21
	Right sup temporal gyrus	41, 22
	Right mid temporal gyrus	21
Anterior	Right cerebellum culmen	
Posterior	Right cerebellum pyramis	
Occipital	Left mid occipital gyrus	37
Female-specific regions		
Sub-Lobar	Left putamen (lentiform nucleus)	
	Left lat glob pallidus (lentiform nucleus)	
	Left claustrum	
	Right putamen (lentiform nucleus)	
	Right insula	13
	Right claustrum	
	Left insula	13
	Left thalamus	
	Left caudate	Caudate body
Frontal	Left precentral gyrus	44
	Right med frontal gyrus	6
	Right mid frontal gyrus	6
Temporal	Right sup temporal gyrus	42
	Right transverse tem gyrus	41

Regions that contained some overlapping area between males and females but also were observed to contain some area specific to male/female network are mentioned in red, regions consisting of ACS–depression seeds are mentioned in violet and regions satisfying both the aforementioned criteria are mentioned in green.

our results demonstrate that the ACS network is distinct from the depression network, future research is needed to investigate whether distinct neural substrates underlie ACS versus thwarted belongingness and perceived burdensomeness. Fourth, we did not investigate whether the ACS network we obtained generalizes across different forms of psychopathology (e.g., bipolar disorder versus major depressive disorder). This is an important avenue for future research. Fifth, deactivations were not considered in these meta-analyses for the following reasons: (a) deactivations are not as frequently reported as activations, and (b) the neural basis of fMRI-based deactivation is yet unclear, i.e., there is still a debate whether deactivations in fMRI are indeed caused by GABAergic inhibition (66, 67). Finally, the limitations of ALE-based meta-analysis, which have been discussed before, also apply to this study (43, 48, 49, 68). For example, we considered studies that examined the psychological construct "fear" and have considered it as equivalent to fearlessness of IPTS dimension. While fear is a basic emotion and involves predominantly limbic structures, fearlessness is an acquired ability and likely involves inputs from higher cortical structures. A similar case can be made with respect to pain and pain tolerance. Given that a Sleuth search on fearlessness (or pain tolerance) returns no relevant papers, we have to assume that both fear and fearlessness are mediated by the same neural structures. While this assumption may not be entirely true, it may be fine since we are using the meta-analyses as a tool for generating hypotheses to be tested with real data,
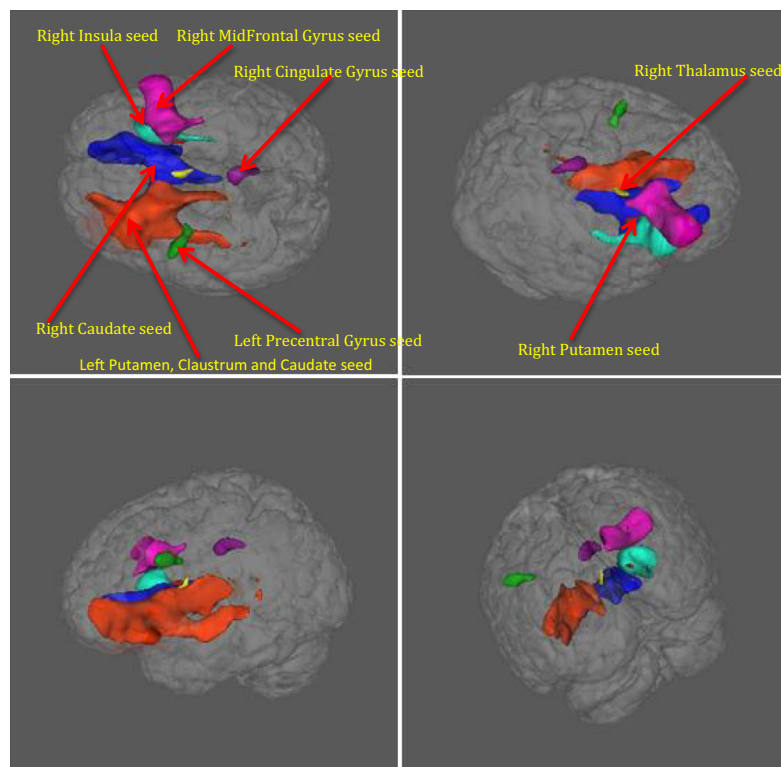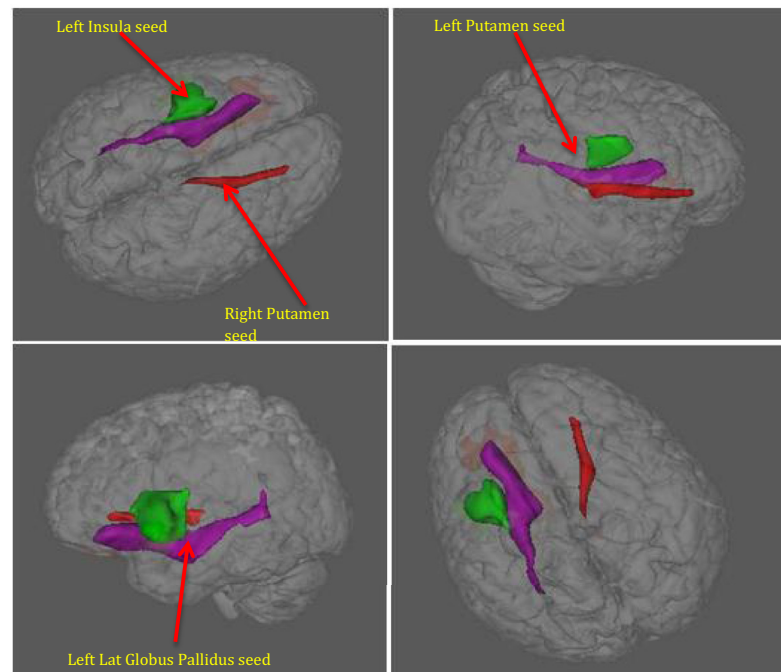
FIGURE 7 | The axonal trajectories derived from the ACS–depression network seeds defined by coactivated voxels from ACS and Depression networks in males (A) as well as females (B). The four panels in **(A,B)** are the different views of the same figure. **(A)** Yellow – fibers from right thalamus, green – fibers from left precentral gyrus, dark blue – fibers from right caudate, purple – fibers from right cingulate gyrus, light blue – fibers from right insula, pink – fibers from right mid frontal gyrus, red – fibers from right putamen, orange – fibers from left putamen, claustrum, caudate. **(B)** Red – fibers from right putamen, green – fibers from left insula, blue – fibers from left putamen (hidden inside the green fibers from left insula, so not seen in the figures), purple – fibers from left globus pallidus.

FIGURE 8 | Fibers from seeds in left and right putamen in males and females both overlaid on a single anatomical. Red – fibers in males, green – fibers in females. Both panels represent different views of the same figure.
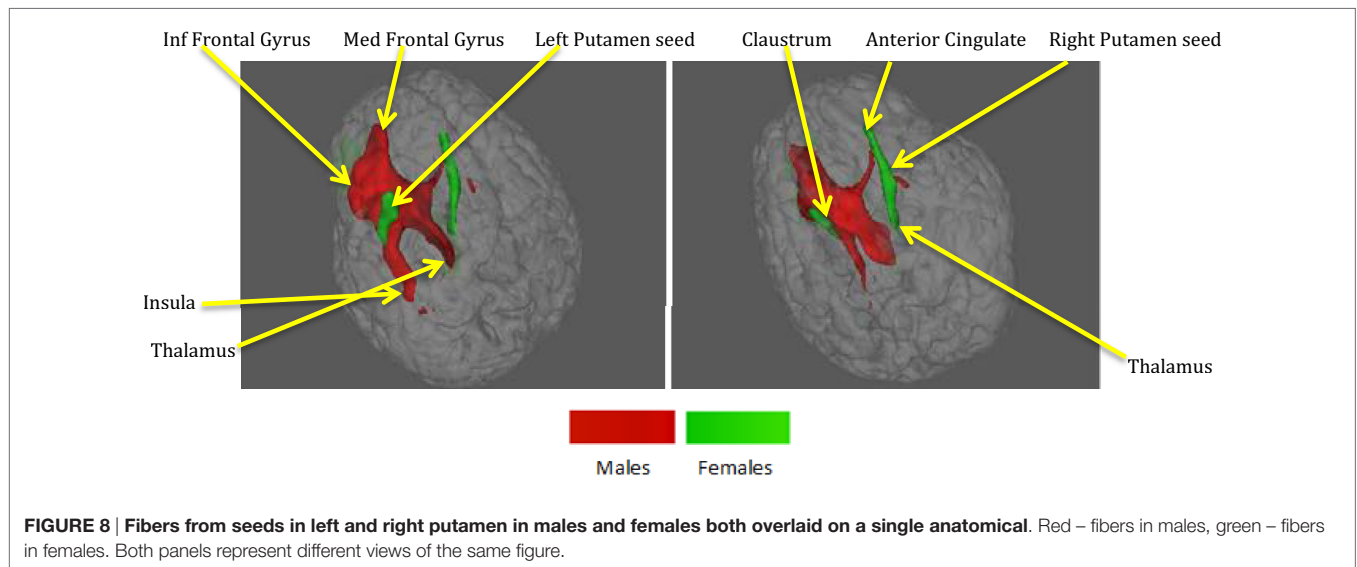
rather than making mechanistic conclusions solely based on the meta-analyses. Despite these limitations, this study provides a useful foundation for future studies of gender differences in the neural basis of SB.

AUTHOR CONTRIBUTIONS

GD, TW, and JR conceived the study. MB performed data analysis under the guidance of GD and JR. GD, MB, TW, and JR wrote the paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Journal/10.3389/fpsyt.2016.00125

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Commentary: A Neural Basis for the Acquired Capacity for Suicide

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A commentary on

A Neural Basis for the Acquired Capability for Suicide

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Every year suicide accounts for nearly 2% or altogether one million deaths, one happening approximately every 40 s (1). Completed suicide happens significantly more frequently in males in all countries except for rural China (2), and in several countries, it is the leading cause of death in males younger than 40 years of age and is also among the leading causes in other age groups (3). In spite of this significant burden, our understanding of suicide is far from complete. Suicide is a complex phenomenon, arising in almost 90% in the framework of psychiatric disorders, mostly associated with affective illness. However, the lack of sufficient understanding of both psychosocial and neuroanatomical contributors and comprehensive biopsychosocial models leaves a huge gap in identifying targets for the early prediction, screening, detection, and intervention in case of suicidal behavior.

As mentioned earlier, completed suicide rates are much higher in men compared to women especially in the young age groups. Therefore, understanding the neurobiological background of the gender difference would be a promising approach for better understanding of the occurrence of this phenomenon and can also give biological support to psychosocial theories which in turn would also utilize biological findings. Although the most frequent precursor of suicide is major depression, which is three times more common in reproductive age women compared to men, males are paradoxically markedly overrepresented among suicide victims. Several clinical correlates of more common suicidal mortality can be identified in men including employment of more highly lethal methods, comorbid alcohol and substance use, less common help-seeking behavior, and increased impulsive aggressive traits (4). These are coupled with poorer treatment compliance and worse response to certain antidepressants in men further hindering recognition and prevention of processes leading to suicide in men (2). Therefore, identification of gender-specific factors in the emergence of suicide needs to be identified to design-specific interventions. Furthermore, understanding the role of gender in differences in the manifestation of behaviors along the suicide spectrum would also yield important new insight concerning the nature of suicide in general.

There are important gender differences in brain processes involved in learning, memory, language, fear, and anxiety as well as significant gender differences in the prevalence rates of several neuropsychiatric disorders, which may result from sex chromosome effects, developmental hormonal effects, or hormonal modulations during adulthood (5) and may also be consequences of gender-related psychosocial effects. So far, gender differences in dopamine and serotonin functions and genetics (6) and associations between cortisol and male suicide have been reported (7, 8). Testosterone also plays an important role in the gender effect observable in suicide, and this effect may also interact

with age (9). Urocortin and BDNF also appear to play a gender-specific role in male suicidal behavior (10), and interestingly there appears to be a gender difference in the putative antisuicidal effect of lithium as well (11). This already complex picture suggests that the investigation of genetic and biological factors in the background of suicide should be conducted from a gender perspective.

In line with this previous knowledge, the present paper (12) focuses on understanding the neural substrates in the background of gender differences in completed suicide by investigating a potential neural network for acquired capability for suicide (ACS), which includes emotional stoicism, sensation-seeking, pain tolerance, fearlessness of death, thus involving neurobiological structures and processes associated with various endophenotypes of suicidal behavior outlined using activation likelihood estimation meta-analysis. The authors report that male-specific neural ACS networks are both more widespread and more diverse compared to female-specific networks and are dominated by motor regions, while female networks show a dominance of limbic regions, explaining why suicidal behavior is manifested more on the action and motor level in males and on the emotional and ideation level in females.

One important aspect of this paper is that while most imaging studies report on suicide attempts, this is one of the rare studies focusing on imaging methodology in completed suicide. As gender shows an inverse association with attempted vs. completed suicide, studies on suicide attempters are unable to address the question of gender sufficiently. Furthermore, the current study uses a psychosocial theory and psychological constructs as a basis for neurobiological research for a comprehensive approach. The results also validate the construct of ACS which may be a key and potentially operationalizable construct in suicidal behavior, by identifying its underlying neural substrates.

This research indeed provides us with important new data on the gender differences in completed suicide; however, the applicability of its method and approach goes way beyond that. Rather than focusing on suicidal behavior as a single entity, or on suicide-related single individual endophenotypes such as impulsiveness or hopelessness, this paper with a unique novel approach targets a complex pathway of behaviors leading to the emerging risk for suicide. Thus, these novel results not only provide a new insight into the gender differences in fatal suicides but also set an example to the complex approach of this complex phenomenon, which may pave the way for the development of more detailed and accurate dynamic models in the understanding of suicidal behavior helping to identify targets for prediction and intervention in both genders.

AUTHOR CONTRIBUTIONS

XG undertook a review of the literature, conceived this general commentary, and wrote and reviewed all drafts.

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The Reciprocal Relationship between Suicidality and Stigma

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Introduction: Although suicidality is frequently the cause of stigma, it is conversely true that stigma may be the cause of suicidality. The present paper focuses on the complex relationships that exist between suicidal behavior and stigmatizing attitudes.

Methods: A narrative review of the topic will be presented on the basis of the relevant literature collected from an electronic search of PubMed, ISI Web of Knowledge, and Scopus databases, using stigma, public stigma, structural stigma, perceived stigma, self-stigma, suicide, attempted suicide, and suicidality as key words.

Results: A negative perception is frequently held of suicidal people, labeling them as weak and unable to cope with their problems, or selfish. Individuals who have attempted suicide are subject to similar processes of stigmatization and "social distancing"; insurance policies include an exclusion clause against death by suicide. Subjects with a direct personal experience of depression or suicide strongly endorse a feeling of self-stigma; those who have attempted suicide are often ashamed and embarrassed by their behavior and tend to hide the occurrence as much as possible. Similar processes are observed among family members of subjects who have committed suicide or made a suicide attempt, with a higher perceived stigma present in those bereaved by suicide. Perceived or internalized stigma produced by mental or physical disorders, or through belonging to a minority group, may represent a significant risk factor for suicide, being severely distressing, reducing self-esteem and acting as a barrier in help-seeking behaviors.

Conclusion: With the aim of preventing suicide, greater efforts should be made to combat the persisting stigmatizing attitudes displayed toward mental disorders and suicide itself. Indeed, the role of stigma as a risk factor for suicide should further motivate and spur more concerted efforts to combat public stigma and support those suffering from perceived or internalized stigma. Experts and scientific societies should form an alliance with the media in an effort to promote a marked change in the societal perception of mental health issues and suicide. As stigma may result in severe consequences, specialist care and psychological interventions should be provided to populations submitted to stigma.

Keywords: stigma, internalized stigma, suicide, mental illness, mental disorders, risk factors, media

INTRODUCTION

Suicide is one of the major public health concerns worldwide, currently listed as the 15th most common cause of death, and accounting for approximately 1.4% of all mortalities; more than 800,000 people die due to suicide, with even higher number of suicide attempts each year (1).

Accordingly, particular consideration should be given to suicide, not only in view of its epidemiological relevance, but particularly as it is one of the human behaviors and conditions at highest risk of stigmatization, on a par with mental disorders, with which suicide is generally associated. Indeed, as reflected in media depictions (2), in the public opinion suicide is largely associated with mental illness; however, average estimates of psychiatric disorders among suicide victims vary from 69.9 to 88.2% in North America and 90.4% in South Asia (3), with a substantial proportion of suicidal cases lacking any association with mental disorders, including subthreshold conditions (4). Although the situation has changed somewhat in recent years, stigmatizing attitudes toward suicide still persist, implying a series of relevant consequences for survivors and their families. Moreover, irrespective of how stigma is determined (suicidality itself and/or mental illness, somatic illness, being part of a minority), it should be viewed as a potent stressor (5), capable of constituting *per se* a risk factor for suicide. Based on these premises, this narrative review aims to focus on the reciprocal relationship between suicidality and stigma and its consequences. After a brief analysis of the historical and religious origins of negative attitudes toward suicide, the review examines the current literature on suicidality as a cause of stigma, both in terms of the nature and extent of stigmatizing attitudes and consequences for suicidal persons and their families. The issue of stigma as a risk factor for suicidality is then considered. Finally, lessons to be drawn from the current literature and problems to be faced are discussed.

METHODS

We performed an electronic search of PubMed, ISI Web of Knowledge, and Scopus databases, without any restriction as regard to time and language, using stigma (i.e., the set of beliefs and attitudes that induce people to refuse, stave off, or fear people perceived as being "different"), religion, public stigma (i.e., the prejudice and discrimination endorsed by the general population), structural stigma (i.e., the set of those practices, regulations or rules, policies of a given social institution in order to restrict the rights and/or opportunities of citizens affected by a mental disorder), perceived stigma (i.e., the discrimination and devaluation by others as perceived by subjects), self-stigma (i.e., the negative public attitudes internalized by people suffering from mental problems), suicide, attempted suicide, and suicidality as key words (**Figure 1**). Only published full papers were examined, including original researches, reviews, and position papers. References found in selected papers were checked in order to identify other papers that could be considered as potentially relevant. Finally, in the case of research contributions, papers were considered on the basis of pertinence of their results to the topics of this narrative

review and of their relevance and/or comprehensiveness in the case of reviews or position papers.

THE HISTORICAL AND RELIGIOUS ORIGINS OF NEGATIVE ATTITUDES TOWARD SUICIDE

Suicide was tolerated by the Greeks and Romans, although considered by Aristotle to be a detriment to the economy and a means of irritating the Gods (6). In the Judeo–Christian tradition, there seems to be no trace of negative attitudes toward suicide (7), and the Bible itself contains no trace of condemnation of suicide (8). Since the times of St. Augustine, who viewed suicide as being incompatible with Christian values, the Catholic Church has condemned suicide, ultimately resulting in the excommunication of suicides and their family members, burial in unhallowed ground, and confiscation of property; this attitude has however gradually been attenuated during the twentieth and twenty-first centuries (9). Indeed, the Compendium of Catechism of the Catholic Church stated not only that "Everyone is responsible for his life before God who has given it to him. It is God who remains the sovereign Master of life. We are obliged to accept life gratefully and preserve it for his honor and the salvation of our souls. We are stewards, not owners, of the life God has entrusted to us. It is not ours to dispose of," but also affirms that "the voluntary cooperation of suicide is contrary to the moral law. Grave psychological disturbances, anguish, or grave fear of trial, suffering, or torture can diminish the responsibility of the one committing suicide. We should not despair of the eternal salvation of persons who have taken their own lives. God, through ways known to Him alone, can provide the opportunity for salutary repentance. The Church prays for persons who have taken their own lives" (10).

Among other Monotheisms, Islam adopts an attitude of condemnation of suicide (7), in the same way as Judaism, which considers the value of human life as supreme (11). Buddhism and Hinduism hold no traditionally negative view of suicide (7), although discordant voices have been raised to this regard (12). Whatever the importance of the different positions held by some religious faiths toward suicidal behavior, they seem to have a certain value in relation to suicide prevention, given that adherence to the norms and moral values dictated by religious beliefs has been associated with a lower risk of suicidality in different clinical conditions (13, 14).

STIGMA TOWARD SUICIDE

Notwithstanding the apparent slight decrease of stigma toward people affected by mental disorders people over the recent years, no similar reduction of the stigma associated with suicide and suicide-survivorship has been reported (15); limited data however appear to show a trend toward the reduction of suicide-associated stigma, particularly with regard to moral disapproval (16). However, prejudicial attitudes toward those who commit suicide are still quite common, as highlighted in recent studies conducted in a series of very different sociocultural contexts using largely heterogeneous designs and methods. An Australian

FIGURE 1 | Literature search flow diagram.
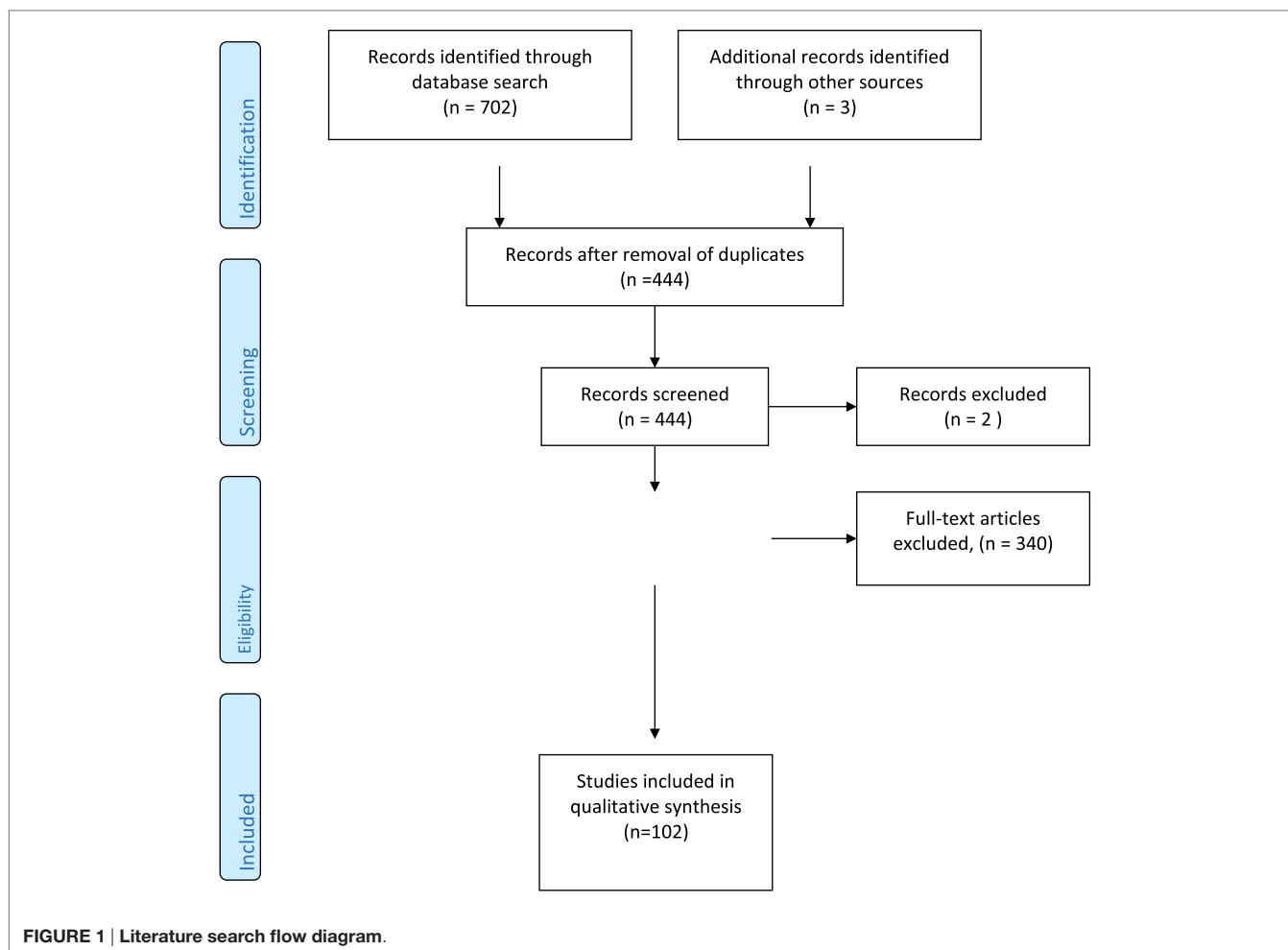
survey conducted on a sample of 676 subjects showed that between 30 and 40% respondents considered suicide as a punitive, selfish, offensive, or reckless act; a 20–30% proportion of the sample saw suicide as a sign of weakness or a thoughtless, irresponsible, cowardly, senseless, or attention-seeking act (17). Suicidal people are generally labeled in a negative sense, as being weak and unable to cope with their problems, or selfish (18). A recent Canadian survey among an adult population regarding stigmatizing attitudes and beliefs about male depression and suicide show how more than a third of responders agreed that men affected by depression are unpredictable, among those who had no direct experience of depression or suicide; overall, more males expressed stigmatizing opinions about depression respect to females; a greater proportion of female respondents endorsed items indicating that men who commit suicide are disconnected, lost, and lonely (19). A large Australian online survey relating to attitudes toward suicide revealed how a lower degree of exposure to suicide, older age, male gender, less education, and culturally diverse backgrounds was associated with poorer knowledge; conversely, stigmatizing attitudes were associated with male gender, younger age, and culturally diverse backgrounds (20). A Korean nationwide community study of factors related to social

stigma of people with a history of suicide, suicide attempts, or depression revealed that older men with lower education and no history of previous suicide attempts predicted the degree of stigmatizing attitudes toward people attempting suicide (21). A recent Chinese paper investigating users' attitudes toward suicide attempts broadcasted on social media (Weibo) showed how more than 33% of posts could be considered as "stigmatizing"; among these, post codes as "deceitful," "pathetic," and "stupid" were, respectively, 22, 16, and 15% (22). Participants randomly assigned to read one of the three fictional obituaries, identical except for the reported cause of death (suicide, cancer, or drug overdose), viewed people listed as succumbing to death by suicide more negatively than those who had died from cancer (23).

Public stigma toward suicide moves parallel to the problem of perceived stigma for both those who have attempted suicide and by the family members of people who have committed or attempted suicide. Data from focus groups comprising a series of diverse stakeholders (suicide attempt survivors, family members of people who have died by suicide and suicide loss therapists) set up to qualitatively investigate suicide stigma revealed an array of stereotypes, prejudices, and discrimination, in particular the fact that those who attempted suicide are predominantly viewed

as attention-seeking, selfish, incompetent, emotionally weak, and immoral (24). In a recent study of individuals with a lifetime history of suicidal behavior recruited through the American Association of Suicidology, respondents reported the highest rates of perceived stigma from a close family member (57.1%) and emergency department personnel (56.6%); the results of the study revealed how subjects who had displayed previous suicidal behavior were more likely to experience stigma, particularly from non-mental health providers and members of their social network (25). Suicide bereavement is perceived differently from natural loss, at times producing a deeply profound effect on the family, friends, and associates of the victim, which goes beyond the suffering inflicted by the immediate loss; indeed, one of the discriminating elements observed in suicide bereavement is the stigma experienced by survivors (26). A cross-sectional study of about 3,400 respondents who had suffered a sudden bereavement (i.e., the death of someone close from the age of 10 years) demonstrated how people bereaved by suicide displayed higher perceived stigma than those bereaved by sudden natural death and people bereaved by other sudden unnatural deaths (27).

CONSEQUENCES OF STIGMA TOWARD SUICIDE

Discrimination is a behavioral response to prejudice and is essentially dependant on the type of emotional reaction associated with the latter. Discrimination may be direct, as shown by studies that demonstrate how people who have attempted suicide are subject to similar processes of "social distancing" as those directed at ethnic or religious minorities (28, 29). Suicides typically leave a total of six or more survivors, with a consequent long-lasting emotional turmoil, which may in some cases end with the survivors' own suicide (30). Family members of individuals who have committed suicide are often judged and blamed for their relatives death (31), with post suicidal bereavement being burdened by the complex psychological impact of the suicide on those close to the victim, fostered by a societal perception that self-given death is considered a failure for those who die by suicide and the family, and by the society blaming the survivors for their losses (26). Indeed, significantly higher feelings of shame, and an increased sense of responsibility and guilt are commonly found in those bereaved by suicide, both in comparison with bereavement by a sudden natural and unnatural death (27).

Structural discrimination comprises the negative consequences resulting from imbalances and injustices experienced in terms of use of facilities and social services, political decisions, and legislation. With specific regard to suicide, probably the most impressive form of discrimination is represented by the fact that throughout the majority of industrialized countries, insurance policies include an exclusion clause against death by suicide and those deemed to be at risk of suicide will not be able to obtain life insurance (32). People with direct personal experience of depression or suicide, both male and female, strongly endorse stigmatizing attitudes toward themselves (18). Self-stigma (or internalized stigma), a self-discrimination process that suicidal individuals (and/or their families) put into effect, is of paramount

importance. Subjects with a direct personal experience of depression or suicide, both male and female, strongly endorse a feeling of self-stigma, while those who have attempted suicide are often ashamed and embarrassed by their behavior and tend to conceal the occurrence as much as possible (33–35). Similar processes are observed among family members of individuals who have attempted suicide (26, 31).

STIGMA AS A RISK FACTOR FOR SUICIDE

Psychological distress due to stigmatizing attitudes may be an exceedingly severe burden and at times result in extreme consequences. Exposure to suicide in someone close has been found to be associated with a series of negative health and social outcomes, including an increased rate of suicide among partners and mothers of people who died by suicide, a more pronounced recourse to psychiatric care by parents bereaved by the self-given death of an offspring, and a higher risk of depression in offspring of parents who had committed suicide (36). However, although adults bereaved by suicide had a higher probability of attempting suicide than those bereaved by sudden natural causes, the significant association between bereavement by suicide and suicide attempt became non-significant when adding perceived stigma, a finding which could be interpreted as indicating stigma as a marker for motivational moderators of suicidality after a negative life event, such as reluctance to seek help, thwarted belongingness or perceived burdensomeness (37). In addition to those specifically relating to suicidality, other forms of stigma should be taken into account due to the severe psychological distress they may cause. Indeed, mental disorders are likely the public health issue featuring the strongest link between stigma and suicide. Indeed, perceived stigma is one of the main factors associated with the risk of suicide among the mentally ill, with suicide at times being seen as a means of escaping from the stigma itself (38, 39). Furthermore, stigma is a highly relevant factor related to suicide among people affected by schizophrenia and other mental disorders (38, 40–46), including people considered at risk of psychosis (47). Confirmation of the link between stigma toward the mentally ill and suicide has been provided by a recent European study (48) showing that age-standardized suicide rates were negatively correlated (beta $= -0.46$, $p = 0.014$) with levels of social acceptance; these findings were derived by crossing data for the indicators of social acceptance of people with mental health problems (Eurobarometer data) and data on suicide rates and socioeconomic indicators (Eurostat) obtained from 25 EU countries for the year 2010. Evidence from this study has been interpreted as implying that stigma contributes toward explaining the risk of suicide and differences in suicide rates detected throughout the different nations; according to the authors, the link between stigma and suicide rates could be explained by a series of assumptions, including the role of stigma as a stressor and cause of social isolation (48). Together with other consequences of stigma such as unemployment, and subjective experiences such as hopelessness, the latter constitutes an important risk factor for suicide among the mentally ill (49). Discrimination is seemingly experienced as a stressor that exceeds coping resources of those who are stigmatized; moreover, this leads to develop a negative

self-image, with the perception of a lack of support by their own social networks; as a consequence, the increased anticipation of future negative events together with the perceived absence of social support may lead the mentally ill into hopelessness and suicidality (43). However, research findings have demonstrated how, in addition to discrimination and perceived stigma, other factors may also contribute toward explaining the rather intricate link between stigma and suicide among people suffering from mental disorders. Indeed, a longitudinal study has highlighted how self-stigma (or internalized stigma) is strongly related to suicidality (50). Levels of insight, depression, and internalized stigma may be associated, at least in schizophrenia, with a higher suicide risk (51). Suicidality related to self-perceived and internalized stigma may be explained by the mediating role of low self-esteem (52, 53). Increased self-labeling as "mentally ill" has been found to be associated with suicidality, being directly and indirectly mediated by social isolation, which in turn is associated with low self-estem (54). Additional information relating to the intriguing link between stigma and suicidality has been gathered from a large community sample examined by means of interviews and self-reports, with the aim of collecting information on perceived stigma, secrecy, hopelessness, and suicidal ideation. Participants who had previously been referred to mental health services were labeled as "mentally ill," with the stigma attached to mental illness contributing toward suicidal ideation in these people; one possible explanation for this association is the relation between perceived stigma and secrecy, which seems to introduce particular negative emotional consequences (55).

Some authors (45) have also hypothesized a "direct" mechanism whereby perceived stigma acts as a "barrier" to accessing mental health services, which should be considered together with the "indirect" mechanism relating to self-stigma. Indeed, one of the most widely accredited explanations of increased suicidality due to stigma is its influence on help-seeking behavior. In a national survey conducted on a sample of the Australian population who were assessed by means of case vignettes depicting depression with or without suicidal intent, the presence of high levels of personal stigma among respondents was a strong, independent predictor of the opinion that depression, both associated and not associated with suicidal thoughts, should best be coped with alone (56). In a web survey of a large sample of medical students from a US university, approximately 14% were found to be affected by depressive disorders ranging from moderate to severe. In particular, throughout the last 2 years of their studies, students reported suicidal thoughts (7.9%); these students indicated statistically more frequent fears of stigmatization (57).

An extensive survey of medical students in the USA revealed that a third of respondents had sought help for a mental health problem over the previous year; respondents with high levels of distress were found to be more likely to agree or strongly agree with 8 of 10 perceived stigma items (58) compared to students who were not distressed. Forty-four percent of college students with a lifetime history of suicidal ideation failed to seek treatment during young adulthood; ambivalence about treatment need or effectiveness, fear of stigma, and financial concerns were found to be the most relevant barriers to treatment (59). Finally, a large survey of undergraduate and graduate students from 15

US Universities demonstrated that correlates of help-seeking and treatment use among individuals referring serious suicidal thoughts over previous years were perceived need, beliefs about treatment effectiveness, contacts with service users, personal stigma and perceived stigma, level of social support, belonging to minorities and ethnicity (60). Although the majority of studies investigating young people highlight the relevance of stigma as a barrier to help seeking, some studies debunk this role. Indeed, a survey conducted among college students who did not seek treatment and deemed to be at high risk for suicide, the most commonly reported barriers included perception that treatment was not needed (68%) lack of time (26.8%) and preference for self-management (18%), while stigma was mentioned by only 12% of students (61); attempting to explain the reasons of these somewhat surprising results, the authors hypothesize that it was possible that students were concerned less about stigma than expected because of ongoing efforts aimed at reducing mental health stigma on college campuses, or that other reasons were simply more salient for these students' help-seeking decisions, particularly when asked to self generate reasons for not seeking help, rather than selecting from an available list of reasons. Another possibility taken into account was that stigma, although not mentioned explicitly, underlies some of the other barriers noted by students, such as not considering problems as warranting professional treatment or preference for self-management, which might reflect an underlying concern about stigma.

Anyway, the role of a reduced help-seeking behavior and fear of stigma among suicidal people, particularly those affected by a mental disorder, has been confirmed by several other studies. Fifty-five percent of people who commit suicide had had no contact with their GP over the previous month, and 68% of suicidal people had not had any contact with mental health services in the last year (62). More than 70% of people with mental disorders fail to seek help or do so very late due largely to non-recognition of having a mental disorder, poor access to care, fear of prejudice, and expectation of being discriminated as people with mental disorders (63). The importance of stigma in reducing help-seeking behavior is particularly consistent in those at higher risk of suicide: only 39% of people at risk had sought help of any kind in the preceding year with the main reasons for not requiring help being, in order: failure to recognize the need for help, the belief that any intervention would be ineffective, and fear of being stigmatized (64). Social, economical, and cultural factors may impinge on help-seeking behavior and subsequently affect suicide rates: 56% of people at risk in high-income countries and only 17% in low-income countries had sought help in the year preceding suicide (63); one study conducted in the Netherlands (65), where suicide rates are quite low, demonstrated an increased openness to calls for help in the presence of psychological problems, a reduced sense of shame and lesser fear of stigma compared to the Flemish population, characterized by higher rates of suicide. Moreover, the levels of perceived stigma were found to be negatively correlated with the propensity to seek informal help in both countries, and with the propensity to seek professional help in Flanders (65). A survey of Asian-American women with a history of depression and suicidality highlighted that the underutilization of mental health services was clearly

correlated to cultural factors such as Asian family stigmatizing attitudes and Asian community contribution to mental health stigma (66). Although the data present in literature support the presence of a credible link between stigma of mental illness and suicide, the limitations of some current studies should be taken into account. These limitations include the cross-sectional nature of the large majority of studies, thus not allowing any firm conclusions to be reached as to the direction of causality between stigma, symptoms, and suicidality, in addition to the fact that as suicide is a relatively rare event, many studies have merely regarded suicidal ideation or suicidal attempts as a proxy (49).

It would be a mistake to confine the role of stigma as a risk factor for suicide to individuals with mental disorders, as the fear of stigma extends to people suffering from somatic disorders or who belong to a minority group. These groups are often burdened by harsh labeling attitudes and discrimination, resulting in an increased risk of suicidality. Indeed, lifetime risk of suicidal ideation and attempts is strongly correlated to perceived discrimination among immigrants, as demonstrated in Hispanic people in the USA (67). Moreover, stigma is one of the major risk factors for depression and suicidality among sexual minorities (68–87) and in patients affected by AIDS (88–91) and obesity (92–94).

CONCLUSION

The main findings emerging from our paper should be read in light of the well-known limitations of narrative reviews, which are mainly due to certain subjectivity respect to other forms of review as regard to the selection of studies (selection bias due to subjective weighing of studies included in the review and to the lack of specificity in inclusion criteria), the method of study analysis chosen and the possibility of misleading conclusions drawn from the studies considered due to a scarce consideration of relationships between the study characteristics and the results, the difficulties in integrating data derived from large set of studies taken into account (95). Even considering these intrinsic limits, some relevant aspects emerge from our review. First of all, a reciprocal relationship exists between stigma and

suicide: suicide may cause stigmatizing attitudes, but stigma toward mental disorders may be a risk factor for suicidality. Both suicide and mental disorders are still today burdened by relevant negative attitudes that can only be tackled by a marked change in societal perception of these issues. Although modest, there is evidence for the effectiveness of antistigma interventions in terms of increasing knowledge and reducing stigmatizing attitudes, at least in the short term (96, 97). A better suicide literacy and low stigmatizing attitudes toward suicide were found to be associated with more pronounced help-seeking attitudes (98), while suicide literacy and stigma reduction programs would benefit community members (99). Mass media interventions may reduce prejudice toward mental disorders, although there is insufficient evidence to determine their effects on discrimination (100); moreover, media may play a significant role in suicide prevention (101). Thus, structured and permanent forms of partnership should be set up between experts, scientific societies, and the media to promote extensive educational efforts aimed at providing deeper insight into mental health issues and thus helping to reduce stigma. The stigma displayed toward suicide may result in severe consequences for people who have attempted suicide or who have been bereaved by suicide; specialist care and specific psychological interventions should be provided to these populations. The role of stigma as a risk factor for suicide should further motivate and spur more concerted efforts aimed at combating public stigma, sustaining self-esteem, reducing isolation and empowering those suffering from perceived or internalized stigma.

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Clinical Characteristics of Diabetes Mellitus and Suicide Risk

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Background: Diabetes mellitus (DM) is a chronic illness with impaired health-related quality of life and a high risk of psychiatric disorders. We carried out a systematic review analyzing the relationship between DM and suicide by providing a qualitative data synthesis of the studies.

Methods: We conducted, in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic search of the literature in PubMed, Scopus, ISI Web of Science, PsycINFO, Google Scholar, and ScienceDirect. Search terms were "suicid*" combined with the Boolean "AND" operator with "diabetes."

Results: The initial search identified 568 citations. A total of 17 research reports met the predefined inclusion criteria and were analyzed. DM was found to be significantly associated with a marked increase in suicidal behaviors and suicidal ideation (SI), especially in patients with depressive symptoms. Insulin therapy, DM of long duration, and unsatisfactory glycemic control were identified as risk factors for SI in Type 1 (T1DM) and Type 2 (T2DM).

Conclusion: Health-care professionals need to be aware of the higher suicidal risk in patient subgroups based on the clinical characteristics of DM; thus, patients with these characteristics warrant special attention. In this regard, clinical management should include efforts to manage emotional distress in DM care.

Keywords: diabetes mellitus, suicidal behavior, suicidal ideation, suicide attempt, depression

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The vast majority of cases of diabetes mellitus (DM) falls into two broad etiopathogenetic categories: Type 1 (T1DM) and Type 2 (T2DM) (1). DM is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control (1) to maintain well-being and quality of life over time, to control risks, to manage disease symptoms, and to reduce the incidence of complications (2).

Patients with DM are at risk of physical and psychological complications. The short-term complications include hypoglycemia, and the long-term complications include cardiovascular disease, neuropathy, nephropathy, and retinopathy.

The prevalence of depression and psychiatric diseases among adults with T1DM or T2DM is approximately double that observed in the general population (3, 4).

Depression has a negative impact on self-care (5) and has been shown to be related to poorer glycemic outcomes and therefore increased risk of complications (6).

The presence of psychopathological symptoms, feeling of hopelessness, and fears of chronic nature of the disease may predispose the patient to the risk of suicidal ideations (SIs) and suicidal behavior, but also to neglect health care and lack motivation to adhere to the medical regimen (7). Suicide risk is considered a major psychiatric emergency in patients diagnosed with chronic illnesses (8). DM and particular aspects of living with DM are known to be associated with greater SI (9–12). Chung et al. found that DM was associated with a marked increase in suicidal behaviors (13).

There are few studies on suicidal risk factors in the patient with DM. The risk factors may be related to the patient's characteristics, such as coping skills, personality profile, additional psychiatric illness including depression and alcohol use, and the feeling of hopelessness. Other risk factors could be a family history of attempted suicide and completed suicide. This is raised by furthermore the chances of suicide are increased by illness-related and situational risk factors such as adverse events, lack of social support, exacerbation of the illness, and gradual increase of DM complications. Another risk factor could be the easy access to means of self-harm by patients with DM (14).

Suicide is one of the highest public health priorities worldwide. The World Health Organization objectives for suicide prevention emphasize identification of high-risk groups (15).

Recognizing the clinical features associated with suicidal risk in patients with DM is crucial in order to realize screening and interventions aimed at prevention that should also take into account SI and suicidal behaviors.

In light of the above, the aim of this manuscript is to provide new insights for performing a systematic review by reporting the most relevant studies analyzing the clinical characteristics of the association between DM and suicide risk.

MATERIALS AND METHODS

Eligibility Criteria

All papers published in English peer-reviewed journals focused on the presence of SI, attempted or committed suicide in patients with T1DM or T2DM with a medical diagnosis were included in the search. Where the title or abstract seems to describe a study eligible for inclusion, the full text was examined to consider its relevance on the basis of the inclusion criteria. Reviews, meta-analyses, commentaries, letters to the editor, books or book chapters, abstracts, and clearly irrelevant papers were excluded. We also excluded abstracts that did not relate to suicide and DM.

Information Sources and Searches

This review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (16). The research was carried out in October 2016 on an electronic database: Scopus, ISI Web of Science, PsycINFO, Google Scholar, ScienceDirect, and PubMed were used to identify published studies.

The following keywords were used: "diabetes" AND "suicid*" [Title/Abstract]. After the initial search was performed, the studies were screened for eligibility, duplicates were identified and

discarded. The relevant studies were assessed using their titles and abstracts first and, finally, the full review of papers. Studies were discarded when the full text was not available. Results were not limited to chronological age of participants. Searching and eligibility of target responses were carried out independently by two investigators.

RESULTS

Based both on inclusion and exclusion criteria, a total of 568 original research studies were identified and selected for inclusion in the systematic review, as reported in the flowchart displayed in **Figure 1**. After removing the duplicates ($N = 77$) 491 papers remained. After that, reviews, meta-analyses, commentaries, letters to the editor, books or book chapters, abstracts, non-English language, clearly irrelevant papers were eliminated ($N = 471$). Twenty full text articles were assessed for eligibility and were read and surveyed by all the authors. Three articles were excluded because they did not respect the eligibility criteria. At the end of this process of examination, 17 studies were included in the qualitative synthesis of the systematic review.

Medical Characteristics of Diabetic Patients with Suicide Risk

Studies conducted with diabetic patients have shown significant associations between suicidality and specific diabetes-related characteristics (see **Table 1** for a detailed description of reviewed

FIGURE 1 | **Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart of the systematic search**.
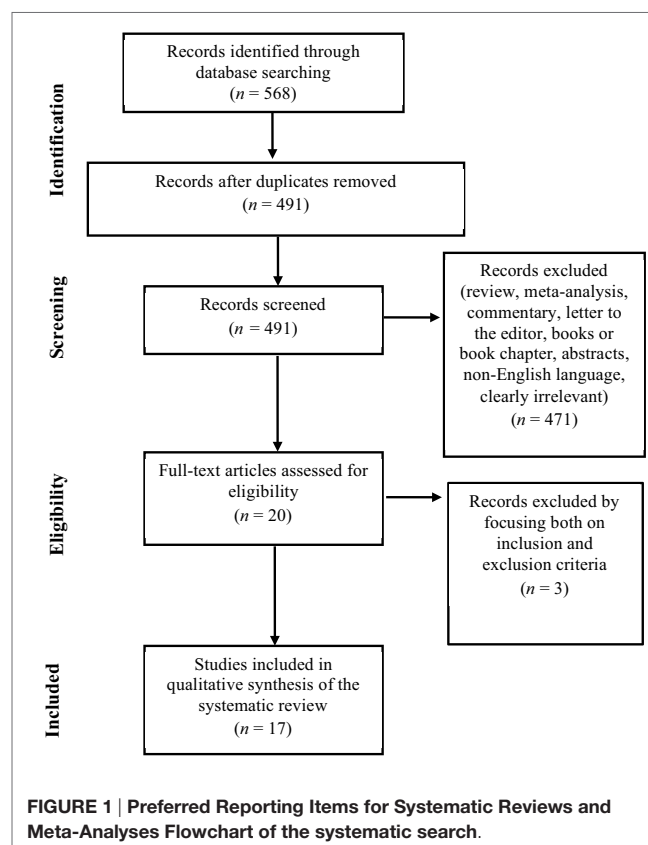
studies). Amer and Hamdan-Mansour (8), by investigating the psychosocial predictors of SI in subjects affected by chronic diseases (T2DM, cardiovascular diseases and cancer), found the highest "seriousness" component among those with T2DM.

Lee et al. (17), in a sample of 9,159 South Korean adults aged 40 years and over, observed a higher rate of SI in subjects with DM than in those without. The study also found an association of SI with the insulin regimen, a longer duration of DM

TABLE 1 | Distribution of the 17 relevant selected studies, including the reference, title, the population target, and the aims of the research.

Reference	Title	Population target and geographic location	Aims
Goldston et al. (7)	Suicidal ideation (SI) and behavior and non-compliance with the medical regimen among diabetic adolescents	$N = 91$ Patients with T1DM. United States	To examine the 1 year and lifetime prevalence of SI and suicidal behavior among adolescents with insulin-dependent diabetes mellitus (DM)
Amer and Hamdan-Mansour (8)	Psychosocial predictors of SI in patients diagnosed with chronic illnesses in Jordan	$N = 442$ Patients with T2DM. Jordan	To investigate the psychosocial predictors of SI among patients with chronic illnesses
Pompili et al. (9)	Quality of life and suicide risk in patients with DM	$N = 100$ Patients with T1DM or T2DM. Italy	To evaluate the perceived quality of life and its association with suicide risk in Italian patients with DM
Fuller-Thomson and Sawyer (10)	Lifetime prevalence of SI in a representative sample of Canadians with Type 1 diabetes	$N = 190$ Patients with T1DM. Canada	To compare the lifetime prevalence of SI among patients with and without T1DM
Ceretta et al. (11)	Increased prevalence of mood disorders and SI in Type 2 diabetic patients	$N = 996$ Patients with T2DM. Brazil	To evaluate the association of mood disorders, SI, and the quality of life in patients with T2DM
Handley et al. (12)	Research: educational and psychological issues SI reported by adults with Type 1 or Type 2 diabetes: results from diabetes MILES-Australia	$N = 3,338$ Patients with T1DM or T2DM. Australia	To examine the prevalence and correlates of SI in a community-based sample of adults with DM
Chung et al. (13)	SI and suicide attempts among DM: The Korea National Health and Nutrition Examination Survey from 2007 to 2012	$N = 3,846$ Patients with T1DM or T2DM. Republic of Korea	To evaluate the mental health of patients with DM and compared it with mental health in the general population
Lee et al. (17)	Risk of SI in diabetes varies by diabetes regimen, diabetes duration, and HbA1c level	$N = 9,159$ Patients with T1DM or T2DM. South Korea	To investigate patient subgroups based on the clinical characteristics of DM to evaluate risk factors for SI
Roy et al. (18)	Suicide attempts and ideation in African-American type 1 diabetic patients	$N = 725$ Patients with T1DM. New Jersey	To examine suicidality and its correlates in T1DM and controls through a semi-structured interview on attempted suicide
Davis et al. (19)	Risk of suicide in Australian adults with diabetes: the Fremantle Diabetes Study	$N = 1,413$ Patients with T1DM. Australia	To evaluate the risk of suicide in Australian adult with T1DM
Westling et al. (20)	High CSF-insulin in violent suicide attempters	$N = 74$ DM patients and MDD disorder. Sweden	To further clarify the role of insulin in patients with suicidal behavior
Löfman et al. (21)	Characteristics of suicide among diabetes patients: a population-based study of suicide victims in Northern Finland	$N = 2,489$ Patients with T1DM or T2DM. Finland	To investigate insulin suicides among DM patients
Avci et al. (22)	Suicide commitment with metformin: our experience with five cases	$N = 5$ cases DM patients with metformin treatment. Turkey	To present five patients who used high doses of metformin for suicide attempt
Myers et al. (23)	Brief report: depression and history of suicide attempts in adults with new-onset Type 2 diabetes	$N = 145$ Patients with T2DM. United States	To assess past suicide attempts in a cohort of adults with T2DM diagnosed within the prior 24 months
Han et al. (24)	Increased risk of SI in Korean adults with both diabetes and depression	$N = 17.065$ Patients with T1DM or T2DM. South Korea	To investigate the association between SI and DM in adults with and without depression
Radobuljac et al. (25)	Lifetime prevalence of suicidal and self-injurious behaviors in a representative cohort of Slovenian adolescents with Type 1 diabetes	$N = 126$ Patients with T1DM. Slovenia	To determine lifetime prevalence of suicidal and self-injurious behaviors in adolescents with T1DM compared with healthy controls
Corathers et al. (26)	Improving depression screening for adolescents with Type 1 diabetes	$N = 528$ Patients with T1DM. United States	To evaluate the prevalence of depressive symptoms and SI in a cohort of adolescents with T1DM

(≥5 years) and a poorer glycemic control (HbA1c levels ≥ 6.5). Another Korean study (13) also reported a marked increase in SI and suicide attempts among participants classified as having DM in comparison with controls. Moreover, mental health problems (depressive mood for two or more continuous weeks, SI, and suicide attempts) increased in association with blood glucose levels.

By focusing on the T1DM population and the risk of suicide attempts, Roy et al. (18) found that African-American T1DM patients were three to four times more likely to attempt suicide during their lifetime than subjects without DM. Davis and colleagues (19), by investigating the suicide risk and associated factors in an older diabetic Australian population, found also that if suicide is a rare event among diabetic adults, compared to the general population, a higher occurrence appeared in subjects with T1DM and a greater diabetes-related disease burden. A bivariate comparison showed also a significant association between suicide with higher presence of retinopathy and greater antidepressant use.

Finally, a previous study (20) measured insulin concentration in cerebrospinal fluid in 74 suicide attempters. The higher cerebrospinal fluid-insulin level detected among patients with a violent suicide attempt than in those with a non-violent attempt, and a similar cerebrospinal fluid–insulin level measured in subjects with or without major depressive disorder, permitted to conclude that cerebrospinal fluid-insulin is involved in violent behavior but not in major depressive disorder.

Suicide Commitment with Antidiabetic Medications

To confirm the prevalence of T1DM and T2DM in the suicide population and to analyze the suicide method adopted, Löfman et al. (21) conducted a study on a Finnish population. Of all suicide victims ($n = 2,489$) 3.1% had DM (T1DM = 34.6% and T2DM = 65.4%). Almost half of the T1DM victims chosen poison as the suicide method, and it was approximately twofold higher than victims without DM; also in T2DM, self-poisoning was more common compared to controls. Among T1DM victims, an insulin overdose was used by half of the self-poisoning cases (6 of 13), whereas by only two patients in the T2DM group (13%) and none in the non-diabetic reference group. Furthermore, during suicide, half of the victims with T1DM were under the influence of alcohol which, taken excessively, could contribute to the risk of hypoglycemia.

Finally, Avci and colleagues (22) described five cases in which subjects attempted suicide with high doses of metformin, an oral anti-hyperglycemic drug that causes a lactate accumulation. The study also describes the interactions of metformin with other drugs or ethanol that could increase the risk of, or cause, lactic acidosis.

Suicide Risk and Mood Disorders in DM

Several studies have shown significant associations between DM, mood disorders, and suicidality (see **Table 1** for a detailed description of reviewed studies).

In 2009, an Italian study conducted by Pompili et al. (9) observing a sample of 100 patients with T1DM and T2DM controlled

for mood disorders found that patients with DM perceived a poor quality of life, which was related to low self-efficacy, high hopelessness, and suicidality.

In 2012, by focusing on a clinical sample consisting of patients with DM and mood disorders, Ceretta et al. (11) demonstrated a high prevalence of depressive disorders, SI, and a poor quality of life in patients with T2DM receiving treatment with insulin.

Löfman and colleagues (21), using a sample of suicide victims, demonstrated the association between DM and suicide mediated by depression.

Myers et al. (23) provided further evidence supporting the prevalence of suicidality and mood disorders in patients with DM by demonstrating that the rate of past suicide attempts in currently depressed patients with DM is 21.8%.

Han et al. (24) investigated, in a large Korean sample, the presence of either DM or depression alone increased the likelihood of SI significantly compared with the general population, by 1.6- and 5.7-fold, respectively. When both conditions were present, the odds of SI were increased more than sevenfold. There was, however, no significant difference in the odds of SI between those with depression only and those with both depression and DM after controlling for factors such as age, gender, and BMI (24).

These results were confirmed by Handley and colleagues in 2015 (12) using a sample of patients with T1DM and T2DM. Particularly, the study showed that elevated rates of SI are largely accounted for by the presence of depressive symptoms, and social support was reported as a significant protective factor for ideations of suicide in these patients.

In order to compare the prevalence of SI in the diabetic South Korean population with that in people without DM, Lee and colleagues (17) compared depressive symptoms, stress, SI, and associated factors using a *chi*-squared test. Depressive symptoms seemed to predict SI, while higher household income, higher education, and being married/cohabiting seemed to play a protective role.

Suicide Risk in Adolescents with DM

Goldston et al. (7) studied the prevalence of SI and suicidal behavior among adolescents with DM in a sample of 91 outpatients. They found that the lifetime prevalence of SI in diabetic youths was 26.4% ($n = 24$ of 91), which appeared to be higher than the rates of the general population. Some clinical characteristics were associated to SI and suicidal behavior in adolescents with DM. The study, using the multivariate logistic model, showed that the duration of T1DM and the presence of psychiatric problems were related to SI in adolescent patients (7). Furthermore, the authors showed that SI during the previous year was related to non-compliance with medical treatment in 63.6% of the subjects; the authors also found that lifetime history of SI was strongly related to non-compliance with medical treatment in 62.5% of the subjects.

In 2009, a study conducted by Radobuljac et al. (25) found that adolescent females with DM reported a higher prevalence of SI compared to males ($p < 0.001$). The authors studied self-injurious behavior in their sample of 126 patients and observed

that 38% of those who committed acts of self-harm used the manipulation of the treatment as a means of self-harm (injecting higher doses of insulin to produce hypoglycemia or omitting insulin to produce hyperglycemia).

Corathers and colleagues (26), using a depression screening tool among patients 13–17 years of age, demonstrated that SI was endorsed in 7% of the sample assessed. In a previous study, Fuller-Thomson and Sawyer (10) had already observed a higher lifetime prevalence of SI among adolescents and adults with T1DM compared to those without, even after adjustment for age and sex; they confirmed the necessity of a consistent screening for SI and depression to promote early identification and intervention in this population.

DISCUSSION

Literature analysis has shown that the severity of DM can increase the risk of mental health disorders, such as depression and suicide risk. Suicide risk is a multifaceted issue that involves bio-psychosocial and cultural factors that interfere with the individual abilities of patients. Taking the potential clinical implications related to suicide risk in diabetic patients, the present study is a review manuscript aimed at systematically investigating the published original research reports evaluating the emerging clinical links between DM and suicidal factors.

Despite limited and contrasting studies, DM *per se* does not appear to be associated with SI and suicide. However, SI is more prominent among patients with DM than in those without [i.e., Ref. (11, 24, 26)], and this prevalence is associated with the depressive symptoms and the severity of illness, such as duration of DM, poor glycemic control, use of insulin treatment (17). In line with these results, a previous study in 2012 (11) showed that patients with more comorbid conditions were more likely to report depressive disorders and SI versus individuals without DM. Chung et al. (13) further demonstrated that depressive mood, SI, and suicide attempts increased in association with blood glucose levels. Furthermore, in 2004, one study (20) measured insulin concentration in cerebrospinal fluid in 74 suicide attempters to clarify the role of insulin in major depressive disorder and violent suicide attempt and found that cerebrospinal fluid insulin is involved in violent behavior but not in major depressive disorder.

When taking into consideration, the duration of DM as a risk factor for suicide, several studies have investigated the incidence of suicidal behavior (i.e., ideation, attempts, and acts) among adults and elderly patients with T1DM (12, 19). Other studies have highlighted that T1DM patients were three to four times more likely to attempt suicide during their lifetime than subjects without DM (18) and that a higher occurrence appeared in subjects with T1DM and a greater diabetes-related disease burden (10, 19).

Chronic disease causes a major emotional impact, which appears most dangerous during adolescence. When focusing on adolescents with T1DM, a hopeless feeling regarding the illness might be associated with risk of suicide attempts, and also with neglect of health care and lack of motivation to adhere to medical instructions (25). The lifetime prevalence of SI in diabetic youths

was 26.4% (7); among patients 13–17 years of age, it was demonstrated that SI was endorsed in 7% of the sample assessed (26).

By focusing on clinical samples consisting of patients with DM and mood disorders, several studies evaluated the association between suicidality and DM. Depressive symptoms were the most prominent predictor of SI in diabetic patients (17). Given the relationships between depression and suicidality, and between depression and DM, some studies examined the mediation role of depressive symptoms, finding that depression mediates the relationship between DM, suicide (21) and non-compliant behavior with the medical regimen (17). In support of these findings, recent studies observed that the coexistence of DM and depression was associated with a much higher risk factor for SI (12, 23) and suicide attempts (13) than with DM alone. In fact, it has also been reported that subjects with an increased prevalence of endocrine abnormalities such as diabetes may be at increased risk of depression and/or anxiety disorders (27). Major depression is also correlated with well-known deficiency in serotonergic neurotransmission, as reported by Müller et al. (28). Neurotransmitter alterations and immune dysregulation lead to an increased generation of proinflammatory cytokines which play a crucial role in anxiety and depression (28, 29). It is interesting that patients with schizophrenia and other severe mental disorders have an increased risk of developing diabetes and hyperlipidemia and initiating medication for these diseases (30).

These findings are important, suggesting that the higher prevalence of suicidal risk observed among people with DM may be attributable to the increased prevalence of depressive symptoms. On the other hand, the study conducted by Pompili et al. (9), observing a sample of patients with DM controlled for mood disorders, found that patients with DM perceived a poor quality of life, which was related to low self-efficacy, high hopelessness, and suicidality. In other terms, the results indicate that DM is associated with an increased risk of suicide, independently from the severity of depressive condition (9).

According to Gois et al. (31), depressive temperament may also be important to better understand the interplay between depression and diabetes.

Protective factors for suicidal risk were higher household income, higher education, social and emotional support (8, 12), and marriage or cohabitation. Being single was a risk factor for suicide (17); furthermore, suicide risk includes also gender, developmental, and substance abuse determinants (18, 21, 23). Recent studies have raised concern on the role of insulin and other antidiabetic medication use as a suicide method in patients with DM (21, 22). Having the means close at hand to commit suicide can represent a major risk for these patients.

Understanding the clinical features that can lead the patient with DM to have SI or suicidal behavior is an important objective to identify patients at higher risk and to promote well-being and adhering to antidiabetic medication. The present review of the relevant literature supports the need for further investigation into the severity and nature of disabilities associated with DM and other chronic diseases (32) and their relationships with SI and suicidal behaviors. From the clinical point of view, when treating patients with DM, it is important to emphasize that only a very

small minority of patients eventually dies from suicide. However, given that DM *per se* is known to increase the risk of suicidal behavior and that depression is one of the most important single risk factors for suicide, it is important to be highly aware of co-occurring depressive symptoms in patients with DM.

These findings have implications for health-care professionals, pointing out the importance of adequate psychological screening and action plans for appropriate follow-up to reduce the suicide risk in diabetic patients.

AUTHOR CONTRIBUTIONS

All authors participated in the concept and writing of this manuscript; approved the final version of the manuscript.

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Suicide during Perinatal Period: Epidemiology, Risk Factors, and Clinical Correlates

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Perinatal period may pose a great challenge for the clinical management and treatment of psychiatric disorders in women. In fact, several mental illnesses can arise during pregnancy and/or following childbirth. Suicide has been considered a relatively rare event during the perinatal period. However, in some mental disorders (i.e., postpartum depression, bipolar disorder, postpartum psychosis, etc.) have been reported a higher risk of suicidal ideation, suicide attempt, or suicide. Therefore, a complete screening of mothers' mental health should also take into account thoughts of suicide and thoughts about harming infants as well. Clinicians should carefully monitor and early identify related clinical manifestations, potential risk factors, and alarm symptoms related to suicide. The present paper aims at providing a focused review about epidemiological data, risk factors, and an overview about the main clinical correlates associated with the suicidal behavior during the pregnancy and postpartum period. Practical recommendations have been provided as well.

Keywords: suicide, suicidal ideation, suicide attempt, pregnancy, perinatal period, puerperium, postpartum

INTRODUCTION

Suicide was worldwide ranked as the 14th leading cause of mortality and morbidity, and it is expected to increase by 50%, becoming the 12th leading cause of mortality by year 2030 (1). Suicide represents a major public health problem, with more than 1,000,000 suicides worldwide (2). A preexisting vulnerability, such as a family history of suicide, impulsivity, and previous and/or current psychiatric diagnoses, may be precipitating risk factors for suicidal ideation (SI) and behavior (3, 4). Specifically, major depressive disorder (MDD) and other affective disorders may represent

strong risk factors for suicide (2). Furthermore, SI and a history of personal suicidal behavior are among the most salient short- and long-term risk factors for suicide (2). The National Institute of Mental Health (NIMH) Developing Centers for Intervention and Prevention of Suicide defined the SI as the wish to die, thoughts of killing oneself, and the intent to kill oneself (5). Thoughts of killing oneself are thoughts, beliefs, images, voices, or other cognitions about intentionally ending one's own life (suicide) and may include the intent to act on such thoughts (2). SI or thoughts may be often associated with suicide attempts and completions (6, 7).

The identification of SI and behavior, as well as high-risk individuals, requires an adequate suicide screening assessment (2), particularly during the perinatal period. Generally, peripartum (including conception, pregnancy, and postpartum) may be a period of considerable vulnerability to MDD and affective disorders as well as it is frequently associated with the onset and/ or recrudescence of a psychiatric illness (8, 9). Overall, approximately 10–15% of newly delivered women experience a major depressive episode; while around 50% of women with a previous mood disorder and 70% with a family history of postpartum psychosis will develop a relapse and/recrudescence following a subsequent delivery (10).

Although suicides and suicidal attempts occur at a lower rate during pregnancy and the postpartum period than in general population (10), the prevalence of SI or thoughts ranges from 5 to 14% (9, 11, 12) and, sometimes, it may result in a suicide attempts and completions (6, 11). In fact, perinatal suicidality, which comprises completed suicides, suicide attempts, SI, and thoughts of self-harm, is nowadays considered one of the leading causes of maternal mortality in the first 12 months postpartum (11, 13–15). Furthermore, it has been documented that women reporting SI and thoughts during pregnancy or during the postpartum period had higher odds for developing postpartum depression (16, 17).

The increasing need of a careful assessment and screening of pregnant and nursing women's mental health should also take into account SI, thoughts of suicide, and thoughts about harming infants as well. Clinicians should carefully monitor and early identify related clinical manifestations, potential risk factors, and alarm symptoms related to suicide. Therefore, the present paper aims at providing a focused review about epidemiological data, risk and protective factors, and an overview about the main clinical correlates associated with the suicidal behavior during the pregnancy and postpartum period.

MATERIALS AND METHODS

The present review was carried out in accordance to the methods recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18). Studies were identified searching the electronic databases MEDLINE, Embase, PsycINFO, and the Cochrane Library. A combined search strategy of free text terms and exploded MESH headings for the topics of suicide and perinatal period as following: ((*suicide* [Title/Abstract] OR *suicide attempt* [Title/Abstract] OR *suicidal ideation* [Title/Abstract]) OR *puerperium*

[Title/Abstract]). ("*suicide*" [MeSH Terms] OR "*suicide*" [Title/Abstract]) AND ("*pregnancy*" [MeSH Terms] OR "*pregnancy*" [Title/Abstract]) OR ("*postpartum period*" [MeSH Terms] OR "*postpartum*" [Title/Abstract] OR "*postpartum period*" [Title/Abstract]) OR Studies published in English through March 20, 2015 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field and or manual search. Identified studies were independently reviewed for eligibility by two authors (Laura Orsolini and Alessandro Valchera) in a two-step based process; a first screening was performed based on title and abstract, while full texts were retrieved for the second screening. At both stages, disagreements by reviewers were resolved by consensus. Data were extracted by two authors (Laura Orsolini and Alessandro Valchera) and supervised by a third author (Cesario Bellantuono) using an *ad hoc* developed data extraction spreadsheet. With the initial set of keywords, 1,567 studies were identified. Of these, 219 were excluded because they were not in English, 1,219 were excluded because they were either duplicated or not consistent with the aims of the review. Of these remaining, 129 were relevant studies. Data were then analyzed according to the epidemiology, risk factors, and clinical correlates.

RESULTS

Epidemiology

A recent 15-year (1997–2012) retrospective study, from the UK National Confidential Inquiry that evaluated all suicides by people who had been in contact with psychiatric services, compared suicides among perinatal and non-perinatal women. Findings reported a suicide in perinatal period in 2% of women aged 16–50 years and in 4% among women aged 20–35 years (19). A register-based cohort Danish study reported, among women with severe postpartum psychiatric disorders, a suicide risk drastically increased when compared with mother with no psychiatric history, by suggesting a strong correlation between perinatal suicidality and psychiatric conditions (20). A retrospective cohort study carried out on perinatal women at 24–28 weeks of gestation and 6 weeks postpartum reported an SI in 3.8% of the women screened with the Edinburgh Postnatal Depression Scale (EPDS), with only 1.1% with a high risk for suicide (i.e., with plan, intent, and access to suicidal means) (21). A register-based Swedish study reported a maternal suicide ratio of 3.7 per 100,000 live births for the period 1980–2007, being higher among women born in low-income countries (22). An audit cohort study evaluated 225 women afferent to a UK perinatal mental health team over a 12-month period. Suicide attempts occurred among women with a previous postpartum depression in 24–49% (10). A prospective study evaluating thoughts of self-harm and SI during the postpartum period among women with mood disorders reported thoughts of self-harm and SI, respectively, in 16.97 and 6.16% of the sample, during the 1-year postpartum period (23). A US community-based study reported a 14-day prevalence of antenatal SI of 2.7% (24). Findings from PND-ReScU reported a rate ranging 6.9–12% of suicidality during pregnancy, while a rate of 4.3–8.6% during the postpartum

period, depending on the assessment tools (25). Women who had major or minor depressive episode during pregnancy showed a prevalence of suicidality of 26.4 and 34.1%, while it was 18.4–30.6% during the postpartum period (25). A prospective cohort study evaluated the prevalence of SI as measured by the EPDS in a primary care population of women at 6–8 weeks postpartum screened for postnatal depressive symptoms. The authors reported that 4% of women in the community had SI occurring sometimes or quite often, while 9% reported any SI (26). Suicide attempts appear to be more frequent in the 1st and 12th months after delivery (27).

Furthermore, according to the NSW Australian Department of Health evaluating a 6-year time period, 73% of suicides by women within 1 year of birth were conducted by violent means (i.e., jumping from high place, lying in front of moving objects, gunshot, strangulation, and suffocation) (14, 22).

Risk Factors

Suicides in the perinatal period appear to be more likely occurring among women who are less likely to be receiving any active treatment at the time of death, younger maternal age, unpartnered relationship status, unplanned pregnancy, non-Caucasian race, with shorter illness duration, preexisting, and/or current psychiatric diagnosis (9, 19, 21, 24, 26, 28–34). Regarding the delivery, severe vaginal laceration was positively correlated with SI risk, while planned cesarean delivery was negatively associated (21). Furthermore, experiencing an intimate partner violence, including emotional abuse, physical, and/or sexual violence, seems to be more likely associated with suicidal thoughts during pregnancy and after childbirth (29, 35–37). A cross-sectional study evaluating a sample of pregnant teenagers found a significant association of suicidality with the 18- to 19-year-old subgroup, low education, prior abortion, physical abuse within the last 12 months, and current psychiatric disorders (38). Women who did not desire or had mixed feelings about being pregnant experienced a higher risk of SI (9). A case–control study comparing 520 women who were hospitalized for a postpartum suicide attempt with 2,204 control women who were not hospitalized for a postpartum suicide attempt concluded that maternal complications (i.e., labor, delivery complications, cesarean delivery, etc.) and adverse infant outcomes (i.e., preterm delivery, low birth weight, congenital malformations, etc.) were not associated with a hospitalization for a suicide attempt within 1 year after delivery (27). A cross-sectional analyses carried out on 234 pregnant women enrolled in a prospective cohort study in Brazil reported a higher likelihood of suicide risk among women with higher arachidonic acid and adrenic acid levels (39). Women who have had a postpartum psychiatric admission have a 70 times greater risk of suicide in their first postpartum year (40, 41).

All risk factors are summarized in **Table 1**.

Clinical Correlates

Women who reported antenatal SI were more likely to experience comorbid antenatal MMD and antenatal panic disorder (24). In particular, preexisting and/or current psychiatric diagnoses

TABLE 1 | Risk factors for perinatal suicidality.

Risk factors for perinatal suicidality	
Individual risk factors	• Younger age (9, 19, 21, 24, 26, 28–34) • Being unmarried (9, 19, 21, 24, 26, 28–34) • Personal and/or family history of psychiatric disorders (9, 19, 21, 24, 25, 28–34, 42–46) • Personal and/or family history of suicidal attempt or suicidal ideation (9, 19, 21, 24, 25, 28–34, 42–46)
Socioeconomical risk factors	• Family conflict (35–37) • Exposure to (domestic) physical/psychological violence (35–37) • Loneliness and lack of social/family/partner support (35–37) • Partner who rejected paternity (35–37)
Environmental risk factors	• Social and gender inequalities (28, 37) • Social and racial discrimination (28, 37) • Belonging to an ethnic or religious minority (28) • Crowded or inadequate housing (24, 28, 37) • Living in rural areas (37) • Exposure to disaster, conflict, war (24)
Gestational risk factors	• Unwanted/unintended pregnancy (9, 17) • Nulliparity (32)
Clinical risk factors	• Previous history of psychiatric disorders (9, 19, 21, 24, 25, 28–34, 42–46) • Previous history of suicidal attempt or suicidal ideation (9, 19, 21, 24, 25, 28–34, 42–46) • Psychiatric comorbidity (9, 19, 21, 24, 25, 28–34, 42–46) • Shorter illness duration (9, 19, 21, 24, 25, 28–34, 42–46) • Psychological symptoms (i.e., premenstrual irritability, perceived pregnancy complications, negative attitude toward the pregnancy, anxiety about birth, distancing pattern of coping, etc.) (9, 21)

represent strong risk factors, being MDD, comorbid anxiety disorders, sleep disturbances, or a substance and/or alcohol use disorder the most frequently identified (9, 19, 21, 24, 25, 28–34). A positive correlation with antenatal depression, lifetime bipolar disorder, and any current anxiety disorder as well as Beck Depression Inventory (BDI) scores ≥15 and EPDS scores ≥11 has been reported (42). Furthermore, poor subjective sleep quality was associated with increased odds of SI as well (43). Women with a dysphoric-dysregulated temperament are more likely to be at risk of suicide after delivering (44). Generally, an abrupt discontinuation of psychotropic medications during pregnancy has been linked to a higher risk of maternal suicidality (45). A history of a previous suicide attempts represents a strong risk for perinatal suicidality (46).

DISCUSSION

Although the incidence of suicide among women who have given birth during the past 12 months is lower than that of women who have not given birth, suicide still remains one of the most common leading causes of maternal death during the 1 year following delivery (22, 40, 47). Perinatal suicide occurs mainly through more violent methods compared to suicide in non-pregnant women (11) and at a higher rate among women with a previous or current mental illness (11, 16).

Despite very limited and contrasting studies, SI and suicides appear to be more likely to occur during pregnancy rather than postpartum (25).

However, the most important cognitive risk factor to consider in determining a risk of making a suicide attempt or dying by suicide is SI. SI predicts later suicidal behavior (including suicide and suicidal attempt) (48).

Therefore, a preventive and careful assessment, screening, and identification for SI should be included during the perinatal period (**Table 2**). However, a specific screening for suicide and SI is almost rare, mainly due to time constraints in prenatal care clinics, the lack of proper screening tools, and the missing collaboration between gynecologists/pediatricians and Mental Health's professionals (24). In fact, SI is usually assessed along with depression screening rather than with specifically designed tools (44, 49–51), such as the Scale for Suicide Ideation (SSRI), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Suicide Probability Scale (SPS) (2). Among the most widely used antepartum depression screening instruments, the Patient Health Questionnaire-9 (PHQ-9) (52) and the EPDS (51) represent easy tools that may be helpful both in primary care and community maternity services to screen perinatal depressive and anxiety disorders as well as SI (53, 54). PHQ-9 is a 9-item, depression screening scale (52). Item 9 ("*thoughts that you would be better off dead, or of hurting yourself*") of the PHQ-9, which assesses SI, has been correlated with item 10 of the EPDS (55). Subjects who answered "*several days,*" "*more than half the days,*" or "*nearly every day*" at item 9 were evaluated at risk of SI. While the EPDS (51), a 10-item self-report questionnaire, is usually administered to screen for postnatal depression. SI was defined as an answer of "*sometimes*" or "*yes, quite often*" to question 10 of the EPDS "*The thought of harming myself has occurred to me.*"

TABLE 2 | Risk assessment.

Risk factors for perinatal suicidality

Clinical risk assessment (9, 19, 21, 24, 25, 28–34, 42–46, 49–51)	• Current presentation of suicidality • Psychiatric disorders • History of current illness • Current medications • Psychosocial environment • Current alcohol and/or drug use • Individual strengths and vulnerabilities
SI risk assessment (9, 19, 21, 24, 25, 28–34, 42–46, 49–51)	• Nature • Timing • Persistence of the desire • Intent of SI
Suicide plan risk assessment (44, 53–55)	• Lethality of the plan • The level of detail and violence • The level of access to means (e.g., weapon or store of medication)
Current or previous suicidal attempt risk assessment (9, 19, 21, 24, 25, 28–34, 42–46, 49–51)	• Timing • Intent • Method • Consequences of the suicidal attempt
Estimating suicide risk (24, 44, 49–51)	• Identification of protective and risk factors • Determination of methods to mitigate/strengthen these risk/protective risks

Further assessment tools may comprise the BDI at item 9 (50) and the Hamilton Rating Scale for Depression (HRSD) at item 3 (49, 56). The BDI is a 21-item self-rated depression scale widely used to screen for depression. The HRSD is a clinician-rated scale. Girardi et al. (44) included the Suicidal History Self-rating Screening Scale in their perinatal assessment of women at risk of suicide.

Furthermore, women who are depressed and/or psychotic for suicide should be assessed for suicide as well. In presence of a SI or suicidal thought, clinicians should promptly developing a safety plan and referring to a specific psychiatric assessment as well as follow up the patient. In some case, hospitalization must be required as well. Urgency of referral depends on several factors including: whether SI is accompanied by a plan, whether there has been a history of suicide attempts, whether symptoms of a psychotic disorder are present. A risk assessment is helpful for identifying mothers at *low-risk* (SI or thought present, with a plan), *medium-risk* (SI with a plan or history of suicide attempt, without an immediate intent), or at *high-risk* (SI with an immediate intent). Warning signs of the risk of imminent suicide may include "feeling trapped," "worthless, hopelessness, talking about death, writing a will, hoarding medication," etc.

Suicide ideation is more likely associated with unplanned pregnancies, current mood and/or comorbid anxiety disorders, previous SI and/or suicidal attempt, and younger maternal age (9, 19, 21, 24, 26, 28–34).

Generally, screening during the perinatal period (particularly during pregnancy) represents an essential clinical tool for identifying women at higher risk of perinatal suicidality. Long-term identification and support of women at particular risk of maternal death due to suicide in the first year following birth may help lower the incidence of late maternal deaths. Overall, it should be proposed to clinicians, particularly gynecologists and primary care physicians, to ask to all pregnant women about their personal mental health history and family history. Women with a previous history of mental disorder (particularly, bipolar and MDDs as well as psychoses) should be offered a mental health assessment antenatally and managed by a psychiatrist. In addition, a regular interview on lifetime SI should be performed. Furthermore, mothers should be regularly monitored and supported for at least 12 months following delivery.

AUTHOR CONTRIBUTIONS

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Suicide in the Early Stage of Schizophrenia

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Suicide is a relevant leading cause of death among patients affected by schizophrenia. Even if suicidal ideation may be present in different stages of disease, some differences have been described between the risk of suicide in patients experiencing first episode of psychosis and those with long-term schizophrenia. It is particularly higher during the first year of illness and reaches a steady decline over the following years. Suicidal ideation and attempts may also be common among subjects with subthreshold psychotic experiences. Factors associated with the risk of suicide in the early phase of schizophrenia are previous suicidal attempts and social aspects: the lack of social support and stable relationships, social drift after the first episode, and social impairment. Also, several psychotic symptoms (suspiciousness, paranoid delusions, mental disintegration and agitation, negative symptoms, depression and hopelessness, and command hallucinations) and substance abuse are associated with higher risk of suicide. It has been described that perfectionism and good levels of insight among individuals who have recently developed psychotic symptoms are significantly associated with higher numbers of suicidal attempts. Moreover, recent evidences show that prefrontal cortex-based circuit dysfunction may be related to suicide in the early stage of schizophrenia. This narrative review summarizes available evidences on suicide in the early stage of schizophrenia and deals with issues to be further studied and discussed.

Keywords: suicide, suicidal attempts, first episode of psychosis, schizophrenia

INTRODUCTION

The risk of suicide can be valued in a multistage continuum, which includes suicidal ideation (ideation, intent, and plans), as a critical initial step, attempted, and completed suicide. The long-term suicide risk in subjects without mental disorders is 0.3%, whereas the risk measured among mentally ill patients ranges from 3.4% for people affected by one mental disorder to 6.2% for people reporting more than one psychiatric disorder: each additional psychiatric diagnosis seems to contribute significantly to increase risk of suicide (1). Suicidal ideation, obviously, is a predictor of suicide and the basis of suicide prevention in schizophrenia (2). Also, suicide is a relevant leading cause of death among patients affected by schizophrenia spectrum disorders, and the rate of attempted suicide in psychotic patients ranges from 10 to 50% (3, 4). Individuals affected by schizophrenia (40–79%) have had suicidal ideation at least one time during the course of illness (5, 6). Also, in schizophrenia, the estimated suicide rate is 579/100,000 person years and the lifetime risk of suicidal death is 5.6% (7, 8). Anyway, rates of completed and attempted suicides among schizophrenia patients are lower

than those reported for patients affected by other psychiatric conditions: 0.24 and 0.74 per 100 person years, respectively (9). In particular, the suicide-related mortality is higher among subjects recently diagnosed with schizophrenia ($\leq$5 years from diagnosis) (9). In fact, the suicide risk is twofold higher at the onset of psychotic illness than in the later course (8, 10, 11). The first episode of psychosis (FEP) can be divided in four phases: (a) prodromic phase or emerging psychosis, (b) untreated psychosis (UP) (the duration of untreated psychosis is labeled as DUP), (c) acute psychosis and its treatment, and (d) post-psychotic recovery. Each phase is characterized by different risk of suicide as summarized in the **Table 1**. In the first phase (that may be called "at-risk mental state" or "prodromic"), suicidal behaviors may be due to the distress caused by unfamiliar emerging pre-psychotic experiences. The delay in accessing the mental health-care system and starting treatment (called DUP) may greatly contribute to increase suicide risk among schizophrenia patients at FEP (12). During the acute phase of schizophrenia, psychotic experiences (distressing delusions, command hallucinations, or passivity phenomena) and feelings, such as fear, stigma, and loss (in patients with some degree of insight), are relevant factors for suicide. Risk of suicide during the following phase of post-psychotic recovery may be related to the loss of role and function mostly due to neurocognitive sequelae (13).

METHOD

This narrative review provides an overview on the links between schizophrenia, FEP, and suicide. We selected and commented significant articles published on the topic during the last decades (from 1997 to 2016) searching through PubMed, Cochrane Library, and Web of Science/Web and Google Scholar. Key words

employed for research were "First Psychotic Episode and Suicide," "Schizophrenia and Suicide," "FEP and Suicide," "FEP," "Suicide," "Schizophrenia self-injury," and "Schizophrenia and self-harm."

INCIDENCE OF SUICIDE IN FEP

A British 10-year follow-up study showed that subjects affected by FEP have died from unnatural causes more than general population (OR: 13). Suicide was recognized to be the cause of these deaths, and most of the suicides occurred in the first 2 years (14). According to the available evidences on rates of suicide in first-admission psychotic patients, 23% of these have already attempted suicide, and 15% attempted it before the hospitalization (15). Recently, some authors aimed to test the progress in the field of suicide prevention and described the change in a 20-year period of suicide risk among FEP schizophrenia patients belonging to the same catchment area. It was found that suicide risk decreased over the two decades with a reduction of suicide rate from 11.0 to 2.4% (4, 11). These data may suggest that early intervention and therapy improve the suicidality among FEP patients, even if they may attempt suicide before their contact with any mental health service: in fact, mortality rates may be underestimated because of complete suicides committed before seeking professional help (8). In addition, the prevalence of deliberate self-harm (DSH) behaviors before psychosis is about 18.4% (16).

SUBTHRESHOLD PSYCHOTIC EXPERIENCES AND SUICIDE IN SCHIZOPHRENIA

In the last decades, the research highlighted the importance of early intervention of FEP in order to reduce the DUP. Longer DUP, in fact, is associated with poor outcome in schizophrenia with higher prevalence of suicidal behaviors (17). A Norwegian study showed that, in the early phases of FEP, 38.8% of patients reported suicidal ideation and 25.9% attempted suicide before any treatment (17).

Authors from the *Bonn School* suggested the classification of "basic symptoms" of psychosis, which are subtle, subclinical, and detectable at an early stage such as distressing self-experienced disturbances in perception, thinking, memory, motility, mood, sense of awareness, and mastering (18, 19). Authors underline the importance of detecting these symptoms in the early stage of psychosis to reduce the period of untreated illness (DUI).

A new psychopathological framework called attenuated psychosis (APS) disorder concerning subthreshold psychotic symptoms in youths was included in the Section 3 of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, as a new putative disorder. The criteria specify that symptoms of APS are sufficiently distressing to call for clinical attention and very helpful to identify young people at risk for psychosis.

The early stages of psychosis were also labeled as "ultra high risk (UHR)," "at risk mental state (ARMS)," and "clinical high risk (CHR)." It is well known that self-harm behaviors and suicidality

TABLE 1 | Risk of suicide during the first psychosis episode (FEP) phases.

Phase	Incidence/epidemiology	Possible risk factors
Prodromic phase or emerging psychosis	About 90% of the young people meeting criteria for an at-risk mental state report suicidal ideation (91)	Distress caused by unfamiliar emerging pre-psychotic experiences
Untreated psychosis (UP-phase) and duration of untreated psychosis (DUP)	Most of patients report suicidal risk during this phase, and 25% have already attempted suicide before seeing a psychiatrist. Rate of completed suicides during the UP is very high (92)	The average delay in accessing health-care system during this phase is 1 year. Suicidality is higher when DUP is longer
Acute psychosis and its treatment (phase)	11% of suicide attempts in the FEP are associated with hallucinations, fear, shame, stigma, guilt, loss, rejection, and despair (76)	Patient's hallucinations, fear, shame, stigma, guilt, loss, rejection, and despair
Post-psychotic recovery (phase)	After an acute episode, 15% of the patients experience high suicidality for the following 18 months (93–96)	Even if the symptoms of psychosis may remit in this phase, neurocognitive deficits may have an impact on studying, working, and recreational activities

are highly prevalent in the UHR population, with rates similar to those observed in samples diagnosed with psychotic disorders (20). In addition, about 50% of young people recognized to be CHR for psychosis have reported current suicidal thoughts (21, 22). The prevalence of suicidal ideation among these samples is 42.9%, and there may also be less severe parasuicidal ideation (22).

A meta-analysis of factors associated with DSH shows that the pooled proportion of patients who reported DSH before any treatment for FEP, during the period of UP, and during the period of clinical follow-up between 1 and 7 years from the clinical diagnosis, was, respectively, 18.4, 9.8, and 11.4% (23).

Psychotic-like experiences (PLEs) are common in the general population and may be associated with poor social outcomes, even if there is no diagnosed psychotic disorder (24). Also, they are important but under-recognized markers of risk for severe psychopathology, including multimorbidity, poor functioning, and suicidal behaviors in young people attending the mental health-care services: in particular, individuals with subthreshold psychotic experiences are at increased risk for suicidal thoughts and behavior, similar to those with schizophrenia and other psychotic disorders, but it is unclear whether the level of risk varies with different types of PLEs (25). Moreover, self-reported auditory hallucinations are associated with twofold risk of suicidal ideation and suicidal plans and fourfold risk of suicide attempts in a non-clinical sample of young adults compared with the general population (26). Hypomania, thought control, paranoia, strange experience, and auditory hallucination in subject without definite psychosis were significantly associated with higher suicidal ideation and suicide attempt (ORs ranging from 3.13; 95% CI 1.99–4.93 to 4.03; 95% CI 1.56–10.42) (27). Furthermore, recent studies demonstrated that only a lifetime history of perceptual abnormalities and persecutory ideation are associated with a higher risk of lifetime suicidality, instead, bizarre experiences were not associated with any suicide variable (28). In conclusion, all-cause mortality is associated with lifetime psychotic experiences among schizophrenia patients over a 24- to 27-year follow-up period (after adjustment for sociodemographic characteristics and psychiatric diagnoses), and suicide seems to report a particularly high hazard ratio (9.16, 95% CI 3.19–26.29) (24).

RISK FACTORS

Several studies have been carried out on predictors of suicide in patients with schizophrenia in order to improve early detection of suicide risk and to provide suggestions for prevention (11).

Age of Onset
The relationship between suicide risk and age of onset of psychotic symptoms is complex. In a recent study conducted in a psychiatric unit for adolescents, most of teenagers who attempted suicide were diagnosed with schizophrenia spectrum disorder (29). Some studies have reported a higher risk of suicide in patients with earlier age of psychotic onset (30–32), whereas some other authors have found a relationship with later age of onset of psychosis (33–36): in all studies, age of onset is considered the only independent risk factor for suicide, with risk of suicide increasing by 1.1% per year (4, 33, 35, 36). Individuals who experience a later

onset of psychosis may find it more difficult to accept since psychosis may impair their previous functioning, plans, and careers (4). Also, patients with a later age of onset in Singapore reported lower risk of suicide probably due to the fact that young people mostly live with parents throughout the years of schooling, and the family environment can be a protective factor against the risk of suicide (34). In addition, it is of interest that several other studies failed in finding any relationship between suicide risk and age of onset of psychotic symptoms (37, 38).

Duration of Untreated Psychosis
As stated above, longer DUP is one of the most commonly reported risk factors of poor outcome and suicide among schizophrenia patients (34). Melle et al. (12) showed that patients coming from a community without an early detection program of FEP had a higher risk of suicide if compared with those coming from "early detection communities" and concluded that early detection reduces the DUP and the rate of suicidal behaviors. They also suggested that early engagement of patients in a treatment program seems to have an independent effect on suicidality beyond any DUP (12). Clarke et al. (39) confirmed that individuals with a longer DUP may have a poorer outcome of illness that is associated with higher suicidality. Moreover, in a recent observational study based on a 10-year period of observation, the association between time for remission from psychosis and mortality was studied and found to be statistically significant when adjusted for age at baseline and sex: authors point out that mortality is not only related to DUP but also to other demographic (e.g., sex and age), personal, and outcome factors (including time for remission), and mortality for "unnatural death" may include not only suicides but also accidents (40).

Gender
Contradictory gender patterns in suicidal behaviors among patients with FEP have been found. Some of these showed no relation with suicide risk, suggesting that the severity of a clinical condition could "override" gender differences in suicidal behaviors (4, 22, 34). In some studies, males seem to be more suicidal than females (41–43), whereas some other reports show that female patients at FEP may show higher risk of suicide and suicidal behaviors (12, 30, 32).

Living Situation
Studies show that only 20% of the patients who attempted suicide report a comfortable living situation; in most of the cases, there may be a concern regarding loneliness: that may suggest that living with others may be a protecting factor (4). In addition, some authors found an increased risk for suicide in patients who experienced the fear of losing their partner or social position (44). In fact, it is clinically relevant to focus psychotherapeutic interventions on the feeling of loss. It is of interest that the risk of unnatural-cause mortality is reduced by 90% when there is a family involvement at intake or first contact with mental health-care services (14). Further researches are also needed because family involvement and family cohesion are relevant factors that impacts on outcome of illness as well as socioeconomic status, level of education, etc. (14).

It would also be very helpful to integrate and include families and caregivers in the early intervention programs in order to improve the outcome of FEP (40).

Cognition and Education

Several evidences report that higher education or higher cognitive functioning is associated with an increased risk of suicide in FEP (2, 4, 36, 45, 46). In particular, some of these studies described the relationship between neurocognitive variables and suicidality in patients with schizophrenia spectrum disorders. Nangle et al. have tested suicide attempters and non-attempters with an extensive neuropsychological battery examining premorbid and current general cognitive functioning, episodic memory, and executive functioning. They found that attempters have higher cognitive functioning than non-attempters. Specifically, higher levels of executive functions may influence the ability to plan suicidal behaviors (31). This is in agreement with previous researches showing that higher cognitive functions, in particular, attention and psychomotor speed, verbal fluency, verbal memory, working memory, and executive function, are associated with greater suicidality (47). Nevertheless, recently Barrett et al. have shown that among patients with schizophrenia spectrum disorders, there are no significant differences in neurocognitive functioning between suicide attempters and non-attempters (17). Even if neural dysfunctions responsible for suicide risk are still obscure, some authors have proposed that the prefrontal cortex (PFC) is involved in suicide based on neuroimaging and post-mortem studies. In particular, PFC activity during the goal representation (an important competency of cognitive control) seems to be related to long-term suicide risk in recent-onset schizophrenia, and suicidal behaviors may derive from impairments in premotor cortex support of action planning as an expression of control (48).

Moreover, Björkenstam et al. found a higher risk of suicide among patients who had completed compulsory school. Some other evidences showed that poorer school performance seems to increase the risk of suicide in the general population (49, 50). This may suggest that patients with higher education may feel more stigmatized and shameful when developing a mental disorder (44) and that this may lead to higher risk of suicide (50).

Psychotic Symptoms in FEP and Suicide

It has been inconsistently shown that negative symptoms may increase suicidal experience in CHR for psychosis individuals (4, 5, 22, 51). Some other authors point out that patients with prominent negative symptoms, in particular, deficits in emotion expressivity, may have significantly impaired ability to experience emotional distress caused by the illness: this may probably reduce the likelihood of developing a sense of hopelessness and suicidal ideation (2). Also, negative symptoms commonly overlap with depressive symptoms, and it is clinically relevant to distinguish the relationship between suicidal ideation and negative symptoms and/or depression among FEP patients. Gill et al. found that negative symptoms remained significantly correlated with severity and intensity of recent suicidal ideation even if adjusted for depression scores (22).

Disorganized symptoms seem to report a poor association with a higher risk of suicide (4). Finally, there is no relevant evidence on the impact of positive symptoms of psychosis and excitement on the risk of suicide (4, 22, 37, 38) even if some studies describe an association between command hallucinations and committed suicides (34, 52). In addition, some authors found that individuals with suicidal ideation during the prodromal phase of schizophrenia report higher scores of negative and positive symptoms than individuals without prodromal suicidal ideation (22, 53).

Affective Symptoms in FEP and Suicide

Depressive symptoms in the prodromal phase of schizophrenia were frequently associated with suicidality during the following 12 months of outcome (54). In particular, depressive symptoms are associated with lifetime as well as current risk for suicidal behaviors (32, 55) with higher rates of depression after the first episode and any relapse of psychosis (56, 57).

Many authors point out that, in FEP patients, depression and suicidal behavior may be a reaction to the perceived persecutors and entrapment (58). Some other authors found that hopelessness was associated with suicidal ideation in FEP individuals and this symptom predicted suicidal ideation (2).

It has also been hypothesized that suicidality in FEP may be linked to patients' altered basic self-awareness or sense of self, called self-disorders: there is a clear association between current suicidality and self-disorders, which appears to be connected by depressive states (59). Previously, Skodlar et al. (6) and Skodlar and Parnas (60) suggested that the effect of self-disorders on FEP was connected to specific feelings of inferiority and loneliness, and these feelings were different from "usual" feelings of low self-esteem or loneliness, since they are characterized by being profoundly dissimilar to other people.

"Mood variability" may also be associated with levels of suicidal thoughts and behaviors among individuals at UHR of developing psychosis through the re-activation of latent suicidal cognitions. In fact, in 2012, Palmier-Claus et al. showed that the variability of negative and positive affect was predictive of the frequency of suicidal thoughts and behaviors, with more variable negative affect associated with severe suicidal ideation and related behaviors. In a later study, they also investigated variability and levels of depressive mood, anxiety, and guilty during the schizophrenia FEP and after this episode. The findings support the hypothesis that variability in depression may contribute to suicidal ideation and related behaviors (61).

Early intervention on depression in FEP is crucial to minimize suicidal ideation and attempts, particularly, in the first years of illness, which seem to be consistently characterized by high risk of suicide (2).

Finally, it has been shown that ARMS and FEP patients had significantly higher scores at the brief psychiatric rating scale-excited component (BPRS-EC) if compared with healthy controls: this may suggest an agitated–aggressive syndrome characterized by impulsivity and increased risk of aggression and suicidality (62).

Schizophrenia and Affective Disorders: The "Continuum" Model

Suicide may significantly occur in the outcome of affective disorders and schizophrenia. Epidemiological data show that unipolar depression, bipolar disorders, and schizophrenia are associated with significant risk of suicide (63). This finding might be explained through the "*continuum*" model in which some characteristics, dimensions, or syndromes (including suicide) are included in different clinical conditions caused by the same underlying mechanism. In fact, several studies proposed a psychopathological *continuum* between schizophrenia and mood disorders (64). In particular, neurobiological data show a relevant overlap between bipolar disorders with psychotic features and schizophrenia. Also, in the early stage of both disorders, genetic vulnerability markers seem to be located on the same chromosomes (65). In addition, schizophrenia and affective disorders present similarities in neurodysfunctions and neuromorphometric characteristics (66, 67). According to this model, risk of suicide may be influenced by different dimensions, such as mood variability and psychoticism, along a spectrum of affective and psychotic disorders.

History of Suicide Attempts

History of suicide attempts suggests an increased risk of suicide since it is supposed to be a strong predictor of later attempted or completed suicides (2, 9, 68).

Similarly, history of self-harm or violent crime is a relevant risk factor for subsequent suicide in patients with FEP: both include some degree of impulsivity, which is associated with an increased risk of suicide (69).

Functioning

It is notable that schizophrenia is associated with a significant impairment in occupational functioning that can start early in the prodromal phase of illness.

Also, individuals with recent suicide ideation have poorer functioning, in particular, they report role deficits and lower scores at global assessment of functioning (GAF) (22, 34, 53).

It has been found that social drift is common in psychotic disorders and individuals with a FEP. They are more likely to be in the lower social classes if compared with the general population. Also, social drift was associated with depression, hopelessness, and suicidality at first presentation of illness. However, the relationship between social class and prognosis is complex: hopelessness may be developed in subjects who maintain their social class or achieve upward social mobility. In addition, individuals who achieve upward social mobility are more likely to be ambitious, hardworking, and motivated, and they may have greater difficulty in coping strategies when their life progression is stopped by a psychotic disorder (70).

Insight

Insight is defined as the awareness of suffering from a mental disorder and needing of treatments. Several studies showed that better insight is associated with suicidal ideation and attempted suicide in FEP patients (71–75), while others specify that insight may influence the risk of suicide if associated with depression and hopelessness (30, 47, 76–79). Conversely, some authors remarked that interventions aimed to improve the insight may also improve the outcome of illness and secondary reduce the risk of attempting suicide (79). In fact, interestingly, it was found that insight at baseline increases the risk for suicide while a good level of insight at 1-year follow-up (due to psychoeducational interventions) decreases the same risk: this may indicate that early insight is qualitatively different from insight after 1 year of treatment. Early insight may imply a negative change in self-image (switching from a healthy person to an ill one) or the awareness of consequences related to a mental disorder and stigma (80). Insight is associated with better treatment adherence in the long term and has a positive impact on the outcome of illness and risk of suicide (81).

In conclusion, authors point out that some domains of insight may increase the risk of suicide such as awareness of mental illness, and also some other factors like being female, longer DUP, and comorbid depression may increase the association between suicide and insight levels.

Trauma

There are few studies on trauma in FEP and its negative impact on clinical outcome. It is well known that traumatic life events may lead to anxiety, depression, and psychotic symptoms and can contribute to the development of an at-risk state for psychosis (82).

Conus et al. described the prevalence of stressful events in 658 FEP outpatients and their associations with premorbid characteristics, baseline, and outcome differences among subjects who did and did not report past sexual and/or physical abuse (SPA). They found that 83% of these patients had been exposed to at least one stressful event during their lifetime and 34% of them to physical and/or sexual abuse (especially females). SPA patients were more likely to report post-traumatic stress disorder (PTSD) and substance use disorder before the onset of the psychosis to have attempted suicide in the past and during the treatment (83).

The effects of trauma and comorbid PTSD may add further risk of suicide in FEP patients. Tarrier et al. (77) investigated all post-traumatic stress symptoms and the effect on suicidal behavior of trauma associated with the psychotic onset. Eighty percent of the patients felt traumatized, and 38% reported criteria for PTSD. Suicidal ideation was reported by 40% of the sample, and 31% reported attempted suicides. Suicidal behavior rates were higher in those suffering from PTSD, even if not statistically significant and significantly associated with the experience of trauma occurred before the onset of psychosis (77).

These results suggest that treatment of early psychosis must consider childhood trauma and comorbid PTSD. Assessment for PTSD has also been suggested in the National Institute for Clinical Excellence (NICE) guidelines in 2014 since it is helpful for further interventions in FEP patients (84).

Other Factors

Other factors may also predict the risk of suicide, although the findings are still inconsistent. Patients who completed suicide within 2 years from FEP showed more passive coping strategies or

high level of neuroticism (4). Also, perfectionist self-presentation was associated with suicide in a case report of a FEP patient (85).

Family history of a first-degree relative hospitalized for schizophrenia or bipolar disorder or substance use disorder or other mental disorders was supposed to be associated with risk of suicide in FEP patients (69). Illicit drug use was associated with a twofold to fourfold increased risk of all- and unnatural-cause mortality, respectively, while controlling for age and sex (40, 86). The relatively high prevalence of concurrent and lifetime substance abuse in the FEP population may increase the rate of suicidal and aggressive behaviors (87).

Medication history is also to be considered among factors influencing suicide risk among schizophrenia patients. Even if evidences about the efficacy of antipsychotics on suicide and FEP are few, there is an agreement on clozapine and its superiority in treating resistant psychotic illness: in fact, clozapine is associated with a significant 3.3-fold lower overall suicidal risk compared with other antipsychotic treatments (63). Also, in December 2002, the Food and Drug Administration (FDA) approved indication for clozapine to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder (63).

LIMITATIONS

Limitations of this review may include the non-systematic approach in selecting the available literature: even if evidences reported were considered as relevant by the authors, any score assessment of the screened results, as well as any consensus statement among authors were employed. Subjectivity in selecting articles may be considered as a selection bias.

CONCLUSION

Suicide is one of the leading causes of premature death among individuals with schizophrenia and psychotic spectrum disorders, and the rate of attempted suicide in these patients is also high (88). This overview confirms that, in recent years, there has been a growing interest in the area of FEP. The most relevant risk factors for suicide in FEP are age of onset of psychotic symptoms, DUP, demographic characteristics, psychopathology, trauma, and insight (a list of risk and protective factors for suicide during FEP is shown in **Table 2**). Clinicians should assess risk of suicide

TABLE 2 | Risk and protective factors for suicide in FEP patients.

Risk factors	Protective factors
Acute psychotic symptoms/experiences (e.g., hallucinations)	At least one close relationship
Mood variability and depression	Family support
Pre-existing or comorbid conditions, such as personality disorder and substance abuse/dependence	Things to live for, e.g., plans for the future, children, pets, etc.
The individual reaction to the impact of the illness	Strong positive cultural/religious/personal values and anti-suicide attitudes
Traumatic life events	Social stability
PTSD features related to earlier trauma or prior suicide attempt	Good service engagement and optimism about recovery (hope)
Trauma associated with an unsatisfactory pathway to care	Compliance to treatments
Lower insight	Good insight
Longer DUP	Shorter DUP

PTSD, post-traumatic stress disorder; DUP, duration of untreated psychosis.

in the prodromal phase with subthreshold symptoms as well as during the FEP and along the entire course of the illness (89). A more exhaustive monitoring with systematic risk assessment should be conducted regularly during these phases to facilitate early detection of high-risk cases and to provide interventions for suicide prevention without any delay (86, 97). Antipsychotic treatment remains crucial for reducing suicide among FEP patients (90). Clozapine has shown superiority in reducing suicide risk among schizophrenia patients (63). Further studies are required to identify specific psychotherapeutic and psychosocial interventions that may offer more benefits for the prevention of suicidal behaviors in such patients. Specialized multidisciplinary early psychosis teams (psychiatrist, psychotherapist, social worker, etc.) could provide the interventions needed for supporting FEP patients and their family in a comprehensive manner.

AUTHOR CONTRIBUTIONS

AV, IB, AG, and ES reviewed the literature and drafted the paper. MM, LS, and AB finalized the paper and provided suggestions to improve it.

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Clinical Characteristics Associated with Suicide Attempts in Clinical Settings: A Comparison of Suicidal and Non-Suicidal Depressed Inpatients

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Introduction: Both psychiatrists and psychiatric nurses are involved in the psychiatric management of suicidal inpatients. One-to-one observation by qualified nurses and the accommodation of the patient in a room close to the infirmary are usually recommended. Suicidal risk should be reassessed periodically to check response to treatment.

Aim: To compare the severity of depressive symptoms in depressed inpatients admitted after an attempted suicide and those admitted for any other reason and to assess the severity of suicide attempts and the management of suicidal risk in clinical settings.

Materials and methods: We divided the sample into two subgroups: patients with a diagnosis of depression admitted because of a recent suicide attempt and depressed patients with no recent history of attempted suicide. Socio-demographic and clinical data were gathered; assessments included the Montgomery-Asberg Depression Rating Scale and the Nurses' Global Assessment of Suicide Risk (NGASR).

Results: Forty-six patients were recruited over a 1-year period: 20 were admitted to the hospital following a suicide attempt; the other 26 had not attempted suicide and were admitted for other depression-related reasons. Multivariate analysis revealed a correlation between use of antidepressants and recent attempted suicide. Attempting suicide was not related to the severity of depressive symptoms. In the recent suicide attempt subgroup, NGASR suicide risk levels were lower at discharge than at admission. Patients with a recent history of attempted suicide had a higher number of suicide attempts in their clinical history than patients with no recent history of attempted suicide.

Conclusion: There were no correlations between psychiatric diagnosis, severity of depressive symptoms, and recent suicide attempt. Antidepressant therapy protected against suicide attempts. History of suicide attempts was one of the best predictors of recent attempted suicide. A more thorough understanding of the complex phenomenon of suicide and the reasons for suicidal behavior is needed.

Keywords: suicide attempt, depression, clinical management, antidepressants, inpatient

Abbreviations: MADRS, the Montgomery–Asberg Depression Rating Scale; NGASR, the Nurses' Global Assessment of Suicide Risk; NSA, non-suicide attempters; SA, suicide attempters.

INTRODUCTION

Suicide is a significant public health problem: more than 800,000 people (11.4/100000) die by suicide every year according to the World Health Organisation (1) and in 2012 suicide was the 15th cause of death worldwide. Attempted suicide is far more common than suicide (2, 3); the prevalence ranges from 0.3% in high income countries to 0.4% in lower income countries (2).

A suicide attempt often leads to admission to a psychiatric ward and it represents a challenge for the whole clinical team. Suicide attempts after hospitalization are also a major cause of morbidity. Arguably risk of attempted or successful suicide is highest at the time of hospitalization (4). Predicting suicide during psychiatric hospitalization remains a challenge (5). Large and Ryan recently claimed that, although it is common to repeat assessments of suicide risk during a hospital stay, this poses several problems of interpretation, and that the predictive value of the risk categories assessed is inevitably low (6). The risk factors most reliably associated with inpatient suicide are "static" ones, and include a diagnosis of affective disorder, a history of suicide attempts, and a suicide attempt in the week before psychiatric admission (7, 8). Although the identification of suicide risk factors does not appear to contribute to a useful probabilistic estimate of inpatient suicide risk, one would expect that some suicides could be prevented by addressing them (6).

According to the 2003 guidelines of the American Psychiatric Association (9), the starting point for the psychiatric management of patients who exhibit suicidal behavior is the establishment and maintenance of a therapeutic alliance involving psychiatrists and psychiatric nurses working in cooperation with the patient's general practitioner, mental health service psychiatrists, and family members or caregivers. Specific precautions are required to ensure patient safety although excessive restraint should be avoided. These might include one-to-one observations by qualified nurses if the risk is severe, and accommodating the patient in a room close to the infirmary is usually recommended. The importance of appropriate clinical management is supported by evidence that inpatient suicide attempts are more likely to occur during shift changes or when staff are less alert (10). Assessment and management of patients who have attempted suicide is complex, and the limited number of effective approaches represents an important problem (11). There is evidence supporting the use of antidepressants, lithium, and other mood stabilizers to reduce symptom-related suicide risk. It is important not to ignore the fact that suicidal behaviors may occur independently from a diagnosis of depression or, in wider terms, any psychiatric diagnosis (12–14). This is an important issue, considering the current zeitgeist and the growing tendency to sue psychiatrists after a patient's suicide. The approach to suicide and suicide attempt should not overlook the philosophical and existential perspective. According to Camus, "There is but one truly serious philosophical problem and that is suicide. Judging whether life is or is not worth living amounts to answering the fundamental question of philosophy. All the rest – whether or not the world has three dimensions, whether the mind has nine or twelve categories – comes afterwards. These are games; one must first answer" (15).

On the basis of this evidence, the aim of our study was to compare socio-demographic, clinical, and treatment variables in depressed inpatients admitted to our psychiatry ward following a suicide attempt and those admitted for any other reason. The clinical implications of our findings are discussed.

MATERIALS AND METHODS

We collected data from all depressed inpatients admitted to the psychiatry ward, A.O.U. "Maggiore della Carità" Novara between November 30, 2014 and November 30, 2015. Inclusion criteria were as follows: diagnosis of depression, age >18 years, adequate understanding of Italian, and willingness to provide written consent to participation. Mental retardation and dementia were exclusion criteria. We divided the sample into two subgroups: patients with a diagnosis of depression admitted due to a recent suicide attempt (recent suicide attempters; RSAs) and patients with a diagnosis of depression who had been admitted for a reason other than attempted suicide (non-suicide attempters; NSAs).

Socio-demographic (age and gender), clinical, and treatment-related information was gathered, including lifetime diagnoses according to DSM-5 criteria (16), comorbid physical illness, suicidal behavior, medication during hospital stay, and length of stay (LOS). Data were gathered using clinical interviews and clinician- and nurse-rated scales. The Montgomery-Asberg Depression Rating Scale (MADRS) (17), a 10-item semi-structured scale, was used to assess the presence and severity of depressive symptoms. MADRS scores are classified as follows: 0–12, minimal depression; 13–19, mild depression; 20–34, moderate depression; ≥35, severe depression. Inter-item reliability for the MADRS is 0.86 (18).

The Nurses' Global Assessment of Suicide Risk (NGASR) was used to evaluate and measure suicidal risk in RSAs during hospitalization (19). The Italian version of the NGASR was filled in by trained nurses for RSAs whenever a change in behavior was observed. Total NGASR score indicates level of suicidal risk: ≤4, low risk (standard daily nursing care; test re-evaluation if needed); 5–8, intermediate risk (standard nursing care three times a day; re-evaluation every 72 h); 9–11, high risk (standard nurse care every 15 min throughout the day and night; re-evaluation every 24 h); ≥12, very high risk (constant, dedicated nursing care or other professional care; re-evaluation every 24 h).

This research project was approved by the Institutional Review Board of the Università del Piemonte Orientale as part of the research duties of the Psychiatry Institute. Informed consent was obtained from all participating patients.

Statistical Analysis

Descriptive statistics, frequencies and percentages for categorical variables and means and SDs for continuous variables were calculated. Group differences were evaluated with the chi-squared test (categorical variables) or t-test (continuous variables). After this, multivariate logistic regression was performed to assess the potential predictors of suicide attempts. The covariates included in the final model were selected using the Hosmer and Lemeshow procedure, by inserting variables with a univariate p-value <0.25 as the main criterion (20). Results are expressed as odds ratios

(ORs) with 95% confidence intervals (95%CIs). The statistical significance level was set at $p \leq 0.05$. Statistical analyses were performed with STATA 11 (21).

RESULTS

During the 1-year period described above, 326 patients were admitted to our psychiatry ward, 46 (23.91% men; 76.09% women) received a diagnosis of depression and were, thus, eligible for our study. Twenty of them (25% men; 75% women) had been admitted to the hospital after attempting suicide, while the other 26 (23.08% men; 76.92% men) had not attempted suicide and were admitted for other reasons related to their depression. The mean age for the whole sample was 49.78 ± 15.81 years (RSA: 49.69 ± 16.00 years; NSA: 49.90 ± 15.98 years). Clinical variables, treatment, and MADRS scores for both groups are reported in **Table 1**.

Psychiatric comorbidities in the RSA group included obsessive compulsive disorder ($n = 1$), substance-related and addictive disorders ($n = 1$), and personality disorders (borderline personality disorders, $n = 2$; narcissistic personality disorder, $n = 3$; histrionic personality disorder, $n = 1$). In the NSA group, psychiatric comorbidities included mental retardation ($n = 1$), substance-related and addictive disorders ($n = 2$), and personality disorders (borderline personality disorders, $n = 1$; histrionic personality disorder, $n = 3$; obsessive personality disorder, $n = 1$; personality disorder not otherwise specified, $n = 1$). We also assessed comorbid cardiovascular, endocrinological, gastrointestinal, neurological and urologic diseases, cancer, and others.

Mean LOS was 14 ± 9.9 days for the RSA group and 14 ± 6.5 days for the NSA group.

TABLE 1 | Group comparison of clinical and treatment variables and MADRS scores.

Variable		RSA (n = 20) %, n	NSA (n = 26) %, n	P
Lifetime diagnosis	Bipolar disorder I	0.00 (0)	3.85 (1)	0.278
	Bipolar disorder II	10.00 (2)	19.23 (5)	
	Major depressive disorder	70.00 (14)	42.31 (11)	
	Dysthymia	20.00 (4)	34.62 (9)	
Psychiatric comorbidity	Yes	40.00 (8)	34.62 (9)	0.708
	No	60.00 (12)	65.38 (17)	
Physical comorbidity	Yes	50.00 (10)	57.69 (15)	0.604
	No	50.00 (10)	42.31 (11)	
Medication	Benzodiazepines	65.00 (13)	80.77 (21)	0.227
	Mood stabilizers	10.00 (2)	23.08 (6)	0.246
	Antipsychotic	40.00 (8)	42.31 (11)	0.875
	Antidepressants	65.00 (13)	84.62 (22)	0.122
Previous suicide attempts	0	30.00 (6)	76.92 (20)	**<0.001**
	1	35.00 (7)	11.54 (3)	
	2	30.00 (6)	11.54 (3)	
	>2	5.00 (1)	0.00 (0)	
MADRS	Minimal symptoms	15.00 (3)	7.69 (2)	0.645
	Mild depression	35.00 (7)	34.62 (9)	
	Moderate depression	40.00 (8)	53.85 (14)	
	Severe depression	10.00 (2)	3.85 (1)	

Bold font means statistically significant results $p \leq 0.05$.

The methods used in recent suicide attempts by the RSA group were drug poisoning (65%; $n = 13$), cutting (20%; $n = 4$), or other methods (drowning, jumping from heights and use of firearms; 15%; $n = 3$). In the RSA group, the distribution of suicide risk on admission based on NGASR scores was as follows: low risk: 10% ($n = 2$); moderate risk: 35% ($n = 7$); high risk: 30% ($n = 6$); very high risk: 25% ($n = 5$). At discharge, the corresponding figures were 65% ($n = 13$), 25% ($n = 5$), 10% ($n = 2$), and 0% ($n = 0$).

Table 2 shows the results of the multivariate analysis for the assessment of potential risk factors related to suicide attempt.

DISCUSSION

Aside from previous suicide attempts, psychopathology is considered one of the most important predictors of suicidal behavior (22, 23). Major depressive episodes associated with major depressive disorder or bipolar disorder account for at least half of all suicide deaths (24). A recent meta-analysis concluded that despite the heterogeneity of relevant studies, there is a stronger association between suicidal behavior and schizophrenia and other psychotic disorders than between suicidal behavior and mood disorders (25).

Patients with physical illnesses, such as chronic obstructive pulmonary disease, cardiovascular diseases, osteoporosis, multiple sclerosis, inflammatory bowel disease, migraine, epilepsy, and traumatic brain injuries, are also at higher risk of suicide than the healthy population (26). In our sample, however, there were no differences between the RSA and NSA groups with respect to physical comorbidities and we also found no correlations between lifetime psychiatric diagnosis (bipolar I, bipolar II, major depressive disorder, dysthymia), psychiatric and physical comorbidity, and suicidal behavior.

Recent suicide attempt was not related to the severity of depressive symptoms as measured with the MADRS ($p = 0.645$). Although the small sample size should not be overlooked when interpreting our results, this nevertheless suggests that suicidal behaviors in depressed patients are linked to factors other than the severity of depressive symptoms. A recent study reported that increased risk of suicide attempts in mood disorders was

TABLE 2 | Predictors of suicide attempt.

Variable		Adjusted OR	95% CI	p
Age		1.01	(0.95–1.09)	0.611
Gender	Female	1.28	(0.17–9.55)	0.811
Psychiatric comorbidity	Yes	0.19	(0.02–1.61)	0.129
Physical comorbidity	Yes	0.36	(0.04–3.06)	0.346
Therapy	Benzodiazepines	1.09	(0.11–10.70)	0.938
	Mood stabilizers	1.23	(0.09–17.68)	0.880
	Antipsychotic	0.12	(0.01–1.44)	0.095
	Antidepressants	0.03	(0.01–0.49)	**0.013**
Previous suicide attempts	0	1		–
	1	88.34	(3.79–2061.28)	**0.005**
	2	53.98	(342–851.98)	**0.005**
	>2	–		–

Bold font means statistically significant results $p \leq 0.05$.

associated with impulsivity and unstable relationships (27). This is consistent with clinical experience which suggests that suicide attempts may be influenced by many other factors in addition to psychiatric diagnosis and severity of psychiatric symptoms, e.g., personality, resilience, personal and cultural factors, and beliefs (12–14).

There were no group differences in use of any of the classes of medication analyzed (benzodiazepines, antidepressants, antipsychotics, mood stabilizers). This is not surprising, given that there is only empirical evidence to support the use of a very limited number of drugs to treat non-suicidal self-injurious behavior (28, 29). This suggests that the RSA and NSA groups would receive similar treatment and, in fact, there was no group difference in LOS.

The only clinical difference between the groups was in number of previous suicide attempts. The number of suicide attempts in the clinical history was higher in the RSA group. This result is consistent with the large body of evidence showing that a history of attempted suicide is a strong risk factor for subsequent suicidal behavior (7, 8, 30–32). Multivariate analysis showed that a history of one (OR = 88.34, $p = 0.005$) or two (OR = 53.98, $p = 0.005$) previous suicide attempts was a strong predictor of current suicidal behavior. There are reports suggesting that 16–34% of people who attempt suicide try again within 1 or 2 years after their first attempt and that there is a history of previous non-fatal suicide attempts in up to 40% of fatal suicides (33). Hence, a history of suicidal behavior, independent of psychiatric diagnosis, is likely to be the strongest risk factor for successful suicide.

Multivariate analysis indicated that, in the RSA group, use of antidepressants was protective against recent suicide attempt (adjusted OR = 0.03, 95% CI: 0.01–0.49), although we should not overlook the fact that the reference category for this analysis was patients not using any psychopharmacological therapy. Evidence on the relationship between use of antidepressants and suicide risk is mixed; although there is broad agreement that selective serotonin reuptake inhibitors (SSRIs) do not increase suicide risk (34), there is no evidence that antidepressants have a specific protective effect with respect to suicidal behavior. For instance, a recent retrospective cohort study comparing depressed patients treated with antidepressants and untreated patients found no difference in suicide rate between the two groups (35). The small number of drugs for which there is empirical evidence of a reduction in non-suicidal self-injurious behavior includes some SSRIs and venlafaxine (36).

Consistent with the literature, patients in our sample with a history of suicide attempts were at greater risk of a further attempt than those without such history and, hence, from a clinical standpoint, behavioral monitoring of this group during hospitalization is essential. Suicidal risk assessment by clinicians and nurses may be helpful in tailoring treatment and assistance to the patient's needs (7, 8, 37, 38).

The literature suggests that patients who have recently attempted suicide should be managed by experienced nurses because suicide and suicidal risk assessment are multifaceted, complex phenomena (39). In our clinical practice, the NGSAR has proved to be useful for assessing suicidal risk and monitoring inpatients. There is evidence that in adult patients suffering from major mood disorders, suicide risk remains high in the hours following a suicide attempt and admission to the emergency department (40) and also in the days following admission to a psychiatric ward (41). Nonetheless in the RSA group, which had a mean LOS of 14 ± 9.9 days, we observed a considerable decrease in NGASR scores between admission to the psychiatric ward and discharge.

Limitations

Some limitations of our study should be underscored. The sample size limits the generalizability of our results, as does the setting, which was limited to a single psychiatric ward. Anyway it should be noted that our ward is part of the Azienda Ospedaliero Universitaria (AOU) Maggiore della Carità Hospital, the second largest hospital in Piedmont, which may be considered representative of the North-Eastern Piedmont area. We also need to point out that the risk of suicide is high in Piedmont, particularly in the north-eastern areas (42–44). The number of variables assessed in this study was limited, and we cannot exclude the possibility that other clinical or socio-demographic factors may predict suicide attempts in depressed patients.

The strength of our research is that we analyzed data from real-life settings. More similar studies are warranted to help and support clinicians in their everyday clinical practice.

CONCLUSION

Notwithstanding the limits noted by Large and Ryan (6), the importance of interventions designed to reduce or prevent suicide during inpatient psychiatric treatment has been recently underscored (45–47). There is still scant evidence on this issue and little research into the effectiveness of prevention strategies (48, 49).

Reduction of suicide risk in psychiatric wards may be achieved by creating a safe environment and ensuring patient visibility; patients should be properly supervised and assessed through teamwork and sharing of viewpoints within the team. Clinicians and nurses should be aware of suicide risk and respect it (50); using structured measures to assess suicide risk may be helpful. Withdrawing from ward activity, wanting to leave the ward without permission and non-compliance with medication regimes should be treated as indicators of risk that warrant early intervention (51).

Interestingly, we found no correlations among psychiatric diagnosis, psychiatric and physical comorbidity, severity of depressive symptoms, and suicidal behavior. On the other hand, antidepressant therapy was found to protect against suicide attempts. A more thorough understanding of the complex phenomenon of suicide and the reasons for suicidal behavior is needed. Consideration should be given to the existential perspective as this may help to de-stigmatize suicide and correct the impression that only psychiatric patients commit suicide.

AUTHOR CONTRIBUTIONS

CG, ET, and PZ were responsible for the conception and design of the work; data collection was carried out by PB, AF, EG,

and DM; data analysis and interpretation by FB and RS; the article was drafted by AF, EG, and CG, and it was revised by PZ. All the authors have approved the final version for publication.

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Acute Mental Discomfort Associated with Suicide Behavior in a Clinical Sample of Patients with Affective Disorders: Ascertaining Critical Variables Using Artificial Intelligence Tools

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Aim: In efforts to develop reliable methods to detect the likelihood of impending suicidal behaviors, we have proposed the following.

Objective: To gain a deeper understanding of the state of suicide risk by determining the combination of variables that distinguishes between groups with and without suicide risk.

Method: A study involving 707 patients consulting for mental health issues in three health centers in Greater Santiago, Chile. Using 345 variables, an analysis was carried out with artificial intelligence tools, Cross Industry Standard Process for Data Mining processes, and decision tree techniques. The basic algorithm was top-down, and the most suitable division produced by the tree was selected by using the lowest Gini index as a criterion and by looping it until the condition of belonging to the group with suicidal behavior was fulfilled.

Results: Four trees distinguishing the groups were obtained, of which the elements of one were analyzed in greater detail, since this tree included both clinical and personality variables. This specific tree consists of six nodes without suicide risk and eight nodes with suicide risk (tree decision 01, accuracy 0.674, precision 0.652, recall 0.678, specificity 0.670, F measure 0.665, receiver operating characteristic (ROC) area under the curve (AUC) 73.35%; tree decision 02, accuracy 0.669, precision 0.642, recall 0.694, specificity 0.647, F measure 0.667, ROC AUC 68.91%; tree decision 03, accuracy 0.681, precision 0.675, recall 0.638, specificity 0.721, F measure, 0.656, ROC AUC 65.86%; tree decision 04, accuracy 0.714, precision 0.734, recall 0.628, specificity 0.792, F measure 0.677, ROC AUC 58.85%).

Conclusion: This study defines the interactions among a group of variables associated with suicidal ideation and behavior. By using these variables, it may be possible to create a quick and easy-to-use tool. As such, psychotherapeutic interventions could be designed to mitigate the impact of these variables on the emotional state of individuals, thereby reducing eventual risk of suicide. Such interventions may reinforce psychological well-being, feelings of self-worth, and reasons for living, for each individual in certain groups of patients.

INTRODUCTION

Suicide is the most feared consequence of mental illness. While there are significant differences between the rates of suicide in many countries, suicide ranks among the top 15 causes of death around the world. Moreover, for every suicide, there are 20 to 30 people who make a suicide attempt (1).

Chile has a suicide rate of 11 for every 100,000 inhabitants (2013). This translates into 6 deaths per day and another 20 who unsuccessfully attempt suicide. This figure is equivalent to the number of deaths in vehicle accidents (2). The situation becomes even more alarming among young Chileans, with a 2009 suicide rate of 7 per 100,000 youths from the ages of 10–19 years, which is expected to increase to 12 per 100,000 inhabitants by the year 2020 (3).

For many years, motivated by the magnitude of this problem, national health authorities and international organizations such as the WHO (1) have explored different strategies to decrease the incidence of this behavior. Like any other important task, in this case too, one must begin by understanding the nature of this behavior.

There is a long tradition of research aimed at shedding light on the distinctive characteristics of suicidal behavior. Without a doubt, when it comes to clinical work with psychiatric patients, one of the greatest difficulties is assessing the short-term suicide risk of subjects who exhibit risk factors, as is the case for most psychiatric patients (4, 5). This limitation is in contrast with the precision of the epidemiological information that can be obtained. The rate of suicide can now be estimated in countries that keep up-to-date epidemiological records. However, we are not yet able to predict—and therefore prevent—suicide in patients who present the clinical features frequently associated with this behavior. Those who suffer from a mood disorder have a risk of suicide of around 7% throughout their lives. Moreover, while a suicide attempt is one of the factors more strongly associated with suicide, most of those who attempt it will die of a different cause (6). On the other hand, approximately 50% of those who do commit suicide never attempt it before.

The above implies that the indicators commonly associated with this behavior have poor short-term predictive value, since they are not particularly specific and are highly sensitive. There is agreement that the complexity of suicide might be attributed to the "multifactorial" nature of this complex behavior. Understanding it as "multifactorial" is to see it as a dynamic process determined by a set of factors with different properties and weights, interacting

simultaneously (7, 8). The models to understand suicidal behavior usually incorporate risk factors into a process—a sequence of stages—that ultimately converge in an individual. Those who elaborate the idea of ending their lives are individuals who suffer for different reasons and, at some moment, cannot find a way to solve them. In the end, it is the individual who chooses to develop this behavior, which emerges as a response to the strain produced by the events that have caused hurt and are experienced as unbearable. This is the period that some authors highlight as the moment in which an individual has "self-destructive or suicidal thoughts" (9) and carries them out in the hope of ending his or her suffering.

Aside from acknowledging that it exists, our knowledge of the moment that precedes any suicide or suicide attempt is very limited (9–11). This serious limitation in our understanding of suicidal behavior has led many authors to question the value of suicide risk assessments in psychiatric patients (4) and to warn of the ineffectiveness of tools that aim at describing a clinical state of "imminent" suicide risk. For some, the use of risk scales or indicators to assess immediate risk should be considered not only pointless but also "dangerous," given the high probability of incorrectly assessing the risk (12, 13). To predict and therefore prevent suicidal behavior in those suffering from mood disorders, it is necessary to study in greater detail how these factors contribute to the "at risk" condition. We understand that the multifactorial nature of suicidal behavior is also dynamic and discontinuous, which is why we have attempted to identify aspects of the interactions between clinical and personality factors that co-occur when an individual chooses to end their life. The aim of this study is to deepen our understanding of this period of great vulnerability, which precedes all suicidal behavior. We are focused on developing more reliable methods to detect the likelihood of impending suicidal behaviors, which could constitute an important step in suicide prevention science nowadays (14).

A deeper understanding of this process may help us to pinpoint the facts, factors, or circumstances that could be changed in order to bring a person out of the risk zone. Our strategy is to describe the patterns that emerge from data structures by using a vast number of variables, without any prior hypothesis. We agree with Oquendo and her colleagues, who suggested that "…Machine Learning 'observes' the data and 'learns' from it to build an understanding and uncover previously unexpected associations. In this way, this computational approach allows exploration of data to identify patterns and structures not

suspected *a priori*, and thus can lead to the generation of new hypotheses…" [Ref. (15), p. 957].

By using mathematical supervised learning mechanisms, this method may enable us to establish decision rules that can recognize a temporary state of acute psychiatric discomfort that occurs before suicidal behavior (16, 17). This multifactorial behavior could be seen as a group of rules for factor interaction, each with their own features within the group. Having previously attempted suicide or being seriously depressed are risk factors for individuals, when they are part of a constellation of variables that contribute to the aforementioned state of risk. While it is highly possible that the configuration of factors may be individual (given the complex human uniqueness of psychological states), it is important to establish if there is a certain configuration that a particular group of subjects may have in common. Over recent years, data mining (DM) techniques have begun to be studied with the aim of facilitating decision-making processes in medicine (18). DM has already been used for a variety of purposes: the automated extraction and processing of emergency consultations to improve estimations of annual visits (19), the identification of adverse reactions to medication using electronic records (20), among others. The multicausal nature of psychological illnesses has led us to believe that DM could be particularly useful in studying the interaction of variables associated with illnesses or some of their manifestations, as in the case of suicide. The few studies that have been carried out with this new methodology suggest that it may be of great utility. For example, DM has been used in existing data on electronic files to estimate suicide risk (21), to establish cases of murder–suicide in the National reporting system for violent deaths (22), and to track suicide risk by following Twitter messages (23). In each of these cases, DM has shown to be an effective strategy for approaching the analysis of large quantities of data with no prior hypotheses, with the aim of identifying variables, or groups of variables that may better characterize groups of patients. Recently, our suicide research team has used a variety of DM techniques to extract variable that allow us to place patients consulting for major depression in what we call the "suicide risk zone" (24). From 345 variables initially gathered from 6 clinical and personality assessment tools, 22 variables were drawn and grouped into an assessment tool. These 22 variables were considered to define the aforementioned suicide risk zone and will be evaluated in a follow-up study with patients in therapy for suicidal behavior. The usefulness of DM for medical decisions is in the early stages of being proven and its applications and limitations are yet to be defined.

PATIENTS AND METHODS

Participants

The sample was composed of 707 mental health patients, ages 14–85 (adolescents, young adults, adults, and seniors) using a consecutive, purposive sampling strategy. The patients were selected according to availability and in consecutive order from throughout the period defined for selecting the sample for this project (June 2010 to December 2014). These patients were undergoing treatment as usual, which, in the case of hospitalized patients, consists of crisis intervention with psychiatric,

psychological, and occupational therapy approaches. For outpatients, treatment consisted of psychiatric and psychological approaches. This paper is not an intervention, but rather a cross-sectional evaluation of a specific moment. **Table 1** presents the sociodemographic characteristics of the participants. Mood disorders and age distribution are shown in **Tables 2** and **3**. They were classified into two groups: (1) a group with suicidal behavior as indicated by consultations relating to a suicide attempt or presenting suicidal ideation in the preceding years and (2) a group without suicidal behavior, who attended mental health consultations without having made a suicide attempt or having presented recent suicidal ideation. Psychiatric diagnoses were made in collaboration with the treating teams, according to the diagnostic criteria set out in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition published by the American Psychiatric Association (25).

Voluntary participation was requested from subjects along with informed consent/assent. This document was designed using the ethical criteria for research using humans (26). The protocol was approved by the institutional ethics committees of the School of Medicine at Universidad Católica de Chile and the Sótero del Río Hospital. The sample comprised patients consulting for mental health issues, between the ages of 14 and 83, at walk-in and inpatient facilities at three health-care centers, serving different socioeconomic levels in the Greater Santiago, Chile. Participant recruitment and data collection were carried out between June 2010 and December 2014.

The inclusion criteria covered subjects consulting for mental health issues, over the age of 14 and into advanced adulthood, of both sexes, who were able to distinguish reality from fantasy and who made informed consent/assent and demonstrated their availability to participate in the study, and who were in a cognitive and emotional state that allowed them to answer the assessment questions. The exclusion criteria, for methodological reasons and in order to control the diagnostic variable, covered subjects consulting for addiction, eating disorders, psychotic disorders, or cognitive disorders. The exclusion of these pathologies was decided in view of the methodological aim of focusing the analysis on mood disorders, even though the pathologies excluded from this study are also highly linked with suicide risk (2, 27, 28). In addition, those who chose not to participate in the study or those who later withdrew having initially accepted were not included.

Using prior qualitative–quantitative studies, results were obtained with regard to selecting the relevant clinical variables and personalities that protect from suicide risk or place someone at risk. These include psychological distress resulting in dysfunctionality, a dysfunctional experience and expression of aggression, reasons that prevent suicidal behavior, destructive depressive experiences, and satisfaction with family functioning (29–31). These findings led to the selection of the instruments detailed below, which introduced 345 study variables overall:

Tools

The validated Spanish version of the Outcome Questionnaire (OQ-45.2) (32, 33) assesses how a person has been feeling over

TABLE 1 | Sociodemographic characteristics of the sample, differences between groups.

Variable	Total	Group without current suicidal behavior	Group with suicidal behavior	Test
N	707	358	349	
Mean	39.68%	42.16%	37.16%	t = −4.4993
				df = 704
				p = 7.975e−06**
SD	14.849	14.459	14.843	
Sex n/%				χ² = 0.029053
Female	564	287	277	df = 1
	79.774	80.168	79.370	
Male n	143	71	72	p = 0.8647
	20.226	19.832	20.630	
Marital status n/%				χ² = 13.12
Married	259	148	110	df = 3
	36.634	41.341	31.519	
Unmarried	33	19	13	p = 0.004378**
	4.668	5.31	3.72	
Single	295	127	169	
	41.726	35.475	48.424	
Divorced or widower	120	64	57	
	16.973	17.877	16.332	
With children n/%	454	248	206	χ² = 8.0851
	64.215	69.274	59.0258	df = 1
				p = 0.004463**
Completed educational level n/%				χ² = 4.0694
With higher education	333	154	179	df = 1
	47.100	43.017	51.289	p = 0.04367*
Without higher education	374	204	170	
	52.900	56.983	48.711	
Occupation n/%				χ² = 25.91
Employed	375	221	154	df = 3
	53.041	61.732	44.126	
Student	157	56	101	p = 9.92e−06**
	22.207	15.642	28.940	
Unemployed	42	20	22	
	5.941	5.587	6.304	
Housewife	133	61	72	
	18.812	17.039	20.630	

*p < 0.05.
**p < 0.001.

TABLE 2 | Mood disorders distribution, differences between groups.

Variable N (%)	Total	Group without current suicidal behavior	Group with suicidal behavior	Test
Major depressive disorder	311	106 (34.08%)	205 (65.93%)	χ² = 67.75
Bipolar disorder	112	62 (55.36%)	50 (44.64%)	
Moderate depressive disorder	53	30 (56.60%)	23 (43.40%)	
Mild depressive disorder	13		1 (6.69%)	df = 8
Anxiety disorder	74	12 (92.31%)	22 (29.73%)	
Mixed episode	14	52 (70.27%)	2 (14.29%)	
Adjustment disorder	73	12 (85.71%)	27 (36.99%)	p = 1.37e−11*
Dysthymia	8	45 (63.01%)	3 (37.50%)	
Others disorders	29	5 (62.50%)	14 (48.28%)	
		15 (51.72%)		
	(n = 687)	(n = 340)	(n = 347)	

*p < 0.001.

TABLE 3 | Age distribution, differences between groups.

Variable N (%)	Total	Group without current suicidal behavior	Group with suicidal behavior	Test
14–19 years	80	25 (31.25%)	55 (68.75%)	$\chi^2 = 28.82$
20–29 years	130	57 (43.85%)	73 (56.15%)	
30–39 years	135	66 (48.89%)	69 (51.11%)	df = 5
40–49 years	142	85 (59.86%)	57 (40.14%)	
50–59 years	156	81 (51.92%)	75 (48.08%)	$p = 2.51e{-}05^*$
60 years and more	63	44 (69.84%)	19 (30.16%)	
	(n = 706)	(n = 358)	(n = 348)	

*$p < 0.001$.

the preceding few days with regard to (a) anxious and depressive symptomatology, (b) interpersonal relationships, and (c) feelings of adaptation to social roles (family roles, employment, and leisure). The internal consistency of the tool validated for Chile shows a Chronbach's alpha of $\alpha = 0.930$ for the overall scale; $\alpha = 0.910$ for the anxious and depressive symptomatology subscale; $\alpha = 0.740$ for the well-being/discomfort in interpersonal relationships subscale, and $\alpha = 0.710$ for the feelings of adaptation to social roles subscale.

The validated Spanish version of the State Trait Anger Expression Inventory (34) assesses the experience of anger from the patient's point of view from two perspectives: (a) state of anger and trait of anger and (b) the expression of anger in three ways: (1) loss of control, (2) overcontrol, and (3) functional control. Its internal consistency shows a Chronbach's alpha for the study sample of $\alpha = 0.779$ for the overall scale; $\alpha = 0.875$ for the state of anger subscale; $\alpha = 0.809$ for the trait of anger subscale; $\alpha = 0.842$ for the control subscale; $\alpha = 0.603$ for the subscale of suppressing anger, and $\alpha = 0.654$ for the expressing anger subscale.

The validated Spanish version of the reasons for living (RFL) scale (35, 36) assesses reasons for not committing suicide from six perspectives according to the importance that the patient him or herself accords to (a) confidence in his or her ability to face difficult situations; (b) fear of death and social disapproval; (c) family responsibility; (d) concern for children; (e) a perception of an inability to commit suicide; and (f) objections of a moral nature: the internal consistency shows a Chronbach's alpha in the sample studied of $\alpha = 0.950$ for the overall scale; $\alpha = 0.956$ for the confidence in one's ability to face difficult situations subscale; $\alpha = 0.750$ for the fear of death and social disapproval subscale; $\alpha = 0.821$ for the family responsibility subscale; $\alpha = 0.872$ for the concern for children subscale; $\alpha = 0.722$ for the perception of an inability to commit suicide subscale, and $\alpha = 0.771$ for the moral objections subscale. This scale has been validated for Chile by our research team and is in the process of being published.

The validated Spanish version of the Depressive Experience Questionnaire (37, 38) measures two factors that relate to vulnerability and are associated with depression: (a) self-criticism and (b) dependence. There is a third factor, which is thought to protect subjects from suicide risk and relates to (c) self-efficacy. The internal consistency shows a Chronbach's alpha for the sample studied of $\alpha = 0.844$ for the overall scale; $\alpha = 0.60$

for the dependency subscale; $\alpha = 0.79$ for the self-criticism subscale, and $\alpha = 0.69$ for the self-efficacy subscale.

The validated Spanish version of the Family APGAR (39, 40) measures satisfaction with family functioning through a general assessment of five aspects of the respondent's family life: (a) adaptability; (b) participation; (c) growth gradient; (d) affection; and (e) resolution. The internal consistency of this tool validated for Chile shows an $\alpha = 0.79$.

A questionnaire containing descriptive information about the patient with regards to their diagnosis and sociodemographic–clinical background has also been used.

Data Collection Procedure

A deliberate sample was chosen based on the availability of patients in the various services, who were then evaluated consecutively. The aforementioned inclusion criteria were taken into account, and the clinical diagnoses were made together with the treating teams. The study was explained, and voluntary participation was requested. Potential subjects were asked to sign the informed consent/assent form, and they were then asked to respond to the questions included in the various tools, guided by specially trained assessors. The informed consent/assent forms were approved in advance by the institutional ethics committees. In the event that participants were minors, the informed consent and signature of the guardian or caregiving father/mother was also requested in addition to the assent and signature. The aim of the study and the methodology were explained as well as the fact that it was unpaid and the costs, risks, voluntary nature of participation, their right to withdraw from the study, and information confidentiality. The authorization of the treating physician was also sought for the participation of patients and any potential deterioration in mental state during the research was to be noted. No incidents were recorded during this study. Participants were also offered the opportunity to further inquire about the study by contacting the head researcher (SM).

Data Analysis Procedure

These were undertaken in multidisciplinary collaboration between clinician-researchers in mental health and mathematical analysts.

Differences were identified between the two defined groups with suicidal behavior (being treated for suicide attempts or suicidal ideation) and without suicidal behavior (receiving

treatment for other reasons without suicide attempts or suicidal ideation). The initial database with its raw data comprised 707 assessments and 345 variables, corresponding to the questions from the assessment tools and the sociodemographic details of the recruited patients.

Classifications were made based on the collected demographic data with regard to the characteristics of the patients, such as the mental health center, gender, marital status, age, level of education, and whether or not they had children.

Analysis was carried out using artificial intelligence and DM tools, which enabled the different variables to be interpreted in a systematic and automated way (41). Given the nature of the problem, supervised learning models were selected from among the techniques in this field to calibrate the algorithms using a series of examples, known as training data, which already have a defined set of variables and are already linked to an answer relating to that set of variables (42). This was used to generate a model that could predict new cases.

The analyses were carried out using two techniques: (1) the Cross Industry Standard Process for Data Mining (CRISP-DM) methodology (43) and decision and (2) decision tree analysis.

Cross Industry Standard Process for Data Mining methodology is widely used to resolve DM problems across a range of industries and has come to be seen as the standard methodology (44). It is usually applied in multidisciplinary contexts when it is necessary to understand both the problem and the analysis technique in all of their detail. It comprises six phases that enable joint collaboration, namely business understanding, data understanding and preparation, modeling, evaluation, and deployment.

Data mining decision trees are an effective predictive model used in artificial intelligence for analyzing the interaction between a large number of explanatory variables including dichotomous and continuous variables, thereby allowing for easy interpretation and clinical application of the results (45). This analytical tool was used to generate logical diagrams categorizing certain conditions for belonging to a configuration of personal and clinical suicide risk variables. It indicates a route to be followed depending on the value that the variable reaches, and it is represented in the form of a tree, whose branches split depending on the values attained by the variables and end in an action: belonging in the risk situation or not.

The analytical process built a series of logical rules (nodes) in order to divide the data based on the group of attributes for each entry (46). The basic algorithm used was a top-down algorithm that looks for different rules to define groups of interest and aims to increase the branching of the first decision tree obtained. In the results that we will present, after showing the decision trees obtained, we have chosen to enter into a deeper explanation of decision tree no 3 for illustrative purposes only. We felt this to be the most suitable example for explaining the model, due to the sufficient quantity of variables and the depth of the clinical aspects from the assessment (45).

Initially, the algorithm assessed all available data and all of the possible divisions that could be carried out. Subsequently, the most appropriate division generated by the tree was chosen according to the Gini index criterion (45).

This index measures the level of purity of a particular node. The aim is to keep the sum of the Gini indices of all of the nodes to a minimum, thereby reducing the probability that a final node will have different types of records (47).

The data were divided into two subgroups and were then looped until any ultimate condition was reached (either belonging to the group with suicidal behavior or belonging to the group without suicidal behavior). The Gini index was calculated for each possible division using, in this case, the two options available for the objective variable. With P1 (shown in the supplied image of decision trees) taken as the proportion of individuals who, given the proposed division would belong to class 1 of the objective variable (without suicidal behavior), and P2 taken as the proportion of individuals belonging to class 2 (with suicidal behavior), the Gini index of the proposed division was calculated as follows:

$$\text{Gini index} = 1 - \left(p_0\right)^2 - \left(p_1\right)^2.$$

$$\text{Gini index} = 1 - \text{probability of obtaining}$$
$$\text{records of the same class.}$$

The criterion was to choose the division that had the lowest Gini index (47). Within the classification conditions, it was established that at a particular node (decision point) all of the records belonged to a single class, the number of observations were below a set amount beyond which division was not attempted. The number of observations belonging to the lowest class in a node was less than a set number or that of the reduction in the overall fit.

This criterion ensures that, for each final node, only records belonging to a single class are obtained and that the number of observations remains below a set number. As a result, no attempt is made to create a division; or to ensure that the number of observations belongs to a lower class or that the overall lack of a node is less than a certain number (48).

The methodological decision was taken to prune the decision trees, removing certain nodes without reducing the overall fit of the model. In order to achieve this, a number of crossed repetitions were carried out. The aim of this was to obtain a series of models that would supply the logic for sequential rules to determine when a certain individual belongs to a suicide risk configuration.

For a model to have good predictive ability, its sensitivity should ideally be high regardless of the cutoff point selected and the FPR ratio. The larger generated "area under the curve" (AUC) is, the greater the predictive abilities of the model (49).

In addition to the ratios described, a receiver operating characteristic (ROC) curve was used to graphically assess the discriminatory abilities of the model that classified observations into two groups (50). Different cutoff points were analyzed as part of this process. Based on these cutoff points, the sensitivity and specificity of the model were calculated. Afterward, "sensitivity" (or TPR) on the "y axis" was represented on a graph against "1-specificity" (or FPR) on the "x axis." For a model with good predictive ability, its sensitivity should ideally always be high, regardless of the cutoff point selected and the FPR ratio. The larger the generated "Area Under the Curve" is, the greater the predictive abilities of the model.

The analysis issue was approached from two perspectives in order to obtain a wider range of rules to contribute to the aims of the study. Each approach that was developed included two stages, and a decision tree was obtained from each. Finally, the models obtained were assessed using cross-validation.

The first approach consisted of using all of the available variables, i.e., both those relating to the sociodemographic profiles of participants and those obtained through the application of the various tools. The second approach only used the variables that resulted from the assessment tools used.

As a first step, each approach was developed with the Gini index as a criterion for dividing the data. Subsequently, during the second phase, the tree was pruned, minimizing its predictive error when faced with a cross-validation technique. This tool trained the analysis for 80% of the data and assessed the rules obtained using the remaining 20% of the data. The procedure was repeated five times in order to use all of the available information to train the analysis undertaken.

Performance Measurements

Sensitivity measurement was defined as the ability of the model to correctly detect which patients were in a suicide-risk configuration. The specificity measurement was the model's ability to correctly detect which patients were not configured as part of the group with suicidal behavior. The accuracy indicator was the ability to correctly classify the group with suicidal behavior. The precision indicator was the proportion of people with suicidal behavior that was correctly classified. In order to calculate the metrics above, a cutoff probability of 0.5 was set to determine

whether an individual would be classified as "belonging to a suicide risk configuration.".

The progressive development of the results obtained from the two lines of analysis is presented below.

The sample comprised 707 consultants, of which 97% were diagnosed with mood disorders (DSM IV-R): with suicidal behavior group—current suicide ideation—current suicide attempt—($n = 349$) and without suicidal behavior group ($n = 358$). The average age was 39.68 ± 14.85 years, with a range of 14–83 years; 79.77% ($n = 564$) were women, and 20.23% ($n = 143$) were men; 36.63% ($n = 259$) were married, and 41.73% ($n = 295$) were single; 47.10% ($n = 333$) had completed higher education, and 53.04% ($n = 375$) were employed (**Table 1**). Mood disorders and age distribution are shown in **Tables 2** and **3**.

Results of the Decision Trees

Regarding the first approach mentioned (the patient's sociodemographic profile and tool variables), the first model obtained is shown in **Figure 1**. It has 12 nodes, 7 of which correspond to tool variables. Five of these correspond to variables associated with the sociodemographic profile of the consulting patient. **Figure 2** presents the ROC curve obtained for this model. The AUC shows a 73.35% of predictive abilities for the model. From this same approach, the model obtained through optimal pruning is shown in **Figure 3**. The ROC curve for this model is shown in **Figure 4**, and the AUC shows a 68.91% of predictive abilities of the model.

For the other analytical approach (assessment tool variables), the first model obtained is presented in **Figure 5**, and its ROC
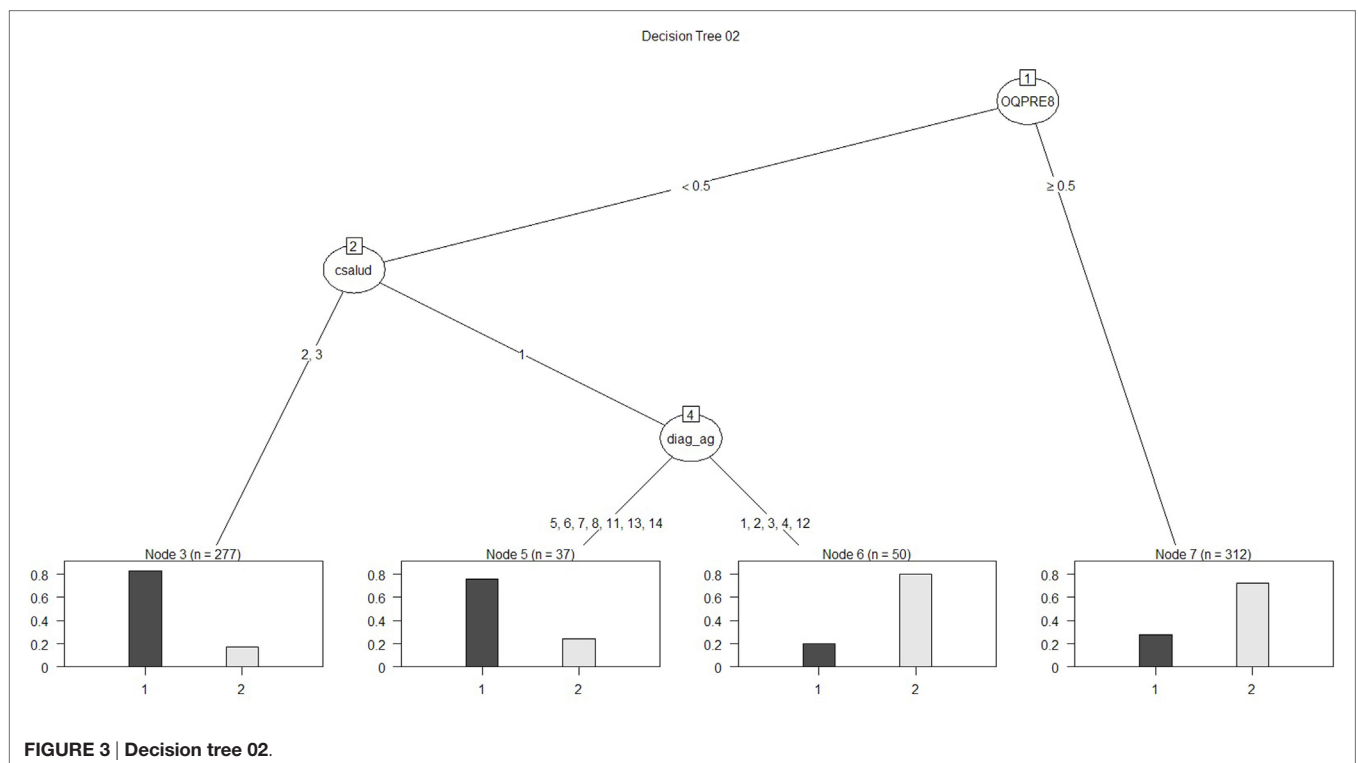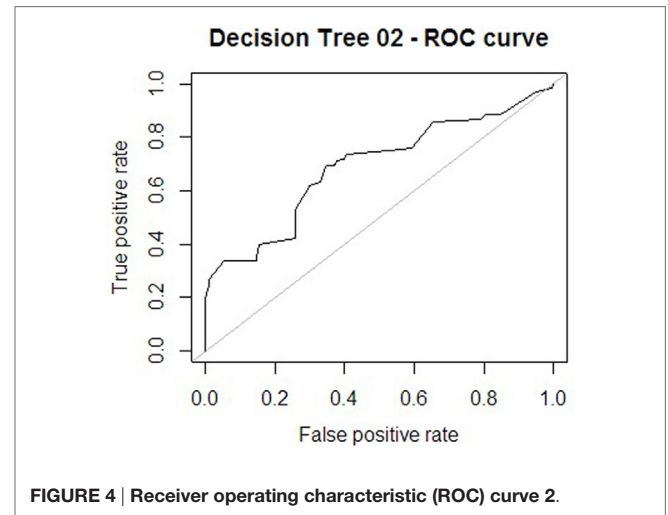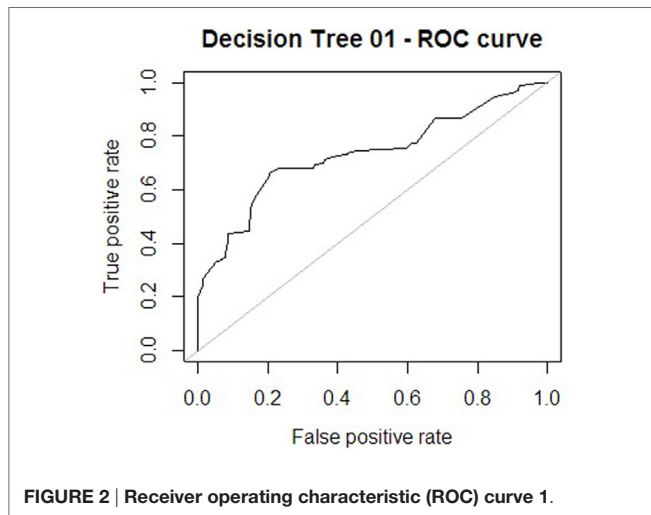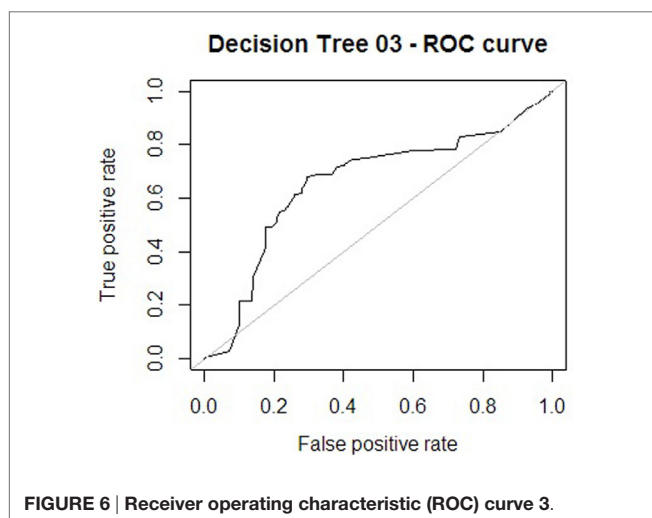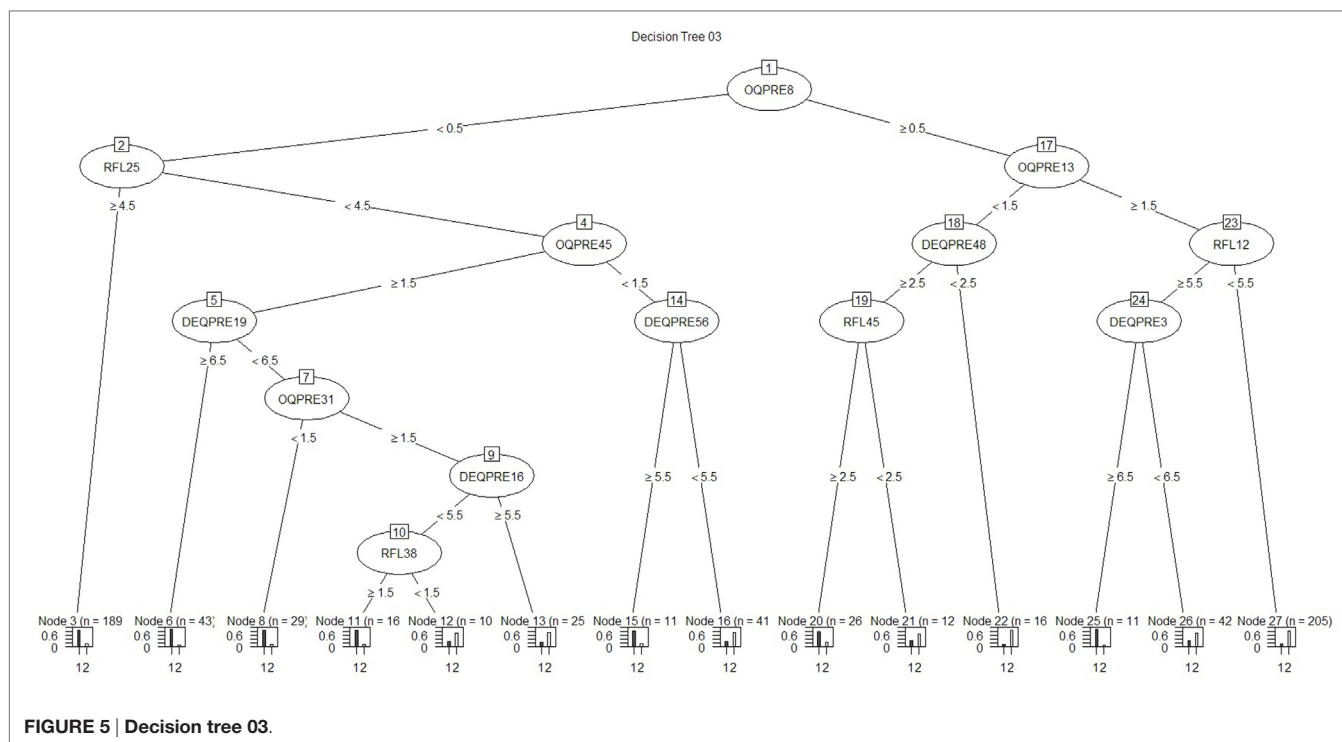

FIGURE 1 | Decision tree 01.
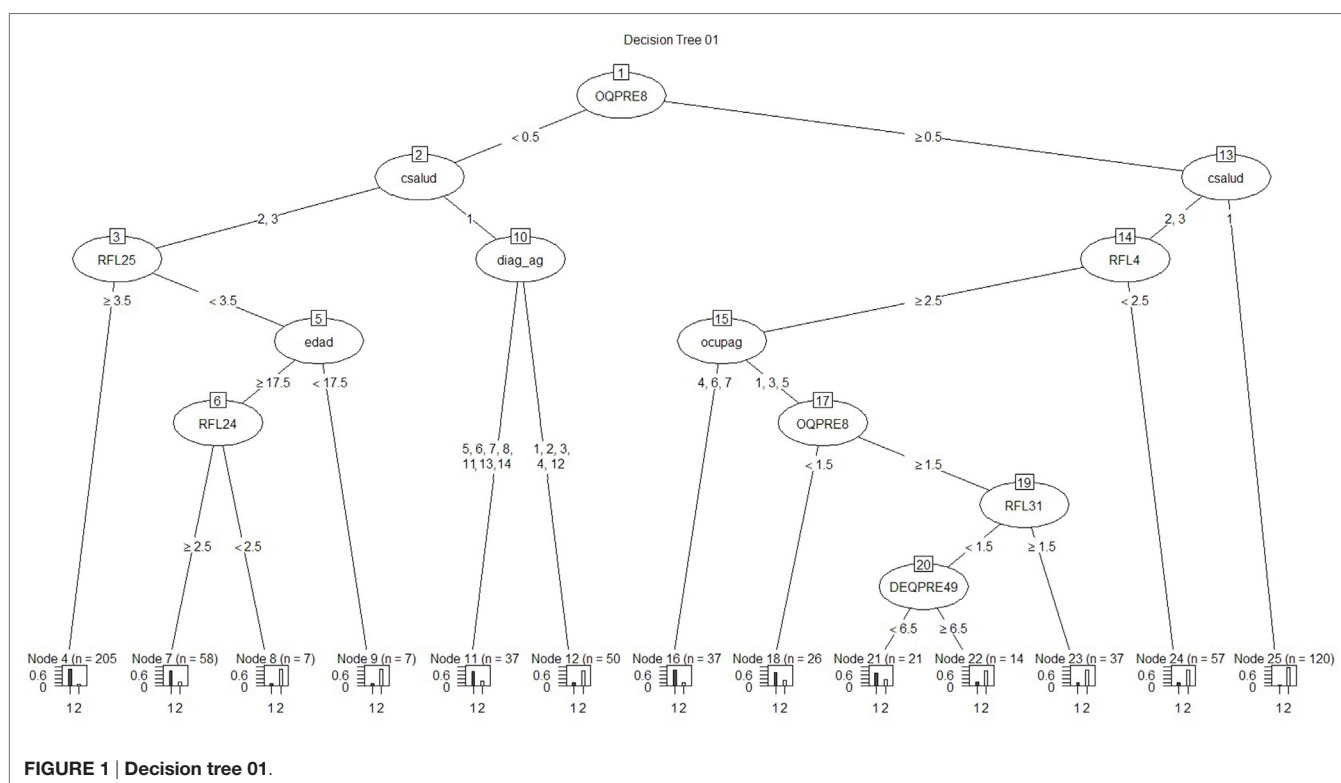
can be seen in **Figure 6**. The AUC shows a 65.86% of predictive abilities for the model. Finally, the model that resulted after the aforementioned model was subjected to optimal pruning is shown in **Figure 7**. The AUC ROC shows a 58.85% of predictive abilities for the model, and its curve is presented in **Figure 8**.

The performance measurements used to compare the different models generated are presented in **Table 4**.

Of the four decision trees obtained using the looping process, the decision was taken to further investigate the substantive aspects of decision tree no 3. This model was preferred for illustrative purposes. While decision tree no 4 ranked higher in terms of both accuracy and *F* measure, and for recall decision tree no 3 performed less well than decision trees no 1 and no 2, it nonetheless appeared to be the example most suited to explaining the model with regard to the sufficient number of variables and the depth of the clinical aspects from the assessments, in order to identify the risk zone in which the patients found themselves. This tree also performed well transversally across the different metrics compared. The decision tree continues to show the flow of responses as a trajectory of psychological variables that constitute the current situation of suicide risk (or otherwise) as described below in **Table 5**.

FIGURE 2 | Receiver operating characteristic (ROC) curve 1.

FIGURE 4 | Receiver operating characteristic (ROC) curve 2.

FIGURE 3 | Decision tree 02.

FIGURE 5 | Decision tree 03.

FIGURE 6 | Receiver operating characteristic (ROC) curve 3.

The variables generated by decision tree no 3 are explained substantively. The decision tree demonstrates the flow of responses in a trajectory of psychological variables that constitute a current state of suicide risk (or otherwise) as described below:

Substantive wording of answers that situate the patient in the not at risk zone (according to decision tree no 3).

Node 3: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is very significant or extremely significant as a reason not to commit suicide.

Node 6: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is insignificant, very insignificant, not very significant, or significant as a reason not to commit suicide; having experienced headaches in the past 7 days at times, frequently, and almost always; not totally agreeing with the statement "I am terrified when I feel alone"; having frequently or almost always felt satisfied with life in the last 7 days.

Node 8: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is insignificant, very insignificant, not very significant, or significant as a reason not to commit suicide; having experienced headaches in the past 7 days at times, frequently, and almost always; not totally agreeing with the statement "I am terrified when I feel alone"; having frequently or almost always felt satisfied with life in the last 7 days.

Node 11: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is very insignificant or not very significant as a reason not to commit suicide; having experienced headaches in the past 7 days frequently and almost always; not totally agreeing with the statement "I am terrified when I feel alone"; having at times, almost never, and never felt satisfied with life in the last 7 days; not totally agreeing with the statement "At times I feel empty inside."

Node 15: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is very insignificant or not very significant as a reason not to commit suicide; never having experienced headaches
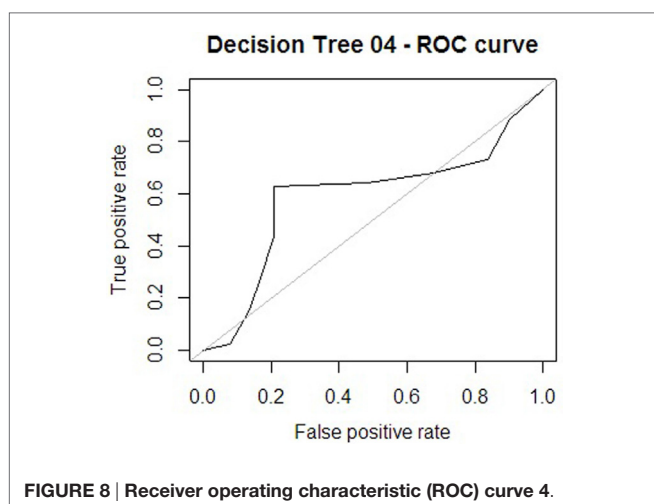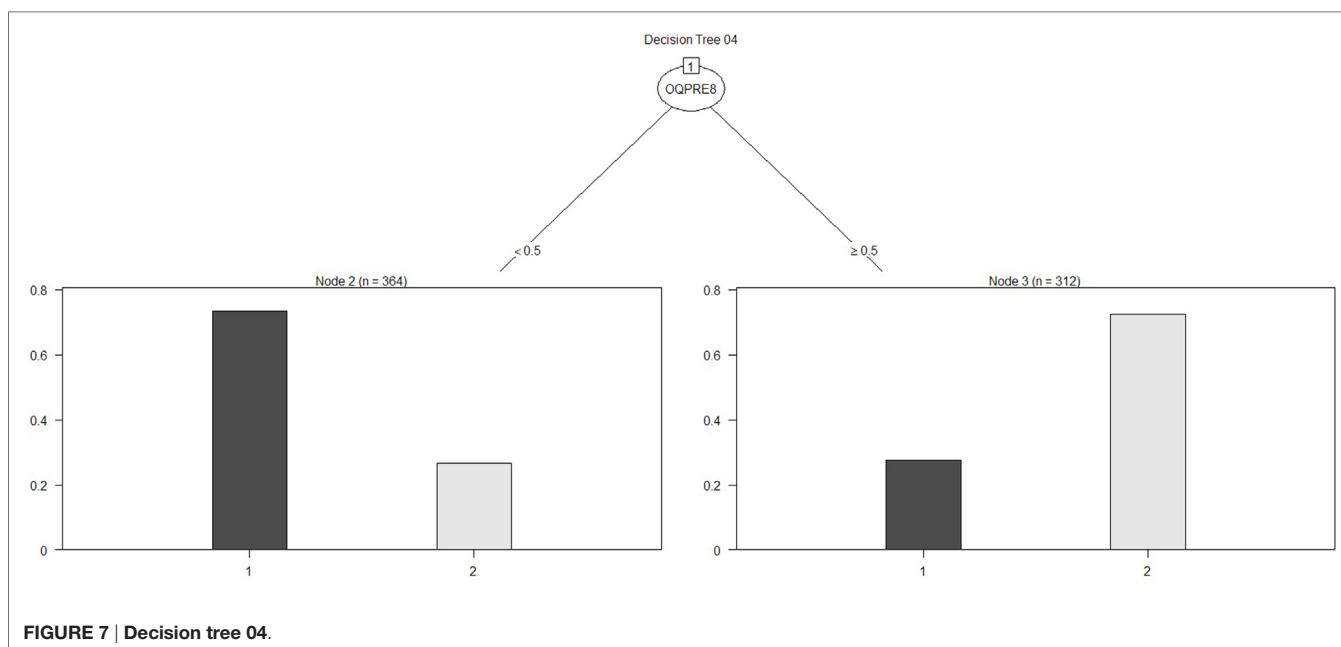
FIGURE 7 | Decision tree 04.

FIGURE 8 | Receiver operating characteristic (ROC) curve 4.

TABLE 4 | Performance measures models.

Metric	Tree decision 01	Tree decision 02	Tree decision 03	Tree decision 04
Accuracy	0.674	0.669	0.681	0.714
Precision	0.652	0.642	0.675	0.734
Recall	0.678	0.694	0.638	0.628
Specificity	0.670	0.647	0.721	0.792
F measure	0.665	0.667	0.656	0.677

in the last 7 days; very much agreeing and totally agreeing with the statement "In my relationships with others I think a lot about what they can give me."

Node 20: never having thought about taking one's life in the last 7 days; frequently and almost always feeling like a happy person; not totally agreeing or totally disagreeing with the statement "I feel great about myself whether I succeed or fail"; considering the sentence "I don't see any reason to bring death forward" as anywhere from not very important to extremely important.

Substantive wording of answers that situate the patient in the not at risk zone (according to decision tree no 3).

Node 12: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is insignificant, very insignificant, not very significant, or significant as a reason not to commit suicide; having experienced headaches in the past 7 days at times, frequently, and almost always; not totally agreeing with the statement "I am terrified when I feel alone"; having at times, almost never, and never felt satisfied with life in the last 7 days; totally disagreeing, very much disagreeing, slightly disagreeing, and agreeing with the statement "At times I feel empty inside"; considering that a fear of committing the act of suicide itself is very insignificant as a reason not to commit suicide.

Node 13: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide is insignificant, very insignificant, not very significant, or significant as a reason not to commit suicide; having experienced headaches in the past 7 days at times, frequently, and almost always; not totally agreeing with the statement "I am terrified when I feel alone"; having at times, almost never, and never felt satisfied with life in the last 7 days; totally agreeing and very much agreeing with the statement "At times I feel empty inside."

Node 16: never having thought about taking one's life in the last 7 days; considering that feeling too stable to commit suicide

TABLE 5 | Detail of variables decision tree.

	Condition	Item	Answer
Node 3 (NSR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	≥4.5	I am too stable to kill myself	Quite important and extremely important
Node 6 (NSR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	≥1.5	I have headaches	Sometimes, frequently, and always
DEQ 19	≥6.5	I become frightened when I feel alone	Strongly agree
Node 8 (NSR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	≥1.5	I have headaches	Sometimes, frequently, and always
DEQ 19	<6.5	I become frightened when I feel alone	Strongly disagree, disagree, fairly agree, agree, and strongly agree
OQ 31	<1.5	I am satisfied with my life	Frequently and always
Node 11 (NSR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	≥1.5	I have headaches	Sometimes, frequently, and always
DEQ 19	<6.5	I become frightened when I feel alone	Strongly disagree, disagree, fairly agree, agree, and strongly agree
OQ 31	≥1.5	I am satisfied with my life	Sometimes, rarely, and never
DEQ 16	<5.5	There are times when I feel "empty" inside	Strongly disagree, disagree, fairly agree, and agree
RFL 38	≥1.5	I am afraid of the actual "act" of killing myself	Quite unimportant, somewhat unimportant, somewhat important, quite important, and extremely important
Node 12 (SR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	≥1.5	I have headaches	Sometimes, frequently, and always
DEQ 19	<6.5	I become frightened when I feel alone	Strongly disagree, disagree, fairly agree, agree, and strongly agree
OQ 31	≥1.5	I am satisfied with my life	Sometimes, rarely, and never
DEQ 16	<5.5	There are times when I feel "empty" inside	Strongly disagree, disagree, fairly agree, and agree
RFL 38	<1.5	I am afraid of the actual "act" of killing myself	Quite unimportant
Node 13 (SR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	≥1.5	I have headaches	Sometimes, frequently, and always
DEQ 19	<6.5	I become frightened when I feel alone	Strongly disagree, disagree, fairly agree, agree, and strongly agree
OQ 31	≥1.5	I am satisfied with my life	Sometimes, rarely, and never
DEQ 16	>5.5	There are times when I feel "empty" inside	Strongly agree
Node 15 (NSR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	<1.5	I have headaches	Never and rarely
DEQ 56	≥5.5	In my relationships with others, I am very concerned about what they can give to me	Strongly agree
Node 16 (SR)			
OQ 8	<0.5	I have thoughts of ending my life	Never
RFL 25	<4.5	I am too stable to kill myself	Not at all important, quite unimportant, somewhat unimportant, and somewhat important
OQ 45	<1.5	I have headaches	Never and rarely
DEQ 56	<5.5	In my relationships with others, I am very concerned about what they can give to me	Strongly disagree, disagree, fairly agree, agree, and strongly agree
Node 20 (NSR)			
OQ 8	≥0.5	I have thoughts of ending my life	Rarely, sometimes, frequently, and always
OQ 13	<1.5	I am a happy person	Frequently and always

(Continued)

TABLE 5 | Continued

	Condition	Item	Answer
DEQ 48	≥2.5	I feel good about myself whether I succeed or fail	Disagree, fairly agree, agree, and strongly agree
RFL 45	≥2.5	I see no reason to hurry death along	Somewhat unimportant, somewhat important, quite important, and extremely important
Node 21 (SR)			
OQ 8	≥0.5	I have thoughts of ending my life	Rarely, sometimes, frequently, and always
OQ 13	<1.5	I am a happy person	Frequently and always
DEQ 48	≥2.5	I feel good about myself whether I succeed or fail	Disagree, fairly agree, agree, and strongly agree
RFL 45	<2.5	I see no reason to hurry death along	Not important and quite unimportant
Node 22 (SR)			
OQ 8	≥0.5	I have thoughts of ending my life	Rarely, sometimes, frequently, and always
OQ 13	<1.5	I am a happy person	Frequently and always
DEQ 48	<2.5	I feel good about myself whether I succeed or fail	Strongly disagree
Node 25 (NSR)			
OQ 8	≥0.5	I have thoughts of ending my life	Rarely, sometimes, frequently, and always
OQ 13	≥1.5	I am a happy person	Never, rarely, and sometimes
RFL 12	≥5.5	Live is all we have and is better than nothing	Extremely important
DEQ 3	≥6.5	I tend to be satisfied with my current plans and goals, rather than striving for higher goals	Strongly agree
Node 26 (SR)			
OQ 8	≥0.5	I have thoughts of ending my life	Rarely, sometimes, frequently, and always
OQ 13	≥1.5	I am a happy person	Never, rarely, and sometimes
RFL 12	≥5.5	Live is all we have and is better than nothing	Extremely important
DEQ 3	<6.5	I tend to be satisfied with my current plans and goals, rather than striving for higher goals	Strongly agree, agree, fairly agree, disagree, strongly disagree, and total disagree
Node 27 (SR)			
OQ8	≥0.5	I have thoughts of ending my life	Rarely, sometimes, frequently, and always
OQ13	≥1.5	I am a happy person	Never, rarely, and sometimes
RFL 12	<5.5	Live is all we have and is better than nothing	Quite unimportant, somewhat unimportant, somewhat important, and quite important

NSR, non-suicide risk (without risk of ideation or attempt); SR, with suicide risk; RFL, reasons for living; OQ, Outcome Questionnaire; DEQ, Depressive Experience Questionnaire.

is insignificant, very insignificant, not very significant, or significant as a reason not to commit suicide; never or almost never having experienced headaches in the past 7 days; not totally agreeing or very much agreeing with the statement "In my relationships with others I think a lot about what they can give me."

Node 21: almost always and frequently having thought about taking one's life in the last 7 days; frequently and almost always feeling like a happy person in the last 7 days; agreeing, slightly agreeing, very much agreeing, or totally agreeing with the statement "I feel good about myself whether I succeed or fail"; considering not seeing any reason to bring death forward as insignificant or very insignificant as a reason not to commit suicide.

Node 22: almost never, at times, and almost always having thought about taking one's life in the last 7 days; frequently and almost always feeling like a happy person in the last 7 days; totally agreeing or very much disagreeing with the statement "I feel good about myself whether I succeed or fail."

Node 25: almost never, at times, frequently, and almost always having thought about taking one's life in the last 7 days; almost never or at times feeling like a happy person in the last 7 days;

feeling that the fact that this life is the only one we've got and it's better than nothing is extremely significant as a reason not to commit suicide; totally agreeing with the statement "I generally feel that I am more suited to my plans and goals than trying to achieve higher objectives."

Node 26: almost never, at times, frequently, and almost always having thought about taking one's life in the last 7 days; almost never or at times feeling like a happy person in the last 7 days; feeling that the fact that this life is the only one we've got and it's better than nothing is extremely significant as a reason not to commit suicide; very much agreeing, agreeing, slightly agreeing, disagreeing, very much disagreeing, or totally disagreeing with the statement "I generally feel that I am satisfied with to my plans and goals rather than trying to achieve higher objectives."

Node 27: almost never, at times, frequently, and almost always having thought about taking one's life in the last 7 days; almost never or at times feeling like a happy person in the last 7 days; feeling that the fact that this life is the only one we've got and it's better than nothing is not significant, very insignificant, not very significant, significant, and very significant as a reason not to commit suicide.

These results translate into the following configuration by group. Without suicide risk: not having thought about taking one's life, feeling good about oneself (whether one succeeds or fails), not feeling empty inside, frequently feeling like a happy person and being satisfied with life, in addition to being highly concerned with what you receive from others. With suicide risk: having thought about taking one's life, having experienced frequent headaches, having been unsatisfied or not very satisfied with life lately, feeling empty inside at times, and not feeling like a happy person.

DISCUSSION

The use of decision tree techniques in artificial intelligence has allowed us to look at the state that precedes suicide. It is a process that is usually temporary, experienced as psychological discomfort, and in some cases, it feels like a psychologically unbearable moment (4, 5, 51). Using 345 variables that correspond to tools assessing subjective well-being, state, trait-expression of anger, depressive lifestyle, satisfaction with family functioning, and RFL, it was possible to generate four decision trees that can distinguish between groups with and without suicidal behavior. In this paper, we focus on one of these trees, which had 14 nodes, 6 of which related to the group without suicidal behavior and the remaining 8 corresponding to the group with suicidal behavior. These analyses have led us to see which factors are useful in detecting a person's vulnerability and can also guide psychotherapeutic interventions that might relieve and reduce the probability of future suicide attempts.

The knowledge contributed by these findings may mark a change in clinical application; through the use of tailored psychotherapeutic interventions to strengthen factors that protect from suicide and minimize factors that make a person vulnerable, for each individual case assessed using the techniques set out in this paper. The analytical methods we have proposed are new, and there are few studies on this topic that make use of DM tools. However, some recent research studies have resulted in similar recommendations that emphasize how these techniques can be applied to clinical practice (15, 52). Regarding the specific variables that we have found in this study, there are some similarities with findings obtained using other, more traditional, statistical techniques, which confirm their significance and strongly encourage clinics to use them not only in their treatment programs but also in the prevention of suicidal behavior.

From decision tree no 3, which was chosen to demonstrate this point, it was possible to distinguish factors using a limited but sufficient number of questions to differentiate the group without suicide risk at a specific moment in time. Among the answers that place patients in the "not at risk group," we found not having thought about taking one's life, feeling good about oneself (whether one succeeds or fails), not feeling empty inside, frequently feeling like a happy person and being satisfied with life, in addition to being highly concerned with what you receive from others. It has been proven that a feeling of satisfaction regarding one's own capabilities and caring for others (while maintaining the boundaries of autonomy and social support) are

experiences that generate psychological well-being and provide resources for development in life (53). These elements of self-worth and interpersonal relationships can be reinforced through psychotherapeutic intervention to promote and develop the patient's resources, including boosting them and adopting them for prevention.

Some of the answers that placed patients in a suicide risk configuration included having thought about taking one's life, having frequently experienced headaches, having felt dissatisfied or not very satisfied with life recently, feeling empty inside at times, and not feeling like a happy person. Factors relating to a depressive lifestyle with their dependent and self-critical style also stand out about being frightened when one feels alone, not worrying a great deal about what relationships with others can offer (54), and not feeling good about oneself whether one succeeds or fails, in addition to not thinking that feeling stable or fearing the act of suicide itself and an absence of reasons to die are significant reasons not to commit suicide (55).

This risk configuration is consistent with the hypothesis that having thoughts about taking one's life are potentially threatening if they are present in an intense and generalized manner (53). If this state is accompanied by the unbearableness of emotional discomfort alongside difficulties with finding adaptive solutions to adverse situations (56), it becomes a risk factor in which a suicide attempt appears as an escape mechanism from a state that is experienced as intolerable (57). For their part, fears of being alone or of being rejected are often associated with a struggle between attempting to be autonomous and being psychologically dependent on others, creating conflicting relationships that create discomfort and dysfunctionality (58).

There are also reasons to carry on living even when a person is going through a painful, demanding, or overwhelming situation. These findings are consistent with those published in the literature with regard to reasons that might be powerful protectors against suicide (1, 59) and might principally be associated with concern for family and a confidence in one's ability to face problems (24, 30, 60, 61).

This limited group of variables will enable the development of an assessment tool to track and detect suicide risk. The assessment of a small number of variables in time, which can be quickly and frequently applied and then evaluated by DM techniques, will enable us to recognize suicide risk behavior over time. Being able to detect the moment of psychological vulnerability, which differs for each patient, and its subsequent psychotherapeutic intervention may not only assist in alleviating the condition but also in preventing the risk of suicide. These interventions may be directed to reinforcing psychological well-being, feelings of self-worth and RFL.

It is important to mention that one of the limitations is that this study was based, for the most part, on patients suffering from mood disorders, which enabled us to control for the psychiatric diagnosis variable. However, these results cannot be generalized to other disorders associated with suicidal behavior, such as psychotic disorders or eating disorders, substance dependency disorders, or cognitive disorders (1, 62). The fact that a small number of the patients who were invited to participate in this research declined to do so, even though they met the inclusion

criteria, is also considered a limitation. These individuals were not taken into account and are not represented in the results.

It is possible that our results could be applied to a subgroup of subjects. We know that a significant proportion of suicides occur without the subject ever having seen a doctor (63). Our aim is to intervene for the group that could benefit from intervention. Like other conditions, such as obesity and metabolic diseases, therapeutic options often do not enable the treatment of all the subjects, rather they focus on groups of subjects who are open to receiving them. Developing a strategy for those that might benefit them is always a good option in an area with so many different needs. As we have mentioned, the usefulness of these results is limited to a population, and it would doubtlessly be extremely interesting to see how this model behaved for a different population.

We feel it is important to mention that the measurements taken were cross-sectional and show the state of the patient at a precise moment. The expression of these characteristics identifies a particular state surrounding suicidal behavior and has allowed us to determine what factors might be relieved and which could be reinforced in that specific moment of time. It will be necessary for future studies to evaluate the trajectory of these configurations of factors with regard the evolution of suicide risk.

This could be carried out through longitudinal studies that would allow us to shed greater light on the evolution of suicide risk (64). This model could subsequently be developed using an assessment tool that would make use of an artificial intelligence methodology to allow for automated learning, generating a model for detecting suicide risk that would update per the trajectory of patient assessments. It would be possible to do this using a smaller quantity of questions than that used in the original study, allowing for quicker application.

New studies that distinguish between protective factors and suicide risk factors, as well as their configurations, will be necessary. It would be of great interest to reach a better understanding of the state of psychological discomfort that is experienced in an acute fashion, the loss of a sense of self, and reasons for staying alive despite adversity.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Comité Ético Científico from Medicin Faculty of Pontificia Universidad Católica de Chile with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Comité Ético Científico de la Facultad de Medicina de la Pontificia Universidad Católica de Chile.

AUTHOR CONTRIBUTIONS

The authors listed bellow have contributed as follows: SM, JB, and OE made substantial contributions to the conception of the work and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; and final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FG and AO made substantial contribution to the analysis of data for the work; revising it critically for important intellectual content; and final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CM, MM, RF. CN, TS, and AT made substantial contribution to the acquisition and interpretation of data for the work; revising it critically for important intellectual content; and final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Responses to Traumatic Brain Injury Screening Questions and Suicide Attempts among Those Seeking Veterans Health Administration Mental Health Services

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Background: Psychometrically sound screening tools available to aid in the identification of lifetime history of traumatic brain injury (TBI) are limited. As such, the Traumatic Brain Injury-4 (TBI-4) was developed and implemented in a Veterans Health Administration (VHA) mental health clinic. To provide information regarding both the predictive validity and clinical utility of the TBI-4, the relationship between screening results and future suicide attempts was evaluated.

Objective: The aim of this study was to determine whether a positive screen on the TBI-4 was associated with increased risk for suicide attempt within 1-year post screening.

Methods: The TBI-4 was administered to 1,097 Veterans at the time of mental health intake. Follow-up data regarding suicide attempts for the year post-mental health intake were obtained from suicide behavior reports (SBRs) in Veteran electronic medical records (EMRs). Fisher's exact tests were used to determine the proportion of suicide attempts by TBI-4 status.

Results: In the year post TBI-4 screening, significantly more Veterans who screened positive had a documented suicide attempt as compared to those who screened negative ($p = 0.003$).

Conclusion: Those with a positive TBI screen at mental health intake had a higher proportion of SBRs than those who screened negative for TBI. Findings provided further psychometric support for the TBI-4. Moreover, results suggest the inclusion of this screen could prove to be helpful in identifying those who may be at risk for future suicide attempt within 1-year post screening.

Keywords: traumatic brain injury, suicide, Veteran, psychometrics, predictive validity, screening

INTRODUCTION

Traumatic brain injury (TBI) is a frequently noted health condition among individuals seeking Veteran's Health Administration (VHA) services. For example, work by Brenner and colleagues (1) suggested that 45% Veterans seeking services at one mental health clinic had a probable history of lifetime TBI. As such, the Department of Veterans Affairs (VA) has made TBI screening, diagnosis, and treatment a priority (2). Although recent attention has been focused on developing a screening tool for deployment-related TBI for Service Members returning from the conflicts in Iraq and Afghanistan (3), there remains a lack of psychometrically sound screening tools for lifetime history of TBI that could be used across Veteran cohorts.

The Traumatic Brain Injury-4 (TBI-4) was developed to address this need and was implemented as part of the mental health intake process in a Veterans Affairs Medical Center Mental Health Clinic (1). It is composed of the following four questions: (1) Have you ever been hospitalized or treated in an emergency room following a head or neck injury?; (2) Have you ever been knocked out or unconscious following an accident or injury?; (3) Have you ever injured your head or neck in a car accident or from some other moving vehicle accident?; and (4) Have you ever injured your head or neck in a fight or fall? The second question, which specifically asks about a loss of consciousness as a result of an accident or injury, contains elements necessary to meet TBI diagnostic criteria (injury event with an associated alteration in consciousness), whereas the other three questions (1, 3, 4) solicit information about risky situations and behaviors that are commonly associated with sustaining a TBI (4). As part of a study, evaluating the prevalence of TBI among Veterans seeking VA mental health services (1) patients' responses to the TBI-4, administered as part of their mental health intake, were compared to their results from the Ohio State University TBI-ID (OSU TBI-ID), a structured clinical interview for identifying lifetime history of TBI (5). The prevalence of probable lifetime history of TBI, defined as a positive response to Q2 of the TBI-4, within the study population was 45% (95% CI, 42–47) (1), which was significantly higher ($p < 0.0001$) than was reported in previous work examining a 1-item TBI screener in individuals seeking substance abuse treatment (31.7%) (6). Using the OSU TBI-ID (5) as the criterion standard for establishing probable lifetime history of TBI and a positive response to Question 2 as the criterion for a positive screen, the sensitivity and specificity of the TBI-4 were 0.58 and 0.77, respectively (1).

It should also be noted that the practice of screening for TBI, particularly among Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans is not without some controversy. According to Vanderploeg and Belanger (7), screening procedures should be implemented "to identify a disease, condition, or risk factor early, thus enabling earlier intervention and management in the hope of reducing mortality and suffering" (p. 212). Regarding history of mild TBI, they suggested that these criteria were not met (e.g., mild TBI is not a progressive condition). In response, Bahraini and Brenner (8) suggested that the costs versus benefits of TBI screening should be evaluated empirically and predicated, at least in part, on whether screening can help identify risk factors for other health conditions. In specific, Bahraini and Brenner (8) suggested that TBI screening may inform prevention strategies aimed at reducing risky behaviors (e.g., suicide attempts).

Moreover, evaluating whether a screening tool is predictive of outcomes often associated with a condition of interest can provide additional psychometric support. For example, Olson-Madden and colleagues (9) found that individuals with a positive screen on the TBI-4 (defined as a positive response to Question 2) had more psychiatric hospital stays than those with a negative screen. The authors suggested that this finding provided support for implementation of this screening tool in VHA mental health settings.

Bahraini et al. (10) performed a systematic review of studies related to TBI and suicide published since the beginning of 2007. Evidence from the review provided support for the association between TBI and elevated suicide risk. Studies included in the review found increased risk for death by suicide following TBI in civilian populations with moderate risk of bias (11) and Veteran populations (12) with low risk of bias. A case–control study examining all suicide deaths among those serving in the United States military with moderate risk of bias did not show a significantly higher rate of TBI among those who died by suicide (13). Two studies examining whether Veterans with comorbid PTSD and mild TBI had an increased likelihood of suicidal behaviors as compared to Veterans with PTSD alone reported non-significant results and had high risk of bias (14, 15). Another study found a significantly higher rate of suicide ideation among patients with TBI as compared to healthy controls with moderate risk of bias (16). Overall, there is evidence suggesting that those with a history of TBI are at risk for suicidal behavior (10, 17). As such, it was hypothesized that Veterans who screened positive to a one-question screen for TBI (Question 2 of the TBI-4), in the context of the 4-question TBI screener, would have more suicide attempts during a 1-year follow-up period then those with a negative screen.

MATERIALS AND METHODS

Cohort

The study sample includes 1,097 Veterans who were given the TBI-4 by a mental health clinician during the standard VA Eastern Colorado Health Care System (ECHCS) mental health intake, between December 2006 and February 2010, and did not seek care at any other VA facility during the 1-year follow-up period. Demographic information was obtained from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW), which is a national repository of data from VHA clinical and administrative systems. The study was approved by the Colorado Multiple Institutional Review Board (COMIRB), as well as the Eastern Colorado Healthcare System Research and Development Service.

Outcome Measures
Traumatic Brain Injury-4
The TBI-4 was used to identify individuals who had probable lifetime history of TBI. The TBI-4 is a four-question screener

used to identify those with a probable lifetime history of TBI. The questions are designed with wording chosen to minimize stigma (i.e., "head" versus "brain") (6). The screen is also consistent with recommendations from the Center for Disease Control and Prevention (18) concerning screening for acute injuries. Individuals who answered "Yes" to the second question on the TBI-4, "Have you ever been knocked out or unconscious following an accident or injury?" were considered to have screened positive. TBI-4 data were collected from local electronic medical records (EMRs).

Suicide Attempts

It is VHA policy that all facilities identify and track patients at high risk for suicide. A suicide behavior report (SBR) is the mandatory documentation completed by VA clinical staff members within a patient's EMR when they become aware of "serious suicidal ideation" or suicidal behaviors (i.e., behavior that is self-directed and deliberately results in injury or the potential for injury to oneself with evidence, either implicit or explicit, that the individual wishes to die, means to kill himself, and understands the probable consequences of his actions or potential actions) (19). Currently, SBR events are tracked in the Suicide Prevention Application Network (SPAN) database (20); however, this database does not capture events that occurred prior to October 1, 2008. It should be noted that within the ECHCS, SBR documentation commenced prior to this date. Given that the earliest TBI-4 screen in this study took place in December 2006, the text integration utilities (TIU) domain in the CDW was utilized to identify clinical notes with SBRs for each of the Veterans in our study cohort. Within the EMR, each clinical note has a title associated with it. Notes with the title of "Suicide Behavior Report" were selected. Additionally, all notes that had the key phrase "Description of event," which is part of the SBR template used in the ECHCS EMR were also selected. Notes were pulled if they met at least one of these two criteria. Once the documents were confirmed to be SBRs, they were reviewed by two study clinicians. Using the Self-Directed Violence Classification System (19), the clinicians classified the SBR events into those that met criteria for a suicide attempt (i.e., a non-fatal self-inflicted potentially injurious behavior with any intent to die as a result of the behavior) and those that did not.

Statistical Analysis

Data were analyzed with SAS 9.2 or higher. Chi-squared, Fisher's exact, or t tests were used as appropriate for demographic comparisons between TBI-4 positive and negative Veterans. Fisher's exact tests were used to determine differences in the proportion of Veterans with a suicide attempt by TBI-4 status, with a significance level of 0.05. Exact Binomial 95% confidence intervals were also calculated.

RESULTS

Data from the CDW were used to determine Veterans' age, sex, marital status, race/ethnicity, period of military service, and eligibility of VA service (**Table 1**). Characteristics of the group that

TABLE 1 | Subject demographics ($n = 1,097$).

	TBI-4 screen		
	Positive ($n = 468$)	Negative ($n = 629$)	p-Value
Mean age	47.8 (±12.9)	48.2 (±13.6)	0.68
Gender			0.0001
Male	94.4% (442)	87.6% (551)	
Female	5.6% (26)	12.4% (78)	
Marital status			0.20
Married	30.8% (144)	35.5% (223)	
Divorced/separated/widowed	45.5% (213)	40.7% (256)	
Single	22.9% (107)	23.1% (145)	
Missing/unknown	0.9% (4)	0.8% (5)	
Race/ethnicity			0.002
Caucasian	76.9% (360)	68.0% (428)	
African-American	10.0% (47)	17.2% (108)	
Hispanic	0.6% (3)	0.5% (3)	
Other	1.9% (9)	3.0% (19)	
Missing	10.5% (49)	11.3% (71)	
Period of service			0.37
Vietnam Era	41.2% (193)	38.2% (240)	
Post-Vietnam	21.4% (100)	21.0% (132)	
Persian Gulf War	32.7% (153)	33.9% (213)	
Other	4.7% (22)	7.0% (44)	
Eligibility			0.69
Non-service connected	34.2% (160)	34.5% (217)	
Non-service connected, pension	5.8% (27)	4.13% (26)	
Service connected <50%	20.3% (95)	22.3% (140)	
Service connected 50–100%	39.3% (184)	38.5% (242)	
Other	0.4% (2)	0.6% (4)	

TABLE 2 | Suicide behavior reports ($n = 1,097$).

	Percentage of sample that had a suicide behavior report (n)	95% exact binomial confidence interval
Question 2 positive ($n = 468$)	1.50 (7)	0.6–3.1
Question 2 negative ($n = 629$)	0.00 (0)	0.0–0.6

Fisher's exact, p = 0.003.

screened positive on the TBI-4 differed from the TBI-4 negative group in gender ($p = 0.001$) and race/ethnicity ($p = 0.002$). Of the participants who screened positive on Question 2 of the TBI-4, 1.50% ($n = 7$) of them had a suicide attempt 1-year post-assessment compared to 0.00% ($n = 0$) of participants who were Question 2 negative (see **Table 2**).

DISCUSSION

In a 2013 publication, Bahraini and Brenner suggested that the costs versus benefits of TBI screening should be evaluated empirically (8). That is, screening for TBI may help to identify those at risk for negative outcomes and facilitate prevention strategies. Findings from this study suggest that among those seeking mental health services, individuals who screen positive for a history of TBI are at increased risk for suicide attempt, as documented

by SBRs, during the 1-year period following intake. These results support both the clinical utility and the predictive validity of the TBI-4. Moreover, when considered in the context of previous findings regarding the screening tool (1, 9), the results provide additional support for implementing the TBI-4 at the time of mental health intake.

Additional follow-up and prevention efforts among this cohort may be warranted. For example, additional and perhaps more intensive efforts aimed at engaging such individuals in treatment are likely indicated. It should be noted that for many who were evaluated, their history of TBI occurred many years prior to the mental health intake. In addition, study participants were not assessed for other comorbidities that are associated with suicidal behavior. As such, it is not clear whether the patients' TBI is directly associated with suicidal behavior. It may have been that this history of TBI created vulnerability that was further exploited by factors that brought these individuals in for mental health treatment. This assertion is consistent with previously published work by Brenner and colleagues (8, 21) regarding the accumulation of disadvantaged risk factors among Veterans with TBI resulting in cascades of physical and psychiatric outcomes. As per Bahraini and Brenner (8) early identification of such risk factors and prevention of future accumulation may help "shift a person's health trajectory away from chronic illness and disability."

Since 2007, the VA has significantly increased efforts to understand Veteran suicide in an effort to reduce its occurrence (20). Data from this study along with other work in the area of TBI and suicide suggest that continued efforts to identify those with a history of TBI seeking mental health services and evaluation of potentially increased suicide risk among this cohort are warranted. Findings regarding the TBI-4 suggest that it may be a useful tool in this process. Further information regarding screening, assessment, and treatment of Veterans with TBI seeking mental health services can be found at http://www.mirecc.va.gov/visn19/tbi_toolkit/.

Study Limitations

Several study limitations should be highlighted including the fact that only records from participants who maintained care within the ECHCS (versus those who transferred care to other VA facilities) were included, which removed 396 individuals from the initial sample. Veterans who sought care outside of ECHCS were not included in data shown here because SBRs may not have existed in the facilities where they were seeking care, as initiation of SBRs nationally did not occur until April 24, 2008. The use of SBRs at ECHCS was not fully implemented until September 2007; thus, SBRs may not have existed for the full year post-TBI-4 for a portion of our cohort. There may also have been suicide attempts that clinicians were aware of, but were not captured by SBRs leading to a possible underestimation of overall suicide attempts; however, there is no evidence suggesting that there would be a difference in reporting suicide attempts through SBRs between those with a history of TBI and those without. Finally, although our findings were significant the total number of individuals with a suicide attempt during the 1-year period was relatively small. As such, if the TBI-4 was used to identify individuals at risk for suicide attempts it would yield a high rate of false positives. However, suicide and suicidal behaviors are rare events; thus, any tool used to screen for suicidal behavior is likely to overestimate the number of individuals at risk. Considering the lack of available screening tools that can be used to identify those at increased risk for suicide, a short screener that can identify most or all individuals that are at risk for suicidal behavior, such as the TBI-4, can be very useful in clinical practice.

Future Research

Strategies for identifying those at risk for suicide attempts and implementing evidence-based prevention interventions continues to be an area of focus within the VHA. Toward this end, future work in this area could include examination of national VHA SBR data for those with a history of TBI over a longer follow-up period. Moreover, as per Bahraini et al. (10), there is a dearth of evidence regarding suicide prevention interventions for those with a history of TBI. Further research aimed at identifying such evidence-based interventions is needed.

ETHICS STATEMENT

This study was approved by Colorado Multiple Institution Review Board (COMIRB) and Eastern Colorado Healthcare System Research and Development Service. A waiver of consent was granted by COMIRB for the research presented in this manuscript.

AUTHOR CONTRIBUTIONS

LB, BH, JO-M, JH, and JF made substantial contributions to the conception and design of this research project. AS and JH were responsible for acquiring results of the TBI-4 screen from patient medical record. TH was responsible for the acquisition of data from national VA data sources. LB and BM provided clinical expertise and interpretation of notes pulled from patient medical records. TH and JF analyzed and interpreted the data for this project. AS and LB drafted this work which was then reviewed and revised by all other authors (TH, JF, BH, JO-M, BM, and JH). All authors approved the final version of the work that is being submitted.

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Suicide Prevention Public Service Announcements Impact Help-Seeking Attitudes: The Message Makes a Difference

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Suicide continues to be one of the most serious public health challenges. Public service announcements (PSAs) are frequently used to address this challenge, but are rarely sufficiently evaluated to determine if they meet the intended goals, or are associated with potential iatrogenic effects. Although it is challenging to assess the relative impact of different PSA modalities, our group previously noted that one billboard message failed to show the same benefits as one TV ad [e.g., Klimes-Dougan and Lee (1)]. The purpose of this study was to extend these findings to test critical aspects of suicide prevention billboard messaging. Although both simulated billboard messages presented had identical supporting messages, we predicted that the more personal billboard message, focused on saving one's life, would cause more favorable help-seeking attitudes than the message focused on suicide. Young adult university students (N = 785) were randomly assigned to one of three conditions; one of two billboard simulations or a TV ad simulation. Help-seeking attitudes, maladaptive coping, and reports of concern and distress were evaluated. The results of this study suggest some relative benefits in endorsement of favorable help-seeking attitudes for one of the billboard conditions – stop depression from taking another life. Although further research is needed to determine what methods will alter the risk for suicide in the population, the results of this study provide a useful first step showing that some billboard messaging may favorably influence help-seeking attitudes.

Keywords: suicide prevention, public service announcements, billboards, universal prevention, young adults, help-seeking

INTRODUCTION

Suicide is a significant contributor to lost years of life among young adults, and it was the second leading cause of death among 15–29 years olds in 2012 (2). The importance of implementing suicide prevention programs is understood and widely accepted, but preventing suicide remains an elusive goal. It is likely that suicide prevention efforts will benefit from the inclusion of a range of efforts from relapse prevention, means restriction, to other universal preventive interventions (3). The focus of this paper is on universal prevention programs, those programs that are dispersed across

a population. Specifically, the focus is on public awareness campaigns. Despite the proliferation of suicide prevention campaigns over the last three decades, many of the campaigns have not been rigorously studied and lack an empirical basis (4, 5). Some suicide prevention efforts fail to produce the desired outcomes. Some approaches may even inadvertently produce iatrogenic effects. Possible iatrogenic effects include messages that normalize suicidal behavior, reinforce biases that prevent individuals from seeking help, or heighten susceptibility for suicide contagion [e.g., Ref. (5, 6)]. More research is needed to validate the effectiveness of suicide prevention campaigns, before taking them to scale.

There are numerous challenges to evaluating suicide prevention programs. For example, it is difficult to show treatment effectiveness among infrequently occurring behaviors, such as deaths by suicide or even suicide attempts (7). The U.S. Surgeon General has called for researchers to develop alternative methods for evaluating suicide prevention efforts beyond simply a reduction in the number of suicides (8). Intermediate measures of intervention effectiveness include assessing changes in help-seeking attitudes and behaviors (9, 10).

Help-seeking is defined as the act of seeking assistance from an informal (e.g., friend) or formal (e.g., mental health professional) source (11). Help-seeking is thought to be a critical step between understanding that there is a problem and seeking out the necessary services for assistance (12). Barriers to help-seeking include stigma and other maladaptive beliefs [e.g., Ref. (13, 14)]. Increased help-seeking is associated with lower suicide risk (15). If prevention programs are to succeed, help-seeking must be promoted. And yet, there is mixed evidence if suicide prevention efforts are effective at increasing help-seeking attitudes and behaviors, especially in those who are at high risk for suicide (9). Similarly, despite the evidence that many individuals who experience depressive symptoms or suicidal ideation use more maladaptive coping and isolative behaviors (15), there is mixed evidence if preventive interventions alter maladaptive coping strategies (16, 17). It is a priority to promote enhanced adaptive attitudes and behaviors.

There is a limited understanding of what features of suicide prevention public awareness campaigns show the most impact. Some strides have been made in assessing the acceptability and impact of public service announcements (PSAs) through the media (e.g., TV ads, radio ads, websites) or printed material (e.g., billboards, flyers, posters). Often these campaigns target white, adult males, the group that accounts for the highest risk of suicide, or target significant others who may serve as sources of referral (e.g., wives, girlfriends, friends). For example, Daigle et al. (18) measured the efficacy of a multimedia-based prevention approach (*via* radio, television, and billboards) intended at reducing suicide rates among males in Quebec, Canada. They exclusively evaluated the results of this campaign and targeted a male audience (e.g., *Pain is not gender-specific – yet 80% of suicides are committed by men*). Male participants exposed to the campaigns gained more knowledge of suicide facts and resources, yet there was no evidence that the campaigns impacted the participant's intention to utilize mental health services.

Given that universal prevention efforts are viewed by all ages, the impact has also been assessed in other groups, even for groups that were not the target of the campaign. That is, while the target group is rarely adolescents or young adults [for an exception, see Ref. (19)], research is needed for this age group as they are at highest risk of iatrogenic effects of suicide prevention efforts [e.g., Ref. (6)]. A series of simulation studies evaluated the benefits and risks associated with viewing a PSA. In one study, high school students were randomly assigned to a billboard, a TV ad, or a no information condition. The results revealed some concerns about the effectiveness of PSAs, particularly the billboard condition with high-risk youth (20). When this study was conducted with college students, those in the billboard condition were less likely to endorse adaptive help-seeking attitudes than those in the no information condition or in the TV ad condition (1). The results of these findings led the authors to conclude that this particular billboard was largely without benefits. The researchers also noted that it remains unclear if the modality (billboard) or message (e.g., content of the message) accounted for the unfavorable outcomes associated with viewing this billboard.

The purpose of this study was to examine individual differences in help-seeking attitudes, knowledge of maladaptive coping behaviors, and reported concerns about PSA exposure among young adults in response to two different simulated billboard messages and a simulated TV ad. Here, our goal was to evaluate if subtle features of the simulated billboard message made a difference. The two messages assessed were identical in every way (e.g., the call to action was *see your doctor*) with the exception of the central message (either the original message – *Prevent Suicide: Treat Depression* or the alternative message – *Stop depression from taking another life*). The wording on the alternative billboard was intended to motivate the viewer by being more personal, by stressing the benefits valued by the intended audience that offset the costs of taking action (21), and by having the viewer consider the implicit directive of acting to save one's life. Additionally, the alternative billboard was intended to decrease psychiatric jargon and avoid the possible stigma associated with the word "suicide" (22). The hope is that this work will promote a better understanding of the utility of campaign messages so that the intended goal of saving lives can be more fully realized.

MATERIALS AND METHODS

Participants

A total of 785 part- or full-time university students between the ages of 18 and 34 years old (M = 21.9; SD = 2.8) served as participants for this study. The sample consisted of primarily upper level undergraduate students (81.6%). The majority of participants were females (79.2%). The majority of participants primarily identified as Caucasian (65.2%), followed by Latin American (21.9%), Native American (6.3%), Asian American (4.5%), and African American (1.4%). Nearly 89% of participants were born in the United States. There were 406 participants in the original billboard group, 279 participants in the alternative billboard group, and 100 participants in the TV ad group. Because the focus of this study is on young adult perceptions, those who were 35 years of age or older were excluded from this study (N = 30).

Dependent Variables
Help-Seeking Attitudes and Maladaptive Coping

The help-seeking attitudes and endorsement of maladaptive coping behavior scales were adapted from Gould et al. (15), who reported Cronbach's alpha coefficients of 0.60 for the help-seeking and 0.54 for the maladaptive coping scale based on scales derived from factor analysis.

The five-item help-seeking attitudes scale required participants to rate their response to a suicidal friend on a five-point scale (0 = "never" to 4 = "always") on a number of help-seeking behaviors (i.e., get advice from another friend, tell my friend to see a mental health professional, tell my friend to call a hotline, talk to an adult about my friend, tell my friend to talk to his or her parents). An average help-seeking score was calculated for each participant. The score used in the analysis, which ranged from 0 to 4, reflects the participant's average endorsement of help-seeking attitudes.

Participants were asked to indicate if they agreed or disagreed with seven statements that reflected maladaptive coping strategies (i.e., people should be able to handle their own problems without outside help, suicide is a possible solution to problems, if you are depressed it is a good idea to keep your feelings to yourself, drugs and alcohol are a good way to help someone stop feeling depressed, keep it a secret, talk to my friend without getting anyone else's help, I would not take it seriously). Three items were on the same five-point scale as the help-seeking questions that were converted to agree-disagree statements. The total number of maladaptive coping behaviors endorsed was calculated for each participant.

Concern or Distress

An additional item was used to evaluate if viewing the PSAs resulted in feelings of concern and/or distress. Participants rated their level of concern using a five-point scale ("none" to "a lot").

Covariates
Demographic/Screening Questionnaire

The Demographic and Screening Questionnaire included questions regarding sex (male = 0; female = 1), age, and race/ethnicity, based on endorsement of one of six groups (European American-Caucasian, African American, Asian American, Latin American/Hispanic, Native American). This was later reduced (non-Caucasian = 0, Caucasian = 1). To assess the experience with depressive symptoms, participants were asked – "Have you felt sad almost all of the time or been depressed?" and if yes, "Have you gone to see someone (your doctor, a counselor, etc.) when you were depressed?" To assess suicide attempts, participants were asked – "Have you ever done anything to try to kill yourself (attempted suicide)?" These items were adapted from the wording of structured diagnostic interviews and a screening tool developed by Kroenke et al. (23). A broader index of risk status was based on those who screened positive for experience with depressive symptoms, and/or suicide attempts were considered high risk (low-risk status = 0 vs. high-risk status = 1). Additionally, a more narrow index of risk status, based on suicide attempt history, was considered for some follow-up analyses (no suicide attempt = 0 vs. suicide attempt = 1).

Simulated PSA Exposure

All types of messaging tested here were developed by Suicide Awareness Voices of Education (SAVE), a Minneapolis-based non-profit suicide prevention agency, as part of a statewide public service campaign. In both billboard conditions, participants were asked to imagine they viewed it while driving in a vehicle. They were then shown a large PowerPoint projection (approximately 3 × 5 ft) of the billboard for 5 s. The original billboard read "*Prevent suicide. Treat depression.*" The alternative billboard read "*Stop depression from taking another life.*" Both billboards provided the directive, "*See your doctor*" and had the SAVE website listed. They also had both, the same depiction of a middle-aged, white male on the right of the billboard and a cardiac rhythm depicted along the bottom border.

Similarly, in the TV ad condition, participants were asked to imagine they saw the PSA while watching television. They were then presented with a 30-s video that featured several adults of different sexes and races. The video described depression as "*a brain illness,*" and noted salient symptoms of depression. The message went on to have components of both billboards ("*If you see the symptoms of depression, get that person to a doctor. With medical help, depression can be treated, suicide can be prevented. Learn how to stop depression from taking another life.*"). The video ended with the printed message "*Prevent suicide. Treat depression.*" with the phone number of SAVE.

Procedure

The Institutional Review Board at the University of Minnesota approved this research proposal. Recruitment took place between 2006 and 2011. Participants were recruited from 17 behavioral science courses at the University of Minnesota. They were told this study examined the impact that PSAs have on suicide and depressive symptom knowledge, perceptions, and behaviors. The experiment was carried out during or after class. Participation was voluntary, and alternative class assignments were available for those who chose not to participate in this study. All participants completed a brief Demographic/Screening Questionnaire. Participants were then randomly assigned to conditions. Students were either randomly assigned to one of the two billboard conditions or one of the three conditions (original billboard, TV ad, and no information). Participants were generally asked to wait outside the classroom when their condition was not being shown.

Immediately after participants were exposed to the simulated PSA (i.e., billboards or TV ad), they were asked to complete the Suicide Awareness Questionnaire. The questionnaire was adapted for this study to evaluate participants' (1) perceptions of the utility of PSAs, (2) knowledge of depressive symptoms, (3) normative beliefs (i.e., estimates of suicidal risk), and (4) knowledge of help-seeking and maladaptive coping attitudes. The focus here is on attitudes, but for more detailed information on the components of the Suicide Awareness Questionnaire, see Ref. (1).

To ensure participant anonymity, consent forms were completed and filed separately from questionnaires. Upon completion of the study, the researchers provided information about the university mental health services in the event that participants experienced distress from participating in research on the topic of suicide. The results pertaining to the no information condition

are reported in Klimes-Dougan et al. (1) and are not included here. Instead, the focus here was on clarifying differences across PSAs. Study participation rate was 92%.

Data Analyses

We used SPSS v. 22 (24) to conduct all the analyses. First, we examined the descriptive statistics for the demographic variables (e.g., sex, age, risk status) for the entire sample and then for the three conditions (see **Table 1**). Second, we calculated product moment correlations, point-biserial correlations, or phi coefficients to estimate the relationship between the potential covariates (i.e., demographic variables) and the dependent variables. Third, we conducted a series of multivariate regression analyses to consider the relationship between PSA conditions and reported help-seeking attitudes, endorsement of maladaptive coping behaviors, and reports of concern/distress after viewing the PSA. We included covariates based on their correlations with the dependent variables (age, sex, and race) and those that differed across group (risk status). Finally, we conducted a series of exploratory follow-up analyses to see if there was a significant interaction between risk status (with both the broad index – low risk vs. high risk and also the narrow index – no suicide attempt vs. suicide attempt) and group membership. We included covariates that were significant predictors from the regression models in these follow-up analyses. For all the analyses, the criterion for statistical significance was set at $p < 0.05$.

RESULTS

Descriptive Statistics and Preliminary Analysis

Demographic information for participants in each condition is presented in **Table 1**. The PSA groups did not differ on the percentage of female participants, the percentage of Caucasian participants, or on the number of reported previous suicide attempts. However, there were significant differences for participant age and the percentage of high-risk participants with previous depression or suicide attempt (although not for the narrowly defined suicide attempts).

Among all participants, the average score on the help-seeking scale was 2.72 (SD = 0.64), suggesting that they were likely to "sometimes" endorse the use of help-seeking behaviors for a friend. Skewness (−0.28) and kurtosis (0.24) statistics, along with visual inspection of a histogram and quartile plots, indicated that participant responses reasonably approximated a normal distribution.

By contrast, responses on the maladaptive coping strategies scale and the concern/distress question were skewed. Participants indicated if they agreed or disagreed with seven statements that represented maladaptive coping strategies. The range of responses was from 0 to 4. Approximately 48% of participants did not endorse a maladaptive coping strategy, 32% of participants endorsed one strategy, 14% endorsed two strategies, 5% endorsed three strategies, and 1% endorsed four strategies. The median response was endorsing one of the seven maladaptive coping strategies. Participants' responses were positively skewed (1.07) and slightly leptokurtic (0.57). For the following analyses, we

TABLE 1 | Participant demographics by condition.

Characteristic	Original billboard	Alternative billboard	Video	F/χ^2	P
N	406	279	100		–
Sex (female)	77.8%	79.2%	85.0%	2.51	0.286
Mean age (SD)	21.8 (2.7)	21.7 (2.7)	22.6 (3.3)	4.39	0.013
Race (Caucasian)	75.8%	75.5%	83.0%	2.61	0.272
Depression/suicide risk[a]	36.2%	27.2%	31.0%	6.17	0.046
Previous suicide attempt[b]	7.4%	6.8%	7.0%	0.08	0.961

[a]Participants who indicated previous experience with depression and/or suicide were identified as high risk.
[b]Participants who indicated a previous suicide attempt were identified as high risk.

recoded the maladaptive coping score as a dichotomous variable (0 = no endorsement of maladaptive strategies; 1 = endorsement of one or more maladaptive coping strategies).

Participants were also asked to rate their level of concern/distress after viewing the PSA on a 1 to 5 scale. The median response was 1 ("none") (M = 1.6, SD = 0.68), indicating a low level of concern or distress after viewing the PSA across all participants. Responses were positively skewed (1.92) and leptokurtic (4.11). Due to the skew of the data, the concern/distress score was recoded as a dichotomous variable (0 = no concern/distress or 1 = at least some concern/distress).

Correlations

As shown in **Table 2**, correlations were generally weak across all variables. In this sample, the males were slightly older; there were more females who endorsed a history of depression or suicidal behavior and more non-Caucasians with a history of suicide attempt. Sex, age, and race were significantly associated with the average help-seeking score. Females, younger adults, and Caucasians were more likely to endorse help-seeking attitudes. Sex, race, and reported history of suicide attempts were significantly associated with the dichotomized maladaptive coping score. Males, non-Caucasians, and those with a history of suicide attempts were more likely to endorse maladaptive coping attitudes. Sex and race were associated with concern/distress after viewing the PSA. Females and Caucasians were more likely to endorse concern/distress. There was a negative relationship between participants' average help-seeking score and dichotomized maladaptive coping score. Concern/distress after viewing the PSA was not associated with the help-seeking attitudes or maladaptive coping strategies.

Help-Seeking Attitudes

For the PSA groups, average help-seeking attitudes were 2.64 (SD = 0.64) for the original billboard group, 2.81 (SD = 0.59) for the alternative billboard group, and 2.83 (SD = 0.68) for the video group. To examine the effect of PSA group, we fit a linear regression model that controlled for participants' sex, age, race, and broad risk status. The overall model was statistically significant, $F(6, 776) = 9.237, p < 0.001$ (see **Table 3**). The covariates accounted for approximately 6% of the variance in participants' help-seeking attitudes. Sex and race were the significant predictors of average

TABLE 2 | Correlations matrix of dependent variables and covariates.

	Sex[a]	Age	Race[b]	High-risk depression/ suicide[c]	High-risk suicide attempt[d]	Average help-seeking scale	Dichotomized maladaptive coping score	Dichotomized concern or distress
Sex (male vs. female)	–							
Age	−0.082*	–						
Race (Non-Caucasian vs. Caucasian)	−0.021	−0.047	–					
High-risk depression/suicide	0.092*	0.069	0.028	–				
High-risk suicide attempt	0.081*	0.023	−0.082*	0.402*	–			
Average help-seeking score	0.177*	−0.080*	0.096*	−0.052	0.010	–		
Dichotomized maladaptive coping score	−0.168*	0.040	−0.147*	0.033	0.086*	−0.233*	–	
Dichotomized concern or distress	0.099*	−0.057	−0.095*	−0.043	−0.017	0.001	−0.001	–

Reported correlations are product moment correlations (between two continuous variables), point-biserial correlations (between a continuous and dichotomous variable), or Phi coefficients (between two dichotomous variables).
[a]*Male = 0, Female = 1.*
[b]*Non-Caucasian = 0, Caucasian = 1.*
[c]*A broader index of risk status was based on those who screened positive for experience with depressive symptoms and/or suicide attempts were considered high-risk.*
[d]*A more narrow index of risk status was based on suicide attempt history was considered for some follow-up analyses.*
*p < .05 (although this is noted in the data analysis section as well).

TABLE 3 | Predictors of help-seeking attitudes.

	B (SE)	95% CI	t	p
Constant	2.645 (0.197)	2.258, 3.033	13.408	<0.001
Group				
Video vs. original billboard	0.167 (0.069)	0.030, 0.303	2.401	0.017
Alternative billboard vs. original billboard	0.152 (0.048)	0.057, 0.247	3.154	0.002
Female (vs. male)	0.283 (0.055)	0.175, 0.391	5.149	<0.001
Age	−0.014 (0.008)	−0.030, 0.002	−1.712	0.087
Caucasian (vs. non-Caucasian)	0.144 (0.052)	0.042, 0.247	2.760	0.006
High-risk depression/ suicide	−0.076 (0.048)	−0.170, 0.170	−1.605	0.109

The overall model was significant, F = 10.55, p < 0.001. The predictors in the model accounted for 5.9% of the variance (adjusted r² = 0.059) in average help-seeking scores.

help-seeking scores. The effect of age or depression/suicide risk was not significant after controlling for the effect of the other covariates in the model. After controlling for the covariates, there were significant differences between the PSA groups. Participants in the alternative billboard group and the TV condition endorsed significantly higher help-seeking attitudes than participants in the original billboard group.

Maladaptive Coping Strategies

Among the PSA groups, approximately 54% of participants in the original billboard group, 53% in the alternative billboard condition, and 42% in the TV ad condition endorsed one or more maladaptive coping strategies. To examine the effect of PSA group, we fit a logistic regression model (using the logit-link function) that included age, sex, race, and risk status as covariates. For the categorical variables, the original billboard group, females, Caucasians, and participants with low risk were coded as the referent groups.

Results from the Hosmer–Lemeshow test suggested that the model adequately fit the data ($\chi^2 = 8.486$, $p = 0.387$). Including

the covariates improved the classification accuracy from the unconditional model by 8.5%. Male participants, OR = 2.46, 95% CI (1.69, 3.58) and non-Caucasian participants, OR = 2.05, 95% CI (1.44, 2.92) had significantly increased odds ($p < 0.001$) of endorsing one or more maladaptive strategies after controlling for other variables in the model. Participants endorsing previous suicide risk were also more likely to endorse one or more maladaptive coping strategies, OR = 2.12, 95% CI (1.17, 3.84), $p = 0.013$. Age was not a significant predictor. After controlling for these covariates in the model, there was no significant difference in the odds of endorsing one or more maladaptive strategies when comparing the original billboard to the TV ad condition (OR = 0.67, $p = 0.08$) or the original billboard to the alternative billboard (OR = 1.00, $p = 0.98$) condition.

Concern/Distress

Some level of concern or distress after viewing the PSAs was endorsed by about a third of the sample. Thirty-one percent of the participants in the original billboard group, 33% in the alternative billboard group, and 29% in the TV ad group reported some concern/distress after viewing the PSAs. We fit a logistic regression model (using the logit-link function) to examine the effect of PSAs after controlling for sex, race, and risk status. Results from the Hosmer–Lemeshow test suggested that the model adequately fit the data ($\chi^2 = 10.59$, $p = 0.16$), but including the covariates did not improve the classification accuracy from the unconditional model. Females, OR = 1.79, 95% CI (1.19, 2.71), $p = 0.005$, and Caucasians were significantly more likely to report concern/distress, OR = 1.57, 95% CI (1.11, 2.23), $p = 0.011$, after controlling for the other variables in the model. Depression/suicide risk did not have a significant effect on the probability of indicating concern or distress, OR = 0.79, $p = 0.17$. After controlling for the covariates, viewing the TV ad condition compared to the original billboard (OR = 0.92, $p = 0.75$) or the alternative billboard compared to the original billboard (OR = 1.08, $p = 0.66$) did not have a significant effect on the odds of reporting concern/distress.

Exploratory Analyses

There were no significant interactions for risk status (either using the broad or narrow index) and group status for any of the outcome variables.

DISCUSSION

Universal suicide prevention efforts hold great promise in reaching many in need. Nevertheless, the lessons learned in research conducted over the last 30 years have curtailed enthusiasm for PSAs, as these campaigns have limitations for communicating critical information and potential iatrogenic risks [e.g., Ref. (5, 25)]. Emerging evidence suggests that theory-driven development and empirical assessment of message content for suicide should be the gold standard (26), but the current state of the field is inchoate (27). Additionally, because PSA exposure may not be limited to the target population, it is also critical to determine the efficacy and safety for other potentially vulnerable populations who may incidentally view PSAs. It is possible that specific formats or messages may have an important impact on the viewer. While progress in developing effective suicide prevention PSAs may be uneven, it is likely that using theoretically guided, practical steps to validate the effectiveness of PSAs will ultimately prove to be beneficial for the society.

The results of this study replicate and extend previous research regarding the utility of PSAs. Specifically, the findings are consistent with previous work showing that the original billboard was not as effective as the TV ad [e.g., Ref. (1, 20)]. The TV ad conveys information about the common symptoms of depression, imbeds the topic of suicide into a broader discussion of depression, and provides more extensive information about services for treating depressive symptoms and preventing suicide. Increasing the individuals' knowledge and awareness of services has been found to be a crucial factor in ensuring media messages are acted on (28).

Importantly, the results of this study suggest that some billboard messages may yield changes in attitudes that are nearly comparable to the TV ad. Specifically, in this study, we showed that attitudes toward help-seeking were favorably influenced by the alternative billboard message ("Stop depression from taking another life"), but not the original message ("Prevent suicide: Treat depression"). Previously, Klimes-Dougan and Lee (1) speculated that some billboards may contain an insufficient "dose" of information for changing attitudes. But the results of this study suggest that the amount of information conveyed in a billboard may not be a critical factor. In this study, all wording was exactly the same in both the billboards other than the central message (so, in total, there were only two words more in the alternative billboard). By contrast, the findings of this study suggest that brief messaging may be useful if the wording of the message is crafted to maximize benefits for the viewer. Some have pointed out the advantages of using a straightforward and succinct message [e.g., Ref. (29)]. It will be important to better understand the features of the alternative billboard message – "*Stop depression from taking another life*" that are most useful. Not only is this message succinct but also it may be more personally relevant, more appealing, and possibly even, inspire intervention. Additionally, the less explicit reference to suicide in the alternative billboard message may be less off-putting. Nevertheless, it remains somewhat surprising that in some respects, the alternative billboard shows similarly favorable outcomes as the TA ad, especially given the depth of information that is conveyed in the TV ad.

Contrary to the predictions, we failed to show that at-risk participants were more vulnerable to the negative effects of any of the simulated PSAs. Previous research with PSAs has shown that those who reported depressive symptoms and/or previous suicide attempts were the least likely to endorse positive help-seeking attitudes and the most likely to see a strong link between depression and suicide, particularly for the original billboard (20). The results of this study fail to show evidence that the responses differed across PSA conditions. However, consistent with other work that shows an association between depressive symptoms and help-seeking attitudes or behaviors (15, 30, 31), the results of this study did suggest that the most vulnerable individuals were more likely to endorse maladaptive coping strategies. Future research should continue to examine the utility of personalization for suicide prevention campaigns, for what might be useful for those at high risk may not be useful for those at low risk for suicide.

There are some important contributions of this study as well as interpretational cautions that should be highlighted. The randomized assignment of the participants to exposure conditions (despite some variations in randomization procedures across classrooms) provides an important design that lends itself to causal implications. Research using a pretest and posttest design may further aid conclusions by showing how outcome variables change after viewing a PSA. Additionally, the relatively large, homogeneous group of young adult participants provided sufficient power to detect small effect sizes. There are measurement issues that need to be addressed in future research, given the moderate internal consistency of the scales (e.g., maladaptive coping), the distribution of responses, and the inconsistent findings across scales (despite the fact that the maladaptive coping scale is related to the help-seeking scale, $r = -0.23$). Additionally, this study examined endorsed attitudes after viewing a PSA, and not the actual behaviors. It would have been ideal to also know if young adults who viewed PSAs were more likely to reach out to family members, friends, or professionals to get help for themselves or others who are struggling with suicidal thoughts. Second, there are limitations regarding generalizability of the results given that the majority of the participants were white, female college students selected from behavioral science courses. In some respects, the characteristics of these participants may have been ideal. Namely, this campaign was specifically intended for females (e.g., friends, spouses etc., of those who are at high risk for suicide – white males) so it may be useful to have a greater proportion of females, particularly at-risk females. However, given that, we know suicide prevention efforts differ for males and females (32, 33) and there are robust sex differences for suicide attempts and deaths, a more equally distributed sample of males and females might have been preferable in some respects.

It will be important to ask the question, how representative are PSA simulation studies of real-world conditions? While simulation designs provide well-controlled exposure (e.g., a 5 s

viewing of the simulated billboard), the exposure is likely to vary significantly under natural conditions. For example, participants viewing a billboard from a car may be focused primarily on traffic, perhaps only briefly glancing at the message or missing the message completely. Increasingly, cluttered media environments make achieving adequate exposure to media campaigns more difficult, rather than making wider exposure easier (28). Also, in this study, there was only one exposure to this simulated billboard message. In real-world contexts, some people may experience repeated exposures to the messaging, potentially based on the placement of the billboards and an individual's transportation patterns or TV viewing patterns. The salience of the messaging is also important. But, while some public health topics provide provocative messaging that is readily recalled (as the recent "Cover your Butt" colonoscopy billboard campaign), it is incumbent upon preventionists to be cautious in suicide prevention messaging. Finally, continued scrutiny of the messages may be worthwhile. For example, contrary to suicide messaging guidelines (34), there may be some ways in which the imperative of the alternative billboard is not ideal. For example, " … *taking another life*" may imply that that lives are "taken" with some regularity and that suicide is normative. It will be important to continue to refine messaging strategies and back these modifications with empirical evidence. Given that messaging may not be uniformly effective across participants, future research should also address the important questions of which suicide prevention approaches are best, and which are best for whom. Due to the

significant impact suicide continues to have on the lives around the world, further research is needed to develop and improve effective suicide prevention campaigns so that more can benefit.

CONCLUSION

Suicide remains a serious public health challenge worldwide and is among the top causes of death for young adults (2). There is great promise in media campaigns as they afford the opportunity to present well-defined messages to large audiences repeatedly, over time, at a low cost. However, this promise is rarely realized because media campaigns can fall short or even backfire (28). In an effort to do something, preventionists have often moved ahead in the absence of firm empirical grounding. The results of this study provide some optimism that carefully crafted billboard messages may favorably influence help-seeking attitudes of participants.

AUTHOR CONTRIBUTIONS

BK-D was the PI on this project and oversaw all aspects of this study and was the primary contributor to the conceptualization and writing of this manuscript. NW conducted preliminary data analysis on a related topic using these data for his thesis and contributed to the preliminary conceptualization, data analysis, and writing of this early version of this manuscript. DK contributed to the conceptualization and data analysis of this manuscript.

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