

## Suicide: A Précis!

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## ABSTRACT

**Background:** Suicide remains a psychiatric emergency, tragedy, a public health burden, and for those aged 15-29, is the second leading cause of death globally. Stigma attached to psychiatric disorders and suicide means many people feel unable to seek help. **Aim of Work:** We highlighted confusing nosology, psychopathology, neurobiological underpinnings, typology, and, risk factor pertinent to suicide. A road-map to the clinical assessment and management of suicide has also been provided. Last, but not least, we tried to dispel the long-held myths about suicide. **Methods:** EMBASE, Ovid MEDLINE, PubMed, Scopus, Web of Science, and Cochrane Database of Systemic Reviews were searched for all relevant studies up to date of Jan, 2020. **Results:** Suicide is self-inflicted death with evidence (explicit/implicit) of intention to die. Suicide reflects many disparate determinants release/relief, response-to the disordered thinking, religious, revenge, rebirth, reunification or rational. 5-HT deficiency appears central to the neurobiology of suicide. Durkheim proposed 4 types of suicide (egoistic, altruistic, anomic, fatalistic). Risk factors for suicide entail both static and dynamic factors. Dynamic factors encompass both clinical and situational variables. Shneidman's concepts of perturbation and psychache are very crucial to consider when assessing the risk. Suicide rating scales are only ancillary with the Modified high-risk construct scale balances vectors of suicidality versus survivality. Myths germane to suicide abound that need to be demystified. Psychiatric management capitalizes on determining a setting for treatment and supervision, attending to patient's safety, as well as working to establish a cooperative and collaborative physician-patient relationship. This entails both psychosocial 'package' and somatic treatments and the best outcomes mandate well-keeled combined approaches. Pharmacologic interventions aim chiefly at acute symptomatic relief. Recently, heaps of data accrue speaking to the idea of ground-breaking 'anti-suicidal' agents that might alleviate suicidal ideation (SI) **Conclusion:** Suicide continues to be a complex public health problem of global calibre. It is variably tied to a myriad of risk factors underscoring likely etiological heterogeneity. That said, suicides can, at least partially, be prevented by restricting access to means of suicide, by training primary care physicians and health workers to identify people at risk as well as to assess and manage respective crises, provide adequate follow-up care and address the way this is portrayed in the media. A host of psychotherapeutic, pharmacological, or neuromodulatory treatments of mental disorders are readily available that can alter this acrimonious trajectory.

**Keywords:** Management, myths, neurobiology, psychopathology, risk factors, scales, suicide

## Prologue

Suicide, as a form of human behavior, is probably as ancient as mankind himself. Attitudes towards those who take their

own lives have veered between condemnation and tolerance throughout the ages.

Analysis of an ancient Egyptian poem by a psychiatrist and an Egyptologist neatly describes the psychopathology of suicide. A "Dispute over suicide" was a poem written by an unnamed Egyptian writer between 2000 and 1740 BC on papyrus in hieroglyphics. The writer known as "The Eloquent Peasant," was commissioned by King Meri-ka-re to write a poem to dissuade people from committing suicide.<sup>[1]</sup>

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## Definitions

Suicide is etymologically derived from Latin *sui-* of self and *caedere-* to cut down.<sup>[2]</sup>

O'Carroll *et al.*<sup>[3]</sup> proposed the following definitions. *Suicide* is a self-inflicted death with evidence, whether explicit or implicit, of intention to die. A *suicidal attempt* is a self-injurious behavior with nonfatal outcomes accompanied by evidence of intention to die. An *aborted suicidal attempt* is potentially self-injurious behavior with evidence of intention to die but was stopped before physical damage occurred. *Suicidal ideation* (SI) is thoughts of serving as the agent of one's death. *Suicidal intent* is subjective expectation and desire for a self-destructive act to end in death. *Lethality of suicidal behavior* is an objective danger to life associated with a suicide method or action. *Deliberate self-harm* (DSH) is a wilful self-inflicting of painful destructive or injurious acts without intention to die.

Some historical terms include apocarterisis to denote suicide by starvation while catabythismus is suicide by drowning.

## Epidemiology

It is estimated that circa 1% of Americans die by suicide<sup>[4]</sup> and over 30,000 people take their own lives each year in the US. Suicide is the 8<sup>th</sup> leading cause of death. Roughly, 8–10 people would attempt suicide for every 1 completes it. US suicide rate averages 12.5 per 100,000 over the past century. It peaked at 17.4 in 1932. It dipped to a nadir of 9.8 in 1957. It has hovered at 12.4 over the past decade. Adolescent rates have tripled over the past 40 years from 4 to 13.2 per 100,000. Suicide is the 3<sup>rd</sup> leading cause of death in this age group. Almost twice as many adolescents die from suicide as dying from all other natural causes combined. More than 12,000 children under 13 years are hospitalized each year for self-destructive acts.<sup>[5]</sup>

WHO recently reported that<sup>[6]</sup> in Europe, particularly Eastern Europe, the highest suicide rates were reported for both genders. The Eastern Mediterranean Region and Central Asia republics have the lowest suicide rates. Nearly 30% of all suicides worldwide occur in India and China. Suicide estimates globally by age are 55% for age between 15 to 44 years and 45% for age 45 years and over. Besides, youth suicide is alarmingly increasing at the greatest rate.<sup>[7]</sup>

## Psychopathology<sup>[8]</sup>

### Early theories of individual suicide

Freud never considered the psychodynamics underlying suicidal behavior to any great extent. Brief mentions of suicidal behavior can be found throughout his writings; however, by 1910, Freud had recognized many clinical features of suicidal behavior such as guilt over death wishes toward others, identification with a suicidal parent, refusal to accept the loss of gratification, suicide as an act of revenge, suicide as an escape from humiliation,

suicide as a form of communication, and the connection between death and sexuality. The more systematic views began with his discussion of melancholia. The essential feature of suicidal behavior is that the person loses a loved object, and the energy withdrawn from this lost loved object is relocated in the ego and used to recreate the loved one as a permanent feature of the self, an identification of the ego with the lost object. Litman called this process ego-splitting. Freud's formulation is phrased in the more archaic version of his theory. In more modern terms, the person has already introjected some of the desires of the loved one. In this way, it is as if part of one's mind is also symbolic of one's loved ones. Once this person is lost (e.g., by death or divorce), a person still possesses those introjected desires, and thus the lost loved one remains symbolically as part of the living person's mind. This process can lead to suicide when the person also harbors hostile wishes toward the lost object, for now, one can turn this anger toward that part of one's mind that is modeled upon and symbolizes the lost object.

A later development in Freud's thought was the postulate of the existence of a death instinct, an instinctual drive toward death that is balanced by the life instinct. The death instinct is primarily masochistic, and the individual tries to externalize the instinct as aggression or sadism. However, when there are cultural forces opposing sadism, the instinct is turned back onto the self. In 1961, the psychoanalyst Samuel Futterman stressed that neither the life instinct nor the death instinct could really function independently of each other, but that they were always fused in variable amounts.<sup>[9]</sup>

### Freud's influence on theorists

#### Menninger

Freud's hypothesis of a death instinct had a great influence on thinking about suicide. For example, in 1938 the psychiatrist Karl Menninger suggested that suicidal motivation can be seen behind behaviors that at first glance are not suicidal. Menninger noted that some people shorten their lives by choosing self-destructive lifestyles, such as alcohol or drug abuse, heavy cigarette smoking, and engaging in other destructive behaviors. He called such behaviors "chronic suicide." He noted that some people appear to focus their self-destructive impulses on specific parts of their bodies, leaving their minds unimpaired. For example, a person may blind himself or lose an arm in an industrial accident. Menninger saw the death instinct behind such behaviors, and he called them "focal suicide" For him, suicide stems from a combination of three wishes: wish to kill, wish to be killed, and wish to die.<sup>[10]</sup>

The result of Menninger's ideas has resulted in some interest on the part of suicidologists in indirect self-destructive behavior, as in Norman Farberow's book *The Many Faces of Suicide*.

#### Farber

Maurice Farber, a psychologist, proposed that the tendency to commit suicide is a function of the extent of the threat to acceptable life conditions experienced by the individual, the

individual's sense of competence, and therefore the individual's degree of hope. Aaron Beck, a psychiatrist, developed the Cognitive-Behavioral Therapy (CBT) for those suffering from depression and anxiety, and his associates later developed an inventory to measure hopelessness. Subsequent research has shown that hopelessness, which is one component of the syndrome of depression, is a much more powerful predictor of subsequent suicidal behavior than other components of the syndrome.<sup>[11]</sup>

### Shneidman

In 1996, Edwin Shneidman, the founder of the American Association of Suicidology, defined "lethality" as the likelihood of an individual committing suicide while "perturbation" referred to the level of upset or distress that the individual was experiencing. Shneidman later called the subjective experience of perturbation "psychache" Shneidman suggested that the way to reduce the lethality of individuals was to reduce their perturbation. He also proposed that all suicides share ten common qualities,<sup>[12]</sup> which include, a common purpose of seeking a solution; the common goal of cessation of consciousness; the common stimulus of unbearable pain; common stressor of frustrated psychological needs; common emotion of hopelessness and helplessness; common cognitive state of ambivalence; common perceptual state of constriction; common action of escape; the common interpersonal act of communication of intention; and common pattern of consistency of lifelong styles.

### The 7 'Rs' of suicide

As with other human behaviors, suicide, whether attempted or completed can reflect many disparate determinants.<sup>[13]</sup> These include a release/relief from hopelessness or despair, a response to the disordered thinking of psychotic decompensation or in a toxic state, religious self-immolation, revenge (you'll be sorry when I'm dead), a rebirth, reunification with a lost love one, or rational suicide (euthanasia).

### Neurobiology

Although results from studies of the biologic basis for suicide vary considerably, some trends and generalizations are informative.<sup>[14]</sup> These include, inter alia, decreased 5-hydroxyindole acetic acid (5-HIAA) in cerebrospinal fluid; increased 5-HT<sub>2A</sub> receptors; polymorphism of 5-HT<sub>2</sub> receptor gene; alteration in hypothalamic-pituitary-adrenal (HPA) axis; altered growth hormone (GH) response to apomorphine; abnormalities in brain-derived neurotrophic factor (BDNF), neutrophin-3 and nerve-growth factor in the hippocampus and prefrontal cortex (PFC); decreased imipramine affinity in brain tissue; and increased RNA editing at a locus in 5-HT<sub>2C</sub> in PFC.

Of note, Mann *et al.*<sup>[15]</sup> concludes that both suicidal behavior and major depressive disorder (MDD) are *independently* related to alteration in serotonergic function and regulation.

This is consistent with the finding of altered kinetics for ligand binding to 5-hydroxytryptamine (5-HT) transporter on

platelets and reduced ligand binding to 5-HT<sub>1A</sub> receptors in the prefrontal cortex (PFC). These changes occur independently of the diagnosis.<sup>[16]</sup>

### Durkheim's four types of suicide

The French sociologist Emile Durkheim proposed these four types of suicide in his famous book titled "Le suicide; étude de sociologie."<sup>[17]</sup> These are namely; egoistic which is committed when the given individual uses suicide as a means to escape facing the consequences of his actions; altruistic where the person is so embedded into a society that they are convinced that suicide is the only means to contribute to the given social group's existence; anomic, here, a person has lost all their social contacts and commits suicide as the result of not belonging anywhere; and fatalistic when a person is convinced that they cannot abide by the rules of the given social group, which they view as unchangeable and irrefutable.

### Risk factors

These include *static* (e.g., demographic variables) and *dynamic* (both clinical and situational variables) risk factors.<sup>[18-20]</sup>

Age: Suicide is increased in the elderly, age group 15–35 years and decreased in the prepubertal age band.

Gender: Suicide is increased in male, and decreased in female.

Suicidality: Increased with frequent, intense and prolonged ideation, plans, intent or attempts, and decreased with infrequent, low intensity and transient ideation, plans, intent, or attempts.

Past suicidal behavior: Increased with multiple, planned, low likelihood of rescue, high intent (*vide infra*), use of the highly lethal method, and availability of means, and decreased for a first attempt, impulsive attempts, high likelihood of rescue, ambivalence, low intent, and low lethal method.

Psychiatric history: Suicide has been tied to major depressive disorder (15%), bipolar mood disorder (10–15%), schizophrenia (10%)<sup>[21]</sup> borderline personality disorder (4-9.5%), antisocial personality disorder (5%), and alcoholism (2%).

Psychopathology: The likelihood of suicide is heightened with hopelessness, severe anhedonia, severe anxiety, or panic attacks, and decreased with optimism, religiosity, and life satisfaction.

Psychosocial history: Suicide has been demonstrated to increase in the divorced, widowed, in the unemployed, in conflictual interpersonal relationships, those with low achievement, in social isolation, with poor interpersonal relationships, with domestic violence, with sexual or physical abuse but decreased in the married, with secured employment, stable relationships, with good achievement, with positive social support, with the positive therapeutic relationship, with a supportive family, and absence of abuse.

Medical history: Human immunodeficiency virus (HIV) ups risk of suicide ( $\times 21-36$ ), epilepsy ( $\times 5$ ), temporal lobe epilepsy ( $\times 25$ ), Huntington's disease ( $\times 5$ ), multiple sclerosis ( $\times 5$ ), porphyria ( $\times 5$ ), Cushing's disease ( $\times 5$ ), spinal cord injury ( $\times 5-10$ ), head injury ( $\times 5$ ), gastrointestinal cancer ( $\times 5$ ), peptic ulcer disease ( $\times 5$ ), and chronic kidney disease on hemodialysis ( $\times 40$ ).

Family history (FH): suicide tends to increase with a history of suicide or mental illness in the first-degree relative and decreased with negative FH.

Personality style: suicide hikes with poor insight, rigid thinking, and poor effective control, and decreased with being insightful, sense of responsibility to family, good reality testing ability, positive coping skills, positive problem-solving skills, flexibility, and ability to manage emotions.

### Role of Family Physician in Suicide

Individuals thinking about suicide can fall through the cracks of fragmented systems. *Primary care physicians* can play an important role in assessing and managing suicide risk given that nearly half those who die by suicide are in contact with a primary care physician within one month of their death<sup>[22]</sup> As a group, doctors can press for social action aimed at influencing conditions rooted in society, but doctors act most effectively in their own offices when they routinely consider depression and suicide potential in their patients. It behooves family physicians to be mindful to spot suicide potential, deal with the patient's family, and tackle the aftermath in attempters.

### Mental Status Examination (MSE) Probing of SI

Just as vital signs are an elemental part of a physical exam, in MSE, assessment of suicidal risk is fundamental. Questions should *not* be restricted to patients who appear depressed. Suicidal impulses may wax and wane, they may be more or less evident so, continuing reassessment may be required for some patients. Inquiry about suicidal concerns and impulses should be conducted systematically, progressing from more general to more specific questions.<sup>[23]</sup>

Typical examples include<sup>[24]</sup> Are you happy with your life?; How often does it get you down?; How depressed do you feel?; Do you ever want to die?; Do you ever think about suicide?; What was going on in your life when you were thinking about dying?; Were these particular things upsetting you that connect to you wanting to die?; Do you think about injuring or killing yourself?; Do the feelings and thoughts last very long?; Has anyone close to you ever attempted suicide or succeeded?; Do you think about acting on your feelings?; Do you have a plan?; Were you ever on the verge of trying to kill yourself but then changed your mind before you acted on your feelings?; Did you ever try to kill yourself?; Did you ever start to kill yourself and then change your mind once you have started to do so?; Are there any guns,

pills or poisons in your house?; and Do you have any reasons that would stop you such as loved ones or religious beliefs?

### Suicide Rating Scales

These are only ancillary and the predictive value is only 3%. Here is a useful battery.<sup>[25,26]</sup> The psychological pain assessment scale; Beck's anxiety inventory which measures Shneidman's perturbation; Beck's hopelessness inventory where scores  $>10$  greatly increase risk of suicide; Beck's scale for suicidal ideation, and the Modified high-risk construct scale. The latter is interviewer-based. It balances vectors of suicidality (negative score) vs. vectors of survival (positive score). Positive items are 5 in number and include adaptability and coping, alternative solution-seeking, abhorrence, anchorage, and stoicism. Negative items are 10 in number; viz. adamance, alcohol or substance use disorder, psychalgia, perturbation, primary psychopathology, helplessness, hopelessness, lethality, impulsivity, and resignation and acceptance of SILC equation (Suicide Is the only Logical Conclusion for me!).

### Suicidal Intent

Kessel<sup>[27]</sup> has proposed four types regarding the intentionality behind a suicide attempt based on Shneidman's classic paper, "orientation towards death: A study of lives" (1984). These are namely; the intended cessation (7% of cases) which is the absolute failed suicide attempt where the patient is alive purely for fortuitous reasons; sub intended cessation (15%) describing those ambivalently hoping for death, possibly turning their suicide attempt into a "trial by ordeal," being prepared to accept the verdict, life or death, either way; intended interruption (40%) denoting those seeking relief from pressure in their lives by temporary oblivion through overdosing and hope things would be better when they wake up; and the intended continuation (37%) representing a "pantomime of suicide" with secondary interpersonal gain. They arrange their acts so that there is a little risk of dying.<sup>[28]</sup>

### Myths and Truths of Suicide

Herein are some long-upheld myths about suicide that should be dispelled. These, inadvertently, subserve to support and sustain the social stigma of suicide.<sup>[29,30]</sup>

Those who talk about suicide are not at serious risk. Most suicide victims communicate their plans or distress before death.

Suicide is an impulsive act with little warning and few clues. *vide supra*.

Suicidal persons are rarely indecisive or ambivalent. They usually seek comfort or help before acting on self-destructive impulses.

Suicidality is inherited. Despite positive family history at times, suicidality does not seem to be inherited predisposition or trait.



Suicidal risk is short-lived and is usually over when signs of improvement appear. This may be deceptive as it may reflect a person's calm after having made a plan, regaining some energy can allow him to act, the post-attempt period could be a vulnerable time.

Suicide is an expected response to stress. Everybody experiences stress but not everybody attempts suicide.

Those committing suicide are selfish and weak. Many of these suffer from mental disorder whether or not have been recognized.

Those who are smart and successful would never commit suicide. Suicide has no cultural, ethnic, racial, or socioeconomic boundaries.

Talking about suicide with a depressed person would instill the idea into his mind. Many of those are relieved by speaking their minds and providing appropriate support and help in lieu.

Nothing could be done for a person who is suicidal. Many may be suffering from a psychiatric disorder that would respond to effective treatment.

Those attempting suicide are attention-seekers. A desperate cry for help is not equivalent to attention-seeking.

## A Decide to Suicide

A continuous debate exists.<sup>[31]</sup> Advocates opine that people have a fundamental right of self-determination as long as exercising that right does not impinge on anyone else's rights and prevention of suicide represents a misguided paternalism that inappropriately violates individual rights. On the other hand, opponents posit that in all but terminally-ill, suicide is symptomatic of treatable mental illness. Even in the terminally-ill, many could suffer from clinical depression. Opinions that suicide is an act of free will sometimes derive from antipathy towards these frequently provocative and covertly furious patients than from objective well-considered desire to further their best interests. Evidence for this position is commonplace in that almost all suicide attempts are subsequently grateful that they did not succeed. Moreover, religious and moral objections abound- "suicide is against Allah's will."<sup>[32,33]</sup>

## Psychiatric Management

### APA recommendations

Psychiatric management of suicide<sup>[34]</sup> includes determining a setting for treatment and supervision; attending to patient's safety, and working to establish a cooperative and collaborative physician-patient relationship. For patients in ongoing treatment, psychiatric management also comprises establishing and maintaining a therapeutic alliance; coordinating treatment provided by multiple clinicians; monitoring patient's progress and response to the treatment plan; and conducting an ongoing assessment of patient's safety, psychiatric status, and level

of functioning. Besides, psychiatric management may foster encouraging treatment adherence and providing education to the patient and when indicated family members and significant others.

In treating suicidal patients particularly those with severe or recurring suicidality or self-injurious behaviors, the psychiatrist should be aware of his own emotions and reactions that may interfere with patient care. Consultation or supervision from a colleague may then help.

The "Suicide prevention contract" is commonly used in clinical practice but should *not* be considered a substitute for careful clinical assessment. Patient's willingness or reluctance to enter into a contract should *not* be viewed as an absolute indicator of suitability for discharge or hospitalization. Besides, such contracts are *not* recommended for use with the agitated; psychotic; impulsive; intoxicated; emergency settings; newly-admitted; and the unknown inpatients.<sup>[35]</sup>

Despite best efforts at suicide assessment and treatment, suicide *can and do occur* in clinical practice. Death of a patient by suicide will often have a significant effect on treating psychiatrist (increased stress and decreased professional self-esteem). The patient's confidentiality extends beyond the patient's death. Conversations with family members may be appropriate to allay grief and aftermath of a loved one's suicide

## Specific treatment modalities

Some generalities to draw are combined somatic and psychosocial interventions have better outcomes; addressing modifiable risk factors is mandatory; therapeutic approaches should target (formerly) axis I and II psychiatric disorders, specifically associated symptoms (e.g., depression, agitation, anxiety, insomnia) and predominant psychodynamic or psychosocial stressors.<sup>[36]</sup>

The goal of *pharmacologic treatment* is to provide *acute* symptom relief. Whilst goals of *psychosocial interventions* are broader, long-term, and entail achieving improvement in interpersonal relationships, coping skills, psychosocial functioning, and, management of effects.

Patient's preference is important to consider when devising an individual treatment plan.

## Somatic interventions

For depressed patients experiencing suicidal thoughts or behaviors, it is advisable to select antidepressants with low risk of lethality on acute overdose-selective serotonin reuptake inhibitors (SSRIs) or newer antidepressants (beware black-box warning for activation of SI for those below 25).<sup>[37]</sup>

For insomniac patients, a sedative antidepressant or adjunctive hypnotic is recommended. Insomnia has been tied recently to suicidality.

For the agitated, short-term (especially long-acting) benzodiazepines (BDZs), trazodone, low dose second-generation antipsychotics can be deployed.

Lithium<sup>[38]</sup> long-term maintenance treatment with lithium is associated with major reductions in suicide risk in bipolar patients and possibly also recurrent unipolar MDD.

Clozapine<sup>[39]</sup> is associated with a significant decrease in suicide rates in schizophrenia/schizoaffective. It is the only FDA-approved drug for that indication. Olanzapine might share these antisuicidal properties. Atypical antipsychotics are generally preferred over conventional.

Ketamine<sup>[40]</sup> can induce fast onset antidepressant effects in patients with depression. It also may rapidly decrease suicidal thinking within 40 min. A sustained decrease in suicidal ideations at 10 days post-infusion has also been reported.

Buprenorphine<sup>[41]</sup> ultra-low-dose sublingual (400 µg) has been tested for safety and efficacy as a time-limited treatment for severe SI in a multisite RCT and was shown to be effective both at week-2 and week-4.

In the pipeline, *Cyclurad*, a combination of d-cycloserine (NMDA modulator) and the atypical antipsychotic lurasidone, is being investigated for acute SI in bipolar depression.<sup>[42]</sup>

ECT<sup>[43]</sup> – Electroconvulsive therapy is associated with a rapid and robust antidepressant response as well as the rapid diminution in associated suicidal thoughts. May also be indicated for suicidal individuals *during* pregnancy or for those who have already failed to respond or tolerate trials of medications.

### Psychosocial interventions

Psychotherapy such as interpersonal and cognitive-behavioral therapy may be considered appropriate treatments for suicidal behavior notably when occurs in the context of depression. For patients with a diagnosis of borderline personality disorder, psychodynamic, or dialectical behavioral therapy (DBT) may be appropriate treatments for suicidal behavior.

### Conclusions

As this paper highlighted, suicide is self-inflicted death with evidence (explicit/implicit) of intention to die. Suicide reflects many disparate determinants release/relief, response-to the disordered thinking, religious, revenge, rebirth, reunification or rational. Serotonin (5-HT) deficiency appears central to the neurobiology of suicide. Durkheim has long proposed 4 types of suicide (egoistic, altruistic, anomic, fatalistic). Risk factors for suicide entail both static and dynamic factors. Dynamic factors encompass both clinical and situational variables. Shneidman's concepts of perturbation and psychache are very crucial to consider when assessing the risk. Suicide rating scales are only ancillary with the Modified high-risk construct scale balances

vectors of suicidality versus survivality. Myths germane to suicide abound that need to be publicly demystified. Psychiatric management capitalizes on determining a setting for treatment and supervision, attending to patient's safety, as well as working to establish a cooperative and collaborative physician-patient relationship. This entails both psychosocial 'package' and somatic treatments and the best outcomes mandate well-keeled combined approaches. Pharmacologic interventions aim chiefly at acute symptomatic relief. Recently, heaps of data accrue speaking to the idea of ground-breaking 'anti-suicidal' agents that might alleviate suicidal ideation (SI). Future holds promise for suicide psychopharmacology as well as biological markers.

## Compliance with Ethical Standards

### Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

### Informed consent

Not applicable. No patients involved.

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### Conflicts of interest

There are no conflicts of interest.

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