Psychological Medicine

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Review Article

Cite this article: Zainal NH (2024). Is combined antidepressant medication (ADM) and psychotherapy better than either monotherapy at preventing suicide attempts and other psychiatric serious adverse events for depressed patients? A rare events meta-analysis. *Psychological Medicine* **54**, 457–472. https://doi.org/10.1017/S0033291723003306

Received: 17 July 2023
Revised: 1 October 2023
Accepted: 13 October 2023
First published online: 15 November 2023

Keywords:
antidepressant medication; combined treatment; comparative efficacy research; psychotherapy; serious psychiatric adverse events; suicide attempt

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Is combined antidepressant medication (ADM) and psychotherapy better than either monotherapy at preventing suicide attempts and other psychiatric serious adverse events for depressed patients? A rare events meta-analysis

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Abstract

Antidepressant medication (ADM)-only, psychotherapy-only, and their combination are the first-line treatment options for major depressive disorder (MDD). Previous meta-analyses of randomized controlled trials (RCTs) established that psychotherapy and combined treatment were superior to ADM-only for MDD treatment remission or response. The current meta-analysis extended previous ones by determining the comparative efficacy of ADM-only, psychotherapy-only, and combined treatment on suicide attempts and other serious psychiatric adverse events (i.e. psychiatric emergency department [ED] visit, psychiatric hospitalization, and/or suicide death; SAEs). Peto odds ratios (ORs) and their 95% confidence intervals were computed from the present random-effects meta-analysis. Thirty-four relevant RCTs were included. Psychotherapy-only was stronger than combined treatment (1.9% *v.* 3.7%; OR 1.96 [1.20–3.20], $p = 0.012$) and ADM-only (3.0% *v.* 5.6%; OR 0.45 [0.30–0.67], $p = 0.001$) in decreasing the likelihood of SAEs in the primary and trim-and-fill sensitivity analyses. Combined treatment was better than ADM-only in reducing the probability of SAEs (6.0% *v.* 8.7%; OR 0.74 [0.56–0.96], $p = 0.029$), but this comparative efficacy finding was non-significant in the sensitivity analyses. Subgroup analyses revealed the advantage of psychotherapy-only over combined treatment and ADM-only for reducing SAE risk among children and adolescents and the benefit of combined treatment over ADM-only among adults. Overall, psychotherapy and combined treatment outperformed ADM-only in reducing the likelihood of SAEs, perhaps by conferring strategies to enhance reasons for living. Plausibly, psychotherapy should be prioritized for high-risk youths and combined treatment for high-risk adults with MDD.

Major depressive disorder (MDD) is a common mental disorder entwined with impaired functioning in academic, occupational, and social domains (Kupferberg, Bicks, & Hasler, 2016) and compromised physical health (Zainal & Newman, 2022) and quality of life (Hohls, Konig, & Hajek, 2023). Economically, MDD imposes a hefty financial burden on government budgets due to substantial healthcare utilization costs, increased absenteeism and presenteeism, and reduced work productivity (Greenberg et al., 2021). One of the most devastating consequences of MDD is mortality due to a suicide attempt and other related causes (Chiu et al., 2023). Determining effective treatments for MDD to reduce the risk for or prevent suicide attempts and other serious psychiatric adverse events is thus essential.

The first-line treatments for MDD include psychotherapy-only, especially cognitive-behavioral and related therapies, antidepressant medication (ADM)-only, and combined treatment (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Meta-analyses of randomized controlled trials (RCTs) that examined MDD treatment response or remission rates as primary outcomes of interest showed that combined treatment conferred a substantially stronger aggregate effect than ADM-only, psychotherapy-only had a better aggregate effect than ADM-only, and the aggregate effect between combined treatment and psychotherapy-only was not different (Cuijpers et al., 2023; Furukawa et al., 2021; Karyotaki et al., 2016). Collectively, such findings might translate to the possibility that MDD treatments that comprise psychotherapy, especially those that embody cognitive-behavioral and related theories, would be associated with reduced risk of suicide attempts and associated serious psychiatric adverse events.

Only six meta-analyses have determined if psychotherapy or ADM monotherapies mitigated the risk for suicide attempts and related serious psychiatric adverse events. Five recent meta-analyses showed that depressed patients randomized to psychotherapy-only, such as cognitive-behavioral therapies (CBT; Calati & Courtet, 2016; Gotzsche & Gotzsche, 2017), dialectical behavioral therapy (Kothgassner, Robinson, Goreis, Ougrin, & Plener, 2020), psychodynamic-oriented therapies (Briggs et al., 2019), and suicide-focused psychotherapies (Riblet, Shiner, Young-Xu, & Watts, 2017), were less likely to engage in suicide attempt, self-harm behaviors, and encounter other serious psychiatric adverse events compared to their counterparts assigned to treatment-as-usual or waitlist. However, another recent meta-analysis showed that the probability for depressed patients randomized to receive ADM to experience any of these serious psychiatric adverse events was not different from those who received placebos (Braun, Bschor, Franklin, & Baethge, 2016). Further, a major limitation of these meta-analyses was the exclusion of RCTs that examined the comparative effects of psychotherapy-only, ADM-only, and combined treatment.

Accordingly, the present exploratory meta-analysis evaluated the comparative effects of psychotherapy-only, ADM-only, and combined treatment on suicide attempts and other serious psychiatric adverse events. Such serious psychiatric adverse events included psychiatric emergency department (ED) visits, psychiatric hospitalization, and/or suicide deaths among depressed patients. Knowing what treatment option works best to decrease the likelihood of suicide attempts and other serious psychiatric adverse events at the aggregate level could aid with successful suicide prevention efforts for depressed patients.

Method

Procedures and eligibility criteria

The present meta-analysis protocol was preregistered on the Open Science Framework (OSF; https://osf.io/c7z8d) and the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023443819). The conventional approach instructed by Cochrane was applied for the analyses, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in reporting the methods and results (Fig. 1; Moher et al., 2015; Page et al., 2021). The inclusion criteria included clinical trials that reported on number of patients with suicide attempts and/or other serious psychiatric adverse events (i.e. psychiatric ED visit, psychiatric hospitalization, or suicide death) at post-treatment in the intervention and control arms. Baseline randomization to psychotherapy-only, ADM-only, or combined treatment and recruitment of patients with a primary diagnosis of a depressive disorder was required. Following best practices, relevant RCTs that reported zero suicide attempts and serious psychiatric adverse events in the treatment and control arms were included, given that this is a more conservative method and enhances the generalizability of the results (Friedrich, Adhikari, & Beyene, 2007). Exclusion criteria included studies that used waitlist, treatment-as-usual, placebo, or another active control (e.g. ketamine) as a comparator, non-RCTs, and RCTs that did not recruit patients with a primary diagnosis of a depressive disorder. Although challenges in utilizing RCTs to examine rare outcomes such as suicide attempts and other serious psychiatric adverse events were acknowledged, RCTs can provide essential information on the comparative risk of such serious psychiatric adverse events when evaluating two or more treatment options. Nonetheless, the present meta-analysis centered on RCTs given that it is the gold standard design to determine comparative effectiveness (or efficacy; Rosen, Manor, Engelhard, & Zucker, 2006), and an adequate number of RCTs (i.e. 34 eligible RCTs; Fig. 1) have examined how psychotherapy-only, ADM-only, and combined treatment might reduce the risk of suicide attempts and other serious psychiatric adverse events. Table 1 summarizes the 34 eligible RCTs in the present meta-analysis and relays information about the number of suicide attempts, psychiatric ED visits, psychiatric hospitalization, and/or suicide deaths extracted from each RCT.

Study selection

Cochrane Library, Google Scholar, PubMed, and ScienceDirect were searched from the inception of each database until 30 June 2023, to identify published articles evaluating our research question. The following search terms and Boolean terms were used: ('suicide attempt') AND ('antidepressant') AND ('psychotherapy') AND ('trial') AND ('depression') AND ('serious adverse events'). A highly sensitive search approach that prioritized the detection of RCTs in these online databases was used (Riblet et al., 2017). Online Supplementary Table S1 details blow-by-blow how each study measured and reported the rates of suicide attempt(s) and/or other serious psychiatric adverse event(s) in each arm.

Intervention arms

Concerning psychotherapy type, the most common face-to-face psychotherapy was individual CBT ($n = 11$, 32.4%), followed by individual, interpersonal psychotherapy ($n = 5$, 14.7%), group CBT ($n = 1$, 2.9%), and psychotherapy without a specified theoretical orientation ($n = 1$, 2.9%). The remaining 16 studies (47.1%) did not use psychotherapy-only as a comparator. Regarding ADM type, most studies did not specify the ADM type ($n = 15$, 44.1%) followed by selective serotonin reuptake inhibitors (i.e. citalopram, fluoxetine, imipramine, sertraline; $n = 12$, 35.3%), and venlafaxine (a serotonin–norepinephrine reuptake inhibitor; $n = 1$, 2.9%). The remaining six studies (17.6%) did not use ADM-only as a comparator.

Data analyses

Using the Peto approach (Bradburn, Deeks, Berlin, & Russell Localio, 2007; Lane, 2013), summary odds ratios (ORs) with 95% confidence intervals (CIs) and p values were computed. Standard meta-analytic techniques (e.g. calculating risk ratio) are not recommended to determine rare outcomes such as suicide attempts and other serious psychiatric adverse events (i.e. psychiatric ED visits, psychiatric hospitalization, and/or suicide death; Bradburn et al., 2007; Lane, 2013). The Peto approach is an appropriate and robust alternative option for meta-analyzing data when event rates are less than 1% (Bradburn et al., 2007; Lane, 2013). No continuity correction for treatment arms with zero negative outcome events was applied since prior research showed that it would bias estimates with the Peto approach (Friedrich et al., 2007; Sweeting, Sutton, & Lambert, 2004).

The *rmeta* *R* package was used to conduct these random-effects meta-analyses for rare events and to generate forest plots. The conventional definition of an OR was used to

https://doi.org/10.1017/S0033291723003306 Published online by Cambridge University Press

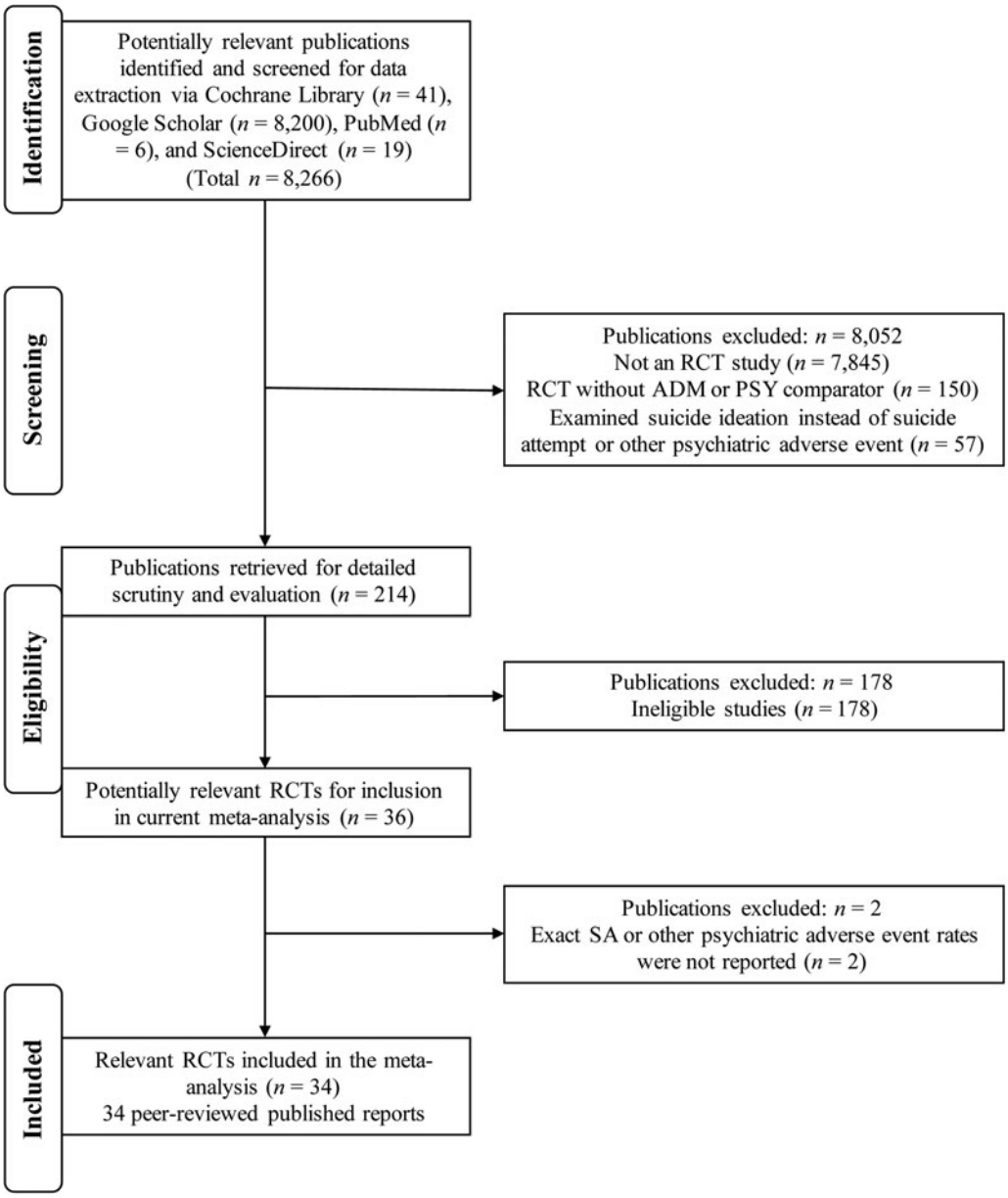

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; ADM, antidepressant medication; PSY, psychotherapy; SA, suicide attempt.

interpret the present findings (i.e. likelihood of the occurrence of suicide attempts and other serious psychiatric adverse events *v.* likelihood of the non-occurrence of suicide attempts and other serious psychiatric adverse events in the intervention arm *v.* comparator arm). An OR value < 1 indicated that the relative odds of suicide attempts and other serious psychiatric adverse events were lower in the treatment arm *v.* comparator arm, and the opposite was true with an OR value > 1. The OR was considered to be statistically significant if the 95% CIs did not cross 1 (Szumilas, 2010). Standard thresholds of Cochrane's Q p value < 0.10 and $I^2 > 50\%$ were used to determine between-study heterogeneity (Deeks, Higgins, & Altman, 2019).

Contour-enhanced funnel plots were created to evaluate publication bias to determine if any funnel plot asymmetry indicated substantial publication bias (Peters, Sutton, Jones, Abrams, & Rushton, 2008). Moreover, Harbord's modified assessment of small study effects was used to test for publication bias for binary outcomes (Harbord, Egger, & Sterne, 2006; Peters, Sutton, Jones, Abrams, & Rushton, 2006) with the *meta R* package (Balduzzi, Rucker, & Schwarzer, 2019). This approach utilized a modified linear regression analysis to detect significant funnel plot asymmetry that would denote publication bias (i.e. with a $p < 0.05$ value; Harbord et al., 2006). The Harbord approach is stronger than other standard tests of publication bias under conditions of few events per RCT (Harbord et al., 2006). Sensitivity analyses were also conducted with Duval and Tweedie trim-and-fill method (Duval & Tweedie, 2000) to determine if the pattern of outcomes from the primary analyses changes after adjusting for any funnel plot asymmetry caused by publication biases. In addition, to assess study quality, the Cochrane Risk of Bias Tool was used (Higgins et al., 2011) with the *robvis R* package to generate risk-of-bias plots (McGuinness & Higgins, 2020).

The heterogeneity of treatment effects was explored in the present meta-analysis. Specifically, we conducted subgroup analyses

https://doi.org/10.1017/S0033291723003306 Published online by Cambridge University Press

Table 1. Summary of RCTs that examined comparative average treatment effect (ATE) of antidepressant medication (ADM) and/or psychotherapy (PSY) predicting suicide attempt (SAs), psychiatric emergency department (ED) visit, psychiatric hospitalization, and/or suicide death

Author(s)	Study design	Target sample	Treatment arm(s)	Control arm(s)	Summary of ATE outcome
Bernstein et al. (2000)	Two-arm RCT	Adolescents with MDD ($n = 63$)	CBT + imipramine ($n = 31$)	CBT-only ($n = 32$)	No significant ATE was observed across treatments in predicting psychiatric hospitalization across arms (1.6%). The RCT did not specify which arm the event occurred.[b]
Bockting et al. (2018)	Three-arm RCT	Adults with MDD ($n = 289$)	ADM + CBT ($n = 104$)	1. CBT-only ($n = 85$) 2. ADM-only ($n = 100$)	No significant ATE was observed across treatments in predicting SA or suicide death rates at 24-month follow-up among patients randomized to ADM-only (1.0%), CBT-only (1.1%), or ADM + CBT (1.0%).
Brent et al. (2009)	Four-arm RCT	Adolescents with MDD who failed first-line ADM-only treatment ($n = 334$)	1. CBT + SSRI ($n = 83$) 2. CBT + venlafaxine ($n = 83$)	1. SSRI-only ($n = 85$) 2. Venlafaxine-only ($n = 83$)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to SSRI-only (11.0%), venlafaxine-only (18.0%), CBT + SSRI (14.2%), or CBT + venlafaxine (14.2%).
Browne et al. (2002)	Three-arm RCT	Adults with MDD ($n = 707$)	Interpersonal PSY + sertraline ($n = 190$)	1. Interpersonal PSY-only ($n = 156$) 2. Sertraline-only ($n = 179$)	No significant ATE was observed across treatments in predicting psychiatric hospitalization rates at 18-month follow-up among patients randomized to interpersonal PSY-only (0%), sertraline-only (3.5%), or interpersonal PSY + sertraline (4.3%).
Cornelius et al. (2009)	Two-arm RCT	Adolescents with MDD + AUD ($n = 50$)	CBT + fluoxetine ($n = 26$)	CBT-only ($n = 24$)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to any of the two treatment arms (0% in all arms).
Davey et al. (2019)	Two-arm RCT	Adolescents and young adults with severe MDD ($n = 153$)	CBT + fluoxetine ($n = 76$)	CBT-only ($n = 77$)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to CBT-only (6.4%) or CBT + fluoxetine (1.3%).
Deas, Randall, Roberts, and Anton (2000)	Two-arm RCT	Adults with MDD ($n = 10$)	CBT + sertraline ($n = 5$)	CBT-only ($n = 5$)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to any of the two treatment arms (0% in all arms).
Dunlop et al. (2019)	Two-arm RCT	Adults with MDD ($n = 250$)	CBT-only ($n = 73$)	ADM-only ($n = 177$)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to ADM-only (0.6%) or CBT-only (0%).
Goodyer et al. (2007)	Two-arm RCT	Adolescents with moderate–severe MDD ($n = 208$)	CBT + SSRI ($n = 105$)	SSRI-only ($n = 103$)	No significant ATE was observed across treatments in predicting SA rates at 7-month follow-up among patients randomized to SSRI-only (6.4%) or CBT + SSRI (7.1%).
Huijbers et al. (2015)	Two-arm RCT	Adults with MDD ($n = 56$)	ADM + MBCT ($n = 32$)	ADM-only ($n = 33$)	No significant ATE was observed across treatments in predicting SA rates at 15-month follow-up among patients randomized to ADM-only (6.1%) or ADM + MBCT (6.3%).

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Table 1. (*Continued.*)

Author(s)	Study design	Target sample	Treatment arm(s)	Control arm(s)	Summary of ATE outcome
Hollon et al. (1992)	Three-arm RCT	Adults with MDD (n = 107)	CT + imipramine (n = 25)	1. Imipramine-only (n = 57) 2. CT-only (n = 25)	No significant ATE was observed across treatments in predicting SA, psychiatric hospitalization, or suicide death rates at 3-month follow-up among patients randomized to CT-only (0%), imipramine-only (8.0%), or CT + imipramine (5.3%).
Iftene, Predescu, Stefan, and David (2015)	Three-arm RCT	Adolescents with MDD (n = 88)	ADM + GCBT (n = 27)	1. ADM-only (n = 33) 2. GCBT-only (n = 28)	No significant ATE was observed across treatments in predicting SA rates at 4-month follow-up among patients randomized to any of the three treatment arms (0% in all arms).
Kennard et al. (2014)	Two-arm RCT	Children and adolescents with MDD (n = 144)	ADM + CBT (n = 95)	ADM-only (n = 69)	No significant ATE was observed across treatments in predicting SA and hospitalization rates at 7-month follow-up among patients randomized to ADM-only (8.7%) or ADM + CBT (6.7%).
Khazanov, Xu, Hollon, DeRubeis, and Thase (2021)	Two-arm RCT	Adults with MDD (n = 445)	ADM + CBT (n = 226)	ADM-only (n = 219)	No significant ATE was observed across treatments in predicting SA rates at 7-month follow-up among patients randomized to ADM-only (0.5%) or ADM + CBT (0.4%).
Kocsis et al. (2007)	Three-arm RCT	Adults with MDD (n = 478)	1. ADM + CBT (n = 195) 2. ADM + SP (n = 189)	ADM-only (n = 94)	No significant ATE was observed across treatments in predicting SA rates at 12-month follow-up among patients randomized to any of the three treatment arms (0% in all arms).
Kuyken et al. (2008)	Two-arm RCT	Adults with MDD (n = 123)	ADM + MBCT (n = 61)	ADM-only (n = 62)	No significant ATE was observed across treatments in predicting SA and suicide death rates at 15-month follow-up among patients randomized to any of the two treatment arms (0% in all arms).
Kuyken et al. (2015)	Two-arm RCT	Adults with recurrent MDD (n = 424)	ADM + MBCT (n = 212)	ADM-only (n = 212)	No significant ATE was observed across treatments in predicting SA rates at 24-month follow-up among patients randomized to ADM-only (0.9%) or ADM + MBCT (0.9%).
Lam et al. (2013)	Two-arm RCT	Adults with MDD (n = 99)	CBT + escitalopram (n = 48)	Escitalopram-only (n = 51)	No significant ATE was observed across treatments in predicting suicide death rates at 3-month among patients randomized to escitalopram-only (2.0%) or CBT + escitalopram (0%).
Lespérance et al. (2007)	Three-arm RCT	Adults with cardiovascular disease and MDD (n = 217)	Citalopram + interpersonal PSY (n = 67)	1. Citalopram-only (n = 75) 2. Interpersonal PSY-only (n = 75)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to citalopram-only (0%), interpersonal PSY-only (1.3%), or citalopram + interpersonal PSY (0%).
Mandoki, Tapia, Tapia, Sumner, and Parker (1997)	Two-arm RCT	Children and adolescents with MDD (n = 40)	CBT + venlafaxine (n = 20)	Venlafaxine-only (n = 20)	No significant ATE was observed across treatments in predicting psychiatric hospitalization rates at 1.5-month follow-up among patients randomized to venlafaxine-only (5%) or CBT + venlafaxine (0%).

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https://doi.org/10.1017/S0033291723003306 Published online by Cambridge University Press

Table 1. (*Continued.*)

Author(s)	Study design	Target sample	Treatment arm(s)	Control arm(s)	Summary of ATE outcome
March et al. (2004)	Three-arm RCT	Adolescents with MDD (*n* = 327)	CBT + fluoxetine (*n* = 107)	1. Fluoxetine-only (*n* = 109) 2. CBT-only (*n* = 111)	No significant ATE was observed across treatments in predicting SA rates at 3-month follow-up among patients randomized to CBT-only (4.5%), fluoxetine-only (11.9%), or CBT + fluoxetine (8.4%).
March et al. (2007)	Three-arm RCT	Adolescents with MDD (*n* = 327)	CBT + fluoxetine (*n* = 107)	1. Fluoxetine-only (*n* = 109) 2. CBT-only (*n* = 111)	Significant ATE was observed, such that SA rates at 9-month follow-up were higher among patients randomized to fluoxetine-only (14.7%) than CBT-only (6.3%) or CBT + fluoxetine (8.4%).
Melvin et al. (2006)	Three-arm RCT	Adolescents with MDD (*n* = 73)	CBT + sertraline (*n* = 25)	1. Sertraline-only (*n* = 26) 2. CBT-only (*n* = 22)	No significant ATE was observed across treatments in predicting SA rates at 6-month follow-up among patients randomized to CBT-only (0%), sertraline-only (15.4%), or CBT + sertraline (4.0%).
Michel, Gysin-Maillart, Breit, Walther, and Pavlidou (2021)	Two-arm RCT	Adults with recurrent MDD (*n* = 120)	ADM + PSY (*n* = 60)	ADM-only (*n* = 60)	Significant ATE was observed, such that SA rates at 24-month follow-up were higher among patients randomized to ADM-only (56.7%) or ADM + PSY (50.0%).
Nakagawa et al. (2017)	Two-arm RCT	Adults with recurrent MDD (*n* = 80)	ADM + PSY (*n* = 40)	ADM-only (*n* = 40)	No significant ATE was observed across treatments in predicting psychiatric hospitalization and suicide death rates at 4-month follow-up among patients randomized to ADM-only (5.0%) or ADM + PSY (0%).
O'Hara et al. (2019)	Three-arm RCT	Adults with MDD (*n* = 67)	Interpersonal PSY-only (*n* = 34)	ADM-only (*n* = 33)	No significant ATE was observed across treatments in predicting SA, psychiatric ED visits, and hospitalization rates at 3-month among patients randomized to ADM-only (30.3%) or interpersonal PSY-only (23.5%).
Riggs et al. (2007)	Two-arm RCT	Adolescents with MDD (*n* = 126)	CBT + fluoxetine hydrochloride (*n* = 63)	CBT-only (*n* = 63)	No significant ATE was observed across treatments in predicting psychiatric ED visit or hospitalization rates at 4-month follow-up among patients randomized to CBT-only (1.6%%), or CBT + fluoxetine hydrochloride (6.3%).
Rucci et al. (2011)	Two-arm RCT	Adults with MDD (*n* = 291)	SSRI-only (*n* = 142)	Interpersonal PSY-only (*n* = 149)	No significant ATE was observed across treatments in predicting SA rates at 4-month follow-up among patients randomized to interpersonal PSY-only (0%) or SSRI-only (0%).
Schramm et al. (2007)	Two-arm RCT	Inpatients with MDD (*n* = 124)	ADM + interpersonal PSY (*n* = 63)	ADM-only (*n* = 61)	No significant ATE was observed across treatments in predicting 12-month psychiatric hospitalization and suicide death rates among patients randomized to ADM-only (9.8%) or ADM + interpersonal PSY (6.3%).
Vitiello et al. (2009)	Three-arm RCT	Adolescents with MDD (*n* = 327)	CBT + fluoxetine (*n* = 107)	1. Fluoxetine-only (*n* = 109) 2. CBT-only (*n* = 111)	No significant ATE was observed across treatments in predicting SA or suicide death rates at 8-month follow-up among patients randomized to CBT-only (3.6%),

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Table 1. (*Continued.*)

Author(s)	Study design	Target sample	Treatment arm(s)	Control arm(s)	Summary of ATE outcome
					fluoxetine-only (6.4%), or CBT + fluoxetine (3.7%).
Vitriol, Ballesteros, Florenzano, Weil, and Benadof (2009)	Two-arm RCT	Adults with MDD (n = 79)	ADM + PSY (n = 39)	PSY-only (n = 40)	No significant ATE was observed across treatments in predicting SA rates at 6-month follow-up among patients randomized to any of the two treatment arms (0% in all arms).
Watanabe et al. (2011)	Two-arm RCT	Adults with MDD and insomnia (n = 37)	ADM + CBT (n = 20)	ADM-only (n = 17)	No significant ATE was observed across treatments in predicting psychiatric hospitalization rates at 2-month follow-up among patients randomized to ADM-only (5.9%) or ADM + CBT (5.0%).
Wei et al. (2013)	Three-arm RCT	Adults with MDD (n = 239)	ADM + CBT (n = 162)	ADM-only (n = 77)	No significant ATE was observed across treatments in predicting SA rates at 12-month follow-up among patients randomized to ADM-only (6.5%) or ADM + CBT (1.2%).
Weitz, Hollon, Kerkhof, and Cuijpers (2014)	Three-arm RCT	Adolescents with MDD (n = 239)	1. CBT-only (n = 33) 2. Interpersonal PSY-only (n = 38)	Imipramine-only (n = 37)	No significant ATE was observed across treatments in SA risk at 4, 6, 12, and 18-month follow-up. The exact rates of SA were not reported in this study.[b]
Wilkinson, Kelvin, Roberts, Dubicka, and Goodyer (2011)	Two-arm RCT	Adolescents with MDD (n = 164)	CBT + SSRI (n = 85)	SSRI-only (n = 79)	No significant ATE was observed across treatments in predicting SA rates at 7-month follow-up among patients randomized to SSRI-only (31.6%) or CBT + SSRI (41.2%).
Zobel et al. (2011)	Two-arm RCT	Adults with MDD (n = 93)	Interpersonal PSY-only (n = 50)	ADM-only (n = 43)	No significant ATE was observed across treatments in predicting SA and psychiatric hospitalization rates among patients randomized to ADM-only (10.0%) or interpersonal PSY-only (14.0%).

ATE, average treatment effect (or efficacy); ADM, antidepressant medication; CBT, individual cognitive behavioral therapy; CI, confidence interval; CT, cognitive therapy; ED, emergency department; GCBT, group CBT; MDD, major depressive disorder; OR, odds ratio; PCP, primary care physician; PSY, psychotherapy; RCT, randomized controlled trial; SA, suicide attempt; SP, supportive psychotherapy; SSRI, selective serotonin reuptake inhibitor.
[a]Online Supplementary Table S1 details blow-by-blow how each study reported the rates of suicide attempt(s) and/or other serious psychiatric adverse event(s) (psychiatric ED visit, psychiatric hospitalization, or suicide death) in each arm.
[b]These RCTs were not included in the current meta-analysis as the exact rates of SA and/or psychiatric hospitalization in each intervention and comparator arm were not reported.

of the comparative treatment effects by age group (adults or youths), study duration (1.5–5, 6–12, or 13–60 months), and treatment setting (outpatient *v.* inpatient). In the case of continuous effect modifiers (moderators), our meta-regression analyses utilized a restricted maximum likelihood model, incorporating the Knapp–Hartung method (Borenstein, Hedges, Higgins, & Rothstein, 2009). Specifically, we determined how mean age, percentage of females, prior suicide attempts, patients with recurrent *v.* first-onset MDD, and any psychiatric comorbidities might modify the average treatment effects.

Results

Study characteristics

Thirty-one out of 34 studies reported baseline sociodemographic variables. The sample age averaged 32.06 years (standard deviation [S.D.] = 14.57, range = 13.80–58.43), and percentage of females was 61.6% across those studies. Regarding study duration, 16 studies (47.1%) reported on 3–5-month follow-up outcomes, another 11 studies (32.4%) on 6–12-month follow-up outcomes, and the remaining seven studies (20.6%) on 13–60-month follow-up outcomes. Concerning RCT design, four were four-arm trials (11.8%), eight were three-arm trials (23.5%), and 22 were two-arm trials (64.7%). Most RCTs occurred within outpatient settings (n = 30, 88.2%) compared to inpatient locations (n = 4, 11.8%). The following variables were regarded as various indices of suicide risk (indexed as percentages): prior suicide attempts (number of studies [k] = 34, observed mean [M] = 17.72, standard deviation [S.D.] = 28.06, range = 0–100), recurrent *v.* first-onset MDD (k = 32, M = 61.60, S.D. = 39.87, range = 0–100), and any psychiatric comorbidities (k = 20, M = 59.32, S.D. = 29.93, range = 5.2–100).

Combined treatment v. psychotherapy-only

Seventeen RCTs determined the comparative treatment effects of combined treatment *v.* psychotherapy-only on suicide attempts

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and other serious psychiatric adverse events. Forty-seven out of 1273 (3.7%) in the combined treatment arm and 24 out of 1240 (1.9%) in the psychotherapy-only arm had suicide attempts and other serious psychiatric adverse events, and this difference was statistically significant (OR 1.96 [1.20–3.20], $p = 0.012$). There was no significant between-study heterogeneity ($Q[df = 11] = 9.29$, $p = 0.595$; $I^2 = 0.0\%$ [0.0–58.3]; $\tau^2 = 0$ [0.00–1.56], $p = 0.60$) when comparing combined treatment to psychotherapy-only (Fig. 2). Subgroup analysis revealed that the average treatment effect of lower suicide attempts and other serious psychiatric adverse events in psychotherapy-only over combined treatment was statistically significant in youths (OR 1.86 [1.07–3.23]) but not in adults (OR 1.95 [0.52–7.35]; Table 2 part A). However, study duration (Table 2 part A), mean age, percentage of females, prior suicide attempts, patients with recurrent MDD, and psychiatric comorbidities (Table 3 part A) were non-significant effect modifiers. All studies within this set of combined treatment *v.* psychotherapy-only comparisons occurred in outpatient treatment settings.

Combined treatment v. *ADM-only*

Twenty-three RCTs examined the comparative treatment effects of combined treatment *v.* ADM-only. In total, 133 out of 2213 (6.0%) in the combined treatment arm and 162 out of 1855 (8.7%) in the ADM-only arm had suicide attempts and other serious psychiatric adverse events, and this difference was statistically significant (OR 0.74 [0.56–0.96], $p = 0.029$). There was no significant between-study heterogeneity ($Q[df = 18] = 15.96$, $p = 0.595$; $I^2 = 0.0\%$ [0.0–48.9]; $\tau^2 = 0.04$ [0.00–0.36], $p = 0.60$) when comparing combined treatment to ADM-only (Fig. 3). Subgroup analysis revealed that the average treatment effect of lower suicide attempts and other serious psychiatric adverse events in combined treatment over ADM-only was statistically significant in adults (OR 0.66 [0.45–0.96]) but not in youths (OR 0.80 [0.51–1.25]), and during follow-ups of 1.5–5 months (OR 0.59 [0.37–0.93]) but not 6–12 months (OR 0.71 [0.44–1.18]) and 13–60 months (OR 0.90 [0.45–1.79]; Table 2 part B). This average treatment effect was significantly stronger as the percentage of females increased ($\beta = 0.030$ [0.004–0.055], $p = 0.026$) and psychiatric comorbidities increased ($\beta = 0.015$ [0.006–0.025], $p = 0.007$; Table 3 part B). However, mean age, percentage of prior suicide attempts, and patients with recurrent MDD were non-significant effect modifiers. There were insufficient studies to determine whether the treatment setting (outpatient *v.* inpatient) might be an effect modifier.

Psychotherapy-only v. *ADM-only*

Thirteen RCTs evaluated the comparative treatment effects of psychotherapy-only *v.* ADM-only. Thirty-one out of 1030 (3.0%) in the psychotherapy-only arm, and 67 out of 1192 (5.6%) in the ADM-only arm had suicide attempts and other serious psychiatric adverse events. This difference was statistically significant (OR 0.45, 95% CI [0.30–0.67], $p = 0.001$). There was no significant between-study heterogeneity ($Q[df = 10] = 7.28$, $p = 0.699$; $I^2 = 0.0\%$ [0.0–60.2]; $\tau^2 = 0$ [0.00–1.50], $p = 0.700$) when comparing psychotherapy-only to ADM-only (Fig. 4). Subgroup analysis revealed that the average treatment effect of lower suicide attempts and other serious psychiatric adverse events in psychotherapy-only over ADM-only was statistically significant in youths (OR 0.39 [0.22–0.71]) but not adults

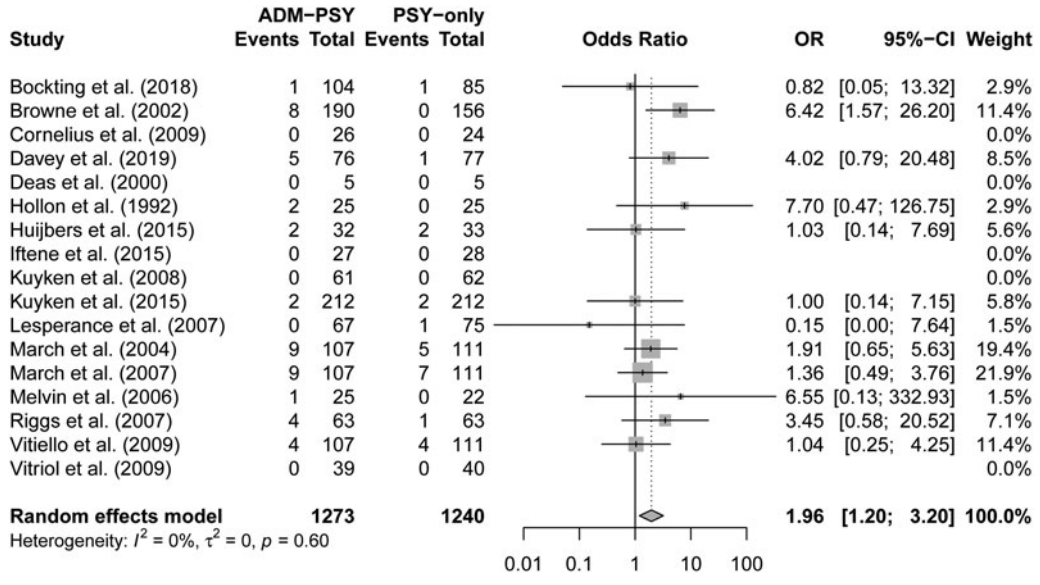

Figure 2. Forest plot for average treatment effect comparing combined treatment *v.* psychotherapy-only[a]. ADM, antidepressant medication; PSY, psychotherapy; OR, Peto odds ratio; CI, confidence interval; I^2, an index of between-study heterogeneity expressed in a percentage, such that higher values indicated more between-study heterogeneity; τ^2, tau-squared statistic, such that a statistically significant τ^2 indicated substantial between-study variance of the underlying distribution of true effect sizes. [a]Events referred to the number of patient(s) (if any) within a specific treatment arm that had a negative treatment outcome (i.e. suicide attempt [SA], psychiatric emergency department [ED] visit, psychiatric hospitalization, and/or suicide death). The random-effects model only pertained to studies that examined SA as an outcome (Bockting et al., 2018; Cornelius et al., 2009; Davey et al., 2019; Deas et al., 2000; Hollon et al., 1992; Iftene et al., 2015; Khazanov et al., 2021; Kuyken et al., 2008; Kuyken et al., 2015; Lespérance et al., 2007; March et al., 2004; March et al., 2007; Melvin et al., 2006; Vitiello et al., 2009; Vitriol et al., 2009). There were too few studies that examined psychiatric ED visit (Riggs et al., 2007), psychiatric hospitalization (Browne et al., 2002; Hollon et al., 1992; Huijbers et al., 2015), and suicide death (Bockting et al., 2018; Hollon et al., 1992; Kuyken et al., 2015; Vitiello et al., 2009) to conduct a random-effects model meta-analysis separately by those adverse outcomes.

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Table 2. Subgroup analysis

	k	OR	[95% CI]	τ^2	Q_{WITHIN}	$Q_{BETWEEN}$	I^2
A. **Combined ADM-psychotherapy *v.* psychotherapy-only**							
Age							
Adults	6	1.95	[0.52–7.35]	0.43	6.43	0.01	22.3%
Youths	6	1.86*	[1.07–3.23]	<0.01	2.75	–	0.0%
Study duration							
1.5–5 months	5	2.52	[0.95–6.66]	<0.01	3.28	2.26	0.0%
6–12 months	3	1.33	[0.45–3.95]	0	0.75	–	0.0%
13–60 months	4	1.95	[0.36–10.51]	0.46	3.87	–	22.5%
B. **Combined ADM-psychotherapy *v.* ADM-only**							
Age							
Adults	11	0.66*	[0.45–0.96]	0	7.69	0.56	0.0%
Youths	8	0.80	[0.51–1.25]	0.08	7.42	–	5.7%
Study duration							
1.5–5 months	7	0.59*	[0.37–0.93]	0	3.34	2.94	0.0%
6–12 months	9	0.71	[0.44–1.18]	0.15	10.65	–	24.9%
13–60 months	3	0.90	[0.45–1.79]	0	0.59	–	0.0%
Setting							
Outpatient	10	0.42*	[0.27–0.66]	0	6.76	0.53	0.0%
Inpatient	1	0.69	[0.20–2.41]	–	0.00	–	–
C. **Psychotherapy-only *v.* ADM-only**							
Age							
Adults	7	0.54	[0.25–1.18]	0	5.42	0.74	0.0%
Youths	4	0.39*	[0.22–0.71]	0	1.33	–	0.0%
Study duration							
1.5–5 months	5	0.50	[0.22–1.15]	0	3.07	0.31	0.0%
6–12 months	3	0.40	[0.12–1.31]	0	1.32	–	0.0%
13–60 months	3	0.43	[0.04–5.14]	0.33	2.68	–	25.3%

k, Number of studies; OR, Peto odds ratio; CI, lower and upper limits of the 95% confidence interval; *Q*, Cochrane's heterogeneity index denoting within-subgroup heterogeneity (Q_{WITHIN}) or between-subgroup heterogeneity ($Q_{BETWEEN}$); I^2, index of between-study heterogeneity; ADM, antidepressant medication.
*Significant estimates at the $p < 0.05$ α level (two-tailed).

(OR 0.54 [0.25–1.18]; Table 2 part C). However, study duration (Table 2 part C), mean age, percentage of females, prior suicide attempts, patients with recurrent MDD, and psychiatric comorbidities (Table 3 part C) were non-significant effect modifiers. All studies within this set of psychotherapy-only *v.* ADM-only comparisons occurred in outpatient settings.

Publication bias and study quality

Harbord's modified test of small study effects suggested that there was no significant publication bias for the analyses that examined combined treatment *v.* psychotherapy-only ($t = -0.09$, degrees of freedom [df] = 10, $p = 0.933$), combined treatment *v.* ADM-only ($t = -1.76$, df = 17, $p = 0.096$), and psychotherapy-only *v.* ADM-only ($t = 0.14$, df = 9, $p = 0.88$; online Supplementary Fig. S1). Trim-and-fill analyses showed that the comparative treatment effects on decreasing the risk for suicide attempts and other serious psychiatric adverse events were significantly better with psychotherapy-only over combined treatment (OR 1.96 [1.20–3.20], $p = 0.012$; Q[df = 11] = 9.29, $p = 0.595$), and psychotherapy-only over ADM-only (OR 0.45 [0.30–0.67], $p = 0.001$; Q[df = 10] = 7.28, $p = 0.699$), but not combined treatment *v.* ADM-only (OR 0.76 [0.58–1.00], $p = 0.052$; Q[df = 21] = 19.03, $p = 0.583$). In addition, the risk-of-bias plots indicated that most study publication biases were due to missing outcome data (Fig. 5).

Discussion

The present novel meta-analysis consistently observed that psychotherapy monotherapy was superior to combined treatment (1.9% *v.* 3.7%) and ADM-only (3.0% *v.* 5.6%) in reducing the probability of suicide attempts and other serious psychiatric adverse events (i.e. psychiatric ED visits, psychiatric hospitalization, and/or suicide death) for MDD patients. The primary meta-analyses indicated that combined treatment was substantially better than ADM-only in decreasing the probability of

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Table 3. Meta-regression analysis

	β	[95% CI]	*p*	df	Moderator *F* statistic
A. **Combined ADM-psychotherapy *v.* psychotherapy-only**					
Mean age (years)	−0.001	[−0.038 to 0.035]	0.933	10	0.01
% Females	0.010	[−0.035 to 0.055]	0.639	10	0.23
% Prior suicide attempts	0.008	[−0.049 to 0.065]	0.768	10	0.09
% Recurrent MDD	0.006	[−0.008 to 0.020]	0.364	9	0.92
% MH Comorbidities	0.022	[−0.015 to 0.059]	0.185	5	2.36
B. **Combined ADM-psychotherapy *v.* ADM-only**					
Mean age (years)	−0.006	[−0.032 to 0.021]	0.662	14	0.20
% Females	0.030*	[0.004–0.055]	0.026	14	6.16
% Prior suicide attempts	−0.005	[−0.014 to 0.004]	0.214	17	1.67
% Recurrent MDD	0.003	[−0.004 to 0.009]	0.383	16	0.80
% MH Comorbidities	0.015*	[0.006–0.025]	0.007	9	12.40
C. **Psychotherapy-only *v.* ADM-only**					
Mean age (years)	0.013	[−0.023 to 0.048]	0.440	9	0.65
% Females	0.008	[−0.016 to 0.032]	0.460	9	0.60
% Prior suicide attempts	0.004	[−0.009 to 0.017]	0.511	9	0.47
% Recurrent MDD	0.002	[−0.011 to 0.014]	0.766	9	0.09
% MH Comorbidities	0.009	[−0.019 to 0.037]	0.440	5	0.70

β, meta-regression estimate; CI, lower and upper limits of the 95% confidence interval; *p*, *p* value associated with *β*; %, percentage of; ADM, antidepressant medication; MDD, major depressive disorder; MH, mental health.
*Significant estimates at the $p < 0.05$ α level (two-tailed).

suicide attempts and other serious psychiatric adverse events (6.0% *v.* 8.7%). However, subsequent trim-and-fill sensitivity analyses suggested that this difference was statistically non-significant. Potential accounts for these outcomes were considered in hypothesis-generating instead of confirmatory ways to catalyze more research in this area.

Why was psychotherapy monotherapy better than combined treatment and ADM alone in the entire sample? Notably, these findings concurred with patterns that emerged when MDD treatment remission or response was the dependent variable of interest in other published meta-analyses of RCTs (Cuijpers et al., 2023; Furukawa et al., 2021; Karyotaki et al., 2016). These results also aligned with evidence of a medium aggregate effect size on depression symptom reduction in support of psychotherapy combined with treatment-as-usual (mostly pharmacotherapy) compared to psychotherapy alone (van Bronswijk, Moopen, Beijers, Ruhe, & Peeters, 2019). Plausibly, psychotherapy (alone or with ADM), but not ADM-only, equipped depressed patients of various suicide risk levels with essential skills to self-monitor, detect early incipient cues (e.g. feelings of loneliness, suicidal thoughts) of suicide attempts, and intervene effectively by recalling and focusing on reasons for living (e.g. community, family, hobbies, religion; Bakhiyi, Calati, Guillaume, & Courtet, 2016) and harnessing other mood-uplifting strategies (e.g. eliciting social support, engaging in valued activities; Bhar & Brown, 2012).

Given these findings, future studies should conduct sophisticated instrumental variable complier average causal effects analyses (Hesser, 2020) to determine if differential engagement might mediate the comparative efficacy of psychotherapy-only *v.* combined treatment and ADM alone on suicide attempts and other serious psychiatric adverse events. Exploring other purported mechanisms of change of efficacy of psychotherapy-only *v.* combined treatment and ADM alone, such as reduced hopelessness (Celano et al., 2017) and self-focused negative repetitive thinking (Chesin et al., 2016), would also advance clinical psychological and related sciences. The growth of effective digitally delivered suicide-focused psychotherapies (Franz et al., 2022; Torous et al., 2018) provides ripe opportunities on these lines of investigation in the near future.

Another noteworthy finding was that the comparative effects of psychotherapy monotherapy over combined treatment and ADM-only in reducing the risk for serious psychiatric adverse events were substantial for children and adolescents instead of adults. These findings aligned with and extended warnings by drug regulators about the risk of ADM to heighten suicide risk, particularly among youths (Sharma, Guski, Freund, & Gotzsche, 2016). Some investigations posit that the maturing brain may exhibit heightened susceptibility to unfavorable drug responses (Andersen & Navalta, 2004, 2011; Murphy et al., 2021; Safer & Zito, 2006), with the underlying mechanisms still shrouded in mystery. Alternatively, the linkage with suicidality may stem from the limited effectiveness of ADMs in clinical trials among suicidal children and adolescents, as implied by RCTs, rather than the ADM use directly amplifying suicidality and risks of other serious psychiatric adverse events (Cipriani, Barbui, & Geddes, 2005; Dragioti et al., 2019). Together, findings suggest that understanding the enduring advantages and potential hazards of ADM (alone or combined with psychotherapy) for depressive disorders among youths is paramount.

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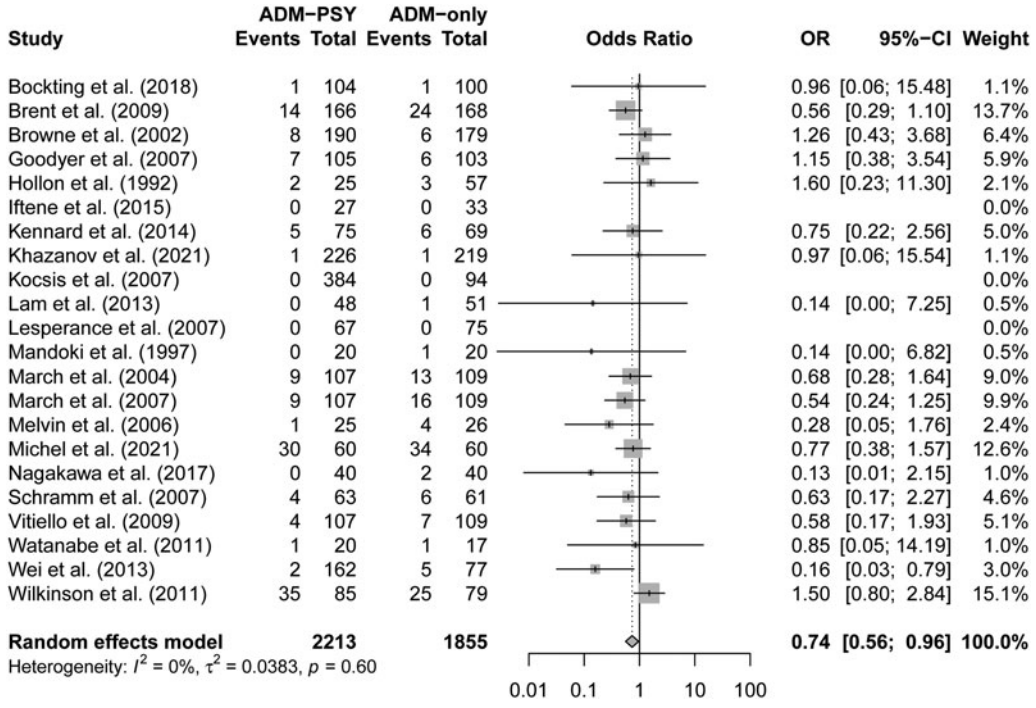

Figure 3. Forest plot for average treatment effect comparing combined treatment *v.* ADM-only[a]. ADM, antidepressant medication; PSY, psychotherapy; OR, Peto odds ratio; CI, confidence interval; I^2, an index of between-study heterogeneity expressed in a percentage, such that higher values indicated more between-study heterogeneity; τ^2, tau-squared statistic, such that a statistically significant τ^2 indicated substantial between-study variance of the underlying distribution of true effect sizes. [a]Events referred to number of patient(s) (if any) within a specific treatment arm that had a negative treatment outcome (i.e. suicide attempt, psychiatric emergency department [ED] visits, psychiatric hospitalization, and/or suicide death). The random-effects model only pertained to studies that examined SA as an outcome (Bockting et al., 2018; Brent et al., 2009; Goodyer et al., 2007; Hollon et al., 1992; Iftene et al., 2015; Kennard et al., 2014; Khazanov et al., 2021; Kocsis et al., 2007; Lespérance et al., 2007; March et al., 2004; March et al., 2007; Melvin et al., 2006; Michel et al., 2021; Schramm et al., 2007; Vitiello et al., 2009; Wei et al., 2013; Wilkinson et al., 2011). There were too few studies that examined psychiatric hospitalization (Browne et al., 2002; Hollon et al., 1992; Kennard et al., 2014; Mandoki et al., 1997; Nakagawa et al., 2017; Schramm et al., 2007) and suicide death (Bockting et al., 2018; Hollon et al., 1992; Nakagawa et al., 2017; Vitiello et al., 2009; Watanabe et al., 2011) to conduct a random-effects model meta-analysis separately by those adverse outcomes. We are unaware of any studies that examined the effect of combined treatment *v.* ADM-only on psychiatric ED visits.

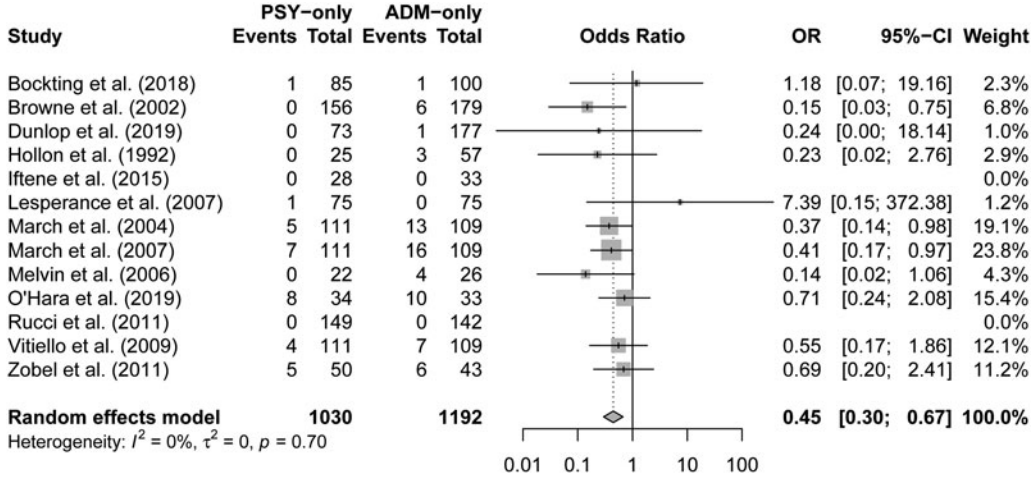

Figure 4. Forest plot for average treatment effect comparing psychotherapy-only *v.* ADM-only[a]. PSY, psychotherapy; ADM, antidepressant medication; OR, Peto odds ratio; CI, confidence interval; I^2, an index of between-study heterogeneity expressed in a percentage, such that higher values indicated more between-study heterogeneity; τ^2, tau-squared statistic, such that a statistically significant τ^2 indicated substantial between-study variance of the underlying distribution of true effect sizes. [a]Events referred to number of patient(s) (if any) within a specific treatment arm that had a negative treatment outcome (i.e. suicide attempt, psychiatric emergency department [ED] visit, psychiatric hospitalization, and/or suicide death). The random-effects model only pertained to studies that examined SA as an outcome (Bockting et al., 2018; Dunlop et al., 2019; Hollon et al., 1992; Iftene et al., 2015; Lespérance et al., 2007; March et al., 2004; March et al., 2007; Melvin et al., 2006; O'Hara et al., 2019; Rucci et al., 2011; Vitiello et al., 2009). Too few studies examined psychiatric hospitalization (Browne et al., 2002; Hollon et al., 1992; O'Hara et al., 2019), and suicide death (Hollon et al., 1992; Vitiello et al., 2009) to conduct a random-effects model meta-analysis separately by those adverse outcomes. We are unaware of any studies that examined the effect of psychotherapy-only *v.* ADM-only on psychiatric ED visits.

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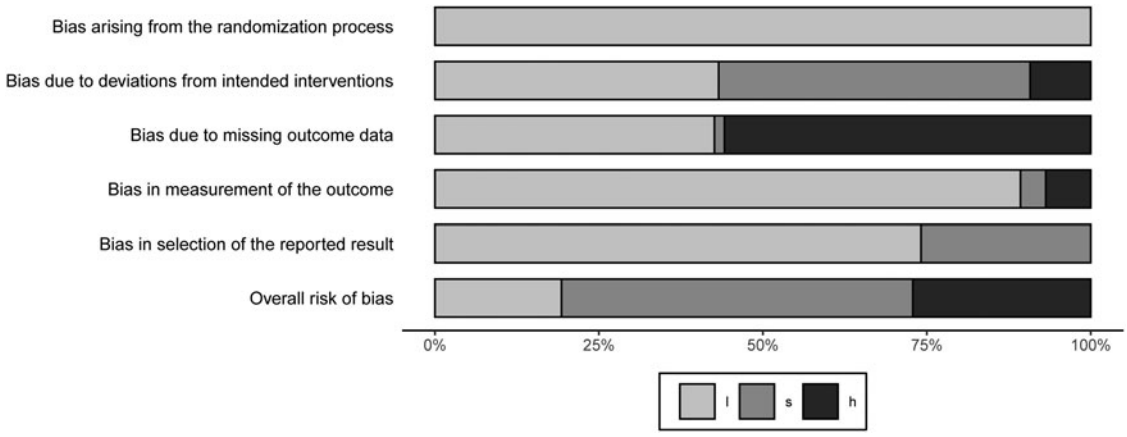

Figure 5. Risk-of-bias plots of the comparative effects of ADM-only, psychotherapy-only, and combined treatment. ADM, antidepressant medication; l, low risk of bias; s, some concerns of bias; h, high risk of bias.

Conversely, the observation that combined treatment worked better than ADM alone for adults, rather than youths, in reducing the probability of suicide attempts and other serious psychiatric adverse events is consistent with clinical guidelines that recommend combined treatment for adult patients with high-risk severe *v.* mild-moderate depression (McQuaid et al., 2022). These findings provide indications of ADMs (particularly when combined with psychotherapy) playing a protective role against suicidality in depressed adults (Barbui, Esposito, & Cipriani, 2009; Craighead & Dunlop, 2014). However, our observed significant average treatment effect between combined treatment and ADM-only did not remain in the trim-and-fill sensitivity analysis, suggesting that publication bias driven by studies with small sample sizes might have influenced the results. Further, numerous studies indicating an elevated suicide risk associated with ADMs will likely stay unpublished. Overall, these results concurred with placebo-controlled RCTs (Braun et al., 2016; Fergusson et al., 2005) and observational studies (Hengartner et al., 2021) that consistently documented a notable elevation in suicide risk among depressed adult patients treated with ADM-only.

Additionally, the meta-regression analyses showed that higher percentage of females was associated with increased risk of suicide attempts and other serious psychiatric adverse events in response to ADM alone over combined treatment. Clinically, gender might be an essential consideration since prior meta-analyses showed that, on average, women responded better to psychotherapy (alone or combined with ADM) *v.* treatment-as-usual than men regarding reduction in depression symptoms (Braun, Gregor, & Tran, 2013) and suicide risk (Calati & Courtet, 2016). Relatedly, growing evidence underscores the heightened risk of repeated suicide attempts among female patients, contrasting with males who frequently choose more lethal means (Corcoran, Keeley, O'Sullivan, & Perry, 2004; Pandey et al., 2022; World Health Organization, 2021). The factors contributing to gender-based variations in treatment effectiveness remain presently uncertain. Nevertheless, there is a paucity of comprehensive investigation into the impact of gender on treatment efficacy on serious psychiatric adverse events, highlighting the necessity for further research in this domain.

Psychiatric comorbidities were also an effect modifier, with higher comorbidities associated with heightened risk of serious psychiatric adverse events in response to ADM-only over combined treatment. These outcomes, coupled with recent meta-analytic evidence on the protective effects of psychotherapies over pharmacotherapies in high-risk subgroups (de la Torre-Luque et al., 2023; Inagaki et al., 2015), suggest that psychotherapy should be prioritized for such patients. Collectively, the number of psychiatric comorbidities might be a salient risk marker concerning the odds of experiencing serious adverse events during and after treatment for depression.

Simultaneously, treatment timing might matter, as we found that combined treatment was more potent than ADM alone in decreasing the likelihood of serious psychiatric adverse events, particularly in studies with follow-up durations of 1.5–5 months rather than 6–60-month follow-ups. This finding extended a prior meta-analysis (Calati & Courtet, 2016), which showed that treatment duration was not an effect modifier of the effect of combined treatment *v.* treatment-as-usual. The present meta-analysis did not find evidence for a higher risk of subsequent suicide attempts the more extended the follow-up duration. A growing body of evidence indicates a rising prevalence of suicide attempts during the initial 6 months following a basal episode (Birtwistle, Kelley, House, & Owens, 2017; Cully et al., 2019; Liu, Lunde, Jia, & Qin, 2020) and that this timeframe might be the most optimal time to intervene to decrease the risk of suicide attempts and other serious psychiatric adverse events (Andreoli, Burnand, Frambati, Manning, & Frances, 2021). Together, these findings might imply the enduring preservation of short-term combined treatment benefits in decreasing suicide risk and improving psychosocial functioning across extended periods.

The current meta-analysis had some limitations. First, the sample size of the current meta-analysis was modest, given the rare nature of the outcome of interest. Such efforts are essential to developing precision treatment models that could guide clinicians to optimize treatment selection for MDD patients (Cohen & DeRubeis, 2018; Kessler & Luedtke, 2021). Second, more than half of the RCTs included herein did not report on their approaches to handling missing data in their population-level intention-to-treat analyses, i.e. a limitation that future similar RCTs should remedy. Third, Peto ORs could generate biased outcomes in the presence of notable differences in sample sizes of the intervention and comparator arms (Lane, 2013). Except for the RCTs by Hollon et al. (1992) and Kocsis et al. (2007), the

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remaining 32 RCTs had well-balanced sample sizes between the intervention and comparator arms. Fourth, while most pharmacological studies included adverse event data, there was considerable variability in the extent of information provided and heterogeneity in the methods employed for adverse event assessment and analysis (Meister et al., 2016). In contrast, psychotherapy studies exhibited a notable dearth in the reporting of adverse event information. In order to enhance the comprehensive reporting of adverse events (including serious ones like suicide attempts examined herein) in published research on psychiatric disorders, researchers must prioritize the meticulous examination of potential harms. Fifth, the sample size was too small to determine if ADM type, such as the prescription of paroxetine in adults (Aursnes, Tvete, Gaasemyr, & Natvig, 2006) and venlafaxine in youths (Cipriani et al., 2016), might be an effect modifier. Relatedly, there was insufficient data to determine how treatment setting (outpatient *v.* inpatient) might be an effect modifier. Future well-powered studies should examine this since the period following discharge from psychiatric hospitalization entails a heightened suicide risk (Kessler et al., 2023). Despite these limitations, fundamental strengths of the current meta-analysis include its novelty and ability to answer an essential question of how three first-line treatment options for MDD (i.e. psychotherapy and/or ADM) could reduce the risk of suicide attempts and other serious psychiatric adverse events.

To conclude, the present meta-analysis consistently found that psychotherapy monotherapy had stronger aggregate effects than combined treatment (1.9% *v.* 3.7%) and ADM-only (3.0% *v.* 5.6%) in decreasing the probability of suicide attempt, psychiatric ED visit, psychiatric hospitalization, and/or suicide death for MDD patients. The observation that combined treatment had better aggregate effect compared to ADM alone to reduce the likelihood of suicide attempts and other psychiatric events (6.0% *v.* 8.7%) did not consistently surpass the statistical significance threshold. On average, psychotherapies, especially those that integrate cognitive-behavioral and related theories, appear to be the best first-line intervention option to mitigate the risk of suicide attempts and other serious psychiatric adverse events in depressed youth and adult populations. Therapists should be cognizant of the absence of conclusive evidence, based on RCTs, regarding the preventive efficacy of ADM monotherapy in mitigating the risk of suicide attempts and other serious psychiatric adverse events, in contrast to prominent assertations (Dragioti et al., 2019). Further, our data underscore the importance of discouraging the routine prescription of ADMs (alone or combined with psychotherapy) for pediatric and adolescent populations, except perhaps for sertraline. Meta-analytic data of placebo-controlled RCTs suggested no increased suicide risk and superior comparative efficacy regarding remission rates with sertraline prescribed to depressed youths (Cipriani et al., 2016). The benefits of utilizing ADMs in adults and older populations, especially in conjunction with psychotherapy, may outweigh manageable safety concerns, considering their effectiveness in addressing a range of psychiatric disorders, including MDD (Calati & Courtet, 2016; Craighead & Dunlop, 2014). Future similar comparative effectiveness research investigating these rare events as the dependent variable of interest could also build on the current meta-analysis by using large, less difficult-to-obtain prospective observational datasets to evaluate aggregate effects (i.e. trial emulation studies; Hernan & Robins, 2016) as a precursor to developing individualized treatment rules for optimizing treatment allocation using RCT designs (Kessler & Luedtke, 2021).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003306

Competing interests. None.

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https://doi.org/10.1017/S0033291723003306 Published online by Cambridge University Press