EMERGENCY IN PSYCHIATRY – THE VARIOUS FACETS OF BEHAVIORAL EMERGENCIES, CRISES AND SUICIDALITY

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EMERGENCY IN PSYCHIATRY – THE VARIOUS FACETS OF BEHAVIORAL EMERGENCIES, CRISES AND SUICIDALITY

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EDITORIAL
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Editorial: Emergency in Psychiatry—The Various Facets of Behavioral Emergencies, Crises, and Suicidality

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Keywords: psychiatry, suicidality, crisis, self-mutilation, emergency, sleep, borderline personality disorder, adolescent psychiatry

Editorial on the Research Article

Editorial: Emergency in Psychiatry—The Various Facets of Behavioral Emergencies, Crises, and Suicidality

Psychiatric emergencies occur every day in various presentations and in various clinical settings. Not only social workers, relatives and teachers can be stunned, overwhelmed and helpless in these situations but also health care professionals are. Social workers and emergency service providers dealing with these highly stressful situations may themselves be traumatized by this confrontation and may suffer significant psychological damage (1–3). In adult as well as in child and adolescent mental health emergencies, self-mutilating and suicidal behavior are within the most frequent challenges as documented in the analyses of Franzen et al. and Slankamenac et al. within this issue. Suicidal crises may trigger feelings of anxiety and anger in those who treat these patients (4). In addition, the acute and long-term treatment of these patients is still demanding–especially in the case of chronic suicidality that often exists in individuals repeatedly being admitted to emergency units with self-mutilation, intoxications, or suicide attempts (5, 6). Unfortunately, the therapist's fear that a patient may commit suicide can threaten clinical judgment, contribute to problems in therapy and may seriously impede the therapist's ability to deal effectively with the danger of suicide (7).

In this issue, we specifically compile articles that focus on interventions and skills that may help individual professionals as well as teams dealing with such emergencies in psychiatry.

Bolsinger et al. stress the importance of a good therapeutic relationship for this endeavor showing special attributes and caveats in an acute psychiatric setting. Across countries, crisis lines have become an inherent part of the crisis management and prevention of suicides. Hoffberg et al. found evidence for the effectiveness of crisis lines but observe that there is still an important gap in the evaluation of this mean of help. Including a medical developmental and systemic perspective, Guedj et al. propose a comprehensive and operational model for the management of adolescents with behavioral problems in an emergency department.

Repetitive transcranial magnetic stimulation has also been discussed in the context of its potential ability to rapidly reduce suicidality (8, 9). Within this special issue, a comprehensive overview (Abdelnaim et al.) of these emergent advances for suicidality in depressed patients is presented. Further, a suggested link between suicidality and sleep disturbances in the context of

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post-traumatic stress disorder (PTSD) as well as its possible therapeutic implications are scrutinized in a thorough literature overview (Weber et al.). Heterogeneous study approaches and diverse outcome parameters hinder a direct comparison of studies examining sleep disturbances, suicidality, and PTSD. However, sleep problems as still underestimated target symptoms may provide preventive strategies with respect to suicidality.

Finally, yet importantly, patients with personality disorders, especially borderline personality disorders (BPD), deserve specific attention as they are typically afflicted with frequent crises including states of acute and chronic suicidality leading to highly frequent usage of psychiatric as well as general emergency services (Slankamenac et al.). Early and focused interventions being of utmost importance in these cases, we discuss promising therapeutic approaches (Hennings) specifically addressing recurrent suicidality in BPD.

AUTHOR CONTRIBUTIONS

JH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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ORIGINAL RESEARCH
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Anti-Suicidal Efficacy of Repetitive Transcranial Magnetic Stimulation in Depressive Patients: A Retrospective Analysis of a Large Sample

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Background: Suicide is a major public health problem. About 90% of suicide victims have one or more major psychiatric disorder, with a reported 20-fold increased risk for suicide in patients with affective disorders in comparison with healthy subjects. Repetitive transcranial magnetic stimulation (rTMS) has been established as an effective alternative or adjunctive treatment option for patients with depressive disorders, but little is known about its effects on suicide risk.

Objective: For the assessment of the effectiveness of rTMS on suicidal ideation and behaviors, we performed a retrospective analysis of a large sample of patients with depressive disorders, who were treated with rTMS.

Methods: We analyzed the records of 711 TMS in- and out-patients with depressive affective disorders in a tertiary referral hospital between 2002 and 2017. Out of these patients we were able to collect Hamilton depression rating scale (HAMD) data of 332 patients (180 females, 152 males; age range 20 to 79 years; mean age 47.3 ± 12.3) for which we analyzed the change of suicidal ideation by using item 3 (suicidality) of HAMD.

Results: Out of all 711 patients treated with rTMS for their depression, one patient (0.1%) committed suicide during the TMS treatment. In the statistical analysis of the subsample with 332 patients there was an overall amelioration of depressive symptoms accompanied by a significant decrease in the suicidality item with a medium effect size. Decrease in suicidality was not inferior to changes in other items as indicated by effect sizes. Forty-seven percent of patients showed an amelioration in suicidality, 41.3% of patients did not show a change in their suicidality's scores, and 11.7% of patients showed an increase in suicidality's scores from baseline to final rating. Correlation of item 3 (suicidality) and item 7 (drive) demonstrated a significant positive association, revealing improved drive with a parallel decreased suicidality.

Conclusion: Based on the proposed data, there is no evidence that rTMS increases the risk for suicide during the course of the treatment. Conversely, rTMS tends to reduce

suicidal ideation. Our findings call for further rTMS controlled studies using large sample sizes and specific suicidality assessment measures to obtain more conclusive results.

Keywords: transcranial magnetic stimulation, suicide, suicidal ideation, depression, brain stimulation, rTMS

INTRODUCTION

Suicide is a major public health problem. World-wide nearly 1 million lives are lost each year because of suicide and 3–5% adults committed at least one suicide attempt at some point in their life (1–3). Although those numbers of people dying of suicide are already high, according to the World Health Organization they are presumably underestimated, and that for each adult who dies by suicide, there may have been more than 20 others attempting suicide (4). Suicidal behavior is a very complex, multi-factorial behavior, involving several medical-biologic, psychosocial, and cultural components (5). The coexistence of mental disorders in suicidal subjects has been widely studied. Psychological autopsy studies from different parts of the world found high prevalence of mental disorders in suicide victims, indicating that around 90% of them have one or more axis I (mostly untreated) major psychiatric disorders at the time of their death (6–8). Among those disorders, mood disorders represent the major risk factor for suicidal ideation and suicide attempts (9, 10, 11). In comparison with healthy subjects, a 20-fold increased risk was reported for the patients with affective disorders (12).

Moreover, affective disorders do not only increase the risk of suicidal ideation and tendency to attempt suicide but also the risk of a suicidal death. It is estimated that between 50 and 70% of all suicide victims are related to depressive and other mood disorders (ICD-10 F3); (13–15), with increased lethality of suicide attempts in patients with major affective disorders being reported (16).

The general recommendation to reduce suicide risk is the effective treatment of the underlying depressive disorder, with medications and psychosocial interventions including psychotherapy being the main therapy modalities (17). However, there exist several difficulties. First, neither antidepressants nor psychotherapy work fast enough for reduction of suicidal ideation. Second, even for medications with well-established reduction in suicidal behavior such as lithium, effectiveness is limited (18). Third, the prescription of antidepressants may offer the depressed patient a potential suicide method, e.g., by intoxication with tricyclic antidepressants, which are known for their cardiotoxicity (19). Fourth, the reporting of an association between increased suicidal ideation and antidepressant treatment in controlled clinical trials of antidepressants has added more difficulty to the connection between depression, its pharmacological treatment, and suicidality (20–23). The mechanism through which antidepressant medication might increase suicidality is yet not understood. A possible explanation for conflicting results concerning the relationship of antidepressant treatment and suicide risk is a transient increase of suicidal behavior after initiation of treatment. In detail, it has been suggested that antidepressants may energize depressed patients before they lead to mood improvement (24). This period of increased impulsivity with ongoing desperation may be related to increased suicidal behavior. Also, side-effects of antidepressants such as worsening of irritability, agitation, and insomnia could ease suicidal ideation and behavior (25, 26). Other results suggested that suicidal behavior in patients taking antidepressants is mostly the consequence of the lack of antidepressant effect and is rarely the result of suicide-inducing potential of antidepressants (27). All of the above-mentioned concerns indicate the need for more safer and more effective interventions to reduce suicide risk.

Beside pharmacotherapy and psychotherapy brain stimulation methods have gained increasing relevance in the treatment of depression during the last decades (28). Electric convulsive therapy (ECT) is an established antidepressant method with clearly proven efficacy for fast improvement of suicidal behavior, however, the use of ECT is limited by safety concerns and adverse effects (29).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique, that has emerged in the last 30 years and is applied in various neuropsychiatric conditions (30). rTMS uses pulsed magnetic fields with an intensity of up to 3T to induce neuronal depolarization in superficial cortical areas. For the treatment of depressions several stimulation protocols have been developed with high frequency rTMS of the left dorsolateral prefrontal cortex being the most established protocol (30).

In 2008, rTMS was approved for use by the FDA as a treatment for major depression for patients who do not respond to at least one antidepressant medication in the current episode (31) (FDA approval K061053).

The efficacy of rTMS is supported by multiple double blind, randomized controlled trials (32–34) that are summarized in several systematic meta-analysis, reviews, and evidence-based guidelines (30, 35). In general, the focus was more set on the efficacy of rTMS in patients with TRD (treatment resistant depression), considering its anti-depressive properties to be "obvious, opening interesting prospects, in particular in the treatment of pharmaco-resistant major depressive patients" (36). However, the effectiveness of rTMS has not only demonstrated in treatment refractory patients. rTMS has also been investigated in less treatment-resistant patients who might benefit even more from TMS than patients with pharmaco-resistant depression (37).

Due to its good tolerability and because it is free of the side effects that commonly accompany antidepressant medications, it would also seem attractive to patients, who are not willing to take a medication (38).

Regarding safety and adverse events of rTMS, side effects like local pain, discomfort, headache, vasovagal syncope are reported, and the induction of an epileptic seizure is the most important safety concern of rTMS treatment (39). However, the incidence of seizures with TMS is relatively low and is less evident than that with current antidepressant medications (40).

In comparison to ECT, although the latter seem to have higher response rates in treatment-resistant depression (41), rTMS does not require anesthesia or muscle relaxation (does not require induction of a seizure). Moreover, the magnetic stimulation is delivered in a focal manner at a chosen cortical target rather than affecting the entire brain as with ECT (42), which significantly reduces side effects (43). Furthermore, there is no evidence of cognitive impairment connected to TMS, also most adverse events of TMS are mild to moderate in intensity, which leads to a low discontinuation rate due to adverse events during the treatment course (40).

These summarized data with respect to efficacy and side effects propose rTMS as promising alternative or additional intervention in the treatment of depression. Some researchers have already reported a decrease of suicidal ideations following treatment with rTMS (33, 44–46). These results however were considered as preliminary because most of them were not sham-controlled with mostly very limited suicide assessment measures and relatively small sample sizes (47). In their study of open-label accelerated TMS (aTMS) over 2 days in 14 depressed patients, Holtzheimer et al. reported that only one patient showed increased suicidal ideation (48).

In a Chinese randomized controlled trial, it has been found that rTMS combined with medications reduces suicidal ideation in elderly patients with depression (49). In their study of applying high frequency TMS to the left dorsolateral prefrontal cortex (DLPFC) on 19 adolescents with treatment-resistant depression, Croarkin et al. reported improvement in suicidal ideation across 30 sessions associated with improvement in depressive symptom severity (50).

Our goal from this study was to investigate the relationship between rTMS and suicidal risk in a more naturalistic sample, which avoids the disadvantage that patients with high risk for suicidality were typically excluded from rTMS treatment studies. We conducted a retrospective analysis of a large dataset from patients that received rTMS for the treatment of depression in a real-world clinical setting of a tertiary referral hospital.

METHODS

The analyses and publication of this retrospective work was approved by the ethic committee of the University of Regensburg (ethic vote: 16-104-0223). We revised and analyzed the records of 711 patients with mood disorders, who were treated with rTMS in the Center for Neuromodulation Regensburg (Germany) between 2002 and 2017 excluding patients receiving sham. One twenty-eight out of them were treated more than one time with rTMS. The patients are referred to us either from our different inpatients' wards or from our outpatient clinic *via* the responsible psychiatrist. Those are typically the patients who failed to show an adequate response to standard therapies. Suicidality is not an exclusion criterion *per se* except for acute suicidality which would be associated with hospitalization in a closed station.

For this sample of 711 patients we report the number of committed suicides within the course of the treatment with rTMS.

In addition, we analyzed a subsample with respect to the effect of rTMS on suicidal ideation based on the Hamilton depression rating scale (HAMD). The inclusion criteria for the retrospective analysis were: rTMS-naïve (only the patient's first treatment with rTMS was considered), primary diagnosis of a depressive disorder [including bipolar disorder currently depressive episode (ICD-10: F31), major depressive disorder (ICD-10: F32), and recurrent depressive disorder (ICD-10: F33)], a complete documented HAMD at beginning and at the end of rTMS treatment, absence of a serious somatic illness. Both in- and outpatients were included.

We were able to collect data of 332 patients, who met the above-mentioned criteria including 180 (54.2%) females and 152 (45.8%) males with an age range between 20 and 79 years (47.3 ± 12.3). Patients were treated with a minimum of 6 up to 50 sessions (17.0 ± 6.5). Patients received different rTMS protocols, most of them received 20 Hz stimulation on the left prefrontal cortex (**Table 1**).

The analysis was based on the scores of the 21-item Hamilton Depression Rating scale (HDRS or HAMD) (51), which is considered to be a reliable depression scale regarding internal consistency, inter-rater and test-retest reliability (52). We focused on the changes in the item 3 (suicidality). This item evaluates the presence and severity of suicidal thoughts/action on a 4-point scale, leveling from absence of suicidal thoughts (score 0) as the lowest score, the feeling that life is not worth living (score 1), presence of death wishes (score 2), suicide ideas (score 3), till suicidal attempts (score 4), as the highest score.

We compared the baseline scores (at beginning of treatment) with those at end of treatment, trying to find out if the scores would increase or decrease after the rTMS treatment. This was done for all single items and also the sum score of the HAMD to

TABLE 1 | Frequency of repetitive transcranial magnetic stimulation protocols performed.

Protocol (frequency—site—daily pulses)	Absolute number of patients	Relative number of patients
20 Hz—left prefrontal—2,000	261	78.6%
10 Hz—left prefrontal—2,000	15	4.5%
10 Hz—left prefrontal—1,000	10	3.0%
20 Hz—right prefrontal—2,000	3	0.9%
1 Hz—right prefrontal—1,000	1	0.3%
10 Hz—anterior cingulate cortex—2,000	12	3.6%
20 Hz—left prefrontal followed by 1 Hz—right prefrontal—2,000	11	3.3%
iTBS—left prefrontal followed by cTBS—right prefrontal—2,400	19	5.7%

investigate whether change in suicidality went in a similar direction as change of other depressive symptoms. For item 3 we also looked in the change of the frequency of the single grades of the question.

We've also tried to correlate the results with the scores of item 7 (work and abilities), which focuses mainly on the patient's energy and drive. The motivation for this analysis was twofold. Firstly, it is assumed that energizing a depressed patient through medication can also increase the risk of suicidality. Secondly, we aimed to investigate whether improvement/worsening the suicidal ideation is attributable to parallel improvement/worsening of patient's energy level. To see if a putative association is specific we did this correlation for all items and also for the sum score.

All data were analyzed using Statistical Package for the Social Sciences (SPSS; IBM SPSS Statistics for Windows, Version 24.0.0.1). The significance level was set at $p < 0.05$ for all analyses. Significant findings which survived correction for multiple comparisons according to Bonferroni were separately marked. For pre-post contrasts we used Wilcoxon rank sum tests. For cross-tab analysis we used the chi-squared test of independence. For correlations we used Spearman correlation coefficients. Effect sizes were reported by Cohen's d (53), and were calculated according to Lenhard & Lenhard (54).

RESULTS

From the above-mentioned 711 patients, only one patient (0.1%) committed suicide during the TMS treatment. In this single case the role of TMS remains unclear. Nine years prior to his suicide, this patient had already received a successful 15-days rTMS treatment course. Re-hospitalization occurred because of another depressive episode. After a short period, the patient was discharged from the hospital. Due to re-emerging of suicidal impulses immediately after hospital discharge the patient was hospitalized again. After a month of hospitalization, because of failed response to antidepressants, and also the prior treatment success of TMS, a new treatment course was proposed. After the first TMS session, he was seen by a doctor. He appeared to be calm, claimed to be in a good mood and denied having any suicidal thoughts. Also, in his conversations with nursing staff and a phone call with a relative afterwards, the patient appeared to be in a stable condition free from suicidal ideation. Later on that day, he left the clinic ward, didn't answer his cell phone anymore and sadly then committed suicide. Finally, the reasons for the suicide remained unclear. To which extent the underlying depressive disorder, the used therapies (medication, psychotherapy, rTMS), or any other factors contributed to the suicide, couldn't be identified.

In the statistical analysis of the subsample with 332 patients there was an overall amelioration of depressive symptoms accompanied by a significant decrease in the suicidality item with a large effect size. Only three items did not survive correction for multiple comparisons. Decrease in suicidality was not inferior to changes in other items as indicated by effect sizes (**Figure 1**). The chi-square test of independence was significant ($\chi^2 = 43.318$; df = 12; $p < 0.001$) showing an association of the severity of depression before and after rTMS.

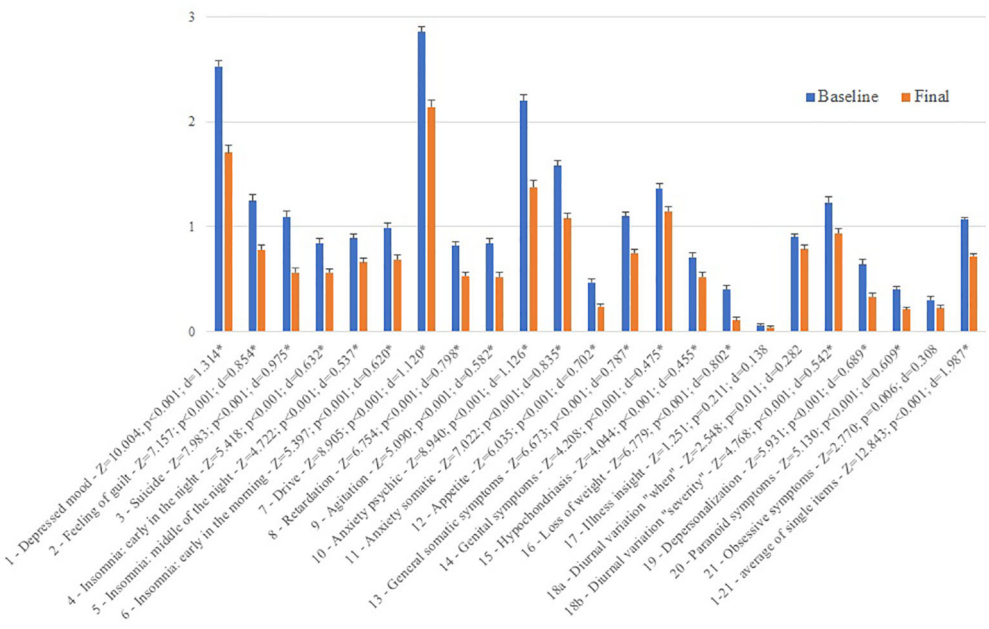

FIGURE 1 | Difference between baseline and final scores of the Hamilton Depression Rating Scale items. *indicate significant Wilcoxon tests which survived correction for multiple comparisons. Z corresponds to the z-value of the test statistic and d to the effect size. Please note that for reasons of similar scale the overall score is shown not as sum but as average score.

The number of patients who scored 0 increased from 118 at the baseline rating, to 208 patients at the final rating. Also, less patients scored 1, 2, and 3 at the final rating (81, 33, 14 respectively) compared to the baseline rating (111, 72, 34 respectively). No patient scored 4 at the final rating compared to three patients at the baseline rating.

One hundred fifty-six (47.0%) patients showed an amelioration in suicidality. One patient showed amelioration of 4 points (0.3%), 15 of 3 points (4.5%), 39 of 2 points (11.8%), and 101 of 1 point (30.4%). One hundred thirty-seven (41.3%) patients did not show a change in their suicidality's scores. Thirty-nine out of the 332 (11.7%) patients showed an increase in suicidality from baseline to final rating as indicated by increase from 0 during baseline to 1, 2, or 3 during the final rating or from 1 during baseline to 2 or 3 during final rating or from 2 during baseline to 3 during final rating. Twenty-nine patients showed worsening of the scoring of 1 point (8.7%), 8 of 2 points (2.4%), and 2 of 3 points (0.6%). No patient increased to the maximum score of 4. For absolute numbers see (**Figure 2**).

Non-parametric Spearman correlation of item 3 (suicidality) and 7 (drive) demonstrate a significant positive association ($r = 0.196$; $p < 0.001$), that means that patients showed improvement of their suicidality alongside with increased drive. Items 1 ($r = 0.263$; $p < 0.001$) and 2 ($r = 0.265$; $p < 0.001$) and sum score ($r = 0.426$; $p < 0.001$) also correlated significantly on a Bonferroni corrected level, the other items not.

DISCUSSION

Suicidal ideation is a severe symptom of depressive disorders and a huge concern for mental health providers. Only few treatments for suicidal ideation and behavior (e.g., lithium, ECT) are available and these are only partially effective. There is an enormous need for more convenient interventions.

Therefore there is a great need to firstly develop new treatment modalities with a rapid effect on suicide risk in order to prevent suicide (18, 47) and to secondly assess the effects of established antidepressant treatments on suicidal ideation.

Transcranial magnetic stimulation represents a non-invasive, feasible, effective, and safe treatment option for depression (55). There are no published reports that TMS increases suicide risk (56). However, there is only relatively few systematic research about the effect of rTMS on suicidality. In our analysis, which comprised a large sample of 711 patients, we found an overall improvement of suicidal ideation represented in item 3 of the HAMD score. The improvement in this item corresponded well to the overall improvement in the total HAMD score; 88.3% of all patients showed either improvement or stability of their suicidal ideation score, compared to 11.7% in which the score worsened under the TMS treatment course. Together with the significant chi-square test, we can conclude that we found no evidence that rTMS systematically increases suicidality.

Also, we found a positive correlation between improved patient's drive (indicated by item-7 score) and improved

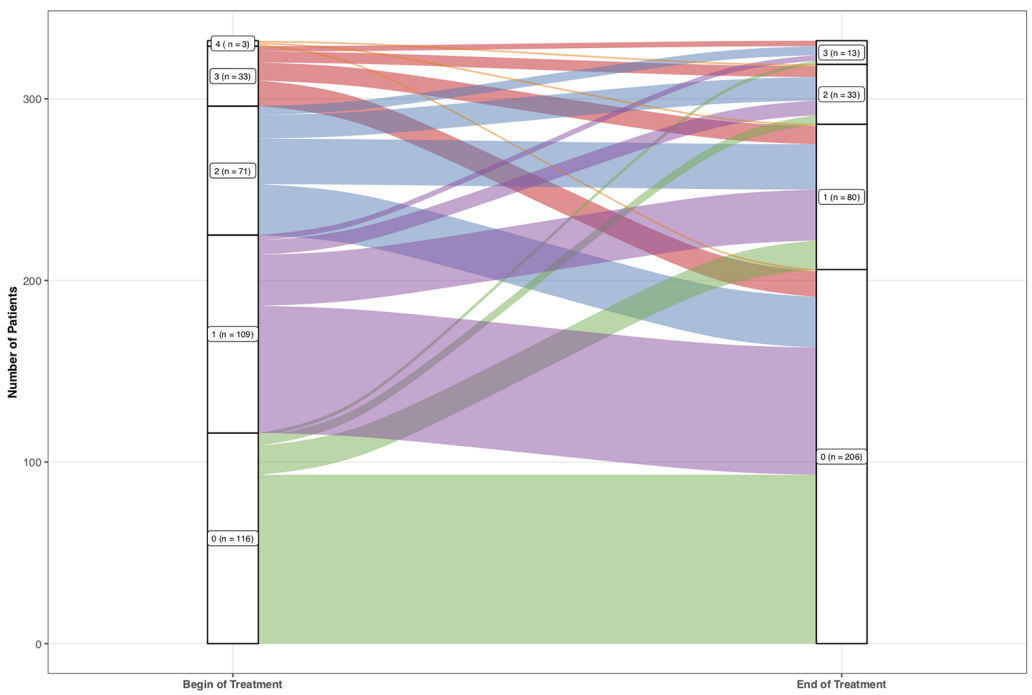

FIGURE 2 | Absolute frequencies of the single values of the suicidality item 3 of the Hamilton Depression Rating Scale.

suicidality (indicated by item-3 score). Changes in suicidality were also significantly associated with change in the total score and with change in the items 1 and 2 (depressed mood and feeling of guilt). The changes of all other items showed smaller and non-significant correlations. We interpret this in a way that change in suicidality is associated with changes in the main symptoms of depression considering that suicidality is also one main symptom of depression. Thus, we found no hint that rTMS induces an energizing effect without improvement of mood and that such a constellation may increase suicidality.

Our results get in line with some prior research revealing alleviation of suicidal ideation under TMS treatment. Hadley et al. reported in their trial on the effect of rTMS in patients with treatment-resistant unipolar or bipolar depression improvement of all measured dimensions, and most importantly, that suicidal ideation diminished in 67% of the patients already after the first week of treatment (57). In another 3 days-trial of delivering high doses of rTMS on left prefrontal cortex in patients with suicidal ideations, a more rapid decline in suicidal thinking has been observed in the active rTMS group compared to the sham group. The rather intense stimulation schedule (delivering 54,000 stimuli over 3 days), was feasible and safe with minimum side effects, and particularly with no worsening of suicidal thinking (58). Desmyter et al. examined in a randomized, sham-controlled trial, the effects and safety of accelerated intermittent Theta Burst Stimulation (iTBS) on suicide risk by using the Beck scale of suicide (BSI). A significant decrease of the BSI score over time was observed for both active and sham stimulation and unrelated to depression-response. There was no worsening of suicidal ideation, and the decrease in suicide risk lasted up to 1 month after baseline, even in depression non-responders (46). Weissmann et al. compared the effect of bilateral, left unilateral DLPFC, and sham rTMS on suicidal ideation in patients with TRD (who failed to respond to at least two antidepressant medications). They found a significant superiority of bilateral rTMS to sham rTMS in reducing suicidal ideation, with only a small portion of this reduction in suicidal ideation attributable to the improvement of overall depressive symptoms (59).

In our sample, among 711 patients that were treated with rTMS there was only one single suicide. For this suicide no obvious causal relation with rTMS treatment could be established. In most of the 711 patients, rTMS was not performed in the context of a clinical trial (where a high suicide risk is frequently an exclusion criterion), but as compassionate use treatment because of treatment resistance to medication and psychotherapy. This means that the sample consisted of treatment resistant patients with a rather high suicide risk. Our findings not only give a powerful indicator for the safety of TMS regarding suicidality, but also present TMS as a potential therapy option to reduce suicidal ideation.

This notion is supported by the presumed mechanism of action of prefrontal TMS namely the improvement of cortical-limbic regulatory control over emotional drive (60). The suicidal crisis has been described as a dysfunctional brain event, related to changes in the prefrontal cortex which leads to deficient regulation of the emotional state (61). Baeken et al. investigated how accelerated iTBS (aiTBS) may influence brain perfusion and suicidal thoughts using arterial spin labeling (ASL) fMRI, they found that both active and sham aiTBS resulted in prompt decreases in suicidal ideation, but specifically sham aiTBS has significantly attenuated frontopolar perfusion in relation to reductions in BSI scores. They interpreted those findings that in accelerated neurostimulation paradigms, placebo responses are related to perfusion decreases in brain areas associated with higher cognitive processes such as the default mode network, resulting in suicidal ideation attenuation (62).

Whereas our results demonstrate the effectivity of rTMS on suicidal ideation, we are aware of several limitations of the study. Firstly, this is a retrospective analysis, secondly rTMS was applied as an add-on treatment. Thirdly there was no sham control and fourthly there were no follow-up measures. Additionally, the study depended on a single item of the HAMD scale and not a specific assessment scale for suicidality e.g., the Beck Scale for Suicidal Ideation (63). Also, only three subjects of the sample had endorsed suicidal behavior (scoring 4 at the item 3 at baseline rating), that means that the analysis was more based on examining suicidal ideation, not suicidal behavior. Despite these limitations, the analysis of this relatively large sample indicates, that there is no hint for an induction of suicidal behavior by rTMS treatment. In contrary our data suggest that during rTMS treatment suicidal risk decreases together with an improvement of other core symptoms of depression.

We call through our work for further prospective studies of rTMS in depression that focus more explicitly on the effect of rTMS on suicidal ideation and suicide risk. Moreover, our data suggest that further studies are warranted that directly investigate the effects of rTMS on suicidal ideation not only in patients with depression, but also in other psychiatric disorders.

CONCLUSION

Based on the proposed data, there is no evidence that rTMS increases the risk for suicidality during the course of the treatment. Conversely, rTMS tends to reduce suicidal ideation. Our findings call for further rTMS controlled studies using large sample sizes and specific suicidality assessment measures to obtain more conclusive results.

DATA AVAILABILITY STATEMENT

The datasets for this manuscript are not publicly available because the approval from the ethic committee of university of Regensburg is restricted to publication of the data results - not the datasets itself - in the corresponding journals. Requests to access the datasets should be directed to: PD Dr. Martin Schecklmann, Email: martin.schecklmann@medbo.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the University of Regensburg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MA, PK, and TP recorded the data. MA, MD, and AM entered it in a database. MS performed the statistical analysis. MA, BL, and MS drafted the manuscript. All the authors designed the study, interpreted the data, and approved the final version of the manuscript.

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SYSTEMATIC REVIEW
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Challenges and Opportunities in Building and Maintaining a Good Therapeutic Relationship in Acute Psychiatric Settings: A Narrative Review

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Background: The therapeutic relationship and its importance for psychotherapy outcome have been the subject of extensive research over the last decades. An acute psychiatric inpatient setting is a unique environment where severely ill patients receive intensive treatment over a limited, relatively short, period of time. This renders establishing a good therapeutic relationship difficult for various reasons. It seems likely, however, that the therapeutic relationship in such a setting plays a vital role on factors such as clinical outcome, patient satisfaction, and rehospitalization rates. Little information is available on special attributes and caveats of building and maintaining a good therapeutic relationship in an acute psychiatric setting, neither on its influence on therapy success.

Methods: An extensive systematic literature search was performed using PubMed, science direct, psyc info, and google scholar databases. Keywords used were therapeutic alliance, therapeutic relationship, psychiatry, emergency, acute, coercion, autonomy, involuntary, closed ward. RCTs, observational studies, reviews, meta-analyses, and economic evaluations were included, case reports and opinion papers were excluded. Factors specific to an acute psychiatric setting were identified, and the available information was categorized and analyzed accordingly. The PRISMA statement guidelines were followed closely upon research and preparation of the present review.

Results: A total of 48 studies were selected based on their relevance as well as design. They demonstrated that several factors related to setting, patient attributes, staff attributes, admission circumstances, and general situation, render building and maintaining a good therapeutic relationship difficult in an acute psychiatric setting compared to scheduled, long-term therapeutic sessions. The available literature on how to overcome this dilemma is scarce. Interventions involving staff and/or patients have been shown to be effective in terms of relevant outcome parameters.

Conclusions: Increasing research efforts, as well as raising awareness and providing specific competencies amongst clinicians and patients in terms of nurturing a good therapeutic relationship in acute settings, are necessary to improve clinical outcome, economic factors, quality of patient care and patient as well as staff satisfaction.

Keywords: therapeutic relationship, psychiatry, emergency, acute, coercion, involuntary admission, closed ward

INTRODUCTION

The therapeutic relationship (TR) has been called the "foundation of mental health practice" (1). A vast body of literature emphasizes the importance of the TR in psychiatry. A positive TR has been consistently shown to be associated with better therapy outcomes in terms of clinical improvement, duration of stay, rehospitalization rate, and patient satisfaction [e.g. (2–6)]. On the other hand, a poor therapeutic relationship is associated with negative therapy outcome, as well as secondary negative effects such as increased risk of violence [e.g. (7)].

In various ways, the TR has been a subject of psychiatric research ever since psychotherapeutic work was first conducted. Most research into the subject of TR stems from psychotherapy in a scheduled, non-acute, long-term one-on-one setting, where the concept was first described (8). One review defined three core aspects of TRs: a collaborative nature, an affective bond between patient and therapist, and a mutual ability to agree on goals (9). It is easily concluded that patient-related, therapist-related, and environmental factors could hinder the establishment of all three of these aspects. For example, one would hypothesize that in the case of involuntary admissions into a closed ward, a patient will be less likely to spontaneously engage in a trustful collaboration with the attending physician. An affective bond between someone in an acute psychiatric crisis and the staff happening to be on duty the day that person is admitted into the hospital will likely be harder to establish than between therapists and their clients getting to know each other in a scheduled appointment agreed upon by both parties. It has also been shown that TR quality is equally important to both staff and patients (10). Being in a mental state that requires emergency in-patient treatment can potentially impede core skills needed in order to define and agree on goals, such as decision-making capacity, standing up for one's own rights, etc. Examining these factors, along with other variables that are likely to cause issues in building and maintaining a stable TR, is crucial in understanding and developing recommendations for clinical practice.

The term "acute psychiatric setting" is relatively unspecific, and it can be defined and understood in a lot of very different ways. In the present review, any environment providing emergency treatment for unscheduled, unforeseen psychiatric conditions is considered an "acute psychiatric setting". These settings provide several unique features that render building and maintaining a TR difficult compared to regularly scheduled psychotherapeutic care. At the same time, with regard both to the emergency setting itself and to secondary positive or negative implications resulting from success or failure of handling these situations, respectively, health care professionals would be well advised to pay particular attention to nurturing a stable and positive TR in an acute setting. However, data on this subject is scarce. Three core questions emerge from this situation: One, what are the potential pitfalls and special challenges of TR building and maintenance in an acute setting? Two, how can these risks be met by staff (and potentially patients/their environment) in order to avoid negative outcomes? Three, in how far does TR quality affect clinical outcome, rehospitalization rate, patient and staff satisfaction, economic balance, or other relevant factors? The present article aims to shed some light on the above questions using a review of available publications.

Abbreviations: TR, Therapeutic relationship.

MATERIALS AND METHODS

A systematic literature review was conducted in web databases (PubMed, science direct, psyc info, and google scholar) between 12/2017 and 11/2018. Keywords used were therapeutic alliance, therapeutic relationship, psychiatry, emergency, acute, coercion, autonomy, involuntary, closed ward. All keywords were used for individual searches, and the keywords "therapeutic alliance" and "therapeutic relationship" were used in a syntax with "AND" and each other keyword, respectively.

RCTs, reviews, meta-analyses, observational studies, opinion papers, and economic evaluations were included, case reports were excluded. No specific time frame for publication was defined. The attached flow diagram (PRISMA-P-guideline-based) (11) gives an overview of the screening, as well as inclusion/exclusion, processes (cf **Supplementary Material, Image 1**). Reasons for exclusion besides not meeting the inclusion criteria were lack of availability of an English full text version, strongly different settings/patient populations (e.g. minors, incarcerated patients), incomparable systems.

Since our study question proved not to lend itself very well to quantitative analysis, we decided to use a narrative approach in the writing process. For this reason, we also decided against an attempt to define the quoted studies in terms of populations, interventions, comparators, outcomes, and study designs (PICOS). Based on the overview of available information gained from the screening process, as well as insights from clinical routine, sub-sections of particular relevance to TR in an acute psychiatric setting were defined. These sections were labelled "Involuntary admission", "Increased symptom severity", "Loss of autonomy", "Coercion", "Role conflict therapist: help vs. assess", "Team work, general setting", "Short duration, lack of continuity".

Study results referring to the previously selected keywords, as well as results adding relevant information on either of the defined sections, were analyzed. The risk of bias was controlled on a study level by critically assessing the available information and, where applicable, discussing it accordingly. There may be a risk of publication bias across studies or selective reporting of supporting evidence for individual viewpoints/favored interventions within studies, which might provide a confounding factor in the present analysis and should be borne in mind accordingly.

The PRISMA-P statement guidelines were followed closely upon research and preparation of the present review) (11).

RESULTS

A total of 48 studies were selected based on their relevance as well as design, as presented in the flow diagram. The information obtained from them is organized and presented in the sections described above. An overview of the main findings from each study can be found in the attached results table (cf **Supplementary Material, Table 1**).

Involuntary Admission

A relatively large proportion of patients receiving treatment in an acute psychiatric setting are admitted through authorities or their treating physician/therapist against their will. A negative association between involuntary admission and the quality of the TR has been repeatedly found (6, 12–16). On the other hand, it has been shown that psychiatric emergencies are handled better if a stable TR is present, enabling less coercive strategies such as "talking down". Verbal and nonverbal communication skills have been shown to have crucial effects in the context of TR building and maintenance (17). (First) encounters with psychiatric services as experienced in an emergency situation have been described as being predictive for views on psychiatry and for the quality of future TRs (18). In a study assessing patients' perceptions of undergoing an involuntary treatment order, four out of the six most frequently described themes were related to staff attitudes and behaviors, indicating that understanding patients' needs and meeting them accordingly can enable the development of a positive TR despite the obstacles posed by involuntary admission (15).

Increased Symptom Severity

Being in need of emergency treatment, patients in acute psychiatric settings will tend to present with a higher and/or more acute degree of suffering from their symptoms, at least initially. Quality ratings of the TR have been consistently shown to decrease with increasing symptom severity (19–21). This may be additionally aggravated by acute deterioration of clinical state or a sudden change of external factors previous to hospitalization. While symptom severity upon admission is beyond the control of the therapist, raising awareness of its negative implications not only on the clinical state but also on the ability to build and maintain a TR may enable the development of strategies to overcome this obstacle.

Loss of Autonomy

Autonomy is a crucial concept for both personal dignity of the patient, as well as for the ability and willingness to engage in a TR. One largely acknowledged definition of autonomy states that "Personal autonomy is, at minimum, self-rule that is free from both controlling interference by others and from limitations, such as inadequate understanding, that prevent meaningful choice" (22). Independently of whether or not a patient was admitted into the hospital voluntarily, it can easily be concluded that acute psychiatric wards have some features that in themselves inevitably restrict a patient's autonomy. Practices such as closed doors, restricted access for visitors, and limited permission to leave the ward in terms of time and/or distance, are likely to meet the criteria for being a "controlling interference" by most definitions. Psychiatric emergencies have been defined as "an acute disturbance of behaviour, thought or mood of a patient which if untreated may lead to harm, either to the individual or to others in the environment" (23). It would again seem likely for either of these conditions to meet the criteria of being a limitation preventing meaningful choice, thus reducing autonomy drastically. This is likely to pose a significant hindrance to building a good TR if not addressed consciously and carefully.

Coercion

As with involuntary admission, a negative association between perceived coercion and TR quality ratings has been established (12, 16, 20, 24). Perceived coercion, however different definitions of the concept may be, certainly involves a subjective loss of control. Practices of forcing medication on patients, physical or chemical restraint or seclusion without consent obviously meet the criteria for such perceived coercion. Further negative consequences may result, for example in the case of medication being refused as a means of protest against not only the drug itself, but also against the loss of autonomy associated with "giving in" to the prescribing therapist. On the other hand, a positive TR has been shown to be a predictor for medication adherence in schizophrenic patients (25–27). Therapists would be well advised to make use of this effect in their efforts to provide patients with the best possible treatment, besides the obvious interpersonal benefits.

Depending on professionals' attitude on coercion, they have been demonstrated to under- or overestimate the extent to which measures are perceived as coercive by patients, respectively (28). Both the presence of coercion in itself and the misjudgment of health care professionals are factors to be addressed in an effort to improve TR building in acute settings.

Role Conflict Therapist: Help vs. Assess

Bearing in mind their responsibility towards the safety and wellbeing of their patients, therapists can run into conflicting requirements negatively impacting a trustful TR. For example, in patients with acute suicidal ideations, a therapist may, despite aiming to be as transparent and open as possible, choose not to disclose additionally disturbing information they have received through third parties (death of a relative, spouse's wish to

divorce, etc). Equally, information that may provoke aggression may be withheld from acutely agitated patients, in line with the previously described principle of prioritizing safety over the TR in specific situations (29). When it comes to applying coercive measures or to evaluating a patient's decision-making capacities, therapists may have to make decisions that they consider to be in their patients' best interest from a medical-professional point of view, yet thus endanger the TR if the patient disagrees with this judgement. Ensuring either the patient's, the therapist's or third parties' safety can also require taking measures that are likely to decrease the TR quality (30). While it has been demonstrated that interpersonal fairness improves TR and compliance (31), the above examples are likely to reduce the perceived degree of fairness on the therapist's part. Sensitive handling of both deciding in these situations and communicating the respective decisions requires adequate training in order to still maintain a good TR.

Team Work, General Setting

The management of acute psychiatric patients is performed by an interdisciplinary team. Professions other than the principal therapist face their own difficulties in building and maintaining a TR in this setting. This has been described most predominantly in the nursing profession [e.g. (32)]. Difficulties in the relationship with one person or profession can have a "spillover-effect", burdening the TR between patient and principal therapist, or they can further conflicts in the multiprofessional team. Some patients may also find it more difficult to engage in a TR with a therapist working in a team (as opposed to seeing an individual therapist in an outpatient practice), feeling intimidated by the loss of privacy following the necessary exchange between team members. Due to the organization of acute wards with shift systems, responsibilities may change, with patients finding themselves in contact with unfamiliar staff repeatedly. This will certainly decrease the probability of establishing a trustful, high-quality TR.

Patients' preferences regarding the gender, personality, background or other attributes of their therapist can hardly be taken into account in an acute psychiatric setting. It has been shown that factors such as communication, cultural sensitivity, and building a TR in an individualized way are pivotal to a good TR and to feeling safe in a therapeutic milieu (24, 33, 34). Bearing this in mind and making conscious efforts to overcome these hindering conditions and meet an individual patient's needs would be well served in facilitating the building of a good TR.

Short Duration, Lack of Continuity

Acute in-patient treatment tends to be short, and decisions may be required to be taken very early after the first encounter between patient and therapist. For example, if an acutely psychotic patient is admitted involuntarily, accompanied by state authorities, the very first interaction between therapist and patient may take place in the presence of these authorities and in the context of coercive measures. Aside from the other difficulties associated with such a setting, both the time to build and to maintain a good TR are thus condensed immensely compared to elective psychotherapy. Besides that, there is usually not a perspective for the patient and the therapist to continue their TR after the patient is discharged. Knowing the temporal limitations of the TR may reduce the level of trust in the therapist that a patient is willing to invest, and likewise may diminish a therapist's readiness to engage in earning that trust.

DISCUSSION

Several points become evident from the above considerations. First, it would seem highly advisable to expand efforts to specifically adapt research methods to examining the TR in an acute setting as opposed to struggling with unsuccessful adaptations of TR research from psychotherapy settings. Most of the above sections defined as influential for TR in an acute setting are not applicable to TR in a psychotherapeutic setting, and thus require research methods more specifically tailored to examine factors related to these sections and their influence on the TR. The need for an adaptation of methods has been pointed out previously (8). Certain efforts have been made to develop scales to objectively measure TR-related factors (35). It has been pointed out that furthering and developing such measures, preferably in a standardized way, would seem reasonable (36).

An association between patient satisfaction and TR quality ratings has been shown (37–39). Aiming to gain a better understanding of the peculiarities and potential pitfalls of building and maintaining a good TR in an acute setting should thus involve patient-focused research, e.g. through satisfaction questionnaires (40, 41), although receiving feedback from patients in severe distress may require some adaptation of standard processes (42). It has been pointed out that a dialog between patients and therapists/staff on delicate subjects such as coercion is possible, useful and desired by patients (43). Establishing transparent communication on these subjects could diminish the probability of misunderstanding and enable more individualized treatment options meeting patients' needs more adequately. It seems plausible to hypothesize that such measures would thus improve the quality of the TR.

In certain patient forums, there are efforts to protect the TR from a patient's perspective for example (44). Internet-based opportunities for exchange and assessment will likely increase, and it has been shown that a TR develops even when there is no direct face-to-face contact (45). Making these efforts known amongst therapists, as well as supporting similar initiatives in different communities, would certainly raise awareness and have beneficial effects on TR quality. Such initiatives should take into account both general factors, those specific to an acute setting, as well as potential diagnosis-related pitfalls (e.g., paranoid fears in schizophrenia, narcissistic wound in personality disorders, lack of motivation in depression, etc). Furthering exchange between therapists and patients might help overcome misunderstandings, as well as reduce the frequently observed disparity between their respective ratings of TR quality [e.g. (46–49)].

It has been pointed out that therapists, on the other hand, should receive specific training (3), for example in verbal and nonverbal communication skills (8, 17, 50) and that awareness of difficult circumstances and situations should be raised, including other professions such as nurses (50). Recommendations have been

made for therapists to minimize perceived coercion and to mediate procedural fairness when attempting to improve patients' treatment adherence (28), which would likely have a positive influence on TR quality, as well. One study observed that the quality of the TR was significantly worse in acute wards than crisis houses, suggesting the latter as an alternative model for suitable patients (51). Examining the reasons for the difference in quality ratings might further therapists' understanding of potential improvements to TR building in an acute ward. Another important development in the management of psychiatric emergencies is the establishment of crisis intervention teams visiting clients in their homes (52). Research on therapeutic relationship in these interventions is scarce, but client satisfaction surveys suggest an overall positive perception, which might point towards positive interactions and thus a good TR in such settings. Further examining the methods used in those home treatment interventions might provide useful insights for building a good TR in acute wards, as well as shedding some light on the preferred mode of intervention in various crisis settings. Additionally, environmental factors such as family and other social contacts might be better accounted for and given a chance to participate in the therapeutic process in more outpatient-directed approaches.

The scarcity of available data on some of the described factors, as well as the paucity of specific research into TR in acute psychiatric settings, also lead to limitations of the present review.

CONCLUSION

As a conclusion, efforts to raise awareness of potential pitfalls in building and maintaining a good TR in an acute setting, conducting more specific research into this area, questioning patients and including them in the process of decision-making wherever possible, defining standardized instruments as well as enabling more specifically tailored procedures, and developing training options for therapists based on these findings would likely increase the chances of improving TR quality in acute psychiatric wards.

Implementing the above measures would likely have positive impacts not only on clinical outcome, duration of stay, rehospitalization rate, and patient satisfaction, but also on experience with and perception of psychiatry, possibly paving the way for a smoother course of disease and treatment in the case of chronic illness as well as reducing stigma.

AUTHOR CONTRIBUTIONS

JB and AT have made substantial contributions to conception and design of the study. JB executed the acquisition of data. JB and AT analyzed the data. JB, PH, MJ, and AT have been involved in the interpretation of data, drafting, and revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIALS

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00965/full#supplementary-material

SUPPLEMENTARY IMAGE 1 | Flow diagram.

SUPPLEMENTARY TABLE 1 | Results table.

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SYSTEMATIC REVIEW
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The Effectiveness of Crisis Line Services: A Systematic Review

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Background: Crisis lines are a standard component of a public health approach to suicide prevention. Clinical aims include reducing individuals' crisis states, psychological distress, and risk of suicide. Efforts may also include enhancing access and facilitating connections to behavioral health care. This review examines models of crisis line services for demonstrated effectiveness.

Methods: Literature searches of Medline, EMBASE, PsycINFO, Web of Science, CINAHL, Cochrane Library, and Google Scholar were conducted from January 1, 1990, to May 7, 2018. Experts were contacted, and references were mined for additional studies. Eligible studies provided health- or utilization-related effectiveness outcome(s). Results were graded according to the Oxford Centre for Evidence-Based Medicine and evaluated for risk of bias using the Effective Public Health Practice Project quality assessment tool for quantitative studies.

Results: Thirty-three studies yielded effectiveness outcomes. In most cases findings regarding crisis calls vs. other modalities were presented. Evaluation approaches included user- and helper-reported data, silent monitoring, and analyses of administrative records. About half of studies reported immediate proximal outcomes (during the crisis service), and the remaining reported distal outcomes (up to four years post-contact). Most studies were rated at Oxford level four evidence and 80% were assessed at high risk of bias.

Conclusions: High quality evidence demonstrating crisis line effectiveness is lacking. Moreover, most approaches to demonstrating impact only measured proximal outcomes. Research should focus on innovative strategies to assess proximal and distal outcomes, with a specific focus on behavioral health treatment engagement and future self-directed violence.

Keywords: systematic review, crisis line, suicide, health services, self-directed violence, prevention, public health, quality of care

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INTRODUCTION

Rationale

In the United States (US), from 1999 through 2017, the age-adjusted suicide rate increased 33% from 10.5 to 14.0 per 100,000 (1) and worldwide suicide remains a pressing concern. Upstream efforts to prevent suicide include crisis line services (e.g., call, chat, text). During such interactions, responders address the crisis at hand with the aim of reducing crisis states, psychological

distress, and risk of suicide. This may include facilitating evaluation of imminent risk by local first responders. In addition, within the context of a crisis line contact, responders may provide resources and strategies to facilitate treatment referrals and engagement in care. Given the key role of crisis lines within a comprehensive public health strategy for suicide prevention, it is critical to know whether they are meeting their intended goals. The primary goal of crisis line effectiveness research is to evaluate the immediate proximal and/or longer-term distal effect(s) of such interventions. These effects may be measured using a wide-range of outcomes, including health- and service use-related client outcomes data regarding prevention of self-directed violence, enhanced mood, satisfaction, compliance with responder interventions, and/or service utilization, as well as outcomes regarding responder responses, such as intervention style and referral recommendations.

Objectives

The purpose of this systematic review is to establish the state of the science on crisis line effectiveness research. This review provides an exhaustive account of published literature, identifying not only strengths and biases present in the evidence, but also gaps, limitations, and future research opportunities. Within this framework, we specifically examined the literature to identify and appraise: (1) immediate proximal as well as longer-term distal outcomes measuring crisis line effects; (2) data collection approaches utilized to measure impact; and (3) study design and risks of bias informing the strength of current evidence.

Research Question

The key question (KQ) of interest inquired whether there are models of service delivery (crisis line phone, chat, or text) with demonstrated effectiveness.

METHODS

Study Design

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2). A completed PRISMA Checklist is available (See **Supplementary Table 3**).

Participants, Interventions, Comparators

For the PRISMA screening and eligibility stages, each study was assessed independently by two reviewers (LAB, KSY) and a third reviewer (ASH) resolved disagreements. Eligibility Criteria were defined according to the PICO(TS) framework: (2, 3)

- Population—Crisis line users consisted of any age.
- Intervention/Exposure—Use of crisis line phone, chat, or text services (see **Supplementary Table 2**). An intervention was not required for inclusion (e.g., surveys or administrative data were included). However, studies were excluded if they only provided results on demographic profiles of crisis line utilizers without effectiveness outcomes as described below.
- Comparison—Not required for inclusion.
- Outcomes—All health- and use-related effectiveness outcomes both immediate proximal and longer-term distal, including SDV, client mood, satisfaction, compliance, and service utilization, as well as responder responses (e.g., referrals, intervention styles) (see **Supplementary Table 2**).
- Timing/Setting—Restrictions were not based on timing, setting, or study design.

Only studies including original data and published in a peer-reviewed journal from January 1, 1990 through May 7, 2018 were included.

Systematic Review Protocol

A protocol for this review is registered in PROSPERO International prospective register of systematic reviews under registration number CRD42019127249 (4).

Search Strategy

Databases were searched using controlled subject heading vocabulary and key words for suicidal self-directed violence (SDV), (5) combined with controlled subject heading vocabulary and key words for crisis line services (see **Supplementary Table 1**). Searches were limited to English language only. Experts were contacted, and references were mined for additional studies. Complete references were exported from each literature source into EndNote X8, duplicates were removed, and the remaining entries were imported into Covidence review software.

Data Sources, Studies Sections, and Data Extraction

The final literature search of OVID Medline, EMBASE, OVID PsycINFO, Web of Science, CINAHL, Cochrane Library, and Google Scholar was conducted on May 7, 2018. Data from included articles were abstracted into evidence tables by two authors (ASH, KSY; conflicts resolved via discussion with LAB). Extracted data from each article included a description of the crisis line service, sample characteristics, study time period, effectiveness domains measured, source of outcome measurements, proximity of outcome measurement to the intervention, and effectiveness findings (see **Supplementary Table 4**).

Included studies were independently evaluated by two reviewers (ASH, KSY) in a custom Research Electronic Data Capture (REDCap) database (6) with disagreements resolved by consensus discussion with a third reviewer (LAB).

Strength of Evidence and Risk of Bias

Included studies were graded by level of evidence according to the Oxford Centre for Evidence-Based Medicine (7) (See **Table 1**). In some cases, "higher level" Oxford grades from well-designed and executed observational studies provided stronger evidence (lower risk of bias) than "lower level" Oxford graded randomized controlled trials (RCT) with extensive biases. To address this limitation and complement the Oxford quality ratings, risk of bias was also assessed independently by two raters using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies (41). The EPHPP

assessment was conducted in a custom REDCap database. The EPHPP tool bias items included selection bias, study design, confounders, blinding, data collection, withdrawals/dropouts, and other sources (e.g., no disclosure of conflicts of interest) (41). To inform the study design appraisal, included studies were classified by study design using the Taxonomy of Study Design Tool (42). Guidance for bias ratings was drawn from the EPHPP data dictionary, and summarized as follows: Selection bias considered to what extent study participants were likely to be representative of the target population, as well as the proportion of selected individuals who agreed to participate in the study; Study design considered the likelihood of bias in the allocation process for experimental designs, and for observational designs, the extent that assessments of exposure and outcome are likely to be independent; Confounding examined to what extent important variables were controlled for in the study design (by matching or stratification), and/or in the analyses; Blinding assessed detection and reporting bias, such as whether the assessors were aware of the research condition and/or the participants were aware of the research question(s); Data collection methods were rated on the validity, reliability and use of standardized outcome measures, including distinctions between self-reported data, objective data retrieved by investigators, and extracted data from administrative records; Withdrawals and drop-outs assessed the proportion of participants remaining in the study through the final data collection period (if applicable); and Other sources of bias included intervention integrity and utilizing appropriate analyses for the research questions (43). Each of these domains, if applicable, was rated as having a low, moderate, or high risk of bias based on these standard guidelines. An overall risk of bias rating was then generated (43, 44). Ratings were based only on information reported in the study. All discrepancies were discussed until reviewers reached consensus regarding the extent of bias present in each domain and overall.

Data Analysis

Variability of study designs and outcome measurement precluded a meta-analytic approach to synthesis. Findings were not quantitatively synthesized because included studies were mostly a mix of observational and quasi-experimental design, and often utilized unstandardized measurement approaches to assess a variety of outcomes across many effectiveness domains. Therefore, a descriptive synthesis approach was utilized.

RESULTS

Study Selection and Characteristics

Of the 757 studies screened, 33 met eligibility criteria and were included in the review (See **Figure 1**). Whereas the vast majority of studies described outcome data measured from crisis calls, three included effectiveness outcomes from crisis chat (21, 30, 35). No studies examined crisis line text outcomes. Crisis line call centers included in the review were staffed by a range of responders (e.g., volunteers, paid employees). Approaches to effectiveness outcome measurement also varied, and included user- and responder-reported outcomes, ratings by silent monitors unobtrusively observing crisis line calls, and coding of administrative records (e.g., from clinical forms, chat logs, and call recordings) (see **Supplementary Tables 2, 4**).

Synthesized Findings and Risk of Bias

The overall risk of bias of included studies was high, and the most frequent Oxford level of evidence was four. Only one study identified was low risk of bias, five studies were rated moderate risk of bias, and the remaining were high risk of bias (See **Table 1**). There were many common sources of bias found in the moderate and high risk of bias studies. Specifically, selection bias was highly prevalent (e.g., many studies excluded crisis line users with the highest [imminent] suicide risk and also inconsistently approached crisis line users for participation). The vast majority of included studies had risks of bias in confounding in the study design and/or analyses, leading to challenges in interpreting potentially spurious associations or findings that could be related to a variable other than the crisis intervention. Furthermore, data collection, measurement, and detection biases (e.g., using unblinded approaches and tools not shown to be valid), as well as attrition bias (e.g., when measuring distal outcomes) contributed to downgraded ratings in the strength of the evidence. Based on these appraisals, the overall strength of evidence for outcomes measuring crisis line effectiveness was determined to be low.

Study Design

Only two studies were RCTs [Gould et al. (29) moderate risk of bias and Mishara et al. (15) high risk of bias; Oxford quality ratings of 1]. Additionally, there were four cohort studies (11, 14, 31, 38), and the remaining studies were a mix of observational and quasi-experimental design, most of which were cross-sectional or single group before-after designs (high risk of bias; Oxford quality ratings of 4).

Immediate Proximal Evidence of Effectiveness

In about half of studies (16 studies) immediate proximal outcomes during and/or at the end of a crisis line service were evaluated (See **Supplementary Table 4**). Immediate proximal evidence consisted almost exclusively of cross-sectional studies of a single measurement timepoint or single-group before-after study designs measuring change from the beginning (pre-) to the end (post-) of the crisis line intervention; one proximal RCT was noted. For the most part, adolescents and adults utilized the crisis lines services evaluated, however there were five adult only samples, which included three US Veteran studies, and four studies in which age was not reported. Regarding location of crisis lines evaluated, eight studies were from the US, two from the United Kingdom (UK), and one each from Australia, Israel, Canada, Amsterdam, and Spain. Proximal outcomes measured included client mood/satisfaction at the end of the call or change from the beginning to the end of the call (nine studies), helper responses/approaches used during the call (eight studies), the provision of referrals (seven studies), and changes in SDV such as suicidal thoughts (four studies).

Approaches to outcome measurement also varied, including six studies that utilized silent monitors or call/chat log ratings

TABLE 1 | Design, sources of bias, overall bias, and oxford quality rating by study.

Study	Study design	Source of bias						Overall bias	Oxford quality rating
		Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals/ dropouts		
de Anda and Smith (8)	Cross-sectional	●	⬤	●	●	⬤	⊖	⬤	4
Daigle and Mishara (9)	Cross-sectional	●	⬤	⬤	●	●	⊖	⬤	4
Jianlin (10)	Before-after	⬤	●	⬤	●	⬤	○	⬤	4
Leenaars and Lester (11)	Retrospective cohort	○	●	⬤	●	○	⊖	●	3
Mishara and Daigle (12)	Before-after	●	●	⬤	●	●	○	⬤	4
King et al. (13)	Before-after	⬤	●	⬤	●	●	○	⬤	4
Leenaars and Lester, Study 1 (14)	Cross-sectional	○	⬤	⬤	●	○	⊖	⬤	4
Leenaars and Lester, Study 2 (14)	Retrospective cohort	○	●	⬤	●	○	⊖	●	3
Mishara et al. (15)	RCT	⬤	●	●	⬤	⬤	●	⬤	1
Latzer and Gilat (16)	Cross-sectional	○	⬤	⬤	●	⬤	⊖	⬤	4
Gould et al. (17)	Before-after	⬤	●	○	⬤	●	⬤	⬤	4
Kalafat et al. (18)	Before-after	⬤	●	○	⬤	●	⬤	⬤	4

(Continued)

TABLE 1 | Continued

Study	Study design	Source of bias						Overall bias	Oxford quality rating
		Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals/ dropouts		
Mishara et al. (19)	Cross-sectional	●	●	●	◌	◌	⊖	●	4
Mishara et al. (20)	Before-after	●	◌	●	●	◌	◌	●	4
Fukkink and Hermanns (21)	Controlled before-after	●	◌	◌	●	●	●	●	4
Witte et al. (22)	Before-after	●	◌	●	●	◌	●	●	4
Chavan et al. (23)	Cross-sectional	○	●	●	◌	◌	⊖	●	4
Coveney et al. (24)	Cross-sectional	●	●	◌	●	●	⊖	●	4
Gould et al. (25)	Cross-sectional	●	●	○	●	◌	⊖	●	4
Knox et al. (26)	Cross-sectional	○	●	●	◌	◌	⊖	●	4
Tan et al. (27)	Cross-sectional	◌	●	◌	◌	◌	⊖	●	4
Britton et al. (28)	Cross-sectional	◌	●	○	◌	●	⊖	●	4
Gould et al. (29)	RCT	◌	◌	◌	◌	◌	○	◌	1

(Continued)

TABLE 1 | Continued

Study	Study design	Source of bias						Overall bias	Oxford quality rating
		Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals/ dropouts		
Pil et al. (30)	N/A	○	⊖	●	⊖	●	⊖	●	4
Britton et al. (31)	Retrospective cohort	●	●	●	●	○	⊖	●	3
Gould et al. (32)	Cross-sectional	●	●	○	●	●	⊖	●	4
Mishara et al., Study 1 (33)	Cross-sectional	●	●	●	●	●	⊖	●	4
Mishara et al., Study 2 (33)	Before-after	●	●	●	●	●	●	●	4
Tyson et al. (34)	Before-after	●	●	●	●	●	⊖	●	4
Mokkenstorm et al. (35)	Before-after	●	●	●	●	●	○	●	4
Ramchand et al. (36)	Controlled before-after	●	●	●	●	●	○	●	4
Rasmussen et al. (37)	Cross-sectional	○	●	●	●	●	⊖	●	4
Chan et al. (38)	Retrospective cohort	○	●	○	●	○	⊖	⊖	3
Gould et al. (39)	Before-after	●	●	●	●	●	●	●	4
Mejias-Martin et al. (40)	Cross-sectional	○	●	●	●	○	⊖	●	4

○, *low;* ●, *moderate;* ●, *high;* ⊖, *not applicable; RCT, Randomized Controlled Trial.*

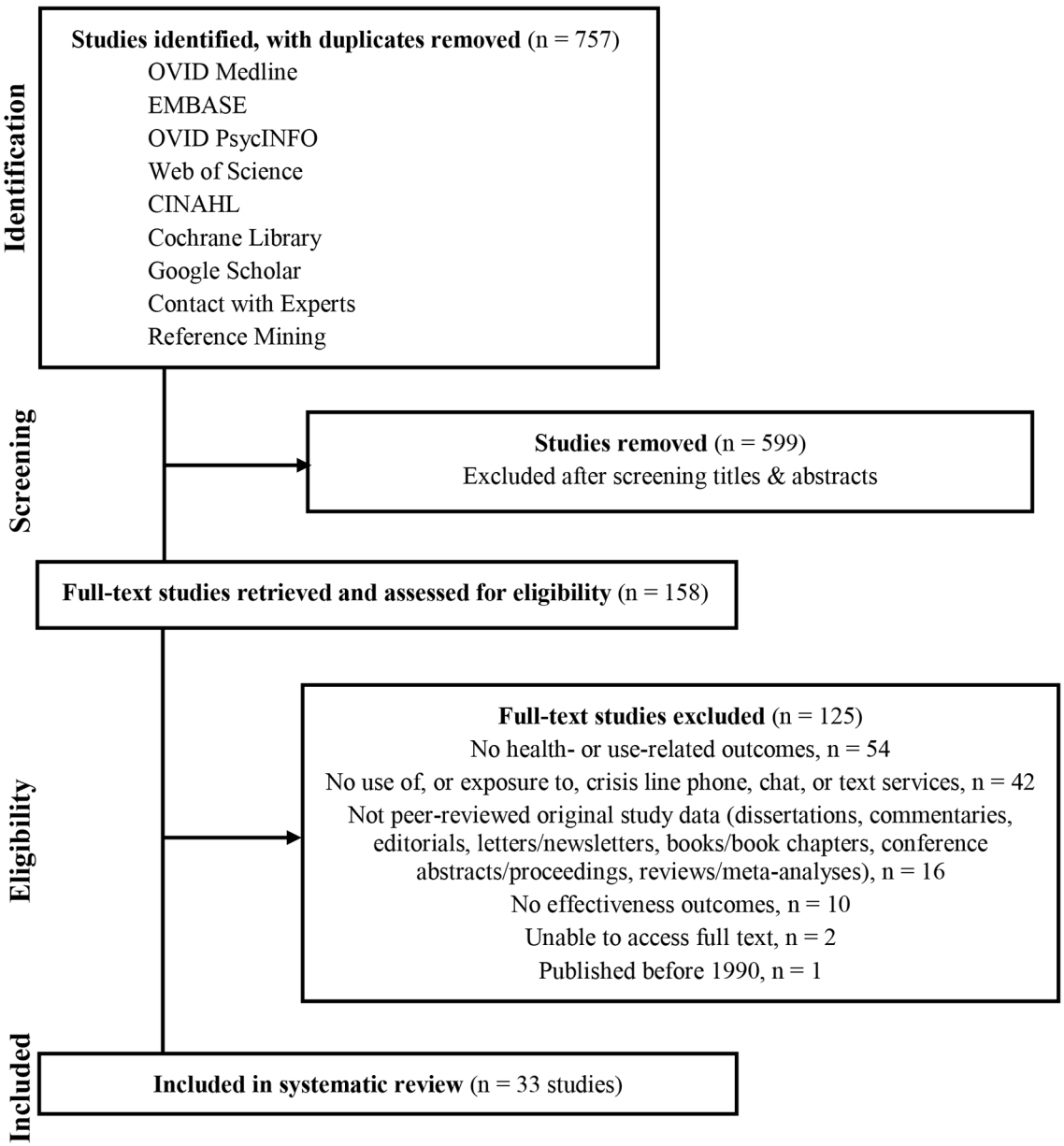

FIGURE 1 | PRISMA literature flow diagram.

that were shown to be reliable, and three studies incorporated validated assessment tools. However, seven studies relied on administrative/clinical records such as routine call sheets completed by responders, and five studies used approaches not shown to be reliable or valid. Note some studies measured effectiveness across more than one domain and using a mixture of validated and unvalidated approaches.

Notable immediate proximal evidence included a before-after study by King et al. (13) (high risk of bias; Oxford quality rating of 4) in which 100 taped calls between March 1998 and March 1999 to the Kids HelpLine in Australia were analyzed. Callers were assessed for suicidal ideation, intent, and mental state using a mixture of standardized and unstandardized approaches, including assessment items adopted from the Mini-International Neuropsychiatric Interview (MINI) Modules A and C (45). Two independent raters analyzed each tape for changes and identified a significant decrease in suicidal ideation and improvement in mental state from the beginning to the end of a call (both $p < 0.0005$). A substantial decrease in the proportion of callers rated imminent risk at the end of calls was also noted. However, 14% of callers remained suicidal at the end of the call (13).

In another study employing reliable independent raters and the use of a validated assessment tool, Mishara and colleagues (19, 20) (high risk of bias; Oxford quality rating of 4) analyzed 1,431

adults crisis calls to the Hopeline Network in the US between August 2003 and May 2004. Caller mood/states and helper responses were evaluated via ratings by two silent monitors observing unobtrusively, and differences between centers were evaluated by the Crisis Call Outcome Rating Scale (CCORS) (46). Reliability analyses were performed for silent monitor observations of helpers, and interrater agreement was found to be quite high throughout (19, 20). They found an overall positive mean effect ($p < 0.001$), but many variables did not significantly change from the beginning to the end of the call according to ratings by the silent observers (19, 20). Responder approaches were found to impact caller outcomes, with a supportive approach and good contact associated with positive mood/state changes ($p < 0.001$). Furthermore, there was significant variability in effectiveness across call centers, measured via the CCORS ($p < 0.03$), and a supportive, collaborative approach with good contact, empathy, and respect were all associated with higher CCORS scores and fewer hang ups (all $p < 0.001$) (19, 20). The authors also noted that 50.5% of callers were not asked about suicidal ideation, and responders failed to meet minimum acceptability standards in 15.6% of calls, including lacking empathy, respect, poor initial contact, and stunningly in four cases the helper told the caller to go ahead and kill himself (19, 20). In two cases, an emergency rescue protocol was initiated by the research team when the helper failed to do so with callers at imminent risk.

A more recent example of a reliable silent monitoring approach was conducted by Ramchand et al. (36) (high risk of bias; Oxford quality rating of 4) in which 241 calls from 10 American Association of Suicidology-accredited hotlines in California during the Spring and Summer of 2014 were monitored. The protocol was developed from existing work by Gould and colleagues (25, 29) and included use of the Lifeline Quality Improvement Monitoring Tool. Monitors identified a mean 43% decreased caller distress from beginning to end of call (range 28–64%), with decreased distress associated with the crisis center NSPL network membership (Odds Ratio [OR] 2.72; $p = 0.024$) (36). Responders at NSPL centers were also more likely to ask about current suicide ideation (77 vs. 52%; OR 3.6; $p < 0.01$), recent ideation (31 vs. 16%; OR 2.5; $p = 0.02$), and past attempts (27 vs. 10%; OR 3.7; $p < 0.01$) (36). The researchers also noted that a mean of 7% of all calls were put on hold (range 0–26% across centers) (36).

In terms of crisis services provided to Veterans, Knox et al. (high risk of bias, Oxford quality rating of 4) analyzed the implementation and early utilization of the Veterans Crisis Line (VCL). Between July 2007 and September 2010, 171,000 calls were made to the VCL. Effectiveness was analyzed via responder referrals to either Suicide Prevention Coordinators (SPC) and/or other Veterans Health Administration (VHA) and community programs. From VCL inception in July 2007 through 2008, approximately 4,000 referrals were made to SPCs, and this increased to 16,000 total referrals by the end of September 2010.

Also of note, in a cross-sectional study of VCL, Britton et al. (high risk of bias; Oxford quality rating of 4) analyzed 646 calls during a 1 week period in 2010 to ascertain responder referral actions at the end of each call (28). Results indicated that 84% of calls ended with a favorable outcome, defined as either resolution during the call or referral to a local health care provider, with the remaining 16% classified as unresolved/declined referral. In the univariate analysis, higher risk callers had significantly higher odds of the call ending in a referral (77 vs. 49%; Relative Risk Ratio [RRR] 2.70; 95% Confidence Interval [CI] 1.64–4.47), and in the multivariate analysis callers at higher risk approached significance in more calls resolved vs. unresolved compared with lower risk callers (RRR 0.56; 95% CI 0.30–1.04; $p = 0.067$). For 54% of callers, responders provided reasons for determining higher vs. lower risk callers, and reported these judgments were based on intent to die (OR 8.47; 95% CI 3.85–18.63) and absence of future plans (OR 10.45; 95% CI 2.84–38.40) (28).

In the most robust proximal evidence of effectiveness, Gould et al. (29) conducted the first national RCT to evaluate the immediate proximal effect of a crisis center intervention and training strategy using a dynamic wait-listed roll-out design across the US National Suicide Prevention Lifeline (NSPL) network of crisis hotline centers. Effectiveness was measured by silent monitoring of 1,507 calls between June 2008 and December 2009 via adapted 4-point rating scales of positive/negative behaviors and affects. They found that counselors with Applied Suicide Intervention Skills Training (ASIST) were significantly more likely to positively impact caller behavioral and affect changes during the call, including callers feeling less depressed (OR 1.31; 95% CI 1.01–1.71; $p < 0.05$), less overwhelmed (OR 1.46; 95% CI 1.18–1.82; $p < 0.05$), less suicidal (OR 1.74; 95% CI 1.39–2.18; $p < 0.001$), and more hopeful (OR 1.35; 95% CI 1.04–1.77; $p < 0.05$), compared with counselors without ASIST (29). Furthermore, counselors with ASIST were significantly more likely to apply positive supportive and collaborative approaches, including exploring reasons for living (OR 1.46; 95% CI 1.03–2.07; $p < 0.05$) and ambivalence about dying (OR 1.65; 95% CI 1.19–2.28; $p < 0.01$). However, those with ASIST were not more likely to ask about suicide plans, preparatory behaviors/actions, intent, and prior suicide thoughts or attempts compared with counselors without ASIST (all $p > 0.05$) (29).

Gould and colleagues (32) (high risk of bias; Oxford quality rating of 4) cross-sectionally analyzed 491 calls to the NSPL between February and September 2012. This study is noteworthy because it consisted entirely of imminent risk callers and provided insights into the utilization of first responders to support crisis line services. Data were drawn from responder self-report questionnaires regarding imminent risk assessments and interventions provided. Interventions were classified according to four levels: active collaborative non-invasive; active collaborative invasive; active non-collaborative invasive; and, active non-collaborative noninvasive (See **Supplementary Table 2**). Collaborative calls included any active engagement by the caller to take action on her or his own behalf to work toward safety, and invasive interventions included the provision of emergency first responder services, sometimes referred to as "emergency rescues." Results indicated that 76.4% of callers were collaborative in securing their own safety, and the remaining 24.6% required a non-collaborative and

involuntary use of emergency services (32). A novel approach to developing risk profiles was also explicated by classifying callers along two continuums based on level of risk and level of engagement.

In the only study focused exclusively on crisis chat outcomes, Mokkenstorm et al. (35) (high risk of bias, Oxford quality rating of 4) analyzed 526 administrative records of chat logs from April to June 2013 to measure immediate proximal change from the beginning to end of a crisis chat, and found that suicidal ambivalence worsened for 15 of the users (2.9%), 156 (29.7%) had no change, and 18 improved (3.4%). Missing data was an issue for this outcome (337; 64.1%). The CCORS was also used to assess chatter's positive and negative experiences and behaviors. The mean score was 114.1 (Standard Deviation [SD] 16.8; range 61–150), though "a mixed picture emerges," (p. 289) with 27.6% of chats rated to be dissatisfied, and 28.7% were satisfied; 33.1% said she or he did not seem to feel better, while 20.2% felt better (35).

In the most recently published study regarding immediate proximal evidence of effectiveness, Mejias-Martin et al. (40) (moderate risk of bias; Oxford quality rating of 4) analyzed 20,942 calls to the EPES public emergency healthcare service of Andalusia, Spain between January 2007 and December 2013. Based on records from the phone operator and healthcare team labeling, the researchers noted 516 caller deaths prior to evacuation (2.46% of analyzed calls), and that males died significantly more frequently than females (4 vs. 0.98%; $p = 0.001$) (40). Almost three-fourths (72.37%) of calls resulted in an emergency rescue evacuation to the emergency department, while 13.05% were resolved *in situ*, 4.61% were referred to a professional, and 1.96% denied to be attended (40). In analyses to understand groups with more frequent evacuation, callers over 65 years old had two times lower likelihood of evacuation compared with younger callers (adjusted OR 0.53; 95% CI 0.47–0.59), and females were more frequently evacuated compared with males ($p = 0.001$), while also having calls more frequently resolved *in situ* (40).

Distal Evidence of Effectiveness

The remaining 17 studies measured more distal outcomes and were categorized by proximity of outcome measurement from the time of crisis line service. Distal evidence ranged from follow-up about 1 week after the crisis line service, to up to 4 years (See **Supplementary Table 4**). For three studies, the outcome measurement was distal but the time elapsed between the call and the follow-up was not clear. Distal evidence consisted largely of single-group before-after study designs measuring initial outcomes during the crisis line intervention, along with a single follow-up assessment after the crisis line service. Several before-after studies included multiple assessment timepoints for distal outcome measurement. One RCT measuring distal outcomes was noted, along with a few retrospective cohort studies. Crisis lines evaluated for distal outcomes also served both adult and adolescent populations, including one adolescent only study, five mixed adult/adolescent samples, seven adult only samples (including one US Veteran study), and four studies in which age was not reported. Distal studies were conducted in Canada (seven studies), the US (six studies), and one each from Amsterdam, China, Hungary, Belgium, and India. Distal outcomes measured included SDV (13 studies), client mood/satisfaction (eight studies), helper responses/approaches (four studies), the provision of referrals (six studies), as well as service utilization (seven studies).

Similar to the proximal studies, approaches to distal outcome measurement varied, including one study that utilized silent monitors, and four studies that incorporated validated assessment tools. However, five studies relied on administrative/clinical records, four studies used approaches not shown to be reliable or valid, and one study did not report source of data. Selected distal results are presented by proximity of the most distal outcome measurement to the crisis line service.

In the most proximal distal study with outcome measurement via follow-up calls at 1 week, Mishara and colleagues Study 2 (33) (high risk of bias; Oxford quality rating of 4) analyzed 1,206 calls to Quebec suicide prevention centers in Canada. Outcome measures included a mix of standardized and unstandardized approaches, including ratings by silent monitors, Helper Response Scales, CCORS, the Psychological Symptom Index (abridged), and the Brasington Indication of Depression. Significant decreases were noted in suicidal urgency from the beginning to the end of the call ($p < 0.001$), although there were no changes in 76% of calls. Additionally, suicidal urgency decreased in 16% of calls, but increased in 7.8% of calls (33). For this study, suicidal urgency was defined along a seven-point scale ranging from one (thinking about suicide with no plan, time frame, or method), to seven (decided to take own life in the next 24 h with a specific method determined and available). Follow-up outcomes regarding distal effectiveness of the crisis line were mixed and consisted of outcome data for just 8.7% of the baseline sample. At 1 week, 69.2% of callers were satisfied with help received, but 31% were not. A substantial proportion (42%) reported they did what they said they would do since the initial calls, but 40.2% admitted they did not (33). The authors also noted gender differences in effectiveness; female callers improved more frequently than males (18.6 vs. 11.8%; $p < 0.05$), and CCORS was significantly higher in females compared with males ($p < 0.001$) (33).

Kalafat et al. (18) (high risk of bias; Oxford quality rating of 4) analyzed 1,617 callers to local crisis hotlines and the 1-800-SUICIDE network from March 2003 to July 2004. Distal outcomes covering a variety of client domains were measured a mean 13 days from the baseline call (range 1–52 days) for about half (49.5%) of baseline callers. Assessment approaches were both standardized and unstandardized, including a 14-item measure adapted from the Profile of Mood States-A Modified (POMS-M) (47) and Likert scales. Findings revealed that 11.7% of callers had suicidal thoughts since the initial call (18). Callers who participated in the follow-up assessment were significantly more overwhelmed and received significantly more referrals compared with callers without follow-up ($p < 0.001$). POMS-M, caller distress, confusion, depression, anger, anxiety, helplessness, feelings of being overwhelmed, and hopelessness all significantly reduced from the beginning of the call to the end of the call and from the end of the call to the follow-up at 2 weeks (all $p < 0.001$) (18). 57.9% of those who completed follow-up initiated an action

plan with their counselor, and among those only 35 had not carried out any of the plan. Among those who completed follow-up and had been referred to a mental health resource (392), 33.2% had kept or made the appointment at follow-up (18). Of the three rescues initiated during the crisis call, two completed follow-up and one did not.

Gould et al. (25) (high risk of bias; Oxford quality rating of 4) analyzed 654 NSPL callers between January 2006 and December 2007 who were referred to health care. Standardized telephone interviews were conducted a mean 14 days after the initial call to the center (range 3–72 days), and they included suicide risk status, Beck Depression Inventory-II (48), along with other unvalidated questions. Overall, 41.9% of callers followed through with their referral, with the highest follow-through rate to mental health providers (25). However, 151 suicidal callers did not follow through with a referral, albeit 25% of those reported accessing a comparable mental health resource. Utilizing a mental health referral was not related to demographics, depression, or suicidal risk profile, although unsurprisingly utilization rates were higher among those with insurance compared with those without insurance (59.6 vs. 35.6%; OR 0.37; 95% CI 0.19–0.72; $p < 0.01$), and among those already in treatment compared with those who were not (76.7 vs. 26.1%; OR 9.32; 95% CI 5,91–14.70; $p < 0.0001$) (25). Perceptions about barriers to utilizing mental health resources among crisis line callers were also explored.

In the only other RCT evaluating crisis line effectiveness (and the only RCT measuring distal effects), Mishara et al. (15) compared the effects of four suicide prevention program arms for crisis line callers between February 2000 and January 2002. This approach was unique in that the study participants were family and friends who had called the crisis line with concern about high-risk suicidal men who did not seek help themselves. Using a mixture of standardized and unstandardized assessment approaches, they found that overall, the crisis line caller participants reported that the suicidal men they were concerned about were significantly less likely to have seriously considered suicide after participation in any of the crisis line programs (at 2 months $p < 0.001$; at 6 months $p < 0.01$), and less frequently attempted suicide in the previous 2 months (at 2 months $p < 0.02$; at six months $p < 0.001$) (15). However, problems with the design and execution of this trial introduced high risks of bias and cast doubt about the validity of these findings. Issues included discrepancies in the reporting of number of participants, errors in the table reporting results, the abandonment of the family session arm of the trial due to lack of participation, and low completion and analysis rates with missing reasons for dropout.

In the most thorough examination of service utilization after a crisis call, Britton et al. (31) (high risk of bias; Oxford quality rating of 3) retrospectively investigated distal VCL effectiveness by examining caller service utilization within 180 days of index referral during the crisis call. Referrals were made for 21,130 callers (20.6% of all calls), and the analysis included 13,444 callers (64% of eligible referrals) during calendar year 2010. Based on precise linkage of VCL call records with VHA medical files, it was revealed that VCL is most frequently used by Veterans already engaged in VHA care (91% of the sample had prior VHA use within the past 5 years). The majority of callers presented for in-person VHA care within seven days of referral (71% of callers without prior VHA use and 91% with prior VHA use). Callers with prior VHA use were more likely to present for same-day care; however, callers without prior VHA use were more likely to present for care after 15 days ($p < 0.0001$) (31). There were few other differences in service utilization observed between the two groups.

The only study across the entire body of evidence rated as low risk of bias was by Chan et al. (38) who conducted a retrospective cohort study analyzing death by suicide among elderly users and non-users of a telephone helpline between January 2012 and December 2015 (Oxford quality rating of 3). Outcomes were assessed via sociodemographic data from the service's computerized system, as well as suicide mortality status from the Coroner's Court matched against crisis line users using the unique Hong Kong Identity Card. In this study, helpline users accounted for 14.4% of known suicides in Hong Kong during the 4 year follow-up period, and the suicide rate among helpline users was far higher than the general Hong Kong older adult population (Males: 86.3 vs. 32.6 per 100,000; Females: 42.8 vs. 16.7 per 100,000; both Incident Rate Ratio [IRR] = 2.6) (38). The majority (60%) of the helpline suicides occurred within 5 years of the service. Significant predictors of suicide among the helpline users included older age, male, living alone, and self-reported mental illness. Protective factors were also identified including skeletal system diseases and brain and nervous system diseases (38).

Work by Pil et al. (30) (moderate risk of bias; Oxford quality rating of 4) was unique in that the team modeled cost-effectiveness of Flemish suicide chat and phone helpline services using 2011 data from 3,785 users in a 10-year simulation to predict distal future effects. Findings suggested that telephone and chat crisis line services could avoid 36% of projected future suicide attempts and provide modest cost-savings.

Volunteer vs. Paid Responders

Two studies provided additional insights into the effects of characteristics of crisis line responders on outcomes. These studies sought to identify differences between volunteer vs. paid responders (both high risk of bias; Oxford quality ratings of 4). In a study by Gould et al. (32) volunteers were significantly less likely to engage in a collaborative active rescue compared with non-volunteers (OR 0.41; 95% CI 0.23–0.74; $p = 0.003$), and volunteers were significantly more likely to implement a non-collaborative active rescue compared with non-volunteers (OR 2.31; 95% CI 1.40-3.81; $p = 0.001$) (see **Supplementary Table 2**). For each additional 4 h per week shift answering calls, helpers had 8% higher odds of collaboratively engaging caller ($p = 0.006$), 8% lower odds of implementing a non-collaborative rescue ($p = 0.008$), and 8% increased odds of reducing a caller's imminent risk so no rescue was needed ($p = 0.03$) (32). Mishara et al. (33) found that overall, there were no significant differences between volunteers and paid employees on outcomes. However, volunteers and paid staff with over 140 h of call experience had significantly better outcomes compared with those with less experience. More experienced helpers (140+ h) were less likely

to have an increase in suicide risk from beginning to end of call (5.4 vs. 12.2%), more likely to have improvement in suicide urgency, defined along a seven-point scale from thinking about suicide with no plan to decide to take own life in the next 24 h with a specific method determined and available (16.8 vs. 14.7%; $p < 0.02$); significantly higher CCORS (46) scores ($p < 0.025$), and were more likely for the safety contract/agreement to be respected (50.1 vs. 31.1%; $p < 0.04$) compared with less experienced helpers (<140 h) (33).

DISCUSSION

Summary of Main Findings

Although the state of the science regarding the effectiveness of crisis response services remains limited, overall results provide support for such services. However, such support is largely from uncontrolled studies indicating the positive effect of crisis line calls on immediate proximal outcome measures (e.g., changes in distress over the course of the crisis line call) and short-term distal effects. Many studies evaluating distal effects after the crisis service suffered from substantial dropout, thereby increasing the risk of bias interpreting findings. However, some distal studies utilizing administrative data were able to retain complete follow-up data [e.g., suicide mortality data (38); medical records (31)], but they did not benefit from participant self-report to contextualize findings. Cautious interpretation of Chan et al. findings is warranted. While the study found significantly higher rates of suicide among crisis line callers, this is not necessarily an indication of lack of crisis line effectiveness. Rather, this study confirmed that crisis line callers are at increased risk for suicide, reinforcing the need for high quality wrap-around services and follow-up care to promote recovery and well-being. While reliability of outcome measurement has been shown in some approaches (e.g., silent monitoring, rating transcripts), further research is needed to establish validity in outcome ascertainment (e.g., measure SDV using standardized assessment tools). Promising approaches to outcome measurement have incorporated validated assessment tools, often modified for brevity (e.g., CCORS, MINI, POMS, BDI); however, more research is needed.

Strengths

The strengths of this review lie in the rigorous methodological approach utilized that is consistent with PRISMA guidelines. An in-depth examination of individual study characteristics combined with a descriptive synthesis of key features and findings contextualize the state of crisis line effectiveness research and illuminate opportunities for future studies. Strengths of the literature include an increased focus over the last decade on crisis line effectiveness evaluation research, in which almost two-thirds of included studies were published since 2010. The evidence is also growing to include research using longitudinal study designs with a comparison group [e.g., (38)], as well as a landmark RCT by Gould et al. (29) that used a dynamic wait-listed roll-out to evaluate a network of call centers. These exemplar studies prove that it is possible to implement rigorous and sophisticated study designs in the understandably complex and complicated field of crisis line evaluation. Current evidence supports the continuation and expansion of crisis line services as an important safety net for comprehensive suicide prevention care.

Limitations

As outlined above, the limitations of the literature are that the overall quality of studies conducted to date are low, and risk of bias is concerning. Significantly less evidence was available to review in terms of crisis chat, and no studies have been conducted to evaluate the effectiveness of text-related services. In addition, there was substantial variability in what outcomes were measured, and the timing of those measurements. A key limitation emerged in defining what truly is effectiveness in crisis line evaluation. The measurement of effectiveness was discerned to be a multi-faceted domain covering much more than the central outcome to prevent suicide and other self-directed violence, and included measures of mood, satisfaction, referrals, and utilization/engagement in care. Furthermore, half of studies measured only immediate proximal outcomes of effectiveness, and studies measuring more distal outcomes widely varied in terms of time to follow-up for outcome measurement (1 week to up to 4 years). The inconsistent use of standardized tools to measure outcomes along with the variety of outcome domains made it challenging to integrate effects across studies, leading to uncertainty in the extent to which crisis line services truly are meeting their intended goals. Also notable are the high losses to follow-up as well as current dearth of evidence regarding the highest risk callers. That being said, such work is complicated by the imminent risk presented by such callers. Exploration of means to evaluate these interactions is warranted (e.g., reviewing recorded interactions).

Additionally, longer-term outcomes would be expected to be improved if crisis line users could be connected to behavioral health services. Most basically, this might include responders offering users resources regarding providers in their community. In particular, opportunities exist in terms of crisis lines following individuals until they engage in treatment. Though ultimately this is an empirical question, models exist, such as Safety Planning Intervention plus follow-up (SPI+) (49), that could be modified to meet the needs of crisis line service users. With that in mind, such interventions are contingent upon users being willing to self-disclose information regarding their identity. This runs counter to the historical anonymous culture of crisis services (50). This culture of anonymity poses clinical and research considerations in regards to challenges associated with providing users with follow-up care and evaluating distal effects of services. Moreover, such interventions are often dependent upon follow-up services being available. Progress on health equity in the US and other countries must remain a priority to meet the behavioral health follow-up service needs of crisis line users (51).

The limitations of this review are that included literature was limited to English language only, and synthesis was not quantitative (e.g., no meta-analysis was performed).

Future Directions

Additional work is needed to evaluate the impact of responder experience on user outcomes. The most robust immediate

proximal evidence from a national RCT indicates that counselors with ASIST had improved user outcomes during the call (29). Findings from both Gould et al. (32) and Mishara et al. (33) suggest that factors associated with responder characteristics impact outcomes. It remains unclear whether paid responders simply have more time to become "experienced." It may also be that those who are paid receive additional resources (e.g., training) that support better outcomes. The evidence to date provides strong indications that responder experience improves outcomes, and it is imperative that all responders are trained to consistently incorporate standardized SDV risk assessment and develop a supportive/collaborative approach to assisting crisis line users. Future studies should incorporate participatory approaches to increase responder engagement in the research process. This will encourage the initiation of study procedures as part of a continuous feedback loop for quality improvement.

Computational linguistics and natural language processing are ripe evaluation paradigms to complement effectiveness research. Various linguistic aspects of conversations can be measured and correlated with crisis service outcomes. Natural language interfaces may be able to assist human responders in linguistic development (52) as well as provide real-time emotional and practical support to responders during crisis chat and text interactions (53, 54). It is critical that a rigorous framework of principles and protocols is applied to ensure the safe and ethical conduct of these research paradigms, as this approach requires the sharing of highly sensitive data between technology companies and crisis line academic researchers, as piloted in the Crisis Text Line platform (55).

Conclusions

Despite the fact that research regarding the effectiveness of crisis line services remains limited, studies overall provide initial support for such services, particularly in terms of calls impacting immediate proximal and short-term distal outcomes. Crisis line callers are a high risk population, confirming the need for competent responders trained in suicide-specific assessment and care. Optimal models of crisis lines should implement proactive follow-up services that incorporate distal evaluation. Additional high quality research is needed particularly among the highest risk callers. Further exploration of proximal and distal outcomes regarding call, chat, and text services will benefit this population.

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AUTHOR CONTRIBUTIONS

LB contributed conception and design of the study, and contributed to the selection of studies, grading of evidence, and interpretation of results. KS-Y contributed to the design of the study, protocol development, selection of studies, and grading of evidence. AH contributed to the design of the study protocol development, selection of studies, grading of evidence, interpretation of results, and wrote the first draft of the manuscript. LB and KS-Y wrote sections of the manuscript and contributed to manuscript revision. All authors have contributed substantially to the paper and read and approved the manuscript and its submission to this journal.

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SUPPLEMENTARY MATERIAL

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Emergency Presentations to Child and Adolescent Psychiatry: Nonsuicidal Self-Injury and Suicidality

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Nonsuicidal Self-Injury (NSSI) and suicidality are common reasons for emergency presentations in child and adolescent psychiatry. Therefore, we focused on reasons for emergency presentations as well as specific characteristics of those presenting with NSSI or suicidality to an emergeny psychiatric service. We analyzed data from a German university hospital regarding emergency presentations during a 78 months' period. NSSI and suicidality were rated according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Data from 546 emergency presentations was recorded, of which 347 (63.5%) presented for NSSI or suicidality. Given the high percentage, thorough assessment of sucidality as well as providing adequate treatment in emergency settings to establish further care, is of utmost importance.

Keywords: nonsuicidal self-injury, self-harm, suicidality, adolescents, emergency, youth

INTRODUCTION

Nonsuicidal Self-Injury (NSSI), defined as repetitive direct self-inflicted damage of one's own body surface without suicidal intent (1), has been described repeatedly as common phenomenon in adolescents, with rates ranging between a lifetime prevalence of 18%–28% in international school samples (2, 3). In clincial samples, rates of NSSI have been reported to be even higher, reaching up to 50% in child and adolescent psychiatric inpatients (4). With regards to suicidality (including both suicidal ideation as well as suicide attempts), rates of suicidal ideation have been reported to be between 19.8% and 24% in youth (5), whereas lifetime prevalence rates between 3.1% and 8.8% have been reported for suicide attempts in minors (5). Germany is—within Europe—among the countries with the highest rates for NSSI in adolescent scool samples, with a lifetime prevalence of 35.1% (3). In addition, a lifetime prevalence rate for suicidal ideation of 39.4% has been reported from a representative sample of German high-school students, with 9% reporting a lifetime suicide attempt (6).

The German clincial guidelines for NSSI and for suicidality in youth recommend assessments for acute suiciality by a child and adolescent psychotherapist or a specialist for child and adolescent psychiatry both in patients presenting with NSSI, as well as in patients with suicidality (7, 8). Therefore, children and adolescents, who report NSSI and suicidality often present themselves to child and adolescents psychiatric emergency services as a first contact to the mental health system. Despite the high prevalence rates and the high clincial relevance of these presentations, so far, only a limited amount of scientic literature has been published about the prevalence and nature of these presentations in child and adolescent psychiatric settings.

An analysis of 1,093 emergency presentations to an Austrian child and adolescent psychiatric service showed suicide attempts to be the most prominent reason (22%) for emergency contacts in female minors with a migration background and the second most common reason in females without migration background (9). A crucial number of similar presentations was also reported from an analysis of 328 mental heath emergencies (in 179 patients) presenting to a pediatric department in Spain (10). Self-harm behavior (defined as intentional act of self-poisoning or self-injury irrespective of degree of suicidal intent) was the second most common reason for presentation in females (29%), following behavior disorder (30%) in rank. In an analysis of clinical data from a Canadian service provider, 468 cases of minors presenting with mental health emergencies were analysed. NSSI within the previous 24 h was recorded in 45% of all cases. Of these, 91% were NSSI only, whereas 5% reported a suicide attempt and 4% involved co-occurring NSSI and suicidality. Those with co-occuring NSSI and suicide attempts showed the highest level of psychopathology (11). In an analysis of 181 youth presenting to an emergency department with suicidal ideation or a suicide attempt, a high overlap between judgement about level of sucidality from the parent´s and the patient´s point of view was described (12)

Given the paucicity of data in this clinically relevant field of child and adolescent psychiatric emergency service provision, we aimed to systematically assess acute child and adolescent psychiatric presentations based on a retrospective chart review. Focusing more specifically on NSSI and suicidality, we decided to classify these incidents based on the Columbia Classification Algorithm (C-CASA). Since emergency presentations call for timely reactions providing a high level of safety, it is of importance to better understand dynamics of these presentations. These analyses could inform a tailored planning of interventions with regards to availability of staff, the need for pediatric health care (e.g., in intoxications) or provision of risk assessment. Given the importance of school in adolescents' daily life, we hypothesized that time patterns of presentations will be influenced by the school year (with lower presentations during the summer and higher number of presentations during exam times). Thereby, we aimed at answering the following questions:

a. What are the reasons for which children and adolescents present to child and adolescent psychiatric emergency services?
b. What are the specific characteristics of presentations for suicidal behavior or NSSI?

MATERIALS AND METHODS

We conducted a retrospective chart review of all children and adolescents presenting to the emergency services at a German University Department of Child and Adolescent Psychiatry and Psychotherapy. The Department serves a region of 402,000 inhabitants as sole provider of inpatient care and emergency child and adolescent psychiatry 24 h for 7 days a week. Electronic records were searched for presentations between 5 pm and 8 am as well as on weekends (outside office hours). Our inclusion criteria were: 1) children and adolescents below the age of 19; 2) Presentation as emergency contact outside of regular working hours to the Department of Child and Adolescent Psychiatry and Psychotherapy at the University of Ulm; and 3) Date of presentation between 01.06.2006 and 31.12.2012.

Based on a search of the hospital´s electronic database, we retrieved each patient record from all patients, who were fulfilling the abovementioned inclusion criteria and aimed to sort information following a pre-defined schedule of search items. Based on the information stored in the records, we classified the cause for the presentations at an emergency child and psychiatric service. In case of presentations, in which self-injuring or sucidal behavior was listed in the context of the emergency presentation, we applied the Columbia Classification Algorithm of Suicide Assessment (C-CASA) classification algorithm. This algorithm was originally developed to classify suicidal behavior in medication trials in minors (13). Given the retrospective nature of the application of this algorithm to pre-existing records, we found it to be perfectly fitting to our approach of data collection and classification. The C-CASA allows for classification in several categories:

- Suicidal (completed suicide, suicide attempt, preparatory action, suicidal ideation)
- Nonsuicidal (nonsuicidal self-injury, other: accidental, psychiatric, medical)
- Indeterminate (self-injury with unknown intent, not enough information)

The original study showed an excellent interrater reliabilty (mean ICC: 0.89) between nine raters (13). In our study, data about those presenting as emergency cases was retrieved and caseness was defined by a consultant child and adolescent psychiatrist. C-CASA classification was first provided by a resident MD, trained with general C-CASA cases. Cases were then presented to a consultant child and adolescent psychiatrist for review. This retrospective chart review was in accordance with the Declaration of Helsinki and was approved by the IRB of the University of Ulm.

RESULTS

Within the searched 78 months' period N = 546 cases (mean age: 14.43; SD: 2.43; age range: 10–17; female: 56.2%) fulfilled the aforementioned criteria and were included in our analysis. Emergency contacts were not evenly distributed across the weekdays (χ^2 = 18.04; p = 0.006), but tests of each weekday

against deviation from the expected value of 78 (14.3%) contacts per weekday revealed that only Saturday (51 = 9.34%) was significantly different (χ^2 = 9.50; p = 0.001). Concerning the month of presentation, there is no overall difference across the months (χ^2 = 16.07; p = 0.139). In single tests, however, there are tendencies for June (58 = 10.6%) having a higher number (χ^2 = 3.37; p = 0.067) and August (33 = 6.0%) having a lower number (χ^2 = 3.57; p = 0.059) than the expected number of presentations of 45.5 (8.3%) per month. Of these contacts, 33.7% were discharged at the same or the following day. The mean treatment duration of those, who were admitted to inpatient care was 28 days (median: 5 days).

With regards to the primary diagnoses, most patients (36.6%) received a diagnosis from the ICD-10 diagnostic group F90–F98 (Behavioural and emotional disorders with onset usually occurring in childhood and adolescence). This was followed by diagnostic group F30–F39 (mood disorders) with 25.5% and F40–F48 (Neurotic, stress-related and somatoform disorders) with 15.3%. While only a minority of patients were receiving psychopharmacological treatment at the time of their emergency contact (12.45%), 43% received a prescription after their contact, with antipsychotics (21.6%), antidepressants (16.2%), and stimulants (8.4%) being the most widely prescribed psychopharmacological agents, with more than one agent prescribed in 102 patients.

We further analysed those patients, who fulfilled at least one category of the C-CASA scheme (n = 347, 63.5% of the whole sample) as reason for presenting to child and adolescent psychiatric services (see **Table 1**). Overall, in each C-CASA category, more female than male patients presented themselves as emergency contacts, with significant sex differences in suicide attempts (χ^2 = 9.94; p < 0.001), preparatory acts (χ^2 = 4.41; p = 0.014), suicidal ideation (χ^2 = 22.02; p < 0.001), and NSSI (χ^2 = 49.88; p < 0.001).

NSSI led to 127 presentations, therefore accounting for 22.52% of all emergency contacts, with youth being predominantely female. Age curves showed two peaks at age 14 and age 16 for presentations.

Presentations for sucide attempts were highest on Mondays (24.49%) and in October (14.28%). Controlling for holidays, we found more presentations with suicide attempts outside of national holidays (p = 0.042). The methods recorded for suicide attempts included (in order of decreasing likelihood): intentional self-poisoning with non-psychopharmacologcial agents (X60+X63) with 32.2%, self posisoning with other substances (X64) with 15.25%, and self-poisoning with psychopharmacological and hallucinogenic agents (X61+X62) with 11.86%. Intentional self-harm with a sharp object (X78) was reported in 15.25%, whereas 8.47% reported intentional self-hanging (X70).

TABLE 1 | C-CASA classification (n = 347).

Category	Number (%)	Female sex (%)
C-CASA 1: Suicidal		
Suicide	0	
Suicide attempt	49 (14.12)	38 (77.55)
Preparatory acts	45 (12.97)	32 (71.10)
Suicidal ideation	120 (34.58)	90 (75.0)
C-CASA 2: Nonsuicidal		
NSSI	127 (36.6)	106 (83.46)
Other nonsuicidal self-harm	2 (0.58)	2 (100.0)
C-CASA 3: Undetermined		
Self-injury undetermined intent	4 (1.15)	3 (75.0)
Not enough information	0	

DISCUSSION

We conducted a retrospective chart review of children and adolescents presenting to a child and adolescent psychiatric emergency service. Our analyses included reasons for presentations as well as further characteristics of the patients and the nature of presentation. We were able to show that NSSI and suicidality are the main reasons for presenting to our child and adolescent psychiatric services. This seems in line with former studies on child and adolescent psychiatric services or pediatric services providing emergency mental health care (9, 10, 14), which also underlined the clinical relevance of these topics for emergency child and adolescent psychiatry. Looking into methods used for suicide attempts, self-poisoning, as well as self-harm with a sharp object and self-hanging was reported. Intoxications are among the most frequently reported methods for suicide attempts in adolesents (5), and intentional self-harm is a common and rising phenomenon in adolescents, also in community samples (15). Self-hanging is the most common method of suicide in the age groups 10–19, whereas there are hardly any suicides in this age groups commited by guns (X72–X74) (16). Although presentations for suicide attempts, represent the three most prevalent methods for suicide attempts in youth (5), it has to be noted that the absence of presentations involving firearms is likely due to legal restrictions on German gun law and may not be comparable to the situation in other countries. We were unable to describe temporal monthly patterns for emergency presentations, although a tendency for more admissions in June and less admissions in August was observed. This pattern could point to an influence of schooling on emergency psychiatric contacts, as June is at the end of the German school year, thus often leading to high work-loads and exam pressure, whereas in August schools are closed for holidays. Interestingly, fewer emergency contacts were observed for Saturdays, which is also a school-free day in Germany.

Given that NSSI and suicidality were found to be among the main reasons for presenting at a child and adolescent emergency psychiatric service, it seems crucial to provide efficiant services at that point of care. This includes thorough assessment (17), as well as adequate follow-up care. Especially in the population of minors with NSSI, high barriers to seeking treatments have been reported (18, 19). It seems crucial to lower these barriers to make healthcare accesible to those with urgent needs, that are in a possibly life-threatening state. This could be achieved by presenting information about child and adolescent psychiatric

services in youth-friendly way (such as for example brochures[1]), by anti-stigma work or by increasing awareness of mental health problems and care providers as well as by increasing mental health literacy (20). Furthermore, adolescents could profit from online interventions and services to lower barriers to treatment. It has been discussed, that the admission to emergency care due to suicidal behavior can be a stressful situation for those seeking acute care (21), especially if specialized services for youth are lacking (22). Youth stressed the importance of information and compassionate clinicians in this situation, and stated that repeated questioning from different clinicians was perceived as negative (23). Due to the retrospective nature of our analysis, we were not able to provide information about patients´ experiences with emergency psychiatric care, although this would clearly help to inform future optimization of assessment and treatment in these situations from a customer´s viepoint. Given the high number of patients, who access emergency psychiatric care, it is of importance to standardize assessment and procedures, allowing for high levels of safety, reduce waiting time and create a flow of information between outpatient assessment and inpatient treatment in those situations where inpatient admissions are necessary.

In addition, it is of utmost importance to make the first contact of young patients to service providers in an acute situation as engaging as possible to secure follow-up care, also in situations in which follow-up is provided in an outpatient setting. This could be achieved by implementing strategies such as Therapeutic Assessment (24), which was designed to engage children and adolescents presenting with NSSI and suicidal behavior in follow-up mental health care. It has been shown, that the likelihood of presenting to follow-up care and the duration of participating in follow-up care can be increased by a simple and short intervention at the first contact (24). Given that there is an increasing evidence for the efficacy of psychotherapy to decrease NSSI or suicidal behavor (25) in youth, efforts must be undertaken to use the first contact to mental health care providers to engage minors in further care.

Following up on this retrospective analysis, future research should focus on the adolescents´ and caregivers´ experience of emergency presentations to child and adolescent psychiatry and use these informations to create optimized procedures, which could result in lowering the threshold of seeking specialist care in mental health crisis situations. Although data about whether adolescents sought help themselves, or were brought to the psychiatric department by their caregivers is not available from our dataset, this could influence willingness to participate in further mental health care and should therefore be assessed in future studies. Building on this information, specific procedures could be tested for their outcome in patient and caregiver satisfaction, as well as for their outcome concering patient safety and further engagement in mental health follow-up care.

[1] https://www.uniklinik-ulm.de/fileadmin/default/Kliniken/Kinder-Jugendpsychiatrie/Dokumente/WebversionWIDSN.pdf (accessed on September 24th, 2019).

LIMITATIONS

We presented data of one department situated in Germany, therefore limiting generalizability of our findings for other settings or countries. We defined emergency presentations as occuring outside of office hours. This neglects the fact that emergency presentations are also possible during office hours. This restriction was based on a lack of possibility to retrieve information about the nature of presentation (acute vs. planned) from retrospective records. We therefore chose to limit our analysis to an intake time, which restricts presentations to those with an acute nature. This approach was based on literature showing that NSSI most often is happening throughout evening hours (26). We are aware that our analysis therefore presents a rather conservative evaluation of emergency contacts, which has to be taken into account when interpreting these findings. Due to the retrospective nature of the study, standardized risk-assessment was not available, creating a risk for misclassification. Therefore, future analyses could benefit from a standardized mean of risk assessment at intake.

CONCLUSIONS

NSSI and suicidal behavior account for a majority of emergency presentations in child and adolescent psychiatry. Therefore, there is a need to put a special emphasis on these situations in the clinical training of residents, as well as provide the best care possible in this specific situation. Apart from providing a thorough risk exam, this should also include motivational aspects, such as in Therapeutic Assessment, among other possible approaches, to increase the likelihood of minors to participate in follow-up care.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical committee of the University of Ulm. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MF conducted the retrospective chart review, with help from FK and PP. PP and RB drafted the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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Efficient Prediction of Vitamin B Deficiencies via Machine-Learning Using Routine Blood Test Results in Patients With Intense Psychiatric Episode

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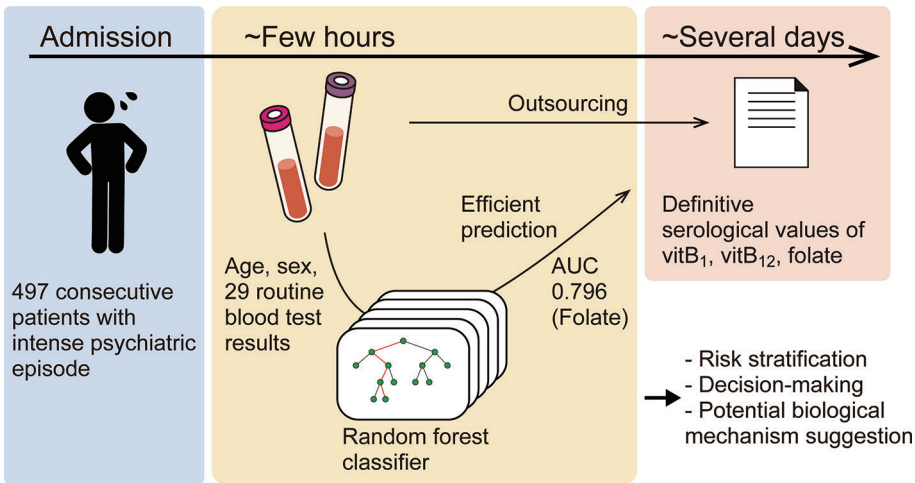
Background: Vitamin B deficiency is common worldwide and may lead to psychiatric symptoms; however, vitamin B deficiency epidemiology in patients with intense psychiatric episode has rarely been examined. Moreover, vitamin deficiency testing is costly and time-consuming, which has hampered effectively ruling out vitamin deficiency-induced intense psychiatric symptoms. In this study, we aimed to clarify the epidemiology of these deficiencies and efficiently predict them using machine-learning models from patient characteristics and routine blood test results that can be obtained within one hour.

Methods: We reviewed 497 consecutive patients, who are deemed to be at imminent risk of seriously harming themselves or others, over a period of 2 years in a single psychiatric tertiary-care center. Machine-learning models (k-nearest neighbors, logistic regression, support vector machine, and random forest) were trained to predict each deficiency from age, sex, and 29 routine blood test results gathered in the period from September 2015 to December 2016. The models were validated using a dataset collected from January 2017 through August 2017.

Results: We found that 112 (22.5%), 80 (16.1%), and 72 (14.5%) patients had vitamin B_1, vitamin B_{12}, and folate (vitamin B_9) deficiency, respectively. Further, the machine-learning models were well generalized to predict deficiency in the future unseen data, especially using random forest; areas under the receiver operating characteristic curves for the validation dataset (i.e., the dataset not used for training the models) were 0.716, 0.599, and 0.796, respectively. The Gini importance of these vitamins provided further evidence of a relationship between these vitamins and the complete blood count, while also indicating a hitherto rarely considered, potential association between these vitamins and alkaline phosphatase (ALP) or thyroid stimulating hormone (TSH).

Discussion: This study demonstrates that machine-learning can efficiently predict some vitamin deficiencies in patients with active psychiatric symptoms, based on the largest cohort to date with intense psychiatric episode. The prediction method may expedite risk stratification and clinical decision-making regarding whether replacement therapy should be prescribed. Further research includes validating its external generalizability in other clinical situations and clarify whether interventions based on this method could improve patient care and cost-effectiveness.

Keywords: machine learning, random forest classifier, vitamin B deficiency, folic acid, early diagnosis, decision support techniques or decision making



GRAPHICAL ABSTRACT |

INTRODUCTION

Vitamin B deficiency is common worldwide and may lead to psychiatric symptoms (1–4). For example, meta-analyses have shown that patients with schizophrenia or first-episode psychosis have lower folate (vitamin B_9) levels than their healthy counterparts (4, 5). Moreover, vitamin therapy can effectively alleviate symptoms in a subgroup of patients with schizophrenia (3, 6–8). However, the epidemiology of vitamin B deficiency in patients with active mental symptoms requiring immediate hospitalization has rarely been examined.

In a psychiatric emergency, psychiatrists should promptly distinguish treatable patients with altered mental status due to a physical disease from patients with an authentic mental disorder (International Statistical Classification of Diseases and Related Health Problems-10, ICD-10 code: F2-9). However, vitamin deficiency testing is very costly (around 60 dollars for each measurement of vitamin B_1 (vitB_1), vitamin B_{12} (vitB_{12}), or folate in the U.S.; 15–25 dollars for each test in Japan) and usually requires at least two days. Therefore, an efficient, cost-effective method of predicting vitamin B deficiency is needed.

Although several studies have applied machine-learning to the prediction of diagnosis or treatment outcomes (9–11), no study using machine-learning has focused on vitamin B deficiencies. We herein explore whether vitB_1, vitB_{12}, and folate deficiencies can be predicted using a machine-learning classifier from patient characteristics and routine blood test results obtained within one hour based on a large cohort of patients requiring urgent psychiatric hospitalization.

METHODS

Medical Chart Review

We reviewed consecutive patients admitted to the Department of Neuropsychiatry at Tokyo Metropolitan Tama Medical Center, one of the biggest psychiatric tertiary-care centers in Japan, between September 2015 and August 2017 under the urgent involuntary hospitalization law, which requires the immediate psychiatric hospitalization of patients at imminent risk of seriously harming themselves or others. The necessity of hospitalization was judged by designated mental health specialists. There were no exclusion criteria. The patient characteristics, ICD-10 codes, and laboratory data were gathered retrospectively.

Since the reference ranges for vitB_1, vitB_{12}, and folate are 70–180 nmol/L (30–77 ng/mL), 180–914 ng/L, and >4.0 μg/L, respectively (12), a deficiency of the nutrients was defined as <30 ng/mL, <180 ng/L, and <4.0 μg/L, respectively, unless otherwise stated. The odds ratios of each deficiency in each ICD-10 code were calculated assuming binomial distribution.

Classifiers and Statistics

We compared four types of standard machine-learning classifiers: k-nearest neighbors, logistic regression, support vector machine, and random forest. Each type of classifier was trained to predict the deficiency of each substance from age, sex, and 29 routine blood variables (described with values in the *Results* section). For developing the models, any missing values were replaced using the mean. The classifiers were trained using the dataset populated in the period from September 2015 to December 2016 (the "Training set"). First, except for logistic regression, we optimized the hyperparameters of the classifier by selecting the best combination of hyperparameters that maximized the "5-fold cross validation" accuracy, among many combinations within appropriate ranges. The cross-validation accuracy was computed as follows: in one session, the classifiers were trained using 80% of the training set and evaluated on the withheld 20% of the training set. This session was performed five times so that every data would be withheld once. The accuracies were finally averaged across sessions to yield the cross-validation accuracy. By incorporating this process, the classifiers were generalized to unseen data (Graphical method is shown in **Figure 1**).

Using the optimized hyperparameters, the classifiers were then validated using data collected from January 2017 through August 2017 (the "Validation set"). We report the classification performance on the validation set in the *Results* section unless otherwise stated.

We quantified the sensitivity, specificity, and accuracy (defined as the average of the sensitivity and the specificity on the optimal operating point) using receiver operating characteristic curves (ROCs). We also quantified the 95% confidence interval of the area under the ROCs (AUCs) and accuracy using 1000-times bootstrapping.

When investigating the Gini importance and the partial dependency (13), we retrained the classifiers using all datasets. All data analyses were performed using Python (2.7.10) with the Scikit-learn package (0.19.0) and R (3.4.2) with the edarf package (1.1.1) and pROC package (1.15.3).

Robustness Verification

We verified the robustness of the prediction performances by three independent approaches. First, we compared the following two prediction performances: random forest classifiers trained and validated using the dataset from the F2 population, and random forest classifiers trained and validated using the dataset from the non-F2 population.

Second, we compared the prediction performances of several random forest classifiers trained and validated using the dataset where different cut-off values were used to define the vitamin deficiency. We chose other two cut-off values for each vitamin based on previous reports (14–16), as well as pre-defined cut-off values (see also *Medical Chart Review* section).

Third, we trained and validated other random forest classifiers where the dataset was split in a different way. Here, the training set consisted of data between 31 January 2016 and August 2017 and the validation set consisted of data between September 2015 and 31 January 2016, so that the sample sizes of the training and validation sets were equal to those in the original split.

Subsampling Analysis

We also examined the relationship between the dataset size and the generalization performance (17). In this analysis, we trained the random forest classifiers using X% of the training set (X = 30, 35, 40, …, 95, and 100), and validated them using the validation set. The hyperparameters were identical to those used in the previous section. To remove sampling bias, this procedure was repeated 100 times for each value of X, where the training dataset was sampled

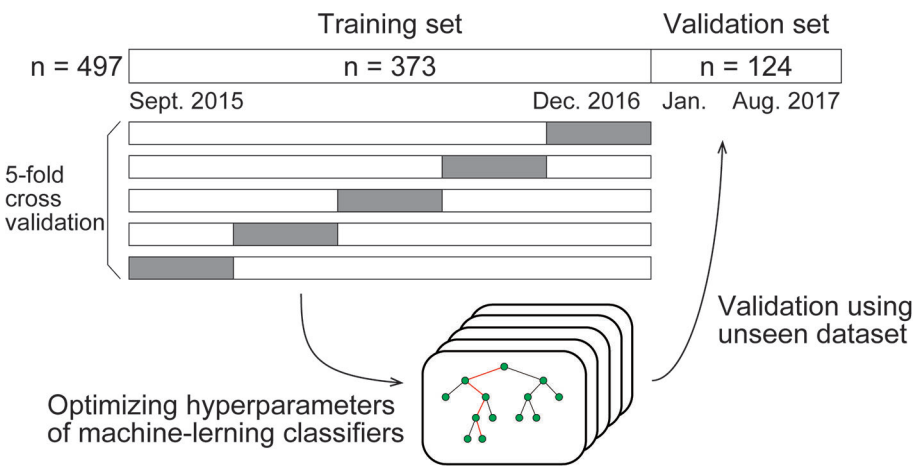


FIGURE 1 | Graphical illustration of method of machine-learning.

randomly for each repetition. This results in obtaining 100 AUC scores for each X and for each vitamin. We plotted the AUC scores (averaged across the 100 repetition) versus X for each vitamin, then the curve was fit with the following saturating function using Levenberg-Marquardt algorithm implemented as "curve_fit" function in the Scipy package (0.19.0).

$$Y = \frac{a*X}{X+b} + 0.5 \quad (1)$$

where Y is the AUC score, and a and b are the parameters to fit. Note that $Y \rightarrow a+0.5$ as $X \rightarrow \infty$ and $Y = 0.5$ as $X = 0$.

Ethical Considerations

Informed consent was obtained from participants using an optout form on the website. The study protocol was approved by the Research Ethics Committee, Tokyo Metropolitan Tama Medical Center (Approval number: 28-8). The study complied with the Declaration of Helsinki and the STROBE statement.

RESULTS

Eligible Patients

During the 2-year study period, 497 consecutive patients (496 were Asian) were enrolled. The mean age (standard deviation, SD) was 42.3 (±15.4) years, and 228 patients (45.9%) were women. F2 (Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders) was diagnosed in over 60% of the patients. The ICD-10 codes of the patients and the number of deficiencies at several cut-off values for $vitB_1$, $vitB_{12}$, and folate are shown in **Table 1**. According to the predefined cut-off values (12), 112 (22.5%), 80 (16.1%), and 72 (14.5%) patients exhibited a deficiency of $vitB_1$ (<30 ng/mL), $vitB_{12}$ (<180 ng/L), and folate (<4.0 μg/L), respectively. Vitamin B deficiencies in sub-groups are shown in **Table 2**. A summary of the full dataset is shown in **Table 3**. Detailed information (sub-datasets) is shown in **Supplementary Tables 1–3** online. Histograms of $vitB_1$, $vitB_{12}$, and folate values are shown in **Figures 2A–C**.

TABLE 1 | Patient distribution data (n = 497).

Age	Sex	Race	ICD-10 code										$VitB_1$ [ng/mL]			$VitB_{12}$ [ng/L]			Folate [μg/L]		
			F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	<20	<28	<30*	<150	<180*	<200	<3.0	<4.0*	<5.0
42.3 (15.4) years	Woman 228 (45.9%) Man 269 (54.1%)	Asian 496 Others 1																			
		N	28	21	300	58	16	0	29	20	24	1	15	81	112	37	80	107	29	72	134
		%	5.6	4.2	60.4	11.7	3.2	0.0	5.8	4.0	4.8	0.2	3.0	16.3	22.5	7.4	16.1	21.5	5.8	14.5	27.0

Age is shown as mean (SD). Asterisks show the predefined cut-off values for vitamin B_1, vitamin B_{12}, and folate (vitamin B_9) based on a reference (12); different cut-off values based on previous reports (14–16) are also presented for further investigation.

ICD-10 codes (Representative disorders in parentheses). F0, Organic, including symptomatic, mental disorders (e.g., dementia and other mental disorders due to brain damage and dysfunction and to physical disease); F1, Mental and behavioral disorders due to psychoactive substance use (e.g., due to use of alcohol, opioids, cannabinoids, and other substances); F2, Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (e.g., acute and transient psychotic disorders); F3, Mood disorders (e.g., depressive episode and bipolar affective disorder); F4, Neurotic, stress-related and somatoform disorders (e.g., anxiety, obsessive-compulsive, stress-related, dissociative, somatoform, and other neurotic disorders); F5, Behavioral syndromes associated with physiological disturbances and physical factors (e.g., eating and nonorganic sleep disorders); F6, Disorders of adult personality and behavior (e.g., emotionally unstable personality disorder); F7, Mental retardation (e.g., intellectual disabilities); F8, Disorders of psychological development (e.g., pervasive and specific developmental disorders); F9, Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (e.g., hyperkinetic, conduct, and tic disorders).

TABLE 2 | Vitamin B deficiencies in sub-groups.

	F0	F1	F2	F3	F4	F6	F7	F8	F9
$vitB_1$ < 30 [ng/mL]	9 (32%)	4 (19%)	70 (23%)	11 (19%)	3 (19%)	7 (24%)	5 (25%)	3 (13%)	0
$vitB_{12}$ < 180 [ng/L]	5 (18%)	4 (19%)	53 (18%)	7 (12%)	3 (19%)	1 (3%)	4 (20%)	3 (13%)	0
Folate < 4.0 [μg/L]	5 (18%)	7 (33%)	38 (13%)	6 (10%)	5 (31%)	3 (10%)	4 (20%)	4 (17%)	0
Odds ratio	**F0**	**F1**	**F2**	**F3**	**F4**	**F6**	**F7**	**F8**	**F9**
$vitB_1$ < 30 [ng/mL]	1.68 [0.74-3.83]	0.80 [0.26-2.43]	1.12 [0.73-1.73]	0.78 [0.39-1.57]	0.79 [0.22-2.81]	1.10 [0.46-2.65]	1.15 [0.41-3.24]	0.48 [0.14-1.63]	0
$vitB_{12}$ < 180 [ng/L]	1.14 [0.42-3.10]	1.24 [0.41-2.43]	1.35 [0.82-2.23]	0.69 [0.30-1.58]	1.21 [0.34-4.35]	0.18 [0.02-1.31]	1.32 [0.43-4.05]	0.73 [0.21-2.52]	0
Folate < 4.0 [μg/L]	1.30 [0.48-3.55]	3.16 [1.23-8.13]	0.70 [0.42-1.15]	0.65 [0.27-1.58]	2.81 [0.95-8.34]	0.59 [0.17-1.98]	1.32 [0.43-4.05]	1.04 [0.35-3.14]	0

Square brackets indicate the 95% confidence interval.
*See **Table 1**.*

TABLE 3 | Summary of full dataset of 29 parameters for machine-learning.

Parameters	Units	Mean	SD
WBC	$\times 10^3/\mu L$	8.2	2.8
Hb	g/dL	13.7	1.7
Hct	%	40.3	4.5
MCV	fL	89	6.6
Plt	$\times 10^4/\mu L$	24.9	6.3
RDW.CV	%	13.5	1.3
Neu	%	70	11
Lym	%	23	10
Mono	%	6	2
Eo	%	1	2
Baso	%	0	0
TP	g/dL	7.2	0.6
Alb	g/dL	4.4	0.4
UN	mg/dL	12.9	6.7
Cre	mg/dL	0.7	0.2
T.bil	mg/dL	0.7	0.4
Na	mmol/L	139	3
Cl	mmol/L	105	4
K	mmol/L	3.7	0.4
cor.Ca	mg/dL	9.1	0.5
CK	IU/L	514	1230
AST	IU/L	31	34
ALT	IU/L	27	24
LDH	IU/L	239	91
ALP	IU/L	224	81
γGTP	IU/L	37	63
Glu	mg/dL	112	40
CRP	mg/dL	0.4	0.9
TSH	μIU/mL	1.7	2.4

Two patients lacked age data (no photo ID was available), and one patient lacked biochemistry data (inappropriate sample processing). For machine-learning, the missing values were replaced using the mean.

WBC, white blood cell count; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; RDW.CV, red blood cell distribution width-coefficient variation; Plt, platelet; Neu, neutrocyte fraction; Lym, lymphocyte fraction; Mono, monocyte fraction; Eo, eosinocyte fraction; Baso, basocyte fraction; TP, total protein; Alb, albumin; UN, urea nitrogen; Cre, creatinine; T.bil, total bilirubin; Na, sodium; Cl, chloride; K, potassium; cor.Ca, corrected calcium; CK, creatine kinase; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γGTP, γ-glutamyltransferase; Glu, plasma glucose; CRP, C-reactive protein; TSH, thyroid-stimulating hormone.

Prediction via Machine-Learning Using Routine Blood Test Results

Machine-learning classifiers were trained to predict the deficiency of each substance from patient characteristics and routine blood test results. The classifiers were trained using the dataset gathered in the period from September 2015 to December 2016 (the "Training set," n = 373), which was then validated from January 2017 through August 2017 (the "Validation set," n = 124). By splitting the whole dataset in this way, the ratio of the training and validation sample size was 3:1, a commonly used ratio in machine-learning analyses.

AUCs for the validation set for each classifier are summarized in **Table 4**. Although the performance of the classifiers was similar except for the k-nearest neighbors, random forest yielded the highest AUC on average. Therefore, we focused on random forest in the following analysis.

The AUCs of the random forest classifiers were 0.716, 0.599, and 0.796, for vitB_1, vitB_{12}, and folate, respectively (**Figures 2D–F** and **Table 4**). With some operative points on the ROC, the sensitivity, specificity, and accuracy for the validation set were calculated (**Table 4**. See also **Supplementary Table 4** for training set and **Supplementary Table 5** for different operating points). The 95% confidence interval (CI) of the AUC and accuracy was quantified using 1000-times bootstrapping. For random forest classifiers, the 95% CI of each value did not include 0.5, except for the AUC of vitB_{12}.

Figure 3 shows the Gini importance (**A–C**) and partial dependency plots (**D–F**) for the eight most important variables for each substance. The results provided further evidence of a relationship between the vitamin B levels and complete blood count while also indicating the hitherto rarely considered, potential association between these vitamins and alkaline phosphatase (ALP) or thyroid stimulating hormone (TSH).

Robustness Verification

We verified the robustness of the results by three independent means. First, we asked if the prediction performance was influenced by the ICD-10 categories. When the prediction performances were compared between the random forest classifiers trained using the dataset from the F2 population and the classifiers trained using the dataset from the other population, the AUC was not statistically different (DeLong's test), except in the case of vitB_1 (see **Supplementary Table 6**).

Second, we used different cut-off values to define the deficiency (14–16). Although the AUC for the validation set, shown in **Supplementary Table 7**, tended to be higher when strict cut-off values were used, the obtained AUCs were not statistically significant ($p > 0.05$, DeLong's test with Bonferroni correction).

Third, we investigated if the prediction performance was influenced by the way the dataset was split into the training and validation set. Here, we trained and evaluated random forest classifiers using a dataset split in a reversed way (see *Methods* section for details). The AUCs for the validation set were 0.771, 0.621, and 0.745 for vitB_1, vitB_{12}, and folate, respectively; none were statistically different from the AUC trained using the original setting (DeLong's test), further demonstrating the robustness of the performance.

Subsampling Analysis

To estimate the number needed to saturate the performance, we examined the relationship between the generalizability and the sample size (17). We randomly sampled X% of the training set, trained random forest classifiers using the dataset, and evaluated the generalization performance by AUCs using the validation set (X = 30, 35, 40, …, 95, and 100; see Methods for details). As shown in **Figure 4**, the relationships between AUC and the training size for vitB_1 and vitB_{12} were almost saturated, whereas that for folate is not saturated. To quantitatively understand this, we fitted each curve using a saturating function formulated in equation (1) (see *Methods* section for details). The fitted parameters of equation (1) were as follows; for vitB_1, a = 0.186 and b = 0.074; for vitB_{12}, a = 0.099 and b = 0.156; and

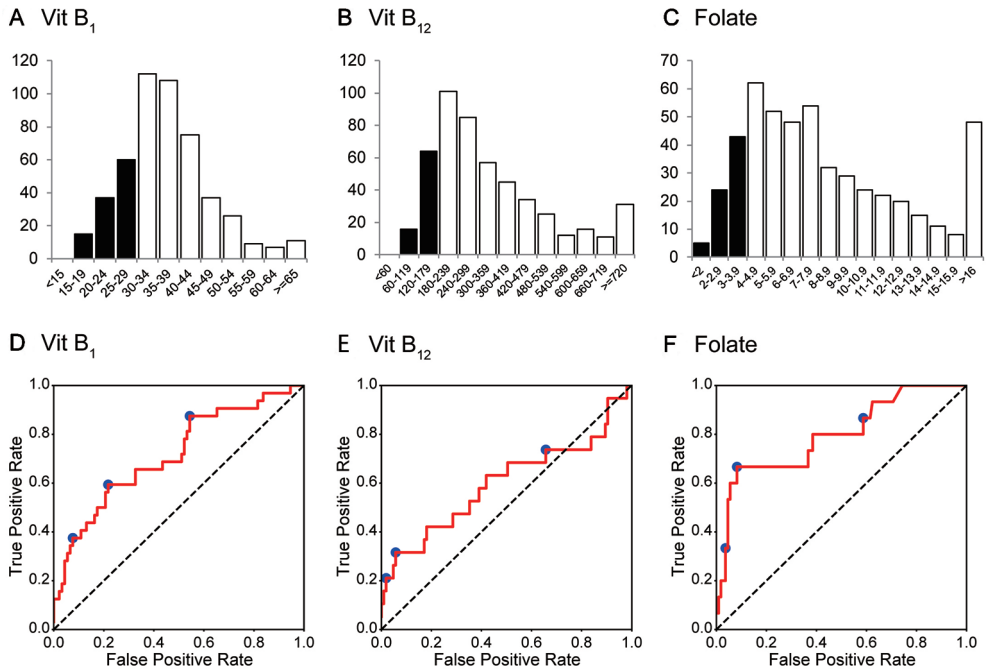


FIGURE 2 | Histogram and ROC curves of each vitamin B value. **(A–C)** The histograms for vitamin B_1, vitamin B_{12}, and folate (vitamin B_9). Their medians (1^{st}–3^{rd} quartile) are 35 (30–42) ng/mL, 285 (206–431) ng/L, and 7.2 (4.9–10.8) μg/L, respectively. **(D–F)** ROC curves for vitamin B_1, vitamin B_{12}, and folate. Operating points used in **Table 4** and **Supplementary Table 5** are depicted in blue. Vit B_1, vitamin B_1; Vit B_{12}, vitamin B_{12}.

TABLE 4 | Summary of AUC, sensitivity, specificity, and accuracy for the validation set.

AUC				
Classifier	**vitB$_1$**	**vitB$_{12}$**	**Folate**	**Average**
k-nearest neighbors	0.596 [0.483–0.702]	0.542 [0.394–0.705]	0.514 [0.383–0.651]	0.551
Logistic regression	0.715 [0.602–0.815]	0.602 [0.454–0.745]	0.754 [0.610–0.877]	0.690
Support vector machine	0.715 [0.613–0.814]	0.620 [0.472–0.763]	0.699 [0.536–0.842]	0.678
Random forest	0.716 [0.610–0.825]	0.599 [0.426–0.755]	0.796 [0.656–0.911]	0.704

Sensitivity, specificity, and accuracy for random forest

	vitB$_1$	**vitB$_{12}$**	**Folate**
Sensitivity	0.594	0.316	0.667
Specificity	0.783	0.943	0.917
Accuracy	0.688 [0.597–0.787]	0.629 [0.523–0.746]	0.792 [0.665–0.909]

*Generalization performance of the classifiers was evaluated using AUC of the validation set for each type of classifiers. For random forest classifiers, sensitivity, specificity, and accuracy of the classification at the optimal operating points that maximized accuracy on the receiver operating characteristic curve of the validation set are also shown (see also **Figures 2D–F**). Accuracy was defined as the average of the sensitivity and specificity. Square brackets indicate the 95% confidence interval. For further information, see **Figure 2** and **Supplementary Table 5**.*
AUC, area under the receiver operating characteristic curve.

for folate, a = 0.291 and b = 0.123. By using these parameter values and extrapolating the curve, we then computed how many additional samples are necessary to reach almost maximum performances. To reach 99% of the maximum performance [i.e., Y = (a + 0.5) × 0.99 in equation (1)], the training dataset to be collected was 92.5%, 143%, and 341% of the training size in this study for vitB$_1$, vitB$_{12}$, and folate, respectively. These quantitative analyses revealed that collecting further similar datasets up to 1,000 patients (e.g. four years × hospitals with similar scale as Tokyo Metropolitan Tama Medical Center) may increase and reproduce the generalizability for folate, while the effect of collecting further dataset is expected to be small for vitB$_1$ and vitB$_{12}$.

DISCUSSION

Relevance of The Present Study

Based on the largest cohort to date of patients at imminent risk of seriously harming themselves or others, this study indicated that deficiency of certain vitamins can be predicted in an efficient manner via machine-learning using routine blood test results. The 29 routine blood variables are available at almost all hospitals/clinics and are necessary to rule out other comorbid physical problems. Given the large number of patients with vitamin B deficiencies, empirical therapy might be acceptable; however, risk stratification is preferred for personalized medicine and shared decision-making. The prediction method presented here may expedite clinical decision-making as to whether vitamins should be prescribed to a patient (**Graphical Abstract**).

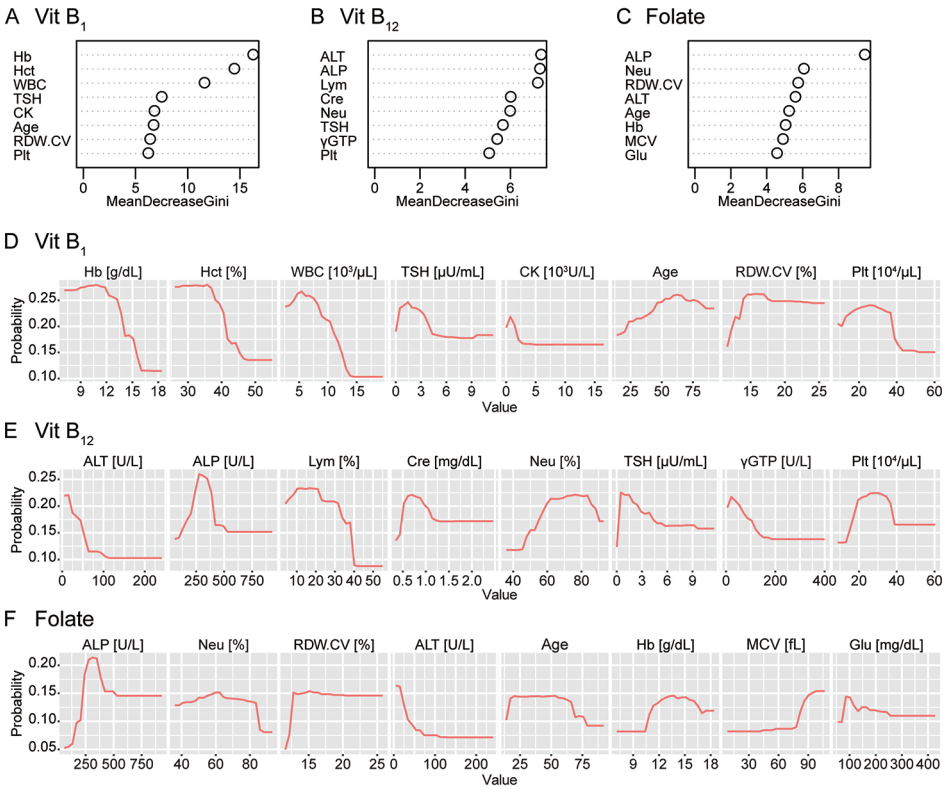


FIGURE 3 | Gini importance and partial dependence plots of vitamin B deficiencies. The Gini importance **(A–C)** and partial dependency plots of the probability of deficiency **(D–F)** are shown for the eight most important variables for vitamin B_1, vitamin B_{12}, and folate (vitamin B_9). Combined with these, this machine-learning classifier without hypothesis also provided further evidence of a relationship between vitamin B levels and the complete blood count while also indicating a potential association between these vitamins and alkaline phosphatase (ALP) or thyroid-stimulating hormone (TSH). Vit B_1, vitamin B_1; Vit B_{12}, vitamin B_{12}; Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell count; CK, creatine kinase; RDW.CV, red blood cell distribution width-coefficient variation; Plt, platelet; ALT, alanine transaminase; Lym, lymphocyte fraction; Cre, creatinine; Neu, neutrocyte fraction; γGTP, γ-glutamyltransferase; MCV, mean corpuscular volume; Glu, plasma glucose.

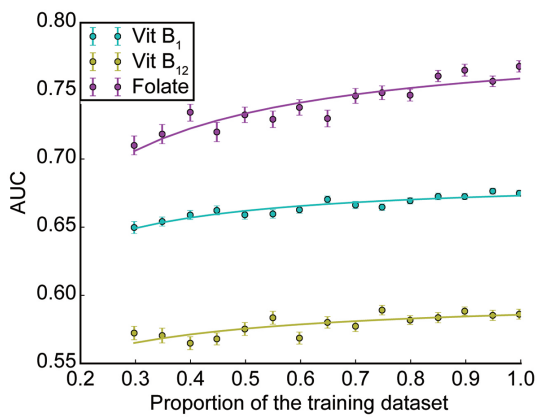


FIGURE 4 | Subsampling analysis. The AUC performances as a function of the dataset size is shown for each vitamin (mean ± SEM across 100 repetitions; see *Methods* for details).

Remarkably, the AUC of folate deficiency was 0.796. The robustness of folate prediction was also suggested by various independent methods and statistics. Folate has a potential to maintain neuronal integrity and is one of the homocysteine-reducing B-vitamins (5). Homocysteine may be linked to the etiology of schizophrenia (18), and vitamin B supplements have been reported to reduce psychiatric symptoms significantly in patients with schizophrenia (7). A recent meta-review has pointed out that the bioactivity of the supplement should be considered (e.g. methylfolate, which successfully crosses the blood-brain barrier, has been reported effective, whereas the effect of other forms of folate is equivocal) (19). As our study does not present longitudinal clinical courses, an intervention effect of folate supplementation to the cohort based on our method remains to be clarified.

Biological Mechanism Prediction

To connect with biological knowledge, we compared four models with high interpretability in this study. Using the random forest

classifiers, as shown in **Figure 3**, we identified several items related to complete blood count as top hits. Notably, our classifier was blind to any biological knowledge, including the well-established association between anemia and vitamin B deficiency, including folate (20). The results provide further evidence of a relationship between vitamin B levels and the complete blood count and support the use of machine-learning to investigate novel, underlying biological mechanisms (21).

ALP and its metabolites indicate the vitamin B_6 status (22); low vitB_{12} is potentially associated with low ALP (23). More generally, ALP may have a close and complicated relationship with the overall vitamin B group. Autoimmune disorders, especially thyroid disease, are commonly associated with pernicious anaemia (24), but there has been no established hypothesis regarding the causal relationships between thyroid disease and vitamin B deficiencies. The potential association between the levels of these vitamins and ALP or TSH awaits further study, both via investigations of populations and basic research (25).

Limitations

This study is subject to several limitations. First, the findings of this single-center retrospective study may have limited external generalizability, though internal generalizability was considered to the maximum extent. Second, the patients' basic characteristics and long-term prognosis were not fully investigated due to administrative restrictions. Though there is similar involuntary treatment/admission in psychiatry worldwide, there is a gap between legislation and practice (26). Therefore, the extent to which this method can expedite clinical decision-making is unclear.

Further, we did not investigate the relationship between serological values and the need for intervention. The lack of data for vitamin B deficiency in the Japanese general population hampered the comparison between the experimental cohort and their counterparts who lacked psychiatric symptoms. Establishing appropriate reference values and an assessment method requires further investigation. Finally, we did not assess the predictive value of other nutritional impairments, including vitamin B_6 and homocysteine deficiency, which were previously shown to have a close link with psychiatric symptoms (3, 5); however, our study provides fundamental data on nutritional impairment based on the largest cohort of patients with intense psychiatric episode ever assembled for this purpose and presents a potential framework for predicting nutritional impairment using machine-learning.

Conclusion

The present report is, to the best of our knowledge, the first to demonstrate that machine-learning can efficiently predict nutritional impairment. This study also provides a possible application of machine-learning to investigate novel, underlying biological mechanisms. Further research is needed to validate the external generalizability of the findings in other clinical situations and clarify whether interventions based on this method can improve patient care and cost-effectiveness.

DATA AVAILABILITY STATEMENT

The source code is available on https://github.com/ukky17/vitaminPrediction. The datasets utilized in the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee, Tokyo Metropolitan Tama Medical Center. Informed consent was obtained from participants using an optout form on the website.

AUTHOR CONTRIBUTIONS

HTam has full access to all data and takes responsibility for the integrity of the data. HTam, JU, KN, and NY conceived the study. HTam, YH, and HTan collected the data. JU performed the statistical analyses. HTam and JU drafted the first version of the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.01029/full#supplementary-material

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ORIGINAL RESEARCH
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Prediction of Recurrent Emergency Department Visits in Patients With Mental Disorders

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Background: Patients with mental disorders are more likely to be frequent emergency department (ED) users than patients with somatic illnesses. There is little information about recurrent ED visitors (≥four ED visits/year) due to mental health problems in Switzerland. Therefore, our aim was to investigate the prevalence of recurrent ED visits due to mental disorders and to determine which mental disorders and risk factors were associated with recurrent ED visits.

Methods: In a retrospective analysis, we investigated patients suffering from mental health problems between January and December 2015 who presented more than once in the ED of a tertiary care hospital. ED patients who sought out the ED due to mental disorders were grouped in a recurrent group with at least four ED visits per year or in a control group visiting the ED twice or three times within a year. The primary endpoint was to assess the prevalence of recurrent ED patients due to acute symptoms of mental disorders. As secondary endpoints, we investigated which mental disorders and risk factors were associated with recurrent ED visits.

Result: Of 33,335 primary ED visits, 642 ED visits (1.9%) were by 177 visitors suffering from acute mental health problems. Forty-five (25.4%) of these 177 patients were recurrent ED visitors; 132 (74.6%) visited the ED twice or three times (control). Patients with personality disorders had a four-times higher risk ($p = 0.011$) of being a recurrent ED visitor. Recurrent ED visitors with mental disorders had significantly more in-house admissions ($p < 0.001$), self-mutilations ($p < 0.001$), acute drug toxicity ($p = 0.007$) and were more often persons of single status ($p = 0.045$). Although recurrent ED visitors more often had an outpatient general physician or psychiatrist, they visited the ED more frequently within office hours ($p < 0.001$).

Conclusion: A quarter of frequent ED users with mental disorders are recurrent ED visitors and were more likely to suffer from personality disorders. Recurrent ED visits are associated with higher rates of self-mutilation, acute drug toxicity, and a greater number of in-house admissions.

Keywords: recurrent emergency department users, mental disorders, personality disorders, risk factors, prediction

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INTRODUCTION

Emergency department (ED) overcrowding is an increasing public health issue and is particularly associated with rising health care costs, longer waiting times, longer overall length of ED stay, decreasing patient satisfaction, and higher mortality (1–4). ED overcrowding has a significantly financial impact on the health care system (5, 6). Reducing ED overcrowding by increasing the transfer to inpatient clinics has potentially saved 10 million dollars in charges in US county hospitals and another 4 million dollars in costs per year in US university hospitals (5).

During the last decade, the overall number of ED visits has continuously increased worldwide, and almost two-thirds of ED users visited the ED more than once within the past year (7). These so-called frequent ED visitors account for a small number of ED patients (4.5 to 8%) but comprise 21 to 28% of all ED visits (7–9).

There is a wide range of definitions for what are termed "frequent visitors." Most often such persons were defined as having four or more ED visits during the past 12 months, but some research groups classify patients as "frequent users" who have just two visits/year, while others set the criterion at 12 visits/year (7, 8, 10–12). Furthermore, there is also no consensus about the designation used for such a category of ED users. Some publications utilize "frequent" while others employ terminology such as "recurrent" or "repeated" visitors (7, 8, 11, 13–15). Despite these terminological differences, all articles investigated patient populations that visited the ED several times in the past year. Recently, our research group made the differentiation between "frequent" and "repeated" ED visitors due to the fact that they found significant differences in the characteristics and risk profiles within this ED population (9). "Repeated" ED users were defined as those who made a visit at least four times in 12 months for identical symptoms and health care problems, whereas "frequent" ED patients visited the ED for various diverse symptoms and issues within a 1-year period (9).

Patients visiting the ED recurrently are more likely to be suffering from chronic somatic diseases, drug and alcohol abuse, as well as mental disorders (2, 8, 9, 11, 12, 14, 16–19). Focusing on the literature about recurrent ED users with acute mental health problems, a 25–30% prevalence of acute mental illness among frequent ED users has been noted (16, 17, 20–25). Personality disorders, depression, and anxiety were the leading psychiatric diagnoses among recurrent ED users with mental disorders (16, 17, 23, 24). Reported predictors for recurrent ED visits due to acute mental health problems were chronic substance abuse, single status, homelessness, and not having a social health insurance (9, 24–26). In Switzerland, no study has been conducted investigating the subpopulation of recurrent ED users due to acute mental health problems.

Therefore, the purpose of this study was to assess the prevalence of ED visits due to mental disorders among frequent ED users and to determine which mental disorders and risk factors were associated with recurrent ED visits.

METHODS

In this retrospective study, all patients were included who visited the ED of a tertiary care hospital due to acute symptoms of mental health problems more than once between January 1st and December 31st, 2015.

The tertiary care ED treats nearly 45,000 adult patients suffering from various disorders (e.g., internal medical problems, surgical, (poly-)trauma, head injuries, and/or psychiatric problems), and provides a full interdisciplinary and inter-professional emergency service 24/7. Of especial importance, a psychiatrist is available 24/7 in the ED; this constitutes a significant difference compared to the surrounding hospitals that do not have a psychiatric physician on staff duty in the ED. In case of acute mental health problems, every patient is treated by an interdisciplinary team of ED physicians, a psychiatrist, and ED nurses. All patients are assessed by means of a structured clinical interview and the final diagnosis of the mental disorder are made by the psychiatrist.

In this study, patients were excluded if they were younger than age 18, or visited the ED only once due to symptoms of mental health problems or for planned follow-up checks. Furthermore, patients were excluded if they suffered from mental disorders as co-morbidities but made a visit due to acute symptoms of somatic disorders. The study was approved by the local ethics committee (BASEC N° Req-2016-00195).

Group Definitions

There are several different thresholds for "recurrent" ED visits (20, 27–31). The most common and established threshold for the definition of recurrent ED visits are four or more visits per year (8).

Therefore, patients making a visit to the ED at least four times per year with any kind of acute mental health symptoms were grouped in the *recurrent group*, whereas ED patients visiting the ED twice or three times within a the span of a year due to mental problems were allocated to the control group.

Endpoints

The primary endpoint was to assess the prevalence of recurrent ED patients with acute symptoms of mental disorders within a subgroup of frequent ED patients of mental illness. As secondary endpoints, we investigated which mental disorders and risk factors were associated with recurrent ED visits. Additionally, we analyzed whether patients of the recurrent group had more hospital admissions due to acute symptoms of mental disorders as compared with the control group.

Assessment and Reporting of Other Parameters

Some clinical and demographic data were recorded from the hospital digital clinical information system in order to characterize the enrolled population. The following parameters were reported: age, gender, primary diagnosis of mental

disorders, co-morbidities, level of triage upon admission by the emergency severity index (ESI) (32), regular medication, regular drug abuse, domestic violence in the past, suicide attempts in the past, ED self-admittance or by paramedics or external doctors, need for fixation due to aggression to self and/or others, and symptoms leading to ED visits. Furthermore, we assessed the presence of a general physician (GP) and psychiatric specialist, and social data such as homelessness, residency (home alone, home with others), marital status (single/married/in partnership/divorced) and widow/-er, level of education (academic, professional qualification, in training, no profession) as well as professional status (differentiating between being employed, unemployed, in training, retired or disabled). Moreover, outcome parameters such as a need for hospital stay, and need for admission to a psychiatric institution were reported and analyzed.

Statistical Analysis

We analyzed the distribution of variables using means and standard deviation (SD) for normally distributed data, and medians and interquartile ranges (IQR) for skewed data. We tested the dataset for normality employing the Kolmogorow-Smirnow test. Categorical data were presented as frequency.

The regression model was used to analyze the association between the dependent variable (outcome) and more independent variables by estimating probabilities. For this, the primary (number of recurrent ED visits) and all other secondary endpoints were compared between the recurrent ED patients (≥4 visits per year) and the control group (two or three visits within a 12-month period) using univariate and multivariable linear as well as logistic regression models. The multivariable model was adjusted for *a priori* defined and known potential confounders such as age, gender, regular drug abuse, and known domestic violence in the past. To investigate which mental disorders and potential risk factors were salient for being a recurrent ED user within this population of ED patients with mental disorders, a multivariable logistic regression analysis was performed. Furthermore, to analyze the association between ED patients having a GP or not and those having an outpatient psychiatric specialist or not, a multivariable logistic regression analysis was also used.

For all results, point estimates, 95% confidence intervals and p-values (<0.05 considered significant) were reported. The statistical analyses were performed using the statistical program STATA SE (version 15, Stata Corp., College Station, Texas).

RESULTS

Among 33,335 primary ED visits annually in 2015, 642 ED visits (1.9%) were made by 177 visitors suffering from mental disorders. These 177 patients visited the ED at least twice or more often due to acute symptoms of mental disorders, with a median number of two ED visits per patient (IQR 2–4). Forty-five patients (25.4%) visited the ED four times or more (recurrent group) and made 302 ED visits, constituting nearly half (47.0%) of all ED visits. An ED visitor from the recurrent group visited the ED on the median five times per year (IQR 4–8). Whereas the remaining 132 ED patients (74.6%) went to the ED twice or three times (control group) during the 1-year period and completed 340 ED visits (52.9%) due to acute symptoms of mental disorders.

Patients' Characteristics and General Social Factors

Table 1 presents patients' characteristics. Patient mean age was 41 years (SD 14) old and 25.4% were female. Almost a third of all patients had been in regular outpatient therapy for underlying mental disorders. In general, patients suffered on the median from two different mental illnesses (IQR 1–3). Every third patient in the recurrent group experienced a suicide attempt in the past, whereas by contrast 18.2% of the control group had attempted suicide once. Among 15.3% of patients, an incident of domestic violence in the patient's history was reported. Additionally, 27.1% of the entire patient population was regularly on drugs.

In sum, the majority of the total patient population was healthy and only a small number of all patients evinced co-morbidities such as coronary heart diseases (4.0%), diabetes (6.2%), chronic obstructive pulmonary diseases (4.0%), or chronic kidney failure (2.3%) (**Table 1**).

Various social parameters are reported in **Table 1**. A general practitioner (GP) was more often recorded in the case of recurrent ED patients as compared to the control group.

The majority of patients lived alone or in a community. Patients of the recurrent group were more often singles, but a similar frequency of children was found compared to the control group. Almost half the population of the recurrent group was unemployed or in the case of 24.4%, individuals with a disability. Patients in the control group were mostly employed or jobless. In both groups, a third of the patients had completed a professional or vocational training course, whereas among recurrent patients 31.1% were without any profession (**Table 1**).

Presentation in the Emergency Department

Table 2 presents patients' parameters upon admission to the ED. Of a total 642 ED visits, 502 (78.2%) were triaged upon ED admission to ESI level three (**Table 2**). Patients of the recurrent group were triaged less often as ESI level 3 (74.2 *vs.* 81.8%) as compared to the control group (**Table 2**).

Furthermore, the recurrent patients had more ED visits made during daytime and late shifts compared to the control group. They also came for a visit more often by self-admittance than via vocational the agency of paramedics (**Table 2**).

Leading Symptoms and Reasons for Emergency Department Visits

Table 3 presents leading symptoms and reasons encountered for ED visits. The three leading acute mental symptoms for frequent ED visits were aggression (20.3%), feeling down, sad or miserable

TABLE 1 | Patients' characteristics.

	All patients N = 177	ED patients with two or three visits/ year (control) N = 132	ED patients with ≥ 4 visits/year (recurrent) N = 45
Age, years	41 (14)	40.3 (13.7)	42.7 (16.0)
Sex (female) (%)	45 (25.4%)	28 (21.2%)	17 (37.8%)
Total number of underlying mental disorders (%)	2 (1–3)	2 (1–3)	3 (1–4)
-Regular outpatient therapy for mental disorders in the history	58 (32.8%)	42 (31.8%)	16 (35.6%)
Suicide attempt in the past (%)	39 (22.0%)	24 (18.2%)	15 (33.3%)
Domestic violence in the history (%)	27 (15.3%)	19 (14.4%)	8 (17.8%)
Coronary heart disease (%)	7 (4.0%)	4 (3.0%)	3 (6.7%)
Diabetes mellitus (%)	11 (6.2%)	4 (3.0%)	7 (15.6%)
Arterial hypertension (%)	18 (10.2%)	8 (6.1%)	10 (22.2%)
Chronic obstructive pulmonary disease (%)	7 (4.0%)	5 (3.9%)	2 (4.4%)
Chronic kidney failure (%)	4 (2.3%)	2 (1.5%)	2 (4.4%)
Chronic liver insufficiency (%)	6 (3.4%)	6 (4.5%)	0%
HIV infection (%)	8 (4.5%)	7 (5.3%)	1 (2.2%)
Regular drug abuse (%)	48 (27.1%)	38 (28.8%)	10 (22.2%)
-Past drug abuse (%)	22 (12.4%)	16 (12.1%)	6 (13.3%)
General physician available (%)	95 (53.7%)	65 (49.2%)	30 (66.7%)
Homelessness (%)	28 (15.8%)	21 (15.9%)	7 (15.6%)
Decaying condition (%)	29 (16.4%)	20 (15.2%)	9 (20%)
Housing (%)			
-Living alone	82 (46.3%)	61 (46.2%)	21 (46.7%)
-Living with others	76 (42.9%)	58 (43.9%)	18 (40%)
-Supervised living	19 (10.7%)	13 (9.8%)	6 (13.3%)
Marital status (%)			
-Single	103 (58.2%)	72 (54.5%)	31 (68.9%)
-Married/in partnership	45 (25.4%)	37 (28.0%)	8 (17.8%)
-Divorced	27 (15.3%)	22 (16.7%)	5 (11.1%)
-Widowed	2 (1.1%)	1 (0.8%)	1 (2.2%)
Children (%)	58 (32.8%)	44 (33.3%)	14 (31.1%)
-Of minor age	32 (18.1%)	26 (19.7%)	6 (13.3%)
Professional/vocational status (%)			
-Employed	47 (26.6%)	41 (31.1%)	6 (13.3%)
-Unemployed	68 (38.4%)	46 (34.8%)	22 (48.9%)
-In training	7 (4.0%)	6 (4.5%)	1 (2.2%)
-Retired	11 (6.2%)	6 (4.5%)	5 (11.1%)
-Disabled	44 (24.9%)	33 (25%)	11 (24.4%)
Level of education (%)			
-Academic	21 (11.9%)	16 (12.1%)	5 (11.1%)
-Professional qualification	57 (32.2%)	41 (31.1%)	16 (35.6%)
-In training	7 (4.0%)	6 (4.5%)	1 (2.2%)
-No profession	40 (22.6%)	26 (19.7%)	14 (31.1%)
-Unknown	52 (29.4%)	43 (32.6%)	9 (20%)

ED, emergency department. Results are presented as mean (standard deviation) or median (25th–75th percentile).

(18.1%), and hallucinations (17.5%). Whereas by contrast, patients of the recurrent group visited the ED repeatedly due to different withdrawal symptoms (26.7%), hallucinations (22.2%), and aggression (17.8%). Additionally, eight recurrent ED patients (17.8%) suffered from chest pain and had negative cardiac diagnostic test results for acute myocardial infarction during examinations in the ED. In addition, no organic etiology for chest pain was found in any of the eight patients complaining of chest pain.

TABLE 2 | Some parameters upon admission as attender/presenter to the emergency department (ED).

	All ED visits N = 642	Two or three ED visits/year N = 340	≥ 4 ED visits/ year N = 302
Triage level upon ED admission by the ESI (%)			
-ESI 1	9 (1.4%)	4 (1.2%)	5 (1.7%)
-ESI 2	51 (7.9%)	21 (6.2%)	30 (9.9%)
-ESI 3	502 (78.2%)	278 (81.8%)	224 (74.2%)
-ESI 4/5	80 (12.5%)	37 (10.9%)	43 (14.2%)
Number of ED visits during:			
-8 am–5 pm	1 (1–2)	1 (0–2)	3 (2–4)
-5 pm–11 pm	1 (0–2)	1 (0–1)	2 (1–3)
-11 pm–8 am	1 (0–1)	0 (0–1)	1 (0–3)
Number of self-admittances	2 (1–3)	2 (1–2)	4 (1–6)
Number of admittances by paramedics	1 (0–2)	0 (0–2)	1 (0–4)
Number of emergency allocations by external doctors	0 (0–1)	0 (0–1)	0 (0–2)
ED admission with police (%)	22 (3.4%)	16 (4.7%)	6 (2.0%)
Need for fixation strategies in the ED (%)	6 (0.9%)	4 (1.1%)	2 (0.7%)

ED, emergency department; ESI, Emergency Severity Index. Results are presented as median (25th–75th percentile).

TABLE 3 | Symptoms or reasons leading to emergency department (ED) visits.

	All patients N = 177	ED patients with two or three visits/year N = 132	ED patients with ≥ 4 visits/ year N = 45
Different symptoms			
Aggression (%)	36 (20.3%)	28 (21.2%)	8 (17.8%)
Feeling down, sad, or miserable (%)	32 (18.1%)	28 (21.2%)	4 (8.9%)
Hallucinations (%)	31 (17.5%)	21 (15.9%)	10 (22.2%)
Anxiety or panic (%)	24 (13.6%)	19 (14.4%)	5 (11.1%)
Different withdrawal symptoms (%)	22 (12.4%)	10 (7.6%)	12 (26.7%)
Increased stress load (%)	17 (9.6%)	13 (9.8%)	4 (8.9%)
Chest pain (%)	13 (7.3%)	5 (3.8%)	8 (17.8%)
Insomnia (%)	6 (3.4%)	4 (3.0%)	2 (4.4%)
Others* (%)	69 (39.0%)	39 (29.5%)	30 (66.7%)
Different reasons			
Acute drug toxicity (%)	90 (50.8%)	62 (47.0%)	28 (62.2%)
-Only alcohol	61 (34.5%)	45 (34.1%)	16 (35.6%)
-Drugs and alcohol	29 (16.4%)	17 (12.9%)	12 (26.7%)
Suicide attempt (%)	54 (30.5%)	38 (28.8%)	16 (35.6%)
Self-mutilation (%)	45 (25.4%)	24 (18.2%)	21 (46.7%)
Foreign body invagination (%)	4 (2.3%)	1 (0.8%)	3 (6.7%)
Wish for a medical prescription (%)	14 (7.9%)	9 (6.8%)	5 (11.1%)
Wish for alcohol or drug withdrawal (%)	12 (6.8%)	6 (4.5%)	6 (13.3%)
Wish for psychiatric admission (%)	8 (4.5%)	4 (3.0%)	4 (8.9%)

It is possible that more than one symptom and/or reason leading to ED visit; ED, emergency department. Others included symptoms of generalized or specific pain (e.g., headache, back, limbs, or abdominal pain), poor appetite, weakness, fatigue, dizziness, trembling or muscle cramps, etc.

The most frequent reason for ED visits was acute drug toxicity (50.8%). Recurrent patients had far more ED visits due to a combination of drug and alcohol toxicity (26.7 *vs.* 12.9%, adjusted OR 4.2, 95% CI 1.5–12.0, p = 0.007) compared to the control group. The rate of acute drug toxicity due solely to alcohol overdose was similar in both groups (adjusted OR 0.97, 95% CI 0.5–2.0, p = 0.93).

Furthermore, recurrent ED patients did not visit significantly more often due to the consequences of a suicide attempt (35.6 *vs.* 28.8%, adjusted OR 1.6, 95% CI 0.7–3.3, p = 0.26). But they visited the ED significantly more often due to the consequences of self-mutilation (46.7 *vs.* 18.2%, adjusted OR 4.2, 95% CI 1.9–8.9, p < 0.001) as compared to patients in the control group.

Only a small number of patients visited the ED frequently with the wish to obtain a medical prescription, for alcohol or drug withdrawal, or desired psychiatric admission (**Table 3**).

Diagnosis of Mental Disorders Leading to Recurrent Emergency Department Visits

Assigning these multiple symptoms to a diagnosis of mental disorders (**Table 4**), the majority of patients visited the ED as a result of psychoactive substance addiction (41.8%). The drug addiction was similarly distributed in both groups.

Furthermore, personality disorders were significantly more often represented among recurrent ED patients (adjusted OR 4.0; 95% CI 1.4–11.8, p = 0.011). A trend was also identified for somatoform disorders (unadjusted OR 6.3, 95% CI 1.1–35.9, p = 0.037), but was weakened by the presence of too few events in both groups (**Table 4**).

TABLE 4 | Leading diagnoses of mental disorders encountered.

	ED patients with two or three visits/ year N = 132	ED patients with ≥ 4 visits/year N = 45	Unadjusted OR (95% CI, p-value)	Adjusted OR (95% CI, p-value)
Psychoactive substance or medical addiction (%)	54 (40.9%)	20 (44.4%)	1.2 (0.7–2.9, p = 0.78)	1.1 (0.5–2.4, p = 0.90)
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (%)	22 (16.7%)	5 (11.1%)	0.6 (0.2–1.8, p = 0.37)	0.6 (0.2–1.8, p = 0.37)
Anxiety, dissociative, stress-related, and other non-psychotic mental disorders (%)	23 (17.4%)	3 (6.7%)	0.3 (0.1–1.2, p = 0.09)	–
Personality disorders (%)	12 (9.1%)	10 (22.2%)	2.9 (1.1–7.2, p = 0.025)	4.0 (1.4–11.8, p = 0.011)
Affective disorder (%)	19 (14.4%)	3 (6.7%)	0.4 (0.1–1.5, p = 0.19)	–
Somatoform disorders (%)	2 (1.5%)	4 (8.9%)	6.3 (1.1–35.9, p = 0.037)	–

ED, emergency department; OR, odds ratio; CI, confidence interval. Results are adjusted for age sex, regular drug consumption, and known domestic violence in the past. No adjustment was performed if fewer than five cases occur in one of the groups.

Social Risk Factors Leading to Recurrent Emergency Department Visits

Analyzing social parameters as potential risk factors for recurrent ED visits due to acute mental symptoms, being single was identified as the only significant predictor (adjusted OR 2.2, 95% CI 1.1–4.8, p = 0.045).

Being unemployed and the fact of never have learned a profession/vocation evinced a trend for increased recurrent ED visits; however, this was not significant (**Table 5**).

Inpatient Admissions due to Acute Symptoms of Mental Disorders

Patients of the recurrent group were significantly more often admitted to an inpatient clinic (2 (IQR 0–4) *vs.* 1 (IQR 0–2); adjusted difference 1.6, 95% CI 1.1–2.0, p < 0.001) as a result of acute symptoms. They were also significantly more often admitted to psychiatric clinics (1 (IQR 0–2) *vs.* 1 (IQR 0–1; adjusted difference 0.8, 95% CI 0.4–1.2, p < 0.001).

Prevalence of General Physician or Outpatient Psychiatrist

In total, 95 patients (53.6%) reported when admitted to the ED that they had a GP. Recurrent ED patients had a GP significantly more often than as compared to the control group (95% CI 1.1–4.4, p = 0.043).

TABLE 5 | Differences and risks for recurrent emergency department (ED) visits.

	ED patients with two or three visits/ year N = 132	ED patients with ≥ 4 visits/year N = 45	Unadjusted OR (95% CI, p-value)	Adjusted OR (95% CI, p-value)
Single status (%)	72 (54.5%)	31 (68.9%)	1.8 (0.9–3.8, p = 0.10)	2.2 (1.1–4.8, p = 0.045)
Unemployed (%)	46 (34.8%)	22 (48.9%)	1.7 (0.9–3.5, p = 0.10)	1.8 (0.9–3.6, p = 0.16)
No profession/ vocation (%)	26 (19.7%)	14 (31.1%)	1.8 (0.9–3.9, p = 0.12)	2.0 (0.9–4.4, p = 0.09)
General physician available (%)	65 (49.2%)	30 (66.7%)	2.0 (1.01–4.2, p = 0.045)	2.1 (1.1–4.4, p = 0.043)
Regular psychiatric outpatient visits (%)	42 (31.8%)	16 (35.6%)	1.2 (0.6–2.4, p = 0.65)	1.3 (0.6–2.7, p = 0.54)
			Unadjusted difference (95% CI, p-value)	**Adjusted difference (95% CI, p-value)**
Number of ED visits during 8 am to 5 pm	1 (0–2)	3 (2–4)	1.5 (1.0–1.9, p < 0.001)	1.5 (1.1–1.9, p < 0.001)
Number of ED visits during 5 to 11 pm	1 (0–1)	2 (1–3)	1.3 (0.9–1.7, p < 0.001)	1.3 (0.9–1.7, p < 0.001)
Number of ED visits during 11 pm to 8 am	0 (0–1)	1 (0–3)	1.3 (0.8–1.8, p < 0.001)	1.4 (0.9–1.9, p < 0.001)

ED, emergency department; OR, odds ratio; CI, confidence interval. Results were presented as median (25th–75th percentile). Results are adjusted for age sex, regular drug consumption and known domestic violence in the past.

Furthermore, 58 patients (32.8%) even had an outpatient psychiatrist. There was no difference between the two groups in the rate of psychiatrists (95% CI 0.6–2.7, p = 0.54) (**Table 5**).

Although recurrent ED visitors had more often a GP or psychiatrist, they presented more ED visits within office hours (adjusted difference 1.5, 95% CI 1.1–1.9, p < 0.001) than the control group (**Table 5**).

DISCUSSION

A quarter of frequent ED users with mental disorders are recurrent ED visitors and were more likely to suffer from personality disorders. Recurrent ED visits are associated with higher rates of self-mutilation, acute drug toxicity, and more in-house admissions. A social risk factor such as being single is more likely to increase the rate of recurrent ED visits. Although recurrent ED visitors more often had an outpatient general physician or psychiatrist, they visited the ED more frequently within office hours.

The general population of frequent ED visitors suffers more often from psychiatric disorders, pain complaints and more frequently, psychoactive substances were misused and the leading cause for recurrent ED visits (2, 8, 9, 11, 12, 14, 16–19). A prevalence of recurrent ED visits of 28–30% has been reported in ED patients making frequent visits due to acute symptoms of mental health problems (16, 17, 33). The prevalence of 25.4% in this current study corresponds with findings in the international literature.

Further findings of this current Swiss study are comparable with the findings in the literature (16, 17, 20–25). Personality disorders, depression and anxiety disorders were the leading psychiatric diagnoses among recurrent ED users with mental disorders (16, 17, 23, 24). Among these, personality disorders were reported to be the most frequent mental illness in recurrent ED users (11, 16, 17, 25). Vandyk et al. reported that 9 of 10 recurrent ED patients with mental disorders visited the ED due to acute symptoms or consequences of antisocial or borderline personality disorder (25). Less frequent but still a high number of borderline effects were recorded in the current study. Almost every second patient presented recurrently in the ED due to consequences of self-mutilation. We reported psychoactive substance addiction, personality disorders, and schizophrenia as the three leading diagnoses for recurrent ED visits. Finally, only ED patients with personality disorders were more likely to have recurrent ED visits. This can be explained by the long-standing course of the disease and its multiple and recurrent exacerbations that lead patients with personality disorders to recurrent ED visits (25, 34). The ED is indeed the accurate place to treat acute consequences of personality disorders by treating cuts and wounds or removing foreign bodies from any body site, for example, but the ED is not the right locus for treatment of the chronic underlying psychiatric disease. Over the long term, it is unclear how ED physicians may assist persons in this vulnerable patient population. In 2017, a randomized controlled trial was performed to investigate whether a brief case management organized by the ED can support these patients with psychiatric diagnosis in order to reduce the number of ED visits (35). Stergiopoulos et al. could not show any effect of the case management on the number of ED visits. A possible solution to reduce the large number of ED visits may be through extended collaboration with outpatient psychiatric services (33). For this specific issue, special outpatient therapies and close support by psychiatrists are needed in the future.

Minassian et al. found that recurrent ED visits due to acute mental health problems were related to alcohol abuse (26). Several articles identified that substance abuse was significantly associated with mental disorders and multiple ED presentations (20, 23, 33, 36). These results reflect the complexity of special needs of these patients and suggest that a well-trained and interdisciplinary team of ED physicians, psychiatrists, and ED nurses need to provide care for this specific population. In the current study, sole alcohol overuse was not associated with recurrent ED visits, whereas drug intake in combination with alcohol led significantly more often to recurrent ED visits. More than 60% of the recurrent patients visited the ED due to acute symptoms of psychoactive substance misuse. The rates for acute symptoms with the need for ED admission due to an alcohol or psychoactive drug overuse are similar in the literature to our current findings (17, 20, 23, 33, 36).

There is a high prevalence of substance abuse (20–25%) in the medical history of recurrent ED patients with mental symptoms (12, 17, 20, 23, 26, 33, 36). The current study also reports that every fifth recurrent ED patient had used drugs regularly in the past.

Acute symptoms of schizophrenia leading to recurrent ED visits were mostly reported among highly frequent ED users (>11 or even 18 visits/year) (17, 18). In the current sample, acute symptoms and consequences of schizophrenia were the third most frequent reason for recurrent ED visits, but there was no significant association between the recurrent ED visitors suffering from schizophrenia and an increased rate of ED visits. Whether schizophrenia is a risk factor in the highly frequent ED population with mental illness is unclear and could not be statistically analyzed in the current study. Only 13 patients had 8 or more ED visits due to acute symptoms of mental disorder. None of these 13 patients suffered from schizophrenia. Therefore, more research is needed in this rare population of highly frequent ED visitors to better understand those vulnerable populations and to identify potential supporting measures.

Recurrent ED patients were more likely to be hospitalized (19–28%) than general ED users (14–16%) (9–11, 33, 37). Hansagi et al. found that 80% of recurrent ED patients needed hospital admission (38). The authors argued that the high rate for hospital admission was due to a large number of severely ill patients with co-morbidities (38). Recurrent ED users with psychiatric disorders have in general fewer co-morbidities and are therefore considered healthier overall. Thus, this might suggest that recurrent ED users suffering from acute mental problems have a lower rate of hospital admission. This was not the case. In the literature as well as in this current study,

recurrent ED users with acute symptoms of mental illness showed a significantly higher number of hospital admissions and admissions to psychiatric clinics compared to the control group. Indeed, those patients were healthier and showed a lower rate of co-morbidities, but they also suffered more frequently from acute symptoms due to alcohol or substance abuse or consequences of self-mutilation that led to a greater number of hospital admissions (33, 36, 39).

The chronic nature of mental disorders impairs the social and occupational functioning, and in addition to the increased rates of exacerbating factors, different social factors were shown to be predictors for recurrent ED presentations. Being a single parent, having single or divorced marital status, being unemployed, having a high school education level or lower and/or low income were associated with an increased number of ED presentations (9, 19, 25, 33, 36). In addition, Chang et al. pointed to other social factors such as homelessness and no social health insurance as predictors for recurrent ED use by patients with acute mental illness (24). In the current study, being of single status was the only social predictor for recurrent ED use. Furthermore, homelessness, divorced marital status, level of education, and professional/vocational status could not be identified as social predictors because the sample in each group was too small. Social health insurance was not evaluated as a predictor because in Switzerland, every patient is required to have at least a general insurance policy that covers medical expenses. Further studies with larger sample sizes and prospective recording of further social factors, such as income, indebtedness, social problems in school, the family, or workplace, are needed.

Strengths and Limitations

There are several limitations in the study conducted. First, it is a single-center study in a region with several surrounding hospitals. Thus, it is likely that the number of recurrent ED patients is overall much higher than reported. Furthermore, recurrent ED patients are likely to pay visits to multiple EDs due to identical problems. This limitation might be negligible, because the surrounding hospitals do not have a psychiatrist in the ED available 24/7. Therefore, as a tertiary care hospital with an interdisciplinary team of ED physicians, a psychiatrist on duty, and ED nurses available on a 24/7 basis, it is the largest sample size of recurrent ED patients with mental disorders in our region, thus representing well the generalizability of our findings.

Furthermore, because of the availability of an electronic clinical information system, the study has only few missing data, and none in the endpoints.

Third, so as to reduce the bias, a randomization was not possible to conduct due to the retrospective nature of the study design. Therefore, we adjusted all our results for potential confounders by using a multivariable regression model. The strict inclusion criteria additionally reduced the selection bias in respect to recurrent ED visitors.

The focus on the subgroup of recurrent ED patients with mental disorders strengthens the findings as a result of the homogeneity of the specified population of vulnerable ED patients.

CONCLUSION

Recurrent ED patients suffering from acute symptoms of mental disorders are a rare subgroup of ED patients but they constitute a fourth of the recurrent ED visitors. Recurrent ED visitors were more likely to suffer from personality disorders. Recurrent ED visits are associated with higher rates of self-mutilation, acute drug toxicity, and more in-house admissions. A possible solution to reduce the ED frequency may be a case management approach for recurrent ED patients with mental disorders. Further prospective studies are required to optimize the future patient-centered care of recurrent ED visitors.

AUTHOR'S NOTE

The abstract with preliminary results of the current study was presented as a poster at: The Annual Conference of Swiss Psychiatrists ("PSY Congress"), Berne, Switzerland, September 5–7, 2018; the 12th European Congress of Emergency Medicine (EUSEM), Glasgow, United Kingdom, September 8–12, 2018; the 13th Annual Conference, Deutsche Gesel lschaft Interdisziplinäre Notfall- und Akutmedizin (DGINA), Leipzig, Germany, September 27–29, 2018; abstract published in Notfall Rettungsmed 2018, 21: 1–22. Preliminary results were presented orally at the Annual Conference, Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), Berlin, Germany, November 28 to December 1, 2018, oral presentation.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available because the ethic committee decision is only positive for the publication of the results and not for the public availability of the dataset.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Canton Zurich, Switzerland. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: KS, DK. Data curation: KS, RH, DK. Formal analysis: KS. Funding acquisition: KS. Investigation: KS, DK. Methodology: KS, DK. Project administration: KS, DK. Supervision: KS, DK. Visualization: KS, RH, DG. Writing – original draft: KS, DK. Writing – review and editing: KS, RH, DK.

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REVIEW
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Sleep Disturbances and Suicidality in Posttraumatic Stress Disorder: An Overview of the Literature

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A causal relationship between sleep disturbances and suicidal behavior has been previously reported. Insomnia and nightmares are considered as hallmarks of posttraumatic stress disorder (PTSD). In addition, patients with PTSD have an increased risk for suicidality. The present article gives an overview about the existing literature on the relationship between sleep disturbances and suicidality in the context of PTSD. It aims to demonstrate that diagnosing and treating sleep problems as still underestimated target symptoms may provide preventive strategies with respect to suicidality. However, heterogeneous study designs, different samples and diverse outcome parameters hinder a direct comparison of studies and a causal relationship cannot be shown. More research is necessary to clarify this complex relationship and to tackle the value of treatment of sleep disturbances for suicide prevention in PTSD.

Keywords: sleep, sleep disorders, suicidality, PTSD (post-traumatic stress disorder), insomnia, nightmares

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INTRODUCTION

Suicide is a leading cause of death worldwide with at least 788,000 annual deaths from suicide around the world in 2015 according to WHO data (1). Sleep disturbances have been shown to be a risk factor for mental disorders for decades, and are an independent risk factor for suicidal behavior (2). However, not only sleep problems in general have evolved as an evidence-based risk factor for suicide (3, 4), but short sleep duration also seems to be associated with suicidality (5, 6). Moreover, insomnia has also been proposed to be an independent risk factor for suicidality (7, 8). However, the association is weaker after controlling for depression (9, 10). Further, there is also evidence for an association between nightmare disorder and suicidality (11–13). However, the specific contributions of nightmare disorder to suicidality remain unclear (14). Unfortunately, nightmares are under-reported, therefore detection and treatment are often insufficient (15).

PTSD and Sleep Disturbances

The lifetime prevalence of posttraumatic stress disorder (PTSD) is estimated to be about 8.0% in the general population (16, 17), and sleep disturbances are considered as a core feature of PTSD (18). There is a high prevalence of nightmares (up to 70%) in patients with PTSD (19), and the rate of sleep disturbances in PTSD is estimated to be in the same range as that of nightmares and insomnia at about 40% (20). A bidirectional relationship between PTSD and sleep disturbances has been purported (21, 22). This is in line with the hypothesis that it is biologically plausible for sleep disturbance to be mechanistically transdiagnostic, suggesting that sleep disturbances are related to the onset and course of several psychiatric disorders. Specifically, increased activity of the

noradrenergic system during rapid-eye-movement-(REM)-sleep, REM-sleep fragmentation and reduced activity of the medial prefrontal cortex during REM-sleep may play a pivotal role with respect to sleep fragmentation and emotion dysregulation in PTSD (23).

Apart from sleep disturbances and nightmares being an integral diagnostic criteria of PTSD, specific sleep disorders such as obstructive sleep apnea syndrome (OSAS), REM-sleep behavior disorder, and periodic limb movement disorder have been reported to be disproportionately frequent in PTSD patients (24). Several studies have shown a high prevalence of OSAS in PTSD patients, and it is suggested that OSAS plays a role in the pathophysiology of PTSD symptoms (25–27). There is also evidence for a positive correlation between effective OSAS treatment and reduced PTSD severity (28, 29). Sleep terrors, nocturnal panic attacks, and simple and complex motor behaviors including vocalizations and acting out dreams may also occur during sleep in patients with PTSD (23). These features were recently described as "Trauma Associated Sleep Disorder" which may also occur without the presence of other typical PTSD symptoms (30, 31).

PTSD and Suicidality

Numerous studies have shown that PTSD represents a risk factor for suicidal thoughts and behaviors (32, 33). In addition, there is evidence for a mediating role of depression in the association of PTSD and suicidality (34). Comorbid depression may amplify the suicide risk synergistically beyond an additive effect (35). Indeed, there is evidence of an increased risk of death by suicide in PTSD patients in general (36, 37) even compared to trauma-exposed people (38, 39). Considering suicide risk, it is noteworthy that PTSD is one of the few psychiatric disorders that distinguish those who think about suicide from those who make suicide attempts (40). A meta-analysis has shown that PTSD is reliably more common in attempters than ideators, but these effects seem to be modest rather than strong (41).

PTSD, Sleep Disturbances and Suicidality

There are only few studies reporting on the relationship between PTSD, sleep disturbances, and suicidality. A meta-analysis of sleep disturbances and suicidal thoughts and behaviors including studies on mixed samples (42) identified only one study on their relationship to PTSD (43); another meta-analysis and systematic review about the association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses (44) also found the same study by Krakow et al. (43). Moreover, a systematic review of the relationship between sleep disturbance, suicidal ideation, suicide attempts, and suicide among adults (45) provided three studies for PTSD (46–48) and seven studies for veterans in consideration of a possible PTSD diagnosis (49–55).

LITERATURE SEARCH AND RESULTS

We conducted a comprehensive search of MEDLINE/PubMed databases using Medical Subject Headings terms in various combinations to identify studies that examined aspects of sleep disorders, suicidality and PTSD. Furthermore, we identified several studies by searching through references of identified studies, reviews and meta-analyses. In total, we identified 30 studies (**Tables 1**–**3**).

Sleep Disturbances (Insomnia)

The respective studies are listed in **Table 1**. One study in military personnel investigated the relationship between insomnia symptoms and suicidal ideation and behavior after controlling for depressive symptom severity, hopelessness, PTSD diagnosis, anxiety symptoms, and drug and alcohol abuse in a cross-sectional as well as longitudinal design (54). It was shown that insomnia symptoms were cross-sectionally associated with suicidal ideation. Using a longitudinal design, insomnia symptoms were unique predictors of suicide attempts after controlling for baseline self-insomnia, depressive symptoms and hopelessness (54). The study is often cited as the prime example of a close link between sleep disturbances and suicidality independent of the presence of depression in PTSD. In addition, another study in veterans found that the association of sleep disturbance with suicidal ideations remained significant after controlling for age, alcohol dependence, depression, and PTSD (49). This was replicated in another study on veterans for poor sleep quality in general, but not for insomnia symptoms (51). A chart review provided evidence for a longitudinal relationship between sleep and suicidality; veterans with sleep disturbance died sooner after their last visit compared to those without sleep disturbance, even after adjusting for the presence of mental health or substance use symptoms (53).

New findings with respect to the longitudinal relationship revealed that pre-deployment insomnia was associated with increased risk of post-deployment PTSD and suicidal ideation

Abbreviations: AIS, Athens Insomnia Scale; AOR, Adjusted odds ratio; AUD, Alcohol use disorder; bCBTi, Brief cognitive behavioral therapy for insomnia; BDI II, Beck Depression Inventory, 2. Edition; BSSI, Beck Scale for Suicidal Ideation; CAF, Canadian Armed Force; CAPS, Clinician-Administered PTSD Scale for DSM-IV; CIDI-Auto, Composite International Diagnostic Interview, version 2.4; C-SSRS, Columbia Suicide Severity Rating Scale; DDNSI, Disturbing Dreams and Nightmare Severity Index; DSI-SS, Depressive Symptom Index-Suicidality Subscale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4. Version; GAD, Generalized anxiety disorder; HRA II, Health Risk Appraisal; IPT, Interpersonal Theory of Suicide; ISI, Insomnia Severity Index; LSD, Long sleep duration; MDD, Major depressive disorder; MINI, Mini International Neuropsychiatric Screen and Interview; MOODS-SR, Mood Spectrum-Self Report; MSSI, Modified Scale for Suicidal Ideationl; mTBI, Mild traumatic brain injury; MUSP, Mater University Study of Pregnancy; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; OIF, Operation Iraqi Freedom; OR, Odds ratio; OSAS, Obstructive sleep apnea syndrome; PCL, Posttraumatic Stress Disorder Symptoms Checklist; PCL-5, Posttraumatic Stress Disorder Checklist for DSM-5; PCL-C, Posttraumatic Stress Disorder Symptoms Checklist—Civilian version; PCL-M, Posttraumatic Stress Disorder Symptoms Checklist—Military version; PC-PTSD, Primary Care PTSD Screen; PD, Panic disorder; PHQ-9, Patient Health Questionnaire 9; PROMIS, Patient-Reported Outcomes Measurement Information System; PSI, Paykel Suicide Items; PSQI, Pittsburgh Sleep Quality Index; PSQI-A, Pittsburgh Sleep Quality Index-Addendum; PSS, PTSD Symptom Scale; PTSD, Posttraumatic stress disorder; RCT, Randomized clinical trial; RDI, Respiratory disturbance index; REM, Rapid eye movement; SA, Suicide attempt; SB, Suicidal behavior; SBQ-R, Suicidal Behaviors Questionnaire-Revised; SCIDI/P, Structured Clinical Interview for DSMIV-TR Axis I Disorders; SI, Suicidal ideation; SSD, Short sleep duration; SSI, Scale for Suicide Ideation; SWS, Suicide warning signs survey; TAU, Treatment as usual; VHA, Veterans Health Administration.

TABLE 1 | Studies referring to PTSD, suicidality and sleep disturbances (insomnia).

References	Core issue	Sample	Sex (male)	Measurements	Main findings
Betts et al. (46)	Association between the risk of SI in individuals with PTSD symptoms on comorbid sleep disturbance	Participants of the MUSP (n = 2,465) with PTSD-symptoms: 9.4%; proportion of those with PTSD-diagnosis not mentioned	48.0%	Single item (SI), shortened version PSQI (sleep quality), CIDI-Auto (PTSD)	- PTSD symptoms did not directly predict SI when adjusting for MDD symptoms, polyvictimization, and gender - PTSD symptoms had an indirect effect on SI via past-month sleep disturbance
Bishop et al. (49)	Association of sleep disturbance with SI after controlling for age, alcohol dependence, depression, and PTSD	Veterans (n = 654), with PTSD: 24.3%	95,3%	PSS (SI), single item PCL (sleep disturbance), PTSD (PCL)	Sleep disturbance was a predictor of SI, even after controlling for age, alcohol dependence, PTSD, and depression
Bishop et al. (56)	Association among sleep disorders and SA after controlling for several mental disorders, medical comorbidity, and obesity	Veterans (data base review) (n = 60,102, 1:1 case control with no SA), with PTSD: 24.7%	87.1%	Data extraction for SA, sleep disturbance, mental disorders	- Insomnia was associated with SA - Sleep medicine visits were associated with a reduced risk of SA in sleep disordered patients
Britton et al. (57)	Associations among insomnia symptoms, PTSD symptoms and depressive symptoms, IPT variables, and risk for SB	Veterans (n = 392), with PTSD: 41.8%	69.6%	SBQ-R (SB), ISI (insomnia), PCL-M (PTSD)	- Insomnia symptoms may be associated with increased PTSD and depressive symptoms - PTSD emerged as a mediator between insomnia and SI
Bryan et al. (50)	Identifying clinical variables (incl. PTSD) associated with suicidality in military personnel with mTBI	Deployed soldiers (n = 158), with mTBI: 85.4%; proportion of PTSD not mentioned	93%	SBQ-R (suicidality), ISI (insomnia), PCL-M (PTSD)	Suicidality was significantly associated with depression and the interaction of depression with PTSD symptoms
Bryan et al. (58)*	Associations of insomnia severity with SI, and SB	3 samples of active duty military (n = 380); proportion of PTSD not mentioned	76.6%	BSSI (SI), ISI (insomnia), PCL (PTSD)	Association between sleep disturbances and SI (concurrent/prospective) in all samples; this effect was no longer present after adjusting for age, gender, depression, and PTSD
Chakravorty et al. (51)	Association between SI and insomnia symptoms adjusted for socio-demographic, psychiatric and addiction-related variables	Outpatient veterans, misusing alcohol (n = 162), with PTSD: 27%	93%	PSI (SI, SB, SA), single item PSQI (sleep quality), PCL (PTSD)	- After controlling for psychopathology, a significant association between insomnia and SI was no longer present; poor sleep quality remained associated with increased SI - SI was not associated with sleep duration
Davidson et al. (48)	Association between exercise and suicide risk including potential mediators (i.e., sleep disturbance, PTSD symptoms, depression)	Veterans admitted to a residential rehabilitation program for PTSD (n = 346)	81%	8 items of BDI II(suicidality), PSQI (sleep quality), PCL-M without sleep item (PTSD)	- Direct negative association between suicide risk and exercise, indirectly through association with depressive symptoms and sleep quality - PTSD symptoms did not mediate the relation between exercise and suicide risk
Dell'Osso et al. (47)	Impact of alterations in rhythmicity and vegetative function (incl. sleep disturbances) as correlates of suicidality	Civilian inpatients/outpatients with PTSD (n = 65); patients with current (n = 20) or former depression (n = 14) were excluded	50.8%	MOOD-SR (SI/SA/sleep disturbances)	All MOODS-SR sub-domains (rhythmicity, sleep, appetite/weight, physical symptoms) were associated with an increased likelihood of SI; changes in appetite/weight were associated with greater OR of SA
Don Richardson et al. (52)	Association between SI and sleep after controlling for probable PTSD, MDD, GAD, AUD	Veterans (n = 324)/active duty military (n = 80), with PTSD: 72.8%	92.4%	Single item PHQ-9 (SI), quantitative single item (sleep disturbances resp. nightmares), PCL-M (PTSD)	- Sleep disturbances did not predict SI - Probable MDD emerged as a significant predictor

(Continued)

TABLE 1 | Continued

References	Core issue	Sample	Sex (male)	Measurements	Main findings
Don Richardson et al. (59)	Mediating role of depression in the relationship between: 1) sleep disturbances and SI, and 2) trauma-related nightmares and SI after controlling for PTSD-, anxiety- and alcohol-use-severity	CAF personnel (17.6%)/veterans (82.4%), ($n = 663$), with PTSD: 72.6%	91%	Single item PHQ-9 (SI), quantitative single item (sleep disturbances resp. nightmares), PCL-M (PTSD)	Sleep disturbances were associated with SI as a function of depressive symptoms
Fisher et al. (60)	The moderating role of agitation within the relationship between insomnia and current SI	U.S. military personnel ($n = 937$); proportion of PTSD is not mentioned	75.3%	BSSI/DSI-SS (SI), ISI (insomnia), PCL-M (PTSD)	- Significant association between insomnia and SI only at high levels of agitation - PTSD symptoms, depressive symptoms, and lifetime number of SA were each associated with greater levels of agitation, insomnia, and current SI
Kachadourian et al. (61)	Association between individual symptoms of PTSD and measures of functioning, quality of life, and SI	U. S. military veterans ($n = 1,484$), with PTSD: 10.9%, trauma-exposed: 85,4%	89.8%	Single item on the PHQ-9 (SI), PCL-5 (sleep difficulties/ nightmares/PTSD)	- Sleep difficulties explained problems in physical functioning/quality of life after adjustment for severity of PTSD/depressive symptoms - No association between SI and sleep difficulties
Kim et al. (62)	The mediating role of AUD and insomnia in the relationship between PTSD symptoms and SI	Korean firefighters ($n = 7,190$), with PTSD: 3.6%	90%	PHQ-9 suicide item (SI), AIS (insomnia), PCL (PTSD)	AUD and insomnia mediated the relationship between PTSD symptoms and SI
Luxton et al. (63)	Prevalence and impact of short sleep duration in redeployed OIF soldiers	Redeployed OIF soldiers ($n = 2,738$), with PTSD: 15.4%	96%	HRA II (SA), 2 items (sleep duration/sleep quality), PC-PTSD (PTSD)	- SSD was a significant predictor of suicide risk - SSD was the strongest predictor of PTSD
McClure et al. (64)	To determine the prevalence of factors that may serve as warnings of acute suicidality risk	Veterans attending an urgent care psychiatric clinic ($n = 473$), with PTSD: 49%	89%	SWS survey (SI/insomnia/ hypersomnia), PC-PTSD (PTSD)	- Past week SI and sleep disturbances were among others a highly prevalent warning sign - 97% endorsed at least one warning sign, participants with MDD and/or PTSD endorsed the largest number of warning signs
Morgan et al. (65)	The relationship between sleep issues, mental health (perceived stress, PTSD symptoms, and depressive symptoms), and SI	Military service members ($n = 891$), with PTSD: 13%	95.5%	Single item (SI), PROMIS (sleep disturbances), PCL-C (PTSD)	PTSD, perceived stress, and depressive symptoms mediated the relationship between sleep issues and SI; after accounting for mental health symptoms, sleep no longer had a direct effect on SI
Pigeon et al. (53)*	Role of sleep disturbance in time to suicide since the last treatment visit among veterans receiving VHA services	Suicide decedents ($n = 423$) Visit of the VHA ($n = 381$); proportion of PTSD is not mentioned	99.7%	Chart review for number of days between last visit and death, sleep disturbances, and psychiatric symptoms	Veterans with sleep disturbance died sooner after their last visit than did those without sleep disturbance, after adjusting for the presence of mental health or substance use symptoms, age, and region
Pigeon et al. (66)*	bCBTi delivered to veterans endorsing SI with a diagnosis of MDD and/or PTSD	Veterans ($n = 54$, RCT 1:1 TAU vs. TAU plus bCBTi); proportion of PTSD not mentioned	80%	C-SSRS (SI), ISI (insomnia), PCL-M (PTSD)	- No significant effect of bCBTi on SI intensity - Effects were large on insomnia and depression with no effect on PTSD
Ribeiro et al. (54)*	Relationship between insomnia symptoms and SI/SB after controlling for depressive symptom severity, hopelessness, PTSD diagnosis, anxiety symptoms, drug and alcohol abuse	Military personnel ($n = 311$), with PTSD: about 20%	82%	MSSI (SI), insomnia symptom index (sleeplessness), diagnosis (PTSD)	- Insomnia symptoms were cross-sectionally associated with SI - Insomnia symptoms were unique predictors of SA longitudinally after controlling for baseline self-insomnia resp. depressive symptoms and hopelessness

(Continued)

TABLE 1 | Continued

References	Core issue	Sample	Sex (male)	Measurements	Main findings
Ribeiro et al. (67)	Association between PTSD status and functional impairment (sleep quality, alcohol use, social problem-solving, work and social adjustment) among suicidal military inpatients	Suicidal military psychiatric inpatients and a lifetime history of at least one SA ($n = 166$), with PTSD: 38%	65%	C-SSRS (SI/SB), PSQI (sleep quality), MINI (PTSD)	- Patients with PTSD reported disturbed sleep and reduced social and work adjustment, association was no longer significant after adjusting for gender and psychiatric comorbidity - Those with a greater number of psychiatric comorbidities demonstrated higher likelihood of meeting PTSD criteria
Richardson et al. (68)	The relationship between insomnia, SI, and past-year mental health status	Canadian Regular Forces personnel ($n = 6,700$), with PTSD: 5.3%	86.1%	Single item (past-year SI/insomnia), WHO-CIDI (PTSD)	- Both insomnia and number of mental health conditions incrementally increased the risk of SI - Insomnia significantly increased the odds of SI, but only among individuals with no or one mental health condition
Selaman et al. (69)	To determine specific DSM-IV symptoms of PTSD that are independently associated with SA	Data from wave 2 of the NESARC ($n = 34,653$), with PTSD: $n = 2,322$	27.9%	Single item (nightmares/sleep disturbances/SA), DSM-IV-criteria (PTSD)	- Increasing numbers of re-experiencing and avoidance symptoms were correlated with SA - No association between SA and sleep disturbances (A)OR about 0,6
Swinkels et al. (55)	Association of sleep duration and sleep quality with mental health and SI	U.S. Afghanistan/Iraq era veterans ($n = 1,640$), with PTSD: 31%	80%	BSSI (SI), PSQI-A (sleep quality/duration), SCIDI/P (PTSD)	- Very SSD ($\leq$ 5 h of sleep) and LSD ($\geq$ 9 h) were each (after adjusting for diverse covariates) associated with increased odds of current PTSD, MDD, and smoking - Poor sleep quality was associated with PTSD, PD, MDD, SI, and risky drinking
Wang et al. (70)*	Association of pre-deployment insomnia with post-deployment PTSD and SI	U. S. Army soldiers ($n = 8,558$, cross-sectional, $n = 4,645$, longitudinal), with PTSD 11.9%	94.7%	C-SSRS (suicidality), items of the Brief Insomnia Questionnaire (insomnia), PCL (PTSD)	Pre-deployment insomnia was associated with increased risk of post-deployment PTSD and SI even after adjusting for socio-demographic characteristics and prior deployment history

**Denotes studies with longitudinal designs; all others are cross-sectional studies.*
Cursive references denotes studies on civilian samples.

even after adjusting for sociodemographic characteristics and prior deployment history (70). This is in line with prior findings. Sleep disturbance is not only a symptom of PTSD, but when existing prior to trauma they may also be a risk factor for developing PTSD in civilians (74) and in military personnel (75–77).

Consistent with these findings, an analysis of a large suicide attempt database from the U.S. Department of Veterans Affairs also revealed an independent association between insomnia and suicide attempts even after controlling for several socio-demographic factors and diverse psychiatric disorders. Furthermore, sleep medicine visits 180 days prior to the index date were associated with a decreased likelihood of suicide attempt for individuals with sleep disorders. Thus, the assessment and treatment of sleep disorders should be considered in context of strategies to augment suicide prevention efforts (56).

A proof-of-concept randomized clinical trial investigated the effects of a brief cognitive behavioral therapy for insomnia in primary care patients with suicidal ideation and insomnia in addition to either major depressive disorder and/or PTSD. The effect size of brief cognitive behavioral therapy for insomnia on suicidal ideation intensity was not significant. Effects were large on insomnia and depression with no effect on PTSD (66).

A birth cohort study in young Australians (the only study with non-veterans in this context) showed that PTSD symptoms indirectly predicted suicidal ideation via comorbid sleep disturbances even when adjusting for major depression symptoms, poly-victimization and gender. Notably, poly-victimization predicted sleep disturbances and suicidal ideation independently of PTSD or major depression (46).

Nightmares

The studies focusing on nightmares are listed in **Table 2**. Two studies focused on the association between suicidality and nightmares in the context of PTSD. In the first study, the authors reported that trauma-related nightmares were highly

TABLE 2 | Studies referring to PTSD, suicidality, and nightmares.

References	Core issue	Sample	Sex (male)	Measurements	Main findings
Bishop et al. (56)	Association among sleep disorders and SA after controlling for several mental disorders, medical comorbidity, and obesity	Veterans (data base review) ($n = 60,102$, 1:1 case control with no SA), with PTSD: 24.7%	87.1%	Data extraction for SA, sleep disturbance, mental disorders	- Nightmares were after controlling for psychiatric disorders no longer associated with SA - Sleep medicine visits were associated with a reduced risk of SA in sleep disordered patients
Don Richardson et al. (52)	Association between SI and sleep after controlling for probable PTSD, MDD, GAD, AUD	Veterans ($n = 324$)/Active duty military ($n = 80$), with PTSD: 72.8%	92.4%	Single item PHQ-9 (SI), quantitative single item (sleep disturbances resp. nightmares), PCL-M (PTSD)	- Nightmares did not predict SI - Probable MDD emerged as the most significant predictor
Don Richardson et al. (59)	Mediating role of depression in the relationship between: (1) sleep disturbances and SI, and (2) trauma-related nightmares and SI after controlling for PTSD-, anxiety-symptom-, and alcohol-use-severity	CAF personnel (17.6%)/ veterans (82.4%) ($n = 663$), with PTSD: 72.6%	91%	Single item PHQ-9 (SI), - quantitative single item (sleep disturbances resp. nightmares), PCL-M (PTSD)	Trauma-related nightmares were associated with SI as a function of depressive symptoms
Littlewood et al. (71)	Mechanism of the relationship between nightmares and SB in consideration of perceptions of defeat, entrapment, and hopelessness	Trauma-exposed patients ($n = 91$) with PTSD-symptoms, with confirmed PTSD: $n = 51$, history of PTSD diagnosis: $n = 36$	26%	SBQ-R (suicidality), in each cases 2 items of CAPS (nightmares/insomnia), CAPS (PTSD)	- SB were higher in participants who experienced nightmares - Nightmares were directly or indirectly associated with SB, through perceptions of defeat, entrapment, and hopelessness, independent of comorbid insomnia and depression.
*McCall et al. (72)**	Examining whether treatment of nightmares with prazosin (nighttime-only) would reduce SI in suicidal PTSD patients	20 adult, suicidal PTSD patients with nightmares in a RCT over 8 weeks; $n = 2$ were militarian	15%	SSI (SI), DDSNSI (nightmares), ISI (insomnia), CAPS (PTSD)	- All psychometric measures improved over 8 weeks - Nighttime measures of nightmares and insomnia showed less improvement in the prazosin group - No significant changes in daytime measures of SI and daytime-only PTSD symptoms
Raskind et al. (73)*	RCT of Prazosin for PTSD for 26 weeks with three primary outcome measures	Veterans with chronic PTSD and frequent nightmares ($n = 304$, 1:1 Placebo/Prazosin)	97.7%	Adverse event (SI), CAPS (nightmares), PSQI (sleep quality), PCL-M (PTSD),	- Prazosin did not improve distressing dreams or sleep quality - Adverse event of new or worsening SI occurred in 8% of participants with prazosin vs. 15% with placebo
Selaman et al. (69)	To determine specific DSM-IV symptoms of PTSD that are independently associated with SA	Data from wave 2 of the NESARC ($n = 34,653$), with PTSD: $n = 2,322$	27.9%	Single item (nightmares/sleep disturbances/SA), DSM-IV criteria (PTSD)	Association between nightmares and SA, this effect disappeared after adjusting for covariables

**Denotes studies with longitudinal designs; all others are cross-sectional studies.*
Cursive references denotes studies on civilian samples.

prevalent (67.9%) but not associated with suicidal ideations. However, in a regression model, the presence of probable PTSD was significantly associated with suicidal ideations, indicating a mediating role of PTSD in the association between nightmares and suicidal ideations. Probable major depressive disorder emerged as the strongest predictor of suicidal ideation (52). These results were confirmed in a subsequent study by the same authors (59). Recently, corresponding results regarding the association between suicide attempts and nightmares were reported in a sample with veterans. After controlling for psychiatric disorders, nightmares were no longer significant associated with suicidal attempts (56).

In contrast to these findings, in a sample of trauma-exposed civilians with PTSD symptoms, nightmares were both directly and indirectly associated with suicidal behavior, through perceptions of defeat, entrapment, and hopelessness, independent of comorbid insomnia and depression (71). Further analyses supported that the relationship between nightmares and suicidal behavior was partially mediated by a multistep pathway via defeat, entrapment, and hopelessness (71).

Prazosin, an α1-adrenergic receptor antagonist, has been effective in alleviating nightmares associated with PTSD in military veterans (78, 79). However, in a randomized clinical trial of prazosin in suicidal PTSD patients there was no

TABLE 3 | Studies referring to PTSD, suicidality, and sleep-related breathing disorders.

Reference	Core issue	Sample	Sex (male)	Measurements	Main findings
Gupta and Jarosz (80)	Diagnosing OSAS by sleep study and SI in patients with PTSD	Civilians with PTSD ($n = 40$)	5%	4 items of the BSI (SI), PSQI PTSD addendum modified (nightmares) PCL-5 (PTSD)	- OSAS severity was directly related to SI - Depression was a significant mediator in the relationship between RDI and SI
Krakow et al. (43)	Prevalence of sleep disorders and the influence on suicidality, and depression severity	Female sexual assault survivors enrolled in a nightmare-treatment program ($n = 153$), with PTSD: 94%	0%	Wisconsin Cohort Sleep Survey (sleep disorders), Nightmare Frequency Questionnaire (nightmares), PSQI (sleep quality), PSS (PTSD)	- Prevalence of sleep breathing disorder: 15% - Prevalence of sleep movement disorder: 29,4% - Association of potential sleep disorders with greater depression and greater suicidality - Prevalence of combination of both disorders: 35,9%; this group suffered from most severe depression and suicidality

Cursive references denotes studies on civilian samples.

significant improvement of suicidal ideation or day time-only PTSD symptoms. In addition, nightmares and insomnia showed significantly less improvement in the prazosin group (72). These findings are in line with a recent multi-center randomized trial on the effect of prazosin in veterans with chronic PTSD, which revealed no effects of prazosin on nightmares or sleep quality (73). Of note, fewer patients in the prazosin group reported suicidal ideation compared with the placebo group.

Sleep-Related Breathing Disorders

The studies focused on sleep-related breathing disorders are listed in **Table 3**. A sample of female sexual assault survivors with PTSD was assessed for subjectively determined sleep related breathing and movement disorders and 80% of the participants presented with such disorders (43). Participants with potential sleep disorders suffered from a higher degree of depression and suicidality in comparison to those without any potential sleep disorder. It was hypothesized that this effect could be mediated through chronic sleep fragmentation. The study was limited insofar as the participants were recruited through a nightmare-treatment program. Nightmares are estimated as a marker for other sleep disorders, therefore nightmares could increase the total prevalence of sleep disorders (43). In a study performed to elucidate the association between suicidal ideations and OSAS, it was found that OSAS severity was directly related to suicidal ideation in (predominately female) PTSD patients who underwent a home sleep apnea monitoring. Depression was a significant mediator in the relationship between respiratory disturbance index and suicidal ideation (80).

Sleep Duration

Sleep duration itself is purported to have an effect on suicidality (5, 6, 81). In redeployed soldiers, after controlling for combat exposure, short sleep duration was associated with symptoms of depression, PTSD, and panic syndrome, and with high-risk health behaviors such as abuse of tobacco and alcohol products, as well as suicide attempts. Short sleep duration emerged as a significant predictor of suicide risk; conversely, short sleep was the strongest predictor of PTSD symptoms (63). Another study in veterans corroborated an association between sleep duration, very short sleep duration ($\leq$5 h of sleep) as well as long sleep duration ($\geq$9 h): after adjusting for covariates, both conditions were associated with increased odds of current PTSD and major depression, but not with suicidal ideation. However, poor sleep quality was associated with PTSD and suicidal ideation as well as with panic disorder, major depressive disorder, and risky drinking (55).

Circadian Aspects

We identified one study in civilian patients with PTSD investigating the effect of alterations in rhythmicity and vegetative function including sleep disturbances as correlates of suicidality. As a result, all lifetime mood spectrum sub-domains (rhythmicity, sleep, appetite/weight, sexual function, physical symptoms) were associated with an increased likelihood of suicidal ideation. Interestingly, another study reported that an eveningness chronotype in PTSD was associated with an increased likelihood of suicidal ideations, but not suicide attempts (47).

MEDIATING FACTORS

Various mediating factors may have an influence on the association between sleep disturbances, suicidality, and PTSD symptoms.

Depression

A study on deployed soldiers with mild trauma brain injury showed a significant association between increased suicidality and depression as well as the interaction of depression with PTSD symptoms. Interestingly, longer duration of loss of consciousness was associated with decreased likelihood for any suicidality (50). Another study found an association between sleep disturbances with concurrent and prospective suicide ideation in three active military samples. When adjusting for age, gender, depression, and PTSD, insomnia severity was no longer directly associated with suicidal ideation either concurrently or prospectively, whereby depression mediated the relation of insomnia severity with suicide risk (58). One study examined the association of suicidal ideation and sleep disturbances after controlling

for probable PTSD, depression, alcohol use disorder (AUD) and generalized anxiety disorder. Neither sleep disturbances nor nightmares significantly predicted suicidal ideation; instead, major depression emerged as the most significant predictor (52). Depression also mediated the relationship between insomnia and nightmares and suicidal ideations (59). Another study investigated the associations among insomnia symptoms, PTSD, and depressive symptoms, interpersonal theory of suicide variables, and risk for suicidal behavior in community veterans and confirmed a mediating effect of depression. In extension to this, PTSD emerged also as a mediator between insomnia and suicidal ideation. The interpersonal theory of suicide variables of thwarted belongingness and perceived burdensomeness mediated the association of depressive and PTSD symptoms with risk for suicidal behavior, indicating a sequential association (57).

Other Mediators

In military service members with PTSD, perceived stress mediated the relationship between sleep issues and suicidal ideation; however, after accounting for mental health symptoms (depression, perceived stress, PTSD symptoms) sleep no longer had a significant direct effect on suicidal ideation (65). In outpatient veterans misusing alcohol the relationship between insomnia symptoms and suicidal ideation was no longer significant after controlling for other mental disorders. However, poor sleep quality remained significantly associated with increased suicidal ideation even after controlling for other risk factors (51). Among suicidal military inpatients, those with PTSD reported more disturbed sleep and reduced social and work adjustment. Still, this association between functionality and PTSD status was no longer significant after adjusting for gender and psychiatric comorbidity as individuals. Patients with a higher number of psychiatric comorbidities demonstrated a higher likelihood of meeting PTSD criteria (67).

Beyond mental health conditions in general, some studies also investigated specific mediators, i.e., AUD (62), agitation (60), and exercise (48) in the context of PTSD, suicidality, and sleep disturbances. Given that AUD und PTSD frequently co-occur (82), evidence for a mediating role of AUD and insomnia in the relationship between PTSD symptoms and suicidal ideation derived from a large sample of Korean firefighters (62). With respect to a moderating role of agitation within the relationship between insomnia and current suicidal ideations, a study on U.S. military personnel showed significant effects only at high levels of agitation. PTSD symptoms, depressive symptoms, and lifetime number of suicide attempts were each associated with greater levels of agitation, insomnia, and current suicidal ideation (60).

PTSD SYMPTOM CLUSTERS AND SUICIDALITY

A burgeoning approach to determine suicide risk in the context of PTSD is the analysis of specific PTSD symptom clusters (69, 83–90) yielding conflicting results. Considering sleep disturbances and nightmares as diagnostic criteria for PTSD, a within-cluster item analysis would be necessary. So far, only one study meets this requirement: reporting that an increased number of re-experiencing and avoidance symptoms significantly correlated with suicide attempts. In addition, a significant association between nightmares and suicide attempts was found; however, this effect was no longer present after controlling for covariates (69). In this study, sleep disturbances (85.0%) and nightmares (77.8%) were highly prevalent, but were evaluated by using a single, dichotomous question only, indicating a possible lack of selectivity. To date, only three studies examined the relationship between PTSD symptom clusters and suicidality in a prospective design (88, 90, 91), with two of them pointing at a unique relationship between alterations in arousal and reactivity and higher suicidality (90, 91). Unfortunately, sleep disturbance as a feature of the cluster "alterations in arousal and reactivity" was not separately considered in these studies. Thus, it is not possible to state, whether sleep disturbances had a significant influence on these results.

A more tailored approach on individual PTSD symptoms a priori has been provided by the use of a more detailed method for the assessment, monitoring, and treatment of PTSD symptoms (61). This study of predominantly trauma-exposed military veterans investigated the association between individual symptoms of PTSD and measures of functioning, quality of life, and suicidal ideation. Among others, sleep difficulties explained problems in physical functioning and quality of life. These findings persisted after adjustment for lifetime trauma burden and severity of PTSD and depressive symptoms. No association was found between suicidal ideations and sleep difficulties (61). However, it should be emphasized that only about 10% of the sample met full PTSD criteria.

DISCUSSION

The present studies revealed heterogeneous and partially contradictory results. A direct association between sleep disturbances and suicidal behavior in patients with PTSD has been reported by a few studies (49, 51, 53, 54, 70),while others found no association after controlling for covariates such as depression (50, 52, 57–59). In a sample of veterans with PTSD and two or more comorbid disorders there was a higher risk of suicidal ideation compared to veterans with PTSD only (92).

The study results should be interpreted with caution because differences in approach and samples, as well as different applied measurements and outcome parameters, hinder direct comparisons. In particular, due to the studies available, various types of sleep disturbances, measured by using different methodologies, were included. Some studies focused on specific sleep disorders such as insomnia, nightmares or sleep related breathing disorders (57, 80, 93) while others measured only sleep quality or sleep duration in a more general approach (43, 48) or used a single sleep item only (59, 69) limiting the comparability. In addition, almost all studies used self-report instruments to assess sleep variables. However, subjective and objective measurements of sleep may differ also in PTSD patients and do not necessarily co-vary (94, 95). The use of sleep diaries could be a more reliable measurement in order to assess

prospectively sleep disorders compared to a selective survey (96). The vast majority of studies used a cross-sectional design, a major limitation for drawing causal conclusions. With respect to suicidality, it can be stated that the outcome parameters vary between suicidal ideation (60), suicidal behavior (57), suicide attempts (56), death by suicide (53), and through combinations of those (51). Thus, "suicidality" does not always carry the same meaning and precludes comparability.

Of importance, an explicit PTSD diagnosis was a primary inclusion criterion only in five studies (27, 47, 48, 72, 73), whereas in all other studies a "possible" PTSD diagnosis was recorded and considered in data analysis with prevalence rates between 3.6% (62) and 94% (43). Therefore, the absolute number of subjects with PTSD was considerably lower than the absolute number of study participants, mitigating the statistical validity. In military samples, the vast majority of participants were men with a proportion of at least 69.6% (57) up to 99.7% (53). In civilian samples, women were overrepresented by trend with a proportion of at least 49.2% (47) up to 100% (43). This remarkable disproportion in gender ratios should be taken into account in light of gender differences in suicidal behavior among persons with PTSD. For example, among veterans with PTSD, women have a lower risk of dying by suicide compared with men (97).

In addition, most studies have included military personnel and veterans. A large cohort study, for example, revealed an association between type and number of traumata with suicidal ideation and suicide attempts in patients with PTSD (98). Among others, peacekeeping traumata had the highest rates of suicidal ideation and suicidal behavior. In the civilian population, however, a broader spectrum of trauma types may occur. Moreover, it remains questionable whether results obtained from veterans can be transferred to the civilian population. Evaluating the risk of death by suicide in military personnel, some specific aspects have to be noted; historically, soldiers have had a markedly lower suicide rate than civilians (99, 100). However, since 2005 the incidence of suicide in Army and Marine personnel has nearly doubled and remained elevated (101, 102). Several studies showed an increased risk of people with PTSD dying by suicide (103–106), while others revealed a decreased risk of death by suicide in military personnel (107–110). The background of these confusing results is discussed in detail in a recently published review (111).

The current overview has some limitations. Most importantly, it does not meet the requirements of a systematic review because we did not perform a systematic literature research. In addition, we had no strict inclusion/exclusion criteria to identify relevant studies. In many studies, the relationship between sleep disturbances, suicidality, and PTSD was a minor issue and evaded a literature search using Medical Subject Headings terms. Therefore, the overview may not cover all studies in the field. Nevertheless, diagnosing and treating sleep disturbances early in the context of trauma exposition may provide preventive strategies regarding the development of PTSD. For example, non-drug interventions such as cognitive behavioral therapy for insomnia has been shown to reduce sleep disturbances and, subsequently, PTSD symptoms (112). It remains to be clarified whether or not suicidal behavior in PTSD can also be improved by treating impaired sleep.

CONCLUSION

Heterogeneous study approaches, different samples and applied measurements, and diverse outcome parameters hinder a direct comparison of studies examining sleep disturbances, suicidality, and PTSD. In addition, due to limited study methodologies, a causal relationship in these entities cannot be shown. Future research including adequately designed studies is necessary to clarify the complex relationship between these parameters. Particularly, more studies in the civilian population are needed also to tackle the value of treatment of sleep disturbances for suicide prevention in PTSD.

AUTHOR CONTRIBUTIONS

FW and TW have made substantial contributions to conception and design of the study and analyzed the data. FW executed the acquisition of data. FW, CN, and TW have been involved in the interpretation of data, drafting and revising the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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PERSPECTIVE
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Function and Psychotherapy of Chronic Suicidality in Borderline Personality Disorder: Using the Reinforcement Model of Suicidality

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Although great advancements in evidence-based therapies, chronic suicidal patients with borderline personality disorder (BPD) still challenge our mental health system. While BPD patients continue suffering from distress and aversive emotions, therapists and relatives feel often stunned and helpless when confronted with suicidality resulting in interruption of therapies, repeated presentations to emergency rooms and referrals to hospitals. Reviewing the current knowledge of the functions and background of non-suicidal self-injury, we learned that reinforcement mechanisms play an important role to understand why individuals act in deliberate self-mutilation. While individual motives for non-suicidal self-injury and suicidal behavior including suicidal ideations can differ, the principle mechanisms appear to be transferrable. Elucidating the individual motives and function of suicidal behavior is an important therapeutic step, giving us access to very central maladaptive schemes and false believes that we need to address in order to reduce chronic suicidality in BPD patients. This Perspective article aims to give a better idea of what is behind and what are the differences between non-suicidal self-injury, suicidal ideations and suicide attempts. It further integrates recent developments of behavioral science in a reinforcement model of suicidality that can provide therapists a practical armamentarium in their work with chronic suicidal clients.

Keywords: suicidality, borderline personality disorder, psychotherapy, reinforcement, behavioral analysis, suicide attempt, non-suicidal self-injury, DBT

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INTRODUCTION

Suicidality is one of the most alerting and urgent symptomatology in mental health. It summarizes a subset of psychopathological phenomena ranging from suicidal ideations (including thinking about, considering and planning suicide) to ambivalent suicide attempt, suicide attempt and suicide (1, 2). Across psychiatric disorders, risk factors for suicidal behavior such as childhood maltreatment, non-suicidal self-injury (NSSI), and previous suicide attempts have been identified (3, 4). Nevertheless, for various reasons [discussed in (5, 6)] the assessment of these factors (derived mostly from cross-

Abbreviations: ACT, acceptance commitment therapy; DBT, dialectical behavioral therapy; HPA, hypothalamic-pituitary-adrenal axis; NSSI, non-suicidal self-injury.

sectional studies) does not sufficiently help predicting suicide risk in a patient at a given time (7). Further, suicide rates even increased in some populations such as adolescent girls during last years (5, 8). On the other hand, mental health care providers often refuse treating suicidal individuals or refer clients that become suicidal, with few evidence that treatment termination, referrals, or even involuntary hospitalization are effective in reducing suicide risk (6). Although we know, that the majority of suicide ideators will never act on their thoughts (9), in clinical practice, we do not have useful indicators (like fearlessness about death, subjective pain tolerance, and objective pain persistence) that help us to differentiate between suicide ideators and attempters (10). Further, NSSI often co-occurs in individuals with suicidal behavior, and although it is by definition not intended to be suicidal, clinical differentiation and appropriate managing can be demanding (3, 11). We further do not have good evidence for any pharmacological approach that addresses suicidality in these individuals (12). Consistently, patients with borderline personality disorder (BPD) that are among the individuals with the highest rates of chronic suicidal ideations (SI), NSSI and repeated suicide attempts, experience both, highly frequent hospitalizations and termination of treatment as a result of their high suicidality (13, 14).

Hence, what is behind chronic suicidality? What are the psychological mechanisms that maintain its chronicity? Can we apply concepts that helped us understanding and treating NSSI also for suicidal behavior? Can or should we do therapy in suicidal patients at all? And if yes, what are useful interventions?

Suicidality and Non-Suicidal Self-Injury in Borderline Personality Disorder

NSSI (e.g., cutting, scratching, head banging, skin burning) is a world-wide phenomenon that occurs not only in BPD (15). Thanks to many studies and more precise definitions (i.e., "not intended to die"; discussed in [16, 17)], we acquired a much better understanding of the motives and background of NSSI during last years, even leading to a distinguished diagnostic entity in Diagnostic and Statistical Manual of Mental Disorders, 5th edition (18). As highlighted in the recent meta-analysis of Taylor et al. (19), we learned that NSSI can have a wide range of underlying functions within an individual (**Table 1**). We can distinguish intrapersonal functions like emotional regulation and self-punishment (escape/avoidance of internal states) from less prevalent interpersonal functions like interpersonal influence and peer bonding (3, 11, 19). Similarly, the different psychic functions of NSSI have been modeled by Nock & Prinstein (22) comparing positive (i.e., involves the addition of a favorable stimulus) versus negative (i.e., involves the removal of an aversive stimulus), and automatic (i.e., intrapersonal; e.g., emotion regulation) versus social (i.e., interpersonal; e.g., attention, avoidance-escape) reinforcing factors.

These observations correlate nicely with recent neurobiological findings of NSSI, so that we can now retrace why patients repeatedly harm themselves - accepting necessity of surgical intervention, subsequent conflicts with their relatives, and even stigmatizing scars on their skin. In particular, NSSI reduces the activity of the amygdala while functional connectivity to the superior frontal gyrus is normalized in resting-state functional magnetic resonance imaging (23). Clinically, aversive tension decreases immediately after NSSI, and patients can think clearer again. It is further assumed that NSSI activates the reward system including the endogenous opioid system, presumably also the endocannabinoid system (24). In a prospective clinical study of frequently self-injuring BPD patients using continuous palmtop assessment of emotional states, Houben et al. (25) have impressively demonstrated the strong contingency between the occurrence of an aversive emotional state and subsequent NSSI. He further showed that beside the negative reinforcement of NSSI to relief emotional pain, NSSI reliably predicts the next aversive emotion (e.g., shame because having self-injured again/failed resolving the stressful situation), and subsequently the next and even further next NSSI during aversive emotional states, entering a vicious circle of repeated NSSI up to several times daily (25).

Clinically, we can use this background knowledge in therapy. For example, behavioral analysis like the stimulus-organismic-

TABLE 1 | Function of non-suicidal self-injury and suicide attempts.

Non-suicidal self-injury (3, 11, 19, 20)	Suicide attempt (20, 21)
Negative affect regulation, emotional regulation (most commonly reported [63–78% in (19)])	Emotional relief, relief of psychological pain [indicated from most patients in (20)]
Self-punishment	Interpersonal influence (may be less than at NSSI)
Anti-dissociation (e.g., causing pain to stop feeling numb)	To make others better off (much more than at NSSI)
Interpersonal influence (e.g., communicate distress; influence others behavior, actively hurt/punish others; less common [(33–56%) in (19)]	Sense of control
Anti-suicide (e.g., stopping suicidal thoughts)	
Sensation-seeking, distraction (e.g., doing something to generate excitement)	
Interpersonal boundaries (e.g., fitting in with others)	

Note that data derive from various means of assessment and item definitions across studies, ranging from structured and validated questionnaires to clinical interviews and case descriptions. For this reason, items that are likely to be related appear in one line. Data are compiled according to Brown et al., 2002, Klonsky (2007), Klonsky et al. (2013), the recent meta-analysis of Taylor et al. (2018), and Tullis (1998) (3, 11, 19–21).

response-contingencies (SORKC or SORC) model of reinforcement-consequence (26) can illustrate to the patient in terms of psychoeducation that NSSI is a negative reinforcer (reduction of aversive tension) increasing the probability of NSSI in the next stressful situation. Most simply like in Dialectic Behavioral Therapy (DBT), the therapist can explain why it is necessary to stop NSSI and develop alternative means ("skills") to reduce aversive tension in order interrupt the reward contingency received by NSSI (14).

Can Suicidality in Borderline Be Conceptualized Similar to Non-Suicidal Self-Injury?

Brown, Comtois, and Linehan (20) were among the first investigating the background of NSSI in comparison to suicide attempts (SA). They found that in both cases, emotional regulation was a predominant function. In a between-person analysis, NSSI was more intended to generate feeling, self-punish, express anger and even distract, while SA was significantly more often intended to make others better off. Interestingly, self-punishment significantly differed between suicide attempters and non-suicidal self-injurers in the between-persons comparison, but not in the within-person comparison. The authors hypothesize that people who engage in non-suicidal acts intend to self-punish with both suicidal and non-suicidal parasuicide. Similarities and differences between NSSI and SA are depicted in **Table 1**.

Nevertheless, suicide attempts are just one symptom of suicidality and patients not conducting SA may still have frequent suicidal ideations or occupy with death and suicide in the internet and exchange suicide methods in social media (27). Indeed, SA typically occur in a circumscribed (early) phase during the course of BPD (28), whereas suicide ideations tend to persist over years (29). Fatally, it also turned out that highest suicide rates occur later in the course of the illness and follow long courses of unsuccessful treatment (30), meaning that patients are not at their highest risk of suicide when they are young and frequent visitors to the emergency room (29). Thus, working in therapy with chronic suicidality (beyond management of NSSI and SA) appears to be mandatory in order to prevent later suicides. At this point, the question rises whether we can simply adapt the reinforcement model described for NSSI to chronic suicidality? Can we assume similar contingency consequences for the appearance of suicide ideations in aversive emotional states? In other words:

Can Thoughts Be Modeled Like Behavior in Psychotherapy?

When we work with behavioral analysis in psychotherapy, we usually focus on (mostly) dysfunctional behavior, i.e., things that we have done, that have some kind of positive or negative consequences. As seen above, these consequences can reinforce me to act similarly the next time: Cutting in a stressful situation, e.g., will immediately reduce aversive tension (negative reinforcement) and may even give me the feeling of control over my emotions (positive reinforcement). But, is being absorbed to suicidal ideations really that different if these suicidal thoughts give me a kind of perspective, relief or just the idea that the current aversive situation will end? Chiles & Strosahl report that adolescents that experience intense emotional pain in response to internal (e.g., thinking of disabilities) or external stimuli can feel a kind of relief from the emotional distress when thinking about suicide (31). Similar to various behavioral patterns assigned to Hayes's so-called Experiential Avoidance (32), like NSSI, eating disorder or substance abuse that function to escape, avoid or modify an experience, suicidality can be regarded as a way to suppress emotions with suicide being the ultimate attempt at controlling psychological pain (33, 34). It was further Hayes (35), who integrated the obvious conceptual gap of internal processes (cognition) and behavior in his Relational Frame Theory (35) and, therapeutically, in the Acceptance and Commitment Therapy (ACT) (32). Assuming, according to the ACT theory, that human behaviors are functional, suicidality including thinking of suicide can be regarded as "a learned method of problem solving that involves escaping from or avoiding intense negative emotions" (31). Hayes states, that compared to classical reinforcement models (e.g., avoidance of closed rooms in agoraphobia, or relief from obsessional thoughts (e.g., contamination) by acting out compulsions (e.g., excessive hand washing), the relief in these situations is not directly conditioned (i.e., persons have not experienced that death releases emotional pain). Instead, individuals may have constructed "if … then" verbal associations [like "If I die, the bullying by my peers will stop" (36)]. This "verbal behavior", enters a long-term conditioning processes, and may have aversive (negative) or appetitive (positive) consequences [see Murrell et al. for overview (33)]. Thus, applying this model to chronic suicidality in BPD, suicidal ideations (the verbal behavior) can reduce hopelessness, helplessness or unbearable anger and act as a negative reinforcer that will increase the probability of similar suicidal associations in an upcoming situation that produce similar aversive tension (**Figure 1**). The individual that experience a relief from suicidal ideations may feel an even bigger reinforcement value when he considers how, when, and where suicide would occur (31), letting him researching suicide methods in the internet, discuss suicide in online platforms, or even, when he prepares a suicide by collecting pills, looking for an appropriate place for hanging or a bridge to jump. The individual who ideates suicide, "from this perspective, experiences the ultimate reinforcement—a way to permanently and completely control difficult emotional experiences" (31).

Contagious Suicidality?

It is frequently observed (for example in acute psychiatric settings) that BPD patients adopt dysfunctional behavior from other BPD patients (e.g., cutting although not having cutting before) indicating that the behavior must have a quite strong (at least short-term) positive consequence (they find out what helps best or they feel connected to peers that understand their need) (37, 38). One can speculate that exchange of suicide topics in online platforms is a similar phenomenon where patients try out different suicidal associations while discussing among each other. Not only can a suicidal association in Hayes's sense act as a

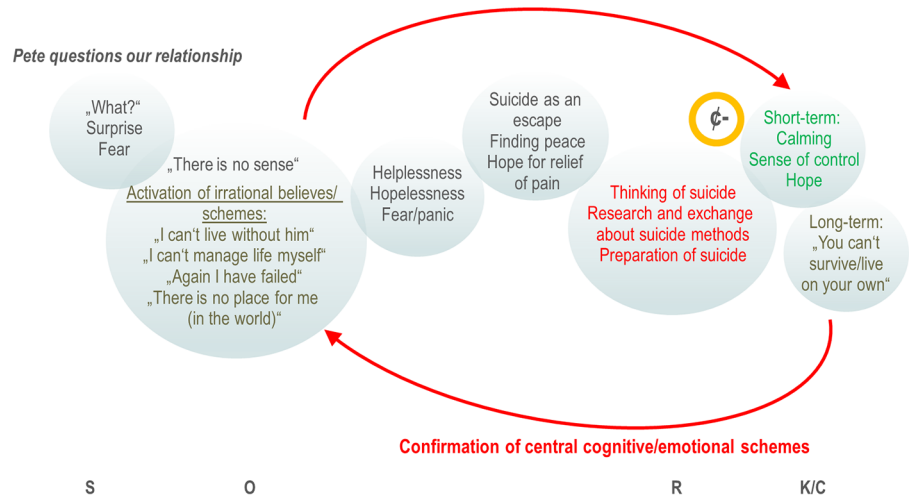

FIGURE 1 | Chain analysis and stimulus-organismic-response-contingencies (SORKC) model of suicidal symptoms: A behavioral (chain) analysis of suicidal symptoms (e.g., suicidal ideation, internet research, preparation of suicide) that occur after the boyfriend of Jess questioned their relationship (cue, S). Jess instantly is surprised and fears losing Pete (primary emotions directly related to the situation; grief would be likely also). The first emotions disappear rapidly while Jess's maladaptive cognitive schemes (O) get activated (her interpretation of the situation against the background of her childhood experiences). These judgements in turn activate secondary emotions (like helplessness, hopelessness, panic) causing significant distress. Of note, these transitions from primary emotions to secondary emotions can be very fast letting patients even not notice their primary emotion at all (14). Thinking of suicide, the visit of suicide chats in the internet and suicidal communication with peers (R) calms Jess down and gives her a kind of feeling of control and hope ("I could escape," "There is a way out," "I must not suffer"). This contingency between psychological pain and relief (K/C) acts as a strong negative reinforcer (¢-) that increases the likelihood of suicidal ideations in the next situation of distress. On the other hand, long-term (i.e., after the immediate relief of pain) emotions like feeling of insufficiency, shame or loneliness occur ("I can't live alone," "I am incapable in relationships," "Anybody likes me," "I am alone in the world") that support in turn the assumptions/maladaptive schemes. The vicious cycle of reinforcement of suicidality and repeated confirmation of central cognitive/emotional schemes results in long-lasting, recurrent, chronic suicidality.

negative reinforcer as described above (e.g., relief of pain), the exchange itself may become a kind of addictive behavior. In his theory of suicide addiction, Tullis (21) nicely describes these observations in his patients: Contemplating suicide can be pleasurable in some people, or, at least can be a break from psychological pain. Suicidal thoughts or behavior can be a form of self-medication in these individuals and reliving previous suicide attempts in thought or imaging death can become a ritual (or even trance-like) behavior providing a sense of control and an optional way out of pain. In his patients, Tullis further observed a calming sensation during suicidal thinking (up to a "rush," "high," "thrill," "exhilaration"), they developed a tolerance to the effects of suicidal thoughts over time and engaged in compulsive rituals and behaviors, including secretly collecting and hoarding paraphernalia for suicide, characteristics we observe similarly in addictive disorders. Hence, these behavioral observations support the hypothesis that in some individuals, occupation with suicide is pleasurable, reduces pain and becomes "a way of life" (39) - psychologically spoken, are object to reinforcement and contingency loops.

Judgments and Beliefs Are the Toxic Ingredients of the Reinforcement Model of Suicidality

When we look out for a new approach addressing suicidality in BPD, then working with the background and motives becomes vital in the proper sense. In the language of behavioral analysis, it is the organism variable that determines how we rate and react upon upcoming stimuli (40, 41). Besides biological factors, the organism variable is largely influenced by experiences we made, messages we became when we were a child or parent models we had (42). Similar to our clinical example in **Figure 1**, suicidal adolescents and BPD frequently share believes of being worthless, inadequate, rejected or blameworthy resulting from invalidation or traumatization (33, 42). Typical examples in these cases are: "I can't live alone," "I am false," "I don't have a place in the world," "I am bad," "I can't handle it." They are robust convictions of themselves and the outside world or automatic thoughts (43) that become activated (in their conscious mind) through internal or external cues (e.g., when they are or feel offended, disappointed, rejected, lonely,…). As shown recently, dependent of the severity of BPD, aversive emotional states can then highly contingently linked to a specific dysfunctional behavior (e.g., intense anger after being offended, or NSSI after being disappointed) (44).

Using behavioral analysis, the therapist may elucidate reinforcing contingencies within the vicious chain of cues, activated faulty believes and subsequent suicidal ideations. He further can look for more adaptive behavioral alternatives or identify possible obstacles that inhibit the application of functional behavior. Typical obstacles can be, e.g., intensive emotions of fear, shame or guilt, or faulty believes and assumptions (e.g., "I am a looser," "I have no right") (14). The

latter is probably the most important aspect that helps understanding the background and function of suicidality in these patients.

Similar to the reinforcer model of NSSI described above, we can speculate that the confirmation of central schemes together with the reinforcement of suicidal ideations stabilizes the dysfunctional system of chronic suicidality. Conversely, in NSSI on the other hand, the rapid dynamic of the next aversive emotional states directly after NSSI exemplified in the Houben study (25) acts as a punishment in the behavioral sense, resulting presumably in an earlier fade out of self-injuring behavior after some time (as frequently observed in the courses of BPD), while chronic suicidality persists.

Interventions Deduced From the Reinforcement Model of Suicidality

Addressing the motives and psychic function behind suicidal behavior depending on specific situations (or triggers) may be a first, but potentially very powerful step in the therapeutic work with suicidal BPD patients. They may feel a substantial validation by going through their individual behavioral analysis and by understanding their own reinforcement mechanisms (**Figure 1**). As described by Murrell (33), normalization of suicidal ideations or behavior with respect to the individual's situation ("If I were in this situation, I would think/feel similar.") and in comparison to others ("Many people at your age have had serious thoughts about killing themselves – it isn't that uncommon or weird.") can reduce shame (about not getting along with the challenges of life, e.g.) and helps establishing acceptability of discussing suicide in an honest and genuine way. Working with faulty believes and assumptions may be one of the most challenging, but on the long run, inevitable approaches in psychotherapy of chronic suicidality. Cognitive techniques as well as emotional exposure in order to reach a cognitive and emotional reappraisal may be applied here (14, 42). As proposed in ACT, so-called defusion techniques (i.e., distancing and disconnecting techniques from thoughts and feelings) can be a highly relevant addressing negative judgements and believes, too (33). Given the high prevalence of traumatization and substantial invalidation experiences in chronic suicidal individuals, exposure-based trauma therapy has an important impact on suicidal symptoms and, according to recent developments in DBT for posttraumatic stress disorder can (and most likely should) start as soon as possible (45, 46). Within this confrontation, time for the grieving process and finally acceptance of what has happened in the past is inevitable. For this process, ACT and the compassion-focused therapy provide useful assistance (32, 47). In parallel, it becomes important to establish alternative non-suicidal behavior that at least at the beginning is reinforced with help from the therapist. On the long run, the goal is to establish a naturally reinforcing system, e.g., by using values of the patient: building up and connection to a circle of friends, feeling of conjointness by taking responsibility and social integration (i.e., volunteering, taking care of a pet,…). According to Hayes, also "verbal behavior" can enter such long-term conditioning processes, like "If I live, my parents might get to see me graduate from college someday," or "If I kill myself, it would really hurt my family to go to my funeral" [taken from (33)]. Without claiming completeness, the **Supplemental Table** gives an overview of possible interventions that can be derived from the behavioral analysis of reinforcement (**Supplemental Table 1**). These interventions comprise standard behavioral techniques as described in DBT, ACT, and compassion-focused therapy, including validation techniques, psychoeducation, cognitive techniques, emotional regulation, and the development of alternative behavior and skills. The proposed approaches are mostly adapted to the clinical example depicted in **Figure 1**, but they may be transferred also to other BPD patients with chronic suicidality.

DISCUSSION

We have seen that similar to NSSI, suicidal ideations and behavior can have various motives and functions. Overall, these functions appear to have in common to significantly reduce mental pain, be it by reducing aversive tension, by giving an idea of a way out of the current situation, or by giving a sense of control of difficult emotions (like guilt, shame, intense anger). Thus, it appears plausible that reinforcement mechanism as presented here are substantially involved not only in NSSI, but also in chronic suicidality. Intriguingly, a recent functional MRI study strongly substantiates this concept from a neurobiological perspective using autobiographic transcripts to recall patients' previous suicidal episodes: In this paradigm, mental pain triggering suicidal behavior is associated with decreased prefrontal activity whereas planning and acting out suicidal impulses (in mind) in response to mental pain is associated with increased activity in the medial prefrontal cortex, the anterior cingulate cortex, and the hippocampus suggesting that goal-directed suicidal behavior is associated with a reduction of mental pain (48).

Nevertheless, there is still a big gap in the literature delineating the continuum from passive suicidal thoughts, ideations of dying or being death to suicide attempt preparation and definite suicidal acts, and the psychological function of each of these suicidal behaviors may be very different within and between individual subjects. Indeed, there is strong evidence from neurobiology, that NSSI, SI, and SA have very distinct (and sustained) effects on the regulation of the hypothalamic-pituitary-adrenal (HPA) hormonal axis, a system that is essentially important in adaptation to challenging situations in life. It has been shown, for example, that cortisol response in the combined dexamethasone suppression/corticotropin releasing hormone stimulation test is attenuated in both, past and recent suicide attempters compared to suicide ideators or non-suicidal patients in major depression (49). In another most recent study, the interaction of a HPA axis response with psychosocial stress differentially predicts suicidal behavior and ideations within 18 months, with, again, a lower cortisol response being associated with suicidal behavior (50). Interestingly in this regard, epigenetic

mechanisms have been claimed to be involved in the neurobiology of suicidality including the HPA axis regulation (51) which may possibly explain some sustained effects observed in recurrent suicide attempters. The meaning of these findings and its implementation to psychological models of suicidality definitively needs further investigation. The challenge of future research will thus be to combine sophisticated methods form both, neurobiology and psychology. In both cases, clear differentiation and definitions of suicidal symptoms is of eminent importance.

From the clinical perspective too, a thorough assessment of all degrees of suicidality becomes crucial for the therapist when estimating the individual patient's risk to proceed from ideating to acting in suicide during treatment. In particular, he wants to know, which factors pushes the patient form ideation to suicidal action. Fearlessness about death and pain tolerance occurs in several suicide models as a factor differentiating suicide ideators from attempters (3, 4, 9, 52, 53), and most robust predictors of SA identified in studies may be closely related to these items as they reflect a previous experience of loss of physical integrity (e.g., NSSI, history of previous SA, childhood maltreatment). They can indeed be helpful for the therapist estimating the patient's individual risk of progression from ideation to attempts, with connectedness being one of the most important protective factor in this respect (52). Nevertheless, the reliability of the prediction (i.e., the negative predictive value in this case) may be too low to exclude a suicide risk, and the results of recent studies have questioned the ability of such factors to robustly distinguish suicide ideators from attempters across diagnostic entities including student samples (10, 54–57). Further, what to do in psychotherapy with BPD patients that are carriers of suicide risk factors? The assessment of predictors alone does not give an answer to this question. But, without doubt, these patients in particular should be subject to a psychotherapy addressing their suicidality. There is a common understanding in third wave behavioral therapies [discussed in (42)], that new behavior or alternative experience can only be learned or made by the brain when it is done in the same or a similar situation that normally would have cued the old (dysfunctional) behavior. In other words, the patient needs to act (or think) differently in a situation he normally becomes suicidal. And, at this point, referral to a hospital would likewise not allow a new experience (but will confirm old assumptions: "I have failed again," "I can't handle it on my own," "I am punished because I behave badly," "suicide is the best option"). Instead, the therapist needs to assist him just then: In the real situation (e.g., during a crisis), or in activated states of critical emotions (of whom the therapist knows its link to the patient's suicidal behavior) in a therapy session, the therapist needs to guide the patient to regulate its emotions, reflect the situation and help applying new behavior. For this purpose, the therapist may offer telephone or online coaching, techniques of emotional regulation and stress tolerance, as well as thorough behavioral analysis of suicidal behavior and thinking. Nevertheless, this kind of work with suicidal patients is demanding and indispensably needs a secure frame also for the therapist. Apart from a common commitment of both sides ("going the new way," "finding a way to stay alive," "being ready for exposure") the use of non-suicide contracts, individual crisis plans and agreements about contingencies (what happens after NSSI, SA, therapy-interfering behavior,…) have been strongly recommended for the psychotherapy of chronic suicidality in BPD (14).

Although we have learned a lot about suicidality during last years and specific programs from different therapeutic schools including behavioral and psychodynamic approaches (58) helped many individuals, the implementation of validated anti-suicidal interventions and suicide prevention for a larger number of affected people is still needed. Educative suicide prevention programs using the internet and social media have now been launched addressing the need of low-threshold communication with individuals at risk and further aiming to increase suicide-prevention-related knowledge (59, 60). Nevertheless, understanding the individual background of suicidality takes time, a trustful therapeutic relation and non-judgmental attitude of the therapist. The proposed reinforcement model of suicidality applies basic behavioral techniques to chronic suicidal BPD patients. It is not a new model. It integrates theoretic concepts that helped us understanding related phenomena like NSSI and suicide attempts. It further includes known interventions that have been efficient in suicidality and the treatment of BPD, such as DBT and ACT. But, it especially stresses the role of reinforcement of suicidal ideations and behavior, thus giving us tools to work with the patient and to find a shared commitment for planned interventions in order to dissolve suicidal contingencies. Albeit, it is of vital importance to further investigate the background of suicidality, especially with respect to all forms of suicidal ideations and behavior in chronic suicidal patients. Precise definitions and assessments appear to be crucial in these studies. Further, many of the here mentioned techniques have not specifically been tested upon its ability to modify central dysfunctional schemes or reinforcements so far. Modern neurobiological techniques like fMRI, neuroendocrinology or epigenetics in combination with appropriate psychological paradigms may help us to further prove our concepts, detect new options for anti-suicidal interventions and hypothetically specifically monitor therapeutic effects.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00199/full#supplementary-material

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Unmet Needs and Classical Pitfalls in the Management of Adolescents With Behavioral Problems in Emergency

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While behavioral problems are the main reasons for adolescents to be referred to an emergency room for mental health problems, their clinical management remain usually heterogenous, poorly standardized, and associated with a low level of patient and family satisfaction. So far, most attention has been paid to the treatment of agitation, and few insights have been provided on the treatment plan of behavioral problems once the crisis is over and a psychiatric or medical condition ruled out. This perspective article represents an attempt to incorporate multiple theoretical approaches to provide a comprehensive and operational model for the management of adolescents with behavioral problems in an emergency department. Short hypothetical case vignettes illustrate the importance of considering several levels of analysis to understand the adolescent's problematic behavior which can be seen as a symptom of a medical/psychiatric condition (medical model), as a maladaptive strategy in a context of vulnerability (developmental model), and finally as a mode of communication in a context of ill-adapted relational patterns (systemic model). As behavioral problems in adolescence are a complex issue, frequently involving the intervention of professionals from various disciplines, being aware of such different levels of understanding could help to preclude any role confusion and to provide better targeted interventions.

Keywords: aggressive behavior, behavioral problem, emergency, crisis-intervention, emergency department, adolescent

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INTRODUCTION

Over the past 15 years, the number of pediatric patients presenting to the emergency room for mental health problems has nearly doubled (1). Behavioral problems are the main reasons for adolescents to be referred to a psychiatric consultation in Pediatric Emergency Department (PED), accounting for 11–55% of all mental health visits (1–3). Heightened awareness of mental health problem in adolescent and the lack of available community resources in most regions has been incriminated to explain this surge (4). In addition, such visits for mental health problems in PED are in most cases the adolescent's first point of contact with a mental health care system (with 53–70% of youths without prior outpatient care) (5–7).

Several authors stressed that a lack of specific training for adolescent psychiatry in PED results in heterogeneous care and low levels of both patient and family satisfaction, in particular due to excessively long wait times (3). In particular, many professionals in PED may feel uncomfortable in caring for adolescents with behavioral problems hastily perceived as not having a "real" urgent medical problem or whose presence in a noisy crowded emergency room is deemed irrelevant or even dangerous for other patients. When the clinician in charge of the psychiatric assessment of such patients in PED is alone, lacking time or having no specific interest in adolescent psychiatry, his/her evaluation might be limited to the following question: "*Has my young patient an acute psychiatric disorder requiring urgent medication or inpatient care?*" Albeit essential, a positive answer only concerns a minority of adolescents with behavioral problems addressed to PED and thus it is not clear what to do with others. A longitudinal study including a systematic assessment of acuity rating for all patients in PED showed that the proportion of non-urgent mental-health related visits increased by 31% between 2003 and 2012 (8). Letting these adolescents go home without any other response certainly miss important needs, paving the way for future referrals.

This perspective article represents an attempt to integrate multiple theoretical approaches of adolescent behavioral problems to provide a series of practical advices for all professionals involved in their care.

DEFINITIONS

Behavioral problems in adolescence is not a homogeneous category. It encompasses a wide array of problematic behaviors ranging from oppositions, aggressive behavior, to antisocial behavior such as theft or runaway from home (9). Some clinical dimensions associated with behavioral problems in adolescents, such as impulsivity or irritability, are continuously distributed in the general population with those at one extreme of the spectrum having a high risk of associated psychiatric disorders. However, adolescents with psychiatric disorders represent only a small proportion of all teenagers with behavioral problems. Adolescent's behavioral problems directly imputable to psychiatric symptoms such as severe anxiety, delusion or dissociation are in fact rather the exception than the rule. In theory, in these cases the adolescent should no longer present any behavioral problems when his/her mental health problems are addressed. In many of cases, the situation are more complex and the adolescent's behavioral problems reflect maladaptive reactions associated with environmental and individual factors that would persist after the ED visit (10, 11). However, while the guidelines for the management of behavioral problems in PED (12, 13) pay particular attention to the treatment of agitation, few insights are provided on the treatment plan of behavioral problems once the crisis is over and a psychiatric or medical condition ruled out.

The term emergency is generally defined as a sudden and dangerous situation which needs immediate action to deal with it (14, 15). The concept can also be approached from a functional perspective, i.e., each presentation at an emergency service should initially be viewed as an emergency (16). Using this second definition, the key question for the clinician is no longer "*Are the reasons for referral of this teenager valid on my medical/psychiatric view?*" but rather "*what dangerous situations were feared by the adolescent and his surroundings and what kind of urgent interventions were expected to motivate the referral in emergency.*" Behavioral problems in adolescents that are not directly caused by a somatic condition or psychiatric symptoms generally consist of outward expressions of relational problems which may be inherent to common aspects of developmental changes in teenagers (17). While a reasonable level of indirect aggressive behavior or defiant attitude in adolescents have been viewed positively as a way for the youths to express their own subjectivity and values (17), it has also been shown that such reactions may tend to perpetuate by themselves through the reaction of the environment and the deterioration of the self-image. It can be postulated that for adolescents with behavioral problems and their surroundings, "emergency" represents the only way out of a persisting relational crisis. In such crises the adolescent and his family lack the internal or external resources to bring about an attitudinal change or, if necessary, a change of the interpersonal setting to find a new balance.

UNDERSTANDING UNMET NEEDS OF ADOLESCENTS WITH BEHAVIORAL PROBLEMS AND THEIR SURROUNDINGS

In this section, we present a hierarchical three-step model for the assessment of adolescents with behavioral problems in PED (**Table 1**). The steps differ in terms of principal aims, level and object of analysis, and the underlying theoretical model. We hypothesized that the low level of a patient's and family's satisfaction in a context of referral to PED for the adolescent's behavioral problems partly result from a discrepancy between the level of the patient's and the family's expectancies and the responses provided by the care system.

The first step of the assessment of adolescents referred to PED for behavioral problems consists in basic medical and psychiatric assessment. The clinical assessment has three objectives: (1) to screen out a psychiatric disorder, a toxic or medical condition that may cause the problematic behavior, (2) to estimate the risk of harm to self or others, and (3) to determine the need for prescription and/or an inpatient treatment. This step is brief and should focus on the determination of priority for treatment (for an illustration see **Table 2**, case 1).

Once the causal role of a somatic condition or a psychiatric disorder in the adolescent's behavioral problems are ruled out, the clinicians may elicit the developmental factors involved in the initiation or the maintenance of the problematic behaviors. In this approach, the clinician pays particular attention to the course of the psychiatric symptom/problematic behaviors, in particular in environmental maintenance factors. In this step, the clinician formulates behavioral problems in terms of disturbances of developmental processes where symptoms are regarded as

TABLE 1 | A proposed three-step approach for the assessment of adolescents with behavioral problems in ED.

Step	**1** **Medical/psychiatric assessment**	**2** **Developmental hypothesis**	**3** **Systemic formulation**
Emergency model	Triage model	Formulation model	Crisis intervention model
Underlying theoretical model	Medical model, i.e., diagnosis, prognosis, and treatment	Developmental psychology	Time-limited psychotherapeutic approach, systemic model
Level of analysis	Adolescent patient	Adolescent and his caregivers	Adolescent within his system
Object of analysis	Psychiatric symptoms	Adaptative and maladaptive emotional and behavioral strategies and family resources	Repetitive relational patterns
Principal aims	Medical decision (assessment, treatment, referral, sometimes short follow-up)	Providing information and guidance	Consultative roles

TABLE 2 | Hypothetical case vignettes synthesized from several real cases of adolescents referred to PED for aggressive behavior.

Clinical vignette 1

M., a 16-year-old boy, was rushed to the hospital for extreme agitation by a social educator. He had lived in foster care placement since he was expelled from his father's house at the age of 6 for unknow reasons. M. had no prior psychiatric or somatic history. He had had a prior visit to PED a few months earlier but ran away before the clinical assessment. The psychiatric assessment revealed severe delusional and paranoid thoughts which gave rise to feelings of hostility. He was deeply convinced of being victim of an injustice in his receiving home. The routine somatic and paraclinical investigations were normal, including toxicologic evaluation. An antipsychotic treatment with sedative effect was prescribed in PED, and the patient was addressed to a psychiatric pediatric inpatient unit for continuation of care. No physical restraint was used. The probabilistic diagnostic at the discharge of the PED was an acute psychotic episode

Clinical vignette 2

L., a 14-year-old girl, was brought to emergency consultation by her parents for severe aggressive behaviors against them. She is a single girl adopted 3 years previously with her biological family still living in Colombia. She had had few psychiatric consultations at age 11 for an anger-management issue. The parents reported that over the last days L. had a resurgence of the same problematic behaviors as at age 11 (mainly irritable and touchy mood) accompanied by new symptoms (secondary enuresis, loss of interest for school and leisure, and marked social withdrawn). In the emergency room, L. is initially mute, still, huddled up. After repeated consultations, alone and with the parents, she reported a first sexual relation with ambivalent consent 2 weeks earlier. Family consultations helped L. and her parents to make sense of her behavior in a context of preexisting difficulties for sharing emotional distress. We also discussed L.'s reluctance to access ambulatory care despite several emergency consultations (about 10 during the past 2 years). As sharing her inner feeling with adults is specifically her core problem, we discussed alternative treatments (family sessions, physical therapy). The probabilistic diagnosis at the discharge of the ED was adjustment disorder with depressive symptoms in a context of prior reactive attachment disorder

Clinical vignette 3

S., a 16-year-old boy, was brought to PED by a social educator after he threatened to strangle another adult. He had been having a psychiatric follow-up since the age of seven and had received the diagnoses of attention deficit disorder, conduct disorder, post-traumatic stress disorder, and borderline intellectual functioning. He had moved into a new foster care 2 months previously with difficulties adjusting to this new environment, with in particular a history of bullying with sexual assault of other residents, both as victim and as perpetrator. He is described as becoming notably more irritable and hostile over the past few days, staying in his room alone, watching television, and avoiding any social contacts. A contract had been formalized with his consulting psychiatrist to plan a hospitalization in the weeks to come. During clinical assessment aggressive behaviors are often minimized with a tendency to place the blame on others. A phone call to his referent educator told us much about the current situation. Following S.'s temper outbursts several adults were frightened of him, avoiding interactions or minimizing educational requirements, with episodic sudden coercive reactions by threating him of being hospitalized. The patient was also not permitted to phone-call his biological family for vague reasons (in response to his behavior or for a problem of administrative authorization). In this context of escalade of retaliatory measures between the adolescent and the educative team, a very short period of separation (12 h) was helpful to gain insight on the systemic contribution of S.'s problematic behaviors and suggest calming measures. In collaborations with a broad array of partners we suggested that at the discharge of the PED, S. might be oriented to a farmhouse for a break before attending to his inpatient admission. The educators were interested to find out how they could develop more consistent educative responses to his transgressive behaviors

maladaptive, blocked, regressive or anti-developmental behaviors (for an illustration see **Table 2**, case 2).

In some situations, the assessment of the adolescent's behavioral problems requires the use of a broad lens to assess the entire system involved with the adolescent. Systemic formulation of the adolescent's behavioral problems aims to better understand the repetition of stereotyped patterns of interaction between members of the system. This approach is therefore particularly useful to analyze recurrent use of PED for mental-health problems. In this step, the clinician formulates problematic behaviors in terms of communication strategies in a specific system. Here, the adolescent's behavioral problems are not regarded as a sign of malfunction (step 1) or as a maladaptive strategy (step 2), but rather as the least bad option for the teenager to maintain a specific balance in his relational system (for an illustration see **Table 2**, case 3).

CLASSICAL PITFALLS IN TREATING ADOLESCENT WITH BEHAVIORAL PROBLEMS IN EMERGENCY

In the following section, we develop a series of recommendations for clinicians involved in the management of adolescents with behavioral problems. These clinical pitfalls also illustrate the fact that correctly addressing these different dimensions involved in the adolescent's problematic behavior may be complex.

Being a Mediator but Not Referee

Context: Sometimes the adolescent and his/her caregiver give radically different descriptions of the situations. Traditionally, the adult's view is systematically balanced by the statement of the adolescent who minimizes or denies implication in problematic behaviors, giving an impression of a "ping-pong" type discussion.

Principles: Clinicians should be careful to not take the side of either the adolescent or the caregiver in this situation. The following prerequisites should be met to help the clinician to have a role of mediator between the two parties and to avoid pointless and time-consuming arguments between the adolescent and his parents.

- Clinicians should be cautious to not try to summarize or synthetize the views of the parents of the adolescent too quickly. The different points of view should be respected and recognized positively as a more adaptative way of expressing conflictual views compared to behavioral manifestations.
- Expression of empathy by the clinician should not be a way to gain an adolescent's attention or an artificial level of trust. The time spent to understand the situations and to provide consistent and detailed explanations of the patient's mental health issue and treatment plan is the best mark of compassionate care (18).
- Clinicians should try to have adolescents and adults express conflicting views of the same situations. The expression of ambivalent emotions and cognitive dissonances represent an opportunity for all family members to take different perspectives and of getting out of Manichean views.

Why this is not easy? In all our medical training we are taught to consider information discrepancies as a source of bias and error. To promote the expression of ambivalent thoughts requires that the clinician accepts that one cannot understand every aspect of the situation, which is far from our traditional medical approach.

Psychiatric Diagnoses Do Not Have the Same Meaning for Everyone

Context: Sometimes the question of a severe psychiatric disorder (usually schizophrenia or bipolar disorder) is raised by the caregivers while no obvious clue supports this view.

Principles: Confusion may exist in the caregivers' perceptions of the severity of the situation in terms of overall functioning and in terms of clinical severity. The severity of the problematic behavior due to its impact on the physical health (e.g., due to physical injury) or social consequence (e.g., family conflict, being expelled from school) is not necessarily correlated with the psychiatric severity. Family and caregivers can press for this diagnosis when it represents an opportunity for hospitalization and thus a separation. Of course, the description of the adolescent's behavior may be partly affected by specific concerns about a psychiatric disorder due, for example, to family history (for example normal mood swings is described as "pathological mood lability").

- We have to accept that sometimes the diagnostic formulation is impossible in emergency consultations, considering the lack of time, objective information about prior functioning, and the difficulties to conduct a clinical assessment when the adolescent is reluctant or outrightly hostile. No diagnosis (with a focus on clinical syndrome or a probabilistic diagnostic) is always a better option than a bad diagnosis. An excessive focus on the most salient behavioral problems may lead to an overdiagnosis of externalizing disorders or borderline personality disorder.
- Sometimes comorbid psychiatric disorder may be essential to consider for risk assessment. For example, in youths with conduct disorder and psychopathic traits, depressive symptoms, albeit rare, may have dramatic consequences with a very high risk of impulsive suicidal attempt.
- For the clinicians the diagnosis is a way to choose the most-appropriate intervention; however, for the family it is expected to shed light on the motivations behind a behavior viewed as aberrant, chaotic and problematic. For most adolescents with behavioral problems the diagnosis is an adult way to talk about things that they truly do not understand.

Why this is not easy? Diagnoses are part of our medical identity; coding diagnosis is also an obligation in most countries to account for our clinical activity in ED.

Being Cautious When There Is an Excessive Emphasis on External Factors

Context: Sometimes the adolescent and his caregivers extensively discuss during the consultation about a stressful life event, generally occurring outside the family (e.g., peer-abuse, medical problem, potentially traumatic events in childhood).

Principles: Some environmental risk factors seem more "concensual" to incriminate than others. In particular, all life events that do not involve one of the persons present in the PED, such as school teachers, a girlfriend, or biological family in a context of foster care. Albeit important to consider, such biographical events should not hide other factors potentially relevant *hic* and *nun* to understand the maintenance of the problematic behaviors. A high level of parental shame about the adolescent's behavioral difficulties may explain that some of these adults are reluctant to talk about what has happened inside the family. External factors could appear as consensual topics of discussion toward which they can turn their blame.

- Above all, it is essential to carefully assess adverse life events when they are mentioned by the family.
- It is preferable to limit the discussion to one or two life events rather than trying to superficially address too many things. To go to the depths means to adopt active listening by making clear facts (*what has happened next?*), feeling (*what did you feel?*), thoughts (*why did you feel that way?*), reactions (*how did you react?*), and expected reactions from the surroundings.
- When parents and adolescents are both reluctant to talk about their own authentic feelings, you can try to get them to discuss about someone else's perceptions ("*how do you expect your parent to behave at this moment? Why?*"). Sometimes adolescents lacking insight on their own emotions may be surprisingly very good at acknowledging a feeling of hopelessness or shame conveyed by one of the parents. Such

an intersubjective game should be practiced with the patient and the parents together.

Why this is not easy? Families may have the feeling that you are trying to find new problems. This resistance reflects how afraid they could be of moving from a stability stance even if this means partially denying the adolescent's problem inside the family.

Is All About Control

Context: All of your suggestions, even the most paradoxical, are rejected by the adolescent. The more you suggest positive solutions, the closer the adolescent gets to discussion.

Principles: At this point, the clinician should keep in mind that behavioral problems represent for many the least bad options vulnerable adolescents have to maintain a sense of control and predictability in their life. Helping to gain a sense of control requires letting the patient have the possibility to address his needs in a different time and a different context. Accepting help from mental health professionals means challenging stigma about mental health problems. All of these may be particularly difficult for adolescents whose attachment issues make them less prone to trust adults and to commit to a therapeutic relationship.

- Talking about resistance and possible stigma in an open way may be more useful than trying to convince an adolescent to accept an intervention (e.g., medication, new referral).
- Doctors are often seen as figures of authority, and "recommendations" may be perceived as being directive or giving an order. Nurse specialists are often considered to be less authoritative, so discussions with them or other non-medical professionals may be worthwhile in an emergency so as not to be confined to a duel scenario, repeating a coercive relational pattern.
- Sometimes it helps to remember that our long-term goals are to decrease stigma about mental health difficulties and help these adolescents to accept a new referral without necessarily resolving the behavioral problems today. Sometimes, it may be useful to explain to the adolescent that compulsory care concerns only very limited and specific situations in psychiatry, and that we cannot force him to accept care.

Why this is not easy? Emergency medicine specifically cares for dependent patients and making decisions on their behalf. Using shared decision making to empower adolescents with a chronic condition is rarely used in a context of emergency. This way of thinking about psychiatric care coexists with other situations, e.g., acute psychotic episode or manic episode, where one will have to decide on behalf of the patient. Switching between this different way of thinking is not always easy.

It Takes a Village…

Context: Many clinicians may be reluctant to consider psychosocial factors on behavioral problems, as they do not want to substitute for social or educative services. Consequently, it is almost certain that clinicians who feel isolated or resourceless in PED (e.g., without the additional help of a dedicated social worker or specialized nurse) will narrow their focus to the identification and treatment of psychiatric disorders.

Principles: Behavioral problems in adolescents stand at the cross-road of various disciplines (medicine, psychiatry, developmental psychology, pedagogy, educative and sometimes judiciary systems). As a result, the management of behavioral problems in adolescence involves the collaboration of many partners, resulting in a significant risk of role confusion between professionals and dilution of responsibilities.

- Considering their knowledge of normal development, psychopathology and care systems, psychiatrists may be at the right place to work collaboratively with a broader array of partners.
- Consultative role does not mean a substitution role, but this certainly requires clear definitions of the roles of each one. Specific meetings with other professionals outside an emergency situation may be useful to clarify this.

Why this is not easy? Such a collaborative role is complex, time-consuming, and requires pedagogic skills that are not always learned in medical school. Caring for patients with poor motivation to change requires a change in our traditional medical setting.

CONCLUSION

Through the article we support the view that the vast majority of adolescents and their families come to the emergency room hoping that more complex and non-strictly medical or psychiatric needs will be addressed. The model presented here can be seen as a blueprint to develop an integrative, developmental, and non-judgmental view of behavioral problems in adolescence. Of note, the practical implications of this comprehensive approach will depend on the extent and availability of adolescent mental health resources locally, regionally, and nationally, both in terms of outpatient, inpatient, and various outreach modalities. While the development of such plan requires specific training, a lot of time and a large dose of collaborative functioning, this will be worthwhile if it helps clinicians to be more aware of the different dimensions involved in the behavioral problem and to feel more comfortable in assessing and treating these patients.

AUTHOR CONTRIBUTIONS

M-JG-B and XB: substantial contributions to the conception and design of the work. M-JG-B, SG, and UP: substantial contributions to the acquisition, analysis, or interpretation of data. M-JG-B, XB, SG, UP, and DC: drafting the work or revising it critically for important intellectual content. M-JG-B, XB, SG, UP, and DC: final approval of the version to be published. M-JG-B, XB, SG, UP, and DC: agreement 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. All authors contributed to the article and approved the submitted version.

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