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Clinical Predictors and Biomarkers of Suicide Attempts in Patients Registered Under the Suicide Risk Protocol: The CODIRISC Project

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Abstract

Background: Suicide is the leading cause of violent death. In 2014, the Catalan Ministry of Health launched a Suicide Risk Protocol, an intervention programme targeting individuals at high risk of suicide. Since 2016 the protocol has covered the whole of Catalonia (Spain).

Objectives: To identify clinical, demographic, neuropsychological and biological factors and stress responses (Psychoneuroendocrine, inflammatory, genetic and neuroimaging markers) associated with suicide attempts.

Method: Analysis of clinical sub-cohorts from a sample of patients registered under the Suicide Risk Protocol (n=900). All participants will undergo clinical assessment (neuropsychological and biomarkers) and be followed up over 18 months. Patients who repeat a suicide attempt will be compared with two groups: patients with a single suicide attempt and healthy controls with no history of attempted suicide.

Discussion and conclusion: The CODIRISC project will also carry out a functional neuroimaging study as proof of concept, thus enabling biological and clinical changes to be correlated with the neuroimaging findings. The resulting model will therefore be both coherent and have predictive capacity.

Keywords: Suicide prevention; Biomarkers; Neuropsychology; Risk factors; Suicide attempt

Introduction

Current state of knowledge

Suicide is the leading cause of violent death and one of the main causes of premature death, with mortality rates well above those for traffic accidents. There is a trend toward an increasing number of deaths by suicide in both genders, especially between the ages of 15 and 44 years, and addressing suicidal behaviour is thus a priority for healthcare systems. There is a strong association between suicide and previous suicide attempts, mental disorders, alcohol consumption and stressful life circumstances, all of which are factors susceptible to intervention. In light of evidence suggesting that suicide is avoidable, research into risk factors and prevention strategies has become a major priority for public health initiatives worldwide [1].

Fortunately, suicide deaths are relatively uncommon in most populations (e.g. the one-year odds of dying by suicide in the USA is around 0.00013 persons/year [2], and even lower in Spain). However, suicide has enormous family and social consequences. Self-inflicted injuries are one of the main causes of loss of disability-adjusted life years (DALYs) worldwide. Furthermore, each youth suicide represents a potential of 60 years of life lost, and suicide attempts have a high potential impact in terms of years lost due to disability [3]. In Spain, there were 3,602 suicide deaths in 2015, equivalent to a rate of 7.76 cases per 100,000 population [4]. Data from the Global Burden of Disease (GBD) study for that same year suggest that, in Spain, death by suicide accounted for 2.52% of premature years of life lost and 1.24% of total DALYs lost [5]. However, there is also evidence to suggest an under-reporting of this cause of death, such that actual rates may be as much as 20% higher [6]. The rate of attempted suicide in Spain has been estimated to be 99.1 cases per 100,000 population [7].

Risk factors

There is good reason to consider that suicide and self-injurious behaviours are avoidable [1]. However, this requires not only proper identification of prevention opportunities in the context of a phenomenon with a complex trajectory, but also an understanding of risk and protective processes at the individual, contextual and environmental levels, as well as of the associated proximal and distal factors.

One of the most important risk factors for suicide is the presence of mental health problems. Between 80% and 90% of suicides [8] occur in the context of a diagnosed mental disorder, most commonly affective disorders. It should be noted, however, that the majority of patients with a mental disorder do not engage in suicidal behaviour [9]. Register-based epidemiological studies show that the prevalence and type of suicidal behaviour differs between subpopulations (gender, age, etc.), and there is evidence that psychological determinants and decision-making abilities play an important role [10].

Recent findings from neuroimaging, genomic and biochemical studies allow the definition of an initial heuristic model for suicidal behaviour that may have predictive value [11]. An increased risk of suicidal behaviour has been associated with a wide range of potential biomarkers (altered serotonin function, inflammation, stress, neuroplasticity and lipids), although a recent meta-analysis of longitudinal studies [12] concluded that only two factors have a significant — and even then, weak — predictive value: cytokines and a diet low in fish oil nutrients. It is acknowledged, however, that there are few longitudinal studies with large samples that analyse the interaction between factors with potential predictive value and greater applicability in clinical practice.

The stress-diathesis model of suicidal behaviour suggests that there may be biomarkers of suicide risk that are independent of biomarkers of psychiatric disorders and which could help to predict suicide risk in response to stressors [13]. The genetic hereditability of suicidal behaviour is 30-55% [14]. Suicidal behaviour has been associated with variants of stress response genes (including those for brain-derived neurotrophic factor, BDNF) and with genes involved in serotonin transmission [15] and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [16]. The evidence suggests an aetiological stress-diathesis model involving genetic and psychological factors that produce neurophysiological and behavioural changes, giving rise to vulnerability that is maintained by altered brain function [17]. Predicting suicide therefore requires an understanding of the interaction between genetic and environmental factors [18], and more population-based studies, such as the one proposed here, are needed.

Dysregulation of the HPA axis appears to be associated with a risk of suicidal behaviour, and there is recent evidence that this can be studied using peripheral markers and that age is an important factor, with suicide risk being associated with elevated cortisol levels in younger patients (<40 years) and with lowered cortisol levels in older patients [19]. Most studies that have examined the role of the HPA axis have focused on baseline cortisol levels (e.g. a single cortisol determination in the morning). Some recent research has measured hair cortisol concentrations, which offers a way of studying cortisol levels retrospectively, and thus for a certain period (usually a few months) prior to the suicide attempt. In one such study, patients who had made a suicide attempt had lower hair cortisol concentrations compared with both healthy controls and patients with suicidal ideation but no history of attempted suicide [20]. Other specific measures of HPA axis activity, such as the cortisol awakening response (CAR), a physiological measure of HPA reactivity, have not been widely studied in relation to suicide. However, it constitutes an excellent measure in the field of biomarkers because dysregulation of the CAR has been associated with life stress [21], vulnerability to major depression [22] and hippocampal damage [23]. When studying the interaction between hormonal (HPA axis) and brain (neuroimaging) biomarkers, the CAR may provide complementary information to that obtained from other baseline cortisol measures (morning or hair cortisol), which are also useful as their ease of collection makes them well-suited to large-scale epidemiological studies. Because the analysis of hair cortisol concentrations allows us to study cortisol levels retrospectively, prior to the suicide attempt, it is possible to establish a correlation which may have predictive value with respect to new attempts in those cases where concentrations do not return to normal following the initial attempt.

Repeated suicide attempts and selective prevention programmes

A recent study in the USA found that 19.7% of people in a cohort who self-harmed but did not complete suicide made another non-fatal attempt during the following year [24]. One meta-analysis estimated the one-year rate of non-fatal repeat self-harm to be 16.3% [25], while the reported rate of death by suicide following a previous attempt ranges between 2% [26] and 5.4% [24]. Hence, prior self-injurious thoughts and behaviours (SITB) are the most important risk factor for self-harm and death by suicide [27-30]. Other risk factors for repeated attempts include a history of sexual abuse, poor global functioning, having a mental disorder and being under psychiatric treatment [28]. Among adolescents and youth there is a clear association between previous SITB and both subsequent self-harm (odds ratio of 3.48) and death by suicide (odds ratio of 22.53) [31]. Biomarkers related to the stress-diathesis model may help to improve risk assessment procedures and guide therapeutic decision making for suicide prevention [13].

Numerous post-crisis prevention programmes have been developed in response to the special risk of repeated suicidal behaviour. Particularly noteworthy are those that include follow-up appointments and active contacting of patients who fail to attend these appointments [32,33], an approach supported by recent meta-analytic findings [34-36]. Other more general programmes that have been developed to prevent SITB include the European Alliance against Depression (EAAD) [37] and self-help online [38], among many others. Although there is evidence that interventions with high-risk individuals (such as those who have just attempted suicide) are effective, at least in the short term, their cost-effectiveness is less clear.

Suicide Risk Protocol in Catalonia (Spain)

In 2014, the Ministry of Health of the Autonomous Region of Catalonia (Spain) with 7,5 M inhabitants, launched a Suicide Risk Protocol (hereinafter, the CRS), comprising a series a healthcare and preventive measures aimed at individuals who, following contact with the public health service in Catalonia (Spain), are considered to be a high suicide risk (normally following a suicide attempt that led them to be assessed by a psychiatrist in an emergency department). The CRS is a selective prevention programme based on active follow-up by different clinical services of high-risk cases detected at any level of the health system, with or without a previous suicide attempt, as well as of cases with concurrent additional risk factors. All such cases are registered in the programme, classified as high suicide risk and

followed up by telephone for a year with the aim of preventing suicidal behaviour. Implementation of the CRS thus involves registration of all those persons who have engaged in self-harm with a explicit suicide purpose or who are at risk of doing so, and it has the following specific objectives:

- To reduce the numbers of deaths by suicide,
- To increase survival rates among persons seen by health services following suicidal behaviour, and
- To prevent repetition of suicide attempts in high-risk cases [39].

Project opportunity

Following its introduction in 2014, the CRS achieved full coverage of Catalonia in 2016, yielding a heterogeneous register across the centres involved. This cohort will be enriched with detailed information from a sub-cohort of new cases recruited through participating centres — specifically, information about clinical and biological variables (cortisol, inflammatory markers and DNA), with clinical and neuropsychological assessment and neuroimaging in a smaller subgroup. The identification of clinical or biological risk factors, or a combination of both, could enable the prediction of repeat suicide attempts in the short or medium term through the development of risk prediction algorithms to target preventive interventions. The project will place particular emphasis on excellence, transferability and dissemination of results.

Hypotheses

1. There are clinical, demographic, neuropsychological and biological characteristics that allow prediction of repeated suicide attempts in patients who have made a previous attempt.

2. In patients who make a further suicide attempt the biological profile associated with the stress response will be different to that of patients who do not make a repeated attempt.

General objective

The project aims to determine the clinical and biological characteristics (biomarkers) that differentiate patients who make a new suicide attempt from those who do not make a repeat attempt and from healthy controls, the ultimate goal being to implement more effective preventive measures in clinical practice.

Specific objectives

1. To identify the clinical, demographic, neuropsychological and biological risk factors that allow us to predict the risk of a repeated suicide attempt in a representative sub-sample of patients registered in the CRS.

2. To study biological differences related to the stress response (psychoneuroendocrine, inflammatory, genetic and neuroimaging markers) between patients who make a repeated suicide attempt and those who do not.

3. To study biological differences related to the stress response (psychoneuroendocrine, inflammatory, genetic and neuroimaging markers) between the two groups of patients registered in the CRS (repeaters and non-repeaters) and a group of healthy controls.

This is a prospective longitudinal cohort study that will include a nested case-control study.

A. Prospective longitudinal study: 12-month follow up of a representative sub-cohort of patients who have attempted suicide and who are registered in the CRS in Catalonia, the aim being to determine the clinical and biological factors that enable the risk of new attempts to be predicted.

B. Nested case-control study within the prospective longitudinal study. We will select patients who make a new suicide attempt during follow up. These will be matched by age and gender with patients who have made a single attempt and who make no repeated attempt during a minimum follow-up period of 12 months. Healthy controls with no history of suicide attempts and matched by age and gender will be included as a reference group.

Participants

The sample will comprise 900 patients aged 18 and over who, following a suicide attempt, are seen in the emergency department of any of the five participating hospitals in Catalonia: a) Corporació Sanitària Parc Taulí (Sabadell, Barcelona), which serves a population of 450,000 people; b) Hospital del Mar (Barcelona), which provides care to a population of 350,000 people; c) Hospital de Sant Pau (Barcelona), with a catchment area of 400,000 people; d) IMAS-Girona mental health service, which serves a population of 700,000 people; and e) the Pere Mata Institute (Reus-Tarragona), with a reference population of 596,000 people. Participation in the study will be governed by a series of inclusion/exclusion criteria, and all participants will be required to sign written informed consent approved by the Clinical Research Ethics Commettee.

Sub-cohort for prospective longitudinal follow-up

Inclusion criteria:

1. Patients of both sexes and aged 18 and over.

2. Registered under the CRS following a suicide attempt, according to DSM-5 criteria.

3. Willing to participate in the study and signing of informed consent.

Exclusion criteria:

1. Younger than 18 years.

2. Learning disability or any serious organic disorder.

3. Not willing to participate in the study and not signing informed consent.

Sample size

For the prospective longitudinal study we will recruit a total of 900 individuals, forming a sub-cohort of cases registered under the CRS during the first year across all participating hospitals (n=180 for each hospital). It is estimated that 900 participants will be required in order to assess at least 135 cases involving a repeated suicide attempt during the 12-month follow up, given that 15-20% of people who attempt suicide make a repeated attempt during the following year, and assuming 25% case attrition during the follow-up period [1].

Nested case-control study

Inclusion criteria: For the nested case-control study we will assign patients from the sub-cohort to one of two groups: a) Case (high risk), defined as patients who make at least one new suicide attempt during

the prospective follow up; and b) Control (low risk), defined as patients who, following their initial suicide attempt and inclusion in the cohort, do not make another attempt during at least the following 12 months. These two groups will be matched by age and gender. We will also recruit a reference group of healthy subjects, matched by age and gender and with no personal or family history of suicidal self-harm according to DSM-5 criteria.

Sample size: The sample size for this study takes into account two factors: the number of subjects included in the prospective study who make a new suicide attempt, and the type of test or determination to be performed. Based on the estimation that 15-20% [2,3] of the 900 patients will make a repeated attempt (n=135), and assuming 25% attrition during follow up [1], the sample for the nested case-control study will comprise around 100 patients who make more than one suicide attempt, and who are therefore considered to be high risk. These patients will be matched with other patients included in the prospective follow-up cohort who have made only one suicide attempt after a minimum of one-year follow up.

A reference group of healthy controls, matched by age and gender and with no personal or family history of suicidal behaviour, will also be included. The neuroimaging study will, for both technical and financial reasons, be limited to the three hospitals in the province of Barcelona, each of which will include an estimated 60 cases, 60 control patients with a single suicide attempt and 60 healthy controls. This number is based on a total of 540 patients under prospective follow up (180 for each of the three hospitals), assuming the presence of a repeat suicide attempt in 15% of patients and an average 25% case attrition.

Assessment

Prospective longitudinal study

All patients who meet the inclusion criteria and who agree to participate in the study will, after signing informed consent, undergo the following clinical and neuropsychological assessment in their first post-discharge appointment (<10 days; at the investigator's discretion the assessment may be carried out over two sessions provided the interval between them is less than 4 days).

Clinical assessment

The MINI-Plus structured interview [4] will be used to diagnose any psychiatric disorders associated with the suicide attempt. Data regarding the main clinical and demographic variables will also be collected.

The following battery of tests will also be administered:

1) Brief Suicide Questionnaire [35];

2) Hamilton Depression Rating Scale-17 items (HDRS-17 [36];

3) Medical Damage Scale (MDS) [37];

4) Suicide Intent Scale (SIS) [38]

5) Childhood Trauma Questionnaire - Short Form (CTQ-SF) [39];

6) Barratt Impulsiveness Scale - 11 (BIS-11) [40];

7) Brown-Goodwin Lifetime History of Aggression (BGLHA) [41];

8) EuroQoL-5D

9) Short Personality and Life Event Scale [42].

Neuropsychological assessment

A brief neuropsychological assessment will be performed, including estimation of intelligence quotient and testing of executive functions, attention, verbal memory and processing speed. The tests used will be: 1) Rey Auditory Verbal Learning Test (RAVLT); 2) Digits forward and backward of the WAIS-IV; 3) Trail Making Test, A and B; 4) Stroop test; 5) Semantic and phonemic fluency; and 6) Vocabulary subtest of the WAIS-IV.

Biological samples

Blood samples: Blood samples will be collected from all participants in order to assess inflammatory markers. A pro-inflammatory score [40-43] will be calculated based on levels of five factors: Interleukin (IL)-6, IL1-B, tumour necrosis factor (TNF)-alpha, gamma interferon (INF) and C-reactive protein. The analysis will be performed using an ELISA Luminex® kit. Genetic analysis will examine different factors related to the HPA axis, including a series of candidate genes for regulation of the stress response: NRC3, FKBP5, BDNF, CRHR1, SK2A, 5-HT2A, 5-HTT and TPH2.

Hair sample: A 3-cm sample of hair will be collected from the posterior vertex of the scalp of all participants. Hair grows at a rate of around 1 cm per month, and hence the most proximal 1 cm corresponds to the past month, and so on. Measurement of cortisol concentration in the hair sample will provide a retrospective measure of exposure to stress. Three 1-cm segments will be cut in the laboratory and adequately preserved. Cortisol levels will be measured using an ELISA kit.

Nested case-control study: Subjects included in the case-control study will undergo a repeat clinical (state measures) and neuropsychological assessment. New samples of blood (pro-inflammatory score) and hair (cortisol) will also be collected. By analysing these repeated measures it will be possible to determine the impact of changes over time in the clinical and/or biological factors (or the absence of changes) on the repetition of suicidal behaviour.

Neuroimaging study: As noted above, neuroimaging will be performed in a smaller number of participants, this decision being driven by both technical (use of a single scan) and logistical/financial considerations (reducing transport and assessment costs). Importantly, the neuroimaging study will serve as a proof of concept, the aim being to establish structural and functional neuroanatomical correlates of the clinical and biological measures. The association between these activity measures (both resting and during a stress task) will add greater validity to the results and will provide more detail about the aetiopathology of suicidal behaviour. For these reasons, we believe it is justified to limit the neuroimaging study to patients seen in the three hospitals in the province of Barcelona.

Neuroimaging will be performed in a diagnostic imaging research centre using a Philips 3 Tesla scanner equipped with a 32-channel head coil. The resonance procedure will take around 40 minutes and will include the following sequences: 3D structural sequence, T2 and FLAIR sequences, resting sequence and a functional task sequence. The T2 and FLAIR sequences are included for ethical reasons and will be evaluated by an external radiologist in order to check for the possibility of structural findings. Stimuli for the functional task will be presented via video goggles, which the subject will wear throughout the resonance procedure. Subjects will use a joystick to respond to the questions that appear on screen during the task.

Sequence characteristics

3D structural sequence: A total of 156 slices will be acquired through a high-resolution 3D SPGR sequence in the axial plane (TR 1600 ms, TE 2.67 ms, flip angle 9°, field of view 12.8 cm, acquisition matrix size 256 × 256 pixels, in-plane resolution 0.5 mm^2, slice thickness 1 mm, without separation).

Functional sequence (resting state and functional task): A total of 22 slices will be acquired through a functional EPI sequence with the following image parameters: TR 2000 ms, TE 35 ms, flip angle 90°, field of view 230 × 230 mm, acquisition matrix size 96 × 96 pixels and slice thickness 4 mm.

Functional task: The Montreal Imaging Stress Task (MIST) is an adaptation for the magnetic resonance setting of the Trier Mental Challenge Test, and it includes a social stress component [5]. The MIST will be used to measure the pattern of brain response to stress under laboratory conditions. It comprises a series of computerized mental arithmetic tasks with an induced failure component. The protocol includes three conditions: rest, control and experimental. In the control condition the subject has to solve a simple arithmetic problem, with no time limit. In the experimental condition each task has a time limit, which is adjusted based on the subject's previous performance. Specifically, the program is set to a time limit that is 10% less than the subject's average response time, thus inducing a high error rate. The time allowed for each task is displayed in the top right corner of the screen, with countdown in real time. Regarding the aforementioned stress component, the subject is told that all the people in the scanner room (investigator, assistants, MR technicians) are going to follow his or her progress on a second monitor in the control room. Finally, during the rest condition the subject merely has to look at a black cross that appears in the centre of the screen. It has been shown that the experimental task robustly activates the fronto-parietal-cingulate network, the cognitive-attentional system, and therefore it allows observation of changes in this network under conditions of stress.

Statistical Analysis

Prospective longitudinal study

The primary outcome variable will be repetition of the suicide attempt (event). Kaplan-Meyer survival curves will be calculated to show survival times following registration of patients in the CRS. Cox regression models will be used to assess the effect of different risk factors on survival time.

Nested case-control study

Cases and controls will be compared in relation to the clinical, neuropsychological and biological variables. Univariate analyses, such as the Student's T test or analysis of covariance, will be used, in addition to repeated measures analysis. These comparisons will be made both between the two patient groups and between patients and the group of healthy controls with no history of attempted suicide. Multivariate analysis, such as logistic regression, will be used to examine predictors of a repeated suicide attempt (the dependent variable). All the variables will be analysed in order to establish predictive models of suicidal behaviour by means of structural equation modelling. Magnetic resonance data will be pre-processed and analysed using SPM8 or SPM12b software (in Matlab 7.0), or the FMRIB Software Library (FSL; for DTI data), following standard procedures. Analysis: VBM and DARTEL for 3D, non-parametric GLM for DTI, and graph-based and seed-based analysis for fMRI.

Justification of the multicentre project

Subjects will be recruited through five hospitals in Catalonia (three in the Barcelona area, one in Girona and one in Tarragona). This multicentre approach to recruitment will: a) Ensure that the required sample size will be achieved; b) yield conclusions that are more generalizable to the whole of the study population; and c) improve the homogeneity and quality of CRS application.

Study Limitations

The study will have the typical limitations associated with cohort studies. As cohort studies are conducted over long periods of time it is likely that subjects will be lost to follow up, which in this case may bias survival rates. In addition, the cohort design does not allow us to study uncommon events, the most relevant in this case being completed suicide. Hence, the study will focus solely on the risk of a repeated suicide attempt, which is the most important known risk factor for completed suicide. These limitations can be partially addressed by conducting the case-control study, which allows for a more detailed, economical and dynamic assessment of the study phenomenon.

Ethical Aspects

The research will be conducted in accordance with the principles set out in the Declaration of Helsinki. Data registers will be pooled in accordance with Spanish legislation (SAS/3470/2009) covering post-authorization observational studies, whereby informed consent is only required in the event that no steps are taken to anonymise data. The project has been evaluated and approved by the Clinical Research Ethics Committee of the Institut d'Investigació e Innovació Parc Taulí (CEIC-I3PT), as well as by the corresponding committee of the other participating centres. All patients included in the study cohort will sign written informed consent.

Discussion

One of the major challenges in preventing suicidal behaviour and death by suicide is that the main risk factors are common in clinical populations [18,44,45], and thus their detection and consideration does not allow effective prediction of what is a relatively uncommon phenomenon (i.e. suicide) in the short or medium term. Although taking into account factors such as male gender, older age, symptoms of depression, current alcohol consumption, previous suicide attempts and the stressors commonly associated with suicidal behaviour can help the clinician in making an individual assessment in an acute situation, they are insufficient to predict the risk of suicide and to enable effective prevention in the medium and long term.

Importantly, none of the risk factors or scales analysed in a recent review [46] were found to be useful for predicting suicide, not even in the short term, and as such their use may lead to overly restrictive treatment of some patients [47].

This inability to predict a relatively rare event such as suicide (despite the concurrent presence of known common risk factors) limits the effectiveness of suicide prevention efforts with the resources currently available to health services. Not all patients identified as a risk will require the same interventions or for the same length of time. Furthermore, the implementation of selective suicide prevention

measures across broad at-risk groups (such as those who have made a previous attempt or simply patients with depression) is not only impossible but may, in some cases, be excessive or even dangerous [47]. If, in addition, these measures need to be maintained for an indefinite period of time, they may become both unsustainable and ineffective. The individualization of effective strategies for preventing suicide is therefore essential in order to avoid unnecessary or even harmful treatments. However, the difficulty of achieving positive outcomes in suicide prevention is clear: suicide rates have barely changed in recent decades, despite improvements in healthcare systems and in people's general living conditions.

The present CODIRISC project will investigate the reliability of clinical and biological markers of suicide risk, based on the stress-diathesis model. It will aim to identify cases likely to repeat suicidal behaviour in the medium term (12 months), based on the results of baseline assessment at the time of the initial suicide attempt. The one-year rate of repeat self-harm is over 14% [29] to 19.7% [14,15]. If patients likely to make a repeat attempt can be distinguished from those who will not, on the basis of baseline stress or inflammation markers (in association with clinical variables), it will be possible to target specific interventions at this high-risk group and reduce or eliminate the risk of suicide, at least in the medium term.

Conclusion

The CODIRISC project will also carry out a functional neuroimaging study as proof of concept, thus enabling biological and clinical changes to be correlated with the neuroimaging findings. The resulting model will therefore be both coherent and have predictive capacity.

This is the first study to propose identifying suicide risk factors under conditions of real clinical practice in people who have survived to a suicide attempt, drawing on the results of previous studies based on the stress-diathesis model. The ultimate goal is to establish specific and more effective and practical interventions than are currently available to prevent suicide re-attempts and reduce the long-term suicide risk.

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