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Beneficial and harmful effects of tricyclic antidepressants for adults with major depressive disorder: a systematic review with meta-analysis and trial sequential analysis

Caroline Barkholt Kamp [ID],[1,2] Johanne Juul Petersen [ID],[1] Pascal Faltermeier,[1,3] Sophie Juul,[1,4] Faiza Siddiqui [ID],[1] Marija Barbateskovic [ID],[1] Andreas Torp Kristensen,[5] Joanna Moncrieff,[6,7] Mark Abie Horowitz [ID],[6,7] Michael Pascal Hengartner [ID],[8] Irving Kirsch,[9] Christian Gluud,[1,2] Janus Christian Jakobsen[1,2]

ABSTRACT

Question Tricyclic antidepressants are used to treat depression worldwide, but the adverse effects have not been systematically assessed. Our objective was to assess the beneficial and harmful effects of all tricyclic antidepressants for adults with major depressive disorder.

Study selection and analysis We conducted a systematic review with meta-analysis and trial sequential analysis. We searched CENTRAL, MEDLINE, Embase, LILACS and other sources from inception to January 2023 for randomised clinical trials comparing tricyclic antidepressants versus placebo or 'active placebo' for adults with major depressive disorder. The primary outcomes were depressive symptoms measured on the 17-item Hamilton Depression Rating Scale (HDRS-17), serious adverse events and quality of life. The minimal important difference was defined as three points on the HDRS-17.

Findings We included 103 trials randomising 10 590 participants. All results were at high risk of bias, and the certainty of the evidence was very low or low. All trials only assessed outcomes at the end of the treatment period at a maximum of 12 weeks after randomisation. Meta-analysis and trial sequential analysis showed evidence of a beneficial effect of tricyclic antidepressants compared with placebo (mean difference −3.77 HDRS-17 points; 95% CI −5.91 to −1.63; 17 trials). Meta-analysis showed evidence of a harmful effect of tricyclic antidepressants compared with placebo on serious adverse events (OR 2.78; 95% CI 2.18 to 3.55; 35 trials), but the required information size was not reached. Only 2 out of 103 trials reported on quality of life and t-tests showed no evidence of a difference.

Conclusions The long-term effects of tricyclic antidepressants and the effects on quality of life are unknown. Short-term results suggest that tricyclic antidepressants may reduce depressive symptoms while also increasing the risks of serious adverse events, but these results were based on low and very low certainty evidence.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tricyclic antidepressants are used to treat major depressive disorder worldwide.
⇒ The National Institute for Health and Care Excellence and the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders recommend tricyclic antidepressants for patients with chronic or melancholic depression or as an alternative for patients who do not benefit from newer antidepressants.
⇒ Previous reviews have not systematically assessed all adverse effects for all tricyclic antidepressants, so it remains unclear whether the potential benefits outweigh the harmful effects of tricyclic antidepressants.

WHAT THIS STUDY ADDS

⇒ The long-term effects of tricyclic antidepressants and the effects on quality of life and suicides or suicide attempts are unknown.
⇒ Short-term results suggest that tricyclic antidepressants may reduce depressive symptoms, while also increasing the risks of serious adverse events, but these results are based on low and very low certainty evidence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It is a cause for concern that there are no data from randomised clinical trials on the long-term effects of tricyclic antidepressants and only low and very low certainty evidence on short-term effects given that so many people use these drugs for several years.

BACKGROUND

Major depressive disorder is a psychiatric condition characterised by depressed mood and diminished interest or pleasure.[1] Major depressive disorder is estimated to affect more than 264 million people globally[2] and is associated with a high risk of suicidal behaviour.[3–5] Tricyclic antidepressants

are used in the treatment of major depressive disorder worldwide.[6–12] Although selective serotonin reuptake inhibitors are generally recommended as first-line treatment for major depressive disorder, the National Institute for Health and Care Excellence (NICE) and the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders recommend tricyclic antidepressants for patients with chronic or melancholic depression or as an alternative for patients who do not benefit from newer antidepressants.[13 14] The WHO Model List of Essential Medicines also includes the tricyclic antidepressant amitriptyline as one of just two essential antidepressants for the treatment of depressive disorders.[15]

It has previously been shown that antidepressants reduce depressive symptoms with statistically significant effects, but it is uncertain how important these effects are to patients and whether they represent genuine pharmacological effects or just amplified placebo effects.[16–18] One systematic review suggests that amitriptyline has larger effects than other antidepressants compared with placebo.[19] However, previous reviews have not systematically assessed suicides, suicide attempts and all serious and non-serious adverse events for all tricyclic antidepressants,[19–23] so it remains unclear whether the harmful effects of tricyclic antidepressants outweigh the potential beneficial effects.

OBJECTIVE
Our objective was to assess the beneficial and harmful effects of all tricyclic antidepressants versus placebo or 'active placebo' in the treatment of adults with major depressive disorder.

STUDY SELECTION AND ANALYSIS
We report this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (online supplemental file 1).[24 25] The methodology used in this systematic review is described in detail in The Cochrane Handbook of Systematic Reviews of Interventions and our protocol,[26 27] which was registered in the PROSPERO database prior to the systematic literature search (ID: CRD42021226161).

Search strategy and selection criteria
Electronic searches
An experienced information specialist searched the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Chinese Biomedical Literature Database (CBM), China Network Knowledge Information (CNKI), Chinese Science Journal Database (VIP), Wafang Database, Conference Proceedings Citation Index—Science (CPCI-S) and Conference Proceedings Citation Index—Social Science and Humanities (CPCI-SSH) to identify relevant trials. We searched all databases from their inception to 27 January 2023. For a detailed search strategy for all electronic databases, see online supplemental file 2.

Searching other resources
To identify unpublished trials, we also searched clinical trial registers, websites of pharmaceutical companies and websites of US Food and Drug Administration (FDA) and European Medicines Agency (EMA). We requested FDA, EMA and national medicines agencies to provide all publicly releasable information about relevant trials of antidepressants submitted for marketing approval, including clinical study reports. Additionally, we hand-searched conference abstracts from psychiatry conferences.

Selection criteria
We included randomised clinical trials irrespective of language, publication status, publication year and publication type. Participants had to be adults with a primary diagnosis of major depressive disorder as defined by standardised diagnostic criteria, such as Diagnostic and Statistical Manual of Mental Disorders[1] or International Classification of Diseases.[28] As experimental intervention, we included any tricyclic antidepressant. As control intervention, we included placebo, 'active placebo' or no intervention.

Data extraction and risk of bias assessment
Two authors (CBK and PF) independently screened relevant trials. Seven authors working in pairs (CBK, PF, JJP, ATK, SJ, FS and MB) independently extracted data using a standardised data extraction sheet and assessed risk of bias based on the Cochrane Risk of Bias tool, V.2 (RoB 2).[29 30] Discrepancies were resolved through internal discussion or, if required, through discussion with a third author (JCJ).

Outcomes and subgroup analyses
The primary outcomes were depressive symptoms measured on the 17-item Hamilton Depression Rating Scale (HDRS-17), serious adverse events (as defined by the International Conference on Harmonisation—Good Clinical Practice (ICH-GCP) guidelines: any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation and resulted in persistent or significant disability or jeopardised the participant)[31] and quality of life. Secondary outcomes were the proportion of participants with either suicides or one or more suicide attempts and non-serious adverse events. Exploratory outcomes were suicidal ideation, depressive symptoms measured on the Montgomery-Asberg Depression Rating Scale (MADRS),[32] the Beck's Depression Inventory (BDI)[33] or HDRS-6,[34 35] treatment response (defined as a 50% reduction from baseline) and remission (as defined by trialists). Outcomes were assessed at the end of treatment and at maximum follow-up. We also planned several subgroup analyses.[27]

When extracting adverse events, we assumed the events were non-serious unless otherwise specified by the trialists. If the trialists did not report the proportion of non-serious adverse events, we used the most common non-serious adverse event for this proportion to potentially avoid double-counting participants with more than one type of non-serious adverse events. When serious adverse events were not reported according to the ICH-GCP definition (ie, if the events were not defined as 'serious adverse events' or if the definition of serious adverse events was unclear),[31] we categorised any adverse event clearly fulfilling the ICH-GCP definition as a serious adverse event. The assessment was made by two review authors who received the full list of all events and discussed the severity of each event. The authors were blinded and therefore did not know whether the events were recorded in an experimental or placebo group. If the authors disagreed on the severity of a specific event, they would discuss this with a third author. We used the same systematic approach in all trials, reflecting standard procedures that have been employed in multiple previous reviews.[36–47] If trialists did not report an overall proportion of serious adverse

events according to the ICH-GCP definition,[31] we used the most common serious adverse event for this proportion to potentially avoid double-counting participants with more than one type of serious adverse events.

Assessment of statistical and clinical significance

We performed meta-analyses according to the Cochrane Handbook for Systematic Reviews of Interventions,[29] Keus *et al*,[48] and the eight-step procedure by Jakobsen *et al*.[49] We planned to assess a total of five main outcomes, and therefore considered a p value of 0.016 or less as the threshold for statistical significance.[49] We assessed the intervention effects with both random-effects (Hartung-Knapp-Sidik-Jonkman)[50] and fixed-effect model meta-analyses (Mantel-Haenszel for dichotomous outcomes and inverse variance for continuous outcomes).[29 51] We primarily reported the most conservative result (highest p value) of the two and considered the less conservative result as a sensitivity analysis.[49] We adjusted for zero-event cells using treatment-arm continuity correction. For trials with multiple relevant experimental groups, we divided the number of events and sample size of the control group for dichotomous outcomes and divided the sample size and kept the mean and SD of the control group for continuous outcomes. If the data could not be equally divided due to an odd number of events, we drew lots to decide which comparison would be favoured. We used the statistical software Stata V.17 to analyse the data.[52] Trial sequential analysis was used to control for random errors by estimating the diversity-adjusted required information size, which is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect.[53–61] To assess clinical significance, we used the lowest estimate based on various methods to determine the minimal important difference as detailed by Hengartner and Plöderl.[17] The lowest empirically derived threshold of clinical significance is three points on the HDRS, which was predefined in our protocol.[27] However, it has previously been questioned whether the true minimal important difference is in fact closer to seven points.[62] We used Grading Recommendations Assessment Development Evaluation (GRADE) to assess the certainty of evidence.[63–65]

DIFFERENCES BETWEEN THE PROTOCOL AND THE REVIEW
Suicidal ideation was predefined as a continuous scale, but the outcome was reported as a dichotomous outcome, and we therefore analysed it accordingly.

FINDINGS
A total of 103 trials randomising 10 590 participants were included (figure 1).[66–223] Most trials (92/103) included both men and women between 18 and 65 years of age with a primary diagnosis of major depressive disorder (online supplemental table S1). Ten trials only included elderly participants (defined by trialists as above 50–65 years).[90 110 144 146 159 170 196 211 213 214] The mean HDRS baseline scores ranged from 17.4 to 45.5 (online supplemental table S1). Both the experimental and the control participants in eight trials also received a co-intervention, such as psychotherapy or other drugs.[78 83 103 131 187 198 211 215] The included trials assessed the effects of different tricyclic antidepressants: imipramine (50 trials),[31 69 84 87 90 98–103 114 117–119 121 123–127 133–136 142 146 150 152–155 163 164 166–170 187 208 210 212–214 217 218 224] amitriptyline (31 trials),[66–68 70–72 74–80 82 83 85–89 91–96 151 221–223 225] nortriptyline (8 trials),[110 131 159 179 196 198 209 211] desipramine (6 trials),[104 130 143 177 178 207] dothiepin (4 trials),[73 93 112 137] tianeptine (4 trial),[117 144 174 201] doxepin (3 trials),[88 112 137] clomipramine

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources
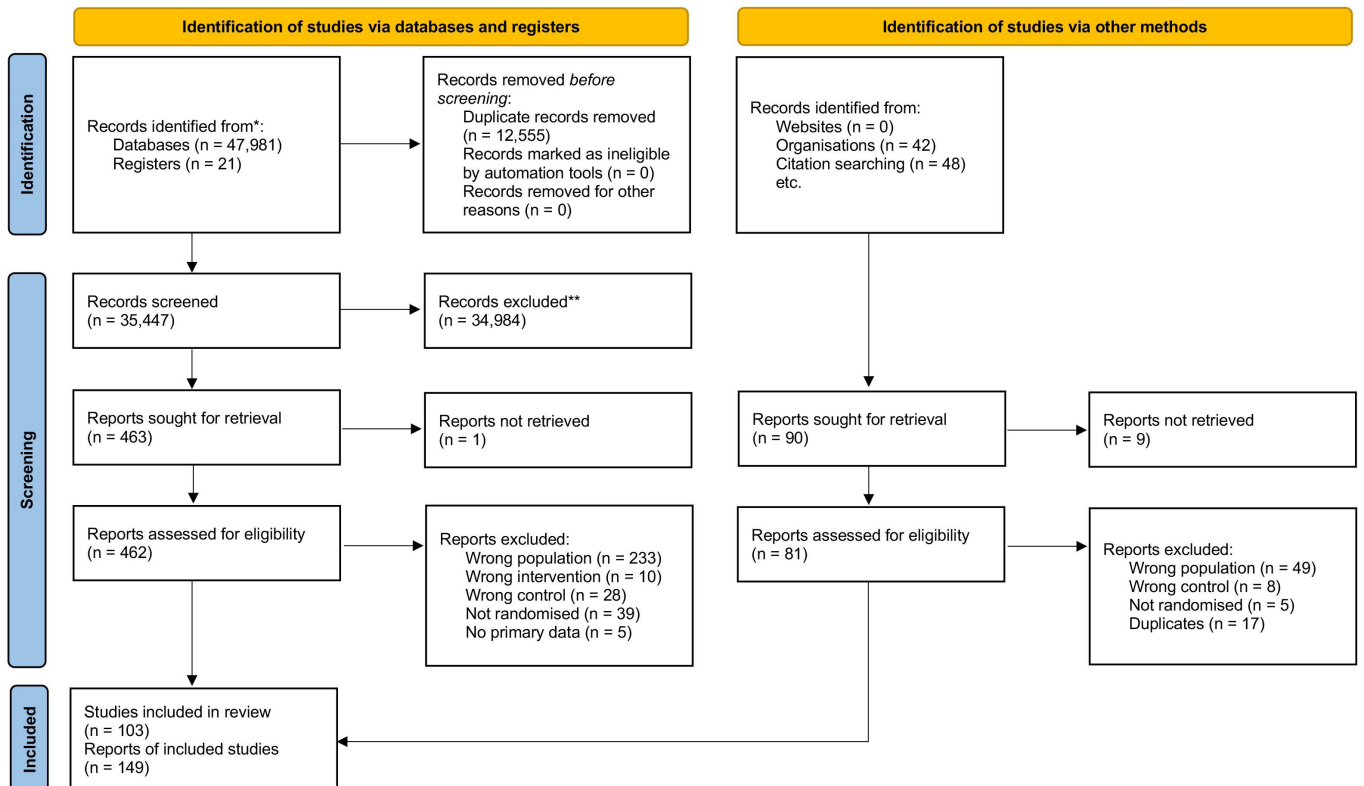
Figure 1 PRISMA flow diagram. From: Page *et al*.[242]

(2 trials),[81 149] amoxapine (1 trial),[150] cianopramine (1 trial),[226] lofepramine (1 trial)[224] and maprotiline (1 trial).[180] Inert placebos were used in 102 trials, while only one trial used 'active placebo' as control intervention.[198] All trials were assessed at overall high risk of bias (figure 2). Ninety-four trials (91%) were at risk of for-profit bias (online supplemental table S1). Most trials did not adequately report the proportion of participants with missing data at follow-up, and it was therefore not possible to perform 'best-worst/worst-best' sensitivity analyses.

Eleven of the included trials assessed outcomes after an extended period of treatment.[67 69 72 90 98 119 134 135 164 211 220] However, in these trials it was either optional to extend the treatment and follow-up period or there were no available data. The trial authors excluded participants from the follow-ups in the extended phase, if they did not wish to extend their treatment, and we therefore chose to exclude these potentially biased data in our analyses. Four other trials assessed outcomes up to 18 months after treatment completion, but no relevant outcomes were reported at these time points.[104 180 184 200]

Primary outcomes
Hamilton Depression Rating Scale, 17 items
Only 17 trials reported results on HDRS-17.[69 82–84 86 91 101 127 130 137 144 152 198 215 221 222] All trials only assessed outcomes at the end of the treatment period, that is, from 4 to 12 weeks after randomisation. Meta-analysis showed evidence of a beneficial effect of tricyclic antidepressants (mean difference (MD) −3.77 HDRS-17 points; 95% CI −5.91 to −1.63; p<0.01; 17 trials; Bayes factor: 0.003) (online supplemental figure S1). Visual inspection of the forest plot and statistical tests (τ=4.4; I^2=91.6%) indicated substantial heterogeneity. When an outlier with a relatively large difference between the HDRS-17 baseline scores (tricyclic group: 38.5, placebo group: 44.2) was removed,[91] meta-analysis showed evidence of a beneficial effect of tricyclic antidepressants (MD −3.16 HDRS-17 points; 95% CI −4.29 to −2.04; p<0.01; τ=1.9; I^2=67.4%; 16 trials) (online supplemental figure S2). Visual inspection of the funnel plot did not show clear signs of asymmetry (online supplemental figure S3). Trial sequential analysis showed that we had enough information to confirm that tricyclic antidepressants reduced the HDRS-17 score (online supplemental figure S4). This outcome result was assessed as overall high risk of bias, and the certainty of the evidence was low (figure 3).

Test of interaction comparing trials using 'active placebo' to trials using inert placebo showed evidence of a difference (p=0.01) (online supplemental figure S5). When the trial using 'active placebo' (atropine and phenobarbital) was analysed separately, meta-analysis showed no evidence of an effect of tricyclic antidepressants (MD 2.47; 95% CI −2.07 to 7.01; p=0.29; 1 trial). When the subgroup of trials using inert placebo was analysed separately, meta-analysis showed evidence of a beneficial effect of tricyclic antidepressants (MD −4.08; 95% CI −6.22 to −1.93; p<0.01; 16 trials).

Tests of interaction comparing the effects of different tricyclic antidepressants (p=0.15), use of placebo washout period (p=0.09) and age groups (p=0.98) showed no evidence of differences (online supplemental figures S6–S8). The remaining predefined subgroup analyses were not possible to perform due to lack of relevant data.

Serious adverse events
None of the included trials reported serious adverse events according to the ICH-GCP definition,[31] and only four trials
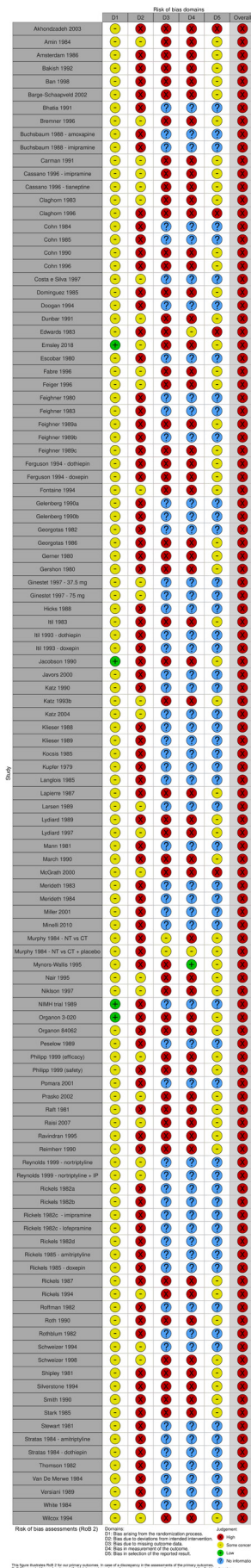

Figure 2 Risk of bias (RoB) assessments.

Summary of findings:

Tricyclic antidepressants compared to control for adults with major depressive disorder

Patient or population: adults with major depressive disorder
Setting:
Intervention: tricyclic antidepressants
Comparison: placebo or active placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with tricyclic antidepressants				
HDRS-17 follow-up: range 4 weeks to 12 weeks		MD **3.77 lower** (5.91 lower to 1.63 lower)	-	2446 (17 RCTs)	⊕⊕◯◯ Low[a]	
Serious adverse events follow-up: range 3 weeks to 9 weeks	42 per 1.000	**108 per 1.000** (87 to 134)	**OR 2.78** (2.18 to 3.55)	4958 (35 RCTs)	⊕◯◯◯ Very low[a,b,c]	
Quality of life follow-up: range 6 to 8 weeks		SMD **0.29 SD higher** (0.01 higher to 0.58 higher)	-	210 (2 RCTs)	⊕◯◯◯ Very low[a,c]	
Suicide/suicide attempts follow-up: range 4 weeks to 8 weeks	22 per 1.000	**12 per 1.000** (4 to 37)	**OR 0.52** (0.16 to 1.67)	584 (5 RCTs)	⊕◯◯◯ Very low[a,c]	
Non-serious adverse events follow-up: range 1 weeks to 10 weeks	322 per 1.000	**676 per 1.000** (573 to 798)	**RR 2.10** (1.78 to 2.48)	7649 (58 RCTs)	⊕◯◯◯ Very low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded 2 for high risk of bias in included studies.
b. Downgraded 1 for indirectness due to differences in measurement of outcome.
c. Downgraded 2 for imprecision due to Trial Sequential Analysis showing that there was not enough information to confirm or reject a relative risk reduction (RRR) of 20% and the accrued number of participants is below 50% of the diversity-adjusted required information size (DARIS).
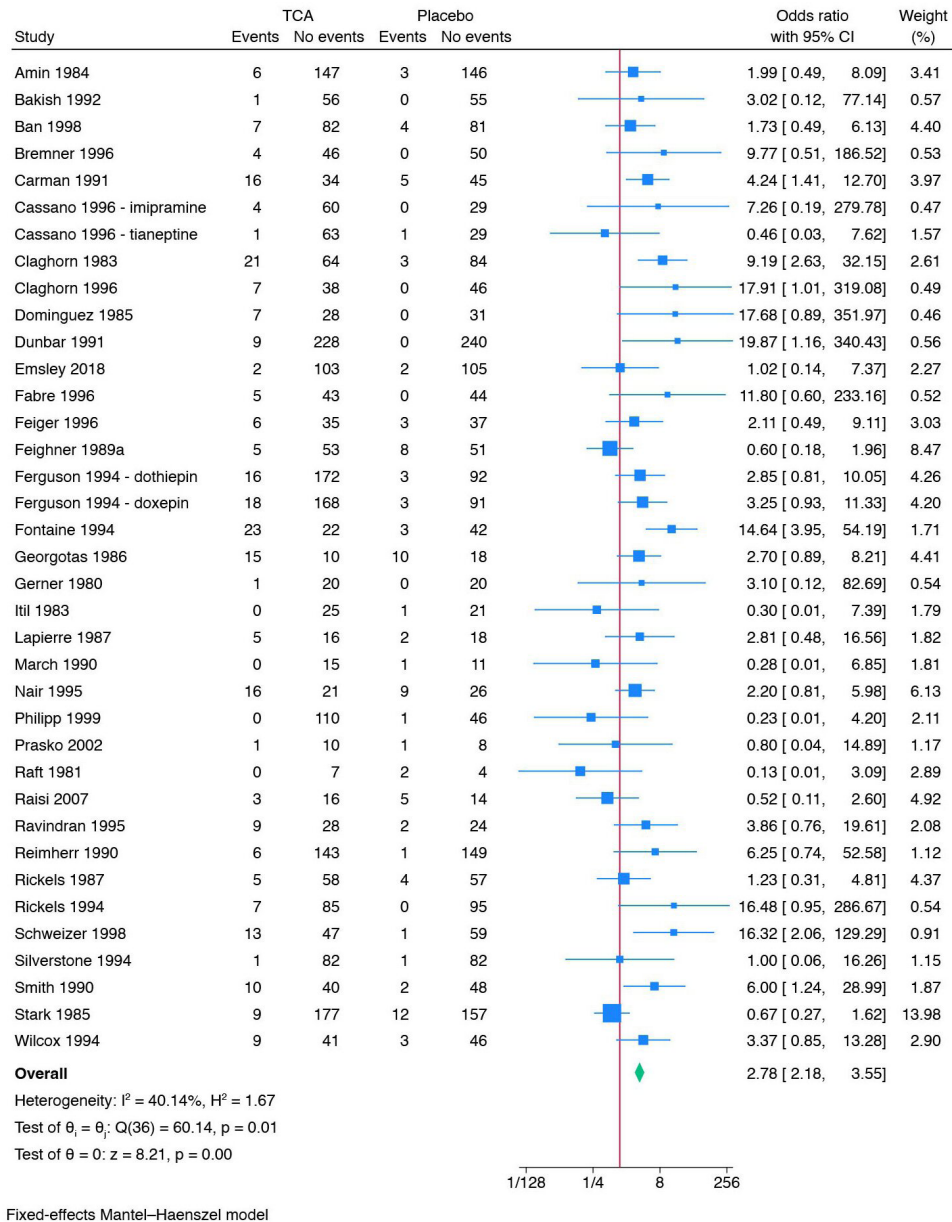
Figure 3 Summary of findings table. HDRS, Hamilton Depression Rating Scale; GRADE, Grading Recommendations Assessment Development Evaluation; RCT, randomised clinical trial.

with few randomised participants and very few events assessed serious adverse events as a composite outcome (online supplemental file 3).

Thirty-five trials reported data that we categorised as serious adverse events based on the ICH-GCP definition (online supplemental table 2).[67 71 72 84–86 90 92 96 98–101 103 104 110 117 118 124 125 131 137 138 142 144 146 153 154 159 163 167 170 202 207 218 220] The trial using 'active placebo' was not included in this meta-analysis. All trials only assessed outcomes at the end of the treatment period, that is, from 3 to 9 weeks after randomisation. A total of 268/2661 (10.1%) experimental participants had one or more serious adverse events compared with 96/2297 (4.2%) control

participants. Meta-analysis showed evidence of a harmful effect of tricyclic antidepressants on serious adverse events (OR 2.78; 95% CI 2.18 to 3.55; p<0.01; 35 trials; Bayes factor: 1.72 E-05) (figure 4). Visual inspection of the forest plot and statistical tests (I²=40.1%) indicated heterogeneity that could not be resolved. Trial sequential analysis showed that we did not have enough information to confirm or reject the hypothesis that tricyclic antidepressants increased the risk of serious adverse events with a relative risk reduction of 20% (online supplemental figure S9). This outcome result was assessed as overall high risk of bias, and the certainty of the evidence was very low (figure 3).

Study	TCA Events	TCA No events	Placebo Events	Placebo No events		Odds ratio with 95% CI	Weight (%)
Amin 1984	6	147	3	146		1.99 [0.49, 8.09]	3.41
Bakish 1992	1	56	0	55		3.02 [0.12, 77.14]	0.57
Ban 1998	7	82	4	81		1.73 [0.49, 6.13]	4.40
Bremner 1996	4	46	0	50		9.77 [0.51, 186.52]	0.53
Carman 1991	16	34	5	45		4.24 [1.41, 12.70]	3.97
Cassano 1996 - imipramine	4	60	0	29		7.26 [0.19, 279.78]	0.47
Cassano 1996 - tianeptine	1	63	1	29		0.46 [0.03, 7.62]	1.57
Claghorn 1983	21	64	3	84		9.19 [2.63, 32.15]	2.61
Claghorn 1996	7	38	0	46		17.91 [1.01, 319.08]	0.49
Dominguez 1985	7	28	0	31		17.68 [0.89, 351.97]	0.46
Dunbar 1991	9	228	0	240		19.87 [1.16, 340.43]	0.56
Emsley 2018	2	103	2	105		1.02 [0.14, 7.37]	2.27
Fabre 1996	5	43	0	44		11.80 [0.60, 233.16]	0.52
Feiger 1996	6	35	3	37		2.11 [0.49, 9.11]	3.03
Feighner 1989a	5	53	8	51		0.60 [0.18, 1.96]	8.47
Ferguson 1994 - dothiepin	16	172	3	92		2.85 [0.81, 10.05]	4.26
Ferguson 1994 - doxepin	18	168	3	91		3.25 [0.93, 11.33]	4.20
Fontaine 1994	23	22	3	42		14.64 [3.95, 54.19]	1.71
Georgotas 1986	15	10	10	18		2.70 [0.89, 8.21]	4.41
Gerner 1980	1	20	0	20		3.10 [0.12, 82.69]	0.54
Itil 1983	0	25	1	21		0.30 [0.01, 7.39]	1.79
Lapierre 1987	5	16	2	18		2.81 [0.48, 16.56]	1.82
March 1990	0	15	1	11		0.28 [0.01, 6.85]	1.81
Nair 1995	16	21	9	26		2.20 [0.81, 5.98]	6.13
Philipp 1999	0	110	1	46		0.23 [0.01, 4.20]	2.11
Prasko 2002	1	10	1	8		0.80 [0.04, 14.89]	1.17
Raft 1981	0	7	2	4		0.13 [0.01, 3.09]	2.89
Raisi 2007	3	16	5	14		0.52 [0.11, 2.60]	4.92
Ravindran 1995	9	28	2	24		3.86 [0.76, 19.61]	2.08
Reimherr 1990	6	143	1	149		6.25 [0.74, 52.58]	1.12
Rickels 1987	5	58	4	57		1.23 [0.31, 4.81]	4.37
Rickels 1994	7	85	0	95		16.48 [0.95, 286.67]	0.54
Schweizer 1998	13	47	1	59		16.32 [2.06, 129.29]	0.91
Silverstone 1994	1	82	1	82		1.00 [0.06, 16.26]	1.15
Smith 1990	10	40	2	48		6.00 [1.24, 28.99]	1.87
Stark 1985	9	177	12	157		0.67 [0.27, 1.62]	13.98
Wilcox 1994	9	41	3	46		3.37 [0.85, 13.28]	2.90
Overall						2.78 [2.18, 3.55]	

Heterogeneity: $I^2 = 40.14\%$, $H^2 = 1.67$

Test of $\theta_i = \theta_j$: $Q(36) = 60.14$, $p = 0.01$

Test of $\theta = 0$: $z = 8.21$, $p = 0.00$

1/128   1/4   8   256

Fixed-effects Mantel–Haenszel model

Figure 4 Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events.

Test of interaction comparing trials at risk of for-profit bias to trials without risk of for-profit bias showed evidence of a difference (p<0.01) (online supplemental figure S10). When the subgroup of trials at risk of for-profit bias was analysed separately, meta-analysis showed evidence of a harmful effect of tricyclic antidepressants (OR 3.01; 95% CI 2.34 to 3.88; p<0.01; 32 trials). When the subgroup of trials without risk of for-profit bias was analysed separately, meta-analysis showed no evidence of a difference (OR 0.43; 95% CI 0.12 to 1.51; p=0.19; 3 trials).

Tests of interaction comparing the effects of different tricyclic antidepressants (p=0.28), age groups (p=0.70) and use of placebo washout period (p=0.55) showed no evidence of differences (online supplemental figures S11–S13). The remaining predefined subgroup analyses were not possible to perform due to lack of relevant data.

When each specific serious adverse event was analysed separately, 5/15 meta-analyses showed evidence of a harmful effect of tricyclic antidepressants on: hypotension (risk ratio (RR) 3.31; 95% CI 1.93 to 5.68; p<0.01; $\tau=0.5$; $I^2=43.6\%$; 10 trials; number needed to harm (NNH): 8 (111/636)) (online supplemental figure S14); urinary retention (RR 6.07; 95% CI 1.66 to 22.19; p<0.01; $\tau=0.9$; $I^2=38.2\%$; five trials; NNH: 8 (36/266)) (online supplemental figure S15); amblyopia (RR 3.32; 95% CI 1.94 to 5.66; p<0.01; $\tau=0.2$; $I^2=6.0\%$; five trials; NNH: 11 (73/574)) (online supplemental figure S16); sexual dysfunction (RR 3.50; 95% CI 1.29 to 9.48; p=0.01; $\tau=0.6$; $I^2=16.8\%$; eight trials; NNH: 31 (25/651)) (online supplemental figure S17); and taste alteration (RR 4.04; 95% CI 1.23 to 13.24; p=0.02; $\tau=0.6$; $I^2=19.9\%$; four trials; NNH: 35 (26/677)) (online supplemental figure S18). The 10 remaining meta-analyses showed no evidence of differences (online supplemental table S3 and figures S19–S28).

Quality of life
Only two trials reported mean scores and SD for quality of life.[69][84] Quality of life was assessed using either a Visual Analogue Scale[69] or the mental component scale of the Short Form 36.[84]

Both trials only assessed outcomes at the end of the treatment period, that is, from 6 to 8 weeks after randomisation. One trial randomised 63 participants, and our t-test showed no evidence of a difference on quality of life (t(57) = 0.95, p=0.35).[69] The other trial randomised 157 participants, and our t-test showed no evidence of a difference on quality of life (t(155) = 1.81, p=0.07).[84] These results were assessed as overall high risk of bias, and the certainty of the evidence was very low (figure 3).

Secondary outcomes

Suicides or suicide attempts

Only 5 of the 103 trials reported on suicides or suicide attempts.[84 101 117 125] All trials only assessed outcomes at the end of the treatment period, that is, from 4 to 8 weeks after randomisation. A total of 3/361 (0.8%) experimental participants had a suicide or suicide attempts compared with 5/223 (2.2%) control participants. Meta-analysis showed no evidence of a difference between tricyclic antidepressants and placebo on suicides or suicide attempts (OR 0.52; 95% CI 0.16 to 1.67; p=0.27; five trials; Bayes factor: 0.71) (online supplemental figure S29). Visual inspection of the forest plot and statistical tests (I^2=0.0%) indicated no clear signs of heterogeneity. Trial sequential analysis showed that we did not have enough information to confirm or reject the hypothesis that tricyclic antidepressants reduced the risk of suicides or suicide attempts with a relative risk reduction of 20% (no graph produced). This outcome result was assessed as overall high risk of bias, and the certainty of the evidence was very low (figure 3).

Non-serious adverse events

Fifty-eight trials reported on non-serious adverse events.[66 67 69–73 76 79 81 82 84–87 89 90 92 96 98–102 104 110 114 117–119 121 124 125 127 129 131 135 137 142 144 146 153 154 159 163 164 167 170 171 174 201 202 207 209 213 218 220 223 224 226] Trials using 'active placebo' were not included in this meta-analysis. All trials only assessed outcomes at the end of the treatment period, that is, from 1 to 10 weeks after randomisation. A total of 2595/4103 (63.2%) experimental participants had one or more non-serious adverse events compared with 1141/3546 (32.2%) control participants. Meta-analysis showed evidence of a harmful effect of tricyclic antidepressants on non-serious adverse events (RR 2.10; 95% CI 1.78 to 2.48; p<0.01; 58 trials; Bayes factor: 6.32 E-08) (figure 5). Visual inspection of the forest plot and statistical tests (τ=0.6; I^2=93.5%) indicated heterogeneity that could not be resolved. Trial sequential analysis showed that we had enough information to confirm that tricyclic antidepressants increased the risk of non-serious adverse events (online supplemental figure S30). This outcome result was assessed as overall high risk of bias and the certainty of the evidence was very low (figure 3).

One trial used another drug, citalopram, as a co-intervention. Test of interaction comparing the effects of drug co-interventions versus no drug co-intervention showed no evidence of a difference (p=0.053) (online supplemental figure S31).
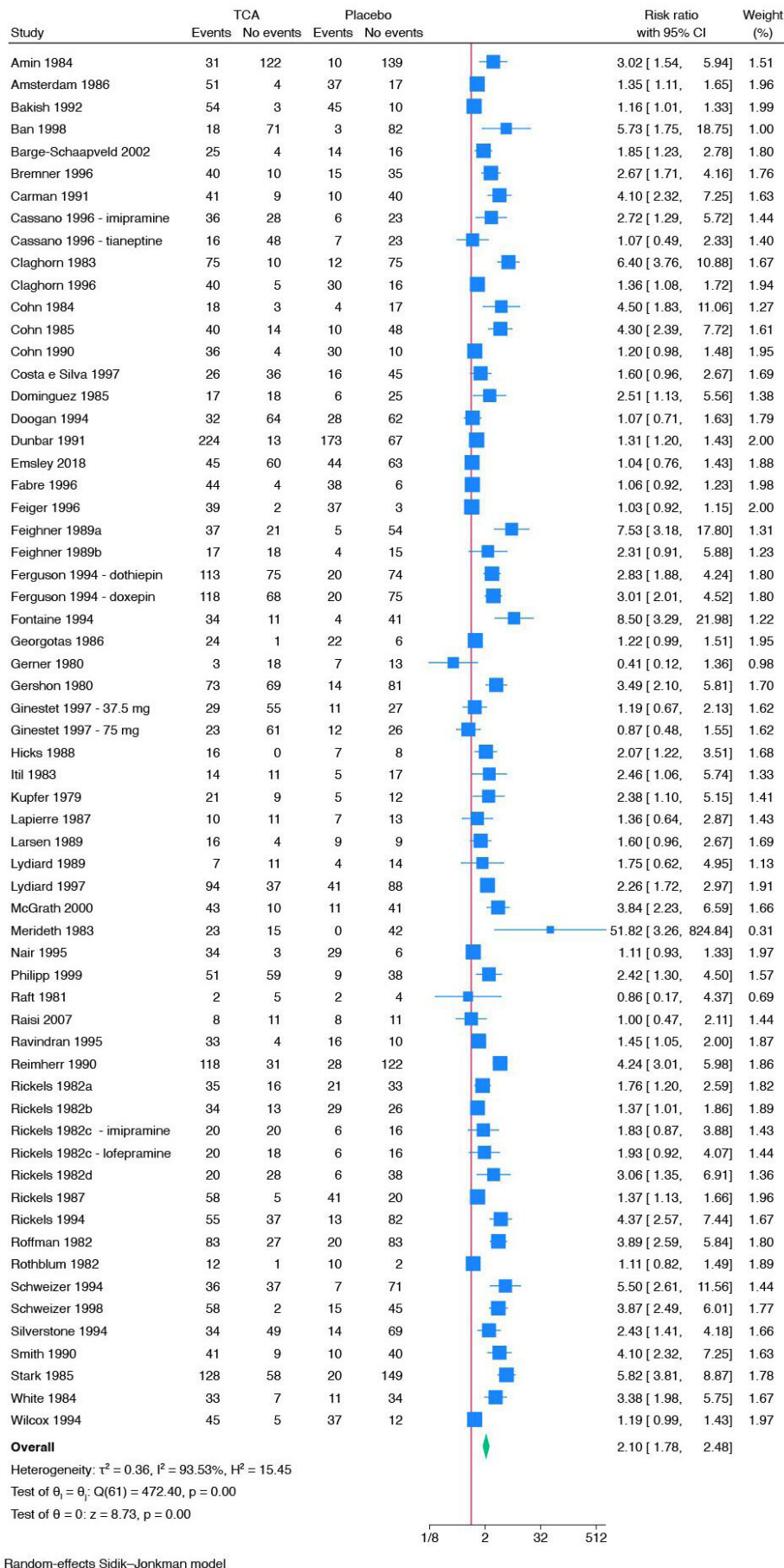
When each specific non-serious adverse event was analysed separately, 23/36 meta-analyses showed evidence of a harmful effect of tricyclic antidepressants on individual non-serious adverse events: dry mouth (45 trials), constipation (38 trials), dizziness (34 trials), somnolence (33 trials), tremor (28 trials), sweating (21 trials), blurred vision (20 trials), asthenia (20 trials), nervousness (14 trials), tachycardia (14 trials), dyspepsia (11 trials), weight gain (8 trials), paraesthesia (7 trials), confusion (7 trials), anticholinergic symptoms (5 trials), sedation (5 trials), increased appetite (5 trials), decreased appetite (4 trials),

micturition disorder (3 trials), flushing (2 trials), abnormal dreams (2 trials), impaired urination (2 trials) and urinary hesitancy (2 trials). The 10 non-serious adverse events with the lowest NNH were dry mouth (RR 3.43; 95% CI 2.87 to 4.10; p<0.01; τ=0.5; I^2=72.1%; 45 trials; NNH: 2 (1863/3399)) (online supplemental figure S32); anticholinergic symptoms (RR 2.35; 95% CI 1.46 to 3.78; p<0.01; τ=0.5; I^2=79.0%; 5 trials; NNH: 3 (184/297)) (online supplemental figure S33); somnolence (RR 2.65; 95% CI 2.20 to 3.21; p<0.01; τ=0.4; I^2=55.9%; 33 trials; NNH: 4 (919/2616)) (online supplemental figure S34); sedation (RR 1.67; 95% CI 1.08 to 2.58; p=0.02; τ=0.4; I^2=49.1%; 5 trials; NNH: 7 (98/301)) (online supplemental figure S35); dizziness (RR 2.37; 95% CI 1.87 to 3.01; p<0.01; τ=0.5; I^2=56.6%; 34 trials; NNH: 7 (584/2753)) (online supplemental figure S36); constipation (RR 2.81; 95% CI 2.16 to 3.65; p<0.01; τ=0.6; I^2=58.6%; 38 trials; NNH: 7 (617/3082)) (online supplemental figure S37); sweating (RR 3.64; 95% CI 2.41 to 5.50; p<0.01; τ=0.6; I^2=42.5%; 21 trials; NNH: 8 (230/1563)) (online supplemental figure S38); tremor (RR 4.70; 95% CI 3.02 to 7.30; p<0.01; τ=0.8; I^2=47.1%; 28 trials; NNH: 9 (300/2321)) (online supplemental figure S39); blurred vision (RR 2.96; 95% CI 2.21 to 3.96; p<0.01; τ=0.2; I^2=14.7%; 19 trials; NNH: 10 (216/1485)) (online supplemental figure S40) and flushing (RR 5.86; 95% CI 1.33 to 25.72; p=0.02; τ=0.7; I^2=41.0%; 2 trials; NNH: 10 (26/231)) (online supplemental figure S41). Two meta-analyses showed evidence of a beneficial effect of tricyclic antidepressants on individual non-serious adverse events: diarrhoea (RR 0.46; 95% CI 0.29 to 0.74; p<0.01; τ=0.4; I^2=25.0%; 13 trials; number needed to treat (NNT): 19 (35/895)) (online supplemental figure S42) and infection (RR 0.41; 95% CI 0.19 to 0.89; p=0.02; τ=0.1; I^2=3.9%; 3 trials; NNT: 21 (9/279)) (online supplemental table S4 and figure S43). The remaining meta-analyses are reported in the online supplemental material (online supplemental table S5 and figures S44–S67). Please see online supplemental file 4 for the list of non-serious adverse events combined for meta-analyses.

The results of the remaining exploratory outcomes, sensitivity analyses and prediction intervals are reported in online supplemental file 3 and online supplemental figures S68–S133.

DISCUSSION

We conducted a systematic review assessing the beneficial and harmful effects of tricyclic antidepressants for adults with major depressive disorder. A total of 103 placebo-controlled trials randomising 10 590 participants were included. In comparison, the network meta-analysis by Cipriani et al[19] included 36 trials assessing the effects of tricyclic antidepressants versus placebo since they only assessed amitriptyline and clomipramine. All present outcome results were at overall high risk of bias and the certainty of evidence was very low or low, particularly due to lack of information, missing data, lack of blinding of outcome assessors, risk of unblinding due to adverse effects, inappropriate analysis methods and poor reporting. All trials only assessed outcomes at the end of the treatment period at a maximum of 12 weeks after randomisation. Meta-analysis and trial sequential analysis showed that tricyclic antidepressants reduced depressive symptoms more than placebo, but the certainty was low. Meta-analysis showed evidence of a harmful effect of tricyclic antidepressants compared with placebo on serious adverse events, but the required information size was not reached and the certainty was very low. The serious adverse events with the lowest NNH were hypotension, urinary retention, amblyopia,

Study	TCA Events	TCA No events	Placebo Events	Placebo No events	Risk ratio with 95% CI	Weight (%)
Amin 1984	31	122	10	139	3.02 [1.54, 5.94]	1.51
Amsterdam 1986	51	4	37	17	1.35 [1.11, 1.65]	1.96
Bakish 1992	54	3	45	10	1.16 [1.01, 1.33]	1.99
Ban 1998	18	71	3	82	5.73 [1.75, 18.75]	1.00
Barge-Schaapveld 2002	25	4	14	16	1.85 [1.23, 2.78]	1.80
Bremner 1996	40	10	15	35	2.67 [1.71, 4.16]	1.76
Carman 1991	41	9	10	40	4.10 [2.32, 7.25]	1.63
Cassano 1996 - imipramine	36	28	6	23	2.72 [1.29, 5.72]	1.44
Cassano 1996 - tianeptine	16	48	7	23	1.07 [0.49, 2.33]	1.40
Claghorn 1983	75	10	12	75	6.40 [3.76, 10.88]	1.67
Claghorn 1996	40	5	30	16	1.36 [1.08, 1.72]	1.94
Cohn 1984	18	3	4	17	4.50 [1.83, 11.06]	1.27
Cohn 1985	40	14	10	48	4.30 [2.39, 7.72]	1.61
Cohn 1990	36	4	30	10	1.20 [0.98, 1.48]	1.95
Costa e Silva 1997	26	36	16	45	1.60 [0.96, 2.67]	1.69
Dominguez 1985	17	18	6	25	2.51 [1.13, 5.56]	1.38
Doogan 1994	32	64	28	62	1.07 [0.71, 1.63]	1.79
Dunbar 1991	224	13	173	67	1.31 [1.20, 1.43]	2.00
Emsley 2018	45	60	44	63	1.04 [0.76, 1.43]	1.88
Fabre 1996	44	4	38	6	1.06 [0.92, 1.23]	1.98
Feiger 1996	39	2	37	3	1.03 [0.92, 1.15]	2.00
Feighner 1989a	37	21	5	54	7.53 [3.18, 17.80]	1.31
Feighner 1989b	17	18	4	15	2.31 [0.91, 5.88]	1.23
Ferguson 1994 - dothiepin	113	75	20	74	2.83 [1.88, 4.24]	1.80
Ferguson 1994 - doxepin	118	68	20	75	3.01 [2.01, 4.52]	1.80
Fontaine 1994	34	11	4	41	8.50 [3.29, 21.98]	1.22
Georgotas 1986	24	1	22	6	1.22 [0.99, 1.51]	1.95
Gerner 1980	3	18	7	13	0.41 [0.12, 1.36]	0.98
Gershon 1980	73	69	14	81	3.49 [2.10, 5.81]	1.70
Ginestet 1997 - 37.5 mg	29	55	11	27	1.19 [0.67, 2.13]	1.62
Ginestet 1997 - 75 mg	23	61	12	26	0.87 [0.48, 1.55]	1.62
Hicks 1988	16	0	7	8	2.07 [1.22, 3.51]	1.68
Itil 1983	14	11	5	17	2.46 [1.06, 5.74]	1.33
Kupfer 1979	21	9	5	12	2.38 [1.10, 5.15]	1.41
Lapierre 1987	10	11	7	13	1.36 [0.64, 2.87]	1.43
Larsen 1989	16	4	9	9	1.60 [0.96, 2.67]	1.69
Lydiard 1989	7	11	4	14	1.75 [0.62, 4.95]	1.13
Lydiard 1997	94	37	41	88	2.26 [1.72, 2.97]	1.91
McGrath 2000	43	10	11	41	3.84 [2.23, 6.59]	1.66
Merideth 1983	23	15	0	42	51.82 [3.26, 824.84]	0.31
Nair 1995	34	3	29	6	1.11 [0.93, 1.33]	1.97
Philipp 1999	51	59	9	38	2.42 [1.30, 4.50]	1.57
Raft 1981	2	5	2	4	0.86 [0.17, 4.37]	0.69
Raisi 2007	8	11	8	11	1.00 [0.47, 2.11]	1.44
Ravindran 1995	33	4	16	10	1.45 [1.05, 2.00]	1.87
Reimherr 1990	118	31	28	122	4.24 [3.01, 5.98]	1.86
Rickels 1982a	35	16	21	33	1.76 [1.20, 2.59]	1.82
Rickels 1982b	34	13	29	26	1.37 [1.01, 1.86]	1.89
Rickels 1982c - imipramine	20	20	6	16	1.83 [0.87, 3.88]	1.43
Rickels 1982c - lofepramine	20	18	6	16	1.93 [0.92, 4.07]	1.44
Rickels 1982d	20	28	6	38	3.06 [1.35, 6.91]	1.36
Rickels 1987	58	5	41	20	1.37 [1.13, 1.66]	1.96
Rickels 1994	55	37	13	82	4.37 [2.57, 7.44]	1.67
Roffman 1982	83	27	20	83	3.89 [2.59, 5.84]	1.80
Rothblum 1982	12	1	10	2	1.11 [0.82, 1.49]	1.89
Schweizer 1994	36	37	7	71	5.50 [2.61, 11.56]	1.44
Schweizer 1998	58	2	15	45	3.87 [2.49, 6.01]	1.77
Silverstone 1994	34	49	14	69	2.43 [1.41, 4.18]	1.66
Smith 1990	41	9	10	40	4.10 [2.32, 7.25]	1.63
Stark 1985	128	58	20	149	5.82 [3.81, 8.87]	1.78
White 1984	33	7	11	34	3.38 [1.98, 5.75]	1.67
Wilcox 1994	45	5	37	12	1.19 [0.99, 1.43]	1.97
Overall					2.10 [1.78, 2.48]	

Heterogeneity: $\tau^2 = 0.36$, $I^2 = 93.53\%$, $H^2 = 15.45$

Test of $\theta_i = \theta_j$: Q(61) = 472.40, p = 0.00

Test of $\theta = 0$: z = 8.73, p = 0.00

Random-effects Sidik–Jonkman model

Figure 5 Meta-analysis of tricyclic antidepressants (TCA) versus placebo on non-serious adverse events.

sexual dysfunction and taste alteration. Only 2 out of 103 trials reported on quality of life, and t-tests showed no evidence of an intervention effect. Meta-analysis and trial sequential analysis showed that we did not have enough information to confirm or reject the effects of tricyclic antidepressants on suicides or suicide attempts. Meta-analysis and trial sequential analysis showed evidence of a harmful effect of tricyclic antidepressants compared with placebo on non-serious adverse events. The non-serious adverse events with the lowest NNH were dry mouth, anticholinergic symptoms, somnolence, sedation and dizziness.

Our meta-analysis showed a mean difference between tricyclic antidepressants and placebo of −3.77 HDRS points or −3.16 HDRS points when an outlier was removed. We predefined the minimal important difference on HDRS as three points, but it has been questioned whether the true minimal important difference is in fact closer to seven points.[62] Moreover, the effect was not above our minimal important difference in the one trial using an 'active placebo'. The high risk of bias of the included trials and the low certainty of the evidence make our results inadequate to determine whether tricyclic antidepressants have a genuine and meaningful short-term antidepressant effect rather than an amplified placebo effect.

Our systematic review has several strengths. Our results are novel, as this is the first systematic review assessing all adverse effects for all tricyclic antidepressants in adults with major depressive disorder. Data on adverse effects are essential for enabling patients and clinician to make informed decisions about the use of any treatment. The predefined methodology was based on the Cochrane Handbook for Systematic Reviews of Interventions,[227] PRISMA,[25] trial sequential analysis,[53 59] the eight-step procedure by Jakobsen et al,[49] the GRADE approach,[63] and risks of systematic and random errors, external validity, publication bias and heterogeneity were taken into account. We increased the statistical power by pooling all tricyclic antidepressants, and we compared the effects of different types of tricyclic antidepressants in subgroup analyses. Furthermore, we searched for both published trials and unpublished data to increase the validity of our results.[227–230]

Our systematic review also has limitations. First, the included trials only reported results at the end of treatment at a maximum of 12 weeks, so the long-term effects of tricyclic antidepressants are unknown. There is a need for trials with long-term follow-up to assess the benefits and harms since, for example, half of patients on antidepressants in the UK and 70% of patients in the USA have used them for more than 2 years.[231 232] This is particularly pertinent for medications that are associated with tolerance and withdrawal effects, which tend to show diminishing effects over time.[233] Second, all included trials were assessed at overall high risk of bias particularly driven by risk of bias due to missing data, lack of blinding of outcome assessors, risk of unblinding due to adverse effects, inappropriate analysis methods and the reporting of the included trials was generally poor. The reporting and assessment of adverse events were especially inadequate. None of the trials assessed adverse events based on the ICH-GCP guidelines,[31] and serious adverse events were generally not systematically assessed. Studies have shown that the adverse effects are generally under-reported in published trials compared with unpublished data, and we therefore aimed to include unpublished data.[227–230] However, in spite of searching systematically for unpublished data, we were only able to identify unpublished data for one trial.[220] Our results are therefore prone to overestimation of benefits and underestimation of harms.[234–241] Third, only five of the included trials reported on suicides or suicide attempts, and there was not enough information to confirm or reject the effects of tricyclic antidepressants on suicides or suicide attempts. This is particularly problematic since major depressive disorder is associated with increased risks of suicidal behaviour.[3–5] There is a need for larger trials at low risk of bias to assess the risks of suicides and suicide attempts. Fourth, only two trials had publicly available protocols or trial registrations, and the certainty of the evidence was very low or low for all outcome results. Fifth, we planned several outcome comparisons, which increased the risk of type I errors. To control the risks of random errors, we adjusted our threshold for significance according to the number of primary and secondary outcomes, but we did not adjust the thresholds for significance according to the total number of comparisons, including exploratory outcomes, subgroup analyses and sensitivity analyses. Sixth, due to poor reporting of the tricyclic antidepressant doses used in the included trials, it was not possible to define meaningful dose subgroups to compare the effects of different doses. Seventh, since we only identified one trial using 'active placebo', we could not adequately assess whether the nature of control intervention impacted results. Eighth, we included one trial using citalopram as a co-intervention, which may lead to different RRs for adverse events compared with other trials, but we assessed the potential differences with subgroup analyses. Ninth, we did not test the inter-rater reliability for our RoB 2 assessments. Tenth, since the included trials did not report serious adverse events according to the ICH-GCP definition and because the definition of serious adverse events was unclear, it was necessary to make a subjective assessment of the severity of the adverse events to decide if each event should be classified as a serious adverse event. However, the subjective assessments may be inaccurate as they rely on the specific adverse events chosen to be reported by the trialists—other serious adverse events might have occurred that the trialists did not assess or report. The information provided by the trialists about specific adverse events was often sparse (ie, adverse events were often only reported in tables and there was rarely information about the patients' specific events). Hence, the present results presumably underestimate the harmful effects of tricyclic antidepressants. A subjective assessment of adverse events based on such information is therefore likely to be incomplete, but nevertheless, important data on adverse effects would not be available without this process. We believe that the present analysis of serious adverse events, a critical outcome of any drug trial, provides useful information regarding the adverse effects of tricyclic antidepressants, and we have assessed serious adverse events using this methodology in several systematic reviews for over a decade.[36–47] Still, the above-mentioned limitations should be considered when interpreting our results.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The long-term effects of tricyclic antidepressants and the effects on quality of life and suicides or suicide attempts are unknown. Short-term results suggest that tricyclic antidepressants may reduce depressive symptoms while also increasing the risks of adverse events, but these results were based on low and very low certainty evidence. It is a cause for concern that there are no data on the long-term adverse effects of tricyclic antidepressants given that so many people use these drugs for several years.

Author affiliations
[1]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
[2]Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

[3]MSH Medical School Hamburg, University of Applied Sciences and Medical University, Hamburg, Germany
[4]Psychotherapeutic Center Stolpegård, Gentofte, Denmark
[5]Department of Cardiology, Gentofte Hospital, Hellerup, Denmark
[6]Division of Psychiatry, University College London (honorary for MAH), London, UK
[7]Department of Research and Development, North East London NHS Foundation Trust, London, UK
[8]Department of Applied Psychology, Zurich Universities of Applied Sciences, Zurich, Switzerland
[9]Program in Placebo Studies, Harvard Medical School, Boston, Massachusetts, USA

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ORCID iDs
Caroline Barkholt Kamp http://orcid.org/0000-0002-7756-4694
Johanne Juul Petersen http://orcid.org/0000-0001-9837-1958
Faiza Siddiqui http://orcid.org/0000-0002-8358-6259
Marija Barbateskovic http://orcid.org/0000-0001-8566-3660
Mark Abie Horowitz http://orcid.org/0000-0003-1318-2029
Michael Pascal Hengartner http://orcid.org/0000-0002-2956-2969

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