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Emerging pharmacological and neuromodulation interventions for suicidal ideation and behaviour

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ABSTRACT

Suicide remains a leading cause of premature mortality worldwide. Current treatments are limited by delayed onset, durability, or poor tolerability. This narrative review, informed by a structured literature search,

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Transcranial magnetic stimulation
N-methyl-D-aspartate receptor antagonists
Opioid agonists

summarises the last decade of evidence on pharmacological and neuromodulation interventions for suicidal ideation (SI) or suicide attempt (SA) that are not approved for these indications. We searched PubMed for studies enrolling adults with SI or SA, including controlled trials and naturalistic/observational studies. Thirty-four studies were included: 22 pharmacological (13 efficacy, nine effectiveness) and 12 using neuromodulation (nine efficacy, three effectiveness). Across controlled trials, SI commonly improved within days to weeks. Some trials reported SI reduction beyond concurrent depression score changes, suggesting partial independence, but evidence remains inconsistent and method-dependent. Encouraging results were reported for NMDA-related drugs (NRX-101 and high-dose D-cycloserine; amantadine in Borna disease virus-1–positive depression), opioid-system modulation (buprenorphine at ultra-low and high doses in distinct populations), ayahuasca in major and treatment-resistant depression, and adjunctive pimavanserin. Smaller effects were observed for vortioxetine augmentation and insomnia-targeted zolpidem. Large observational datasets reported associations between lower suicidality and folic acid, benztropine, testosterone initiation in transgender adults, and non-vitamin K oral anticoagulants versus warfarin, whereas non-medical cannabis use was associated with worse SI trajectories. Neuromodulation evidence implicated accelerated or targeted repetitive transcranial magnetic stimulation, theta-burst stimulation, and magnetic seizure therapy for SI reduction, with longer-term observational support for vagus nerve stimulation. Future trials should prespecify suicide-related outcomes, test independence from mood change, and assess durability and high-risk transition periods to advance suicide-specific treatment development.

1. Introduction

Suicide remains a major global public health concern, accounting for >720,000 deaths each year worldwide and ranking as the third leading cause of death among individuals aged 15–29 (WHO, 2025). In Europe, age-adjusted suicide mortality rates have been reported at approximately 10.2 deaths per 100,000 people, with variation across countries and demographic subgroups in recent years (Zuin and De Leo, 2025). Sex differences show a stable pattern across studies and countries. Women generally show higher rates of non-fatal attempts and ideation, while men account for two- to eight-fold more deaths due to more lethal methods and lower help-seeking (Schrijvers et al., 2012). Estimates of the economic consequences of suicide in European contexts, based on indirect productivity losses, include €9.07 billion in productivity losses for suicide deaths across the EU-28 in 2015 and approximately €750 million per year in Sweden when including both fatal and non-fatal outcomes (productivity and direct costs) in 2022 (Feldman, 2025; Łyszczarz, 2021). Much of this burden is concentrated in clinical populations.

Psychiatric disorders are a major predictor of suicidal ideation (SI) and suicide attempt (SA). In major depressive disorder (MDD), the pooled lifetime prevalence of SAs reaches 31% (95% CI: 27–34%), which is over six times higher than in the general population (Jiang et al., 2024). Similar rates are observed in bipolar disorder (BD), psychotic, and substance use disorders (SUD) (Franklin et al., 2017). Beyond diagnostic associations, recent evidence from genetic studies suggests substantial pleiotropy between SI/SA phenotypes and a range of correlated psychiatric and non-psychiatric traits, which may help refine mechanistic targets for intervention development (Martone et al., 2025). Initial evidence also suggests that SI may not simply represent a quantitative correlate of depressive symptom severity. Rather, it may follow partially different temporal and clinical patterns, with changes that may precede or occur independently of mood improvement (Batterham et al., 2019). Specifically, SI may emerge, improve, or recur on timescales that do not necessarily parallel broader mood trajectories, contributing to growing interest in suicide-specific therapeutic targets and interventions (Grunebaum et al., 2018).

A broad spectrum of clinical strategies was implemented to reduce suicide risk in these populations. Psychotherapeutic interventions, whether direct (i.e., explicitly targeting SI and SA) or indirect (i.e., addressing suicide-related outcomes as a secondary outcome in the treatment of a psychiatric disorder), showed small-to-moderate efficacy, with *Hedges' g* ~ 0.30–0.39 for SI and a relative risk reduction of approximately 28–32% for SA (Van Ballegooijen et al., 2025). Recent digital psychotherapy has shown comparable efficacy (*Hedges' g* ~ 0.48) in reducing SI, while offering scalable solutions that bypass barriers related to stigma and geographic accessibility (Oh et al., 2024).

Despite these advancements, pharmacological treatments remain the most widely adopted method for reducing suicidality (Zisook et al., 2023). Among these, antidepressants are commonly prescribed, yet their therapeutic effects commonly start after several weeks. They may also increase suicide risk in children and adolescents, as well as adults during the early stages of treatment (Hetrick et al., 2012). Lithium has shown efficacy in mood disorders, reducing suicide risk by nearly 80% compared to placebo (Cipriani et al., 2013). Clozapine remains the only medication specifically approved for suicide prevention in schizophrenia, though its use is limited by serious haematological, metabolic, and cardiovascular adverse events (Masdrakis and Baldwin, 2023; Lee et al., 2023). Finally, sub-anaesthetic ketamine and intranasal esketamine can reduce SI rapidly, but effects are typically short-lived (Shen et al., 2024).

These constraints have motivated the evaluation of novel compounds targeting GABAergic, orexinergic, inflammatory, metabolic, and psychedelic systems beyond the traditional monoaminergic system, with the aim of achieving rapid and broad antisuicidal effects independent of improvement of mood or psychotic symptoms (Scala et al., 2023). In parallel, advances in device-based interventions have increased interest in neuromodulation, broadly defined as the intentional alteration of nervous system activity through electrical, magnetic, or chemical stimuli. This concept extends beyond the narrower scope of neurostimulation, which primarily refers to focal energy delivery (De Ridder et al., 2021). From electroconvulsive therapy (ECT) to advanced techniques such as deep brain stimulation, vagus nerve stimulation, repetitive transcranial magnetic stimulation, and transcranial direct-current stimulation, a wide range of neuromodulation strategies have been explored. However, evidence for suicidality-specific effects remains inconclusive (Kucuker et al., 2021).

Given the persistent burden of suicidality and the limitations of current treatments, this review synthesises recent evidence on emerging pharmacological and neuromodulation-based strategies with potential effects in reducing SI or SA. We focus specifically on therapeutic interventions that have not yet received regulatory approval for suicide prevention but have shown preliminary efficacy in controlled research settings and/or potential effectiveness in real-world clinical settings.

2. Methods

2.1. Literature search

This article is a narrative review informed by a structured literature search. Two reviewers (M.S. and E.M.) conducted an independent structured search on PubMed (National Library of Medicine), retrieving

eligible articles published over the last 10 years up to February 2025. Keywords related to investigational compounds with potential effects in reducing SI or SA and recent neuromodulation techniques were combined using the Boolean operator OR, and then linked to suicidality-related terms using AND. A full list of the pharmacological, neuromodulatory, and suicide-related terms used in the search is provided in **Supplementary Materials, Appendix I**. Medical Subject Headings (MeSH) terms were also used when appropriate to enhance retrieval sensitivity. Reference lists of previous reviews and relevant articles were scanned for additional records. Any discrepancies were resolved by a senior reviewer (G.F.).

2.2. Eligibility criteria

Studies were included if they met the following criteria: 1) published in English in a peer-reviewed journal over the last 10 years; 2) involved adult individuals aged over 18 years with SI or SA; 3) provided data on the efficacy (i.e., the ability to reduce SI or SA under ideal and controlled conditions, such as in randomised clinical trials [RCTs]) or effectiveness (i.e., the ability to reduce SI or SA in real-world clinical settings, accounting for patient diversity and clinical variability) of pharmacological or neuromodulatory treatment either as monotherapy or adjunctive therapy; 4) suicide-related outcomes were assessed with: a) validated scales or scale items (i.e., the Columbia-Suicide Severity Rating Scale [C-SSRS], specific SI and SA items from the Hamilton Depression Rating Scale [HAMD], Montgomery-Åsberg Depression Rating Scale- Suicidal Ideation [MADRS-SI], Beck Scale for Suicide Ideation [BSSI or BSI], Scale for Suicide Ideation [SSI], Suicidal Ideation Attributes Scale [SIDAS], Clinical Global Impression of Severity for Suicide [CGI-SS], Quick Inventory of Depressive Symptomatology–Self Report [QIDS-SR]); or b) objective clinical measures (i.e., documented SA or SA frequency).

There were no restrictions based on study type (i.e., observational or interventional study), sex, study duration, diagnosis of psychiatric illness, or inpatient/outpatient status of the participants.

We excluded: 1) studies that only reported the lack of an increase in SI as part of safety and tolerability assessments for a pharmacotherapy; 2) studies on ketamine/esketamine (studies evaluating non-ketamine interventions [e.g., NRX-101] in post-ketamine stabilisation/maintenance designs were still eligible), clozapine, or lithium due to their established anti-suicidal effects as this review focuses on novel interventions (Masdrakis and Baldwin, 2023; Shen et al., 2024; Cipriani et al., 2013); 3) books, editorials, letters to the editor, corrigenda, literature reviews, meta-analyses, clinical vignettes, conference proceedings, theoretical articles, qualitative studies, grey literature, and newsletters, as well as conference abstracts.

2.3. Data extraction and presentation of results

Data from the included studies were extracted independently by two reviewers (M.S. and E.M.), collecting the following information: study type, design and duration, diagnosis, prescribed daily dose, route of administration, treatment modality (monotherapy or adjunctive treatment), and treatment duration. For neuromodulation interventions, additional data were extracted on stimulation modality and related parameters. The primary outcome was the efficacy or effectiveness of the drug or neuromodulation intervention in reducing SI or SA. Any discrepancies between reviewers were resolved by a senior reviewer (G.F.).

The data were organised and presented in both tabular and narrative formats, according to the review question. Given heterogeneity in study designs, populations, and suicide-related outcome definitions, a narrative review informed by a structured search was selected *a priori*. We did not perform a quantitative synthesis or formal risk-of-bias assessment because the available evidence combined randomised trials, post hoc analyses, open-label studies, observational cohorts, and survey-based studies, with variable ascertainment of suicidal ideation and behaviour. Further restriction of the inclusion criteria would have excluded relevant early-phase and exploratory interventions. The narrative approach was considered the most appropriate method to address the breadth and methodological heterogeneity of the emerging literature and to facilitate an integrated interpretation of the available data. Findings are therefore presented descriptively, with controlled trials and observational studies interpreted separately.

3. Results

Thirty-four studies met the inclusion criteria: 22 investigated pharmacological agents (13 efficacy trials, nine effectiveness studies) and 12 examined neuromodulation approaches (nine efficacy, three effectiveness in naturalistic settings). Study-level details are provided in Table 1.

Participants included individuals with MDD, including treatment-resistant depression (TRD), BD, borderline personality disorder (BPD), SUD, schizophrenia, and gender dysphoria. Six of the 34 included studies (17.6%) enrolled adults with primary SI without a psychiatric disease (Yovell et al., 2016; Nolan et al., 2023; Gibbons et al., 2022; Jones and Nock, 2022; Yang et al., 2022; Li et al., 2024a). Fig. 1 shows diagnostic distributions across drug and neuromodulation studies. Fig. 2 summarises intervention duration, follow-up length, and, when reported, the earliest timepoint of a statistically significant anti-suicidal effect, in efficacy studies. Due to heterogeneity in study design and inconsistent reporting of temporal information, data for effectiveness studies are presented in the **Supplementary Figure S1**.

3.1. Pharmacotherapy

Pharmacological strategies targeted multiple mechanisms, including N-methyl-D-aspartate (NMDA) receptor modulation (NRX-101, amantadine, D-cycloserine [DCS]), classic and novel psychedelics (ayahuasca, psilocybin, lysergic acid diethylamide [LSD], 3,4-methylenedioxymethamphetamine [MDMA], other tryptamines), opioid-system modulation (buprenorphine), monoaminergic agents (paroxetine, bupropion, vortioxetine), serotonin/dopamine receptor modulators (pimavanserin, brexpiprazole), and GABA-A receptor positive allosteric modulators (zolpidem). Additional agents comprised folic acid, benztropine, testosterone therapy, cardiovascular drugs (non-vitamin K oral anticoagulants [NOACs] vs. warfarin), and cannabis. Secondary outcome domains reported across pharmacological studies are summarised in Fig. 3.

3.1.1. NMDA receptor–related strategies

Three RCTs investigated the efficacy of NMDA receptor modulation as a strategy to reduce SI.

NRX-101, an oral combination of high-dose DCS (350–950 mg) and lurasidone (16.5–66 mg), produced greater SI reductions than lurasidone alone in bipolar depression after ketamine response, at both 4 and 6 weeks, with consistent effects across C-SSRS ($\Delta = -1.5$, $p = 0.02$) and CGI-SS ($\Delta = -2.9$, $p = 0.02$) (Nierenberg et al., 2023). Similarly, adjunctive high-dose DCS alone (250–1000 mg) in TRD (MDD and BD) led to greater reductions in HAMD item 3 over 6 weeks vs. placebo ($F(1, 26) = 7.91$, $p = 0.01$), though no antidepressant effects were observed (Chen et al., 2019). In contrast, amantadine (200 mg/day), tested in MDD/BD for Borna disease virus 1 (BDV-1)–positive patients, showed a progressive and large effect on SI (HAMD-3), with Cohen's d increasing from 0.66 at week 2 to 1.02 at week 7, and global superiority across HAMD items (Cohen's $d = 1.05$) (Dietrich et al., 2020).

Overall, NMDA-related interventions were associated with reductions in SI over weeks in controlled designs, with variable evidence for separation from overall depressive symptom change.

3.1.2. Psychedelics

Two clinical trials investigated the efficacy of ayahuasca for rapidly reducing SI. In an open-label study, a single oral dose (2.2 mL/kg) in

Table 1
Summary of included studies published in peer-reviewed journals until February 2025 assessing the effect of pharmacological and neuromodulation treatments on suicidal ideation (SI) and suicide attempt (SA). Table 1a presents studies evaluating the efficacy of pharmacological treatments, while Table 1b includes studies assessing the effectiveness of pharmacotherapy in reducing SI/SA in real-world clinical contexts. Table 1c presents studies evaluating the efficacy of neuromodulation treatments, and Table 1d includes studies assessing the effectiveness of neuromodulatory interventions in routine clinical practice.

Table 1a
PHARMACOTHERAPY

Study, category, and intervention	Diagnosis	Intervention details and treatment context	Study design and registration	Duration and follow-up	Baseline suicidality measure (s)	Sample characteristics	Efficacy on SI/SA
Study: Nierenberg et al., 2023; Category: NMDA modulation; Intervention: NRX-101 (D-cycloserine + lurasidone).	BD	Dose/route: DCS 350–950 mg + lurasidone 16.5–66 mg, oral; Modality: sequential oral treatment after initial ketamine response.	Study type/registration: phase 2 RCT; NCT02974010; Design: phase 2 randomised oral-treatment comparison after initial ketamine response: lurasidone (n = 5) versus NRX-101 (n = 12).	Stage 1: initial ketamine-response phase on day 1; Stage 2: oral treatment from day 2 to day 42 (6 weeks); Assessments/follow-up: days 28 and 42; Hospitalisation: 48-hour supervision during the initial ketamine-response phase.	C-SSRS at start of Stage 2 (day 2): lurasidone group = 2.4; NRX-101 group = 3.0.	N enrolled (sex): 22 (6 F/16 M); Stage 2 efficacy sample: n = 17 (NRX-101 n = 12; lurasidone n = 5); Mean age, years: 39.5 ± 11.43.	NRX-101 ↓ SI versus lurasidone alone at day 28 (C-SSRS least-squares mean Δ: −1.3, p = 0.04; CGI-SS least-squares mean Δ: −2.9, p = 0.05) and day 42 (C-SSRS Δ: −1.5, p = 0.02; CGI-SS Δ: −2.9, p = 0.02) under LOCF.
Study: Dietrich et al., 2020; Category: NMDA modulation; Intervention: Amantadine sulfate.	MDD or BD; all BDV-1 seropositive	Dose/route: 200 mg/day, oral; Modality: adjunctive treatment, with pre-existing therapeutic regimens maintained unchanged where present.	Study type/registration: Phase II RCT; DRKS00007649; Design: Randomised N = 36, 18 per arm; Period I analysed sample: N = 33, amantadine n = 16 and placebo n = 17; Period II cross-over: placebo n = 15 and amantadine n = 16; Cross-over completers: N = 31.	Intervention: two 7-week periods, each including 6 weeks of treatment plus 1 week washout; total double-blind cross-over phase: 14 weeks. Follow-up: 12 months with optional amantadine treatment.	HAM-D item 3; baseline suicidality score not reported.	Period I analysed sample N (sex): 33 (21 F/12 M); Mean age, years: 52.79 ± 9.94.	Amantadine ↓ SI over the first 2 weeks (Cohen's d = 0.66, p = 0.04), with growing effect size at week 4 (d = 0.97) and week 7 (d = 1.02); After 7 weeks amantadine was superior to placebo on all HAM-D items (mean d = 1.05). Item 3: Δ score amantadine = −1.63 ± 0.9 versus placebo = −1 ± 1, p = 0.039.
Study: Chen et al., 2019; Category: NMDA modulation; Intervention: DCS.	TRD in MDD or BD	Dose/route: DCS 250 mg, 500 mg, 750 mg, 1000 mg, oral; Modality: adjunctive to current medication.	Study type/registration: two-stage study; Stage 1 open-label ketamine phase; Stage 2 RCT; R000027142-UMIN000023581; Design: Stage 2 included ketamine responders randomised to DCS (n = 16) versus placebo (n = 16).	Stage 1: 1 week; Stage 2: 6-week intervention with weekly follow-up/assessment.	Baseline HAM-D item 3: DCS group = 0.31 ± 0.48; placebo group = 0.19 ± 0.54; between-group p = 0.495.	N (sex): 32 (24 F/8 M); Mean age, years: 46.2 (SD not reported).	DCS group showed ↓ HAM-D item 3 scores across time versus placebo (F(1, 26) = 7.91, p = 0.01); day 0: 0.31 (0.48) versus 0.19 (0.54); day 42: 0.44 (0.63) versus 0.38 (0.62).
Study: Zeifman et al., 2021; Category: Psychedelics; Intervention: Ayahuasca.	MDD	Dose/route: 2.2 mL/kg, oral, single dose; Modality: monotherapy.	Study type/registration: open-label trial; Design: single-dose, one-treatment-group inpatient study; SI assessed at baseline, 40, 80, and 180 minutes post-administration, and at days 1, 7, 14, and 21.	Intervention: single administration; Follow-up: 21 days.	Baseline MADRS item 10 (SI): 2.4 ± 1.35.	Full trial sample N (sex): 17 (14 F/3 M); Mean age, years: 42.71 ± 12.11. Suicidality analysis sample n = 15, after excluding 2 participants with baseline MADRS item 10 (SI) = 0.	Ayahuasca produced acute and sustained ↓ in SI. Post-acute effect sizes were large, Hedges' g = 1.31–1.75, with the largest effect at day 21, Hedges' g = 1.75.
Study: Zeifman et al., 2019; Category: Psychedelics; Intervention: Ayahuasca.	TRD	Dose/route: 1 mL/kg, oral; Modality: monotherapy after 2-week washout.	Study type/registration: RCT; NCT02914769; Design: Arm 1: ayahuasca (n = 14); Arm 2: placebo (n = 15); Setting: mainly outpatient care.	Intervention: single administration; Follow-up: 7 days.	Baseline MADRS item 10 (SI): ayahuasca = 3.36 ± 1.65; placebo = 1.40 ± 1.68.	N (sex): 29 (16 F/13 M); Mean age, years: 42.04 ± 11.66.	Group effect approached significance (p = 0.088); Medium between-group effect sizes: d = 0.58 (Day 1), d = 0.56 (Day 2), d = 0.67 (Day 7); Large within-group effects for ayahuasca: d = 1.33 (Day 1), 1.42 (Day 2), 1.19 (Day 7)

(*continued on next page*)

Table 1 (*continued*)

Study: Ahmadi et al., 2018; Category: Opioid agonism; Intervention: Buprenorphine (sublingual).	MDD and OUD	Dose/route: 32 mg, 64 mg, or 96 mg, sublingual; Modality: monotherapy.	Study type/registration: RCT; IRCT20160713251 60N4; Design: randomised N = 51, 17 per group; treated/analysed N = 47 after 4 refused dosing; analysed groups: 32 mg n = 16, 64 mg n = 17, 96 mg n = 14; Setting: inpatient care.	Intervention: 3 days; Follow-up: 14 days.	Baseline BSSI: 32 mg group = 8.50 ± 8.53; 64 mg group = 11.05 ± 9.58; 96 mg group = 8.24 ± 6.08.	N (sex): 47 (0 F/47 M); Mean age, years: 32.87 ± 7.50.	↓ in SI within all groups from baseline to day 3 ($p < 0.01$); No difference between doses ($p = 0.408$); No patients reported SI at 2-week follow-up; No placebo arm, so efficacy versus nonspecific inpatient or withdrawal-related effects cannot be estimated.
Study: Yovell et al., 2016; Category: Opioid agonism; Intervention: Buprenorphine (sublingual).	SI without SUD	Dose/route: 0.44 mg/day, sublingual; Modality: adjunctive to ongoing clinical care; antidepressants were used by 70.2% of buprenorphine patients and 71.0% of placebo patients during the study.	Study type/registration: RCT; NCT01046851; Design: randomised 2:1 to buprenorphine or placebo (randomised: buprenorphine n = 57; placebo n = 31; modified ITT efficacy sample: buprenorphine n = 40; placebo n = 22); outpatient and inpatient care.	Intervention: 4 weeks; Assessments/follow-up: weekly from week 1 to week 4.	Baseline BSSI: buprenorphine = 19.7 ± 4.9, placebo = 19.6 ± 5.4; Baseline SPS: buprenorphine = 92.1 ± 18.1, placebo = 91.3 ± 16.5.	N (sex): 88 (63 F/25 M); Mean age, years: 37.3 ± 13.9. Modified ITT efficacy sample: n = 62.	BSSI ↓ greater in buprenorphine versus placebo at week 2: MD = −4.3 (95% CI: −8.5 to −0.2; $p = 0.04$); at week 4: MD = −7.1 (95% CI: −12.0 to −2.3; $p = 0.004$); SPS score also ↓: MD = −10.4 (95% CI: −19.7 to −1.0; $p = 0.03$); SA: 1/57 buprenorphine and 1/31 placebo. No withdrawal symptoms reported at 1-week follow-up.
Study: Shelton et al., 2020; Category: Antipsychotics; Intervention: Pimavanserin.	MDD with inadequate response to ongoing SSRI or SNRI therapy	Dose/route: pimavanserin 34 mg/day, oral; Modality: adjunctive to background SSRI or SNRI.	Study type/registration: Post hoc suicidality analysis of the CLARITY randomised, double-blind, placebo-controlled Phase 2 trial; NCT03018340; Design: sequential parallel-comparison design; stage 1: placebo versus pimavanserin, randomised 3:1 for 5 weeks; placebo non-responders were re-randomised 1:1 in Stage 2 for another 5 weeks.	Intervention: 10 weeks total, with two 5-week stages; 30-day safety follow-up; Assessments/follow-up: weekly from week 1 to week 10.	HAMD-17 item 3; C-SSRS. Stage 1 baseline HAMD item 3: placebo = 0.4; pimavanserin = 0.5. Baseline C-SSRS suicidal ideation, questions 1–3: placebo 30/155, pimavanserin 15/52.	Stage 1 C-SSRS sample: placebo n = 155; pimavanserin n = 52. Stage 1 HAMD item 3 shift/sample denominator: placebo n = 152; pimavanserin n = 51. Stage 2: placebo n = 29; pimavanserin n = 29. Sex and mean age were not reported in this post hoc paper.	Stage 1 HAMD item 3 decreased more with pimavanserin than placebo at week 3, least squares mean difference = −0.2, SE = 0.08, $p = 0.012$, Cohen's $d = 0.431$. Among patients with baseline HAMD item 3 ≥1, week-3 reduction also favoured pimavanserin, least squares mean difference = −0.5, SE = 0.21, $p = 0.038$, Cohen's $d = 0.598$; No increase in SI was observed on C-SSRS.
Study: Keilp et al., 2018; Category: Antidepressants; Intervention: paroxetine and bupropion.	MDD with SI and/or prior SA	Dose/route: paroxetine 25, 37.5, or 50 mg; bupropion 150, 300, or 450 mg, oral; Modality: monotherapy.	Study type/registration: RCT; secondary analysis of Grunebaum et al., 2012; Design: Arm 1: paroxetine (n = 36); Arm 2: bupropion (n = 38); Setting: outpatient care.	Intervention: 8 weeks; Assessments/follow-up: weekly from week 1 to week 8.	Baseline SSI: 9.0 ± 7.1.	N (sex): 74 (42 F/32 M); Mean age, years: 36.5 ± 12.7.	Both treatments ↓ SI, no between-group difference; Improvement was associated with change in subjective depressive symptoms (i.e., hopelessness); $R^2 = 0.20$, $p = 0.0006$ for subjective domain versus suicidality change, but not cognitive or somatic domains.
Study: Gorlyn et al., 2015; Category: Antidepressants; Intervention: paroxetine and bupropion.	MDD with SI and/or prior SA	Dose/route: paroxetine 25, 37.5, or 50 mg; bupropion 150, 300, or 450 mg, oral; Modality: monotherapy.	Study type/registration: RCT; secondary analysis of Grunebaum et al., 2012; Design: Arm 1: paroxetine (n = 30); Arm 2:	Intervention: 8 weeks; Assessments/follow-up: weekly from week 1 to week 8.	Baseline SSI: bupropion = 11.0 ± 7.7; paroxetine = 7.3 ± 6.5.	N (sex): 57 (30 F/27 M); Mean age, years: bupropion = 38.9 ± 11.5, paroxetine = 36.3 ± 12.5.	Changes in HDRS-23 scores and Buschke SRT memory performance significantly predicted changes in SSI

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Table 1 (*continued*)

			bupropion (n = 27); Setting: outpatient care.			scores (Multiple R = 0.63; F = 16.63; p < 0.001).
Study: Parris et al., 2018; Category: Antidepressants; Intervention: paroxetine and bupropion.	MDD with SI and/or prior SA	Dose/route: paroxetine 25, 37.5, or 50 mg; bupropion 150, 300, or 450 mg, oral; Modality: monotherapy.	Study type/registration: RCT; secondary analysis of Grunebaum et al., 2012; Design: Arm 1: paroxetine (n = 36); Arm 2: bupropion (n = 38); Setting: outpatient care.	Intervention: 8 weeks; Assessments/follow-up: weekly from week 1 to week 8.	Baseline SSI: bupropion = 10.0 ± 7.4; paroxetine = 8.0 ± 6.7. HDRS-24 suicide item: bupropion = 1.95 ± 1.09; paroxetine = 1.75 ± 1.23. Columbia Suicide History Form: bupropion = 22/38, 57.9%; paroxetine = 21/36, 58.3%.	N (sex): 74 (42 F/32 M); Mean age, years: bupropion = 38.0 ± 12.0; paroxetine = 35.2 ± 12.7.	Patients with higher baseline anxiety experienced greater ↓ in SI with paroxetine compared to bupropion (t = 2.03, p = 0.047); Weekly anxiety scores were positively associated with concurrent SSI scores (Estimate = 0.32, 95% CI: 0.07–0.57, t = 2.54, p = 0.012); In the high-anxiety group, predicted reduction in SSI was greater for paroxetine (ΔSSI = −4.36, SE = 1.71, p = 0.010; bootstrap p = 0.055).
Study: McCall et al., 2019; Category: hypnotics/z-drugs; Intervention: zolpidem CR.	MDD with insomnia and SI	Dose/route: 6.25 mg – 12.50 mg, oral; Modality: adjunctive to open-label SSRI initiated at randomisation.	Study type/registration: RCT; NCT01689909; Design: SSRI + zolpidem CR (n = 51) versus SSRI + placebo (n = 52); Setting: outpatient care.	Intervention: 8 weeks; Assessments/follow-up: in-person visits at weeks 1, 2, 4, 6, and 8, followed by telephone safety/clinical follow-up for 2 weeks after randomised treatment.	SSI and C-SSRS (SI); Baseline SSI: zolpidem-CR = 12.2 ± 5.3; placebo = 11.8 ± 5.3; Baseline C-SSRS past-week ideation intensity: zolpidem-CR = 1.71 ± 1.03; placebo = 1.58 ± 1.02.	N (sex): 103 (64 F/39 M); Mean age, years: 40.5 ± 13.2.	No significant treatment effect on SSI, least-squares mean estimate = −0.56, SE = 0.83, 95% CI: −2.19 to 1.08, p = 0.50, Cohen's d = −0.11. C-SSRS ideation intensity showed a significant advantage for zolpidem-CR, least-squares mean estimate = −0.26, SE = 0.12, 95% CI: −0.50 to −0.02, p = 0.035, Cohen's d = −0.26. The C-SSRS advantage was numerically larger in participants with severe baseline insomnia. Improvement in insomnia was longitudinally associated with reduced SSI after accounting for depressive symptoms excluding sleep and suicide items. No deaths or SA occurred.
Study: Nolan et al., 2023; Category: Hormones; Intervention: testosterone.	SI in gender dysphoria	Dose/route: IM testosterone undecanoate 1000 mg or transdermal testosterone gel 1% (12.5 mg/actuation), 4 pumps daily; Modality: monotherapy.	Study type/registration: Open-label trial; ACTRN1262100016864; Design: Arm 1: immediate initiation of testosterone (n = 31); Arm 2: standard care with a 3-month waiting period before testosterone initiation (n = 31); Setting: outpatient care.	Intervention: immediate testosterone initiation versus 3-month waiting-list standard care. Follow-up/assessment: baseline and month 3.	Baseline SIDAS: mean score not reported.	N: 62; Sex: not reported; Median age, years: 22.5 (IQR 20-27).	Immediate testosterone initiation ↓ SI versus delayed treatment; mean difference in SIDAS score = −6.5 points (95% CI: −8.2 to −4.8, p < 0.001).

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Some data (e.g., trial registration numbers, intervention duration, follow-up period, baseline suicidality scale scores, effect sizes, p values, and confidence intervals) were unavailable for some studies and are therefore not reported.
Abbreviations = BD: bipolar disorder; BDV-1: Borna disease virus 1; BSSI: Beck Scale for Suicidal Ideation; CGI-SS: Clinical Global Impression of Severity for Suicide; CI: confidence interval; CR: controlled release; C-SSRS: Columbia-Suicide Severity Rating Scale; DCS: D-cycloserine; HAM-D or HDRS: Hamilton Depression Rating Scale; IM: intramuscular; IQR: interquartile range; LOCF: last observation carried forward; MADRS: Montgomery-Åsberg Depression Rating Scale; MD: mean difference; MDD: major depressive disorder; NMDA: N-methyl-D-aspartate; NRX-101: D-cycloserine and lurasidone combination; OUD: opioid use disorder; RCT: randomised controlled trial; SA: suicide attempt; SD: standard deviation; SE: standard error; SI: suicidal ideation; SIDAS: Suicide Ideation Attributes Scale; SNRI: serotonin-noradrenaline reuptake inhibitor; SPS: Suicide Probability Scale; SRT: Selective Reminding Test; SSI: Scale for Suicidal Ideation; SSRI: selective serotonin reuptake inhibitor; SUD: substance use disorder; TRD: treatment-resistant depression.

Table 1b
PHARMACOTHERAPY

Study, category, and intervention	Diagnosis	Intervention details and treatment context	Study design and registration	Duration and follow-up	Baseline suicidality measure (s)	Sample characteristics	Effectiveness on SI/SA
Study: Gibbons et al., 2023; Category: Anticholinergics; Intervention: benztropine.	44% BD; 19% schizophrenia; 2% Parkinson's disease	Dose/route: 55% 1 mg, 29% 0.5 mg; 16% 2 mg, oral; Modality: adjunctive to antipsychotics.	Study type/registration: Retrospective cohort observational study; Design: Within-person exposure-only cohort design; Setting: outpatient care.	Follow-up window: up to 8 years.	Not applicable.	N (sex): 62,493 (33,934 F/ 28,559 M); Mean age, years: 39.22 (SD not reported).	Benztropine ↓ suicidal events (SA) (HR = 0.63, 95% CI: 0.50–0.80, $p < 0.001$); Duration-dose relationship observed with 6% reduction in suicidal events per 1 mg equivalent dosage per month; 486 total suicidal events (0.8%) during follow-up.
Study: De Berardis et al., 2020; Category: Antidepressants; Intervention: vortioxetine.	SSRI-resistant MDD	Dose/route: 5–20 mg, oral; Modality: adjunctive to SSRI.	Study type/registration: Retrospective chart-review study; Design: Retrospective analysis of adult outpatients' charts.	Intervention: 8 weeks. Follow-up/assessment: 8 weeks.	HAM-D; SSI = 13.6 ± 4.4.	N (sex): 36 (14 F/22 M); Mean age, years: 31.1 ± 5.8.	↓ in SSI ($t = 9.1$, $df = 35$, $p < 0.001$); 55.7% ↓ in SI scores; 41.7% response rate, 33.3% remission on HAM-D.
Study: Francis et al., 2024; Category: Antipsychotics; Intervention: brexpiprazole.	BPD and cyclothymia with SI	Dose/route: 2 mg, oral; Modality: monotherapy (cross-tapered with quetiapine)	Study type/registration: Case report; Design: Single patient case report of a psychiatric inpatient.	Intervention: 3 weeks; Follow-up: not reported.	Not applicable.	N (sex): 1 (1 F/0 M); Mean age, years: 26.0.	Gradual ↓ of SI and emotional instability after 1 week of starting brexpiprazole; Full remission with no SI or self-harm at 3-week follow-up.
Study: Gibbons et al., 2022; Category: Vitamins; Intervention: folic acid.	Not reported; general population with private insurance who filled a prescription for folic acid	Dose/route: 1 mg, oral; Modality: adjunctive.	Study type/registration: observational exposure-only cohort design; Design: within-person comparison of suicidal event rates before and after folic acid exposure; cyanocobalamin (vitamin B12) used as a negative control exposure; outpatient care.	Observation period: 2 years.	Not applicable.	N (sex): 866,586 (704,514 F/162,072 M); Mean age, years: not reported.	Folic acid was associated with ↓ SA (HR = 0.56, 95% CI: 0.48–0.65, $p < 0.001$). Dose-response relationship: 5% monthly ↓ in suicidal events per 1 mg/day (HR = 0.95, 95% CI: 0.93–0.97, $p < 0.001$). Negative control cyanocobalamin: no association with SA (HR = 1.01, 95% CI: 0.80–1.27).
Study: Padmanathan et al., 2022; Category: Opioid agonism; Intervention/exposure: methadone or buprenorphine prescribed as OAT.	SUD; opioid dependence	Dose/route: methadone or buprenorphine as OAT, oral; specific dose not reported; Modality: observational exposure to OAT.	Study type/registration: Retrospective cohort study using primary care records linked to hospital admission and mortality data; Design: Comparison of suicide and self-harm risk during, before, and after OAT in a national UK outpatients' cohort.	Total follow-up 40,599 person-years for self-harm analyses and 40,098 person-years for suicide analyses. Median patient follow-up, years: 3.4, IQR 1.2–7.4. Median OAT episode duration: 84 days, IQR 20–318; mean OAT episode duration, days: 327 ± 626.	Not applicable.	N (sex): 8,070 (2,476 F/ 5,594 M); Median age, years: 33.3 (IQR 27.6–39.9).	46 deaths by suicide during study, rate 0.11 per 100 person-years; OAT did not significantly affect suicide risk (aRR = 1.21, 95% CI: 0.64–2.28, $p > 0.6$); Suicide/ self-harm risk highest in 4 weeks after OAT discontinuation: self-harm aRR = 2.60, 95% CI: 1.83–3.70; suicide aRR = 4.68, 95% CI: 1.63–13.42. The suicide standardised mortality ratio

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Table 1 (*continued*)

							versus the general population was 7.5, 95% CI: 5.5–10.0.
Study: Bahorik et al., 2018; Category: Cannabinoids; Intervention: marijuana.	MDD	Dose/route: not applicable (observational marijuana-use exposure); Modality: not applicable.	Study type/registration: Longitudinal observational study; Design: Arm 1: medical marijuana users; Arm 2: non-medical marijuana users; Arm 3: no marijuana users (reference group); Setting: outpatient care.	Observation period: 1 year.	PHQ-9 item 9 (SI)	N (sex): 307 (215 F/92 M); Mean age, years: 37.2 ± 13.8.	Non-medical marijuana use was associated with ↑ SI at baseline (B = 1.08, p = 0.002) and poorer mental health functioning (B = −3.79, p = 0.015). Over 1 year, non-medical users showed less improvement in SI (B = 1.08, p = 0.003) and depressive symptoms (B = 1.49, p = 0.026), compared to non-users.
Study: Jones et al., 2022; Category: Psychedelics; Intervention/exposure: MDMA, psilocybin.	Not applicable (general population survey)	Dose/route: not applicable (population survey of lifetime psychedelic use); Modality: not applicable.	Study type/registration: Cross-sectional observational study; Design: Analysis of lifetime psychedelic use and past-year suicidality using survey data (NSDUH, 2008–2019)	Time frame: lifetime psychedelic use and past-year suicidality assessed in cross-sectional survey.	Not applicable.	N: 484,732; Sex: not reported; Age: ≥18 years.	Lifetime MDMA use associated with ↓ odds of past-year SI (OR = 0.90, 95% CI: 0.84–0.97, p < 0.01); MDMA also linked to ↓ odds of past-year suicidal planning (OR = 0.88, 95% CI: 0.78–0.99, p < 0.05); Psilocybin use associated with ↓ odds of SI (OR = 0.90, 95% CI: 0.83–0.96, p < 0.01)
Study: Yang et al., 2022; Category: Psychedelics; Intervention/exposure: LSD, DMT/AMT/Foxy, Salvia divinorum, MDMA, ketamine.	Not applicable (population-based survey)	Dose/route: not applicable (population survey of psychedelic use); Modality: not applicable.	Study type/registration: Cross-sectional observational study; Design: Analysis using survey data (NSDUH 2015–2020)	Time frame: psychedelic use and suicidality assessed in cross-sectional survey.	Not applicable.	N: 241,675; Sex: not reported; Age: ≥18 years.	MDMA: associated with ↓ risk of suicidal thinking (aPR = 0.86; 95% CI: 0.75–0.99); LSD: ↑ likelihood of suicidal thinking (aPR = 1.21; 95% CI: 1.09–1.34); Salvia divinorum: associated with a ↑ likelihood of suicidal thinking (aPR = 1.41; 95% CI: 1.00–1.97); DMT/AMT/Foxy: strongly associated with ↑ risk of suicidal thinking (aPR = 1.81; 95% CI: 1.17–2.81)
Study: Li et al., 2024a; Category: Anticoagulants; Intervention/exposure: NOACs (71.74%) versus warfarin (28.26%).	AF	Dose/route: oral anticoagulant exposure; dose not reported; Modality: observational comparison of anticoagulant strategy for AF.	Study type/registration: Retrospective study using Taiwan NHIRD and Cause of Death Registry; target trial emulation framework; NCKU HREC-E-110–453-2; Design: new-user comparison of NOACs versus warfarin; Setting: nationwide real-world outpatient, inpatient, and emergency claims data.	Mean follow-up: NOACs = 2.75 years; warfarin = 4.31 years. On-treatment sensitivity analysis mean follow-up: NOACs = 1.67 years; warfarin = 0.91 years.	Not applicable; patients with previous suicide-related events were excluded.	N (sex): 144,645 (62,772 F/81,873 M), NOACs n = 103,768, warfarin n = 40,877; Mean age, years: 72.5 ± 11.8.	Patients on NOACs had lower risk of suicide-related outcomes compared with those on warfarin (HR = 0.82, 95% CI: 0.69–0.96, p = 0.015). This was driven by SA: HR = 0.79, 95% CI: 0.67–0.93.

Some data (e.g., trial registration numbers, intervention duration, follow-up period, baseline suicidality scale scores, effect sizes, p values, and confidence intervals) were unavailable for some studies and are therefore not reported.

Abbreviations = AF: atrial fibrillation; AMT: alpha-methyltryptamine; aPR: adjusted prevalence ratio; aRR: adjusted risk ratio; BD: bipolar disorder; B: unstandardised regression coefficient; BPD: borderline personality disorder; CI: confidence interval; DMT: dimethyltryptamine; Foxy: 5-methoxy-N,N-diisopropyltryptamine; HAM-D: Hamilton Rating Scale for Depression; HR: hazard ratio; IQR: interquartile range; LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; MDD: major depressive disorder; NOACs: non-vitamin K oral anticoagulants; NSDUH: National Survey on Drug Use and Health; OAT: opioid agonist therapy; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9; SA: suicide attempt; SD: standard deviation; SI: suicidal ideation; SSI: Scale for Suicidal Ideation; SSRI: selective serotonin reuptake inhibitor; SUD: substance use disorder.

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Table 1c
NEUROMODULATION

Study, category, and intervention	Diagnosis	Intervention details and treatment context	Study design and registration	Duration and follow-up	Baseline suicidality measure (s)	Sample characteristics	Efficacy on SI/SA
Study: Zhao et al., 2024; Category: theta-burst stimulation; Intervention: a-cTBS versus a-iTBS.	TRD with SI	Dose/route: 10 sessions/day, 1800 pulses/session, for 5 consecutive days; total 90,000 pulses. a-iTBS targeted the left DLPFC; a-cTBS targeted the right DLPFC using neuronavigation. Modality: active neuromodulation comparison while patients remained on a stable antidepressant regimen.	Study type/registration: RCT; ChiCTR2200055320; Design: a-cTBS versus a-iTBS.	Intervention: 5 days; Follow-up: 4 weeks.	Baseline BSI: a-iTBS = 21.09 ± 6.15; a-cTBS = 18.86 ± 6.08; Baseline HAMD-24 item 3: a-iTBS = 3.18 ± 0.39; a-cTBS = 3.27 ± 0.46.	N (sex): 44 (33 F/11 M); Mean age, years: a-iTBS = 18.59 ± 5.81, a-cTBS = 21.59 ± 7.83.	a-cTBS: greater SI ↓ over time than a-iTBS ($p < 0.05$, Bonferroni-corrected); Remission at week 5: a-cTBS = 72.73% versus a-iTBS = 31.82% ($p < 0.01$, corrected)
Study: Desmyter et al., 2016; Category: theta-burst stimulation; Intervention: a-iTBS.	TRD (MDD)	Dose/route: neuronavigated left DLPFC a-iTBS; 110% resting motor threshold; 1,620 pulses/session; 5 sessions/day over 4 days per treatment week, for 20 sessions and 32,400 pulses per active treatment week; Modality: monotherapy.	Study type/registration: RCT; NCT01832805; Design: crossover trial; week 1: active a-iTBS then sham, or sham then active a-iTBS in week 2.	Intervention: two 1-week crossover periods; each treatment condition consisted of 20 sessions delivered over 4 days; Follow-up: 4 weeks.	Baseline BSI: 13.3 ± 6.78.	N (sex): 46 (32 F/14 M); Mean age, years: 41.9 ± 11.8.	↓ in BSI scores over time in suicidal subgroup: 13.31 at T1, 8.22 at T2, 7.53 at T3, 5.26 at T4. Significant T1–T2 decrease in mixed model, $p < 0.01$; post hoc T1–T2, T1–T3, and T1–T4 decreases all $p < 0.05$. No treatment-order effect, $p = 0.66$; no order × time interaction, $p = 0.45$; reduction unrelated to HDRS response, $p = 0.378$ for response status and $p = 0.19$ for interaction. No worsening of SI; no suicide up to 6 months.
Study: Baeken et al., 2019; Category: theta-burst stimulation; Intervention: a-iTBS.	MDD	Dose/route: 5 sessions/day for 4 days (32,400 stimuli), left DLPFC; Modality: monotherapy.	Study type/registration: RCT; NCT01832805; Design: crossover trial; week 1: active a-iTBS then sham, or sham then active a-iTBS in week 2.	Intervention period: 2 weeks; Follow-up: 4 weeks.	Baseline median BSI: 10.00 (IQR 16.00).	N (sex): 45 (33 F/12 M); Median age, years: 44.00 (IQR 19.00).	No significant difference in BSI score changes between active and sham ($p = 0.62$); improvement in SI correlated with ↓ perfusion in PFC.
Study: Wang et al., 2024; Category: tDCS; Intervention: tDCS.	BD with SI	Dose/route: 30-min, 2-mA tDCS; twice daily on weekdays during week 1, then once daily on weekdays during weeks 2–3, over left DLPFC; Modality: adjunctive to quetiapine 300 mg.	Study type/registration: RCT; NCT0559646; Design: Arm 1: quetiapine + active tDCS; Arm 2: quetiapine + sham tDCS; Setting: outpatient or inpatient care.	Intervention: 3 weeks, consisting of a 1-week acute phase plus a 2-week maintenance phase.	Baseline BSSI: score not reported.	N (sex): 31 (18 F/13 M); Mean age, years: active tDCS = 19.38 ± 6.19; sham tDCS = 17.60 ± 2.35.	Significant ↓ in suicidality (SI) in both groups ($p < 0.001$); Active tDCS > sham on BSSI reduction ($p < 0.05$); No difference in HDRS-17 or MADRS scores ($p > 0.05$)

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Study: Pan et al., 2020; Category: rTMS; Intervention: rTMS.	MDD with SI	Dose/route: 1 session/day for 7 consecutive days; each session included 120 trains of 5 s at 10 Hz, 6000 pulses/session, 100% resting motor threshold, MRI-neuronavigated to left DLPFC BA46. Modality: adjunctive to escitalopram 10 mg.	Study type/registration: RCT; ChiCTR1800017458; Design: Arm 1 (n = 21): escitalopram 10 mg + active rTMS; arm 2 (n = 21): escitalopram 10 mg + sham rTMS.	Intervention: 1 week; Assessments/follow-up: baseline, day 3, and day 7.	Baseline BSSI: active rTMS = 19.00 ± 5.94; sham rTMS = 21.48 ± 5.91; between-group p = 0.183.	N (sex): 42 (35 F/7 M); Mean age, years: active rTMS = 18.14 ± 3.94; sham rTMS = 21.43 ± 6.79.	Active rTMS group had significantly greater BSI ↓ versus sham at days 3 and 7 ($p < 0.001$); By day 7, 57.14% in active group scored 0 on BSI; none in sham.
Study: Weissman et al., 2020; Category: MST; Intervention: MST.	TRD with suicidality (SI)	Dose/route: MST delivered at PFC with low (25 Hz), moderate (50–60 Hz), or high (100 Hz); up to 24 sessions; Modality: adjunctive to stable antidepressant treatment.	Study type/registration: Open-label, secondary analysis; NCT01596608; Design: Arm 1 (n = 29): MST 25 Hz; arm 2 (n = 22): MST 50–60 Hz; arm 3 (n = 16): MST 100 Hz.	Intervention: up to 24 MST sessions, delivered 2–3 times per week; Follow-up: 6 months.	Baseline BSSI: MST 25 Hz = 10.3 ± 5.5; MST 50–60 Hz = 11.0 ± 4.8; MST 100 Hz = 12.1 ± 3.9.	N (sex): 67 (40 F/27 M); Mean age, years: 46.3 ± 15.3.	47.8% achieved remission; Large effect sizes (↓ SI) in low (d = 1.43; 95% CI: 0.59–1.88) and moderate (d = 0.87; 95% CI: 0.28–1.35) groups; Effect in high-frequency group not significant (d = 0.42; 95% CI: −0.35 to 1.04)
Study: Sun et al., 2016; Category: MST; Intervention: MST.	TRD	Dose/route: MST administered under general anaesthesia using a MagPro MST stimulator with twin coil; stimulation delivered over the frontal cortex at the midline position over Fz; patients were treated for up to 24 sessions or until remission of depressive symptoms; Modality: procedural neuromodulation treatment; concomitant pharmacotherapy not specified in this secondary analysis.	Study type/registration: open-label trial; Design: single-arm, pre-post study.	Baseline TMS-EEG assessment: within 1 week before MST initiation. Treatment course: up to 24 sessions or until remission of depressive symptoms; mean number of MST sessions = 16.9 ± 7.0. Suicidality assessment: SSI before MST and after completion of MST.	Baseline SSI: 9.0 ± 6.8; 30% scored 0.	N (sex): 27 (15 F/12 M); Mean age, years: 46.0 ± 15.3.	↓ SI; Post-treatment SSI mean: 4.2 (SD 6.3); pre-post difference: 4.8 (SD 6.7), $t(26) = 3.72$, $p = 0.001$. Remission (SSI = 0) achieved in 53% (10/19 with baseline SSI ≥ 1); Baseline frontal N100 and LICI predicted remission (89% accuracy, AUC = 0.90, $p = 0.003$).
Study: Sun et al., 2018; Category: MST; Intervention: MST.	TRD	Dose/route: 24 sessions or until remission of depressive symptoms (under general anaesthesia and neuromuscular blocker); EEG collected 1 week before and 2 days after treatment; Modality: procedural neuromodulation treatment; concomitant pharmacotherapy not specified in this secondary analysis.	Study type/registration: Open-label clinical trial; NCT01596608; Design: single-arm MST study in patients with TRD.	Intervention/follow-up: MST course up to 24 sessions or until depressive-symptom remission; no longer-term SSI follow-up reported.	Baseline SSI: 9.3 ± 6.3.	N (sex): 23 (12 F/11 M); Mean age, years: 45.0 ± 12.2.	↓ SI; SSI decreased from 9.3 ± 6.3 to 4.3 ± 5.6 after MST, $Z = 3.44$, $p < 0.001$; Among patients with baseline SI, 8/18 (44.4%) had resolution of SI, defined as post-treatment SSI = 0.
Study: Li et al., 2024b; Category: accelerated rTMS; Intervention: SAINT (rTMS).	MDD with SI	Dose/route: MRI-navigated, sgACC functional-connectivity-guided DLPFC iTBS; 10 sessions/day for 5 consecutive days; 50-minute inter-session intervals; 18,000 pulses/day; 90,000 total pulses;	Study type/registration: single-arm open-label trial; NCT04653337; Design: SAINT in patients with MDD and moderate-to-severe SI.	Intervention: 5 days; Follow-up: immediately after treatment, 2 weeks, and 4 weeks.	Baseline BSI-CV = 17.63 ± 7.06; HAMD-17 item 3 = 3.00 ± 0.00; MADRS item 10 = 3.90 ± 0.30.	N: 32; Sex: not reported; Mean age, years: 27.66 ± 20.38.	SAINT ↓ SI as measured by the BSI-CV ($F = 81.34$, $df = 2, 61$, $p < 0.001$), item 3 of the HAMD-17 ($F = 317.90$, $df = 2, 66$, $p < 0.001$), and item 10 of the MADRS ($F = 314.72$, $df = 2, 64$, $p < 0.001$) across follow-up assessments; Response rates for SI were

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		90% resting motor threshold; Modality: adjunctive to antidepressant medication (venlafaxine 75 mg/day or duloxetine 30 mg/day).					65.63% after treatment, 78.13% at 2 weeks, and 90.63% at 4 weeks.

Some data (e.g., trial registration numbers, intervention duration, follow-up period, baseline suicidality scale scores, effect sizes, p values, and confidence intervals) were unavailable for some studies and are therefore not reported.

Abbreviations = a-cTBS: accelerated continuous theta-burst stimulation; a-iTBS: accelerated intermittent theta-burst stimulation; AUC: area under the curve; BD: bipolar disorder; BSI/BSSI: Beck Scale for Suicidal Ideation; BSI-CV: Beck Scale for Suicidal Ideation, Chinese Version; cTBS: continuous theta-burst stimulation; DLPFC: dorsolateral prefrontal cortex; EEG: electroencephalogram; HAM-D/HDRS: Hamilton Depression Rating Scale; HAMD-17: 17-item Hamilton Depression Rating Scale; HDRS-17: 17-item Hamilton Depression Rating Scale; iTBS: intermittent theta-burst stimulation; LICI: long-interval cortical inhibition; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MRI: magnetic resonance imaging; MST: magnetic seizure therapy; N100: N100 cortical evoked potential component; PFC: prefrontal cortex; RCT: randomised controlled trial; rTMS: repetitive transcranial magnetic stimulation; SA: suicide attempt; SD: standard deviation; SAINT: Stanford Accelerated Intelligent Neuromodulation Therapy; sgACC: subgenual anterior cingulate cortex; SI: suicidal ideation; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; TRD: treatment-resistant depression.

Table 1d
NEUROMODULATION

Study, category, and intervention	Diagnosis	Intervention details and treatment context	Study design and registration	Duration and follow-up	Baseline suicidality measure (s)	Sample characteristics	Effectiveness on SI/SA
Study: Abdelnaim et al., 2020; Category: rTMS; Intervention: rTMS.	Mood disorders (MDD, BD, depressive episode)	Dose/route: 6–50 rTMS sessions (mean 17.0 ± 6.5); mostly 20 Hz, 2000 pulses/day; Modality: not reported.	Study type/registration: Retrospective cohort observational study; Design: Retrospective analysis of inpatients and outpatients receiving rTMS.	Treatment course: 6–50 sessions; Follow-up: not reported.	HAM-D item 3: baseline score not reported.	N (sex): 332 (180 F/152 M); Mean age, years: 47.3 ± 12.3.	↓ SI (HAM-D item 3), surviving Bonferroni correction; 47% of patients showing improvement.
Study: Weissman et al., 2018; Category: rTMS; Intervention: rTMS.	TRD (MDD)	Dose/route: 15 sessions of either bilateral or left unilateral TMS or sham; Modality: adjunctive.	Study type/registration: Retrospective pooled analysis of RCTs; NCT01515215 and NCT00305045; Design: To compare the effectiveness of bilateral, left unilateral or sham rTMS on suicidality.	Intervention: 3 weeks; Follow-up: 6 weeks.	Baseline HDRS item 3: bilateral rTMS = 1.96 ± 0.6; left unilateral rTMS = 1.91 ± 0.6; sham = 1.88 ± 0.6.	N (sex): 156 (97 F/59 M); Mean age, years: 47.1 ± 13.9.	↓ SI; Bilateral rTMS was more effective than sham in reducing SI (OR = 3.03, 95% CI: 1.19–7.71, p = 0.02); Modest correlation between change in SI and change in depression severity (Pearson r = 0.38; p < 0.001).
Study: Aaronson et al., 2017; Category: VNS; Intervention: VNS.	TRD (MDD and BD)	Dose/route: implanted VNS pulse-generator; stimulation parameters individually titrated; Modality: adjunctive to TAU.	Study type/registration: Prospective, open-label, non-randomised observational study; NCT00320372; Design: TAU + VNS versus TAU alone; Setting: outpatient and specialty depression registry sites.	Planned follow-up visits: months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60; Total follow-up: 5 years.	QIDS-SR item 12 ≥ 2; MADRS item 10 ≥ 4; investigator-completed suicidality assessment for suicidal gesture/attempt since last visit.	N (sex): VNS safety population = 494 (350 F/144 M); TAU safety population = 301 (211 F/90 M). VNS mean age, years: 48.9 ± 10.1; TAU mean age, years: 49.9 ± 11.1.	Greater ↓ in suicidality (SI and SA) versus TAU: QIDS-SR item 12 OR = 2.11 (95% CI: 1.28–3.48, p = 0.035) and investigator assessment OR = 2.04 (95% CI: 1.08–3.86, p = 0.029); The effect on MADRS item 10 did not achieve statistical significance (OR = 1.67, 95% CI: 0.98–2.83, p = 0.058); Deaths by suicide were numerically lower with VNS than with TAU, 1.01 versus 2.20 per 1,000 person-years, with 2 deaths by suicide in each arm.

Some data (e.g., trial registration numbers, intervention duration, follow-up period, baseline suicidality scale scores, effect sizes, p values, and confidence intervals) were unavailable for some studies and are therefore not reported.

Abbreviations = BD: bipolar disorder; HAM-D/HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; OR: odds ratio; QIDS-SR: Quick Inventory of Depressive Symptomatology–Self Report; RCT: randomised controlled trial; rTMS: repetitive transcranial magnetic stimulation; SA: suicide attempt; SD: standard deviation; SI: suicidal ideation; TAU: treatment as usual; TMS: transcranial magnetic stimulation; TRD: treatment-resistant depression; VNS: vagus nerve stimulation.

patients with MDD led to acute and sustained SI reduction, peaking at day 21 with a large effect size (Cohen's d = 1.75, p = 0.05) on MADRS-SI (Zeifman et al., 2021). A parallel RCT in TRD using a lower dose (1 mL/kg) similarly found rapid within-group SI improvements (day 1 d = 1.33, day 7 d = 1.19), with medium between-group effects versus placebo (d = 0.67 at day 7), though statistical significance was not reached (p = 0.088) (Zeifman et al., 2019).

In contrast, effectiveness data from large-scale surveys suggest variable associations between lifetime psychedelic use and suicidality. Analysis of nearly 485,000 adults found that MDMA and psilocybin use were associated with significantly lower odds of past-year SI (MDMA OR = 0.90, 95% CI: 0.84–0.97; psilocybin OR = 0.90, 95% CI: 0.83–0.96), while other hallucinogens showed no consistent associations (Jones and Nock, 2022). A separate population-based study confirmed MDMA's protective association (aPR = 0.86, 95% CI: 0.75–0.99) but identified increased SI risk with LSD (aPR = 1.21, 95% CI: 1.09–1.34), salvia divinorum (aPR = 1.41, 95% CI: 1.00–1.97), and higher odds of suicidal planning with dimethyltryptamine/alpha-methyltryptamine/Foxy (aPR = 1.81, 95% CI: 1.17–2.81) (Yang et al., 2022).

Overall, ayahuasca trials suggested rapid within-group reductions in SI, while population surveys reported mixed associations that varied across compounds and patterns of use.

3.1.3. Opioid-system modulation

Two RCTs assessed the efficacy of sublingual buprenorphine (partial agonist on μ receptor, antagonist on κ, δ receptors) in reducing SI, with different dosing strategies and populations.

In hospitalised men with comorbid MDD and opioid use disorder (OUD), high-dose buprenorphine (32–96 mg) produced rapid reductions in SI across all dose groups by day 3 (p < 0.01), with full remission in all participants at two weeks. No dose-response differences were observed (p = 0.408) (Ahmadi et al., 2018). Ultra-low-dose buprenorphine (0.44 mg/day) administered as an adjunct to antidepressants in adults with severe SI without substance use, many with BPD, was associated with significantly greater SI reductions compared to placebo. At week 2, BSSI scores showed a mean difference of –4.3 (95% CI: −8.5 to −0.2, p = 0.04), increasing to –7.1 at week 4 (95% CI: −12.0 to −2.3, p = 0.004) (Yovell et al., 2016).

In contrast, a large cohort study comparing buprenorphine and methadone for OUD found no overall protective effect of drugs against suicide during treatment (aRR = 1.21, 95% CI: 0.64–2.28, p > 0.6), but suicide death and non-fatal self-harm (including SAs) rates were highest during the four weeks following treatment discontinuation (Padmanathan et al., 2022).

Across study types, buprenorphine showed rapid reductions in SI in controlled trials, whereas observational data highlighted heightened risk during the post-discontinuation period.

3.1.4. Antipsychotics

Two studies explored the role of antipsychotics in suicidality, with divergent levels of evidence.

In a post hoc subgroup analysis of a RCT, pimavanserin (receptor antagonist (5-HT2A); 34 mg/day) administered as an adjunctive treatment in patients with MDD unresponsive to selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs), was associated with greater reductions in suicidality and related depressive symptoms compared with placebo, with significant effects by week 3 as measured by HAMD item 3 (suicidality) and item 9 (feelings of worthlessness), with a Cohen's d = 0.431 (p = 0.012) (Shelton et al., 2020).

Effectiveness data are limited to a single case report describing a 26-year-old inpatient with BPD and cyclothymia. Brexpiprazole (dopamine, serotonin receptor partial agonist (D2, 5-HT1A) receptor antagonist (5-HT2A); 2 mg/day, oral) after cross-tapering from quetiapine was associated with a gradual reduction of SI and emotional instability within the first week, reaching full remission by week three (Francis et al., 2024).

Overall, evidence for antipsychotics in suicidality outcomes was sparse, with one RCT post hoc signal for pimavanserin and only anecdotal data for brexpiprazole.

3.1.5. Antidepressants

Three post hoc analyses of a single efficacy trial (Grunebaum et al., 2012) evaluated paroxetine (SSRI; 25–50 mg/day) and bupropion (norepinephrine, dopamine reuptake inhibitor and releaser; 150–450 mg/day) in MDD patients with active SI or history of SAs. Both agents reduced SI over 8 weeks, with no between-group differences. Reductions in SI were significantly predicted by subjective depressive symptoms such as hopelessness (R^2 = 0.20, p = 0.0006), but not by cognitive or somatic symptom change (Keilp et al., 2018). A related analysis found that improvements in verbal memory (the Buschke selective reminding test [SRT]) and depressive symptoms jointly predicted SI reduction (R = 0.63; F = 16.63; p < 0.001) (Gorlyn et al., 2015). Finally, among patients with high baseline anxiety, paroxetine showed greater SI reduction than bupropion (ΔSSI = –4.36, SE = 1.71, p = 0.010). Weekly anxiety severity was independently associated with concurrent SI (estimate = 0.32, 95% CI: 0.07–0.57; p = 0.012) (Parris et al., 2018).

Complementing these findings, a small effectiveness study retrospectively examined vortioxetine (serotonin reuptake inhibitor, partial agonist on serotonin receptor 1A (5-HT1A), antagonist on serotonin receptor 3 (5-HT3); 5–20 mg/day) as adjunctive treatment in SSRI-resistant depression. Over 8 weeks, SSI scores decreased by 55.7% (t = 9.1, df = 35, p < 0.001), with 33.3% achieving remission and 41.7% showing HAM-D response (De Berardis et al., 2020).

Across post hoc analyses and one naturalistic study, SI generally decreased over weeks, with potential effect modification by anxiety and signals linking ideation change to selected cognitive and depressive symptom domains.

3.1.6. Hypnotics

A single efficacy trial assessed zolpidem-controlled release (CR) (6.25–12.5 mg/day) as an adjunct to SSRIs in patients with MDD, insomnia, and SI. Over 8 weeks, zolpidem-CR had no significant effect on SI as measured by the SSI (Cohen's d = –0.11), but produced modest yet significant reductions on the C-SSRS suicidal ideation score (Cohen's d = –0.26), with a numerically greater effect among participants with severe baseline insomnia (McCall et al., 2019). Improvements in insomnia correlated with reductions in SI, indicating a possible indirect pathway via sleep normalization.

3.1.7. Hormones, anticholinergics, vitamins, cannabinoids, NOACs

A range of pharmacological interventions beyond conventional psychotropics has been explored for their potential to reduce SI, with varying levels of evidence.

Testosterone is the only agent tested under efficacy conditions. In a randomised open-label trial, immediate initiation in transgender individuals led to greater reductions in SI over three months compared to delayed treatment (SIDAS Δ = –6.5, 95% CI: −8.2 to −4.8, p < 0.001), supporting the rapid benefit of early gender-affirming care (Nolan et al., 2023).

Effectiveness data emerged from large-scale observational studies, three of which were population-based, including one exposure-only cohort design (Gibbons et al., 2022) and two retrospective cohort studies (Gibbons et al., 2023; Li et al., 2024a).

Folic acid use (1 mg/day) in over 860,000 adults was linked to fewer SAs over two years (HR = 0.56, p < 0.001), with a dose-response effect (HR = 0.95, p < 0.001), while no benefit emerged for cyanocobalamin (HR = 1.01, 95% CI: 0.80–1.27) (Gibbons et al., 2022). Similarly, long-term exposure to benztropine was associated with reduced suicidal events (HR = 0.63, 95% CI: 0.50–0.80, p < 0.001) in psychiatric and neurological populations, with an additional 6% reduction per 1 mg/month increase in dose (Gibbons et al., 2023). Beyond these agents,

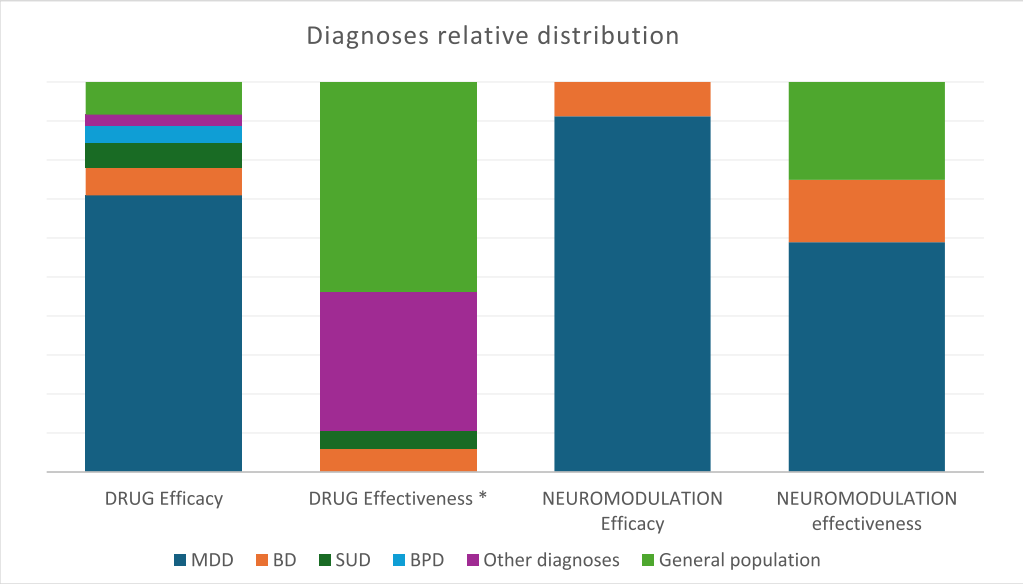

Fig. 1. Relative distribution of diagnostic groups across studies of drug efficacy, drug effectiveness, neuromodulation efficacy, and neuromodulation effectiveness. Each column is divided into coloured segments, with each colour representing one diagnostic category; absolute patient numbers are reported within each segment. *For the effectiveness group, the prevalence of patients with missing diagnostic information (NA) was adjusted to allow clearer graphical representation; the actual number of patients with NA diagnosis is 1,592,993.
Abbreviations: BPD = Borderline Personality Disorder; BD = Bipolar Disorder; MDD = Major Depressive Disorder; NA = Not Applicable; SUD = Substance Use Disorder.

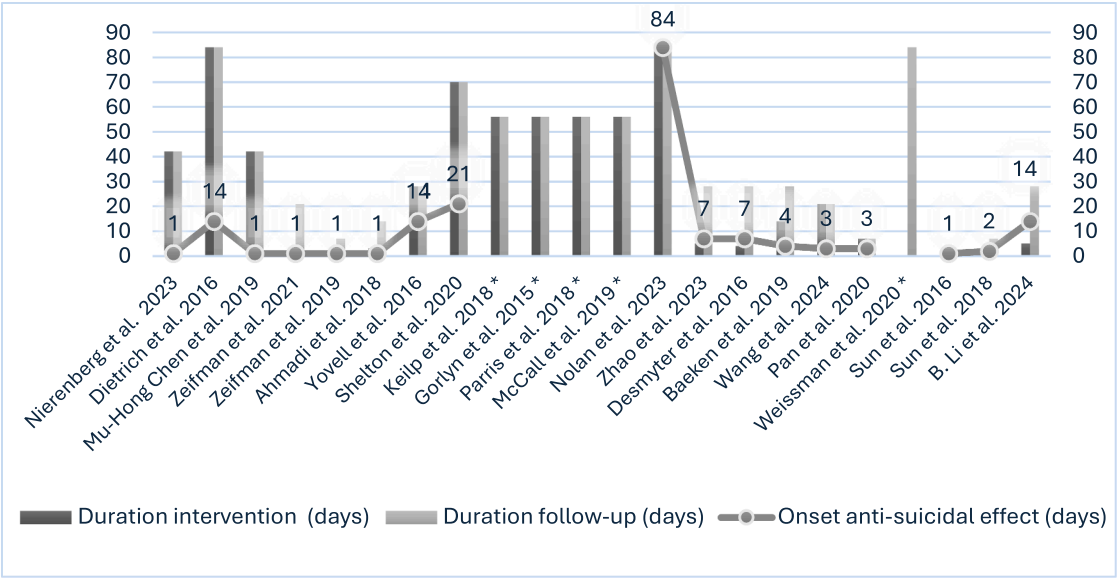

Fig. 2. Efficacy studies are represented with two bars per trial, indicating the duration of the intervention and the follow-up period. When available, a dot on the intervention bar marks the day on which a statistically significant anti-suicidal effect was first observed.
Data on the onset of anti-suicidal effects were missing for some studies. In Weissman et al. (2020), the duration of the intervention was not specified.

cardiovascular medications have also been implicated: among >140,000 patients with atrial fibrillation (AF), use of novel oral anticoagulants (NOACs) was associated with a significantly lower risk of suicide-related outcomes compared to warfarin (HR = 0.82, 95% CI: 0.69–0.96, p = 0.015), although rates of completed suicide did not differ (Li et al., 2024a). Finally, evidence regarding cannabinoids indicated a divergent association with suicidality. In MDD, non-medical cannabis users showed higher SI at baseline (B = 1.08, p = 0.002) and less improvement in both SI (B = 1.08, p = 0.003) and depressive symptoms (B = 1.49, p = 0.026) compared to non-users over 1 year. Medical cannabis users showed more variable patterns, without consistent risk elevation (Bahorik et al., 2018).

Overall, these signals were largely observational and heterogeneous, ranging from associations with lower suicide-related outcomes for folic acid, benztropine, testosterone initiation, and NOACs, to worse ideation trajectories with non-medical cannabis use.

3.2. Neuromodulation

Several neuromodulation strategies have been tested in patients with depression and SI, including accelerated and standard theta-burst stimulation (intermittent [iTBS] and continuous [cTBS]), high-

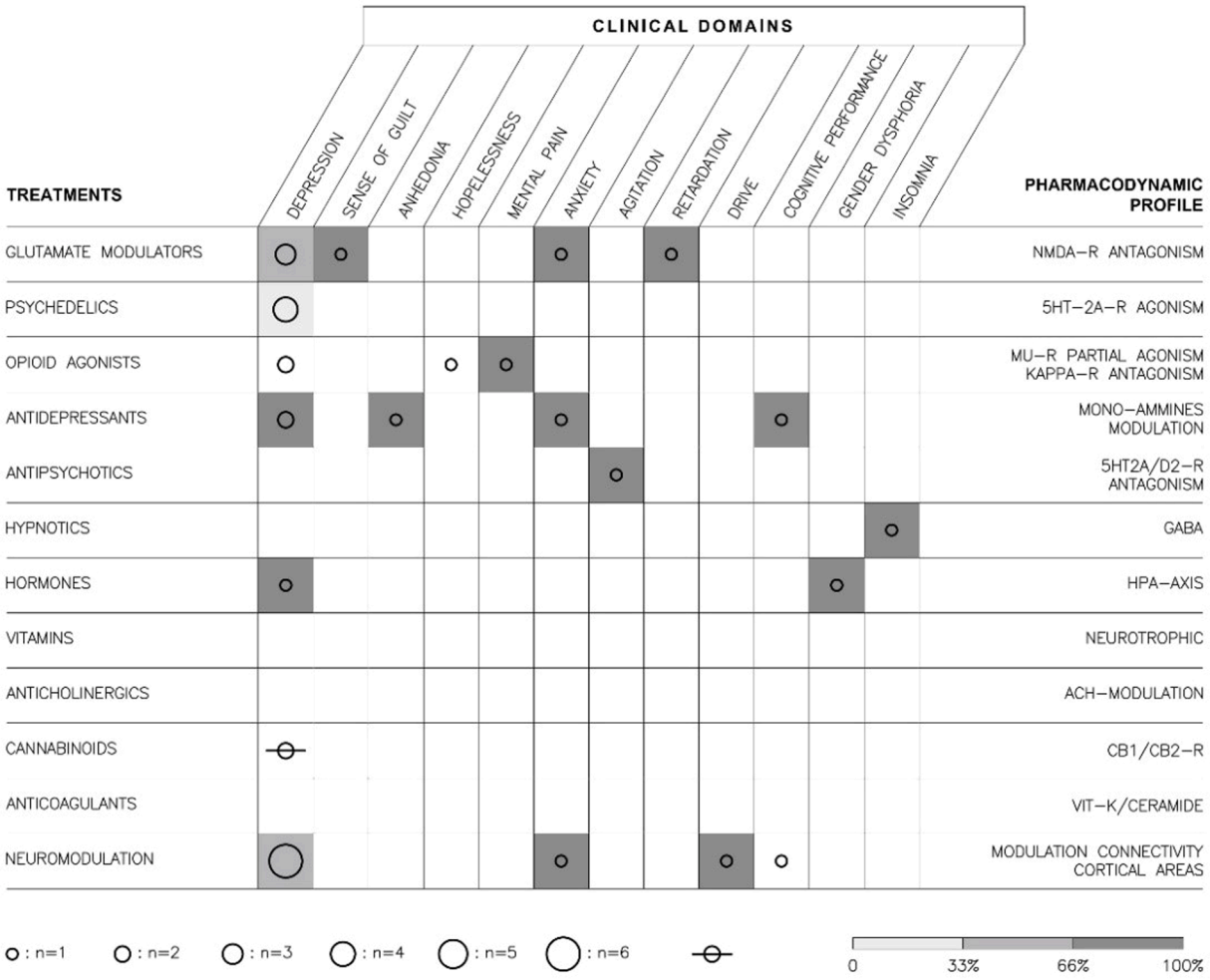

Fig. 3. Clinical features other than suicidal ideation or behaviour targeted by novel anti-suicidal agents, based on studies reporting these domains as secondary outcomes. Empty boxes indicate the absence of studies, while larger circles denote a greater number of studies exploring the given symptom. Increasingly darker shades of grey represent a higher proportion of studies showing a positive effect within that domain, whereas barred circles indicate a negative result.
Abbreviations: Ach = Acetylcholine; CB1/CB2 = Cannabinoid Receptor 1/2; GABA = γ-Aminobutyric Acid; HPA = Hypothalamic–Pituitary–Adrenal Axis; NMDA-R = N-Methyl-D-Aspartate Receptor; Vit. K = Vitamin K.

frequency or bilateral repetitive transcranial magnetic stimulation (rTMS), magnetic resonance imaging (MRI)-guided protocols, bifrontal transcranial direct current stimulation (tDCS), magnetic seizure therapy (MST) at different frequencies, and long-term vagus nerve stimulation (VNS).

In efficacy trials, SI reductions were often rapid, particularly in accelerated protocols (i.e., several sessions per day). In TRD, accelerated cTBS over the right dorsolateral prefrontal cortex (DLPFC) reduced SI more than iTBS (remission at week 5: 72.7% vs 31.8%, $p < 0.01$) (Zhao et al., 2024). Similarly, four days of iTBS decreased BSI scores ($p < 0.01$) in TRD, with effects persisting at four weeks, although improvements were also observed after sham stimulation, suggesting strong placebo contributions (Desmyter et al., 2016). Subsequent neuroimaging analyses confirmed that these placebo-related improvements were linked to perfusion decreases in frontopolar cortices (Baeken et al., 2019).

In MDD, neuronavigation-guided high-dose rTMS combined with escitalopram 10 mg/day reduced SI by day 3, with 57% remission at day 7 versus none in the sham group ($p < 0.001$) (Pan et al., 2020). Another rTMS intervention delivered over five days in patients with MDD and SI demonstrated rapid and sustained improvements, lowering BSI and MADRS/HAM-D suicidality scores ($p < 0.001$), with remission rates rising from 65.6% post-treatment to 90.63% at four weeks (Li et al., 2024b).

MST in patients with TRD and suicidality produced consistent anti-suicidal effects: SI decreased significantly post-treatment (mean SSI reduction 4.8, $p = 0.001$), with remission in 53% of patients (Sun et al., 2016), and around half in a subsequent trial (Sun et al., 2018). Further analyses indicated that low- and moderate-frequency MST yielded larger effect sizes ($d = 1.43$; 0.87) compared to high frequency ($d = 0.42$) (Weissman et al., 2020).

In bipolar depression, active tDCS plus quetiapine reduced BSSI scores more than sham by day 3 ($p = 0.043$), without changes in depressive symptoms (Wang et al., 2024).

Under effectiveness conditions, VNS provided sustained benefits: over five years, patients with TRD receiving adjunctive stimulation had lower SI than treatment as usual (QIDS-SR item 12 OR = 2.11, 95% CI: 1.28, 3.48; $p = 0.035$) and fewer suicides (1.01 vs 2.20 per 1000 person-years) (Aaronson et al., 2017). Naturalistic rTMS studies also showed meaningful improvements in HDRS-item 3, with 47% of patients with mood disorders showing a reduction in SI in routine care (Abdelnaim et al., 2020) and bilateral rTMS proving superior to sham (OR = 3.03, 95% CI: 1.19–7.71, $p = 0.02$) (Weissman et al., 2018).

Across studies, rTMS and theta-burst protocols showed the most consistent short-term reductions in SI, with reproducible post-treatment effects reported for magnetic seizure therapy and longer-term observational support for VNS.

4. Discussion

This review synthesises adult clinical studies of emerging pharmacological and neuromodulation interventions evaluated for SI and SA, spanning controlled trials and naturalistic studies. We excluded lithium, ketamine/esketamine, and clozapine as primary interventions because their anti-suicidal effects have been clearly proven and extensively synthesised elsewhere (Cipriani et al., 2013; Masdrakis and Baldwin, 2023; Lee et al., 2023; Shen et al., 2024). **Supplementary Table 1** provides a structured overview of the clinical characteristics and mechanisms of action of these well-known anti-suicidal agents.

Across mechanistically heterogeneous strategies, efficacy studies suggest that SI may change over short timeframes, sometimes without being fully accounted for by concurrent changes in depressive symptom severity (Batterham et al., 2019; Grunebaum et al., 2018). However, as summarised in Table 2, the relationship between SI improvement and depressive symptoms change was not consistently assessed across included studies. Evidence for partially dissociable effects therefore remains preliminary. Some studies reported parallel improvements in SI and depressive symptoms (Bahorik et al., 2018; Dietrich et al., 2020; De Berardis et al., 2020; Francis et al., 2024; Gorlyn et al., 2015; Keilp et al., 2018; McCall et al., 2019; Parris et al., 2018; Shelton et al., 2020), whereas others observed reductions in SI despite limited or absent antidepressant effects (Chen et al., 2019; Wang et al., 2024). These findings support, but do not establish, the hypothesis that SI can partly dissociate from global mood severity and should be directly measured as a treatment outcome in trials of pharmacological and neuromodulatory interventions. This interpretation is consistent with suicide-focused interventional neuroscience models, which argue that suicide-relevant states may require temporally sensitive assessment and direct interrogation of neurocognitive circuits involved in acute suicidal crises, rather than relying only on global depressive symptom change as a proxy outcome (Barredo et al., 2021).

The evidence base spans efficacy designs, including randomised or otherwise tightly controlled trials, and effectiveness data derived from naturalistic or observational studies. In suicidality research, this distinction is interpretive as well as methodological. Controlled trials provide the strongest basis for causal inference under defined conditions, whereas observational associations are primarily hypothesis-generating given residual confounding, indication effects, and contextual influences. Findings from controlled trials are interpreted as supporting potentially modifiable treatment targets under defined conditions, whereas observational associations are treated as hypothesis-generating, particularly when treatment allocation is influenced by baseline risk or illness severity (Sendor and Stürmer, 2022; Langan et al., 2018).

4.1. NMDA-related strategies

Among pharmacological approaches, glutamatergic modulation—particularly NMDA receptor–related strategies—has been widely studied given converging links between synaptic plasticity, stress-related neuroadaptation, and SI (Hanson et al., 2024). Ketamine and esketamine provide evidence that SI can improve within hours, but these agents were outside the scope of the present synthesis because their anti-suicidal effects are already supported by meta-analytic evidence and have entered clinical practice in several settings (Shamabadi et al., 2022; Ballard et al., 2021; Shen et al., 2024).

Building on this evidence base, the studies reviewed here suggest that next-generation NMDA-related approaches may contribute to sustaining or consolidating early improvement in SI after initial response. High-dose D-cycloserine (DCS; partial agonist at the NMDA receptor glycine site), as monotherapy or as part of NRX-101 (i.e., DCS plus lurasidone), was associated with greater reductions in suicidality measures than comparator conditions in controlled designs (Nierenberg et al., 2023; Chen et al., 2019). Notably, these effects emerged over weeks rather than hours, raising the hypothesis that NMDA partial agonism may act on consolidation of cognitive–affective change rather than immediate symptom improvement.

Mechanistic experimental and interventional studies provide convergent support. DCS has been associated with modulation of cognitive domains relevant to SI, including positive emotional memory and autobiographical memory specificity (Chen et al., 2021). In addition, DCS combined with intermittent theta-burst stimulation in MDD was associated with reductions in SI and changes in an implicit suicide-risk marker measured by the death/suicide Implicit Association Test (Sohn et al., 2025). Together, these findings justify larger trials that prespecify suicidality endpoints, formally test independence from depressive symptom change, and extend follow-up to assess durability and relapse (Lucido and Dunlop, 2025).

4.2. Opioid-system modulation and transition risk

Opioid-system modulation has drawn interest partly because affective distress and mental pain may act as proximal drivers of SI in some individuals (Rajkumar 2022). The most direct efficacy evidence comes from a multisite double-blind placebo-controlled RCT in which ultra-low-dose buprenorphine (initial 0.1 mg once or twice daily; mean final dose 0.44 mg/day) was associated with greater reductions in SI than placebo over 2 and 4 weeks in severely suicidal adults without OUD (Yovell et al., 2016). This is compatible with a suicide-relevant mechanism not fully explained by conventional antidepressant pathways.

Clinical translation, however, requires careful attention to safety and to treatment transitions. Even at low doses, buprenorphine carries risks related to misuse liability, physiological dependence, and discontinuation. Observational evidence consistently shows that suicide and self-harm rates peak in the weeks following opioid agonist treatment discontinuation, identifying cessation as a high-risk period rather than a neutral endpoint (Padmanathan et al., 2022). These findings have direct implications for trial design: tapering procedures, structured follow-up during discontinuation, and predefined safeguards during treatment changes should be considered core protocol elements. Evidence on μ-opioid receptor modulation suggests potential anti-suicidal effects, but indicates that any efficacy signals must be carefully weighed against safety considerations (Rajkumar 2022).

4.3. Adjunctive psychotropics and hypothesis-generating signals

Evidence on several adjunctive psychotropics remains limited and often derives from post hoc analyses or observational designs. For pimavanserin, available signals arise primarily from subgroup analyses reporting reductions in suicidality-related ratings over weeks (Shelton et al., 2020), warranting prospective confirmation in trials powered for suicide-related outcomes and designed to test independence from depressive symptom change. For vortioxetine, pooled safety analyses indicate no increased risk of SI or SA relative to placebo (Mahableshwarkar et al., 2020), supporting a neutral suicidality safety profile; direct evidence for a suicide-specific therapeutic effect remains sparse.

Large observational datasets also report associations between suicide-related outcomes and medications not conventionally framed as anti-suicidal treatments. Prescription folic acid was associated with lower rates of SAs or intentional self-harm in an electronic health record (EHR)–based cohort (Gibbons et al., 2022), consistent with biological links between one-carbon metabolism, folate pathways, and depression-related phenotypes (Liwinski and Lang, 2023; Susam et al., 2024). Long-term benztropine exposure has also been associated with fewer suicidal events (Gibbons et al., 2023), although these findings remain hypothesis-generating given plausible confounding and the known cognitive and medical risks of anticholinergic exposure (Vanegas-Arroyave et al., 2024). Additional randomised and quasi-experimental evidence suggests that timely testosterone initiation

Table 2
Relationship between suicidal ideation (SI) change and depressive or related clinical outcomes across included studies. The table distinguishes studies reporting parallel changes in SI and depressive or related symptoms, studies suggesting SI reduction without clear antidepressant effects, and studies in which this relationship was not formally assessed or not reported. 'Not assessed/reported' indicates that the study did not provide sufficient data to infer whether SI changes were independent of depressive symptom change.

Author, year	Intervention		Relationship between SI and other clinical outcomes
Nierenberg et al., 2023	NMDA modulation	NRX-101	Not assessed/reported
Chen et al., 2019		DCS	↓ SI without antidepressant effects
Dietrich et al., 2020		Amantadine	↓ SI accompanied by global HAMD improvement
Zeifman et al., 2021	Psychedelics	Ayahuasca	Not assessed/reported
Zeifman et al., 2019		Ayahuasca	Not assessed/reported
Jones and Nock, 2022		MDMA / psilocybin	Not assessed/reported
Yang et al., 2022		MDMA/ LSD/ Salvia divinorum/ DMT/ AMT/Foxy	Not assessed/reported
Ahmadi et al., 2018	Opioid agonism	Buprenorphine	Not assessed/reported
Yovell et al., 2016		Buprenorphine	Not assessed/reported
Padmanathan et al., 2022		Buprenorphine/methadone discontinuation	Not assessed/reported
Shelton et al., 2020	Antipsychotics	Pimavanserin	↓ SI and depressive symptoms
Francis et al., 2024		Brexpiprazole	↓ SI and emotional instability
Keilp et al., 2018	Antidepressants	Paroxetine/bupropion	↓ SI more strongly associated with subjective depressive symptoms than somatic symptoms
Gorlyn et al., 2015		Paroxetine/bupropion	↓ SI and depressive symptoms and ↑ verbal memory
Parris et al., 2018		Paroxetine/bupropion	SI associated with anxiety severity
De Berardis et al., 2020		Vortioxetine	↓ SI and depressive symptoms
McCall et al., 2019	Hypnotics	Zolpidem-CR	↓ SI and insomnia
Nolan et al., 2023	Hormones	Testosterone	Not assessed/reported
Gibbons et al., 2022	Vitamins	Folic acid	Not assessed/reported
Gibbons et al., 2023	Anticholinergics	Benztropine	Not assessed/reported
Li et al., 2024a	Anticoagulants	NOACs vs warfarin	Not assessed/reported
Bahorik et al., 2018	Cannabis	Marijuana	SI and depressive symptoms showed less improvement compared to non-users
Zhao et al., 2024	Neuromodulation	cTBS/iTBS	SI, depression, and anxiety improved; a-cTBS superiority for SI was attenuated after controlling for anxiety
Desmyter et al., 2016		iTBS/sham stimulation	Not assessed/reported
Baeken et al., 2019		Placebo aiTBS/neuroimaging	Not assessed/reported
Pan et al., 2020		rTMS + escitalopram	Not assessed/reported
Li et al., 2024b		rTMS	Not assessed/reported
Sun et al., 2016		MST	Not assessed/reported
Sun et al., 2018		MST	Not assessed/reported
Weissman et al., 2020		MST frequencies	Not assessed/reported
Wang et al., 2024		tDCS + quetiapine	↓ SI; no changes in depressive symptoms
Aaronson et al., 2017		VNS	Not assessed/reported
Abdelnaim et al., 2020		Naturalistic rTMS	Not assessed/reported
Weissman et al., 2018		Bilateral rTMS	Not assessed/reported

Abbreviations: aiTBS = Accelerated Intermittent Theta-Burst Stimulation; DCS = D-cycloserine; CR = Controlled Release; cTBS = Continuous Theta-Burst Stimulation; iTBS = Intermittent Theta-Burst Stimulation; MDMA = 3,4-methylenedioxymethamphetamine; MST = Magnetic Seizure Therapy; NOACs = Non-Vitamin K Oral Anticoagulants; rTMS = Repetitive Transcranial Magnetic Stimulation; SI = Suicidal Ideation; tDCS = Transcranial Direct Current Stimulation; VNS = Vagus Nerve Stimulation.

in transgender adults is associated with reductions in SI (Nolan et al., 2023; Doyle et al., 2023), while target trial emulation analyses in atrial fibrillation report lower risk of suicide-related outcomes with NOACs compared with warfarin, without differences in completed suicide (Li et al., 2024a). These diverse signals highlight opportunities for mechanism-driven repurposing but do not substitute for suicidality-focused trials. By contrast, the cannabis literature remains cautionary, with consistent associations between non-medical use and higher suicidality, particularly in younger populations and individuals with mood disorders (Shamabadi et al., 2023).

4.4. Neuromodulation as intervention and mechanistic probe

Neuromodulation offers a particularly informative line of evidence because it directly perturbs neural circuitry implicated in cognitive control, affect regulation, and threat processing. Among non-invasive approaches, rTMS shows the most consistent association with reductions in SI. Meta-analyses report significant effects in MDD, with smaller and more variable effects in treatment-resistant populations (Cui et al., 2022; Chen et al., 2022). Several trials describe improvement within days and accelerated or theta-burst protocols further support a temporal dissociation between effects on SI and broader mood change.

Specificity is central. Studies that adjust for depressive symptom severity provide stronger support for suicide-specific effects, implicating modulation of prefrontal–limbic circuitry beyond global mood mechanisms (Weissman et al., 2018). Transcranial direct current stimulation has shown reductions in SI in small trials, sometimes without concurrent mood improvement, but heterogeneity in stimulation parameters and limited samples constrain inference. Also, some studies reported reductions in SI after sham stimulation (Desmyter et al., 2016; Wang et al., 2024; Weissman et al., 2018), suggesting that treatment expectations, intensive clinical monitoring, and repeated therapeutic contact may contribute to improvement, particularly in accelerated protocols. Notably, placebo-related improvements were associated with measurable changes in frontopolar activity (Baeken et al., 2019), raising the possibility that expectancy effects may modulate neural systems implicated in affect regulation and suicidality, rather than representing only psychological or methodological artefacts. This is consistent with magnetoencephalographic models showing that affective processing depends on dynamic interactions across distributed cortico-limbic and large-scale brain networks (Scala et al., 2026), which may be sensitive not only to direct neuromodulatory interventions but also to contextual and expectancy-related influences. Future studies should improve control of expectancy-related effects through more rigorous sham conditions, systematic assessment of blinding integrity and patient expectations, and designs specifically aimed at determining whether

reductions in SI remain dissociable from broader antidepressant responses.

Seizure-based neuromodulation offers complementary evidence. MST has demonstrated reproducible reductions in SI in TRD, with protocol-dependent effects. ECT remains the reference standard; recent large-scale evidence reports robust reductions in suicidality and all-cause mortality in refractory populations (Odermatt et al., 2025). VNS occupies a distinct niche: randomised evidence specific to suicidality is limited, but long-term observational cohorts report durable reductions in SI and lower suicide mortality over years, distinguishing VNS from other strategies with shorter-term evidence (Camacho-Conde et al., 2023).

4.5. Psychedelic-based interventions

Evidence for psychedelic-based interventions remains preliminary. Small clinical studies suggest that psilocybin, MDMA-assisted therapy, and ayahuasca may reduce SI in selected populations, but trials are scarce, performed in small samples, and suicidality is rarely prespecified as a primary endpoint. Systematic reviews report moderate effect sizes in controlled therapeutic settings, whereas observational studies—particularly those focused on recreational or lifetime use—yield heterogeneous and sometimes conflicting associations with suicidality (Meshkat et al., 2025). A central limitation is the difficulty of separating pharmacological effects from contextual influences. Outcomes appear closely linked to patient selection, preparation, therapeutic support, and environmental conditions, which are inconsistently reported and limit reproducibility (Estric et al., 2025). High-risk individuals are frequently excluded, limiting generalisability. Current consensus emphasises that any clinical integration requires clearer safety, ethical, and training standards before wider implementation (Herwig et al., 2025). At present, evidence on psychedelic interventions should be regarded as early and methodologically heterogeneous, rather than support their use as near-term suicide prevention strategies.

4.6. Cross-cutting synthesis

Across intervention classes, three observations have direct implications for trial design and clinical translation. First, SI can change rapidly, often within days, and in some studies without parallel improvement in depressive symptoms. This temporal profile has been reported for NMDA-related pharmacological strategies and for neuromodulation approaches, including accelerated rTMS and accelerated theta-burst protocols (Li et al., 2024b; Desmyter et al., 2016; Chen et al., 2019; Nierenberg et al., 2023). Second, early response is often not durable. Follow-up trajectories are heterogeneous, with attenuation or relapse after the acute phase in a subset of participants (Kucuker et al., 2021). Together, these features support a two-phase model, an acute phase targeting near-term reduction in SI and a continuation phase targeting persistence, relapse, and transition risks. Third, treatment transitions represent a clinically important risk window. In OUD cohorts, suicide and self-harm rates peak during the first month after cessation of opioid agonist treatment, supporting active monitoring and support during tapering, discontinuation, and post-discontinuation follow-up (Padmanathan et al., 2022; Colledge-Frisby et al., 2023). Contemporary models conceptualize suicidality as a dynamic process defined by rapid fluctuations in risk states rather than a static clinical condition (Barredo et al., 2021). Accordingly, treatment initiation, dose escalation, tapering, discontinuation, and post-intervention phases may be associated with transient increases in vulnerability due to withdrawal phenomena, rebound affective distress, reduced therapeutic benefit, or impaired emotional regulation. Observational evidence further supports the clinical relevance of these transition phases, with the highest risk of suicide attempt observed during treatment initiation (Valuck et al., 2009). These findings may be especially relevant for rapidly acting interventions targeting SI, where short-term symptomatic improvement may not translate into sustained protection against suicidal behaviour. Similar concerns emerge in the neuromodulation literature. Interventions such as rTMS, tDCS, and ECT often show promising short-term reductions in SI, although follow-up duration, durability of effects, and transition-phase monitoring remain heterogeneous across studies (Kucuker et al., 2021). Importantly, methodological reviews note that clinical trials fail to capture temporal fluctuations in suicidality during high-risk periods, limiting interpretation of treatment effects on suicidal behaviour (Barredo et al., 2021; Yao and McCall, 2023). Future studies should incorporate structured transition-sensitive monitoring strategies, including repeated suicide-risk assessments during treatment changes, predefined tapering protocols, scheduled follow-up after discontinuation, safety-planning procedures, and rapid access to crisis intervention when symptom worsening emerges.

Comparative interpretation across modalities should also account for differences in evidence strength and implementation requirements. Among pharmacological strategies, NMDA-related agents and opioid-system modulation have the most direct short-term efficacy evidence for SI outcomes, whereas folic acid, benztropine, NOACs, and cannabis-related findings derive largely from observational or survey-based data and should be considered hypothesis-generating; testosterone initiation is supported by limited open-label trial evidence. Among neuromodulatory interventions, accelerated rTMS and theta-burst protocols provide controlled evidence for short-term SI reduction, whereas VNS has mainly longer-term naturalistic support.

Safety and implementation constraints differ across intervention classes and should be considered when evaluating clinical translation. For non-invasive neuromodulation, rTMS and theta-burst protocols have an established safety framework, but accelerated schedules increase treatment intensity and service demands, and seizure risk and contraindications remain relevant in routine care (Rossi et al., 2021). Seizure-based procedures (MST and ECT) require anaesthesia-level infrastructure and systematic monitoring, and VNS adds surgical considerations and long-term device management. For opioid-system modulation, any efficacy signal must be weighed against misuse liability, physiological dependence, and elevated risk around discontinuation, which is consistently identified as a high-risk period in observational datasets (Padmanathan et al., 2022; Vakkalanka et al., 2021). For psychedelic-assisted interventions, acute physiological risk is generally manageable in controlled settings, but psychological risk management, participant selection, therapist training, and governance standards are central to safety and scalability (McGuire et al., 2024; Scala et al., 2024). Finally, findings arise from medications with clinically relevant adverse-effect profiles in real-world populations, including cognitive and medical harms associated with cumulative anticholinergic exposure and safety concerns around hypnotics in older or medically frail individuals (Coupland et al., 2019; Pieper et al., 2020; Cho et al., 2020; American Geriatrics Society, 2023).

4.7. Limitations and priorities for the next generation of trials

The available evidence should be interpreted considering several limitations, including small sample sizes and substantial heterogeneity across multiple domains. First, study designs comprised RCT (efficacy) and observational or naturalistic studies (effectiveness), as well as post hoc versus primary analyses. Second, patient samples were highly heterogeneous, including different diagnostic groups (e.g., MDD, BD, BPD, SUD, schizophrenia, and gender dysphoria), variability in treatment resistance, and inclusion of individuals with primary SI without a formal psychiatric diagnosis. Third, interventions varied widely, including pharmacological and neuromodulation approaches, with heterogeneous mechanisms of action (i.e., NMDA modulation, opioid system modulation, psychedelics, monoaminergic agents), as well as variability in treatment modality (monotherapy vs adjunctive), dosing, and administration. Fourth, follow-up duration and temporal outcome assessment also varied, with inconsistent reporting of onset and durability. Hence,

the persistence of effects cannot be directly inferred, given the absence of repeated measures of SI, limited reporting of effect sizes across multiple timepoints, and the lack of explicit analyses of maintenance versus relapse. This is particularly evident in observational studies, typically population- or survey-based, which lack within-individual longitudinal assessment. Finally, outcome measurement heterogeneity limits cross-study comparability. Many studies relied on single items embedded within depression scales (e.g., HAMD item 3; MADRS suicidality item), whereas others used dedicated instruments such as the C-SSRS or SSI/BSSI, which differ in anchors, time windows, and thresholds for clinically meaningful change (Posner et al., 2011; FDA, 2012). Findings based on single-item approaches may be pragmatic but should be interpreted with greater caution than those derived from validated, dedicated suicidality instruments. Single-item measures may increase misclassification, reduce statistical power, particularly for SA endpoints, and inadequately distinguish passive death wishes from active ideation, preparatory acts, and SAs (Millner et al., 2015). At the same time, rapid-acting intervention trials require SI instruments that are sensitive to short-term change, because different single-item and multi-item measures may vary in their ability to detect rapid reductions in suicidal thoughts (Ballard et al., 2015). Because these methodological differences precluded quantitative synthesis, findings were presented descriptively and interpreted according to study design and measurement robustness.

Consistent with regulatory guidance, future trials should prespecify a suicidality endpoint hierarchy, include both SI and SA ascertainment with standardised definitions, and report rater training and adjudication procedures when behavioural events are outcomes (Posner et al., 2011; FDA, 2012).

Observational studies provided useful results but remain exposed to confounding and reverse causality, particularly in clinical populations where baseline risk and treatment allocation are closely linked. Across interventions, evidence on moderators of response remains sparse, but available signals suggest that baseline anxiety, insomnia severity, and clinical context may shape SI trajectories and should be prespecified as effect modifiers. Placebo and contextual effects are also relevant. In neuromodulation, sham-associated improvements in suicide risk and SI have been reported, with neuroimaging evidence consistent with expectancy-related change (Desmyter et al., 2016; Baeken et al., 2019). Only a minority of studies formally test whether anti-suicidal effects persist after accounting for concurrent changes in depressive symptoms or correlated domains such as anxiety, insomnia, or affective distress.

Individuals at highest imminent risk are often excluded, limiting generalisability to settings where suicide prevention is most urgent (Lawrence et al., 2025; Ballard et al., 2017). Accordingly, future investigations should implement ethically responsible inclusion strategies, including intensive safety monitoring, rapid clinical response protocols, frequent suicidality assessments, predefined rescue interventions, and shorter placebo exposure when feasible. Adaptive and pragmatic trial designs conducted in highly supervised clinical settings may also improve the balance between participant safety and external validity, improving real-world clinical applicability. Across included studies, suicide-related endpoints were predominantly ideation-based, whereas SA outcomes were infrequently captured and typically underpowered. Therefore, observed changes in SI should not be interpreted as evidence of reduced SA without dedicated behavioural endpoints and follow-up that spans high-risk periods. Of note, the reviewed studies did not assess differential effects on outward- versus self-directed aggression (e.g., hostility vs. SI/SA), limiting understanding of shared anti-aggressive mechanisms (Scala et al., 2025).

Finally, the literature on anti-suicidal interventions is limited to adult populations, with minimal representation of adolescents and elderly individuals. Therefore, age-related differences in neurobiology, clinical presentation, and treatment response may influence the efficacy and safety of these interventions (Casey et al., 2008), limiting their generalisability across age groups.

These limitations point to concrete next steps. Trials intended to inform suicide prevention should prespecify SI, SA, or mortality as primary outcomes; apply analytic plans that test independence from mood change (including covariate-adjusted and mediation frameworks where appropriate); incorporate age-stratified study designs; and extend beyond acute response to explicitly evaluate continuation strategies (repeated dosing, maintenance neuromodulation, or structured integration with psychotherapy). Treatment transitions should be treated as protocol-defined high-risk phases with predefined monitoring and mitigation, rather than as administrative endpoints.

5. Conclusions

The evidence reviewed here supports a reappraisal of suicide-related outcomes as a treatment target in its own right. Across pharmacological and neuromodulatory interventions, the most consistent finding is that SI can change rapidly—often within days—and, in several studies, without parallel improvement in depressive symptoms. This temporal dissociation is observed most reliably for glutamatergic strategies and for neuromodulation approaches such as accelerated rTMS, theta-burst stimulation, and seizure-based interventions (Li et al., 2024b; Kucuker et al., 2021; Cui et al., 2022; Chen et al., 2022; Camacho-Conde et al., 2023; Odermatt et al., 2025). By contrast, the duration of early effects has been scarcely investigated, and relapse after acute phases is common. Transition periods, particularly discontinuation phases, carry heightened risk and remain insufficiently addressed in many trial designs. Progress in suicide prevention will require moving beyond depression-centred endpoints. Trials should prespecify suicide-related outcomes, test independence from mood change, and incorporate designs that address onset, maintenance, and transitions. Clinically, early reductions in SI should not be equated with sustained risk mitigation. The current evidence suggests that SI may follow partially distinct trajectories, respond on a different timescale than depressive symptoms, and warrant direct evaluation as a treatment target in pharmacological and neuromodulatory trials.

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Statement of ethics

This review used published data only; ethics approval was not required.

Data statement

All data reported in this review were extracted from publicly available publications. The extracted datasets and all related materials are included in the manuscript and its supplementary files. No new raw data were generated.

Contributors

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References

Aaronson, S.T., Sears, P., Ruvuna, F., Bunker, M., Conway, C.R., Dougherty, D.D., Reimherr, F.W., Schwartz, T.L., Zajecka, J.M., 2017. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am. J. Psychiatry 174 (7), 640–648. https://doi.org/10.1176/appi.ajp.2017.16010034.

Abdelnaim, M.A., Langguth, B., Deppe, M., Mohonko, A., Kreuzer, P.M., Poeppl, T.B., Hebel, T., Schecklmann, M., 2020. Anti-suicidal efficacy of repetitive transcranial magnetic stimulation in depressive patients: a retrospective analysis of a large sample. Front. Psychiatry 10, 929. https://doi.org/10.3389/fpsyt.2019.00929.

Ahmadi, J., Jahromi, M.S., Ehsaei, Z., 2018. The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: a randomized, double-blind, clinical trial. Trials 19 (1), 462. https://doi.org/10.1186/s13063-018-2843-9.

American Geriatrics Society, 2023. updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 71 (7), 2052–2081. https://doi.org/10.1111/jgs.18372.

Baeken, C., Wu, G.-R., Van Heeringen, K., 2019. Placebo aiTBS attenuates suicidal ideation and frontopolar cortical perfusion in major depression. Transl. Psychiatry 9 (1), 38. https://doi.org/10.1038/s41398-019-0377-x.

Bahorik, A.L., Sterling, S.A., Campbell, C.I., Weisner, C., Ramo, D., Satre, D.D., 2018. Medical and non-medical marijuana use in depression: longitudinal associations with suicidal ideation, everyday functioning, and psychiatry service utilization. J. Affect. Disord. 241, 8–14. https://doi.org/10.1016/j.jad.2018.05.065.

Ballard, E.D., Luckenbaugh, D.A., Richards, E.M., Walls, T.L., Brutsché, N.E., Ameli, R., Niciu, M.J., Vande Voort, J.L., Zarate Jr., C.A., 2015. Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. J. Psychiatr. Res. 68, 68–73. https://doi.org/10.1016/j.jpsychires.2015.06.003.

Ballard, E.D., Snider, S.L., Nugent, A.C., Luckenbaugh, D.A., Park, L., Zarate, C.A., 2017. Active suicidal ideation during clinical antidepressant trials. Psychiatry Res. 257, 303–308. https://doi.org/10.1016/j.psychres.2017.07.065.

Ballard, E.D., Fields, J., Farmer, C.A., Zarate, C.A., 2021. Clinical trials for rapid changes in suicidal ideation: lessons from ketamine. Suicide Life-Threat. Behav. 51 (1), 27–35. https://doi.org/10.1111/sltb.12663.

Barredo, J., Bozzay, M.L., Primack, J.M., Schatten, H.T., Armey, M.F., Carpenter, L.L., Philip, N.S., 2021. Translating interventional neuroscience to suicide: it's about time. Biol. Psychiatry 89 (11), 1073–1083. https://doi.org/10.1016/j.biopsych.2021.01.013.

Batterham, P.J., Spijker, B.A.J., Mackinnon, A.J., Calear, A.L., Wong, Q., Christensen, H., 2019. Consistency of trajectories of suicidal ideation and depression symptoms: evidence from a randomized controlled trial. Depress. Anxiety 36 (4), 321–329. https://doi.org/10.1002/da.22863.

Camacho-Conde, J.A., Del Rosario Gonzalez-Bermudez, M., Carretero-Rey, M., Khan, Z. U., 2023. Therapeutic potential of brain stimulation techniques in the treatment of mental, psychiatric, and cognitive disorders. CNS Neurosci. Ther 29 (1), 8–23. https://doi.org/10.1111/cns.13971.

Casey, B.J., Jones, R.M., Hare, T.A., 2008. The adolescent brain. Ann. N. Y. Acad. Sci. 1124, 111–126. https://doi.org/10.1196/annals.1440.010.

Chen, G.-W., Hsu, T.-W., Ching, P.-Y., Pan, C.-C., Chou, P.-H., Chu, C.-S., 2022. Efficacy and tolerability of repetitive transcranial magnetic stimulation on suicidal ideation: a systemic review and meta-analysis. Front. Psychiatry 13, 884390. https://doi.org/10.3389/fpsyt.2022.884390.

Chen, M.-H., Cheng, C.-M., Gueorguieva, R., Lin, W.-C., Li, C.-T., Hong, C.-J., Tu, P.-C., Bai, Y.-M., Tsai, S.-J., Krystal, J.H., Su, T.-P., 2019. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo–control study. Neuropsychopharmacology 44 (12), 2112–2118. https://doi.org/10.1038/s41386-019-0480-y.

Chen, R., Capitão, L.P., Cowen, P.J., Harmer, C.J., 2021. Effect of the NMDA receptor partial agonist, D-cycloserine, on emotional processing and autobiographical memory. Psychol. Med. 51 (15), 2657–2665. https://doi.org/10.1017/S0033291720001221.

Cho, C.-H., Jee, H.-J., Nam, Y.-J., An, H., Kim, L., Lee, H.-J., 2020. Temporal association between zolpidem medication and the risk of suicide: a 12-year population-based, retrospective cohort study. Sci. Rep. 10 (1), 4875. https://doi.org/10.1038/s41598-020-61694-9.

Cipriani, A., Hawton, K., Stockton, S., Geddes, J.R., 2013. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 346 (jun27 4), f3646. https://doi.org/10.1136/bmj.f3646.

Colledge-Frisby, S., Jones, N., Degenhardt, L., Hickman, M., Padmanathan, P., Santo, T., Farrell, M., Gisev, N., 2023. Incidence of suicide and self-harm among people with opioid use disorder and the impact of opioid agonist treatment: a retrospective data linkage study. Drug Alcohol Depend. 246, 109851. https://doi.org/10.1016/j.drugalcdep.2023.109851.

Coupland, C.A.C., Hill, T., Dening, T., Morriss, R., Moore, M., Hippisley-Cox, J., 2019. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern. Med 179 (8), 1084. https://doi.org/10.1001/jamainternmed.2019.0677.

Cui, Y., Fang, H., Bao, C., Geng, W., Yu, F., Li, X., 2022. Efficacy of transcranial magnetic stimulation for reducing suicidal ideation in depression: a meta-analysis. Front. Psychiatry 12, 764183. https://doi.org/10.3389/fpsyt.2021.764183.

De Berardis, D., Fornaro, M., Anastasia, A., Vellante, F., Olivieri, L., Rapini, G., Serroni, N., Orsolini, L., Valchera, A., Carano, A., Tomasetti, C., Ventriglio, A., Bustini, M., Pompili, M., Serafini, G., Perna, G., Iasevoli, F., Martinotti, G., Di Giannantonio, M., 2020. Adjunctive vortioxetine for SSRI-resistant major depressive disorder: a "real-world" chart review study. Braz. J. Psychiatry 42 (3), 317–321. https://doi.org/10.1590/1516-4446-2019-0690.

De Ridder, D., Maciaczyk, J., Vanneste, S., 2021. The future of neuromodulation: smart neuromodulation. Expert Rev. Med. Devices 18 (4), 307–317. https://doi.org/10.1080/17434440.2021.1909470.

Desmyter, S., Duprat, R., Baeken, C., Van Autreve, S., Audenaert, K., Van Heeringen, K., 2016. Accelerated intermittent theta burst stimulation for suicide risk in therapy-resistant depressed patients: a randomized, sham-controlled trial. Fronti. Hum. Neurosci. 10. https://doi.org/10.3389/fnhum.2016.00480.

Dietrich, D.E., Bode, L., Spannhuth, C.W., Hecker, H., Ludwig, H., Emrich, H.M., 2020. Antiviral treatment perspective against Borna disease virus 1 infection in major depression: a double-blind placebo-controlled randomized clinical trial. BMC Pharmacol. Toxicol 21 (1), 12. https://doi.org/10.1186/s40360-020-0391-x.

Doyle, D.M., Lewis, T.O.G., Barreto, M., 2023. A systematic review of psychosocial functioning changes after gender-affirming hormone therapy among transgender people. Nat. Hum. Behav. 7 (8), 1320–1331. https://doi.org/10.1038/s41562-023-01605-w.

Estric, C., Duron, T., Kabani, S., Lopez-Castroman, J., 2025. Set and setting of psychedelics for therapeutic use in psychiatry: a systematic review. J. Psychopharmacol. 39 (9), 910–929. https://doi.org/10.1177/02698811251338214.

FDA, 2012. Guidance for industry suicidal ideation and behavior: prospective assessment of occurrence in clinical trials.

Feldman, I., 2025. Economic burden of suicide in Sweden in 2022. Eur. J. Public Health 35 (Supplement_4). https://doi.org/10.1093/eurpub/ckaf161.1888 ckaf161.1888.

Francis, B., Ganasan, V.A., Sulaiman, A.R.B., 2024. Brexpiprazole attenuates aggression, suicidality and substance use in Borderline Personality Disorder: a case series. Medicina (B Aires) 60 (2), 283. https://doi.org/10.3390/medicina60020283.

Franklin, J.C., Ribeiro, J.D., Fox, K.R., Bentley, K.H., Kleiman, E.M., Huang, X., Musacchio, K.M., Jaroszewski, A.C., Chang, B.P., Nock, M.K., 2017. Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychol. Bull. 143 (2), 187–232. https://doi.org/10.1037/bul0000084.

Gibbons, R.D., Hur, K., Lavigne, J.E., Mann, J.J., 2022. Association between folic acid prescription fills and suicide attempts and intentional self-harm among privately insured US adults. JAMA Psychiatry 79 (11), 1118. https://doi.org/10.1001/JAMApsychiatry.2022.2990.

Gibbons, R.D., Hur, K., Lavigne, J.E., Mann, J.J., 2023. Benztropine and suicide attempts and intentional self-harm. Psychiatry Res. 320, 115054. https://doi.org/10.1016/j.psychres.2023.115054.

Gorlyn, M., Keilp, J., Burke, A., Oquendo, M., Mann, J.J., Grunebaum, M., 2015. Treatment-related improvement in neuropsychological functioning in suicidal depressed patients: paroxetine vs. bupropion. Psychiatry Res. 225 (3), 407–412. https://doi.org/10.1016/j.psychres.2014.12.004.

Grunebaum, M.F., Ellis, S.P., Duan, N., Burke, A.K., Oquendo, M.A., John Mann, J., 2012. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. Neuropsychopharmacology 37 (3), 697–706. https://doi.org/10.1038/npp.2011.247.

Grunebaum, M.F., Galfalvy, H.C., Choo, T.-H., Keilp, J.G., Moitra, V.K., Parris, M.S., Marver, J.E., Burke, A.K., Milak, M.S., Sublette, M.E., Oquendo, M.A., Mann, J.J., 2018. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am. J. Psychiatry 175 (4), 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647.

Hanson, J.E., Yuan, H., Perszyk, R.E., Banke, T.G., Xing, H., Tsai, M.-C., Menniti, F.S., Traynelis, S.F., 2024. Therapeutic potential of N-methyl-D-aspartate receptor modulators in psychiatry. Neuropsychopharmacology 49 (1), 51–66. https://doi.org/10.1038/s41386-023-01614-3.

Herwig, U., Schnell, K., Daumann, J., Jungaberle, A., Koller, G., Mertens, L.J., Borgwardt, S., 2025. Psychedelika in der psychiatrie: eine offene debatte. Fortschr. Neurol. Psychiatr. 93 (09), 343–351. https://doi.org/10.1055/a-2453-0910.

Hetrick, S.E., McKenzie, J.E., Cox, G.R., Simmons, M.B., Merry, S.N., 2012. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst. Rev. 2021 (11), CD004851. https://doi.org/10.1002/14651858.CD004851.pub3.

Jiang, T., Nagy, D., Rosellini, A.J., Horváth-Puhó, E., Keyes, K.M., Lash, T.L., Galea, S., Sørensen, H.T., Gradus, J.L., 2024. Prediction of suicide attempts among persons with depression: a population-based case cohort study. Am. J. Epidemiol. 193 (6), 827–834. https://doi.org/10.1093/aje/kwad237.

Jones, G.M., Nock, M.K., 2022. MDMA/ecstasy use and psilocybin use are associated with lowered odds of psychological distress and suicidal thoughts in a sample of US adults. J. Psychopharmacol. 36 (1), 46–56. https://doi.org/10.1177/02698811211058923.

Keilp, J.G., Ellis, S.P., Gorlyn, M., Burke, A.K., Oquendo, M.A., Mann, J.J., Grunebaum, M.F., 2018. Suicidal ideation declines with improvement in the subjective symptoms of major depression. J. Affect. Disord. 227, 65–70. https://doi.org/10.1016/j.jad.2017.09.018.

Kucuker, M.U., Almorsy, A.G., Sonmez, A.I., Ligezka, A.N., Doruk Camsari, D., Lewis, C. P., Croarkin, P.E., 2021. A systematic review of neuromodulation treatment effects on suicidality. Front. Hum. Neurosci. 15, 660926. https://doi.org/10.3389/fnhum.2021.660926.

Langan, S.M., Schmidt, S.A., Wing, K., Ehrenstein, V., Nicholls, S.G., Filion, K.B., Klungel, O., Petersen, I., Sorensen, H.T., Dixon, W.G., Guttmann, A., Harron, K., Hemkens, L.G., Moher, D., Schneeweiss, S., Smeeth, L., Sturkenboom, M., Von Elm, E., Wang, S.V., Benchimol, E.I., 2018. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ k3532. https://doi.org/10.1136/bmj.k3532.

Lawrence, R.E., Jaffe, C., Zhao, Y., Wang, Y., Goldberg, T.E., 2025. Clinical trials studying suicide risk reduction: who is excluded from participation. Arch. Suicide Res. 29 (1), 77–90. https://doi.org/10.1080/13811118.2024.2322128.

Lee, B.J., Cotes, R.O., Mojtabai, R., Margolis, R.L., Nucifora, F.C., Nestadt, P.S., 2023. The protective effect of clozapine on suicide: a population mortality study of statewide autopsy records in Maryland. J. Clin. Psychiatry 84 (3), 22m14587. https://doi.org/10.4088/JCP.22m14587.

Li, B.M.-H., Yang, A.S.-H., Cheng, M.C.-Y., Huang, H.-K., Lai, E.C.-C., 2024a. Risk of suicide in patients with atrial fibrillation receiving different oral anticoagulants: a nationwide analysis using target trial emulation framework. BMC Med. 22 (1), 451. https://doi.org/10.1186/s12916-024-03645-z.

Li, B., Zhao, N., Tang, N., Friston, K.J., Zhai, W., Wu, D., Liu, J., Chen, Y., Min, Y., Qiao, Y., Liu, W., Shu, W., Liu, M., Zhou, P., Guo, L., Qi, S., Cui, L.-B., Wang, H., 2024b. Targeting suicidal ideation in major depressive disorder with MRI-navigated Stanford accelerated intelligent neuromodulation therapy. Transl. Psychiatry 14 (1), 21. https://doi.org/10.1038/s41398-023-02707-9.

Liwinski, T., Lang, U.E., 2023. Folate and its significance in depressive disorders and suicidality: a comprehensive narrative review. Nutrients. 15 (17), 3859. https://doi.org/10.3390/nu15173859.

Lucido, M.J., Dunlop, B.W., 2025. Emerging medications for treatment-resistant depression: a review with perspective on mechanisms and challenges. Brain Sci. 15 (2), 161. https://doi.org/10.3390/brainsci15020161.

Łyszczarz, B., 2021. Production losses attributable to suicide deaths in European Union. BMC Public Health 21 (1), 950. https://doi.org/10.1186/s12889-021-11010-5.

Mahableshwarkar, A.R., Affinito, J., Reines, E.H., Xu, J., Nomikos, G., Jacobsen, P.L., 2020. Suicidal ideation and behavior in adults with major depressive disorder treated with vortioxetine: post hoc pooled analyses of randomized, placebo-controlled, short-term and open-label, long-term extension trials. CNS. Spectr. 25 (3), 352–362. https://doi.org/10.1017/S109285291900097X.

Martone, A., Folego-Temoteo, I., Fries, G.R., Docherty, A.R., Ashley-Koch, A.E., European College of Neuropsychopharmacology Network on Suicide Research and Prevention, Bandeira, C.E., Grevet, E.H., Bau, C.H.D., Bralten, J., Fabbri, C., Serretti, A., Rovaris, D.L., Fanelli, G., 2025. *Dissecting the pleiotropic genetic architecture of suicide attempt, suicidal ideation, and thirteen correlated traits*. https://doi.org/10.64898/2025.12.07.25341749.

Masdrakis, V.G., Baldwin, D.S., 2023. Prevention of suicide by clozapine in mental disorders: systematic review. Eur. Neuropsychopharmacol. 69, 4–23. https://doi.org/10.1016/j.euroneuro.2022.12.011.

McCall, W.V., Benca, R.M., Rosenquist, P.B., Youssef, N.A., McCloud, L., Newman, J.C., Case, D., Rumble, M.E., Szabo, S.T., Phillips, M., Krystal, A.D., 2019. Reducing suicidal ideation through insomnia treatment (REST-IT): a randomized clinical trial. Am. J. Psychiatry 176 (11), 957–965. https://doi.org/10.1176/appi.ajp.2019.19030267.

McGuire, A.L., Cohen, I.G., Sisti, D., Baggott, M., Celidwen, Y., Devenot, N., Gracias, S., Grob, C., Harvey, I., Kious, B., Marks, M., Mithoefer, M., Nielson, E., Öngür, D., Pallas, A., Peterson, A., Schenberg, E.E., Summergrad, P., Waters, B., Yaden, D.B., 2024. Developing an ethics and policy framework for psychedelic clinical care: a consensus statement. JAMA Netw. Open. 7 (6), e2414650. https://doi.org/10.1001/JAMAnetworkopen.2024.14650.

Meshkat, S., Malik, T., Zeifman, R., Swainson, J., Zhang, Y., Burback, L., Winkler, O., Greenshaw, A.J., Claire Reichelt, A., Vermetten, E., Erritzoe, D., Jha, M.K., Dunn, W., Jetly, R., Husain, M.I., Bhat, V., 2025. Psychedelics and suicide-related outcomes: a systematic review. J. Clin. Med. 14 (5), 1416. https://doi.org/10.3390/jcm14051416.

Millner, A.J., Lee, M.D., Nock, M.K., 2015. Single-item measurement of suicidal behaviors: validity and consequences of misclassification. PLoS. One 10 (10), e0141606. https://doi.org/10.1371/journal.pone.0141606.

Nierenberg, A., Lavin, P., Javitt, D.C., Shelton, R., Sapko, M.T., Mathew, S., Besthof, R.E., Javitt, J.C., 2023. NRX-101 (D-cycloserine plus lurasidone) vs. lurasidone for the maintenance of initial stabilization after ketamine in patients with severe bipolar depression with acute suicidal ideation and behavior: a randomized prospective phase 2 trial. Int. J. Bipolar. Disord. 11 (1), 28. https://doi.org/10.1186/s40345-023-00308-5.

Nolan, B.J., Zwickl, S., Locke, P., Zajac, J.D., Cheung, A.S., 2023. Early access to testosterone therapy in transgender and gender-diverse adults seeking masculinization: a randomized clinical trial. JAMA Netw. Open. 6 (9), e2331919. https://doi.org/10.1001/JAMAnetworkopen.2023.31919.

Odermatt, J., Sarlon, J., Schaefer, N., Ulrich, S., Ridder, M., Schneider, E., Lang, U.E., Liwinski, T., Brühl, A.B., 2025. Electroconvulsive therapy reduces suicidality and all-cause mortality in refractory depression: a systematic review and meta-analysis of neurostimulation studies. Neurosci. Appl. 4, 105520. https://doi.org/10.1016/j.nsa.2025.105520.

Oh, J., Ho, J., Lee, S., Park, J.-H., 2024. Effects of digital psychotherapy on suicide: a systematic review and meta-analysis. Healthcare 12 (14), 1435. https://doi.org/10.3390/healthcare12141435.

Padmanathan, P., Forbes, H., Redaniel, M.T., Gunnell, D., Lewer, D., Moran, P., Watson, B., Degenhardt, L., Hickman, M., 2022. Self-harm and suicide during and after opioid agonist treatment among primary care patients in England: a cohort study. Lancet Psychiatry 9 (2), 151–159. https://doi.org/10.1016/S2215-0366(21)00392-8.

Pan, F., Shen, Z., Jiao, J., Chen, J., Li, S., Lu, J., Duan, J., Wei, N., Shang, D., Hu, S., Xu, Y., Huang, M., 2020. Neuronavigation-guided rTMS for the treatment of depressive patients with suicidal ideation: a double-blind, randomized, sham-controlled trial. Clin. Pharmacol. Ther. 108 (4), 826–832. https://doi.org/10.1002/cpt.1858.

Parris, M.S., Marver, J.E., Chaudhury, S.R., Ellis, S.P., Metts, A.V., Keilp, J.G., Burke, A. K., Oquendo, M.A., Mann, J.J., Grunebaum, M.F., 2018. Effects of anxiety on suicidal ideation: exploratory analysis of a paroxetine versus bupropion randomized trial. Int. Clin. Psychopharmacol. 33 (5), 249–254. https://doi.org/10.1097/YIC.0000000000000225.

Pieper, N.T., Grossi, C.M., Chan, W.-Y., Loke, Y.K., Savva, G.M., Haroulis, C., Steel, N., Fox, C., Maidment, I.D., Arthur, A.J., Myint, P.K., Smith, T.O., Robinson, L., Matthews, F.E., Brayne, C., Richardson, K., 2020. Anticholinergic drugs and incident dementia, mild cognitive impairment and cognitive decline: a meta-analysis. Age Ageing 49 (6), 939–947. https://doi.org/10.1093/ageing/afaa090.

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia–Suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168 (12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704.

Rajkumar, R.P., 2022. Pharmacological strategies for suicide prevention based on the social pain model: a scoping review. Psych. 4 (3), 494–515. https://doi.org/10.3390/psych4030038.

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L.L., Cincotta, M., Chen, R., Daskalakis, J.D., Di Lazzaro, V., Fox, M.D., George, M.S., Gilbert, D., Kimiskidis, V.K., Koch, G., Ilmoniemi, R.J., Lefaucheur, J.P., Leocani, L., Hallett, M., 2021. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: expert Guidelines. Clin. Neurophysiol. 132 (1), 269–306. https://doi.org/10.1016/j.clinph.2020.10.003.

Scala, M., Dukart, J., De Simone, G., Fanelli, G., Arroyo Iturra, R., Bordignon, S., Fabbri, C., Serretti, A., 2026. Magnetoencephalographic signatures of facial emotion processing in schizophrenia and major depressive disorder: a systematic review. Neuropsychobiol 1–21. https://doi.org/10.1159/000550903.

MNESYS - Mood and Psychosis Sub-Project (Spoke 5) Scala, M., Fabbri, C., Fusar-Poli, P., Di Lorenzo, G., Ferrara, M., Amerio, A., Fusar-Poli, L., Pichiecchio, A., Asteggiano, C., Menchetti, M., De Ronchi, D., Fanelli, G., Serretti, A., 2024. The revival of psilocybin between scientific excitement, evidence of efficacy, and real-world challenges. CNS Spectr. 29 (6), 570–584. https://doi.org/10.1017/S1092852924002268.

Scala, M., Fanelli, G., De Ronchi, D., Serretti, A., Fabbri, C., 2023. Clinical specificity profile for novel rapid acting antidepressant drugs. Int. Clin. Psychopharmacol. 38 (5), 297–328. https://doi.org/10.1097/YIC.0000000000000488.

Scala, M., Fanelli, G., Fabbri, C., Serretti, A., 2025. Asenapine for aggressive behaviours in psychiatric disorders: a systematic review of efficacy and real-world effectiveness. Int. J. Psychiatry Clin. Pract. 29, 179–192. https://doi.org/10.1080/13651501.2025.2560357.

Schrijvers, D.L., Bollen, J., Sabbe, B.G.C., 2012. The gender paradox in suicidal behavior and its impact on the suicidal process. J. Affect. Disord. 138 (1–2), 19–26. https://doi.org/10.1016/j.jad.2011.03.050.

Sendor, R., Stürmer, T., 2022. Core concepts in pharmacoepidemiology: confounding by indication and the role of active comparators. Pharmacoepidemiol. Drug Saf. 31 (3), 261–269. https://doi.org/10.1002/pds.5407.

Shamabadi, A., Ahmadzade, A., Hasanzadeh, A., 2022. Ketamine for suicidality: an umbrella review. Br. J. Clin. Pharmacol. 88 (9), 3990–4018. https://doi.org/10.1111/bcp.15360.

Shamabadi, A., Ahmadzade, A., Pirahesh, K., Hasanzadeh, A., Asadigandomani, H., 2023. Suicidality risk after using cannabis and cannabinoids: an umbrella review. Dialogues Clin. Neurosci. 25 (1), 50–63. https://doi.org/10.1080/19585969.2023.2231466.

Shelton, R.C., Fava, M., Freeman, M.P., Thase, M.E., Papakostas, G.I., Jha, M.K., Trivedi, M.H., Dirks, B., Liu, K., Stankovic, S., 2020. Effect of adjunctive pimavanserin on suicidal ideation in patients with major depression: analysis of the CLARITY study. J. Affect. Disord. 277, 478–485. https://doi.org/10.1016/j.jad.2020.08.051.

Shen, Z., Gao, D., Lv, X., Wang, H., Yue, W., 2024. A meta-analysis of the effects of ketamine on suicidal ideation in depression patients. Transl. Psychiatry 14 (1), 248. https://doi.org/10.1038/s41398-024-02973-1.

Sohn, M.N., Cole, J., Bray, S.L., McGirr, A., 2025. Intermittent theta-burst stimulation with adjunctive D-cycloserine rapidly resolves suicidal ideation and decreases implicit association with death/suicide. Psychol. Med. 55, e13. https://doi.org/10.1017/S0033291724003313.

Sun, Y., Farzan, F., Mulsant, B.H., Rajji, T.K., Fitzgerald, P.B., Barr, M.S., Downar, J., Wong, W., Blumberger, D.M., Daskalakis, Z.J., 2016. Indicators for remission of suicidal ideation following magnetic seizure therapy in patients with treatment-resistant depression. JAMA Psychiatry 73 (4), 337. https://doi.org/10.1001/JAMApsychiatry.2015.3097.

Sun, Y., Blumberger, D.M., Mulsant, B.H., Rajji, T.K., Fitzgerald, P.B., Barr, M.S., Downar, J., Wong, W., Farzan, F., Daskalakis, Z.J., 2018. Magnetic seizure therapy reduces suicidal ideation and produces neuroplasticity in treatment-resistant depression. Transl. Psychiatry 8 (1), 253. https://doi.org/10.1038/s41398-018-0302-8.

Susam, S., İlhan, N., Bodur, A., Çıkım, G., Canpolat, Ö., 2024. Is serum homocysteine level a biomarker of suicide attempts: a preliminary study. J. Psychiatr. Res. 175, 455–460. https://doi.org/10.1016/j.jpsychires.2024.05.043.

Vakkalanka, P., Lund, B.C., Arndt, S., Field, W., Charlton, M., Ward, M.M., Carnahan, R. M., 2021. Association between buprenorphine for opioid use disorder and mortality risk. Am. J. Prev. Med. 61 (3), 418–427. https://doi.org/10.1016/j.amepre.2021.02.026.

Valuck, R.J., Orton, H.D., Libby, A.M., 2009. Antidepressant discontinuation and risk of suicide attempt: a retrospective, nested case-control study. J. Clin. Psychiatry 70 (8), 1069–1077. https://doi.org/10.4088/JCP.08m04943.

Van Ballegooijen, W., Rawee, J., Palantza, C., Miguel, C., Harrer, M., Cristea, I., De Winter, R., Gilissen, R., Eikelenboom, M., Beekman, A., Cuijpers, P., 2025. Suicidal ideation and suicide attempts after direct or indirect psychotherapy: a systematic review and meta-analysis. JAMA Psychiatry 82 (1), 31. https://doi.org/10.1001/JAMApsychiatry.2024.2854.

Vanegas-Arroyave, N., Caroff, S.N., Citrome, L., Crasta, J., McIntyre, R.S., Meyer, J.M., Patel, A., Smith, J.M., Farahmand, K., Manahan, R., Lundt, L., Cicero, S.A., 2024. An evidence-based update on anticholinergic use for drug-induced movement disorders. CNS Drugs 38 (4), 239–254. https://doi.org/10.1007/s40263-024-01078-z.

Wang, D., Guo, X., Huang, Q., Wang, Z., Chen, J., Hu, S., 2024. Efficacy and safety of transcranial direct current stimulation as an add-on trial treatment for acute bipolar depression patients with suicidal ideation. CNS. Neurosci. Ther. 30 (10), e70077. https://doi.org/10.1111/cns.70077.

Weissman, C.R., Blumberger, D.M., Brown, P.E., Isserles, M., Rajji, T.K., Downar, J., Mulsant, B.H., Fitzgerald, P.B., Daskalakis, Z.J., 2018. Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. J. Clin. Psychiatry 79 (3). https://doi.org/10.4088/JCP.17m11692.

Weissman, C.R., Blumberger, D.M., Dimitrova, J., Throop, A., Voineskos, D., Downar, J., Mulsant, B.H., Rajji, T.K., Fitzgerald, P.B., Daskalakis, Z.J., 2020. Magnetic seizure therapy for suicidality in treatment-resistant depression. JAMA Netw. Open. 3 (8), e207434. https://doi.org/10.1001/JAMAnetworkopen.2020.7434.

World Health Organization, 2025. Suicide. https://www.who.int/news-room/fact-sheets/detail/suicide.

Yang, K.H., Han, B.H., Palamar, J.J., 2022. Past-year hallucinogen use in relation to psychological distress, depression, and suicidality among US adults. Addict. Behav. 132, 107343. https://doi.org/10.1016/j.addbeh.2022.107343.

Yao, Z., McCall, W.V., 2023. Designing clinical trials to assess the impact of pharmacological treatment for suicidal ideation/behavior: issues and potential solutions. Pharmaceut. Med. 37 (3), 221–232. https://doi.org/10.1007/s40290-023-00467-x.

Yovell, Y., Bar, G., Mashiah, M., Baruch, Y., Briskman, I., Asherov, J., Lotan, A., Rigbi, A., Panksepp, J., 2016. Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. Am. J. Psychiatry 173 (5), 491–498. https://doi.org/10.1176/appi.ajp.2015.15040535.

Zeifman, R.J., Palhano-Fontes, F., Hallak, J., Arcoverde, E., Maia-Oliveira, J.P., Araujo, D.B., 2019. The impact of Ayahuasca on suicidality: results from a randomized controlled trial. Front. Pharmacol. 10, 1325. https://doi.org/10.3389/fphar.2019.01325.

Zeifman, R.J., Singhal, N., Dos Santos, R.G., Sanches, R.F., De Lima Osório, F., Hallak, J. E.C., Weissman, C.R., 2021. Rapid and sustained decreases in suicidality following a single dose of ayahuasca among individuals with recurrent major depressive disorder: results from an open-label trial. Psychopharmacology (Berl) 238 (2), 453–459. https://doi.org/10.1007/s00213-020-05692-9.

Zhao, H., Jiang, C., Zhao, M., Ye, Y., Yu, L., Li, Y., Luan, H., Zhang, S., Xu, P., Chen, X., Pan, F., Shang, D., Hu, X., Jin, K., Chen, J., Mou, T., Hu, S., Fitzgibbon, B.M., Fitzgerald, P.B., Huang, M., 2024. Comparisons of accelerated continuous and intermittent theta burst stimulation for treatment-resistant depression and suicidal ideation. Biol. Psychiatry 96 (1), 26–33. https://doi.org/10.1016/j.biopsych.2023.12.013.

Zisook, S., Domingues, I., Compton, J., 2023. Pharmacologic approaches to suicide prevention. Focus (Madison) 21 (2), 137–144. https://doi.org/10.1176/appi.focus.20220076.

Zuin, M., De Leo, D., 2025. Suicide-related mortality trends in Europe, 2012–2021. Int. J. Environ. Res. Public Health 22 (6), 890. https://doi.org/10.3390/ijerph22060890.