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REVIEW ARTICLE

Designing Clinical Trials to Assess the Impact of Pharmacological Treatment for Suicidal Ideation/Behavior: Issues and Potential Solutions

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Abstract
Suicide is a serious and growing public health concern yet randomized controlled trials (RCTs) that inform pharmacologic treatment remain limited. We emphasize the overall need for such trials and review the literature to highlight examples of trials that have aimed to study patients at elevated risk of suicide. We discuss key examples of existing psychotropic medication trials as well as psychotherapy intervention studies that can yield important design insights. Medications that have been studied in individuals at risk for suicide include lithium, clozapine, zolpidem, prazosin, ketamine, esketamine, and aripiprazole. While important design challenges should be considered—RCTs to study suicide are feasible and much needed. Issues such as overall trial design, patient-selection criteria, and the scales/tools used to assess suicidality are discussed.

Key Points

Pharmacotherapy randomized controlled trials (RCTs) in patients at risk for suicide are needed.

Research in this patient population requires extra consideration but can be practical.

1 Introduction

Suicide is a serious and growing public health concern with population incidence rates in the USA increasing 33% from 1999 to 2019 to approximately 14/10,000 persons annually [1]. This concern is even greater in younger populations where suicide is the second leading cause of death from ages 10–34 years [1]. Rates of suicidal ideation (SI) have also increased during the COVID-19 pandemic [2]. A wealth of literature exists pertaining to population data, demographics, and risk factors associated with suicide [3–6]. This has been used to develop innovative strategies such as the social media screening and prevention tools [7, 8]. However, research that informs choice of pharmacologic treatment—especially regarding patients most at risk for suicide—remains limited. Although there are important considerations, drug trials with suicidal patients are feasible and much needed. Pharmacology is often used in an attempt to mitigate suicide risk; however, the lack of rigorous randomized controlled trials (RCTs) may place patients under undue risk in the absence of scientifically informed decision making. The scope of this paper will be limited to adults. Other technologies such as therapeutic brain stimulation are also outside the main focus of this paper.

2 Making the Case for RCTs in Patients at Risk for Suicide

Antidepressants are frequently prescribed to patients who struggle with suicidal thoughts or behaviors; however, the direct effect of antidepressants on suicide remains unclear [9]. Moreover, patients most at risk for suicide are often excluded from RCTs. For example, a 2017 Cochrane review [10] that found vortioxetine has greater efficacy than placebo in treating depression, but all referenced trials excluded patients at elevated risk for suicide. This problem applies to

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many antidepressants on the market. A 2020 review found that of all the efficacy trials described on 14 FDA-approved antidepressants, 30 do not mention suicide in the inclusion or exclusion criteria, 33 specifically exclude suicidal patients (by various criteria, some using validated instruments, others by more vague means), and only 1 trial included patients at risk for suicide. This was a placebo-controlled RCT of nefazodone in patients with major depressive disorder (MDD) where the inclusion criteria required patients to be hospitalized and one of the reasons for hospitalization could be the risk for suicide [11, 12]. A similar trend was observed for antipsychotics—for example in Phase 3 efficacy trials of brexpiprazole: (i) one placebo-controlled study in patients with schizophrenia made no mention of suicide in inclusion/exclusion criteria but Columbia-Suicide Severity Rating Scale (C-SSRS) was used and the article only reports 3 patients with SI or behaviors at Week 1 (presumably 0 at baseline) [13]. (ii) A second placebo-controlled study in patients with schizophrenia made no mention of suicide in inclusion/exclusion criteria and only commented briefly that "the incidence of suicidality was low (as measured by the C-SSRS) and similar across all treatment groups" with no further details published [14]. (iii) An augmentation study in patients with MDD excluded "serious risk of suicide", no suicidal behaviors were reported on C-SSRS and 7 patients reported worsening SI (not clear how many had SI at baseline) [15]. (iv) A second study of augmenting brexpiprazole in patients with MDD also excluded "serious risk of suicide", no suicidal behavior was reported on C-SSRS, and baseline SI was not reported [16].

Sometimes favored treatments do not prove effective when subjected to RCTs. For example, nightmares are a well-known risk factor for suicide [17]. Prazosin is commonly used in the treatment of post-traumatic stress disorder (PTSD) with the goal of reducing nightmares with meta-analysis supporting a positive effect [18]. It would logically follow that prazosin may be beneficial in reducing suicide risk. However, in a study of patients with PTSD and SI, the effect was opposite that expected—prazosin was associated with worse nightmares and insomnia [19]. This study illustrates the need for rigorous RCTs involving patients most at risk of suicide as efficacy may not be as expected with non-suicidal patients.

3 Literature Review of Clinical Trials Involving Patients at Risk for Suicide

There are a few examples of medications as well as non-pharmacological interventions that have been formally studied in RCTs involving patients at risk of suicide. While this article focuses on pharmacologic trial design, non-pharmacologic RCTs can also serve as practical models as many psychotherapeutic interventions have been studied in patients at risk of suicide. This paper is a narrative review and hence did not follow the comprehensive steps as would happen in a systematic review. Nevertheless, we queried PubMed on papers with suicide or suicidal in their titles or abstracts, then filtered these to only randomized clinical trials, and then examined the abstracts to find relevant papers with a pharmacology focus.

3.1 Non-Pharmacologic RCTs

A meta-analysis of 10 RCTs of cognitive behavioral therapy (CBT, of various types, outlined in Table 1) versus treatment as usual involving patients who had attempted suicide within 6 months prior to trial, found that CBT reduces the risk of a new suicide attempt (risk ratio, 0.47, 95% confidence interval [CI] 0.30–0.73) [20]. Many of these trials recruited participants in emergency departments immediately after a suicide attempt. Pertinent details of sub-studies are highlighted in Table 1. A similar meta-analysis found that CBT is effective in reducing SI (standardized mean difference [SMD] = −0.24, 95% CI −0.41 to −0.07 for trials reporting a continuous outcome measure and risk ratio = 0.62, 95% CI 0.44 to 0.88 for studies reporting a dichotomous outcome measure [21]. Another meta-analysis attempting to quantify suicide prevention found that the World Health Organization brief intervention and contact reduced risk of death by suicide (odds ratio [OR] = 0.20, 95% CI 0.09–0.42); however, CBT was not found to be significant (OR = 0.34, 95% CI 0.12–1.03) [22]. Dialectical Behavioral Therapy (DBT) has also been studied in patients at risk for suicide. One meta-analysis concluded that DBT was effective in reducing self-directed violence (weighted mean effect size, $d = -0.237$, 95% CI = −0.369 to −0.104) and need for psychiatric crisis services ($d = -0.336$, 95% CI = −0.587 to −0.086), but was not significant for effect on SI ($d = -0.247$, 95% CI = −0.555 to 0.060) [23]. A Cochrane review of psychotherapies for patients with borderline personality disorder found that DBT was superior to treatment as usual in reducing self-harm (SMD −0.28, 95% CI −0.48 to −0.07); however, quality of evidence was rated to be low [24].

3.2 Pharmacologic RCTs

Here are examples of pharmacologic trials that planned to investigate anti-suicide effects. Key details are summarized in Table 2.

3.2.1 Lithium

Lithium is among the most well studied medications for anti-suicide effects. Meta-analysis of RCTs in patients with mood disorders shows that lithium (levels ranging from

Table 1 Cognitive behavioral therapy randomized clinical trials in patients with suicidal ideation and behavior

Reference	Patient recruitment site and number of participants	Suicide criteria	Comparators	Precautions	Emergency management	Suicide attempts treatment vs control	Findings RR and 95% CI
(Brown et al, 2005) [41]	ED *N*=120	A suicide attempt within 48 h prior to being evaluated at the emergency department	CBT (10 sessions) vs TAU (both groups received care of "clinicians in the community" and case management)	Case management 1wk to 1 mo routine contact Permission to contact collaterals (family, friends, clergy, probation officers, and mental health workers)	Pts at imminent risk were sent to ED If hospitalized patients were allowed to continue study after discharge	13 vs 23	RR 0.50 [0.33, 0.85]
(Dubois et al, 1999) [42]	ED *N*=102	Attended emergency department following a suicide attempt	5 sessions of psychotherapy in 1 mo vs TAU (assessment by clinical psychiatrist, follow-up by a psychiatrist or psychologist)	Excluded if patients required hospitalizing for more than 24 h	Not specified	8 vs 10	RR 0.76 [0.33, 1.74]
(Gibbons et al, 1978) [43]	ED *N*=400	Deliberate self-poisoning	Problem solving therapy and social work services for up to 3 mo vs TAU (psychiatry or general practitioner referral)	Interview by psychiatrist at recruitment – excluded if "they had a formal psychiatric illness requiring immediate psychiatric treatment" or "if they were judged, from scores on a predetermined scale to be an immediate suicide risk"	Limited follow-up interview at 4 mo Repeated SA endpoint evaluated by review of medical records at 1 y	27 vs 29	RR 0.93 [0.57, 1.51]
(Guthrie et al, 2001) [44]	ED *N*=119	Deliberate self-poisoning, did not need inpatient psychiatric treatment	4 weekly sessions of interpersonal therapy vs TAU (assessment and referral to psychiatry, addition services, or general practitioner)	Therapist assessed patient for suicide risk at each visit	Not specified	5 vs 17	RR 0.31 [0.12, 0.78]
(Gysin-Maillart, Schwab, Soravia, Megert, & Michel, 2016) [65]	ED *N*=120	SA presenting to ED	3 CBT sessions + personalized letters for 2y vs TAU	Suicide risk assessments sent to patient's follow-up providers	Inpatient vs day patient services as determined by clinicians	5 vs 41 Suicide deaths: 1 vs 1	RR 0.12 [0.05, 0.29]

Table 1 (continued)

Reference	Patient recruitment site and number of participants	Suicide criteria	Comparators	Precautions	Emergency management	Suicide attempts treatment vs control	Findings RR and 95% CI
(Husain et al, 2014) [66]	Hospital *N*=213	Admitted to medical unit due to self-harm – and did not require further inpatient psychiatric treatment	Problem solving therapy 3 sessions in 3 mo vs TAU	Assessment at 3 and 6 mo	Not specified	1 vs 1	RR 1.09 [0.07, 17.17]
(Rudd et al, 2015) [67]	Active-duty army base *N*=116	SA or SI with intent referred from behavioral health team, ED reports, or on discharge from inpatient psychiatric hospitalization	12 sessions of CBT vs TAU	Follow-up assessments at 3, 6, 12, 18, 24 mo	Not specified	6 vs 14 Suicide deaths: 1 vs 1	RR 0.41 [0.17, 1.00]
(Salkovskis, Atha, & Storer, 1990) [68]	General hospital *N*=20	SA presenting to the hospital	5 sessions problem solving CBT vs TAU (discharge to general practitioner follow-up)	Interview by psychiatrist at recruitment – excluded if requiring immediate psychiatric treatment In home follow up assessments at 1 wk, 1 mo, 3 mo, 6 mo, 1y	Not specified	3 vs 4	RR 0.5 [0.15, 1.66]
(Stewart, Quinn, Plever, & Emmerson, 2009) [69]	ED *N*=32	SA presenting to ED	4 sessions of CBT or 7 sessions of problem-solving therapy vs TAU (follow-up by the Health Service District Acute Care Team)	Acute care team follow up consisted of phone calls, home visits, and psychiatry appointments "proportional to the client's level of risk upon discharge"	Not specified	4 vs 2	RR 0.78 [0.17, 3.55]
(Wei et al, 2013) [70]	ED *N*=52	SA presenting to ED	10 sessions of CBT vs TAU (medication as advised by psychiatrist)	At least 1 contact person to enable follow-up 3-, 6-, 12-mo phone follow-up	Not specified	1 vs 5	RR 0.22 [0.03, 1.72]

CBT cognitive behavioral therapy, *CI* confidence interval, *ED* emergency department, *RR* relative risk, *SA* suicide attempt *TAU* treatment as usual

Table 2 Pharmacologic randomized clinical trials in patients at risk of suicide

Reference	Recruitment site	Suicide criteria	Comparator	Precautions	Emergency management	Suicide related Adverse events	Outcomes
InterSePT (Meltzer et al, 2003) [27]	67 medical centers in 11 countries	(1) A history of previous attempts or hospitalizations to prevent a SA in the 3 y before enrollment, (2) moderate to severe current SI with depressive symptoms, or (3) command hallucinations for self-harm within 1 wk of enrollment	Clozapine vs olanzapine	Randomized, open-label trial with masked ratings – so that clinicians could respond appropriately	Clinicians were allowed to make any interventions necessary to prevent the occurrence of SAs, including changing dosages, adding other medications, switching medications, and increasing surveillance	34 vs 55 SA 5 vs 3 suicide deaths	Suicidal behavior was significantly less in patients treated with clozapine vs olanzapine (HR, 0.76; 95% CI, 0.58-0.97
Ketamine meta-nalysis (Samuel T. Wilkinson et al., 2018) [29]		10 RCTs Meta-analysis included only patients with SI at baseline	IV ketamine vs saline placebo or midazolam control	Heterogeneous sub studies	Heterogeneous sub studies		Ketamine reduces SI with moderate to large effect size (Cohen's d=0.51–0.85)
Ketamine (Fan et al, 2017) [31]	Hospital	Newly diagnosed cancer within 3 mo with SI SI/SA could not precede diagnosis	IV ketamine vs IV midazolam	None specified	None specified	0	Ketamine reduces SI on Beck SSI (9.53 ± 9.53 vs 16.79 ± 7.07, $p = 0.0474$)
Ketamine (Michael & Grunebaum et al, 2018) [30]	Community advertisements and clinician referrals	Beck SSI ≥4	IV ketamine vs IV midazolam	Require voluntary admission to inpatient research unit	None specified	3 vs 1 SA 2 suicide deaths post study from ketamine group – 6 vs 2 6 mo later	Beck SSI is reduced 4.96 points after Day 1 in ketamine group (95% CI 2.33 to 7.59, t=3.75, df=77, $p = 0.0003$)
Esketamine Aspire I (Fu et al, 2020) [32]	Candidates screened from ED or inpatient psychiatric unit	SI and intent to act on thoughts of killing yourself within 24 h of randomization and imminent risk requiring hospitalization	Non-investigational antidepressant treatment + esketamine/placebo	9-wk post-treatment follow-up	Hospitalization required to enter study	4 vs 3 SA 1 vs 0 suicide deaths	Esketamine improved MADRS total score, but no significant difference in severity of suicidality

Table 2 (continued)

Reference	Recruitment site	Suicide criteria	Comparator	Precautions	Emergency management	Suicide related Adverse events	Outcomes
Esketamine ASPIRE II (Ionescu et al, 2021) [33]	Candidates screened from ED or inpatient psychiatric unit	SI and intent to act on thoughts of killing yourself within 24 h of randomization and imminent risk requiring hospitalization	Non-investigational antidepressant treatment + esketamine/placebo	9-wk post-treatment follow-up	Supervised inpatient unit or ED required to enter study	7 vs 4 SA	Esketamine improved MADRS total score, but no significant difference in severity of suicidality
REST-IT (McCall et al, 2019) [28]	Outpatient advertising and self-referrals to care	Score of at least 3 on Beck SSI, but less than 4 on ideation dimension of C-SSRS	SSRI (open-label fluoxetine, sertraline, or citalopram) + zolpidem/placebo	Two planned interim analyses with stopping rules (futility or an early significant effect) routine follow-ups at 1-, 2-, 4-, 6-, 8 wk	None specified	0	No significant treatment effect was observed on the Beck SSI (LSM estimate 20.56, SE 0.83, 95% CI 22.19, 1.08) The C-SSRS indicated that zolpidem-CR had a significant treatment effect (LSM estimate 20.26, SE 0.12, 95% CI 20.50, 20.02)
Prazosin pilot (McCall et al, 2018) [19]	Outpatient clinic	Score of at least 3 on Beck SSI, but less than 5 on ideation dimension of C-SSRS	Stable doses of mood disorder medication + prazosin qhs/placebo	None specified	None specified	0	No significant effect on SSI score (treatment effect 0.65 ± 2.52, 95% CI −4.36 to 5.67)
Venlafaxine + aripiprazole augmentation (Lenze et al, 2015) [35]	Multisite academic centers	Suicide not specified in inclusion/exclusion criteria Patients with SI on SSI were included for subgroup analysis	Venlafaxine + aripiprazole/placebo	None specified	None specified	1 vs 0 suicide death	Higher rate of resolved SI with treatment (Wald $\chi^2 = 5.2$, p=0.02)

CI confidence interval, *CR* controlled-release, *C-SSRS* Columbia Suicide Severity Rating Scale, *HR* hazard ratio, *LSM* least square mean, *qhs* at bedtime, *SA* suicide attempt, *SI* suicidal ideation, *SSI* Scale for Suicide Ideation

0.3–1.5 mEq/L with treatment at a minimum of 14 weeks) was superior to placebo in reducing the number of suicides (OR 0.13, 95% CI 0.03 to 0.66) [25]. Meta-analysis of ecological studies has also shown that lithium in drinking water (concentrations range from 3.8 to 123 μg/L) is linked with reduced suicide in the general population (OR = 0.42; 95% CI: 0.27–0.67; *p*-value <0.01) [26].

3.2.2 Clozapine

The InterSePT trial compared clozapine versus olanzapine treatment for suicidal behavior in patients with schizophrenia or schizoaffective disorder at high risk of suicide and found that clozapine decreased suicide attempts and the hospitalizations needed to prevent suicide attempts (hazard ratio [HR], 0.76; 95% CI 0.58–0.97) [27]. Authors of this study defined inclusion criteria as either history of suicide attempt or hospitalization to prevent an attempt in the last 3 years, command hallucinations instructing self-harm within the last week, or current suicidal ideation with depressive symptoms at time of enrollment.

3.2.3 Zolpidem

The REST-IT trial compared open-label selective serotonin reuptake inhibitor (SSRI) plus either zolpidem controlled-release (CR) or placebo in suicidal patients with insomnia [28]. All patients had to have SI for inclusion with a Scale for Suicide Ideation (SSI) score of at least 3 but could not have active plans (C-SSRS had to be less than 4 on the ideation dimension). Evidence was somewhat mixed as a mixed-model analysis of variance of post-treatment score of the SSI showed no difference while the C-SSRS SI subscale showed that zolpidem CR reduced SI over placebo (least squares mean estimate [LSM] = − 0.26, SE = 0.12, 95% CI = − 0.50 to 0.02).

3.2.4 Ketamine/Esketamine

A meta-analysis of several RCTs of single-dose intravenous ketamine found that ketamine quickly reduces SI (within 1 day up to 1 week) with moderate to large effect size (Cohen's $d = 0.51–0.85$) [29]. Very short periods of follow-up were intentionally picked to demonstrate the very rapid onset of effect. One study in particular studied IV ketamine versus IV midazolam in patients with a Beck SSI score of at least 4 and used a within-patient ANCOVA of changes in SSI from baseline. Findings showed that ketamine reduced SSI by 4.96 points (95% CI 2.33 to 7.59) on Day 1. A secondary analysis that used ANCOVA models to test for differential change between groups in SSI scores versus changes in the Profile of Mood States (POMS), found that there was partial mediation (33.6%) of ketamine's effect on Day 1 through its effect in the POMS depression rating [30]. A similar trend was found in newly diagnosed cancer patients with SI where IV ketamine was more effective than IV midazolam in reducing Beck SSI (BSI: 9.53 ± 9.53 vs 16.79 ± 7.07, $p = 0.0474$) [31]. Two multicenter trials of esketamine in hospitalized patients with active suicidal intent compared with placebo (both groups received standard of care antidepressant with or without augmentation agent at investigators' discretion) showed that esketamine improved Montgomery Åsberg Depression Rating Scale (MADRS) scores but did not differ from placebo regarding severity of SI [32, 33]. It remains unclear whether these results are due to insufficient power or if there is an inherent difference in the efficacy of racemic ketamine versus esketamine for suicidality (comparative meta-analysis does suggest that response and remission rates of racemic ketamine are superior to esketamine for depression) [34].

3.2.5 Prazosin

A trial of bed-time prazosin against placebo in patients with PTSD and SI found that prazosin had no statistical effect on SSI, but surprisingly worsened nightmares and insomnia [19]. All patients had to have mild-moderate SI for inclusion, which was defined as a Beck SSI score of at least 3, but C-SSRS had to be less than 5 on the ideation dimension.

3.2.6 Aripiprazole

In a study of patients aged ≥ 60 years with treatment-resistant depression, patients who failed to respond to venlafaxine were randomized to receive the addition of aripiprazole augmentation or placebo. Patients with SI at baseline were included for subgroup analysis, which showed that venlafaxine + aripiprazole augmentation resulted in greater resolution of SI – 30/91 (33.0%) participants on aripiprazole and 25/90 (27.8%) on placebo had SI at baseline, which resolved in 22/30 (73.3%) versus 11/25 (44.0%) (Wald χ^2 [1] =5.2, $p = 0.02$) [35]. The patients with SI were a smaller subset of the original study population so subgroup analysis may be less precise.

4 Design Considerations for Future Trials

4.1 Inclusion Criteria and Randomization Strategies

Suicide risk assessment is limited by reliance on clinical and demographic features such as male gender, Caucasian ethnicity, advanced age, living alone, depressive, and psychotic illness, medical illness, substance abuse, impulsivity, and insomnia [36–39]. Suicide is a complex phenomenon to be understood in the context of a socioecological model that

includes psychological stress, discrimination, poor quality housing, unemployment, lower level of parental education, community or domestic violence, childhood adversity, and access to lethal means. There are various degrees of risk for suicide—some more severe than others. Even at a relatively low-moderate risk, the inclusion of patients with current passive SI or history of suicide attempt would increase generalizability over many existing pharmacologic RCTs. Existing psychometric instruments for the measurement of suicide risk vary in complexity, e.g., from the single suicide items of the Hamilton Rating Scale for Depression (HRSD) to the self-rated Beck Scale for Suicide Ideation (SSI), to the observer administered C-SSRS. We have argued that the SI subscale of the C-SSRS is perhaps the most intuitive for identifying unacceptably high risk for the purpose of participation in a clinical trial, with a scores of 4 or 5 indicating unacceptable risk [40]. Psychotherapy RCTs have shown that it is feasible to conduct studies with patients at relatively high risk of suicide such as immediately post-suicide attempt on recruitment from an emergency department [41–44]. The InterSePT trial also included relatively high-risk individuals with command auditory hallucinations instructing self-harm [27]. Even patients at imminent risk of suicide—e.g. those with active SI with specified plan—have been studied in RCT of ketamine [33]. Patients who have been discharged from a psychiatric hospitalization are also at increased risk [45] and warrant study. Accepting various levels of risk may be useful in increasing sample size; however, greater variance within the study population may also introduce confounding factors and detrimentally affect power. Rather than exclusively sampling patients with SI, another strategy is to perform subset analysis on patients at risk for suicide present amongst a larger sample of participants, for example the aripiprazole augmentation trial [35]. Adaptive designs are a potentially attractive solution towards maximizing benefit to the study participants while increasing the likelihood of proving the stated hypotheses. An adaptive randomization design is one example and could include planning interim analyses for the purpose of early detection of the best treatment arm within a RCT, and then increasing the proportion of randomized participants into the most promising treatment arm. However, this strategy can potentially undermine the basic statistical assumptions in the sample size and also undermine the original statistical plan at the end of the study [46].

While there have been advances in public acceptance of mental health problems—suicide remains a stigmatized topic [47, 48]. This stigma carries over to research as patients with SI may be thought of as unreliable candidates—a myth that is readily disproven by adherence rates in existing trials, for example, participants in the ReST-IT trial attended 90% of scheduled visits and were highly adherent with taking 91% of prescribed study drug and 94% of prescribed SSRIs [28].

4.2 Control Group

Placebo-only comparators may not be ethically sound as non-treatment could place patients at undue risk of harm. A common solution is to pair placebo with treatment as usual that is otherwise the standard of care: for example, both groups receive a reasonable first-line treatment and either study medication or placebo control is added on—such as the REST-IT trial where zolpidem or placebo was added to an antidepressant [28]. In RCTs of non-pharmacologic interventions, treatment as usual by independent clinicians is a common control group [20]. Structured psychotherapy paired with placebo may be a reasonable control for medication trials. Frequency of interactions between patients and research staff (whether with case managers, assessors, therapists, or prescribers) is also an important factor to control between groups.

4.3 Home Medications

Some RCTs require patients to stop taking home medications prior to study. While there are legitimate concerns of additional variance and drug interaction safety; investigators interested in studying suicide must also contend with the risk of decompensation following discontinuation. In a retrospective case-control study of over 50,000 patients pulled from a claims database of managed care enrollees, discontinuation of antidepressants had a statistically significant risk for suicide attempt (OR = 1.61, $p < 0.05$) but less risk than other factors such as antidepressant initiation (OR = 3.42, $p < 0.05$) [49]. The risk of medication discontinuation may be greater in patients with severe mental illness—as case series of patients with schizophrenia have highlighted completed suicide following discontinuation of clozapine because of side effects [50].

4.4 Endpoints

While the ultimate goal is suicide prevention—using suicide deaths as a primary outcome measure may be unrealistic for RCTs. Due to the relatively low rate of suicide deaths and an ethical obligation to employ monitoring and intervention strategies during investigation—sufficiently powered studies would require massive sample sizes (for example the InterSePT trial estimated $N = 20{,}000$ patients to detect a 20% relative risk reduction in suicide deaths, while a sample size in the order of several thousand was sufficient to detect a difference in suicide attempts [27]. Reducing suicidal behavior is the desired goal and reducing SI is less than ideal. There is a practical need to rely on more common proxy outcome measures that precede suicide such as SI, suicidal behaviors, suicide attempts, hospitalization, or increased monitoring to prevent suicide. Another strategy

is a 'composite suicide risk event' measure that aggregates various components of the above. Even in well-studied agents such as lithium, individual trials have had difficulties in achieving sufficient power [51, 52]. Ideally, endpoints should be measured within 1–2 weeks after initiation of the experimental intervention to detect early improvement in SI or suicidal behavior for those treatments that may have rapid onset of therapeutic effect, and also employ longer-term measurement to capture less-common endpoints such as suicide attempts.

4.5 Instruments to Measure Suicide Risk

Well-validated observer-rated instruments for SI and behaviors that are commonly used in research include the C-SSRS [53-55]. Well validated self-rated scales include the Beck SSI [56], and the self-rated version of the MADRS-S, which does generally agree with its observer-rated counterpart [57]. In a head-to-head comparison of the SSI, C-SSRS, and HRSD conducted as a secondary analysis of a RCT all three instruments were highly correlated ($rs > 0.60$, $ps < 0.001$) and performed well in detecting high levels of SI but were equally limited in distinguishing low from very low levels [40]. The Collaborative assessment and management of suicidality (CAMS) [58] is another interesting option that instructs patient and observer to work together in evaluation of suicide risk factors and co-author a crisis response plan [59].

4.6 Risk Mitigation

Appropriate monitoring and intervention plans should be put in place to maximize safety. Safety protocols need to be tailored to appropriate risk level and may vary by treatment setting—emergency department versus locked inpatient versus outpatient. In the case of outpatient follow-up, a common strategy is to employ case management, which has been shown to reduce suicide attempts [60, 61] and deaths [61]. Follow-up timeframes should be tailored to level of risk along with a plan to increase monitoring frequency when needed. Participants may also be required to provide authorization to contact friends/family in case of missed check-ins or other acute safety concerns. Safety and crisis response plans should be made in collaboration with staff, patient, and their support networks. Patients and staff should be educated on emergency protocol including involuntary hospitalization. It should also be considered what events are considered exit conditions—i.e., will patients be welcomed back into the study after crisis intervention, hospitalization, or suicide attempt? There is at least one example of a psychotherapy trial where patients continued enrollment after mid-trial hospitalization [41]. Prior to trial inclusion and at checkpoints during the investigation, patients should be informed of alternative treatments. A discussion of reasonable alternatives should include highly effective and rapid-acting interventions such as ketamine or electroconvulsive therapy [62]. The safety of potential candidates that fall short of inclusion should also be accounted for with appropriate referrals to care. A comprehensive overview of safety considerations can be found through the National Institute of Mental Health considerations for researchers investigating suicide (NIMH). A safety methodology is also available which shows how the ReST-IT trial satisfied NIMH guidelines [63, 64].

5 Conclusion

Patients at risk of suicide are underrepresented in existing RCTs. While important design challenges need to be considered—trials to study suicide are feasible. Trials of pharmacological and psychological interventions serve as practical examples of potential solutions. We have outlined some proposed solutions, but exact methodology will need to be tailored for specific patient populations, interventions, and treatment settings.

Declarations

Authors' contributions We confirm that all authors meet the four ICMJE criteria for authorship. We also confirm that all authors have read and approved the final submitted manuscript and agree to be accountable for the work.

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