REVIEW

Annals of Internal Medicine

# Treatments for the Prevention and Management of Suicide

## A Systematic Review

**Kristen E. D'Anci, PhD; Stacey Uhl, MS; Gina Giradi, MS; and Constance Martin, BA**

**Background:** Suicide is a growing public health problem, with the national rate in the United States increasing by 30% from 2000 to 2016.

**Purpose:** To assess the benefits and harms of nonpharmacologic and pharmacologic interventions to prevent suicide and reduce suicide behaviors in at-risk adults.

**Data Sources:** MEDLINE, EMBASE, PsycINFO, and other databases from November 2011 through May 2018.

**Study Selection:** Systematic reviews (SRs) and randomized controlled trials (RCTs) that assessed nonpharmacologic or pharmacologic therapies for adults at risk for suicide.

**Data Extraction:** One investigator abstracted data and assessed study quality, and a second investigator checked abstractions and assessments for accuracy.

**Data Synthesis:** Eight SRs and 15 RCTs were included. The evidence for psychological interventions suggests that cognitive behavioral therapy (CBT) reduces suicide attempts, suicidal ideation, and hopelessness compared with treatment as usual (TAU). Limited evidence suggests that dialectical behavior therapy (DBT) reduces suicidal ideation compared with wait-list control or crisis planning. The evidence for pharmacologic treatments suggests that ketamine reduces suicidal ideation with minimal adverse events compared with placebo or midazolam. Lithium reduces rates of suicide among patients with unipolar or bipolar mood disorders compared with placebo. However, no differences were observed between lithium and other medications in reducing suicide.

**Limitation:** Qualitative synthesis of new evidence with existing meta-analyses, methodological shortcomings of studies, heterogeneity of nonpharmacologic interventions, and limited evidence for pharmacologic treatments and harms.

**Conclusion:** Both CBT and DBT showed modest benefit in reducing suicidal ideation compared with TAU or wait-list control, and CBT also reduced suicide attempts compared with TAU. Ketamine and lithium reduced the rate of suicide compared with placebo, but there was limited information on harms. Limited data are available to support the efficacy of other nonpharmacologic or pharmacologic interventions.

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For author affiliations, see end of text.

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Suicide is a growing public health problem, with the national rate in the United States increasing by 30% from 2000 to 2016 (1). According to data from the Centers for Disease Control and Prevention, the national suicide rate increased from 10.4 to 13.5 per 100 000 persons, with average annual increases of 1% from 2000 to 2006 and 2% from 2006 to 2016. Findings from a 2017 survey by the Substance Abuse and Mental Health Services Administration (SAMHSA) suggest that suicidal ideation, suicide planning, and suicide attempts have especially increased over the past 10 years among persons aged 18 to 25 years (2). The SAMHSA notes that these increases have co-occurred with an increase in the prevalence of mental health conditions that cause significant impairment in daily functioning, especially major depressive episodes and chronic substance abuse.

This systematic review (SR) served to update the 2013 clinical practice guideline (CPG) from the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD) on assessment and management of suicide risk. Because this SR supports an update, the literature searches were intended to cover the period from the previous CPG searches to immediately before the guideline panel meeting. The key questions (KQs) addressed in this review were developed by the VA/DoD workgroup for the suicide management CPG. The specific questions are listed in the Appendix (available at Annals.org). The full CPG covers a range of recommendations pertaining to screening, assessment of risk factors, and interventions and treatments intended to mitigate risk for suicide. This article focuses specifically on the evidence from that review that assessed the benefits and harms of nonpharmacologic and pharmacologic treatments for persons at risk for suicide.

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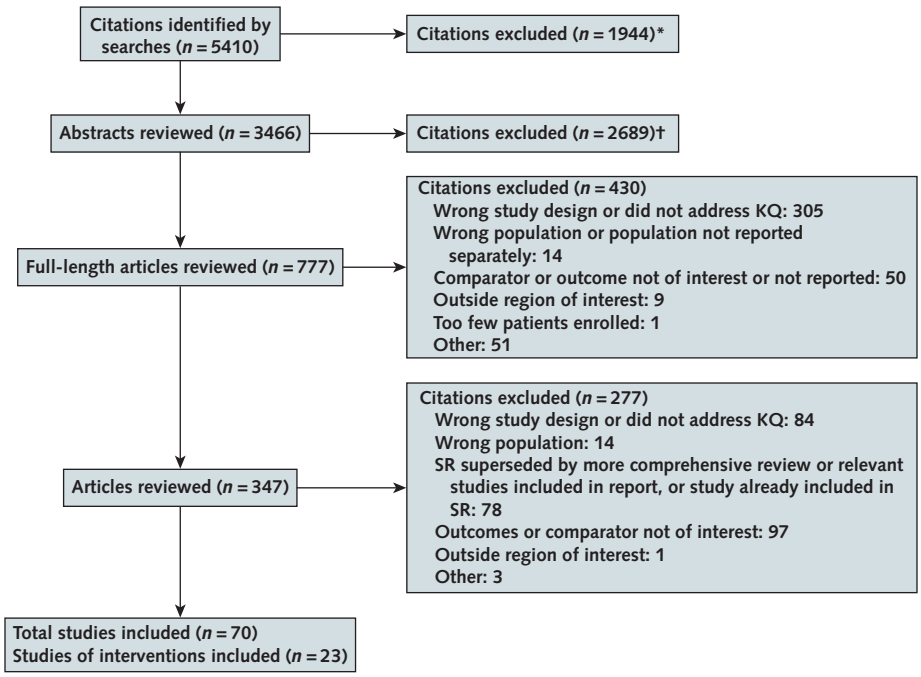
Supplement

## Methods

This SR focused on various nonpharmacologic and pharmacologic interventions compared with no intervention, wait-list control, placebo, other active medication or nonpharmacologic intervention, or combination medication plus nonpharmacologic treatment. Consistent with the methods outlined in the VA/DoD Guideline for Guidelines (3), the first line of evidence was previously published SRs. For interventions of interest, we selected the most recent, relevant, and comprehensive SR that was rated by a validated assessment tool as

***Figure.*** Evidence search and selection.




KQ = key question; SR = systematic review.
* Not relevant to topic, not published in English, or published before inclusion date.
† Not clinical trial or SR, did not address KQ, did not report on outcome of interest, or outside publication cutoff dates.

having good methodological quality (4). If there were multiple good-quality SRs for a given intervention with similar arrays of included studies, we chose the most comprehensive (in terms of the number of high-quality studies included) and/or recent SR for our evidence synthesis to avoid multiple ratings of a similar evidence base. Systematic reviews were supplemented with subsequently published randomized controlled trials (RCTs). Any RCTs that were included in the SRs were not considered independently as evidence in this review. For interventions for which no SR was available, we summarized the overall findings of RCTs that addressed the intervention and reported on at least 1 outcome of interest.

## Data Sources and Searches

The current review serves to update the evidence supporting the VA/DoD's previous CPG on assessment and management of suicide risk. The end date of the literature search in the previous guideline was 18 November 2011; our searches encompassed this period and extended through May 2018. We searched MEDLINE and EMBASE (via Embase.com), MEDLINE In-Process and PubMed-unique content (via PubMed .gov), PsycINFO, the PILOTS (Published International Literature on Traumatic Stress) database, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database. A search of ClinicalTrials.gov through February 2019 did not identify any additional relevant studies. Clinical experts serving as members of the guideline workgroup were also asked to identify any important publications published after our search date during the guideline development process. Search terms are provided in Appendix Tables 1 to 3 (available at Annals.org).

## Study Selection

Literature was screened using DistillerSR (Evidence Partners). The titles and abstracts identified in the literature search were screened for relevancy against the inclusion and exclusion criteria, and relevant titles underwent full-text review. All disagreements were resolved by consensus between 2 screeners.

We used a PICOTS (population, intervention, comparator, outcomes, timing of outcomes measurement, and setting) approach to identify studies that met our inclusion criteria. The population of interest was adults (aged ≥18 years) at risk for suicide. Interventions included nonpharmacologic and pharmacologic therapies. Nonpharmacologic interventions of interest were psychotherapies, crisis response planning (CRP), and community support programs. Pharmacologic interventions of interest were antidepressants and anxiety medications, lithium, antipsychotics, ketamine, and naloxone. Comparators of interest were no treatment (for example, placebo or wait list), other active therapies or combination medication, and nonpharmacologic treatments. Critical outcomes included suicides, suicide attempts, suicidal ideation, harms (such as reduction of health-seeking behavior and effect on patient–provider

*Table 1.* Nonpharmacologic Interventions for Suicide Prevention*

| Intervention | Suicide Attempts | | | Suicidal Ideation | | |
|---|---|---|---|---|---|---|
| | Evidence Base (Reference) | Findings | SOE | Evidence Base (Reference) | Findings | SOE |
| CBT vs. TAU | 10 RCTs from 1 SR (6) | Favors intervention | Moderate | 27 RCTs from 2 SRs (7, 10) and 1 additional RCT (19) | Favors intervention | Moderate |
| e-CBT vs. face-to-face CBT or TAU | – | NR | – | 3 RCTs from 1 SR (7) | ND | Very low |
| e-CBT vs. other controls | – | NR | – | 2 RCTs from 1 SR (7) | Favors intervention | Very low |
| DBT vs. wait-list control | – | – | – | 1 RCT from 1 SR (10) | Favors intervention | Low |
| Brief intervention vs. active control | – | NR | – | – | NR | – |
| E-CRP vs. TAU | 1 RCT (18) | Favors intervention | Low | – | NR | – |
| E-CRP vs. standard CRP | 1 RCT (18) | ND | Low | – | NR | – |
| Window to Hope vs. wait-list control | – | NR | – | 1 RCT (11) | ND | Low |

CBT = cognitive behavioral therapy; CRP = crisis response planning; DBT = dialectical behavior therapy; e-CBT = Internet-delivered cognitive behavioral therapy; E-CRP = enhanced crisis response planning; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ND = no difference between intervention and control; NR = not reported; RCT = randomized controlled trial; SOE = strength of evidence; SR = systematic review; TAU = treatment as usual.
* Supplement Table 1 (available at Annals.org) provides reasons for the GRADE ratings.

relationship, career, social relationships, and functioning), overdose, and hopelessness.

Studies were limited to English-language SRs or RCTs with no minimum follow-up that took place in an outpatient health care setting, including primary care, emergency care, VA, community, and specialty care settings.

### Data Extraction and Risk-of-Bias Assessment

One investigator extracted study data, and a senior reviewer verified the accuracy of the extractions. For individual RCTs not included in the SRs, we abstracted the following study-level details: country, purpose, and risk-of-bias (ROB) rating. For SRs, we reported on the search strategy; study selection criteria; and overall information about the evidence base, including the number of included studies, the overall number of patients enrolled, and the ROB assessment. For RCTs and SRs, we also abstracted data on the population, interventions, and results.

One investigator assessed the ROB of each SR using criteria developed by the U.S. Preventive Services Task Force (USPSTF) for SRs (4). The ROB of individual RCTs not included in the SRs was rated as good, fair, or poor using criteria developed by the USPSTF for randomized trials (4). For studies included in SRs, we relied on the quality assessments performed in the reviews and used the overall rating that was reported (good, fair, or poor). A senior reviewer verified the accuracy of the ROB ratings. Disagreements were resolved through discussion. Appendix Table 4 (available at Annals.org) shows ROB assessments.

### Data Synthesis and Analysis

We used a narrative approach to synthesize the evidence for each intervention. We reported on meta-analysis results from SRs and examined the degree of heterogeneity identified through the analysis. Rather than conducting an updated meta-analysis, we examined whether the results of new studies were consistent (same direction and similar magnitude) with the findings of the prior SRs. The overall quality of the body of evidence supporting the findings for the outcomes of interest was assessed by the authors using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (5). A senior reviewer verified the accuracy of the GRADE ratings. Disagreements were resolved through discussion.

### Role of the Funding Source

This review was funded by the VA to support an update of the CPG on assessment and management of patients at risk for suicide to be used in VA and DoD clinical practice. These agencies helped refine the scope, informed KQ development, and reviewed a draft report of the findings. The authors are solely responsible for the content preparation, writing the manuscript, and the decision to submit the manuscript for publication.

## RESULTS

Literature searches identified 5410 citations potentially addressing all of the KQs of interest for the guideline evidence review (see the Figure for the study flow). Overall, 70 studies addressed 1 or more of the KQs and were considered as evidence in the guideline review encompassing treatment, risk factors, and screening. Twenty-three articles were relevant to this SR.

### Nonpharmacologic Interventions

Five SRs and 12 RCTs examined nonpharmacologic interventions for suicide prevention. These covered a range of interventions delivered one-to-one, within a small group or in a community setting (Tables 1 and 2). Included interventions were provided face-to-face, via the Internet, or through mobile telephone applications. Using the USPSTF criteria for SRs, we rated the quality of the 5 SRs as good. The overall quality of the included studies was rated as fair in 4 SRs (6–9) and poor in 1 SR (10). Study limitations included concerns about blinding, allocation concealment, participant attrition, and potential for reporting bias. Table 1 shows quality ratings for the body of evidence for each intervention. The

*Table 1*–Continued

| Suicide | | | Hopelessness | | |
|---|---|---|---|---|---|
| **Evidence Base (Reference)** | **Findings** | **SOE** | **Evidence Base (Reference)** | **Findings** | **SOE** |
| 6 RCTs from 1 SR (8) | ND | Low | 7 RCTs from 1 SR (10) | Favors intervention | Moderate |
| – | NR | – | – | NR | – |
| – | NR | – | – | NR | – |
| 2 RCTs (13, 14) | ND | Low | 1 RCT from 1 SR (10) | ND | Low |
| 3 RCTs from 1 SR (8) | Favors intervention | Low | – | NR | – |
| – | NR | – | – | NR | – |
| – | NR | – | – | NR | – |
| – | NR | – | 1 RCT (11) | Favors intervention | Low |

quality of the included individual trials ranged from good to poor according to the USPSTF criteria. Two trials were rated as good (11, 12), 6 were rated as fair (13–18), and 4 were rated as poor (19–22). Study limitations were related primarily to moderate to high participant attrition, lack of clarity about allocation concealment and blinding, and potential reporting bias. Supplement Tables 1 to 3 (available at Annals.org) provide full GRADE ratings and study information.

### *Cognitive Behavioral Therapy*

Four SRs and 1 additional RCT examined treatment with cognitive behavioral therapy (CBT) for suicide behavior and prevention. One SR (10 RCTs; $n = 1241$) focused on the effects of CBT compared with treatment as usual (TAU) on suicide attempts in adults who had attempted suicide within 6 months of the study (6). Another SR (22 RCTs; $n = 1977$) evaluated the effect of CBT delivered face-to-face or via the Internet compared with TAU or, in some studies, a nondirective control (for example, wait list or befriending) on suicidal ideation (7). A third SR (6 RCTs; $n = 1040$) focused on the effect of CBT versus TAU on suicide prevention (8). The final SR (18 RCTs; $n = 3458$) assessed the effect of CBT compared with TAU on hopelessness, suicidal ideation, and suicide (10).

The RCT assessed the effectiveness of CBT compared with an attention-control program for prevention of suicidal ideation among medical interns with a mean age of 25 years (19). Participants in the CBT group ($n = 100$) received 4 weekly Web-based sessions lasting 30 minutes each, and those in the attention-control group ($n = 99$) received 4 weekly e-mails containing information about depression and suicide and contact information for local mental health services.

The findings suggest that CBT reduced suicide attempts (risk ratio [RR], 0.47 [95% CI, 0.30 to 0.73]; $P = 0.0009$) (6), suicidal ideation (standardized mean difference [SMD], −0.24 [CI, −0.41 to −0.07] in 15 studies [7] and −0.32 [CI, −0.53 to −0.11] in 8 studies [10]), and hopelessness (SMD, −0.31 [CI, −0.51 to −0.10]) (10) compared with TAU. The strength of the evidence for these outcomes was moderate (Table 1). However, CBT did not seem to prevent or reduce suicide (8, 10); the strength of evidence for this outcome was low. No harms related to CBT were reported in the included evidence. Further data (7) suggest a modest benefit of Internet-delivered CBT compared with nondirective

*Table 2.* Evidence for Other Nonpharmacologic Interventions*

| Intervention | Evidence Base (Reference) | Outcomes | SOE |
|---|---|---|---|
| Partial hospitalization vs. control | 2 RCTs from 1 SR (8) | Suicide | Very low |
| Case management vs. TAU | 4 RCTs from 1 SR (10) | Suicide | Low |
| Mixed multimodal therapy vs. TAU | 1 RCT from 1 SR (10) | Suicide, hopelessness | Low |
| Self-help (Web-based) vs. attention control | 1 RCT (15) | Suicide attempt, suicidal ideation | Low |
| CAMS vs. TAU | 1 RCT (16) | Suicide attempt, suicidal ideation | Low |
| Active visit and treatment vs. TAU | 1 RCT (17) | Suicide attempt, suicidal ideation | Low |
| Abandonment therapy vs. TAU | 1 RCT (12) | Suicide attempt, suicidal ideation | Low |
| Other electronically delivered psychotherapies | 14 RCTs from 1 SR (9) | Suicide attempt, suicidal ideation | Low |
| Community-based programs | 2 RCTs (21, 22) | Suicide, suicide attempt | Very low |

CAMS = Collaborative Assessment and Management of Suicidality framework; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; SOE = strength of evidence; SR = systematic review; TAU = treatment as usual.
* Supplement Table 1 (available at Annals.org) provides reasons for the GRADE ratings.

*Table 3.* Pharmacologic Interventions for Suicide Prevention*

| Intervention | Suicide Attempts | | | Suicidal Ideation | | |
|---|---|---|---|---|---|---|
| | Evidence Base (Reference) | Findings | SOE | Evidence Base (Reference) | Findings | SOE |
| Buprenorphine vs. placebo† | 1 RCT (26) | ND‡ | Very low | 1 RCT (26) | Favors intervention | Very low |
| Ketamine vs. control | – | – | – | 1 SR (23) and 2 RCTs (27, 28) | Favors intervention | Moderate |
| Lithium vs. placebo | – | NR | – | – | NR | – |
| Lithium vs. active medication | – | NR | – | – | NR | – |
| NGA vs. placebo† | – | NR | – | – | NR | – |

GRADE = Grading of Recommendations Assessment, Development and Evaluation; ND = no difference between intervention and control; NGA = newer-generation antidepressant; NR = not reported; RCT = randomized controlled trial; SOE = strength of evidence; SR = systematic review.
* Supplement Table 4 (available at Annals.org) provides reasons for the GRADE ratings.
† Data not used to inform any recommendations.
‡ Only 1 event per group.

controls (very low strength of evidence), but not when compared with TAU or CBT delivered face-to-face.

### *Dialectical Behavior Therapy*

Dialectical behavior therapy (DBT) combines elements of CBT, skills training, and mindfulness techniques with the aim of helping persons with borderline personality disorder (BPD) develop skills in emotion regulation, interpersonal effectiveness, and distress tolerance. One SR (10) and 3 RCTs (13, 14, 20) assessed the efficacy of DBT for suicide behavior and prevention.

The SR included 5 RCTs ($n$ = 222) that examined the efficacy of DBT among patients with BPD who were at high risk for suicide (10). The included RCTs compared DBT with TAU (3 trials), client-oriented therapy (1 trial), less directive psychotherapy (1 trial), and DBT plus prolonged exposure therapy (1 trial). Two of the additional RCTs also assessed the efficacy of DBT in reducing suicidal behavior among patients diagnosed with BPD. One compared DBT skills training plus TAU ($n$ = 42) versus TAU alone ($n$ = 42) (13), and the other compared DBT plus the Collaborative Assessment and Management of Suicidality framework (CAMS) ($n$ = 57) versus CAMS alone ($n$ = 51) (14). The final RCT assessed the efficacy of DBT among veterans at high risk for suicide without a diagnosis of BPD (20). Veterans were randomly assigned to standard DBT for 6 months ($n$ = 46) or treatment according to the recommendations of their mental health team ($n$ = 45).

The findings for DBT suggest that it is more effective than client-oriented therapy (MD, −7.75 [CI, −14.66 to −0.84] in 1 RCT [$n$ = 24] in the SR [10]) and wait-list control (1 RCT [$n$ = 84]; $P$ < 0.04) (13) in reducing suicidal ideation. However, the overall quality of the evidence supporting this outcome was low. No differences were found between DBT and TAU, "expert-led" psychotherapy, or CAMS for suicidal ideation. Similarly, no differences were found between DBT and TAU or other psychotherapeutic interventions for hopelessness, suicide attempts, or death.

### *Brief Intervention*

One SR included 3 RCTs ($n$ = 2028) that compared the World Health Organization's Brief Intervention and Contact method (WHO-BIC) with an active control condition for suicide prevention (8). The intervention included an educational session on suicide prevention followed by regular contact with a trained provider by telephone or in person for up to 18 months. The findings suggest that WHO-BIC reduced the incidence of suicide compared with the control condition (3 of 1041 vs. 24 of 987; odds ratio [OR], 0.20 [CI, 0.09 to 0.42]; $P$ < 0.001).

### *Crisis Response Planning*

An RCT evaluated the effectiveness of enhanced CRP (E-CRP) ($n$ = 33) versus standard CRP ($n$ = 32) or TAU ($n$ = 32) for prevention of suicide attempts in patients with active suicidal ideation or a history of suicide attempt (18). The TAU group used a verbal contract for safety along with risk assessment, supportive listening, and provision of crisis resources. The standard CRP group used the same components as the TAU group, but without the verbal contract for safety. The E-CRP group used the same components as the standard CRP group but also included an explicit discussion of the patient's reasons for living. The findings suggest a difference in the number and proportion of suicide attempts that favored CRP of either type versus TAU (hazard ratio, 0.24 [CI, 0.06 to 0.96]; $P$ = 0.028) but no difference between E-CRP and standard CRP.

### *Window to Hope*

One RCT evaluated the efficacy of a group psychological intervention called Window to Hope in reducing hopelessness and suicidal ideation among veterans with moderate to severe traumatic brain injury (11). Participants were randomly assigned to receipt of ten 2-hour weekly sessions of Window to Hope ($n$ = 15) or to a wait-list control ($n$ = 20). The wait-list group continued to receive usual care from the VA until the start of group therapy. The average age of the veterans in this study was 51 years, and follow-up was 3 months. The findings suggest that Window to Hope improved hopelessness (MD, 4.4 [CI, 0.52 to 8.3]; $P$ = 0.03) but not suicidal ideation (MD, 3.8 [CI, −0.29 to 8.0]; $P$ = 0.07) compared with the wait-list control.

*Table 3*–Continued

| Suicide | | | Adverse Events | | |
|---|---|---|---|---|---|
| **Evidence Base (Reference)** | **Findings** | **SOE** | **Evidence Base (Reference)** | **Findings** | **SOE** |
| – | NR | – | 1 RCT (26) | Favors control | Very low |
| – | NR | – | 1 RCT (28) | Favors control | Moderate |
| 1 SR (24) | Favors intervention | Moderate | – | NR | – |
| 1 SR (24) | ND | Low | – | NR | – |
| 1 SR (25) | ND | Low | – | NR | – |

### *Other Interventions*

The evidence base for the interventions presented in Table 2 was small and was not used to inform any recommendations because of concerns about the low certainty of the evidence. Overall, the findings suggest no difference between the interventions and the control conditions.

## Pharmacologic Interventions

Three SRs (23–25) and 3 RCTs (26–28) evaluated the effectiveness of a range of pharmacotherapies for adult patients at risk for suicide (Table 3). Using the USPSTF criteria, we rated the quality of the SRs as good. The quality of the included studies was rated as fair overall in the 3 SRs. Study limitations were primarily related to lack of clarity surrounding randomization, allocation concealment, and blinding in the original trials, as well as study attrition and possible selective reporting of outcomes. Table 3 shows quality ratings for the body of evidence for each medication. Quality ratings ranged from fair to poor across the individual RCTs. Limitations of the studies rated as fair included lack of blinding of some patients (28) and lack of clarity about allocation concealment and blinding of outcome assessors (27). Limitations of the RCT rated as poor (26) included high attrition rates and unexplained diagnostic, pharmacologic, and therapeutic heterogeneity of the study population. Supplement Tables 4 to 6 (available at Annals.org) provide full GRADE ratings and study information.

### *Ketamine*

A meta-analysis used individual patient–level data ($n$ = 167) to compare a single intravenous dose of ketamine with placebo or midazolam for reducing suicidal ideation (23). Two additional RCTs examined the efficacy and safety of a subanesthetic dose of racemic ketamine hydrochloride (0.5 mg/kg of body weight) over 40 minutes ($n$ = 60) versus midazolam (0.02 mg/kg [$n$ = 40] or 0.05 mg/kg [$n$ = 19]) (27, 28). In all studies, suicidal ideation (clinician-assessed and self-reported) was reduced with ketamine. Only 1 study reported on adverse events and showed a transient increase in blood pressure during administration, with a return to normal within approximately 15 minutes after the infusion (systolic: $t = -6.22$ [$P < 0.001$]; diastolic: $t = -5.85$ [$P < 0.001$]) (28).

### *Lithium*

A large SR ($n$ = 6674) sought to determine the efficacy of lithium versus other active treatments (25 RCTs) or placebo (23 RCTs) in preventing suicide in patients with unipolar or bipolar mood disorders over a range of 4 to 48 months (24). Rates of suicide were statistically significantly lower with lithium than with placebo (OR, 0.13 [CI, 0.03 to 0.66]). There were no differences between lithium and other active treatments (ORs: amitriptyline, 0.13 [CI, 0.01 to 2.05]; carbamazepine, 0.37 [CI, 0.09 to 1.51]; lamotrigine, 1.35 [CI, 0.08 to 22.91]; olanzapine, 7.49 [CI, 0.15 to 377.68]). Harms were not reported.

### *Other Medications*

Two additional studies of pharmacologic treatments were identified but were not used to inform any recommendations because of concerns about very low certainty of the evidence, adverse effect profile, and lack of applicability to a U.S.-based patient population. One RCT examined the safety and efficacy of very low dosages of sublingual buprenorphine as a time-limited treatment for suicidal ideation, suicide attempt, and adverse events (26). The buprenorphine group had a greater reduction in Beck Scale for Suicide Ideation score than the placebo group after 4 weeks (MD, −7.1 [CI, −12.0 to −2.3]; $P$ = 0.004). There was 1 suicide attempt in each group (difference not significant). Rates of treatment-related adverse events were higher in the buprenorphine group, and the most common adverse events were fatigue, nausea, dry mouth, and constipation. Finally, an SR compared a range of pharmacologic and natural products for patients with a history of self-harm (25). The authors noted that data were not reported numerically in many of the included studies, which limited their ability to analyze outcomes. We report on the most complete available data on newer-generation antidepressants (NGAs), which include mianserin, nomifensine, and paroxetine. The findings suggest that there were no significant differences between NGAs and placebo (OR, 0.32 [CI, 0.01 to 8.04])

in suicide or hopelessness. The authors of an included trial stated that hopelessness scores did not differ between NGAs and placebo, but no numerical data were reported. Our searches for other medications did not yield any new publications that met inclusion criteria. Therefore, the workgroup retained the recommendations related to other medications in the previous CPG.

## DISCUSSION

In this SR, we reviewed and synthesized evidence from 8 SRs and 15 RCTs of nonpharmacologic and pharmacologic interventions intended to prevent suicide in at-risk persons. These interventions are a subset of topics included in the updated VA/DoD 2019 CPG for assessment and management of patients at risk for suicide. The full final guideline is available from the VA Web site (www.healthquality.va.gov).

Nonpharmacologic interventions encompassed a range of approaches delivered either face-to-face or via the Internet or other technology. We found moderate-strength evidence supporting the use of face-to-face or Internet-delivered CBT in reducing suicide attempts, suicidal ideation, and hopelessness compared with TAU. We found low-strength evidence suggesting that CBT was not effective in reducing suicides. However, rates of suicide were generally low in the included studies, which limits our ability to draw firm conclusions about this outcome. Data from small studies provide low-strength evidence supporting the use of DBT over client-oriented therapy or control for reducing suicidal ideation. For other outcomes and other comparisons, we found no benefit of DBT. There was low-strength evidence supporting use of WHO-BIC to reduce suicide, CRP to reduce suicide attempts, and Window to Hope to reduce suicidal ideation and hopelessness.

We found moderate-strength evidence supporting use of short-term intravenous ketamine for reducing suicidal ideation and use of lithium for reducing suicide. Patients in a meta-analysis that used individual patient–level data (23) had diagnoses of major depressive disorder, bipolar disorder, or posttraumatic stress disorder with baseline suicidal ideation. Patients in 1 RCT had a diagnosis of major depressive disorder (28), and those in another RCT had recently been diagnosed with cancer (27). All trials in the meta-analysis and the RCTs excluded patients with a history of substance use disorder or past or current psychotic disorders, which limits generalizability to these high-risk populations. In a large SR, risk for suicide was significantly lower with lithium than placebo in patients with unipolar or bipolar mood disorders. However, compared with other active treatments for mood disorders, no benefits of lithium use were found. The data for these comparisons were highly variable and do not suggest that the treatments are equivalent.

Our review has several limitations. The methods underlying the SRs for VA/DoD guidelines rely on previously published SRs. Although a benefit of this is the ability to perform rapid reviews for formulating evidence-based recommendations, we were limited by what was reported in the SRs. When SRs addressing a question or outcome of interest were not available, we incorporated and synthesized data from published clinical trials. However, the time frame for conducting the SR did not allow us to perform quantitative synthesis; therefore, we provide a qualitative, narrative synthesis of the literature. In addition, our time frame did not allow for dual screening or dual ROB assessment. We addressed the former issue by using the DistillerAI function (Evidence Partners) to confirm that no studies were missed in the database and relied on iterative feedback from the guideline panel. To address the latter concern, a senior reviewer checked all ratings and made corrections as needed. Finally, the methods outlined in the VA/DoD Guideline for Guidelines (3) direct the approach of using existing SRs as the primary source of evidence in reviews supporting the VA/DoD CPGs. Using previously published SRs could result in potential bias, either by overrepresenting studies if they are reported in more than 1 review included in the final evidence synthesis or by missing important studies (29). We recognized this and attempted to reduce bias by including the most comprehensive, recent SRs with high methodological rigor; by also including studies that were published subsequent to the review; and by carefully assessing areas of overlap. We occasionally included reviews that overlapped provided that they reported on different outcomes or subgroups of interest. Typically, overlap in reviews is highlighted for the CPG workgroup panel to assist them in interpreting the overall findings.

Given the need for interventions to mitigate risk for suicide, particularly in the veteran and active military populations, the lack of evidence to support current nonpharmacologic and pharmacologic interventions and the lack of information on potential harms is significant. We found modest benefit of CBT and DBT in reducing suicidal ideation compared with TAU or wait-list control, and CBT also reduced suicide attempts compared with TAU. Both ketamine and lithium had modest benefit in reducing the rate of suicide compared with placebo. The data on ketamine are short-term, with follow-up of only 1 to 7 days in the SR and up to 6 weeks in 1 small RCT, and long-term information on patients treated with ketamine is not available. Recently, the U.S. Food and Drug Administration cleared the s-enantiomer of ketamine, esketamine, as a nasal spray for use in patients with treatment-resistant depression, and long-term follow-up studies may better inform future guideline recommendations. Adverse events related to ketamine administration in 1 included study were limited to transient increases in blood pressure. Although adverse events were not measured in the trials examining use of lithium, it has a low therapeutic index and requires patient safety monitoring. Finally, several gaps in the literature merit further study. These are described extensively in the full CPG, which is available at the Web site for the VA/DoD CPGs (30).

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**Corresponding Author:** Kristen E. D'Anci, PhD, Senior Associate Director, Center for Clinical Evidence and Guidelines, ECRI Institute, 5200 Butler Pike, Plymouth Meeting, PA 19462-1298; e-mail, kdanci@ecri.org.

Current author addresses and author contributions are available at Annals.org.

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**Current Author Addresses:** Dr. D'Anci, Ms. Uhl, Ms. Giradi, and Ms. Martin: Center for Clinical Evidence and Guidelines, ECRI Institute, 5200 Butler Pike, Plymouth Meeting, PA 19462-1298.

**Author Contributions:** Conception and design: K.E. D'Anci, S. Uhl.
Analysis and interpretation of the data: K.E. D'Anci, S. Uhl.
Drafting of the article: K.E. D'Anci, S. Uhl, G. Giradi, C. Martin.
Critical revision of the article for important intellectual content: K.E. D'Anci.
Final approval of the article: K.E. D'Anci, S. Uhl, G. Giradi, C. Martin.
Statistical expertise: K.E. D'Anci.
Collection and assembly of data: K.E. D'Anci, S. Uhl, G. Giradi, C. Martin.

## Appendix: Key Questions

### KQs Addressed in the Review

1. For adults identified as being at increased risk for suicide, what non-pharmacologic/behaviorally based interventions improve health outcomes (decreased suicide attempts, decreased suicide deaths, improved functional status and quality of life, or health status) or intermediate outcomes (decreased suicidal ideation, depressive symptomatology, or hopelessness)?
    a. Does the effect of the interventions vary by level of risk?
    b. Does the effect of the interventions vary by population characteristics?
    c. What are the potential harms of the intervention and do the harms vary by population?
2. For adults identified as being at increased risk for suicide, what pharmacological interventions improve health outcomes (decreased suicide attempts, decreased suicide deaths, improved functional status and quality of life, or health status) or intermediate outcomes (decreased suicidal ideation, depressive symptomatology, or hopelessness)?
    a. Does the effect of the interventions vary by level of risk?
    b. Does the effect of the interventions vary by population characteristics?
    c. What are the potential harms of the intervention and do the harms vary by population?
3. In adult patients at risk for suicide, what community-based interventions and/or social support programs are effective at reducing risk of suicide?
4. In adult patients at risk for suicide, what is the effectiveness of telehealth modalities compared to a usual care setting?
5. In adult patients at risk for suicide, what is the effectiveness of technology-based interventions as an adjunct to usual care in improving outcomes?

### KQs Addressed in the Full CPG

1. In adults, do screening programs to detect suicide risk improve health outcomes (decreased suicide attempts, decreased suicide deaths, improved functioning, improved quality of life, or improved health status) or intermediate outcomes (decreased suicidal ideation, depressive symptomatology, or hopelessness)?
    a. Does the effect of screening programs vary by population characteristics?
        i. Population characteristics include: gender, age, race/ethnicity, post-deployment status, populations at high risk for suicide, chronic medical or mental health co-morbidities (PTSD, TBI)
    b. Does the effect of screening programs vary by healthcare setting (primary care, mental health, ED, community-based setting, Vet centers, specialty care [e.g., oncology])?
    c. Are there potential harms or unintended consequences associated with screening for suicide risk in healthcare settings?
2. In adults, do instruments used in healthcare settings to screen for increased risk for suicide accurately identify those who are at increased risk?
    a. Does the accuracy of the screening instruments vary by population characteristics?
    b. How often and by whom should these instruments be administered?
    c. Are structured assessment tools superior to unstructured clinical assessment interviews?
    d. In what settings and populations does the positive predictive value of instruments support their utility in practice?
3. What methods are most effective in stratifying risk of suicide behavior and suicide?
    a. Are structured assessment tools superior to unstructured clinical assessment interviews?
4. For patients identified as being at risk for suicide, what are the most effective treatment approaches?
    a. Does the effect of the interventions vary by level of risk?
    b. Does the effect of the interventions vary by population characteristics?
    c. What are the potential harms of the intervention and do the harms vary by population?
5. In adults with suicide ideation/attempt, what are the most effective post-acute care approaches?
    a. What follow-up plan is most effective immediately after discharge (e.g. intervention, frequency, timing, assessments, location)?
    b. What are the most effective interventions for managing long-term risk in an adult who was hospitalized?
6. In adult patients at risk for suicide, what factors can increase risk or reduce or protect against suicidal behavior?
7. What community-based interventions are effective at reducing population-level risk of suicide?

*Appendix Table 1.* Literature Search Strategy: EMBASE Syntax

| Set | Concept | Strategy |
|---|---|---|
| **Nonpharmacologic/ behavior-based interventions** | | |
| #1 | Problem (suicide) | 'suicidal behavior'/exp/mj OR sdv:ti,ab OR 'self-directed violence':ti OR 'self-directed violent':ti OR 'self-harm':ti OR 'self-inflicted':ti OR 'self injur*':ti OR suicid*:ti |
| #2 | Nonpharmacologic/behavior-based interventions | 'behavior therapy'/exp OR 'cognitive therapy'/exp OR 'narrative therapy'/mj OR 'virtual reality exposure therapy'/mj OR 'accelerated resolution therapy':ab,ti OR art:ab,ti OR 'behavior therapy':ti,ab OR 'behaviour therap':ti,ab OR 'behavioral therapy':ti,ab OR 'behavioural therapy':ti,ab OR 'bep tg':ab,ti OR cbct:ab,ti OR cbt:ab,ti OR 'cognitive behavioral conjoint therapy':ab,ti OR 'cognitive behavioral therapy':ab,ti OR 'cognitive behavioural therapy':ab,ti OR 'cognitive processing therapy':ab,ti OR 'cognitive therapy':ab,ti OR eclectic:ab,ti OR ehlers:ab,ti OR emdr:ab,ti OR 'emotional freedom':ab,ti OR 'exposure therapy':ab,ti OR 'eye movement desensitization':ab,ti OR 'imagery rehearsal therapy':ab,ti OR 'implosive therapy':ab,ti OR mindfulness:ab,ti OR 'narrative therapy':ab,ti OR 'prolonged exposure therapy':ab,ti OR 'thought field therapy':ab,ti OR 'trauma focused':ab,ti OR 'virtual reality':ab,ti OR 'written exposure therapy':ab,ti |
| #3 | Nonpharmacologic/behavior-based interventions | 'acceptance and commitment therapy'/exp OR 'family therapy'/exp OR 'marital therapy'/exp OR 'mindfulness'/exp OR 'psychodynamic psychotherapy'/exp OR 'psychotherapy'/exp OR 'acceptance and commitment therapy':ti,ab OR act:ti,ab OR 'behavioral activation':ti,ab OR 'behavioural activation':ti,ab OR 'couples counseling':ti,ab OR 'couples therapy':ti,ab OR 'emotion focused couples therapy':ti,ab OR 'family therapy':ti,ab OR 'interpersonal therapy':ti,ab OR ipt:ti,ab OR 'marital therapy':ti,ab OR 'marriage therapy':ti,ab OR mindfulness:ti,ab OR 'neurolinguistic programming':ti,ab OR pct:ti,ab OR 'present centered therapy':ti,ab OR 'problem solving therapy':ti,ab OR psychoanalysis:ti,ab OR psychodynamic*:ti,ab OR psychotherap*:ti,ab OR relaxation:ti,ab OR 'seeking safety':ti,ab OR sit:ti,ab OR 'socioenvironmental therapy':ti,ab OR 'stress inoculation therapy':ti,ab OR 'supportive counseling':ti,ab OR "home visit*":ti,ab OR "environmental change*":ti,ab OR "coping skills":ti,ab OR "caring contacts":ti,ab OR "care environment change*":ti,ab OR |
| #4 | CAM interventions | 'acupuncture'/exp OR 'alternative medicine'/exp OR 'animal assisted therapy'/exp OR 'art therapy'/de OR 'dance therapy'/de OR 'diet supplementation'/de OR 'exercise'/exp OR 'herbal medicine'/de OR 'homeopathic agent'/de OR 'integrative medicine'/de OR 'meditation'/de OR 'mindfulness'/de OR 'music therapy'/de OR 'phytotherapy'/de OR 'psychodrama'/de OR 'recreational therapy'/de OR 'tai chi'/de OR 'transcendental meditation'/de OR 'yoga'/de |
| #5 | CAM interventions | Acupuncture:ti,ab OR (("animal assisted" OR art OR "creative art" OR "creative arts" OR dance OR drama OR movement OR music OR recreational) NEAR/2 therap*):ti,ab OR ((alternative OR complementary OR integrative) NEAR/2 medicine):ti,ab OR (dietary NEAR/2 supplement*):ti,ab OR exercise:ti,ab OR fishing:ti,ab OR herbs:ti,ab OR herbal:ti,ab OR Homeopath*:ti,ab OR mantram:ti,ab OR meditation:ti,ab OR meditate*:ti,ab OR mindbody:ti,ab OR "mind body":ti,ab OR mindfulness:ti,ab OR phytotherapy:ti,ab OR "progressive muscle relaxation":ti,ab OR Psychodrama:ti,ab OR relaxation:ti,ab OR "Tai Chi":ti,ab OR "Tai Ji":ti,ab OR Yoga:ti,ab |
| #6 | Safety planning | ((safety OR crisis) NEAR/2 plan*):ti,ab |
| #7 | Lethal means restriction | ('lethal means':ti,ab OR gun*:ti,ab OR firearm*:ti,ab) AND restrict*:ti,ab |
| #8 | Combine interventions | #2 OR #3 OR #4 OR #5 OR #6 OR #7 |
| #9 | Combine sets | #1 AND #8 |
| #10 | Meta-analyses and systematic reviews | See hedge at end of table |
| #11 | RCTs | See hedge at end of table |
| #12 | Combine sets | #10 OR #11 |

*Continued on following page*

*Appendix Table 1*–Continued

| Set | Concept | Strategy |
|---|---|---|
| **Pharmacologic interventions** | | |
| #1 | Problem (suicide) | 'suicidal behavior'/exp/mj OR sdv:ti,ab OR 'self-directed violence':ti OR 'self-directed violent':ti OR 'self-harm':ti OR 'self-inflicted':ti OR 'self injur*':ti OR suicid*:ti |
| #2 | Pharmacotherapy: general | 'drug therapy'/exp OR ((drug* OR pharma*) NEAR/2 (therap* OR treatment*)) OR pharmacological OR 'pharmaco-therapy' OR 'pharmaco-therapies' OR pharmacotherapy* |
| #3 | Pharmacotherapy: antipsychotics | 'neuroleptic agent'/exp OR 'anti psychotic' OR 'anti psychotics' OR antipsychotic* OR chlorpromazine OR fluphenazine OR haloperidol OR loxapine OR neuroleptic OR perphenazine OR pimozide OR thioridazine OR thiothixene OR trifluoperazine |
| #4 | Pharmacotherapy: atypical antipsychotics | 'atypical antipsychotic agent'/mj OR aripiprazole OR asenapine OR brexpiprazole OR clozapine OR iloperidone OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR ziprasidone |
| #5 | Pharmacotherapy: mood stabilizers | 'anticonvulsive agent'/mj OR anticonvuls* OR carbamazepine OR divalproex OR gabapentin OR lamotrigine OR lithium OR 'mood stabilizer*' OR oxcarbazepine OR pregabalin OR tiagabine OR topiramate OR valproate OR 'valproic acid' |
| #6 | Sedatives | 'hypnotic sedative agent'/mj OR 'sedative agent'/mj OR 'anti anxiety' OR antianxiety OR buspirone OR clonidine OR diphenhydramine OR eszopiclone OR guanfacine OR hydroxizine OR hypnotic* OR ramelteon OR sedative* OR suvorexant OR tasimelteon OR zaleplon OR zolpidem OR zopiclone |
| #7 | Pharmacotherapy: antidepressants | 'antidepressant agent'/exp/mj OR 'serotonin noradrenalin reuptake inhibitor'/exp/mj OR 'serotonin uptake inhibitor'/exp/mj OR 'tricyclic antidepressant agent'/exp/mj OR 'triple reuptake inhibitor'/exp/mj OR amitriptyline OR amoxapine OR buproprion OR 'anti-depressant' OR 'anti-depressants' OR antidepressant* OR citalopram OR clomipramine OR desipramine OR desvenlafaxine OR doxepin OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR hydroxizine OR imipramine OR levomilnacipran OR maprotiline OR milnacipran OR mirtazapine OR nefazodone OR nortriptyline OR paroxetine OR protriptyline OR 'selective serotonin reuptake inhibitor' OR 'selective serotonin reuptake inhibitors' OR 'serotonin noradrenaline reuptake inhibitor' OR 'serotonin noradrenaline reuptake inhibitors' OR 'serotonin norepinephrine reuptake inhibitor' OR 'serotonin norepinephrine reuptake inhibitors' OR sertraline OR snri* OR ssri* OR trazodone OR trimipramine OR venlafaxine OR vilazodone OR vortioxetine OR (tricyclic NEAR/2 antidepressant*) |
| #8 | Pharmacotherapy | ketamine OR naloxone OR 'medication assisted treatment' OR MAT |
| #9 | Combine interventions | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| #10 | Combine sets | #1 AND #9 |
| #11 | Meta-analyses and systematic reviews | See hedge at end of table |
| #12 | RCTs | See hedge at end of table |
| #13 | Combine sets | #11 OR #12 |
| **Community-based interventions** | | |
| #1 | Problem (suicide) | 'suicidal behavior'/exp/mj OR sdv:ti,ab OR 'self-directed violence':ti OR 'self-directed violent':ti OR 'self-harm':ti OR 'self-inflicted':ti OR 'self injur*':ti OR suicid*:ti |
| #2 | Community-based interventions | 'community intervention'/exp OR 'health literacy'/exp OR "community resources" OR "community support" OR "health literacy" OR 'patient education'/exp OR "family education" OR "patient education" OR "provider education" OR 'public health campaign'/exp OR (community NEAR/2 intervention*) OR (stigma NEAR/2 reduc*) |
| #3 | Community-based interventions | 'clergy'/exp OR 'social support'/exp OR clergy OR chaplain* OR 'family support'/exp OR (peer* NEAR/2 (program* OR support)) OR "Confidential care" OR "Vet centers" OR "Be there" OR "social support" |
| #4 | Combine sets | #2 OR #3 |
| #5 | Combine sets | #1 AND #4 |
| #6 | Meta-analyses and systematic reviews | See hedge at end of table |
| #7 | RCTs | See hedge at end of table |
| #8 | Combine sets | #6 OR #7 |

*Continued on following page*

*Appendix Table 1*–Continued

| Set | Concept | Strategy |
|---|---|---|
| **Telehealth modalities/technology** | | |
| #1 | Problem (suicide) | 'suicidal behavior'/exp/mj OR sdv:ti,ab OR 'self-directed violence':ti OR 'self-directed violent':ti OR 'self-harm':ti OR 'self-inflicted':ti OR 'self injur*':ti OR suicid*:ti |
| #2 | Telehealth | 'telehealth'/exp OR mobile OR phone OR remote OR telemedicine OR telenursing OR telehealth* OR telephone OR virtual |
| #3 | Technology | 'mobile application'/exp OR apps OR "crisis line*" OR "text line*" OR "caring contact" OR "Technology supported management" OR "technology based intervention*" OR "web-based" |
| #4 | Combine sets | #2 OR #3 |
| #5 | Combine sets | #1 AND #4 |
| #6 | Meta-analyses and systematic reviews | See hedge at end of table |
| #7 | RCTs | See hedge at end of table |
| #8 | Combine sets | #6 OR #7 |
| **General hedges applied to each search** | Limit to English-language publications | AND [English]/lim |
| | Remove undesired age ranges | NOT child*:ti |
| | Remove undesired publication types (e.g., conferences, editorials) | NOT (abstract:nc OR annual:nc OR 'book'/exp OR 'case study'/exp OR conference:nc OR 'conference abstract':it OR 'conference paper'/exp OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR 'editorial'/exp OR editorial:it OR 'erratum'/exp OR letter:it OR 'note'/exp OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/exp OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR 'case report'/de OR 'case report':ti OR 'a case':ti OR 'a patient':ti OR 'year old':ti,ab) |
| | Limit by publication date within range | AND [18-11-2011]/sd NOT [11-4-2018]/sd |
| **Study type hedges applied as needed** | Limit to meta-analyses and systematic reviews | AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR ((systematic* NEAR/2 review*):ab,ti) OR metaanaly*:ab,ti OR 'meta analysis':ab,ti OR 'meta analyses':ab,ti OR search*:ab) |
| | Limit to RCTs | AND ('random sample'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR randomization/de OR random*:ti,ab) |

CAM = complementary and alternative medicine; RCT = randomized controlled trial.

*Appendix Table 2.* Literature Search Strategy: PsycINFO Syntax

| Set | Concept | Strategy |
|---|---|---|
| **Nonpharmacologic/ behavior-based interventions** | | |
| #1 | Problem (suicide) | *SUICIDE/ or sdv.ti,ab. or "self-directed violence".ti. or "self-directed violent".ti. or "self-inflicted".ti. or suicid*.ti. |
| #2 | Nonpharmacologic/behavior-based interventions | exp Cognitive Therapy/ OR Eye Movement Desensitization Reprocessing/ OR Virtual Reality Exposure Therapy/ OR exp Behavior Therapy/ OR exp Cognitive Behavior Therapy/ OR Cognitive Therapy/ OR Eclectic Psychotherapy/ OR exp Exposure Therapy/ OR Eye Movement Desensitization Therapy/ OR Virtual Reality/ OR (Accelerated Resolution Therapy OR ART OR (Behavior* ADJ2 therap*) OR (behaviour* ADJ2 therap*) OR BEP-TG OR Brief eclectic psychotherapy OR CBCT OR CBT OR cognitive behavioral conjoint therapy OR cognitive behavioral therapy OR Cognitive Processing Therapy OR (cognitive ADJ2 therap*) OR Ehlers OR EMDR OR emotional freedom OR exposure therapy OR Eye Movement Desensitization OR imagery rehearsal OR Mindfulness OR Narrative Therapy OR Prolonged Exposure Therapy OR thought field therapy OR trauma focused OR virtual reality exposure OR Written Exposure Therapy).ti,ab. |
| #3 | Nonpharmacologic/behavior-based interventions | Acceptance and Commitment Therapy/ OR Family Therapy/ OR exp Mind-Body Therapies/ OR mindfulness/ OR Neurolinguistic Programming/ OR exp psychotherapy/ OR Psychotherapy, Psychodynamic/ OR px.fs OR Relaxation Therapy/ OR exp Socioenvironmental Therapy/ OR th.fs OR Acceptance and Commitment Therapy/ OR Brief Psychotherapy/ OR exp Cognitive Behavior Therapy/ OR Cognitive Therapy/ OR Conjoint Therapy/ OR Couples Therapy/ OR Emotion Focused Therapy/ OR exp Family Therapy/ OR Interpersonal Psychotherapy/ OR exp Marriage Counseling/ OR Meditation/ OR mindfulness/ OR Neurolinguistic Programming/ OR exp Psychoanalysis/ OR Psychodynamic Psychotherapy/ OR Psychotherapy/ OR Relaxation/ OR exp Relaxation Therapy/ OR (acceptance and commitment therapy OR behavioral activation OR couples therapy OR emotion focused couples therapy OR family therapy OR interpersonal therapy OR IPT OR marital therapy OR marriage therapy OR meditation OR mindfulness OR Neurolinguistic programming OR PCT OR Present Centered Therapy OR Problem Solving Therapy OR Psychoanalysis OR psychodynamic* OR psychotherap* OR relaxation OR Seeking Safety OR SIT OR Socioenvironmental Therapy OR Stress Inoculation Therapy OR supportive counseling).ti,ab. OR ("home visit*" OR "environmental change" OR "coping skills" OR "caring contacts").ti,ab. |
| #4 | CAM interventions | Acupuncture/ OR Acupuncture Therapy/ OR Animal Assisted Therapy/ OR Art Therapy/ OR Dance Therapy/ OR Dietary Supplements/ OR exp Exercise/ OR Herbal Medicine/ OR Homeopathy/ OR Integrative Medicine/ OR Meditation/ OR exp Mind-Body Therapies/ OR Music Therapy/ OR Plants, Medicinal/ OR Psychodrama/ OR Recreation Therapy/ OR Relaxation/ OR Relaxation Therapy/ OR Tai Ji/ OR yoga/ OR Acupuncture/ OR exp Alternative Medicine/ OR Art Therapy/ OR Animal Assisted Therapy/ OR exp Creative Arts Therapy/ OR Dietary Supplements/ OR exp Exercise/ OR Holistic Health/ OR Martial Arts/ OR exp "medicinal herbs and plants"/ OR Mind Body Therapy/ OR Mindfulness/ OR Meditation/ OR Movement Therapy/ OR Music Therapy/ OR Progressive Relaxation Therapy/ OR Psychodrama/ OR Recreation Therapy/ OR Relaxation/ OR Relaxation Therapy/ OR Yoga/ |
| #5 | CAM interventions | Acupuncture.ti,ab. OR (("animal assisted" OR art OR "creative art" OR "creative arts" OR dance OR drama OR movement OR music OR recreational) ADJ2 therap*).ti,ab. OR ((alternative OR complementary OR integrative) ADJ2 medicine).ti,ab. OR (dietary ADJ2 supplement*).ti,ab. OR exercise.ti,ab. OR fishing.ti,ab. OR herbs.ti,ab. OR herbal.ti,ab. OR Homeopath*.ti,ab. OR mantram.ti,ab. OR meditation.ti,ab. OR meditate*.ti,ab. OR mind-body.ti,ab. OR mindfulness.ti,ab. OR phytotherapy.ti,ab. OR "progressive muscle relaxation".ti,ab. OR Psychodrama.ti,ab. OR relaxation.ti,ab. OR "Tai Chi".ti,ab. OR "Tai Ji".ti,ab. OR Yoga.ti,ab. |
| #6 | Safety planning | ((safety OR crisis) ADJ2 plan*).ti,ab. |
| #7 | Lethal means restriction | (("lethal means" OR gun* OR firearm*) AND restrict*).ti,ab. |
| #8 | Combine interventions | 2 OR 3 OR 4 OR 5 OR 6 OR 7 |
| #9 | Combine sets | 1 AND 8 |
| #10 | Meta-analyses and systematic reviews | See hedge at end of table |
| #11 | RCTs | See hedge at end of table |
| #12 | Combine sets | 10 OR 11 |

*Continued on following page*

*Appendix Table 2*–Continued

| Set | Concept | Strategy |
|---|---|---|
| **Pharmacologic interventions** | | |
| #1 | Problem (suicide) | *SUICIDE/ or sdv.ti,ab. or "self-directed violence".ti. or "self-directed violent".ti. or "self-inflicted".ti. or suicid*.ti. |
| #2 | Pharmacotherapy: general | dt.fs or exp Drug Therapy/ OR (drug* ADJ2 (therap* OR treatment*)).ti,ab. or pharmacological.ti,ab. or pharmaco-therap*.ti,ab. or pharmacotherap*.ti,ab. |
| #3 | Pharmacotherapy: antipsychotics | Antipsychotic Agents/ OR chlorpromazine/ OR fluphenazine/ OR haloperidol/ OR loxapine/ OR perphenazine/ OR pimozide/ OR thioridazine/ OR thiothixene/ OR trifluoperazine/ OR exp Neuroleptic Drugs/ OR (anti-psychotic* OR antipsychotic* OR chlorpromazine OR fluphenazine OR haloperidol OR loxapine OR neuroleptic OR perphenazine OR pimozide OR thioridazine OR thiothixene OR trifluoperazine).ti,ab. |
| #4 | Pharmacotherapy: atypical antipsychotics | Antipsychotic Agents/ OR aripiprazole/ OR clozapine/ OR lurasidone hydrochloride/ OR paliperidone palmitate/ OR quetiapine fumarate/ OR risperidone/ OR aripiprazole/ OR exp Neuroleptic Drugs/ OR (aripiprazole OR asenapine OR brexpiprazole OR clozapine OR iloperidone OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR ziprasidone).ti,ab. |
| #5 | Pharmacotherapy: mood stabilizers | carbamazepine/ OR clonidine/ OR lithium/ OR pregabalin/ OR valproic acid/ OR anticonvulsive drugs/ OR Carbamazepine/ OR exp Lithium/ OR Mood Stabilizers/ OR Valproic Acid/ OR (anticonvuls* OR carbamazepine OR divalproex OR gabapentin OR lamotrigine OR lithium OR (mood ADJ2 stabiliz*) OR oxcarbazepine OR pregabalin OR tiagabine OR topiramate OR valproate OR valproic acid).ti,ab. |
| #6 | Sedatives | anti-anxiety agents/ OR buspirone/ OR diphenhydramine/ OR eszopiclone/ OR guanfacine/ OR Hypnotics and Sedatives/ OR exp sedatives/ OR (buspirone OR clonidine OR diphenhydramine OR eszopiclone OR guanfacine OR hydroxizine OR hypnotic* OR ramelteon OR sedative* OR suvorexant OR tasimelteon OR zaleplon OR zolpidem OR zopiclone).ti,ab. |
| #7 | Pharmacotherapy: antidepressants | amitriptyline/ OR amoxapine/ OR exp Antidepressive Agents/ OR Antidepressive Agents, Tricyclic/ OR citalopram/ OR clomipramine/ OR desipramine/ OR Desvenlafaxine Succinate/ OR doxepin/ OR Duloxetine Hydrochloride/ OR fluoxetine/ OR fluvoxamine/ OR imipramine/ OR maprotiline/ OR nortriptyline/ OR paroxetine/ OR protriptyline/ OR Serotonin and Noradrenaline Reuptake Inhibitors/ OR exp serotonin uptake inhibitors/ OR sertraline/ OR trazodone/ OR trimipramine/ OR Venlafaxine Hydrochloride/ OR Vilazodone Hydrochloride/ OR exp Antidepressant Drugs/ OR exp Serotonin Norepinephrine Reuptake Inhibitors/ OR exp Serotonin Reuptake Inhibitors/ OR exp Tricyclic Antidepressant Drugs/ OR (amitriptyline OR amoxapine OR buproprion OR anti-depressant* OR antidepressant* OR citalopram OR clomipramine OR desipramine OR desvenlafaxine OR doxepin OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR hydroxizine OR imipramine OR levomilnacipran OR maprotiline OR milnacipran OR mirtazapine OR nefazodone OR nortriptyline OR paroxetine OR protriptyline OR selective serotonin reuptake inhibitor* OR serotonin noradrenaline reuptake inhibitor* OR Serotonin norepinephrine reuptake inhibitor* OR sertraline OR SNRI* OR SSRI* OR trazodone OR tricyclic antidepressant* OR trimipramine OR venlafaxine OR vilazodone OR vortioxetine).ti,ab. |
| #8 | Pharmacotherapy | (ketamine OR naloxone OR 'medication assisted treatment' OR MAT).ti,ab. |
| #9 | Combine interventions | 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 |
| #10 | Combine sets | 1 AND 9 |
| #11 | Meta-analyses and systematic reviews | See hedge at end of table |
| #12 | RCTs | See hedge at end of table |
| #13 | Combine sets | 11 OR 12 |
| **Community-based interventions** | | |
| #1 | Problem (suicide) | *SUICIDE/ or sdv.ti,ab. or "self-directed violence".ti. or "self-directed violent".ti. or "self-inflicted".ti. or suicid*.ti. |

*Continued on following page*

*Appendix Table 2*–Continued

| Set | Concept | Strategy |
|---|---|---|
| #2 | Community-based interventions | exp Community Services/ or Health Promotion/ or exp Community Mental Health Services/ or Health Education/ or exp Public Health/ or "community resources".mp. or "community support".mp. or "health literacy".mp. or "family education".mp. or "patient education".mp. or "provider education".mp. or (community adj2 intervention*).mp. or (stigma adj2 reduc*).mp. |
| #3 | Community-based interventions | exp clergy/ or exp social support/ or clergy.mp. or chaplain*.mp. or ((family or peer* or spouse or parent*) adj2 (program* or support)).mp. or "Confidential care".mp. or "Vet centers".mp. or "Be there".mp. or "social support".mp. |
| #4 | Combine sets | 2 OR 3 |
| #5 | Combine sets | 1 AND 4 |
| #6 | Meta-analyses and systematic reviews | See hedge at end of table |
| #7 | RCTs | See hedge at end of table |
| #8 | Combine sets | 6 OR 7 |
| **Telehealth modalities/ technology** | | |
| #1 | Problem (suicide) | *SUICIDE/ or sdv.ti,ab. or "self-directed violence".ti. or "self-directed violent".ti. or "self-inflicted".ti. or suicid*.ti. |
| #2 | Telehealth | exp Telemedicine/ or mobile.mp. or phone.mp. or remote.mp. or telemedicine.mp. or telenursing.mp. or telehealth*.mp. or telephone.mp. or virtual.mp. |
| #3 | Technology | exp Mobile Devices/ or exp Computer Applications/ or exp Technology/ or apps.mp. or "crisis line".mp. or "text line".mp. or "caring contact".mp. or "Technology supported management".mp. or "technology based intervention".mp. or "web-based".mp. |
| #4 | Combine sets | 2 OR 3 |
| #5 | Combine sets | 1 AND 4 |
| #6 | Meta-analyses and systematic reviews | See hedge at end of table |
| #7 | RCTs | See hedge at end of table |
| #8 | Combine sets | 6 OR 7 |
| **General hedges applied to each search** | Limit to English-language publications | limit # to english language |
| | Remove undesired publication types (e.g., conferences, editorials) | not ((authored book or autobiography or biography or book or case reports or comment or conference* or dissertation abstract edited book or editorial or encyclopedia or lectures or letter or news or note or proceeding or video-audio media or webcasts).pt. or (bibliography or chapter or column/opinion or comment/reply or dissertation or editorial or encyclopedia entry or letter or obituary or review-book).dt. or child.ti.) |
| | Limit by publication date within range | limit # to yr="2011 - 2018" |
| **Study type hedges applied as needed** | Limit to meta-analyses and systematic reviews | and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt. or literature review/))) |
| | Limit to RCTs | and ((Randomized controlled trials or random allocation).de. or random$.ti,ab.) |

CAM = complementary and alternative medicine; RCT = randomized controlled trial.

*Appendix Table 3.* Literature Search Strategy: PILOTS Database Syntax

| Set | Concept | Strategy |
|---|---|---|
| #1 | Problem (suicide) | (MAINSUBJECT(suicidality) OR ti(suicid*) |
| #2 | Publication type | (stype.exact("Scholarly Journals") |
| #3 | Date range | pd(20111118-20180410))) |
| #4 | Combine sets | #1 AND #2 AND #3 |

PILOTS = Published International Literature on Traumatic Stress.

*Appendix Table 4.* Study Quality Checklist for RCTs, Based on USPSTF Criteria

| Study, Year (Reference) | Adequate Randomization* | Group Comparability Maintained Throughout Study† | Potential for Measurement Bias Minimized‡ | Proper Analysis of Trial Data§ | Overall Rating‖ |
|---|---|---|---|---|---|
| **Nonpharmacologic interventions** | | | | | |
| Guille et al, 2015 (19) | Yes | No; >20% attrition | Some concern; use of self-reported outcomes | Yes | Poor |
| McMain et al, 2017 (13) | Yes | Yes | Some concern; self-reported outcomes | Some concern; ancillary treatments not excluded | Fair |
| Andreasson et al, 2016 (14) | Yes | Some concern; moderate attrition in DBT group | Some concern; patient and therapist not masked | Yes | Fair |
| Goodman et al, 2016 (20) | Some concern; allocation concealment not reported | No; >20% attrition | Some concern; not reported whether outcome assessor masked | Yes | Poor |
| Brenner et al, 2018 (11) | Yes | Yes | Yes | Yes | Good |
| Bryan et al, 2017 (18) | Some concern; recruitment suspended for 1 y | Yes | Yes | Yes | Fair |
| van Spijker et al, 2018 (15) | Yes | Some concern; moderate attrition | Some concern; selective reporting bias | Yes | Fair |
| Mousavi et al, 2017 (17) | Some concern; allocation concealment not reported | Yes | Some concern; not reported whether outcome assessor masked | Yes | Fair |
| Jobes et al, 2017 (16) | Some concern; allocation concealment not reported | Yes | Some concern; not reported whether outcome assessor masked | Yes | Fair |
| Andreoli et al, 2016 (12) | Yes | Yes | Yes | Yes | Good |
| Collings et al, 2018 (22) | Yes | Yes | No; outcome assessors not blinded and data on suicides from public records | Yes | Poor |
| Aquin et al, 2017 (21) | Yes | Some concern; control group may have received partial intervention | No; outcome assessor not masked | Yes | Poor |
| **Pharmacologic interventions** | | | | | |
| Yovell et al, 2016 (26) | No; baseline heterogeneity | No; >20% attrition | Yes | Some concern; modified intention-to-treat analysis | Poor |
| Fan et al, 2017 (27) | Some concern; allocation concealment not reported | Yes | Some concern; not reported whether outcome assessor masked | Yes | Fair |
| Grunebaum et al, 2018 (28) | Yes | Some concern; moderate attrition | Some concern; remitters not masked | Yes | Fair |

DBT = dialectical behavior therapy; RCT = randomized controlled trial; USPSTF = U.S. Preventive Services Task Force.
* Includes adequate allocation sequence and concealment and equal distribution of baseline confounders.
† Includes overall and between-group attrition, adherence, crossover, and contamination.
‡ Includes measurement of all important outcomes, use of reliable and valid instrument, and masking of outcome assessors.
§ For example, intention-to-treat analysis and proper consideration of confounders.
‖ Quality is rated as "good" if the study meets all of the following criteria: comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%); reliable and valid measurement instruments are used and applied equally in all groups; interventions are spelled out clearly; all important outcomes are considered; appropriate attention is paid to confounders in analysis; and, for RCTs, intention-to-treat analysis is used. Quality is rated as "fair" if any of the following problems occur (without the fatal flaws noted in the "poor" category): generally comparable groups are assembled initially, but questions remain about whether some (not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and are generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs. Quality is rated as "poor" if any of the following fatal flaws exist: groups assembled initially are not close to being comparable or are not maintained throughout the study; unreliable or invalid measurement instruments are used or are not applied equally among groups (including unmasked outcome assessment); key confounders are given little or no attention; and, for RCTs, intention-to-treat analysis is lacking.