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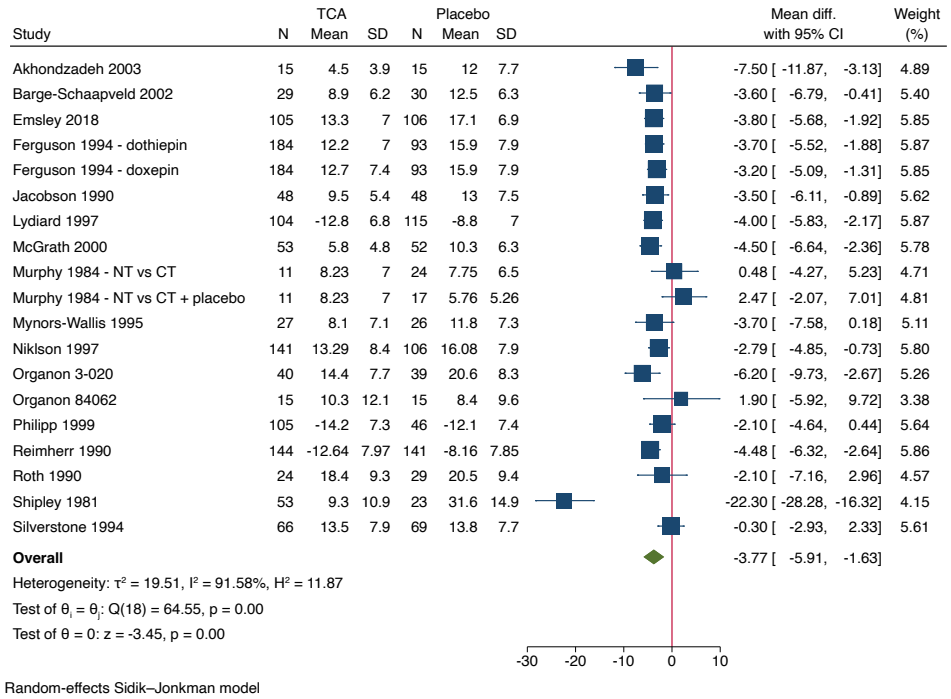

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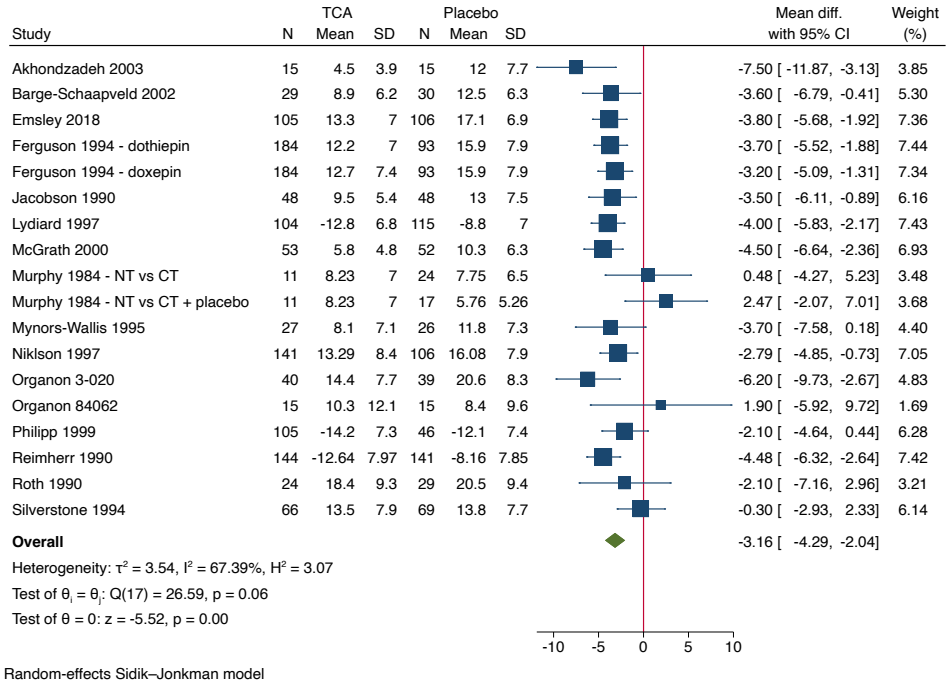

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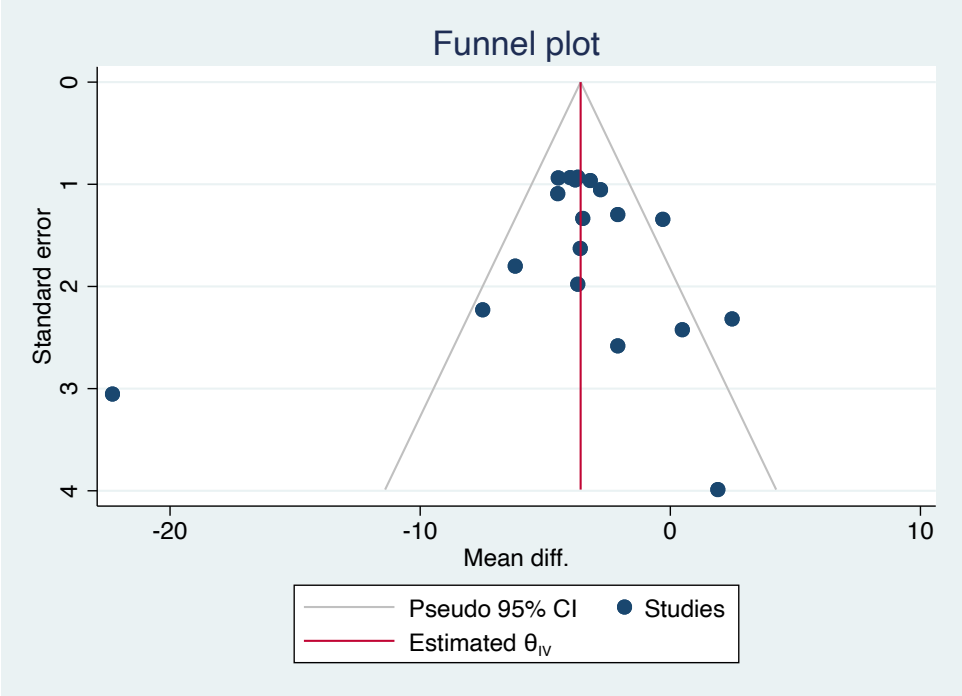

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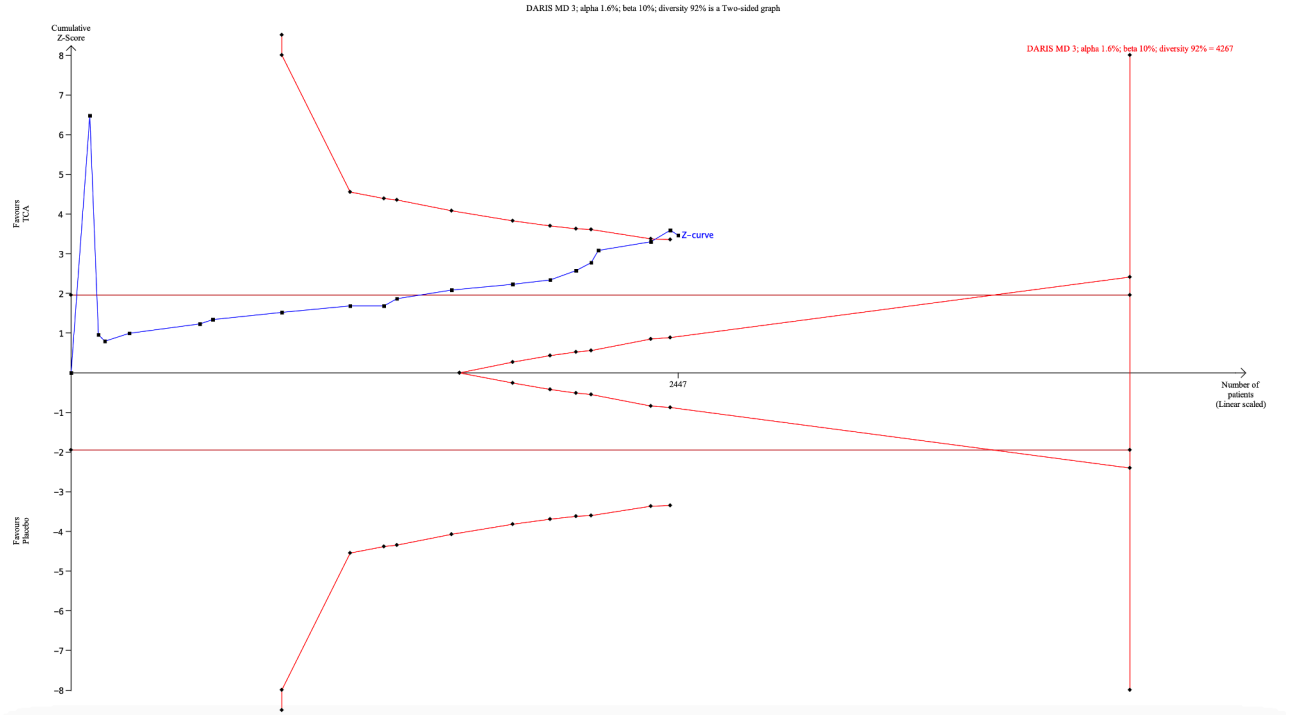

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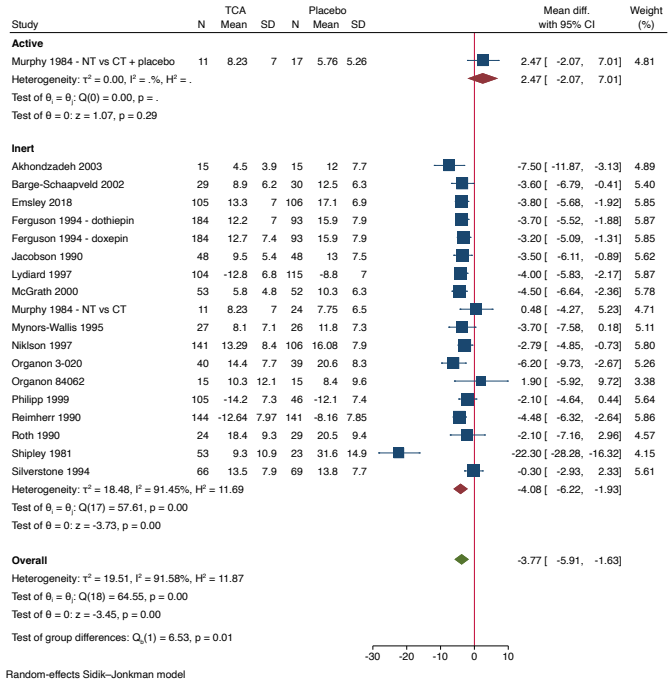

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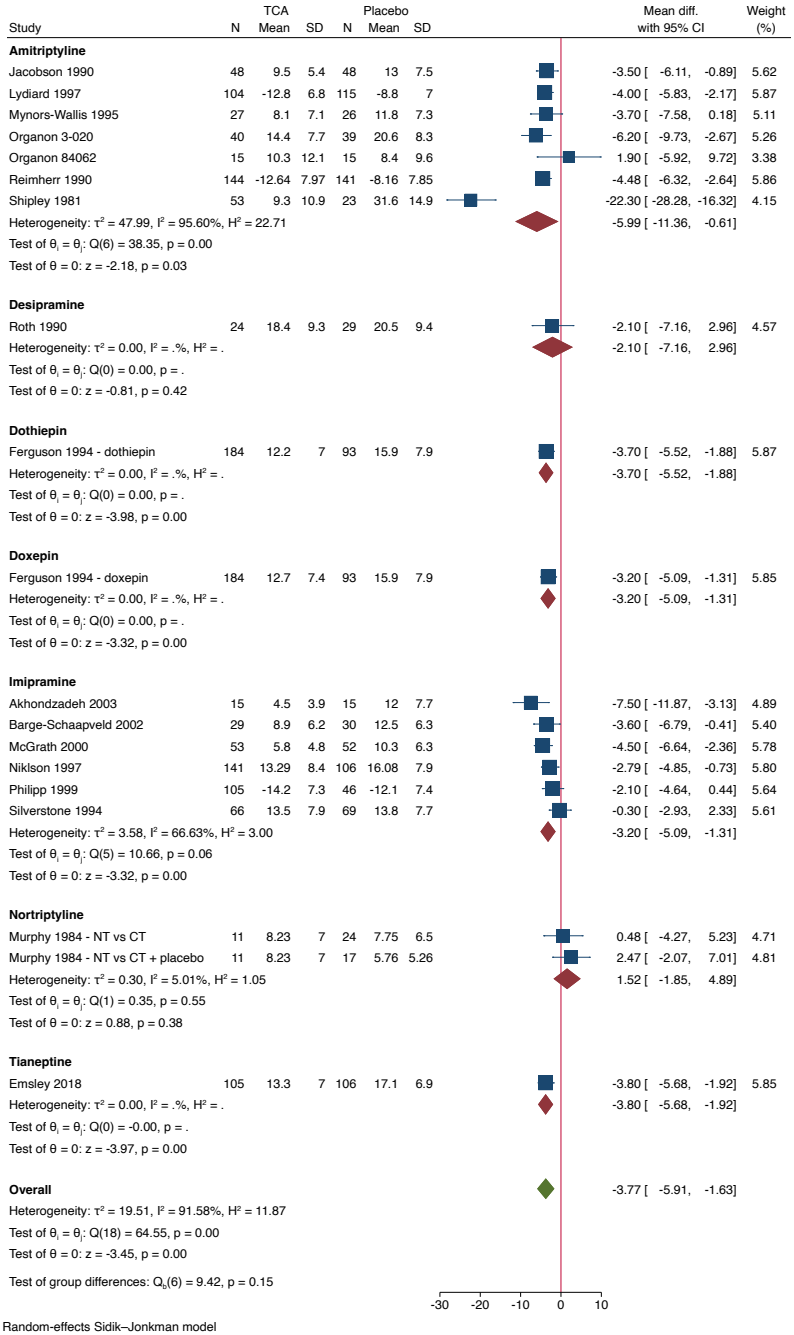

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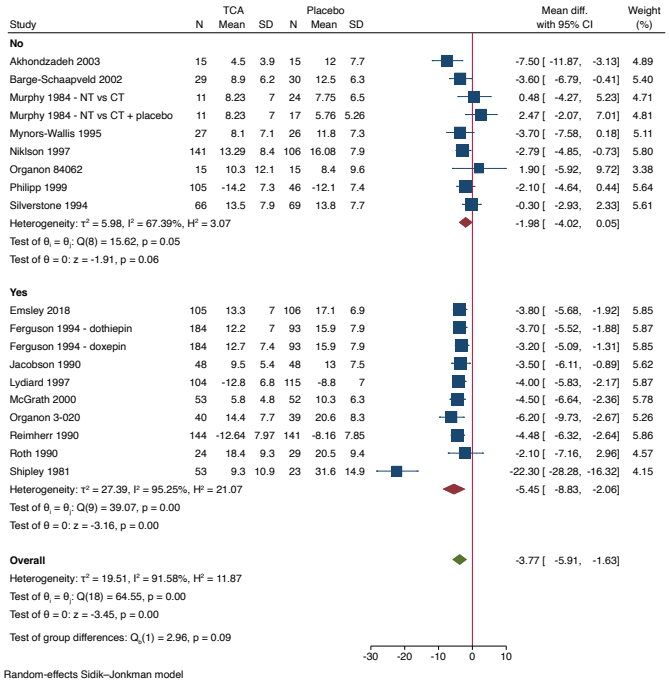

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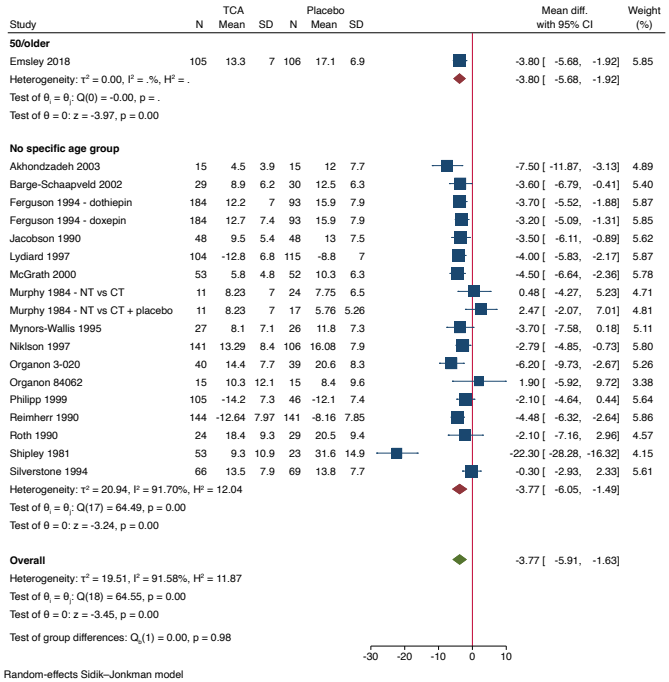
Graph 22/05/2023, 11.02



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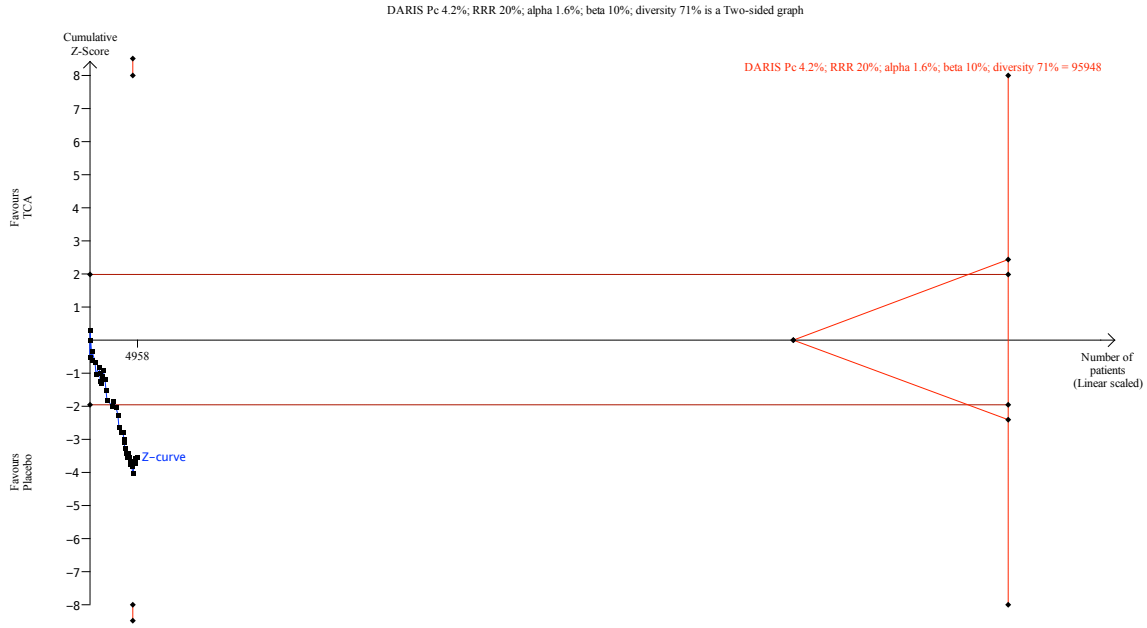

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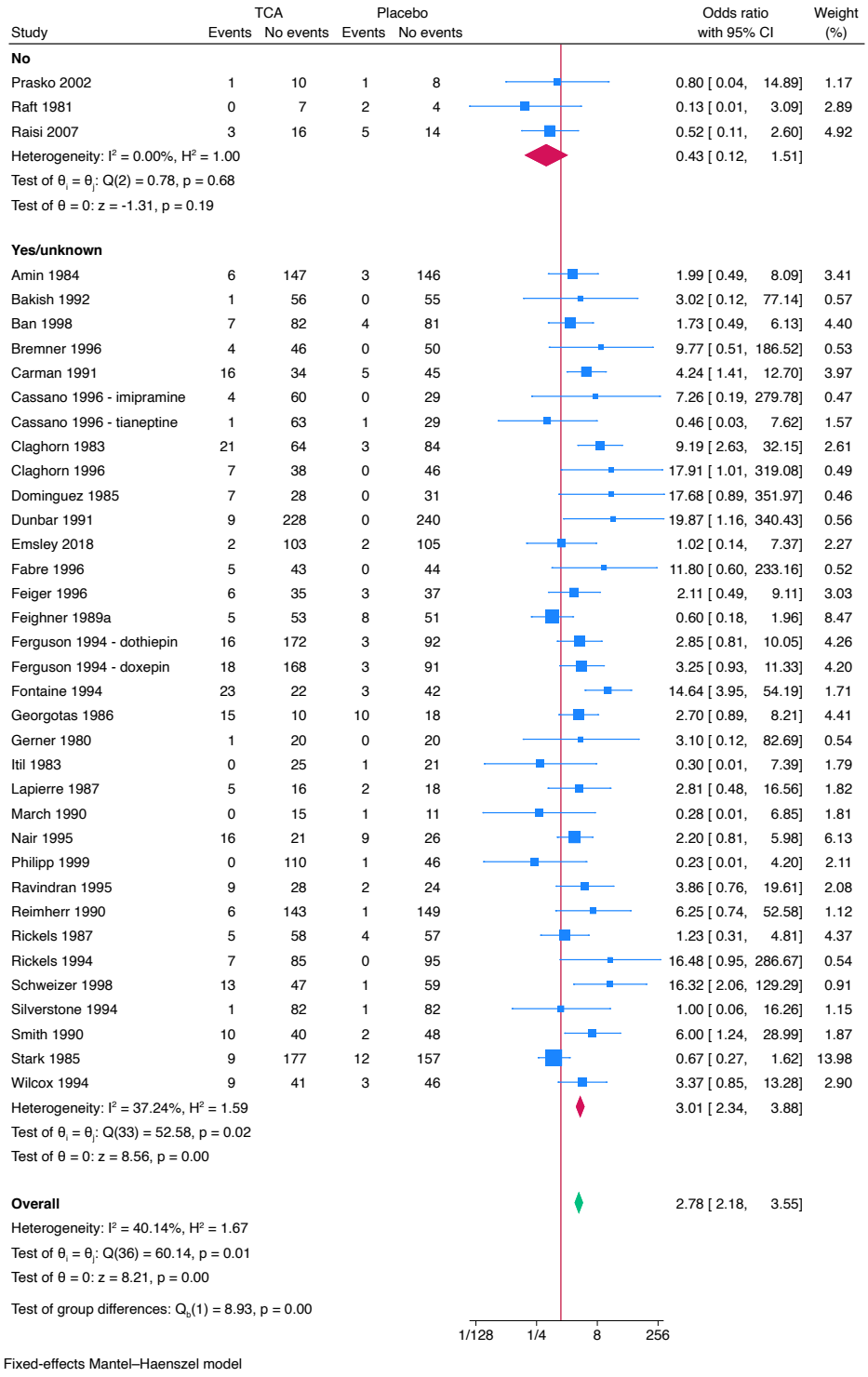

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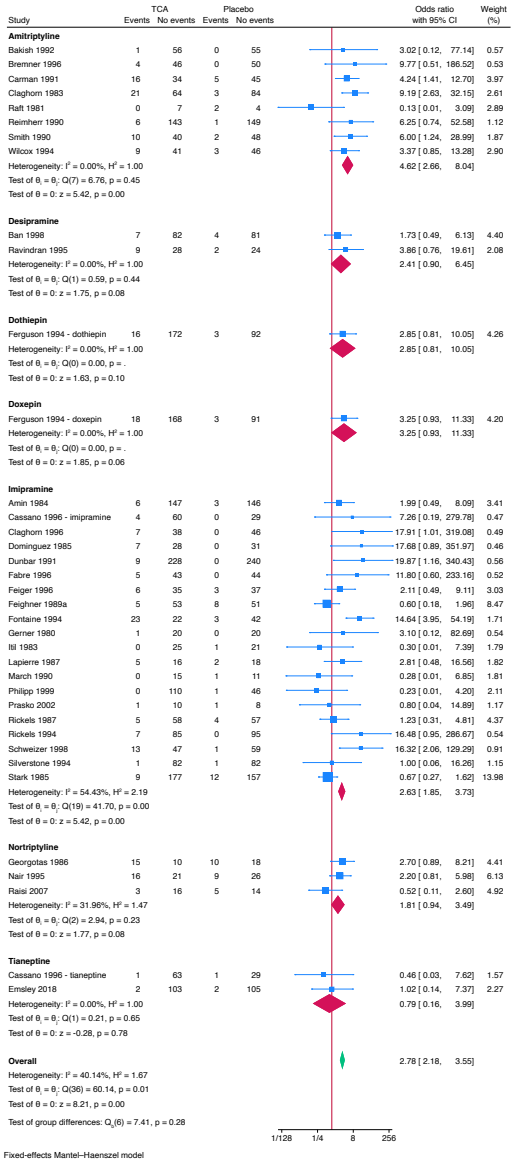

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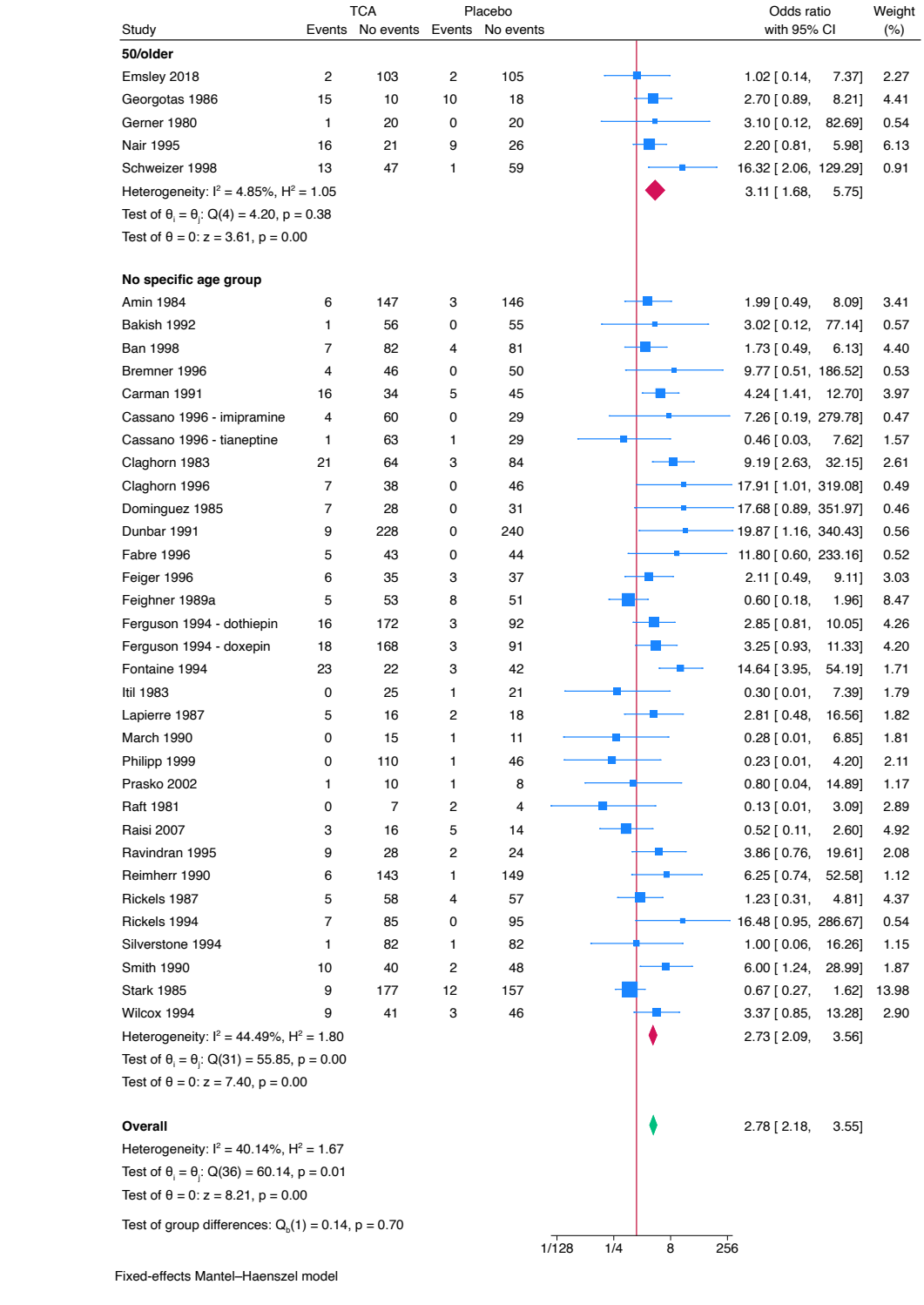

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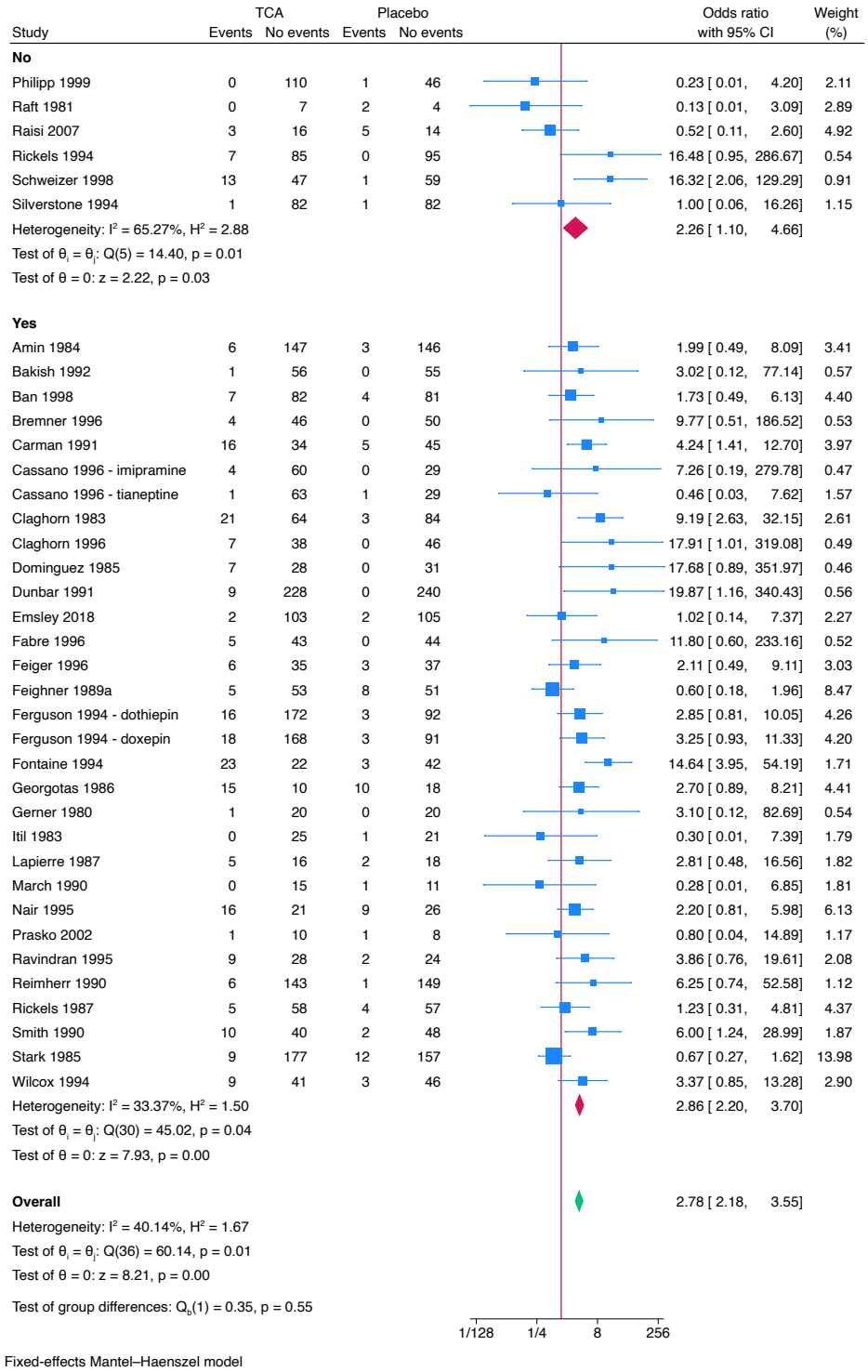

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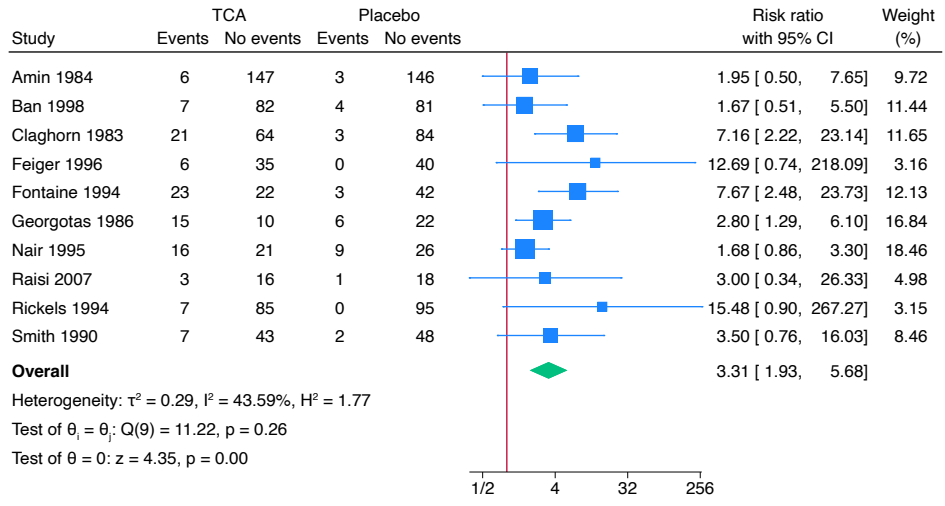

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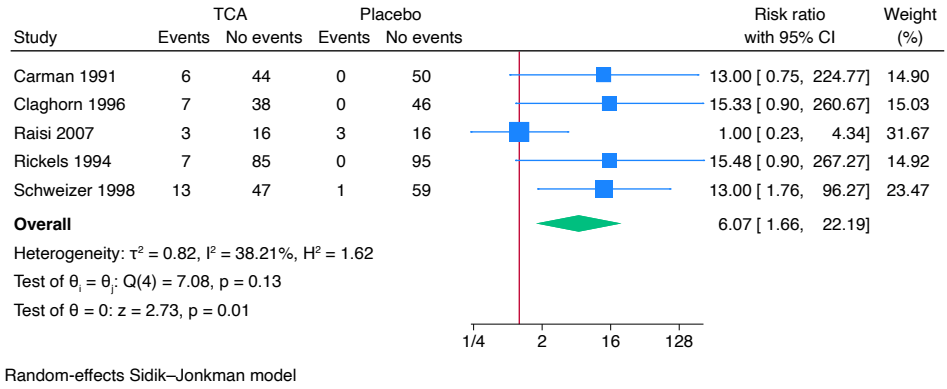

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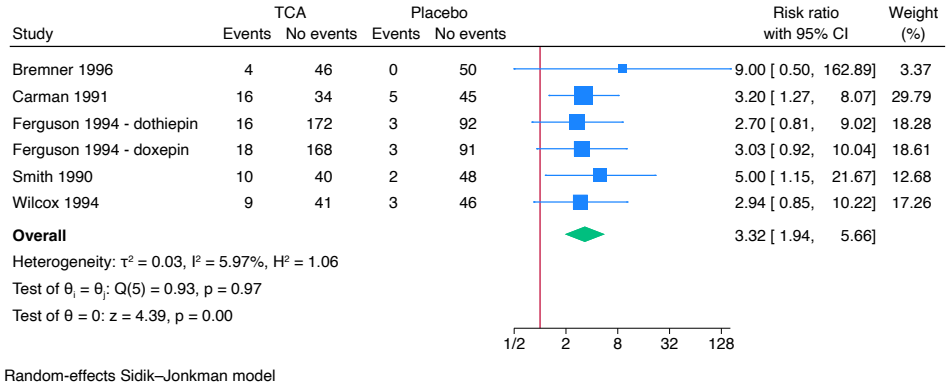

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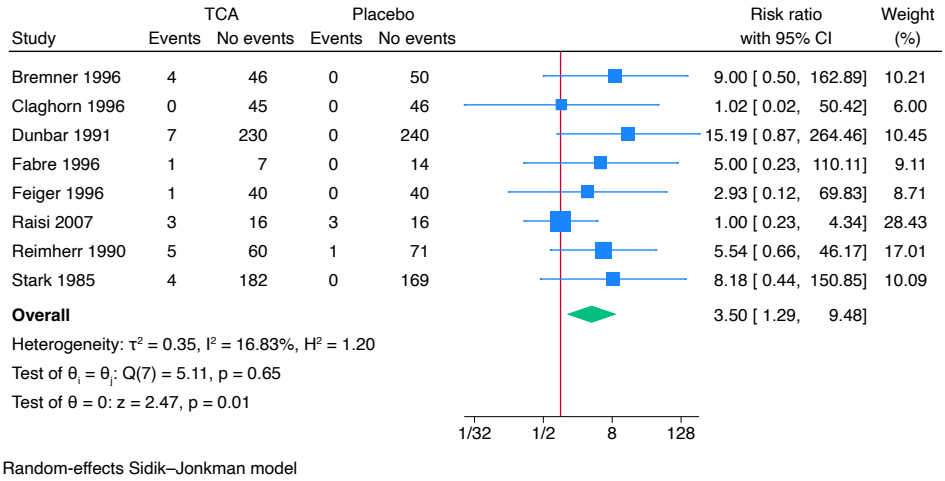

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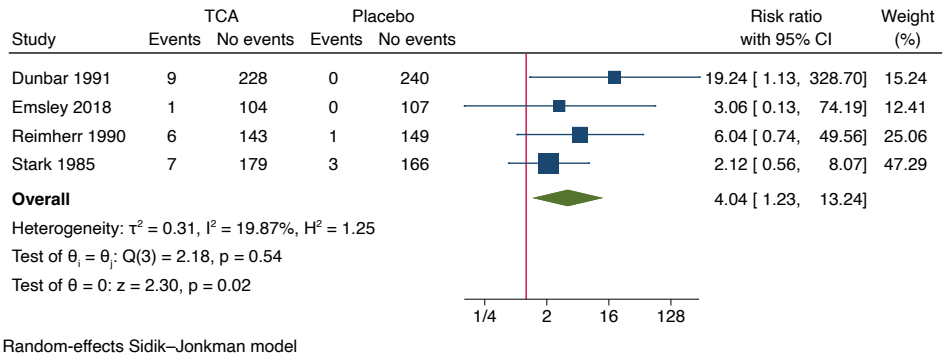

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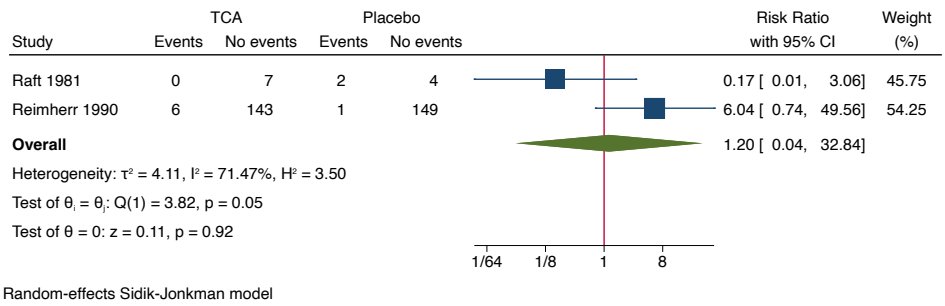

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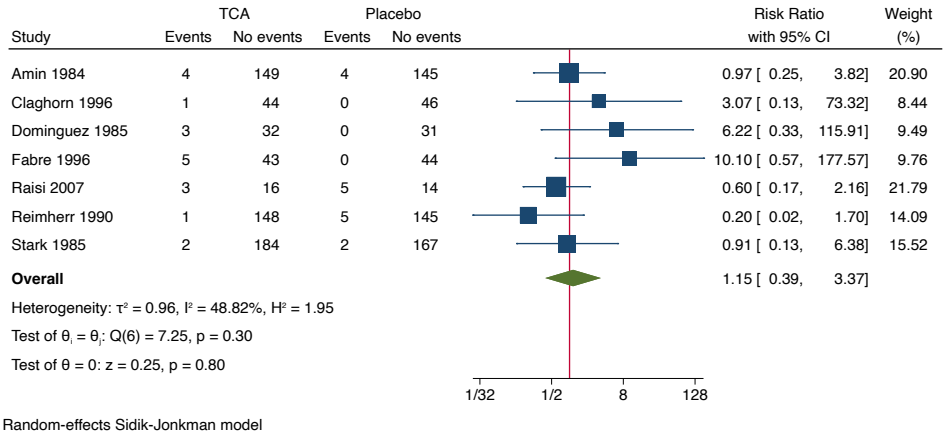

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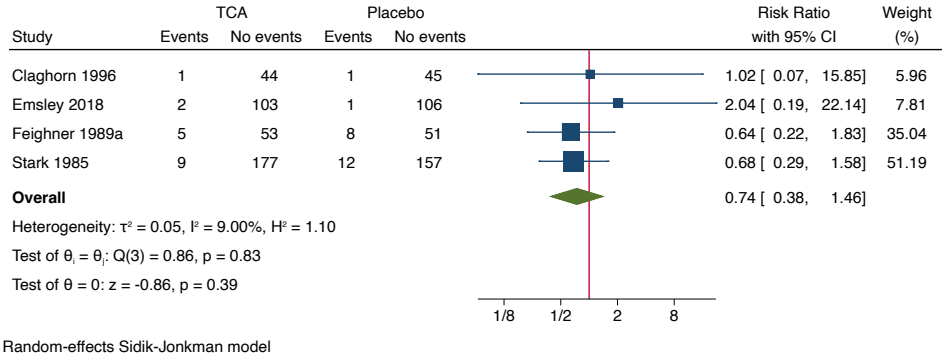

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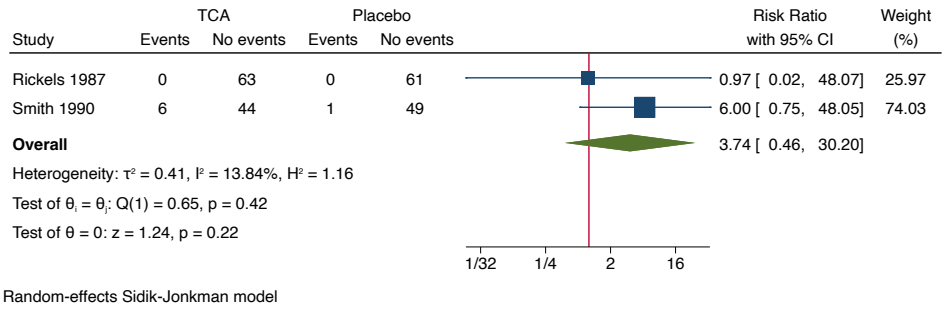

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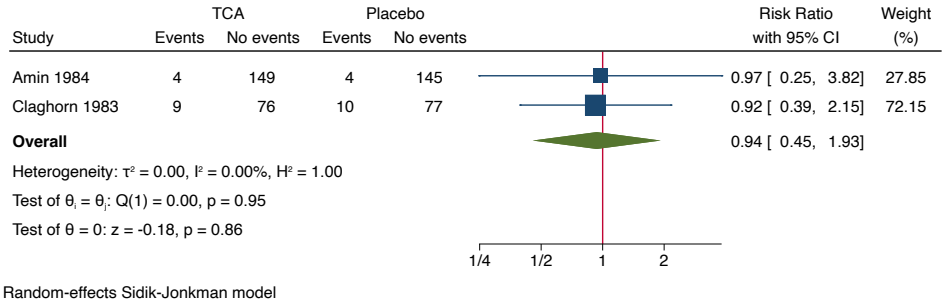

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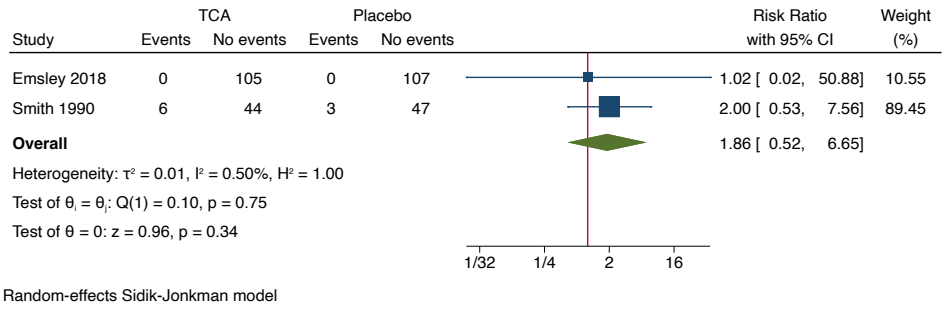

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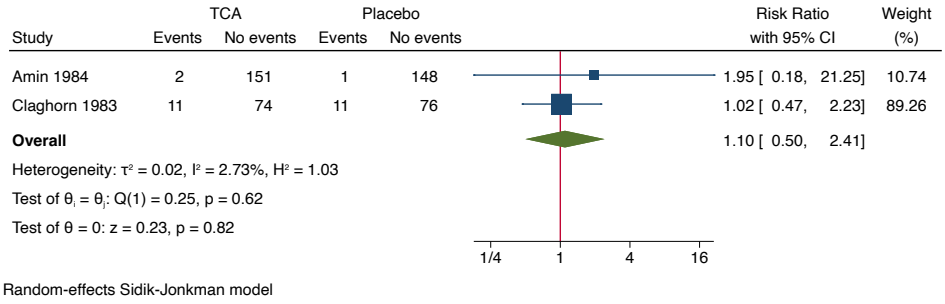

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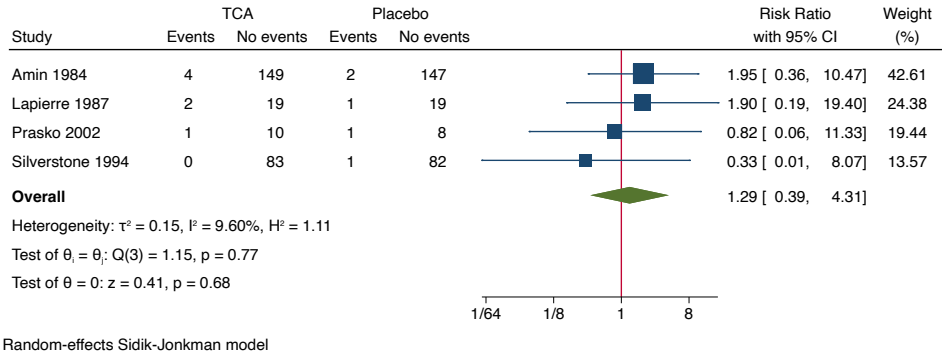

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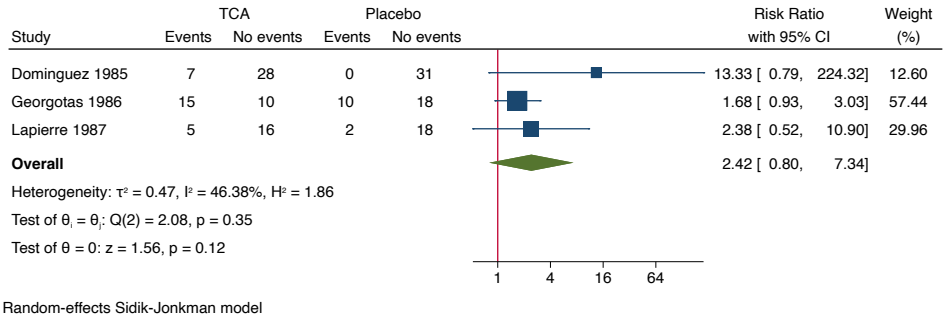

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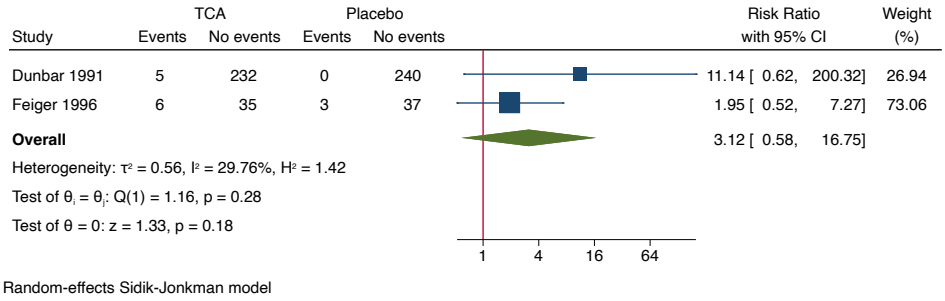

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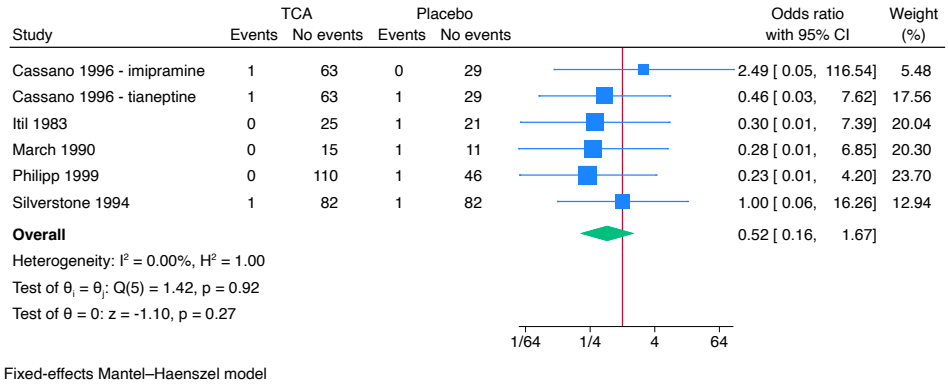

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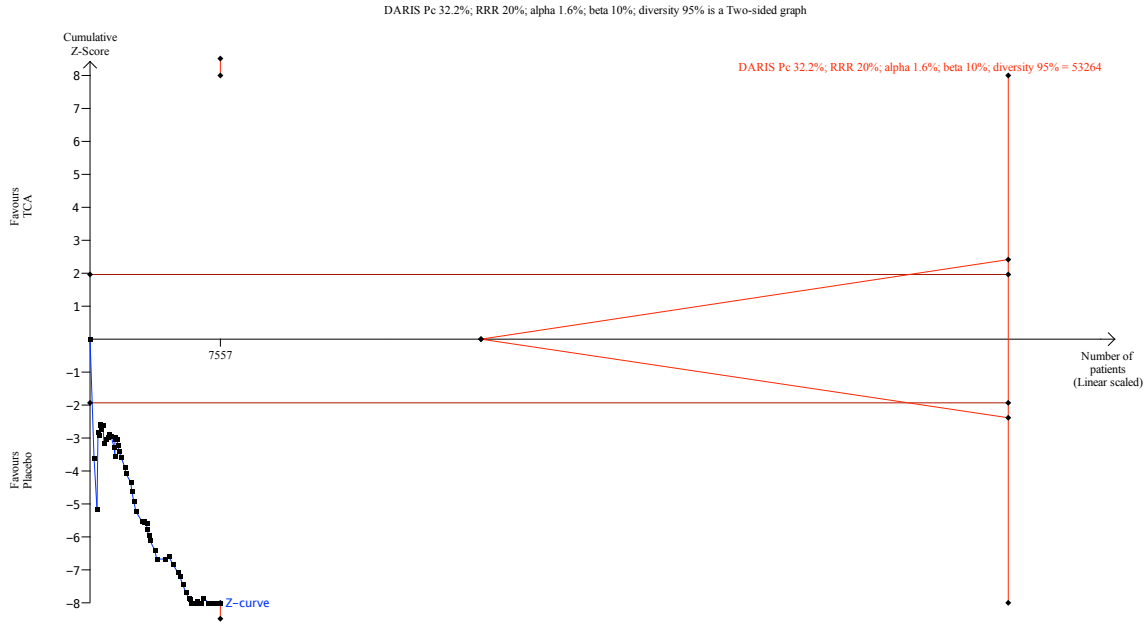

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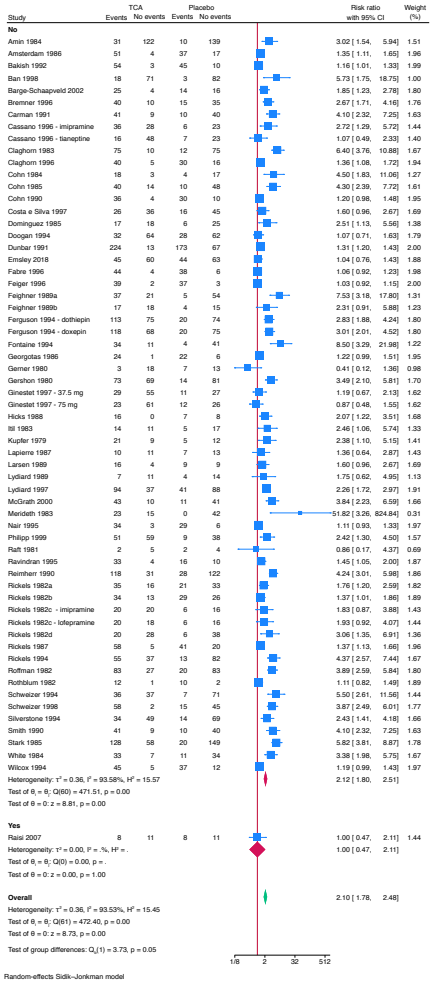

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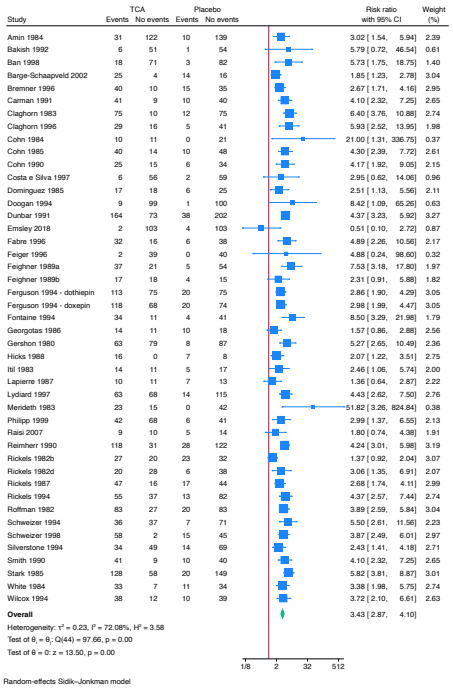

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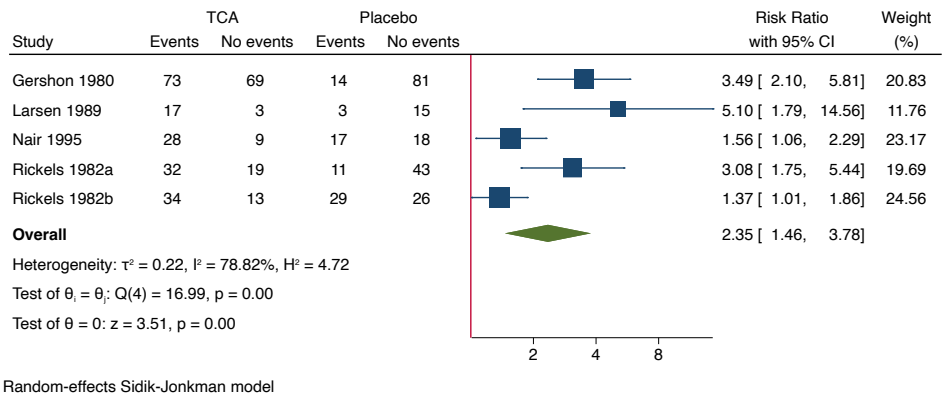

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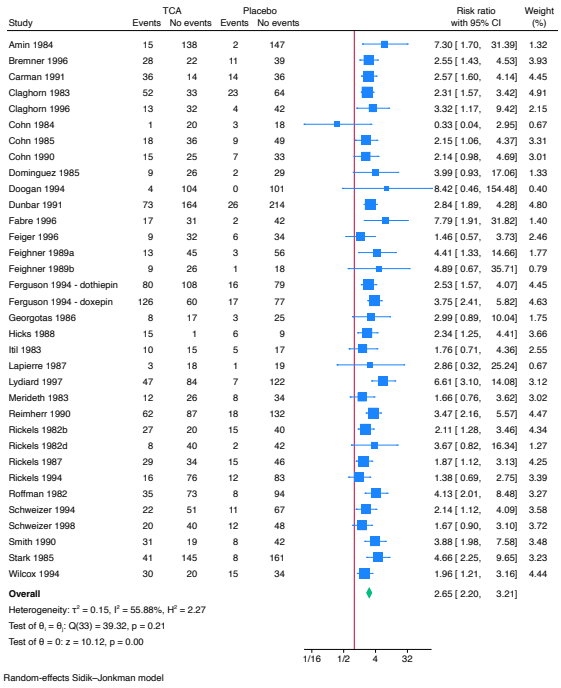

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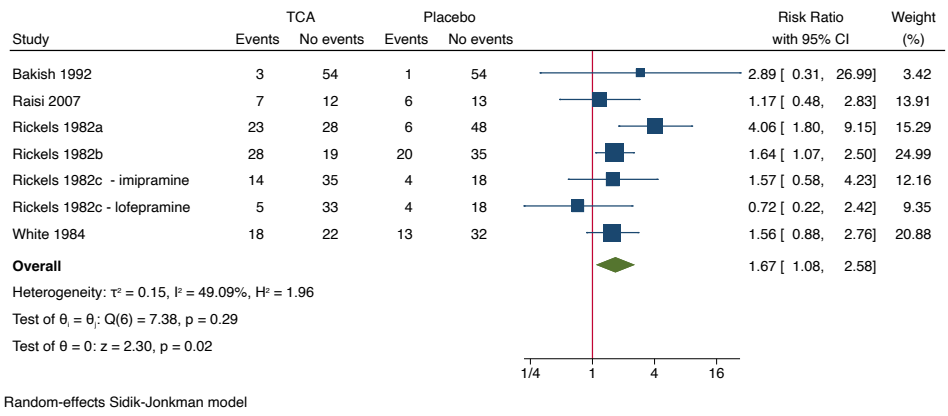

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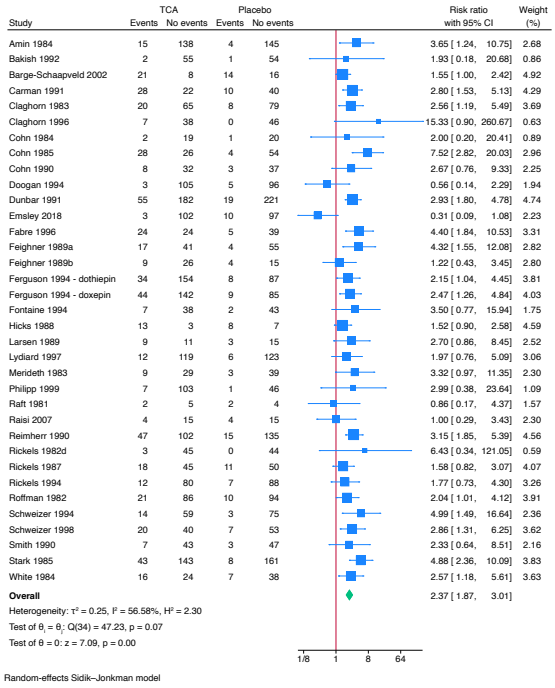

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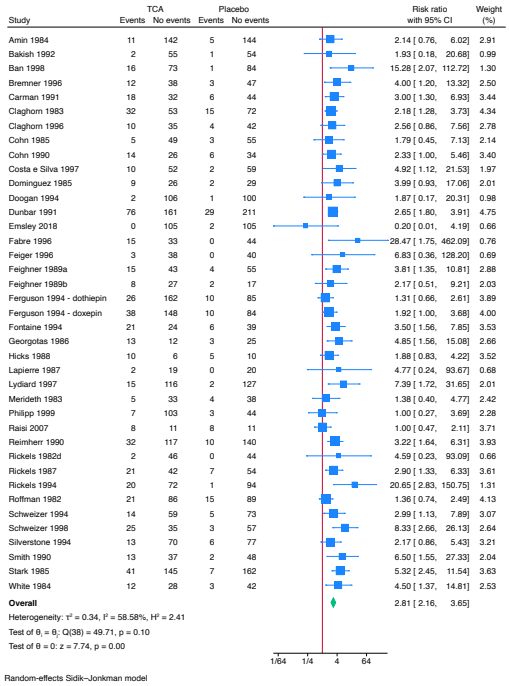

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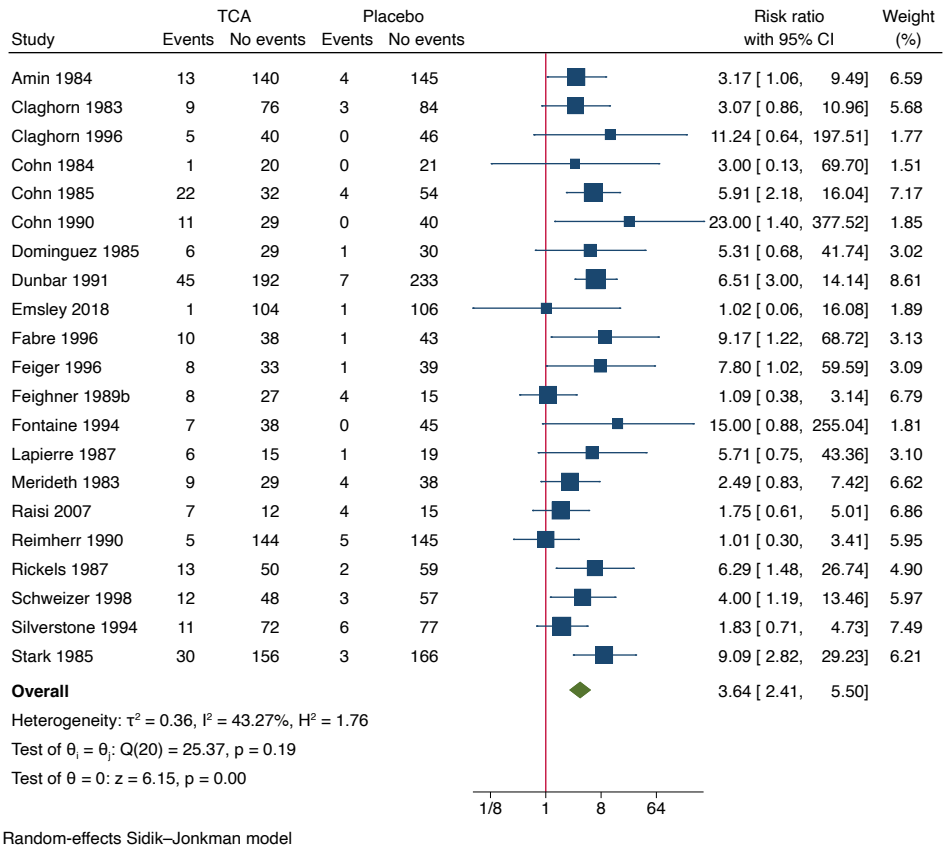

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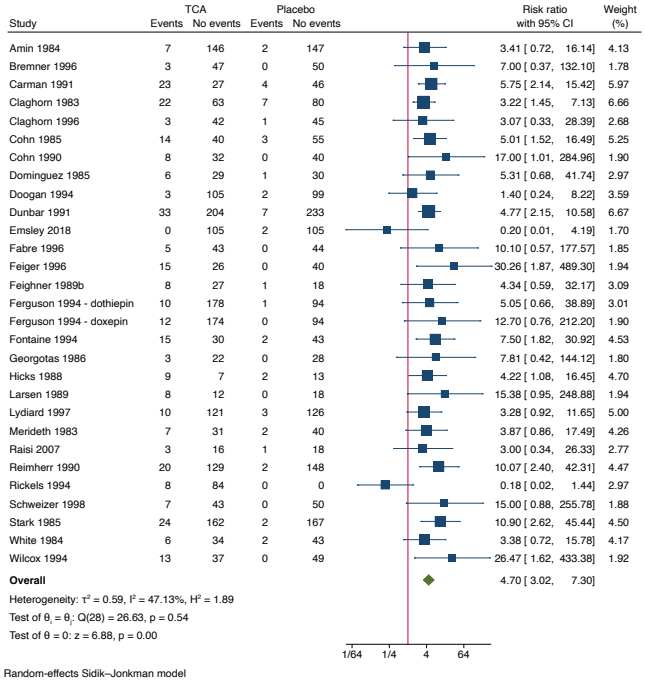
Graph 22/05/2023, 12.59



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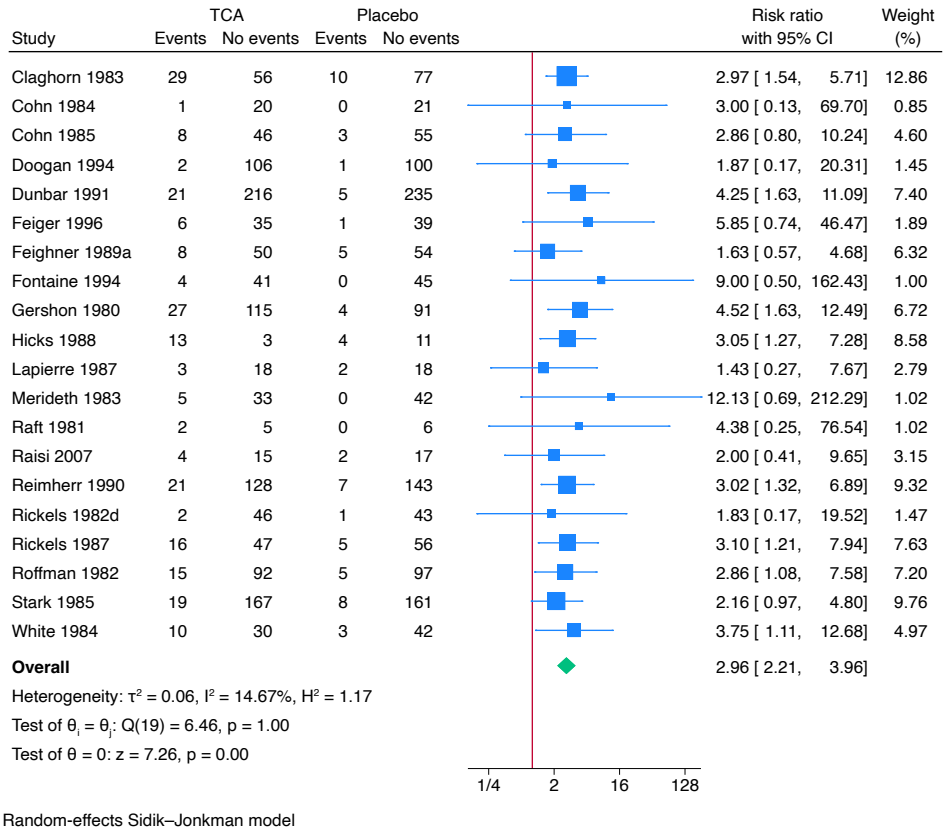

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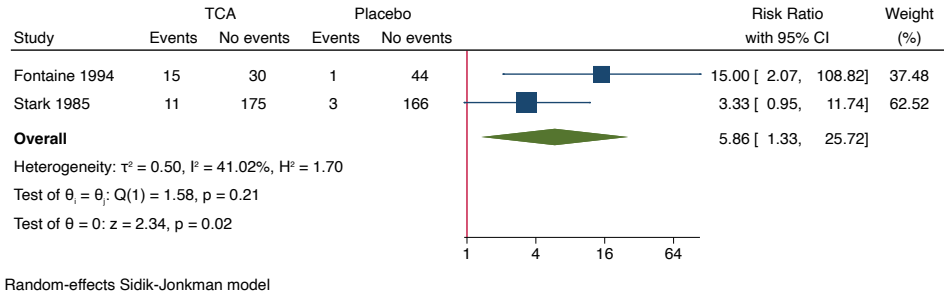

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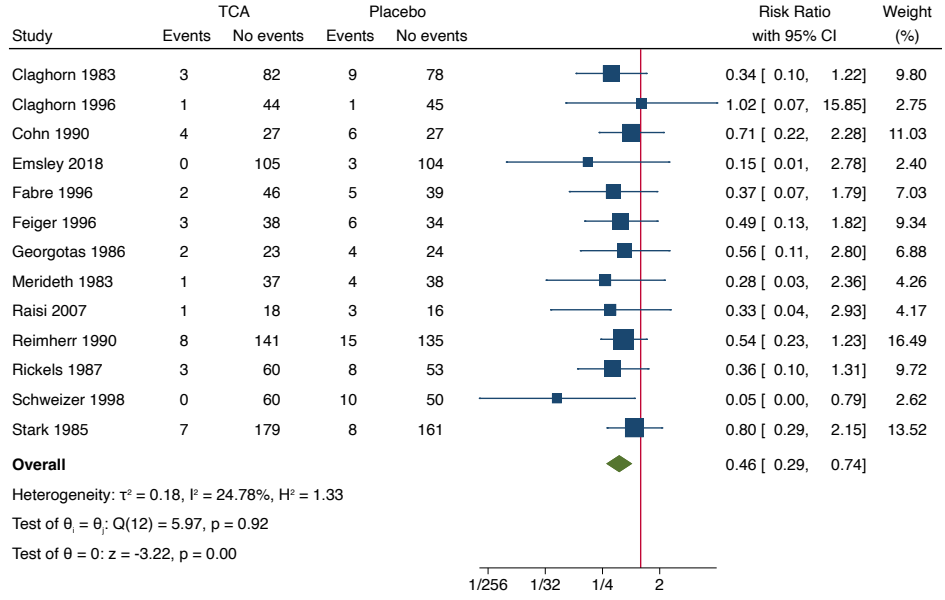

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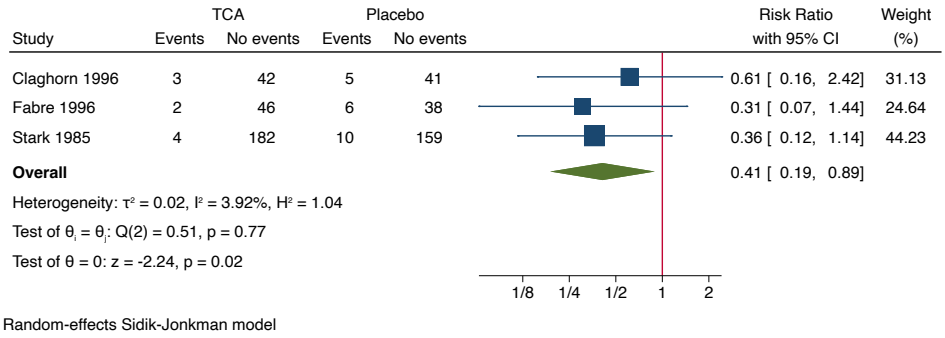

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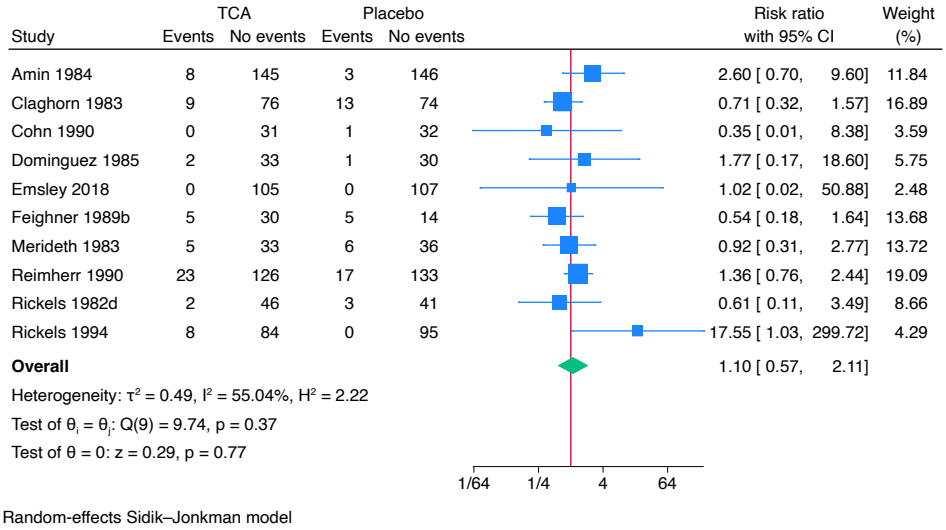

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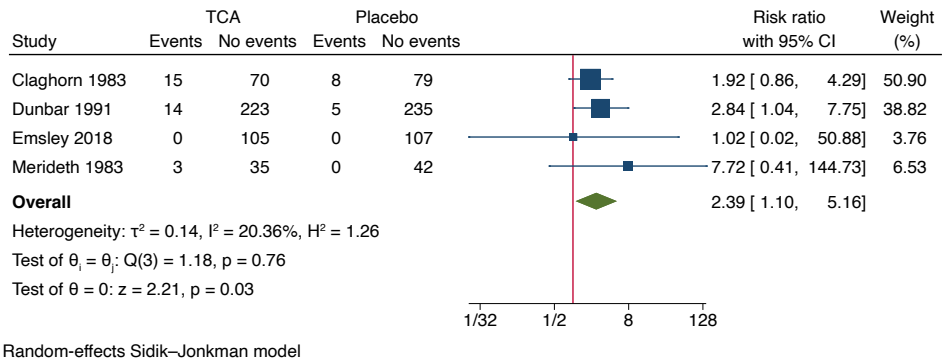

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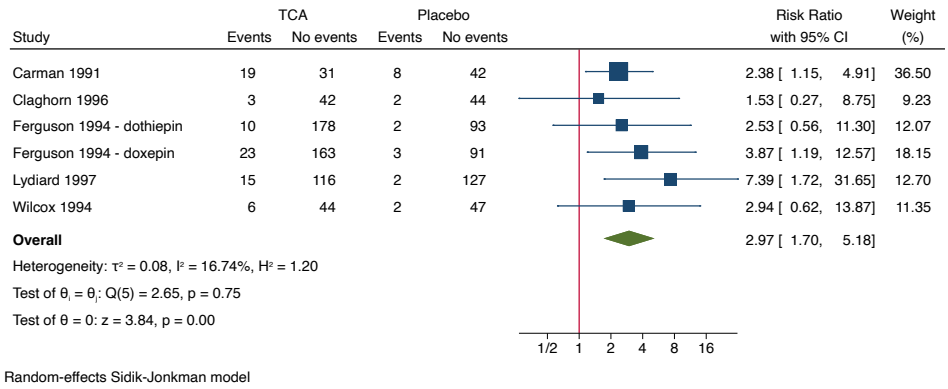

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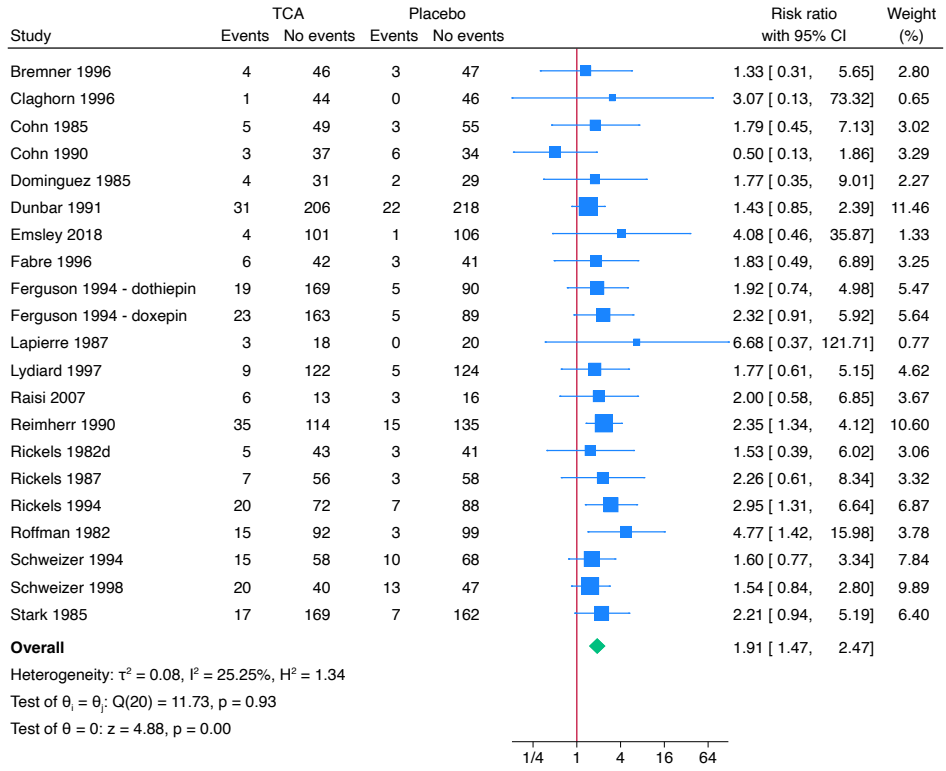

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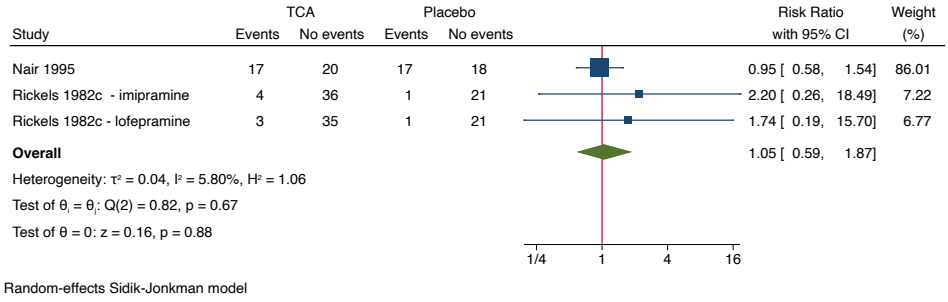

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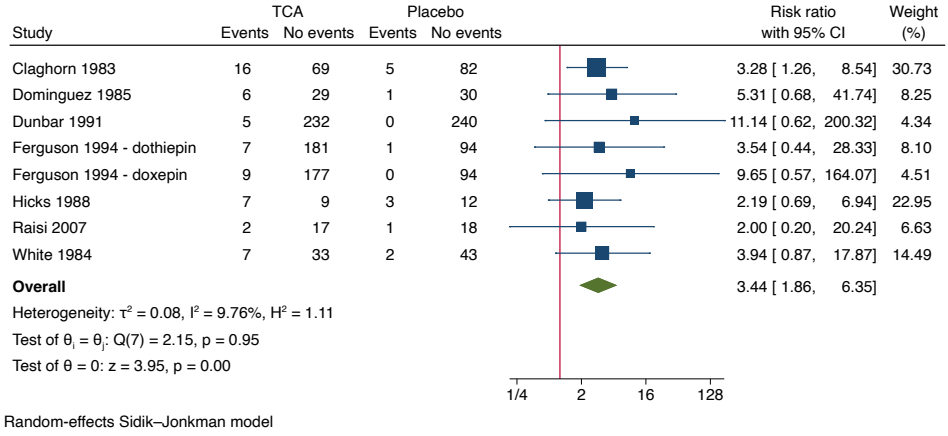

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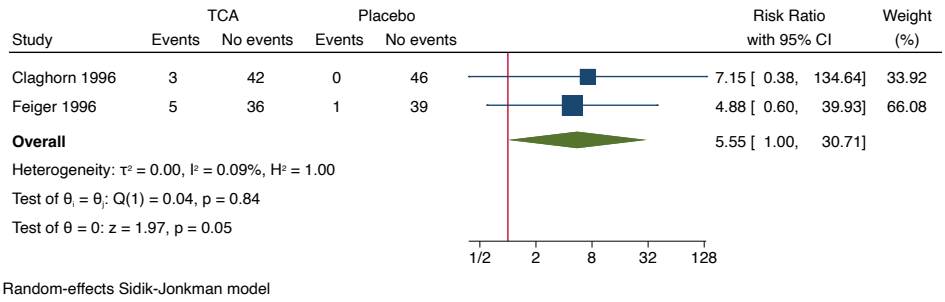

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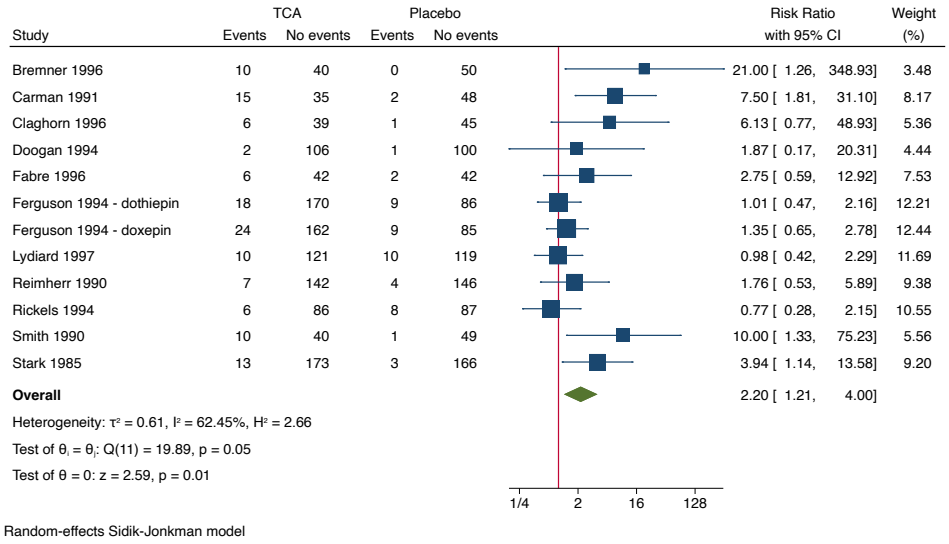
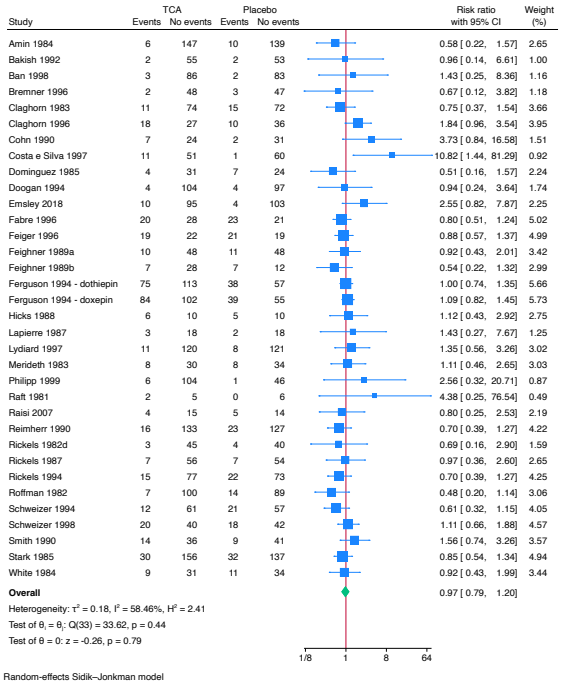
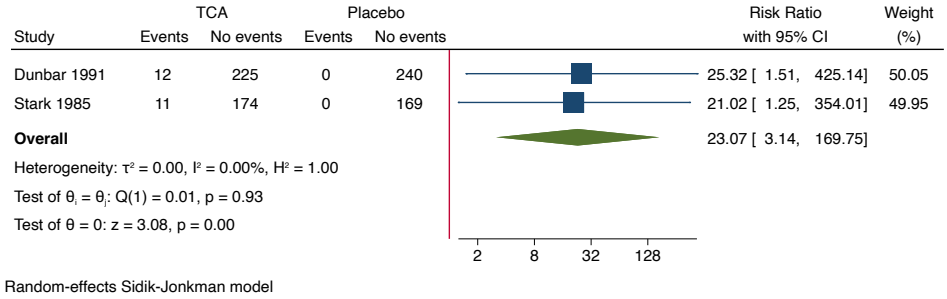


Supplementary figure S52: Meta-analysis of tricyclic antidepressants versus placebo on headache.

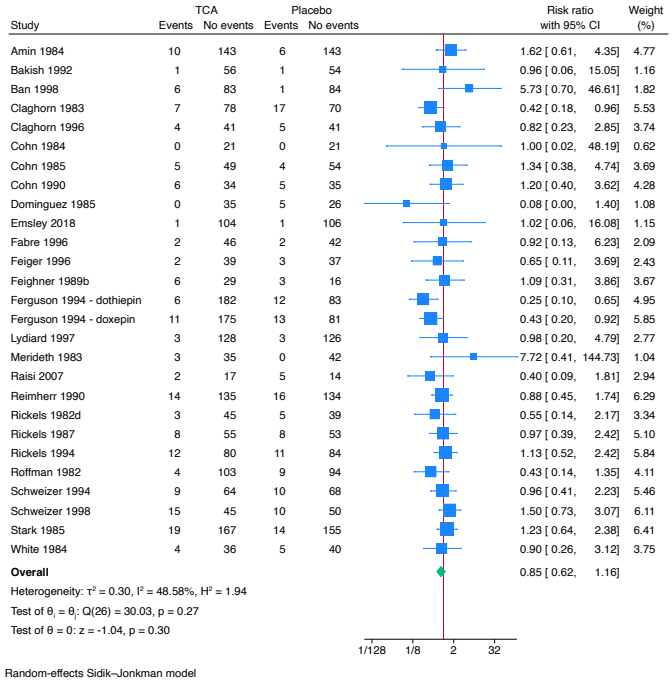
Graph 11/08/2023, 21.33



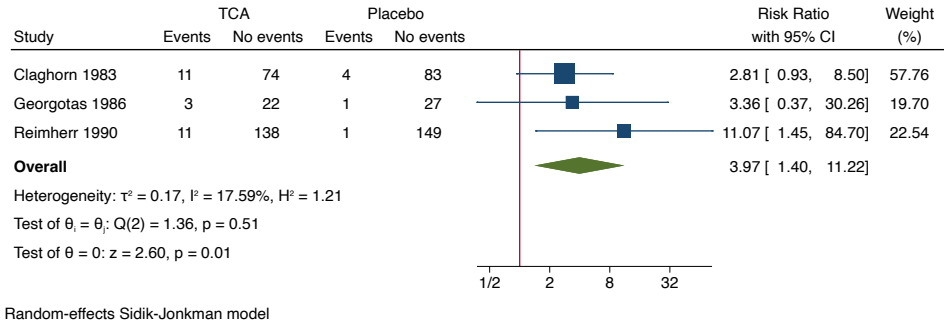
Supplementary figure S53: Meta-analysis of tricyclic antidepressants versus placebo on impaired urination.



Supplementary figure S54: Meta-analysis of tricyclic antidepressants versus placebo on insomnia.

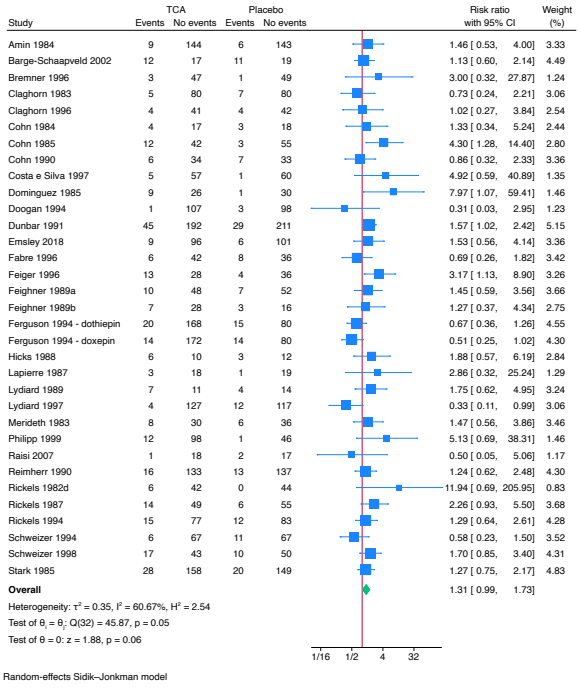


Supplementary figure S55: Meta-analysis of tricyclic antidepressants versus placebo on micturition disorder.

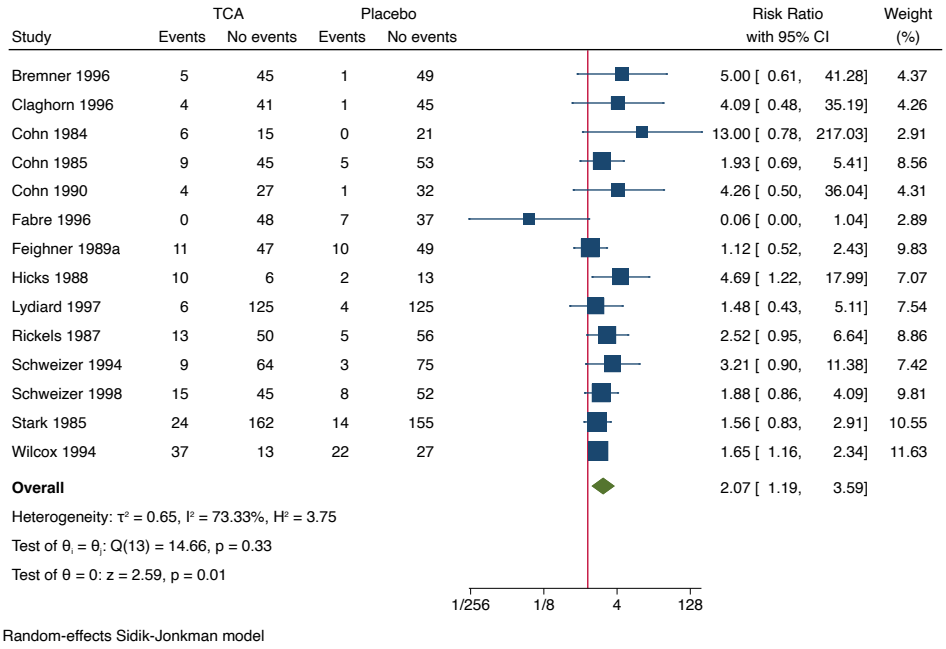


Supplementary figure S56: Meta-analysis of tricyclic antidepressants versus placebo on nausea.

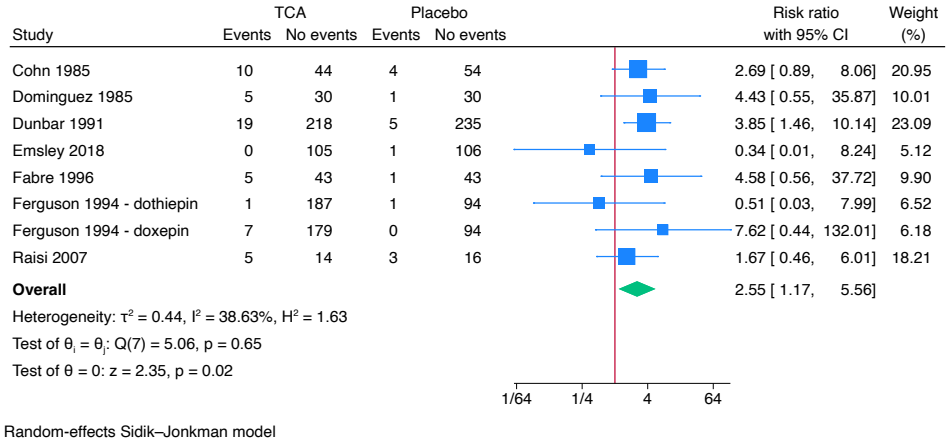
Graph 11/08/2023, 21.26



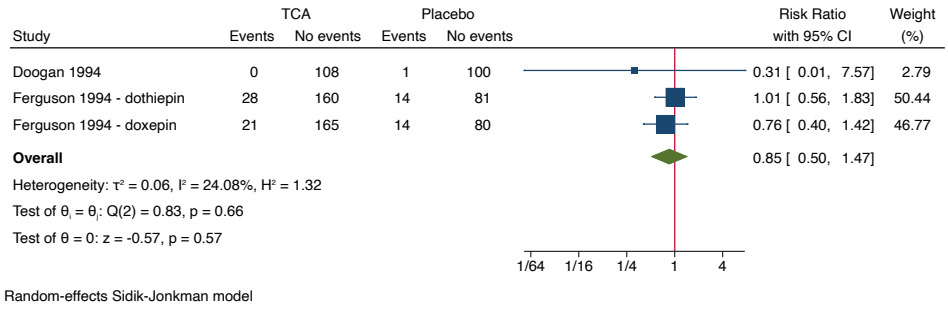
Supplementary figure S57: Meta-analysis of tricyclic antidepressants versus placebo on nervousness.



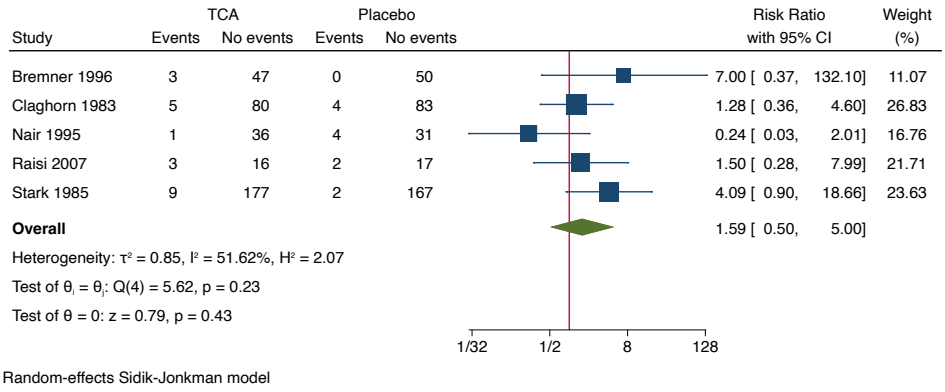
Supplementary figure S58: Meta-analysis of tricyclic antidepressants versus placebo on paraesthesia.



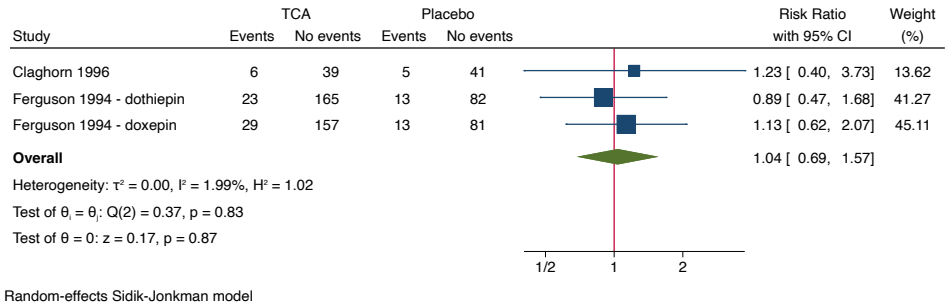
Supplementary figure S59: Meta-analysis of tricyclic antidepressants versus placebo on pharyngitis.



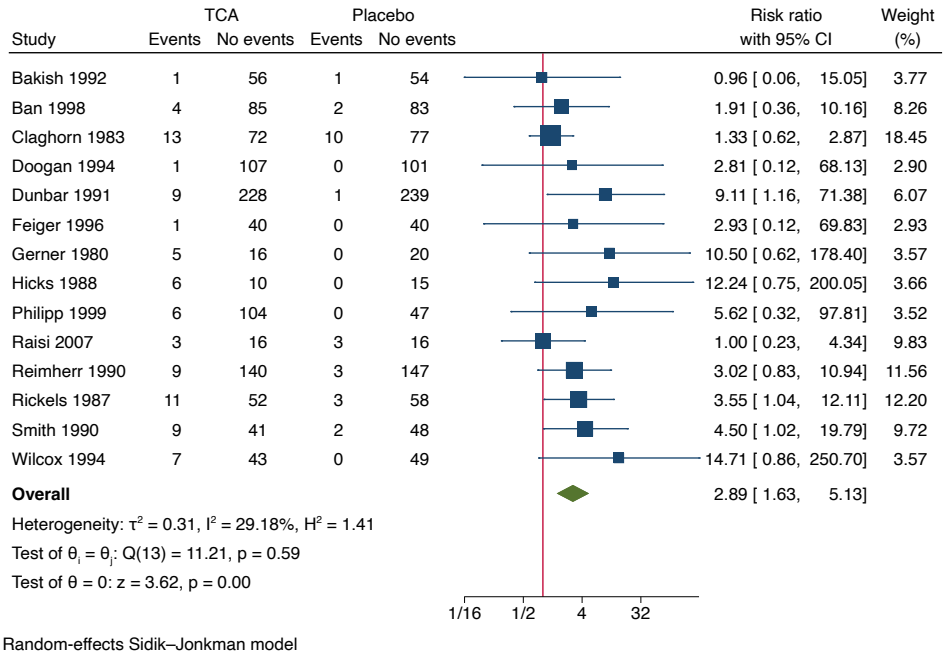
Supplementary figure S60: Meta-analysis of tricyclic antidepressants versus placebo on rash.



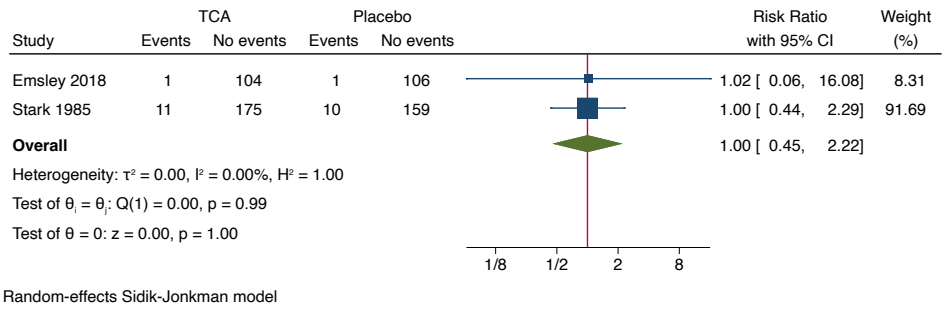
Supplementary figure S61: Meta-analysis of tricyclic antidepressants versus placebo on rhinitis.



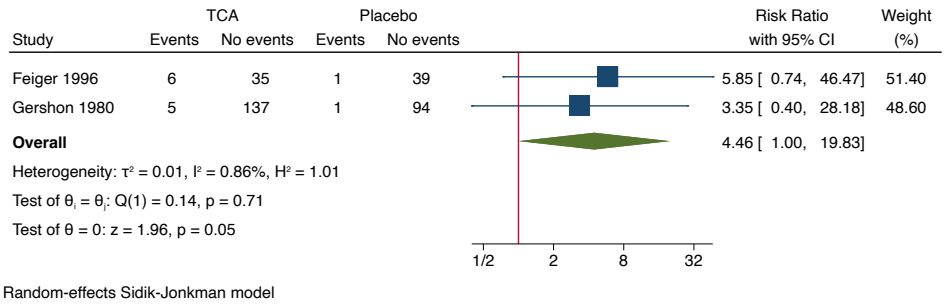
Supplementary figure S62: Meta-analysis of tricyclic antidepressants versus placebo on tachycardia.



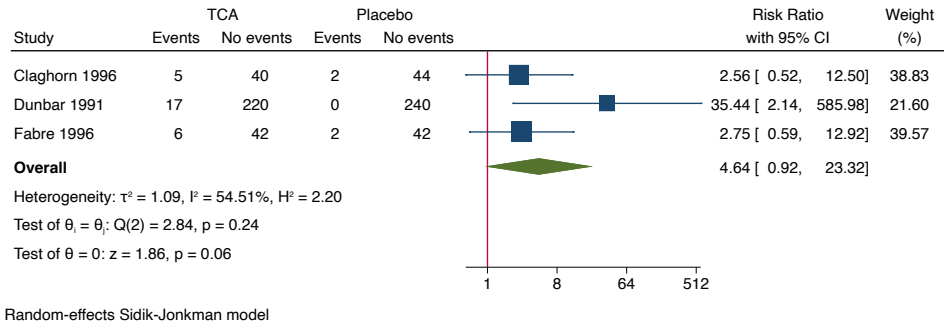
Supplementary figure S63: Meta-analysis of tricyclic antidepressants versus placebo on upper respiratory tract infection.



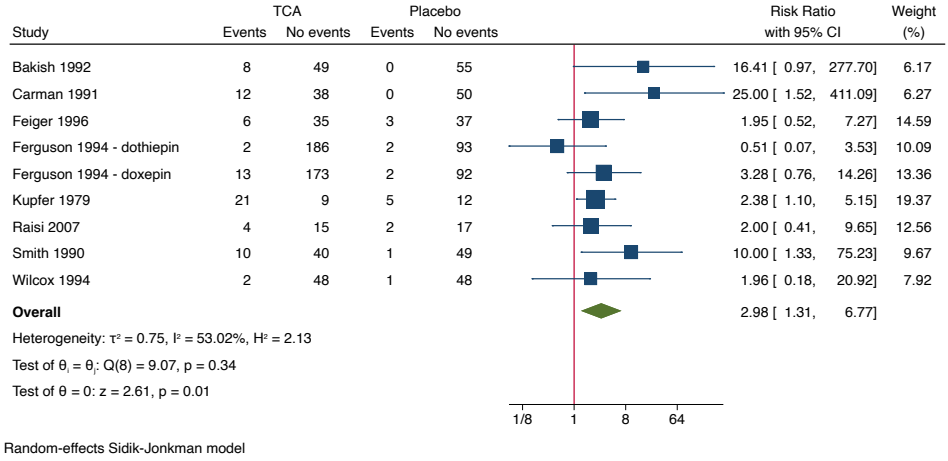
Supplementary figure S64: Meta-analysis of tricyclic antidepressants versus placebo on urinary hesitancy.



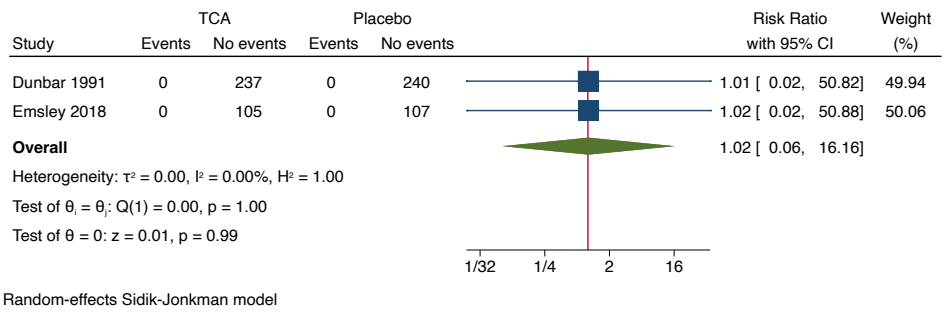
Supplementary figure S65: Meta-analysis of tricyclic antidepressants versus placebo on vasodilatation.



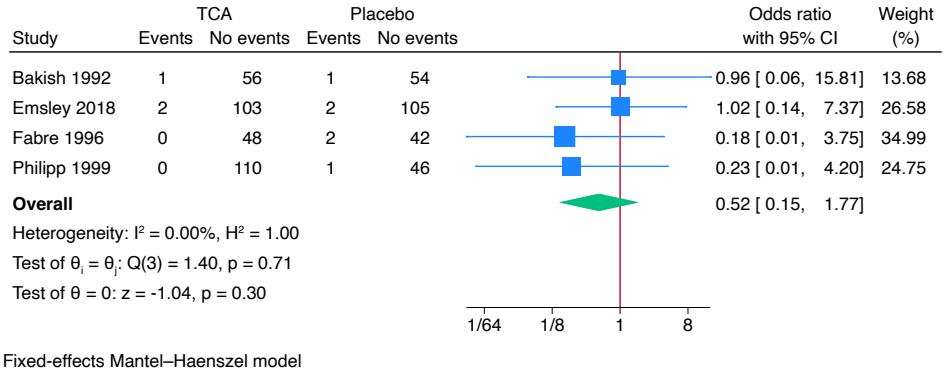
Supplementary figure S66: Meta-analysis of tricyclic antidepressants versus placebo on weight gain.



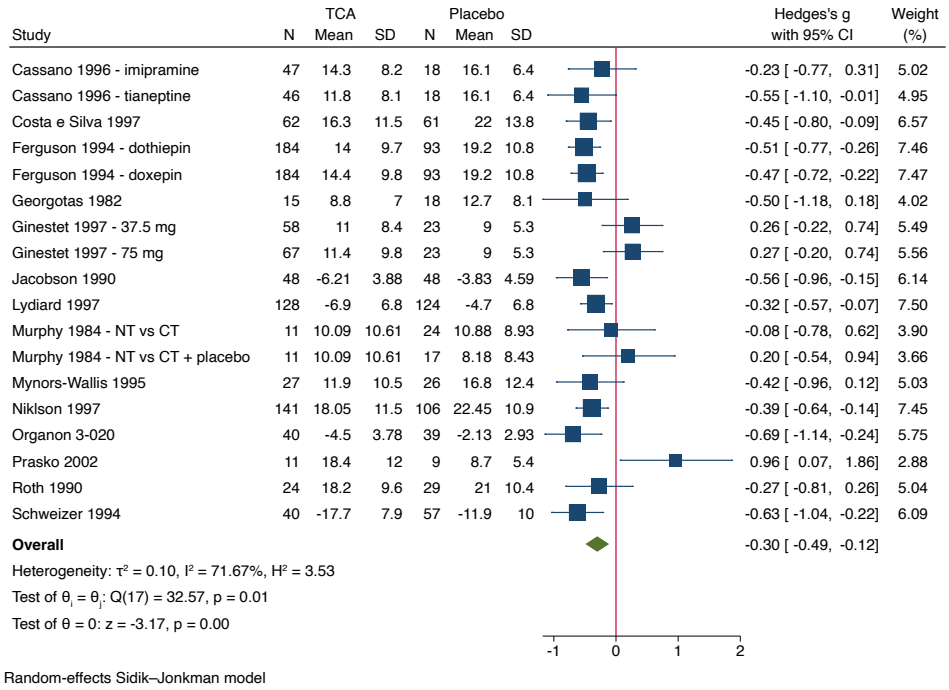
Supplementary figure S67: Meta-analysis of tricyclic antidepressants versus placebo on yawning.



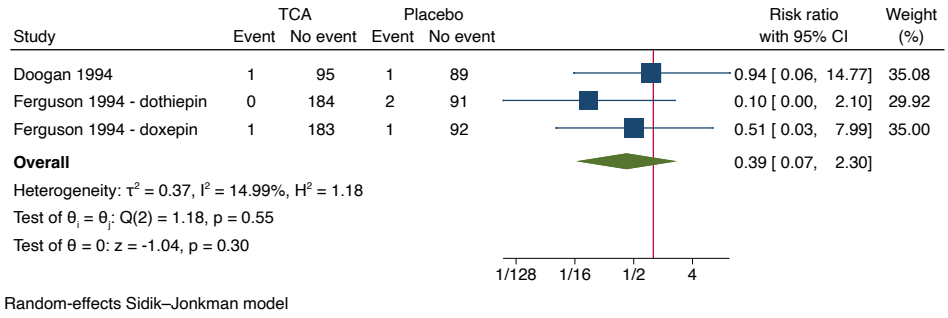
Supplementary figure S68: Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events (as reported by trialists).



Supplementary figure S69: Meta-analysis of tricyclic antidepressants versus placebo on MADRS, BDI, and HDRS-6.

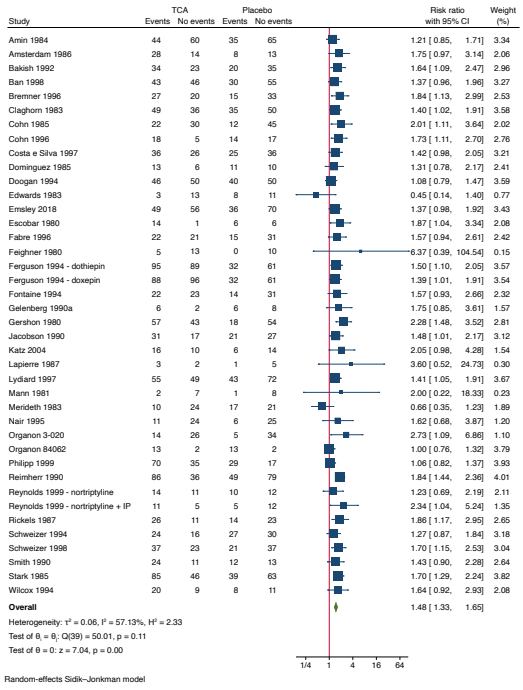


Supplementary figure S70: Meta-analysis of tricyclic antidepressants versus placebo on suicidal ideation.

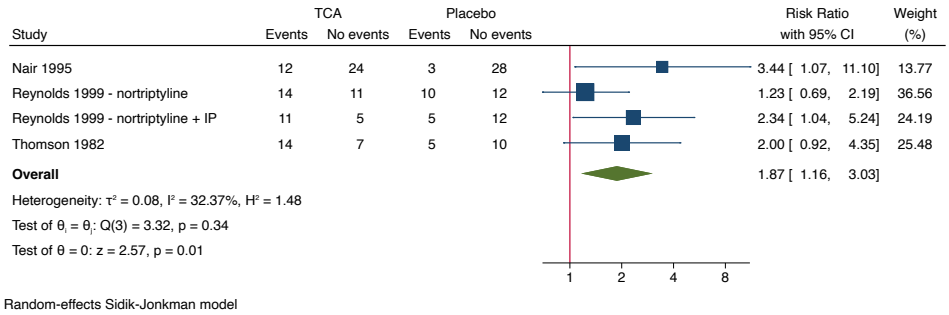


Supplementary figure S71: Meta-analysis of tricyclic antidepressants versus placebo on response.

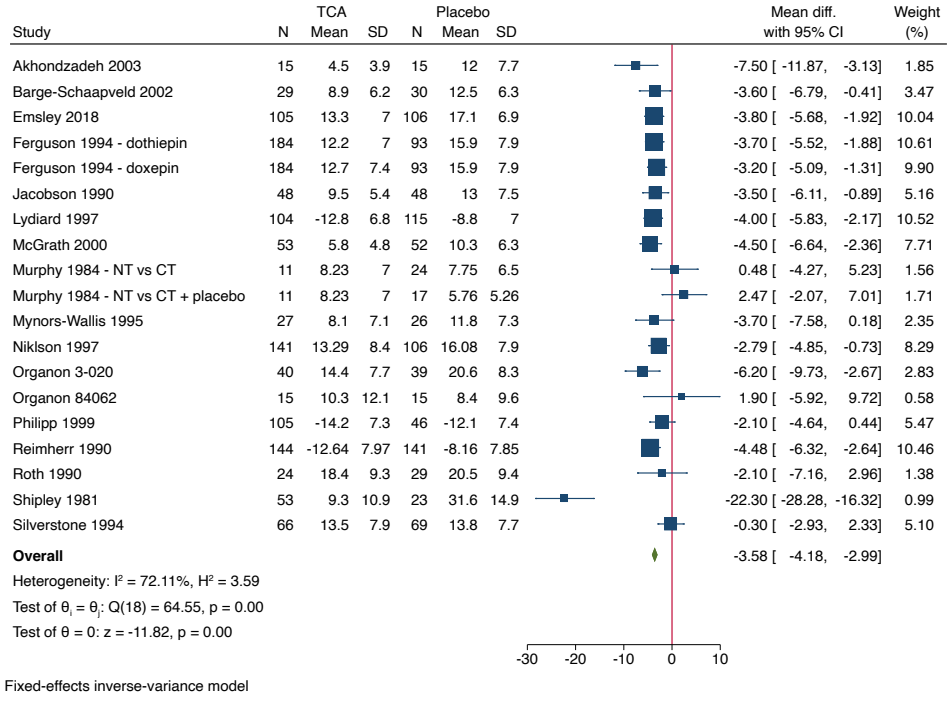
Graph 22/05/2023, 11.41



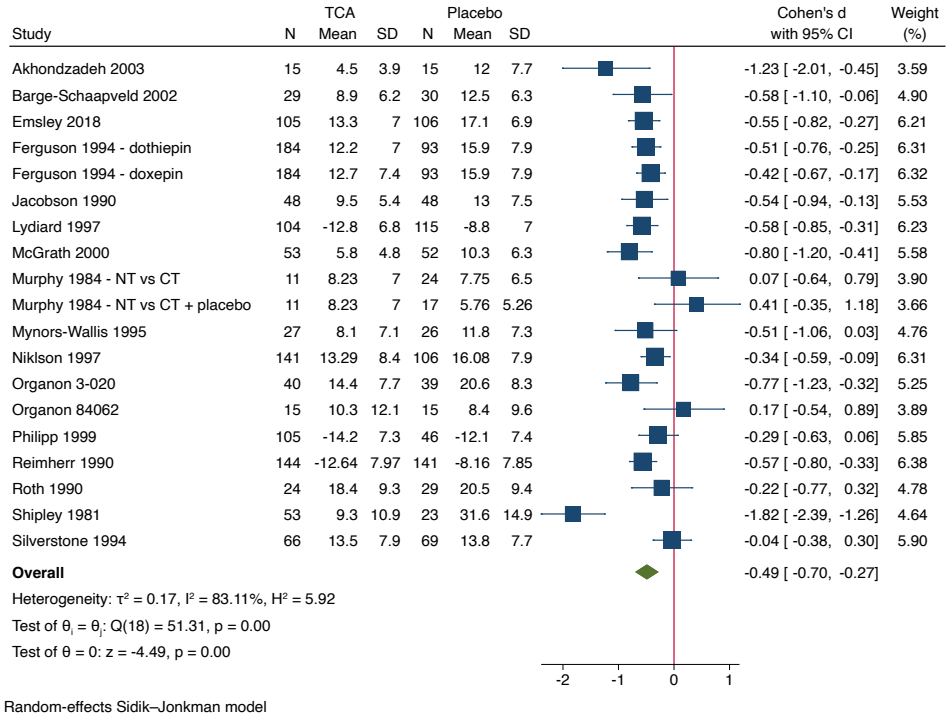
Supplementary figure S72: Meta-analysis of tricyclic antidepressants versus placebo on remission.



Supplementary figure S73: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (sensitivity analysis).

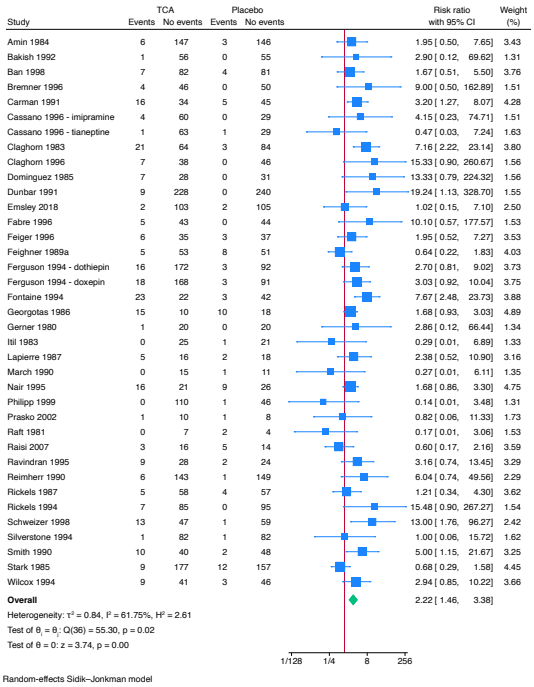


Supplementary figure S74: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (standardised mean difference).

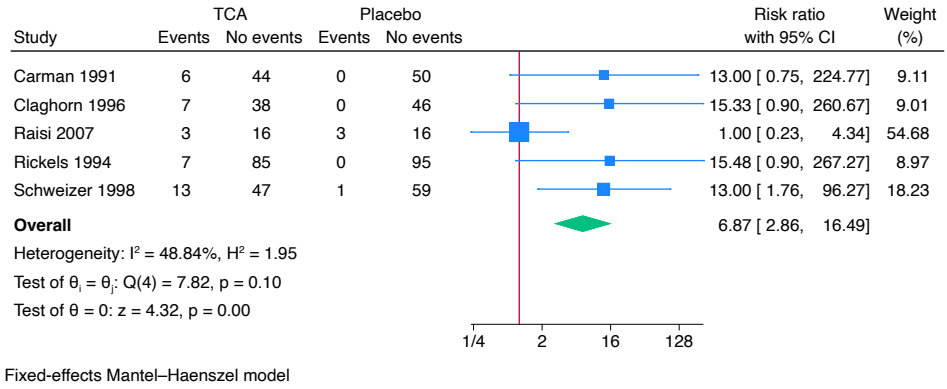


Supplementary figure S75: Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events (sensitivity analysis).

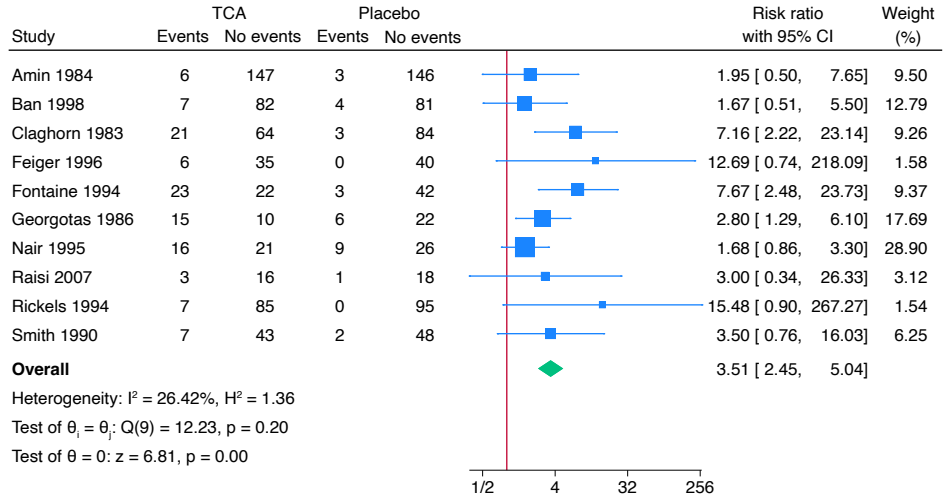
Graph 16/08/2023, 08.56



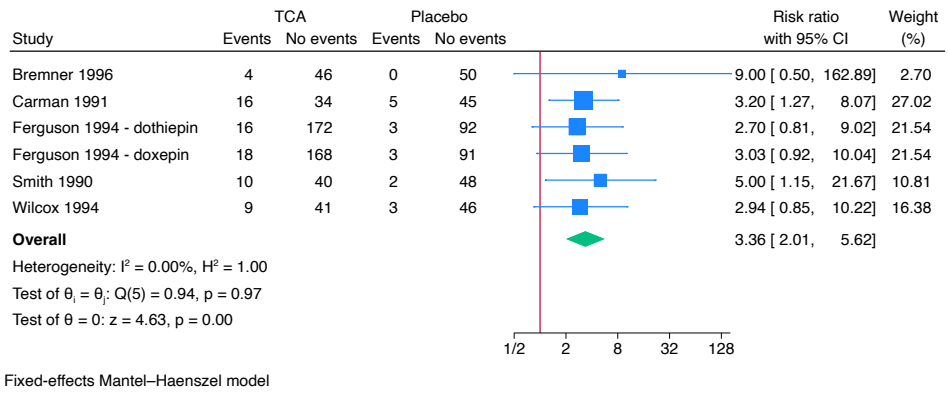
Supplementary figure S76: Meta-analysis of tricyclic antidepressants versus placebo on urinary retention (sensitivity analysis).



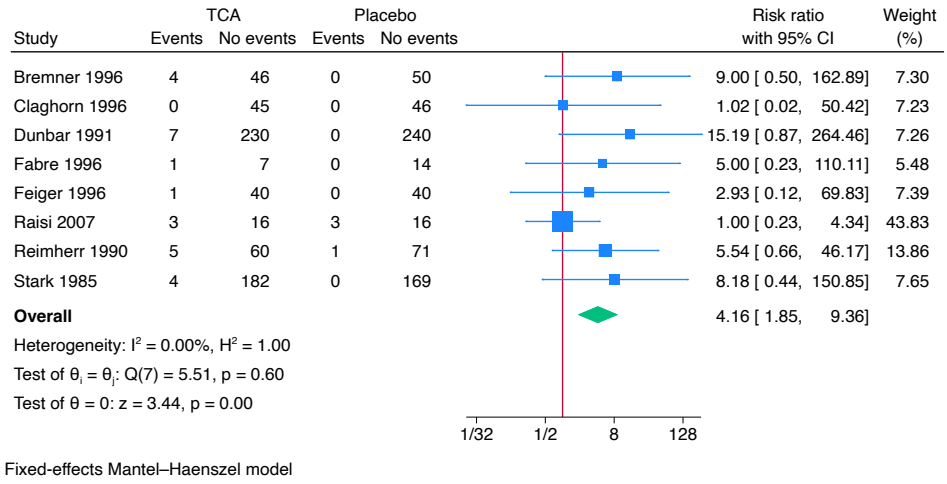
Supplementary figure S77: Meta-analysis of tricyclic antidepressants versus placebo on hypotension (sensitivity analysis).



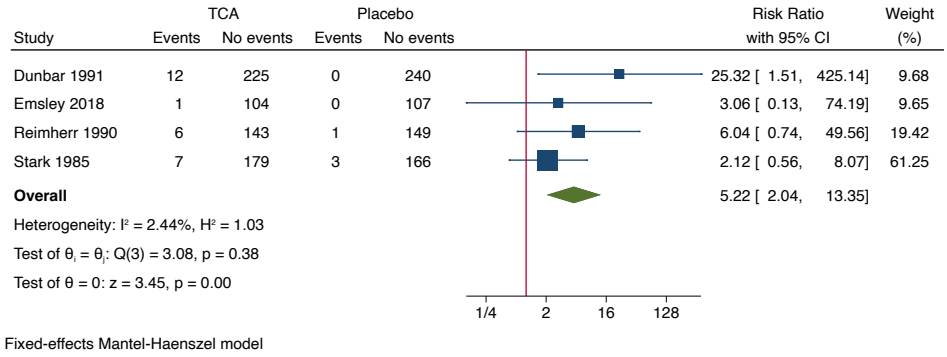
Supplementary figure S78: Meta-analysis of tricyclic antidepressants versus placebo on amblyopia (sensitivity analysis).



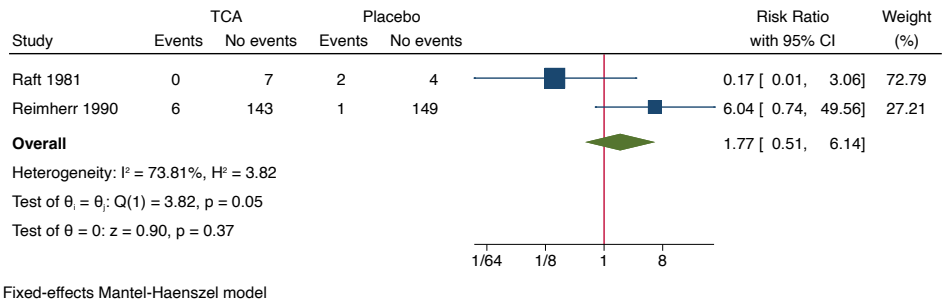
Supplementary figure S79: Meta-analysis of tricyclic antidepressants versus placebo on sexual dysfunction (sensitivity analysis).



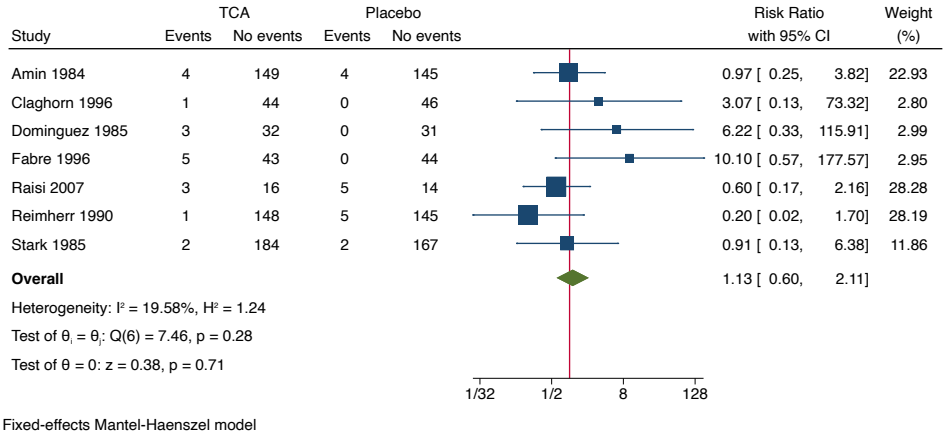
Supplementary figure S80: Meta-analysis of tricyclic antidepressants versus placebo on taste alteration (sensitivity analysis).



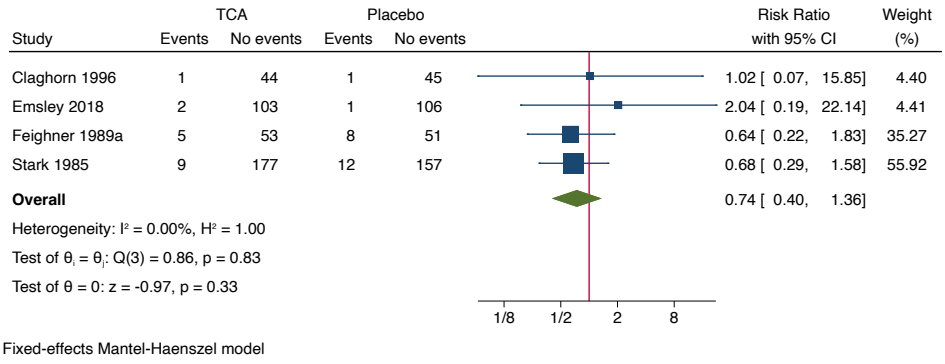
Supplementary figure S81: Meta-analysis of tricyclic antidepressants versus placebo on amnesia (sensitivity analysis).



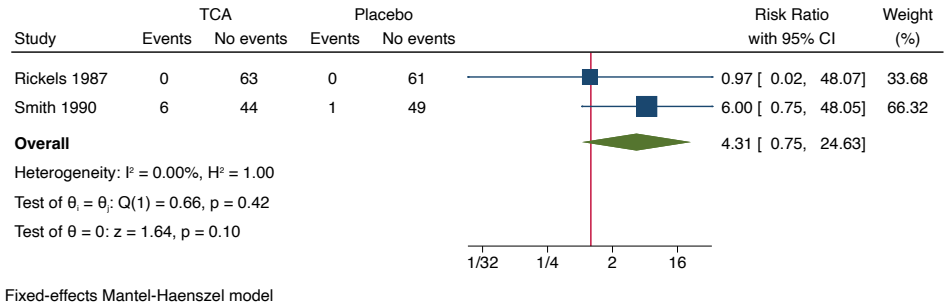
Supplementary figure S82: Meta-analysis of tricyclic antidepressants versus placebo on anorexia (sensitivity analysis).



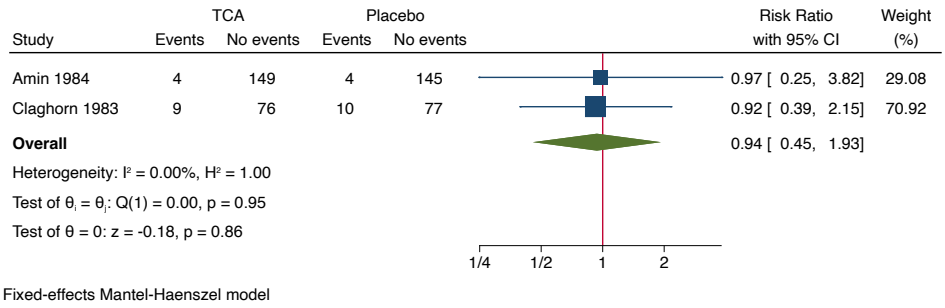
Supplementary figure S83: Meta-analysis of tricyclic antidepressants versus placebo on anxiety (sensitivity analysis).



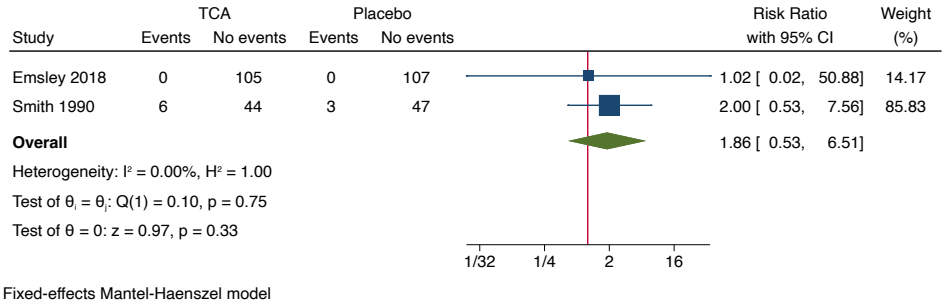
Supplementary figure S84: Meta-analysis of tricyclic antidepressants versus placebo on dyscoordination (sensitivity analysis).



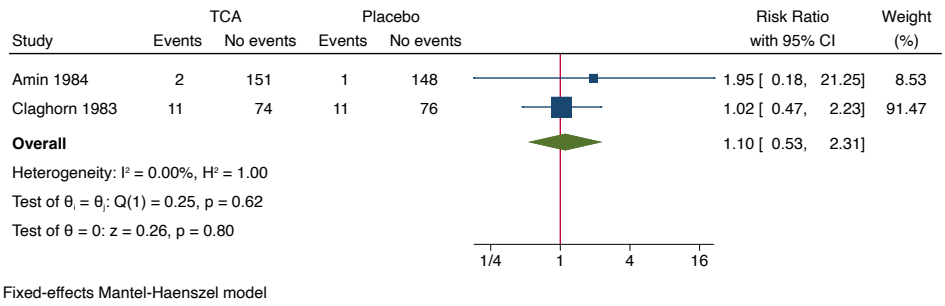
Supplementary figure S85: Meta-analysis of tricyclic antidepressants versus placebo on hyperkinesia (sensitivity analysis).



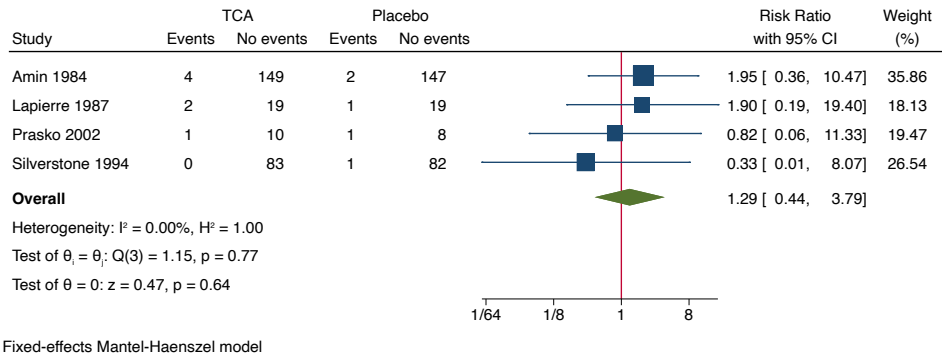
Supplementary figure S86: Meta-analysis of tricyclic antidepressants versus placebo on hypertension (sensitivity analysis).



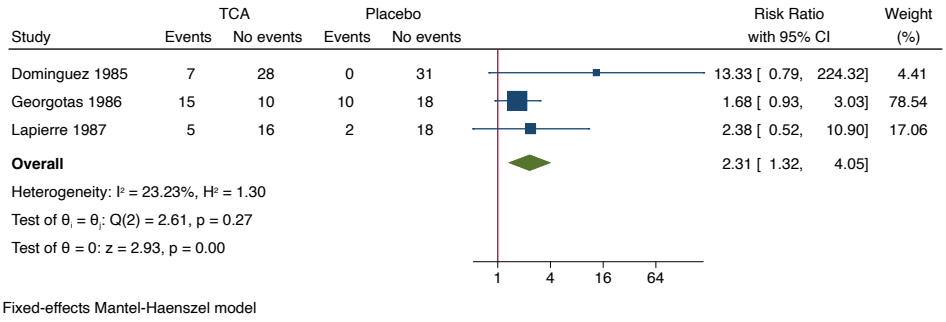
Supplementary figure S87: Meta-analysis of tricyclic antidepressants versus placebo on hypokinesia (sensitivity analysis).



Supplementary figure S88: Meta-analysis of tricyclic antidepressants versus placebo on mania (sensitivity analysis).

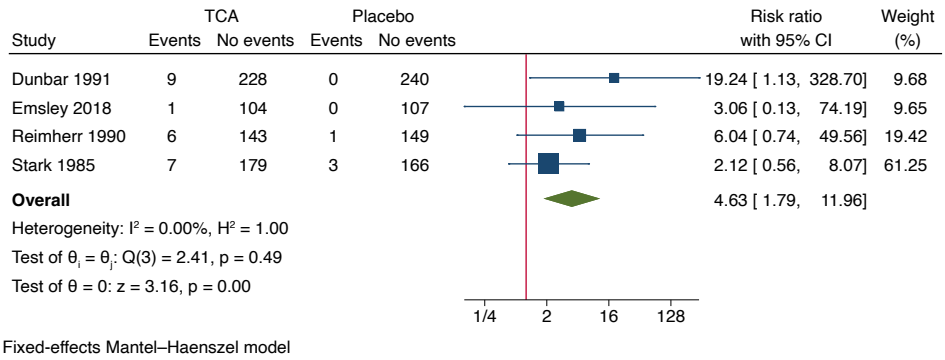


Supplementary figure S89: Meta-analysis of tricyclic antidepressants versus placebo on syncope (sensitivity analysis).

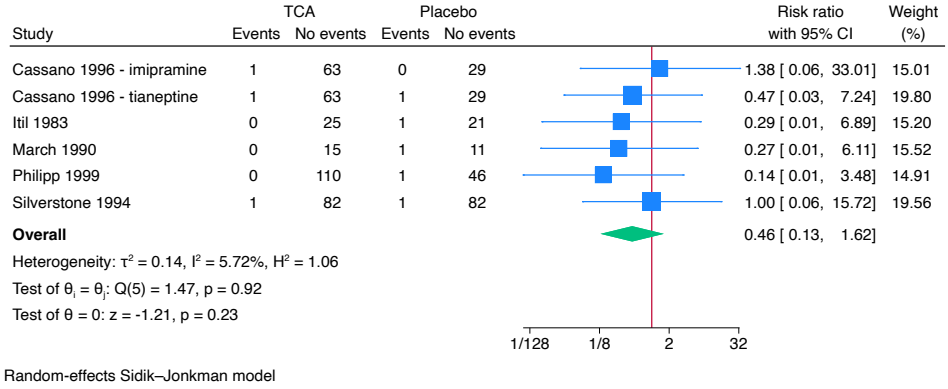


Fixed-effects Mantel-Haenszel model

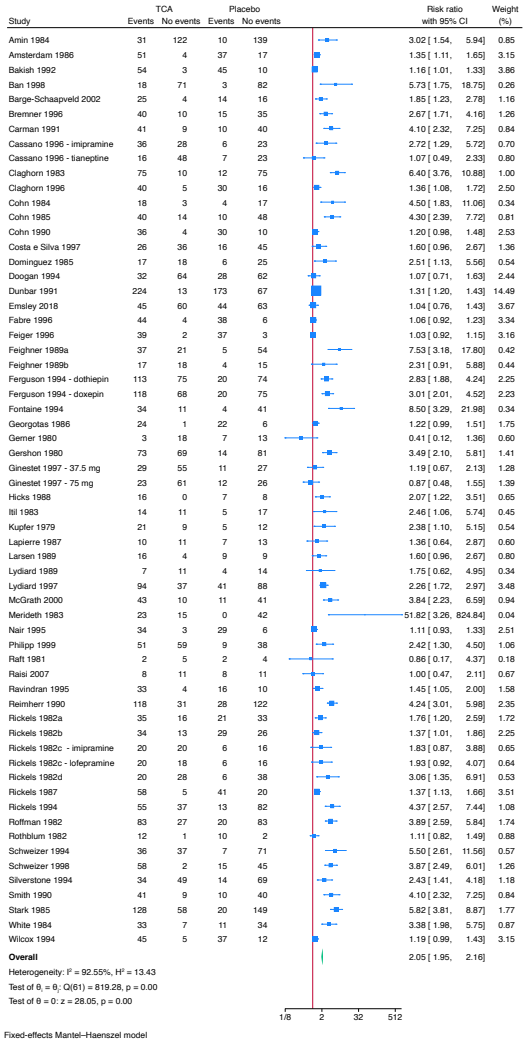
Supplementary figure S90: Meta-analysis of tricyclic antidepressants versus placebo on tinnitus (sensitivity analysis).



Supplementary figure S91: Meta-analysis of tricyclic antidepressants versus placebo on suicides or suicide attempts (sensitivity analysis).

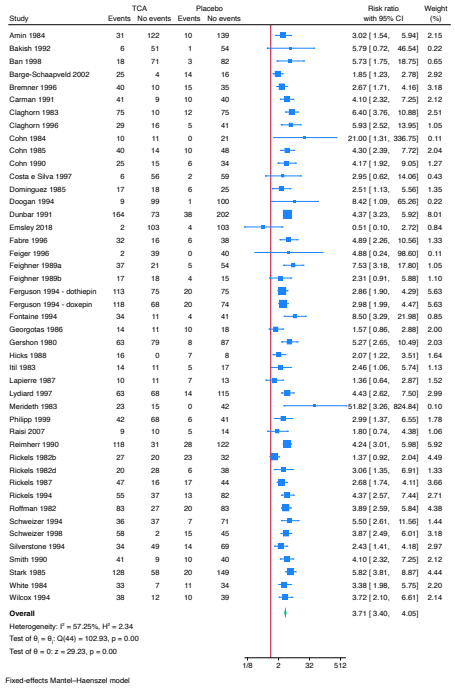


Supplementary figure S92: Meta-analysis of tricyclic antidepressants versus placebo on non-serious adverse events (sensitivity analysis).

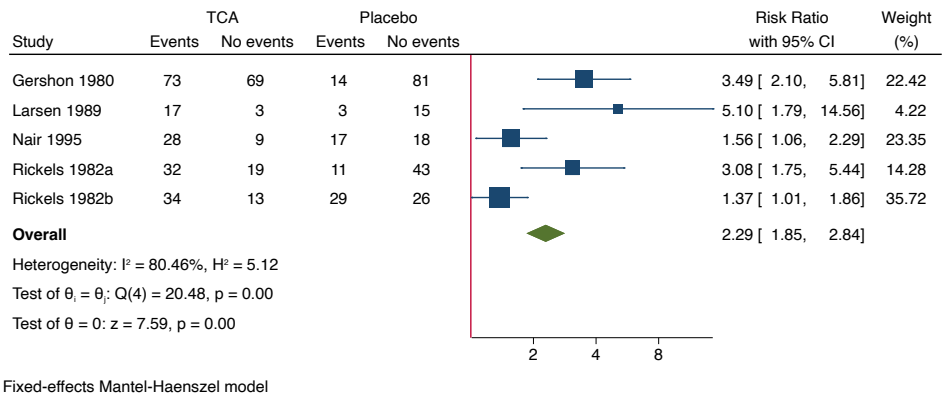


Supplementary figure S93: Meta-analysis of tricyclic antidepressants versus placebo on dry mouth (sensitivity analysis).

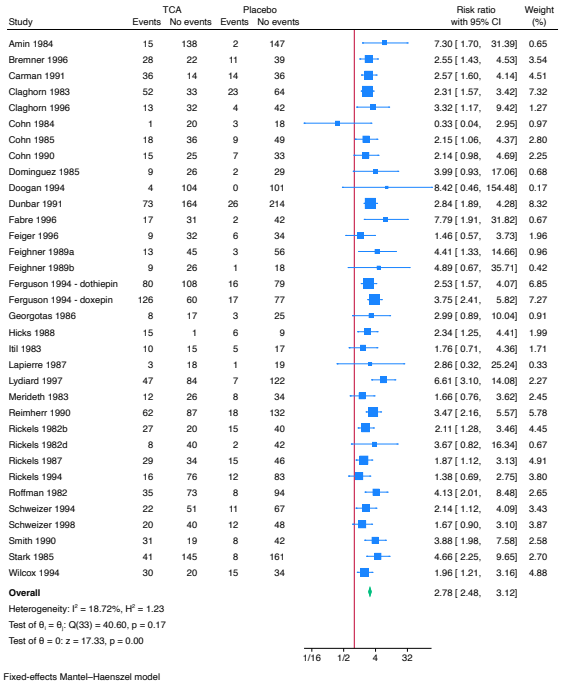
Graph 11/08/2023, 21.08



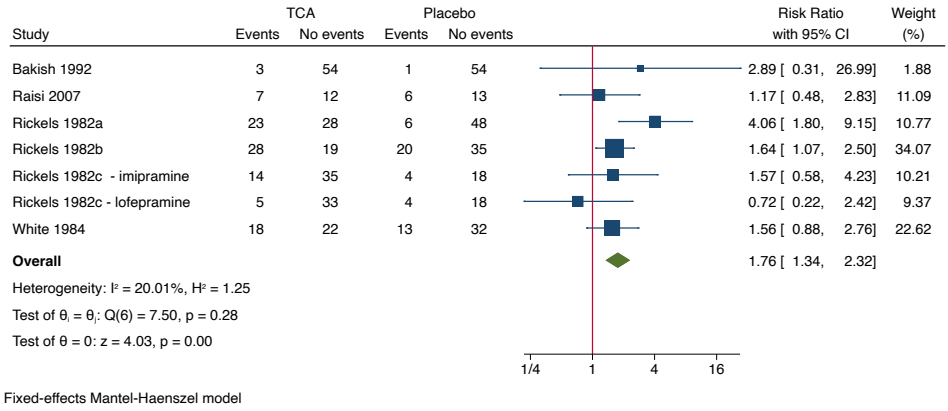
Supplementary figure S94: Meta-analysis of tricyclic antidepressants versus placebo on anticholinergic symptoms (sensitivity analysis).



Supplementary figure S95: Meta-analysis of tricyclic antidepressants versus placebo on somnolence (sensitivity analysis).

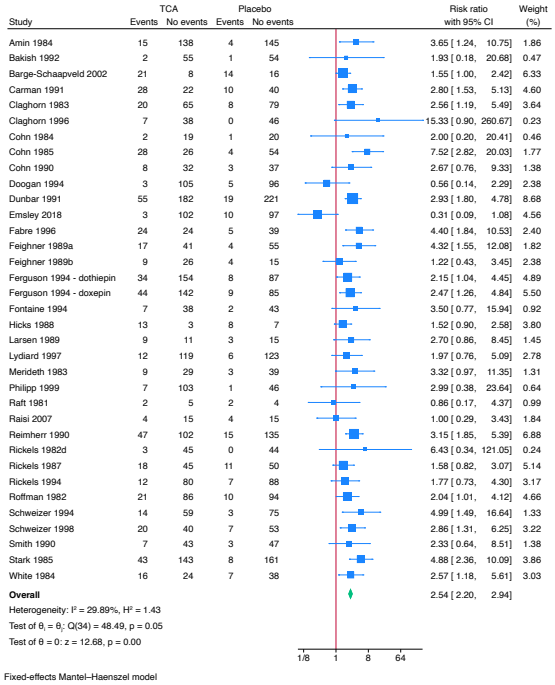


Supplementary figure S96: Meta-analysis of tricyclic antidepressants versus placebo on sedation (sensitivity analysis).

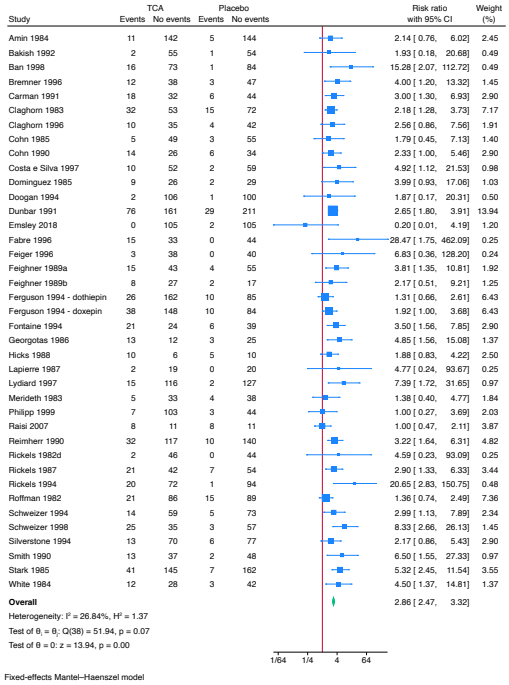


Supplementary figure S97: Meta-analysis of tricyclic antidepressants versus placebo on dizziness (sensitivity analysis).

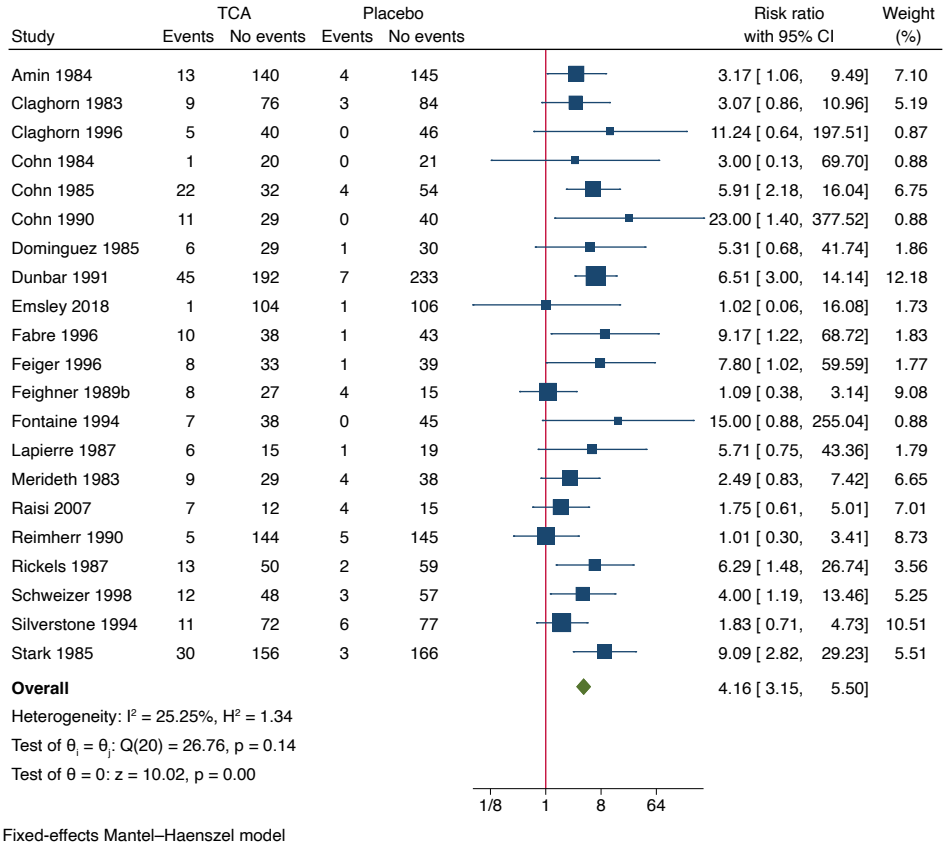
Graph 11/08/2023, 21.43



Supplementary figure S98: Meta-analysis of tricyclic antidepressants versus placebo on constipation (sensitivity analysis).

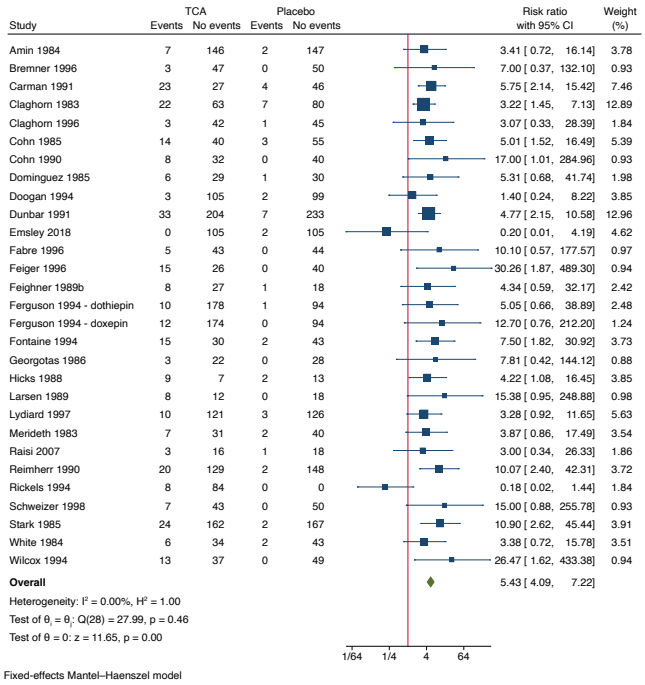


Supplementary figure S99: Meta-analysis of tricyclic antidepressants versus placebo on sweating (sensitivity analysis).

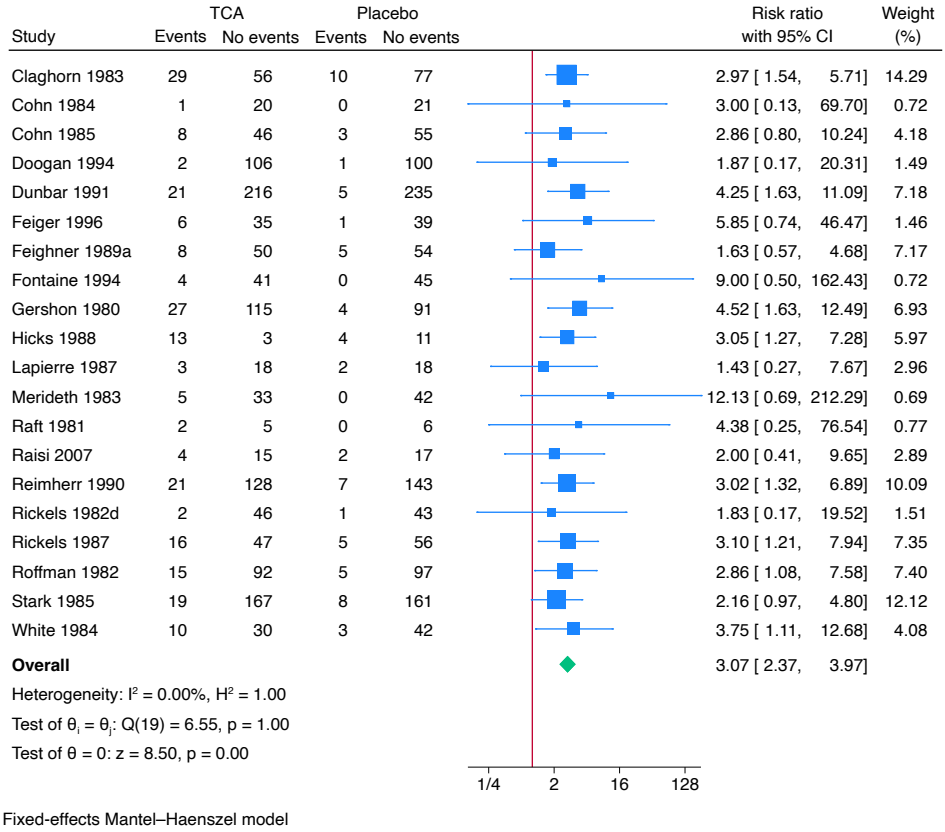


Supplementary figure S100: Meta-analysis of tricyclic antidepressants versus placebo on tremor (sensitivity analysis).

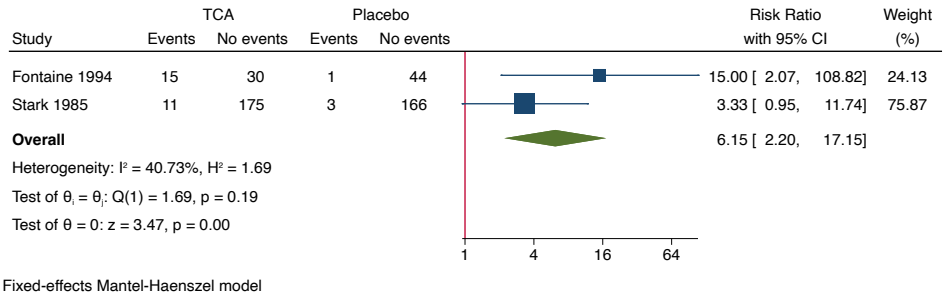
Graph 22/05/2023, 12.59



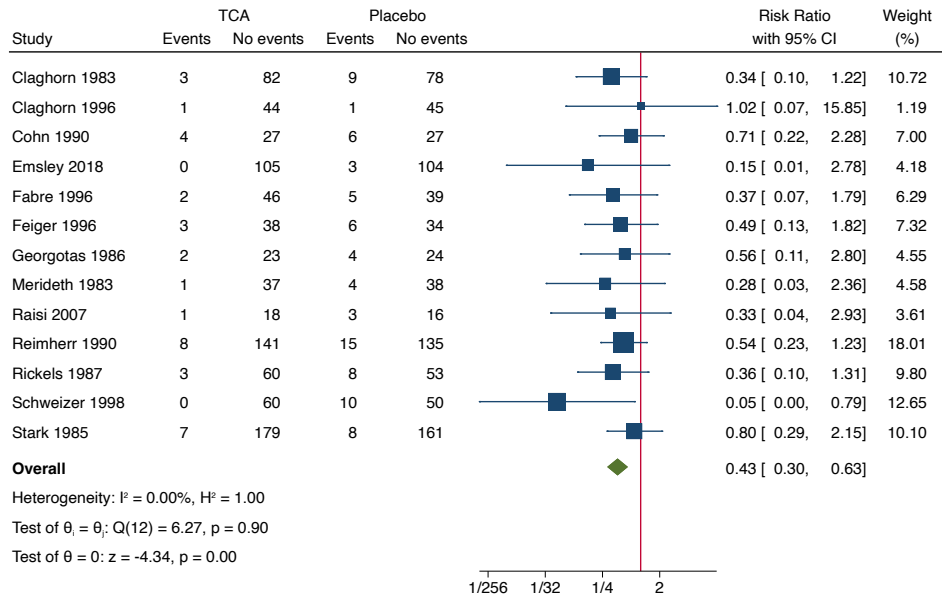
Supplementary figure S101: Meta-analysis of tricyclic antidepressants versus placebo on blurred vision (sensitivity analysis).



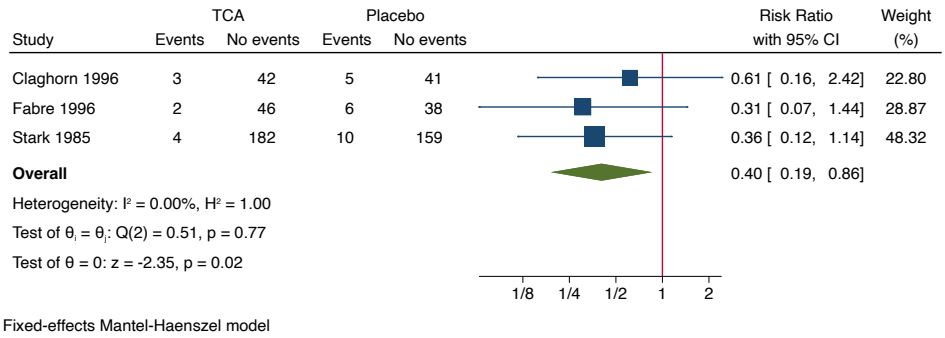
Supplementary figure S102: Meta-analysis of tricyclic antidepressants versus placebo on flushing (sensitivity analysis).



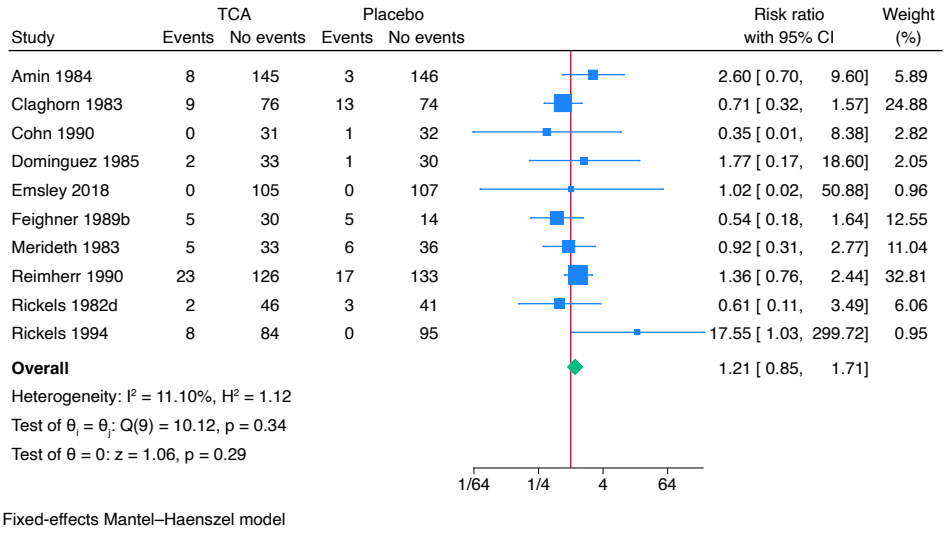
Supplementary figure S103: Meta-analysis of tricyclic antidepressants versus placebo on diarrhoea (sensitivity analysis).



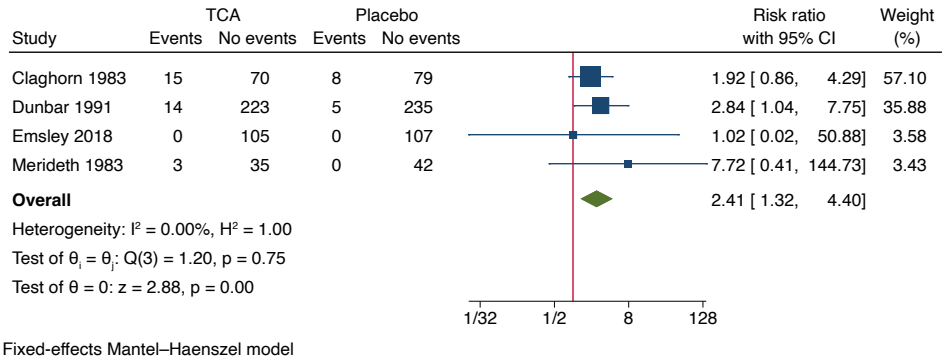
Supplementary figure S104: Meta-analysis of tricyclic antidepressants versus placebo on infection (sensitivity analysis).



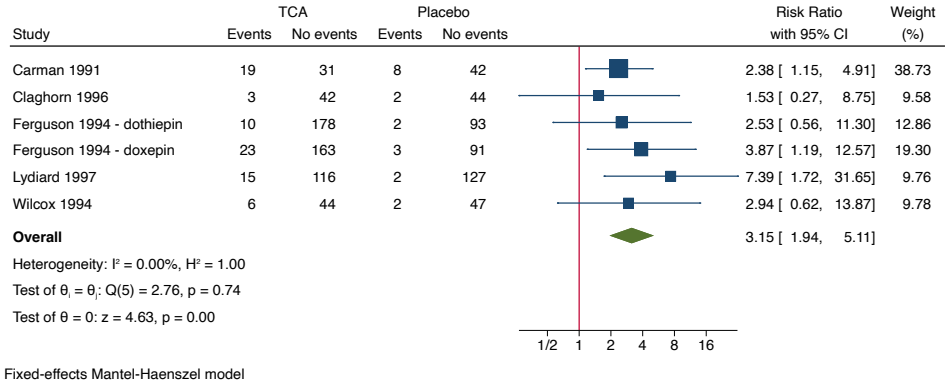
Supplementary figure S105: Meta-analysis of tricyclic antidepressants versus placebo on agitation (sensitivity analysis).



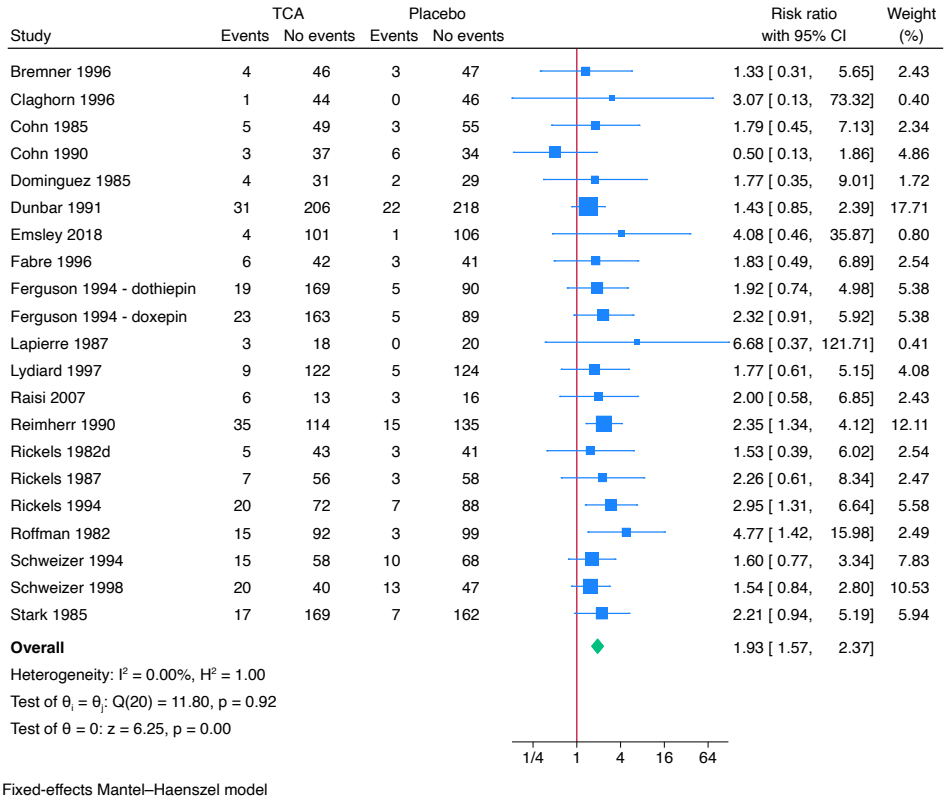
Supplementary figure S106: Meta-analysis of tricyclic antidepressants versus placebo on decreased appetite (sensitivity analysis).



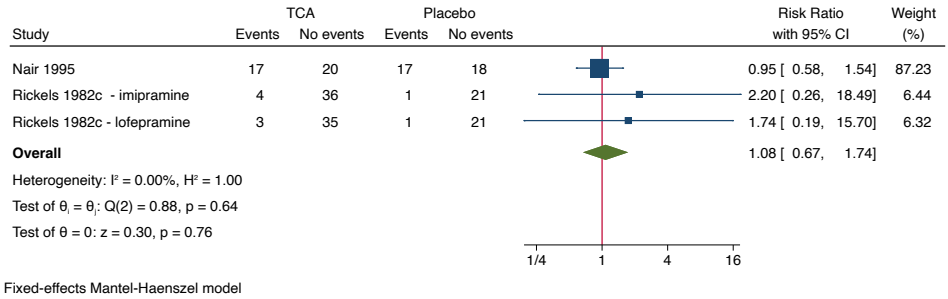
Supplementary figure S107: Meta-analysis of tricyclic antidepressants versus placebo on increased appetite (sensitivity analysis).



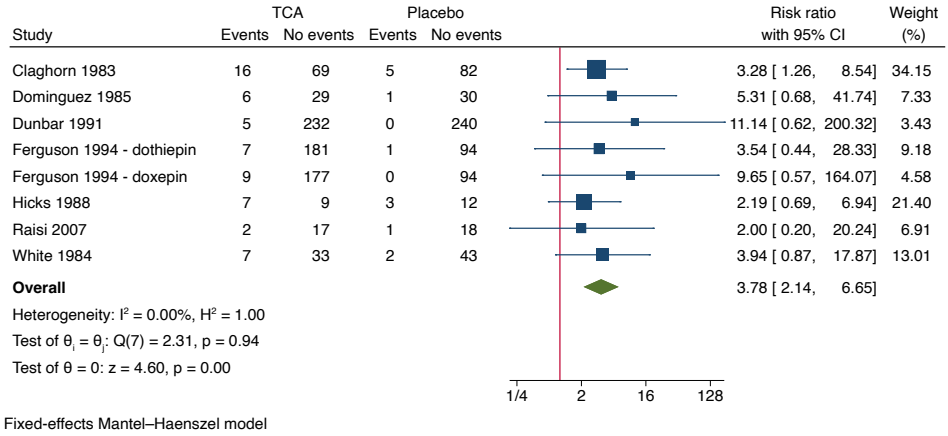
Supplementary figure S108: Meta-analysis of tricyclic antidepressants versus placebo on asthenia (sensitivity analysis).



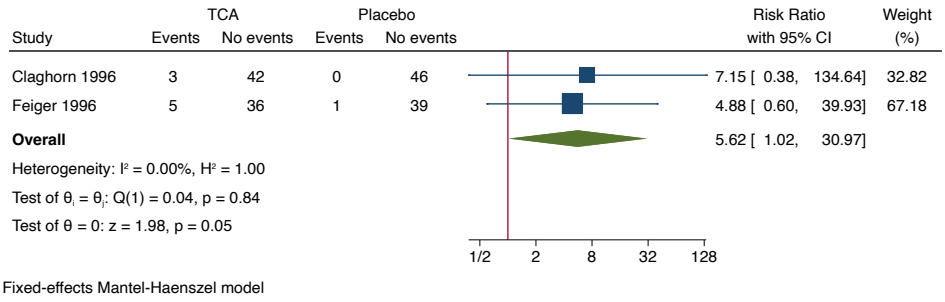
Supplementary figure S109: Meta-analysis of tricyclic antidepressants versus placebo on CNS (sensitivity analysis).



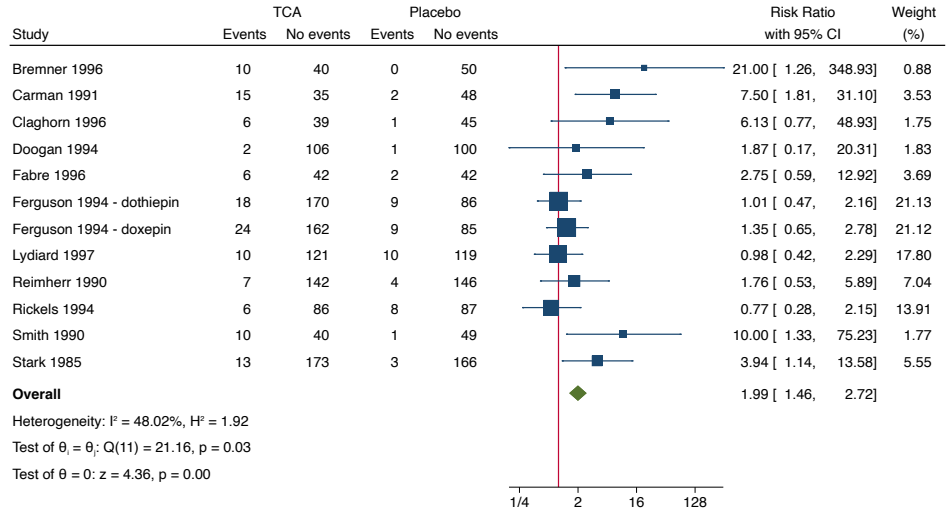
Supplementary figure S110: Meta-analysis of tricyclic antidepressants versus placebo on confusion (sensitivity analysis).



Supplementary figure S111: Meta-analysis of tricyclic antidepressants versus placebo on abnormal dreams (sensitivity analysis).

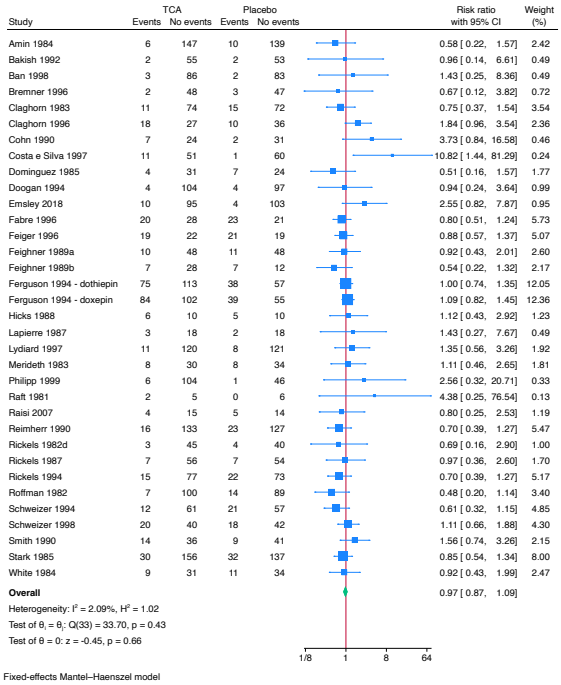


Supplementary figure S112: Meta-analysis of tricyclic antidepressants versus placebo on dyspepsia (sensitivity analysis).

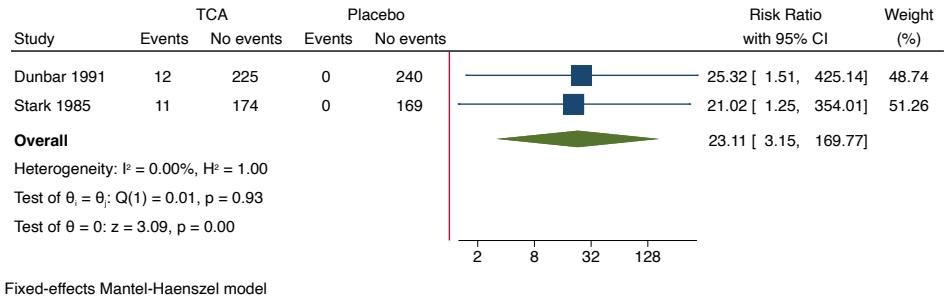


Supplementary figure S113: Meta-analysis of tricyclic antidepressants versus placebo on headache (sensitivity analysis).

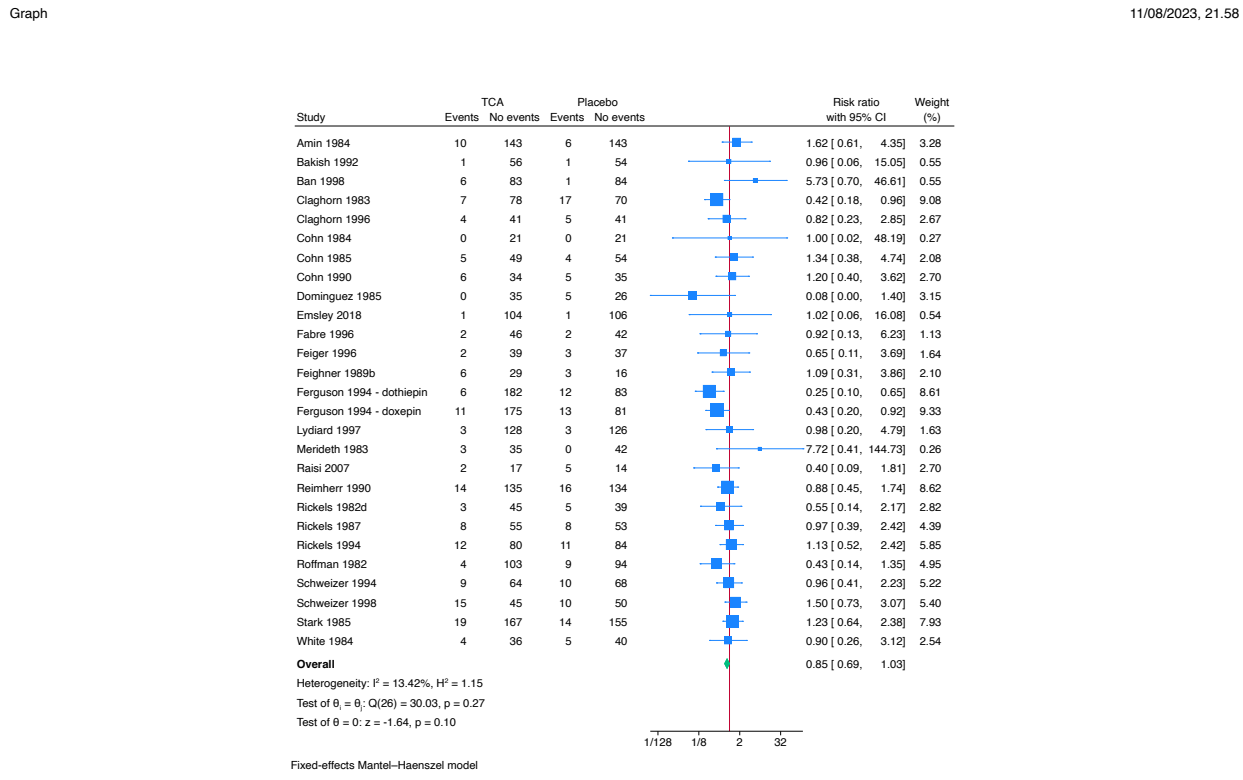
Graph 11/08/2023, 21.34



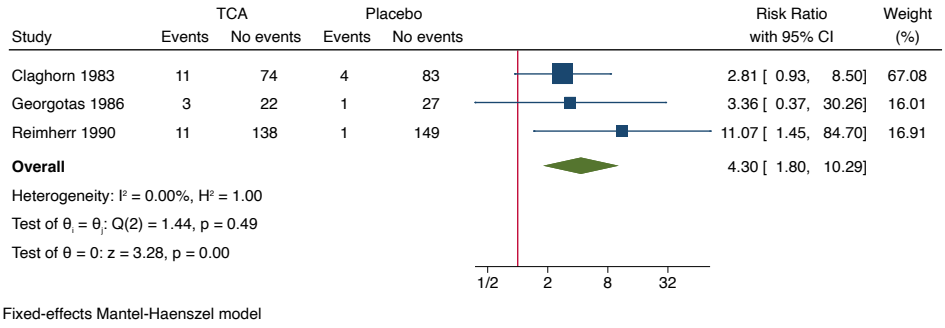
Supplementary figure S114: Meta-analysis of tricyclic antidepressants versus placebo on impaired urination (sensitivity analysis).



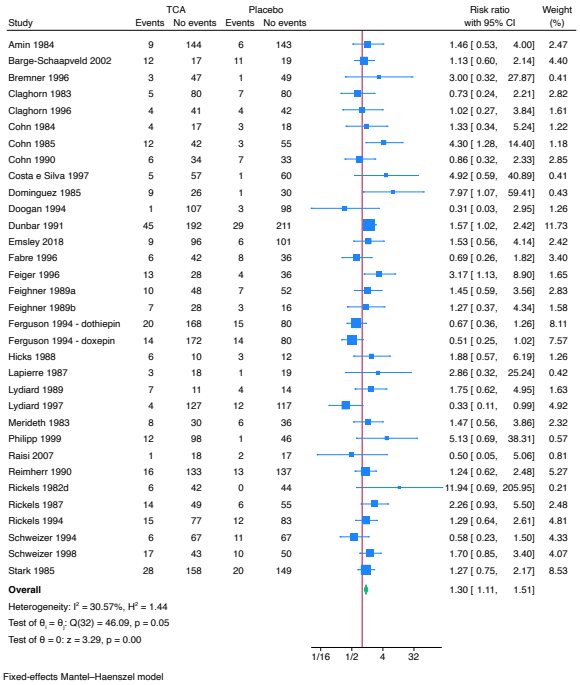
Supplementary figure S115: Meta-analysis of tricyclic antidepressants versus placebo on insomnia (sensitivity analysis).



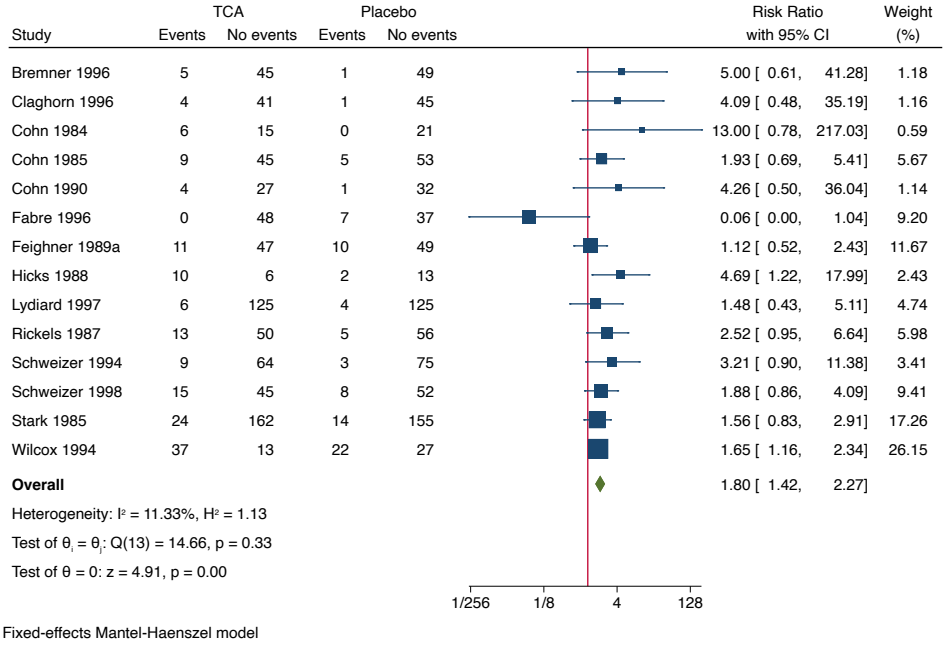
Supplementary figure S116: Meta-analysis of tricyclic antidepressants versus placebo on micturition disorder (sensitivity analysis).



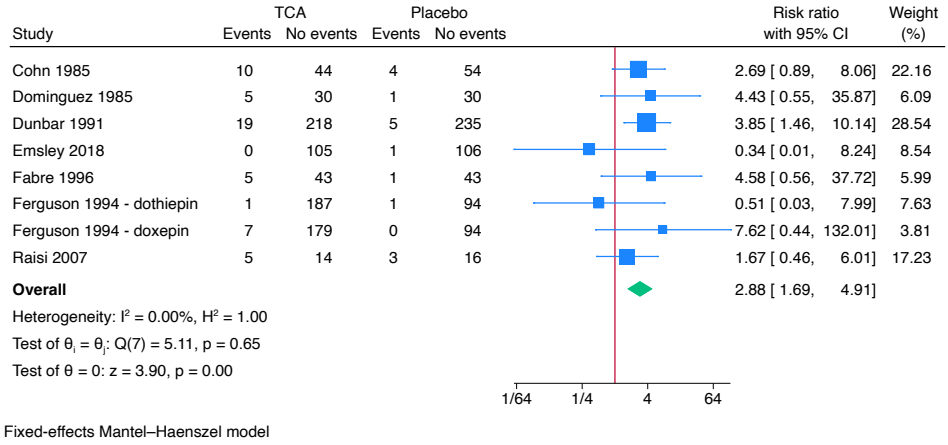
Supplementary figure S117: Meta-analysis of tricyclic antidepressants versus placebo on nausea (sensitivity analysis).



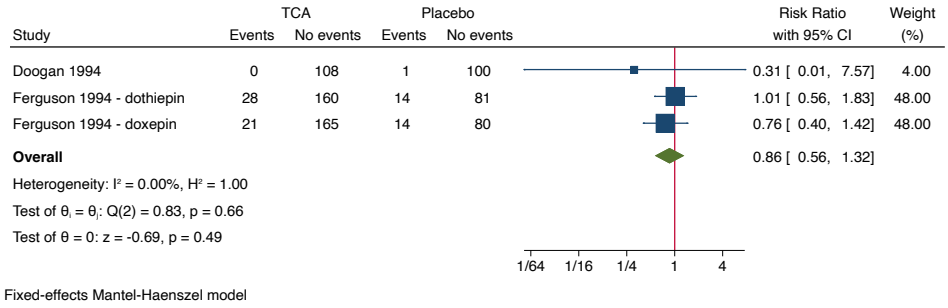
Supplementary figure S118: Meta-analysis of tricyclic antidepressants versus placebo on nervousness (sensitivity analysis).



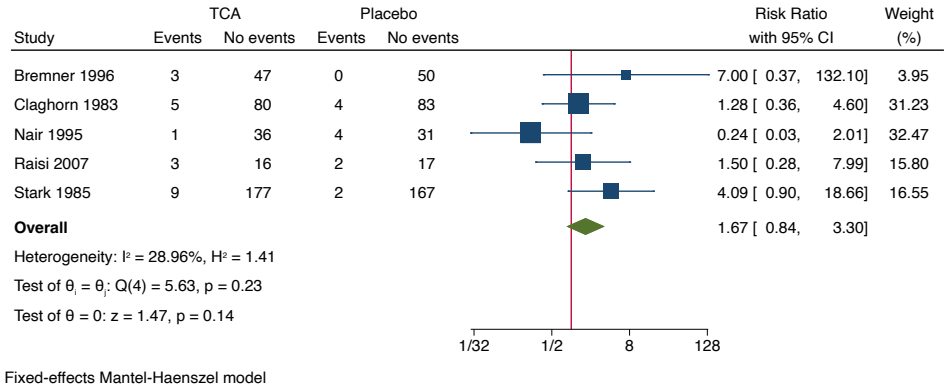
Supplementary figure S119: Meta-analysis of tricyclic antidepressants versus placebo on paraesthesia (sensitivity analysis).



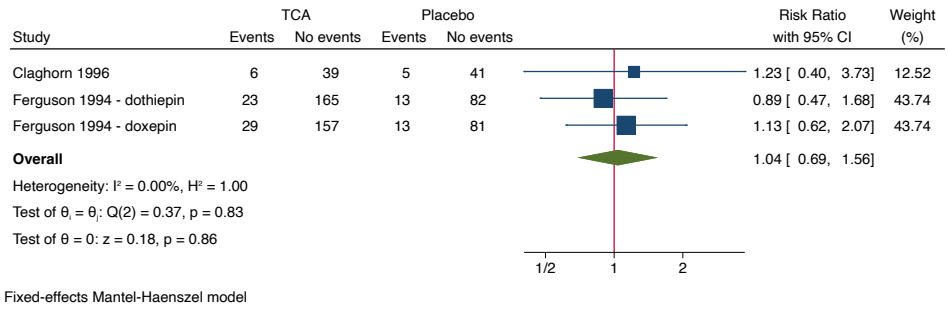
Supplementary figure S120: Meta-analysis of tricyclic antidepressants versus placebo on pharyngitis (sensitivity analysis).



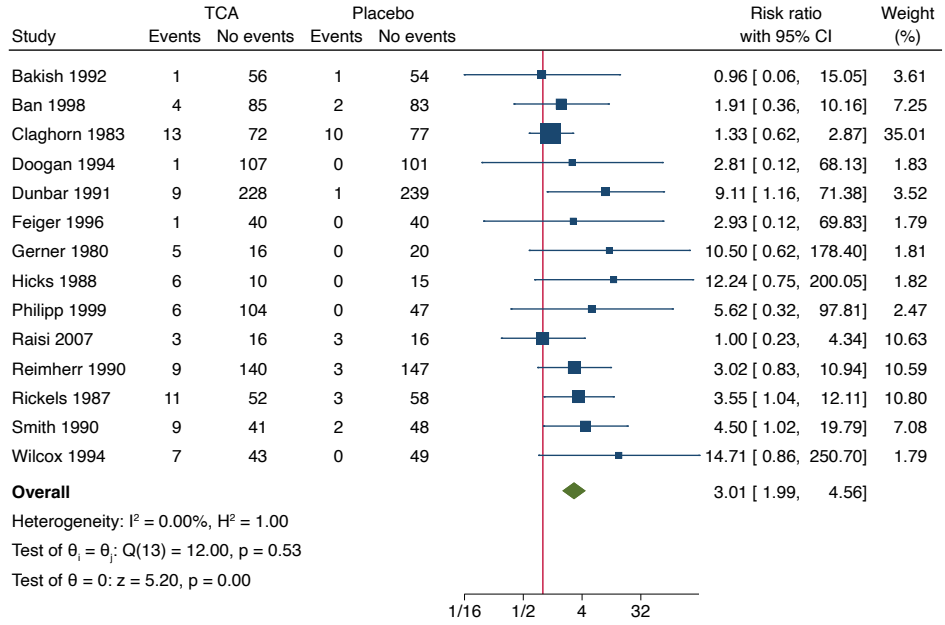
Supplementary figure S121: Meta-analysis of tricyclic antidepressants versus placebo on rash (sensitivity analysis).



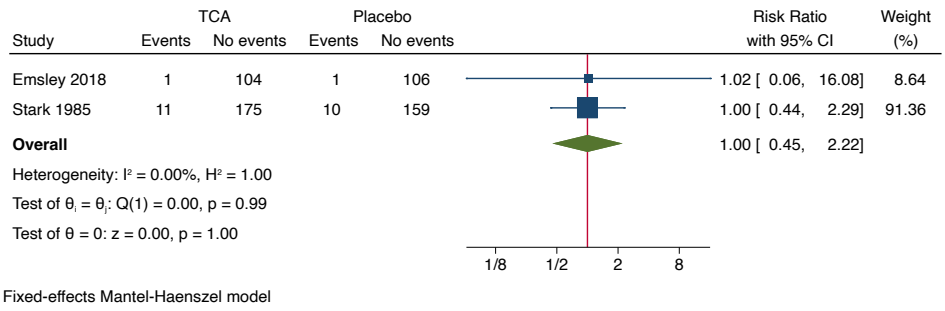
Supplementary figure S122: Meta-analysis of tricyclic antidepressants versus placebo on rhinitis (sensitivity analysis).



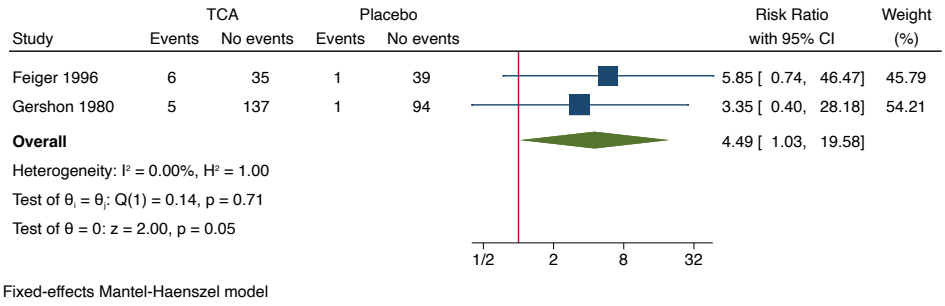
Supplementary figure S123: Meta-analysis of tricyclic antidepressants versus placebo on tachycardia (sensitivity analysis).



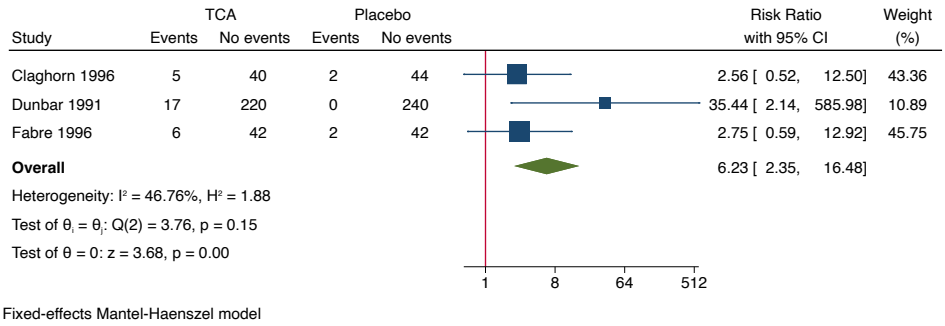
Supplementary figure S124: Meta-analysis of tricyclic antidepressants versus placebo on upper respiratory tract infection (sensitivity analysis).



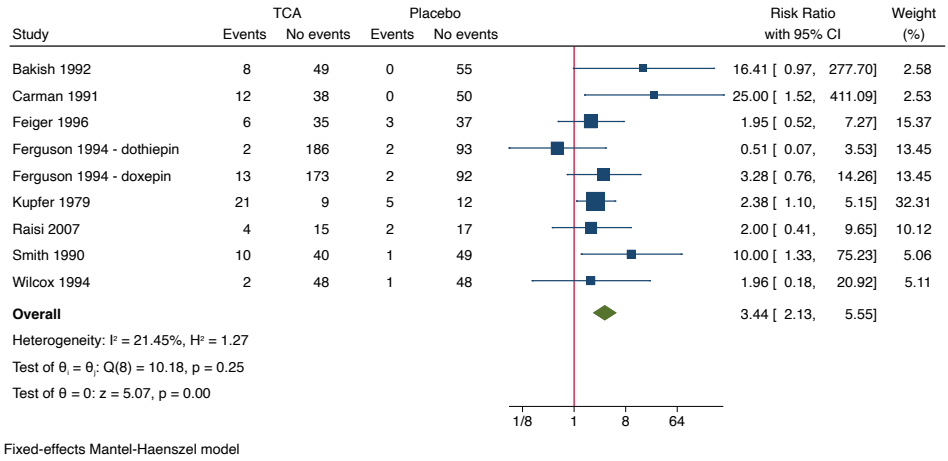
Supplementary figure S125: Meta-analysis of tricyclic antidepressants versus placebo on urinary hesitancy (sensitivity analysis).



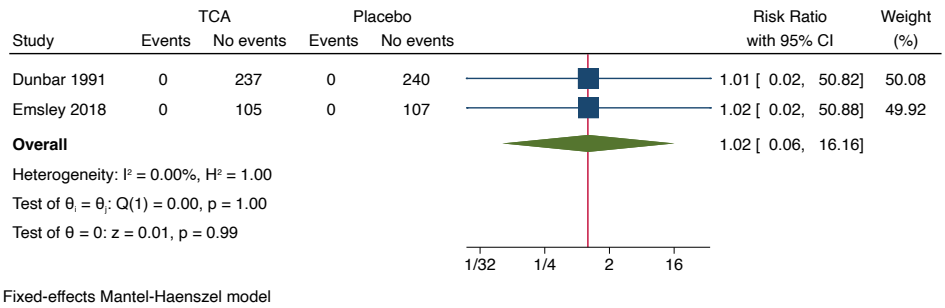
Supplementary figure S126: Meta-analysis of tricyclic antidepressants versus placebo on vasodilatation (sensitivity analysis).



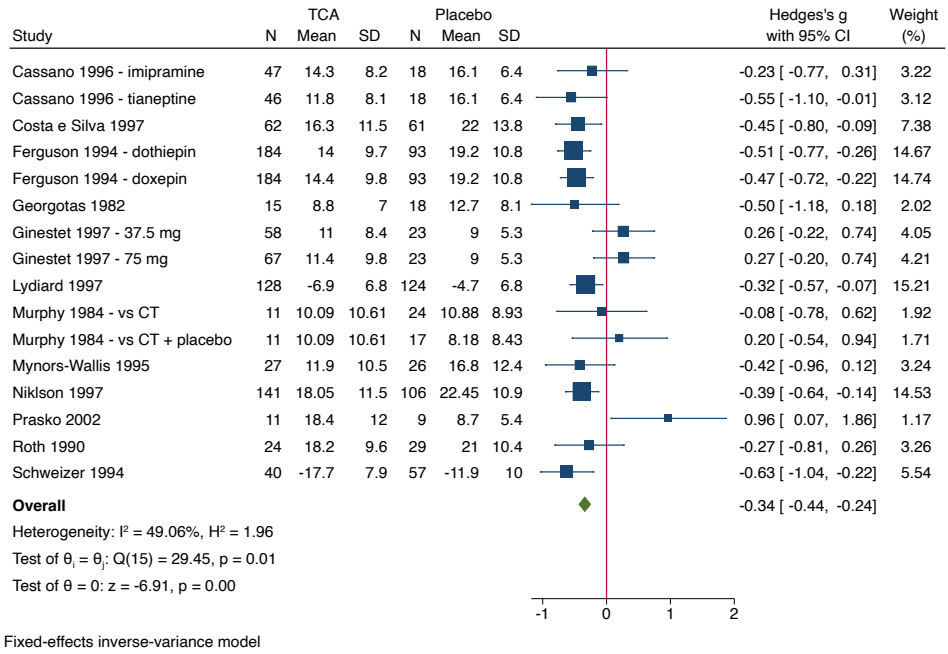
Supplementary figure S127: Meta-analysis of tricyclic antidepressants versus placebo on weight gain (sensitivity analysis).



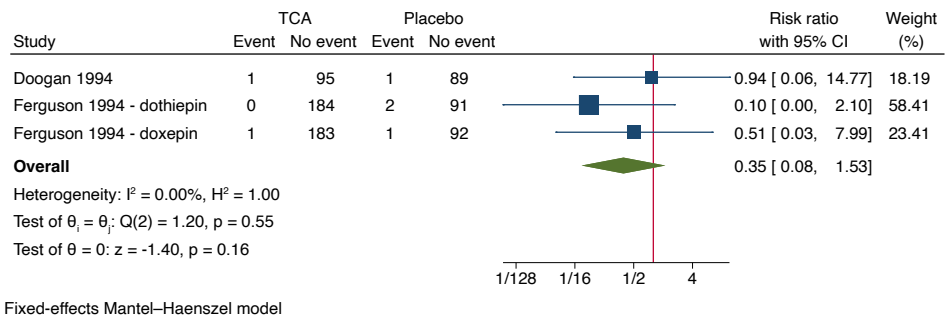
Supplementary figure S128: Meta-analysis of tricyclic antidepressants versus placebo on yawning (sensitivity analysis).



Supplementary figure S129: Meta-analysis of tricyclic antidepressants versus placebo on MADRS, BDI, and HDRS-6 (sensitivity analysis).

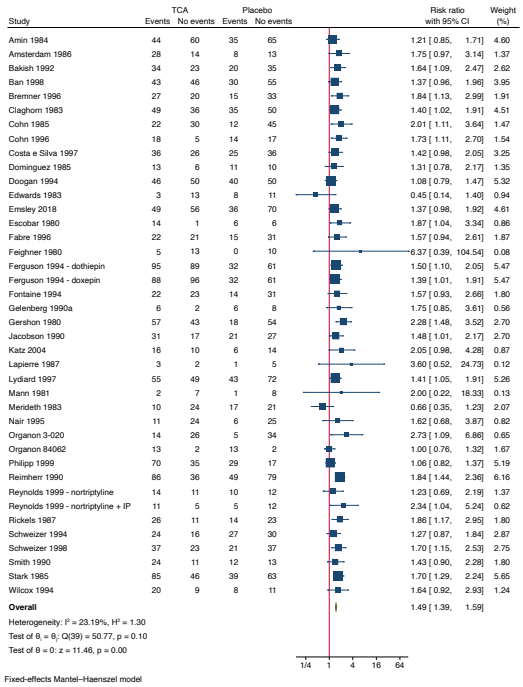


Supplementary figure S130: Meta-analysis of tricyclic antidepressants versus placebo on suicidal ideation (sensitivity analysis).

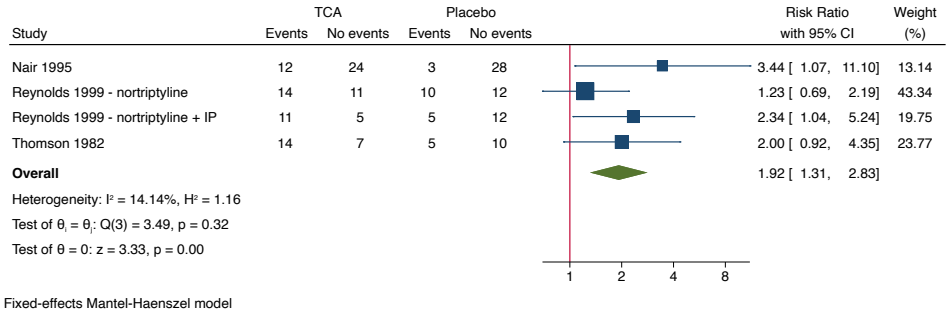


Supplementary figure S131: Meta-analysis of tricyclic antidepressants versus placebo on response (sensitivity analysis).

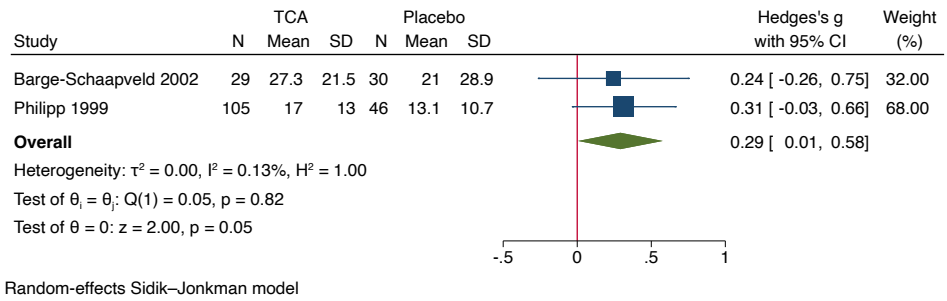
Graph 22/05/2023, 11.42



Supplementary figure S132: Meta-analysis of tricyclic antidepressants versus placebo on remission (sensitivity analysis).



Supplementary figure S133: Meta-analysis of tricyclic antidepressants versus placebo on quality of life (standardised mean difference).



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Selection criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy and selection criteria
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Outcomes and subgroup analyses
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Protocol
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Protocol
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Protocol
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Protocol
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Protocol or Assessment of statistical and clinical significance
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Assessment of statistical and clinical significance
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Outcomes and subgroup analyses
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Protocol
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Protocol + data extraction and risk of bias assessment

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. Assessment of statistical and clinical significance	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplementary
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results + supplementary
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results + supplementary
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results + supplementary
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract + methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Abstract + methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Differences between the protocol and the review
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71

For more information, visit: **www.prisma-statement.org**.

Search strategies for
'Tricyclic antidepressants for major depressive disorder'
(C Kamp)
Updated searches performed 27 January 2023

Total number of records identified:	**47981 records**
Number of duplicates excluded:	**15478 records**
Number of records in final list:	**32483 records**
Number of new records sent to authors:	**8334 records**

Cochrane Central Register of Controlled Trials (2023; Issue 1) in the Cochrane Library (10093 hits)

#1 MeSH descriptor: [Antidepressive Agents] explode all trees
#2 (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*)
#3 (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Depressive Disorder, Major] explode all trees
#6 MeSH descriptor: [Depressive Disorder] this term only
#7 MeSH descriptor: [Seasonal Affective Disorder] explode all trees
#8 MeSH descriptor: [Dysthymic Disorder] explode all trees
#9 MeSH descriptor: [Depression] explode all trees
#10 MeSH descriptor: [Affective Symptoms] this term only
#11 ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
#12 #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 #4 and #12

MEDLINE Ovid (1946 to 27 January 2023) (11606 hits)

1. exp Antidepressive Agents/
2. (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. 1 or 2 or 3
5. exp Depressive Disorder, Major/
6. Depressive Disorder/
7. exp Seasonal Affective Disorder/
8. exp Dysthymic Disorder/
9. exp Depression/
10. Affective Symptoms/
11. ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 4 and 12
14. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti.

15. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. 13 and (14 or 15)
17. limit 16 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

Embase Ovid (1974 to 27 January 2023) (16488 hits)
1. exp antidepressant agent/
2. (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. 1 or 2 or 3
5. exp major depression/
6. depression/
7. exp seasonal affective disorder/
8. exp dysthymia/
9. emotional disorder/
10. ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. Randomized controlled trial/ or Controlled clinical study/ or trial.ti.
14. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
15. 12 and (13 or 14)
16. limit 15 to (adult <18 to 64 years> or aged <65+ years>)

LILACS (VHL Regional Portal; 1982 to 27 January 2023) (1161 hits)
((antidepress* OR (moodstimula* OR mood-stimula*) OR thymoanaleptic* OR thymoleptic*) OR (amineptine OR amitriptyline OR amoxapine OR butriptyline OR clomipramine OR desipramine OR dibenzepin OR dosulepin OR doxepin OR imipramine OR iprindole OR lofepramine OR maprotiline OR nortriptyline OR opipramol OR protriptyline OR tianeptine OR trimipramine OR cianopramine OR demexiptiline OR dothiepin OR melitracen OR metapramine OR noxiptiline OR quinupramine)) AND (((depress* OR affective OR dysthym*) AND (disorder* OR disease* OR symptom*))) AND (db:("LILACS"))

PsycINFO (EBSCO host; 1806 to 27 January 2023) (3693 hits)
S17 S15 AND S16
S16 TI adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged OR AB adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged
S15 S13 AND S14
S14 TX ((random* or blind* or placebo* or meta-analys*)) OR TI trial*
S13 S4 AND S12
S12 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11 TX ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
S10 MA Affective Symptoms
S9 MA Depression

S8 MA Dysthymic Disorder
S7 MA Seasonal Affective Disorder
S6 MA Depressive Disorder Expanders
S5 MA Depressive Disorder, Major
S4 S1 OR S2 OR S3
S3 TX (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine)
S2 TX (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*)
S1 MA Antidepressive Agents

Science Citation Index Expanded (Web of Science; 1900 to 27 January 2023); Conference Proceedings Citation Index – Science (Web of Science; 1990 to 27 January 2023); Social Sciences Citation Index (Web of Science; 1956 to 27 January 2023), and Conference Proceedings Citation Index- Social Science & Humanities (Web of Science; 1990 to 27 January 2023) (4940 hits)
#9 #8 AND #7
#8 TS=(adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged)
#7 #6 AND #5
#6 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)
#5 #4 AND #3
#4 TS=((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
#3 #2 OR #1
#2 TS=(amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine)
#1 TS=(antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*)

Exploratory outcomes

Serious adverse events (as reported by trialists)

Four trials reported serious adverse events as a composite outcome (**supplementary table S2**).[1-4] Trials using 'active placebo' were not included in this meta-analysis. All trials only assessed outcomes at the end of the treatment period, i.e. from six to eight weeks after randomisation. A total of 3/320 (0.9%) experimental participants had one or more serious adverse events compared with 6/253 (2.4%) control participants. Meta-analysis showed no evidence of a difference between tricyclic antidepressants and placebo on serious adverse events (odds ratio (OR) 0.52; 95% CI 0.15 to 1.77; $p = 0.30$; 4 trials) (**supplementary figure S68**). 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 increased the risk of serious adverse events with a relative risk reduction of 20% (no graph produced as we only had 1.15% of the required information size). This outcome result was assessed as overall high risk of bias.

MADRS, BDI, and HDRS-6

Fourteen trials reported results on MADRS, BDI, or HDRS-6.[5-19] All trials only assessed outcomes at the end of the treatment period, i.e. from 3 to 12 weeks after randomisation. Meta-analysis using standardised mean difference (SMD) showed evidence of a beneficial effect of tricyclic antidepressants on the MADRS and BDI scores (SMD -0.30; 95% CI -0.49 to -0.12; $p < 0.01$; 14 trials) (**supplementary figure S69**). Visual inspection of the forest plot and statistical tests ($\tau = 0.3$; $I^2 = 72.0\%$) indicated heterogeneity that could not be resolved. This outcome result was assessed as overall high risk of bias.

Suicidal ideation

Two trials reported suicidal ideation [10, 20]. All trials only assessed outcomes at the end of the treatment period, i.e. from six to nine weeks after randomisation. Meta-analysis showed no evidence of a difference between tricyclic antidepressants and placebo on suicidal ideation (RR 0.39; 95% CI 0.07 to 2.30; $p = 0.30$; 2 trials) (**supplementary figure S70**). Visual inspection of the forest plot and statistical tests ($\tau = 0.6$; $I^2 = 15.0\%$) indicated no clear signs of heterogeneity. This outcome result was assessed as overall high risk of bias.

Response

Thirty-five trials reported on response [1-4, 7, 9, 10, 15, 20-46]. All trials only assessed outcomes at the end of the treatment period, i.e. from four to nine weeks after randomisation. Meta-analysis showed evidence of a beneficial effect of tricyclic antidepressants on response (RR 1.49; 95% CI 1.33 to 1.67; $p < 0.01$; 35 trials) (**supplementary figure S71**). Visual inspection of the forest plot and statistical tests ($\tau = 0.2$; $I^2 = 55.3\%$) indicated heterogeneity that could not be resolved. This outcome result was assessed as overall high risk of bias.

Remission

Three trials reported on remission [38, 40, 47]. All trials only assessed outcomes at the end of the treatment period, i.e., from 7 to 12 weeks after randomisation. Meta-analysis showed evidence of a beneficial effect of tricyclic antidepressants on remission (RR 1.87; 95% CI 1.16 to 3.03; $p = 0.01$; 3 trials) (**supplementary figure S72**). Visual inspection of the forest plot and statistical tests ($\tau = 0.3$; $I^2 = 32.4\%$) indicated heterogeneity that could not be resolved. This outcome result was assessed as overall high risk of bias.

Remaining results

We performed all meta-analyses as both fixed-effect and random-effects meta-analyses and reported the most conservative results as the main results. For the less conservative results, please see **supplementary figures S73-S133**.

95% prediction intervals

Tricyclic antidepressants versus placebo on HDRS-17: -10.97 to 3.51

Tricyclic antidepressants versus placebo on mania: 0.06 to 29.81

Tricyclic antidepressants versus placebo on anxiety: 0.13 to 4.38

Tricyclic antidepressants versus placebo on urinary retention: 0.17 to 215.00

Tricyclic antidepressants versus placebo on sexual dysfunction: 0.52 to 23.50

Tricyclic antidepressants versus placebo on anorexia: 0.06 to 20.62

Tricyclic antidepressants versus placebo on taste alteration: 0.12 to 139.81

Tricyclic antidepressants versus placebo on hypotension: 0.82 to 13.41

Tricyclic antidepressants versus placebo on syncope: 0.00 to 1.9e+05

Tricyclic antidepressants versus placebo on amblyopia: 1.37 to 8.05

Tricyclic antidepressants versus placebo on non-serious adverse events: 0.63 to 7.05

Tricyclic antidepressants versus placebo on dry mouth: 1.28 to 9.20

Tricyclic antidepressants versus placebo on somnolence: 1.18 to 5.99

Tricyclic antidepressants versus placebo on constipation: 0.84 to 9.39

Tricyclic antidepressants versus placebo on dyspepsia: 0.34 to 14.23

Tricyclic antidepressants versus placebo on nervousness: 0.32 to 13.25

Tricyclic antidepressants versus placebo on asthenia: 0.98 to 3.71

Tricyclic antidepressants versus placebo on nausea: 0.38 to 4.51

Tricyclic antidepressants versus placebo on tremor: 0.91 to 24.39

Tricyclic antidepressants versus placebo on rash: 0.05 to 51.42

Tricyclic antidepressants versus placebo on headache: 0.40 to 2.36

Tricyclic antidepressants versus placebo on increased appetite: 0.97 to 9.13

Tricyclic antidepressants versus placebo on dizziness: 0.83 to 6.75

Tricyclic antidepressants versus placebo on weight gain: 0.31 to 28.87

Tricyclic antidepressants versus placebo on blurred vision: 1.61 to 5.44

Tricyclic antidepressants versus placebo on pharyngitis: 0.01 to 89.56

Tricyclic antidepressants versus placebo on confusion: 1.23 to 9.61

Tricyclic antidepressants versus placebo on tachycardia: 0.73 to 11.40

Tricyclic antidepressants versus placebo on agitation: 0.18 to 6.61

Tricyclic antidepressants versus placebo on diarrhoea: 0.16 to 1.34

Tricyclic antidepressants versus placebo on sweating: 0.97 to 13.70

Tricyclic antidepressants versus placebo on anticholinergic symptoms: 0.44 to 12.48

Tricyclic antidepressants versus placebo on micturition disorder: 0.00 to 2.0e+04

Tricyclic antidepressants versus placebo on sedation: 0.53 to 5.30

Tricyclic antidepressants versus placebo on decreased appetite: 0.24 to 24.28

Tricyclic antidepressants versus placebo on paraesthesia: 0.38 to 16.96

Tricyclic antidepressants versus placebo on rhinitis: 0.07 to 16.40

Tricyclic antidepressants versus placebo on vasodilatation: 0.00 to 1.0e+08

Tricyclic antidepressants versus placebo on infection: 0.00 to 86.51

Tricyclic antidepressants versus placebo on CNS: 0.01 to 99.48

Tricyclic antidepressants versus placebo on MADRS, BDI, or HDRS-6: -1.02 to 0.41

Tricyclic antidepressants versus placebo on suicidal ideation: 0.00 to 4.2e+05

Tricyclic antidepressants versus placebo on remission: 0.38 to 9.24

Tricyclic antidepressants versus placebo on response: 0.89 to 2.48

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List of non-serious adverse events combined for meta-analyses:

- Nausea + nausea/vomiting + vomiting
- Somnolence + drowsiness
- Blurred vision + vision abnormalities + visual disorder
- Rash + skin rash + skin
- Dizziness + lightheaded
- Weight gain + weight increase
- Tachycardia + palpitations
- Agitation + motor agitation
- Sweating + increased sweating + hyperhidrosis
- Anticholinergic symptoms + Anticholinergic, composite + anticholinergic adverse events
- Urination impaired + Impaired urination
- Vivid dreams + abnormal dreaming
- Infection + viral infection

Characteristics of the included trials.

Trial ID	Registry/ published protocol	Risk of for-profit bias	Inclusion criteria	Exclusion criteria	Experimental intervention	Dose range (mg/day)	Control intervention	Placebo washout	Length of intervention period	No. randomised to TCA	No. randomised to control	Baseline HDRS TCA	Baseline HDRS control	Co-interventions
Akhondzadeh 2003	No	Yes	Patients have a baseline Hamilton Rating Scale for Depression (HAM-D 17-item) (Hamilton, 1960) score of at least 18.	Prospective participants with the following DSM IV diagnosis were excluded: current cognitive disorder in the last year, or current or past history of bipolar disorder, schizophrenia, and schizotypal personality disorder. Patients were required to be free of all psychotropic medications for at least 4 weeks before study entry. Patients were selected to range in age from 18 to 54 years of age. As depression is a serious and potentially life-threatening condition and the participants were outpatients, extensive safeguards were needed. Patients were excluded, if they posed a significant risk of suicide at any time during participation. Persons who scored greater than 2 on the suicide item of the HAM-D, or who were judged to have significant suicidal ideation or potential in the view of an investigator were excluded. Further, any clinically significant deterioration in the condition of the subject from baseline would result in exclusion. Pregnant women or women not using medically accepted means of birth control were excluded.	Imipramine	100	Placebo	No	4 weeks	Unclear	Unclear	19.5	19.5	Lavandula angustifolia (lamiacae)
Amin 1984	No	Yes	Each test center investigated either outpatients or hospitalized patients. Criteria for inclusion were a diagnosis of a major depression (major affective disorder, depressive episode) after DSM III (American Psychiatric Association, 1980), the presence of 4 of the eighner criteria for depression [Feighner, 1972] and a total score of > 15 in the 17-item version of the Hamilton Rating Scale for Depression (HAMD). The depressive disorder was to be pathological, and not curable by social contact alone.	Excluded from the study were recognizable suicidal, psychotic and alcohol- or drug- dependent patients; further exclusion criteria were serious cardiac, renal or hepatic diseases and any interfering concomitant medication that could not be discontinued for medical reasons. Pregnant women and women ofchild-bearing age not practising a reliable form of contraception were also excluded. Finally, patients who had received electroconvulsive therapy in the previous 4 weeks, MAO inhibitors in the previous 2 weeks, lithium prepa- rations in the previous week, or tricyclic antidepressants on the 3 days preceding the study were excluded from participation in the study.	Imipramine	Mean: 149	Placebo	Yes	4-6 weeks	Unclear	Unclear	25.92	25.60	No
Amsterdam 1986	No	Yes	All patients were suffering from a moderate to severe mixed anxiety/depression syndrome, for which an antidepressant medication appeared the treatment of choice. However, the subjects also fulfilled an RDC diagnosis for major depression, had a minimum Hamilton Depression Rating score (HDRS) of at least 18 on a 21-item scale, a minimum score of 9 on the Raskin Depression scale and an 8 on the Covi Anxiety scale after the placebo elimination period. Symptoms of anxiety were also assessed by the Hamilton Anxiety Rating Scale (HARS).	Patients were excluded if they had symptoms or a history of schizophrenia, acute mania (or a history of bipolar I disorder), dementia, mental retardation, substance abuse, significant medical illness which might contraindicate the use of a TCA, significant hepatic, renal, endocrine or cardiovascular disorders.	Amitriptyline	100-300	Placebo	Yes	4 weeks	55	54	24.5	23.4	No
Bakish 1992	No	Yes	Out-patients of either sex, aged 18-65 years, suffering from a major depressive episode, according to DSM III-R and scoring a minimum of 18 points on the 17-item Hamilton Depression Scale (HAM-D) were included. Patients had to weigh within 20% of the norm of their height.	The main exclusion criteria were high suicidal risk, depression associated with mood-incongruent psychotic features, manic or acute confusional states, significant organic disease, alcohol or drug abuse and recent treatment with MAO inhibitors (within the past 2 weeks), tricyclic antidepressants (within the past week) or electroconvulsive treatment (within the past 6 months). Women with childbearing potential who were not using an effective form of contraception (oral contraceptives) and women who were pregnant or lactating were also excluded. Concomitant use of antihypertensive, diuretic, anticholinergic or sympathomimetic agents was prohibited. All patients gave written informed consent to their participation in the study.	Amitriptyline	50-150	Placebo	Yes	6 weeks	58	56	22.81	23.04	No
Ban 1998	No	Yes	Hospitalised patients between the age of 18 and 65 years with a DSM-III-R diagnosis of major depression of at least 1 month duration and a total score of 16 or higher on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) were eligible for admission.	Excluded from the experimental population were patients with a history of hypersensitivity to psychotropic drugs or with an anomaly that was known to interfere with the absorption, distribution, metabolism or excretion of drugs. Excluded also were patients treated with electroconvulsive therapy within a period of 6 months immediately prior to recruitment, patients with a history of seizures and/or brain injury and patients with clinically relevant abnormal findings in the clinical examination, laboratory tests or the ECG.	Desipramine	100-200	Placebo	Yes	4 weeks	Unclear	Unclear	26	25	No
Barge-Schaapveld 2002	No	Yes	83 patients with a DSM-III-R/DSM-IV diagnosis of current major depressive disorder were recruited in 8 primary care practices in the Netherlands. Age between 18 and 65 years, a score at entry of >/= 18 on the HAMD-17 and a score of >/= 4 on the CGI.	Exclusion criteria included current use of psychotropic medations and major medical disorders.	Imipramine	50-200	Placebo	No	6 weeks	32	31	24.0	23.5	No
Bhatia 1991	No	Yes	In order to be eligible for the study each patient had to fulfill the DSM-III criteria for major depression with melancholia as determined by the screening and initial evaluations. In addition, each patient was required to have a Hamilton (Hamilton, 1967) Depression Rating Scale score of >/= 26 and a Raskin Depression Scale (Raskin et.al., 1967) of >/= 10. Each patient was evaluated with a complete physical examination, electrocardiogram, and laboratory tests for hepatic, renal, pancreatic, hematopoietic and thyroid function. They were included in the study if assessed to be free of significant medical disorders. A serum human chorionic gonadotropin was evaluated in order to exclude pregnant females.	Patients and control volunteers were excluded from the study if they required other psychotropic medications, opiate analgesics, adrenergic agonists or antagonists. A patient could not have received electroconvulsive therapy or monoamine oxidase inhibitors for 2 weeks or tricyclic antidepressants for 3 days prior to the investigation. A urine drug screen was utilized to determine the reliability of the patient drug history and to exclude patients with positive results for abused drugs including alcohol.	Amitriptyline	200-300	Placebo	No	8 weeks	Unclear	Unclear	Unclear	Unclear	No
Bremner 1996	No	Yes	Outpatients of both sexes at least 18-years-old with a DSM-III diagnosis of a moderate-to-severe major de- pressive episode (296.2 or 296.3) and total score >/= 18 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) who were assessed as able to complete the Zung Self-Rating Depression Scale (SDS) entered the study. A fixed upper age limit was not incorporated in the inclusion criteria for this study.	Exclusion criteria included a primary diagnosis of schizophrenia (atypical depressive type), bipolar disorder, or adjustment disorder; anxiety as the primary disorder; known active suicidal tendencies; known cognitive deficiencies; and known alcohol or drug abuse during the last 6 months. Patients with symptoms or a history of the following diseases were also excluded: relevant renal, hepatic, respiratory, cardiovascular, or cerebrovascular diseases; narrow-angle glaucoma; clinically significant pros- tatic hypertrophy; seizure disorders; drug allergy or other hypersensitivity reaction to tricyclic antidepressants or related compounds; hyperthyroidism; and clinically significant abnormal EEG. Women who were pregnant or intended to become pregnant during the study or were practicing a method of birth control assessed as unreliable by the investigators and nursing mothers did not participate in the study. In addition, patients who required treatment with concomitant psychotropic medication including benzodiazepines and those treated with electroconvulsive therapy within 3 months of baseline, study medication within 30 days of baseline, monoamine oxidase inhibitors within 14 days prior to baseline, or other psychotropic medication including antidepressants within 7 days of baseline were excluded as well as patients with a total HAM-D score reduction of >20% in a 7-day placebo washout period. The only permitted psychotropic medication during the study was chloral hydrate (500 mg h.s.).	Amitriptyline	40-280	Placebo	Yes	6 weeks	Unclear	Unclear	27.3	26.6	No
Buchsbaum 1988 - amoxapine	No	Yes	All patients had been free of psychoactive medication for a minimum of 2 weeks before the study began (confirmed by history and urine-drug screening) and were in good health based on medical history, physical examination, and laboratory analyses. Patients were diagnosed according to DSM-III criteria by a psychiatrist before the study, and all had a minimum score of 20 on the Hamilton Rating Scale for Depression, a minimum score of 8 on the Raskin Scale, and a minimum score of 45 on the Zung Self-Rating Scale for Depression.	-	Amoxapine	150	Placebo	No	2 days	7	3	Unclear	Unclear	No
Buchsbaum 1988 - imipramine	No	Yes	All patients had been free of psychoactive medication for a minimum of 2 weeks before the study began (confirmed by history and urine-drug screening) and were in good health based on medical history, physical examination, and laboratory analyses. Patients were diagnosed according to DSM-III criteria by a psychiatrist before the study, and all had a minimum score of 20 on the Hamilton Rating Scale for Depression, a minimum score of 8 on the Raskin Scale, and a minimum score of 45 on the Zung Self-Rating Scale for Depression.	-	Imipramine	100	Placebo	No	2 days	6	4	Unclear	Unclear	No
Carman 1991	No	Yes	This study was a randomized, double-blind, active- and placebo-controlled investigation of mianserin in a population of moderately to severely depressed outpatients, age 18 years or older, with the diagnosis of major depression according to DSM-III (American Psychiatric Association 1980). All patients gave informed consent in writing. All fertile females used adequate contraceptive means throughout. All patients were free of major or unstable medical problems and were free of other primary psychiatric diagnoses. Eligible patients underwent a 1-week placebo washout and were subsequently randomized to one of three treatment groups if their total 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) score was 18 or greater, and the total HAM-D 21-item scale had not been reduced by 20 percent or more from its screen value.	-	Amitriptyline	60-300	Placebo	Yes	6 weeks	50	50	27.6	26.7	No
Cassano 1996 - imipramine	No	Yes	Patients of both sexes, aged between 18 and 60 years, had to fulfil DSM-III-R criteria for MDD (single episode or recurrent) or bipolar disorder (depressed), without psychotic features or melancholia. Initial severity of the depression was controlled by a MADRS score greater than or equal to 25.	Other types of depression, acute or chronic psychosis, non-responders to two different antidepressants for the current episode, necessity of ECT, treatement within seven days of pre-inclusion with non MAOI, treatement withing 14 days of pre-inclusion with a reverseible MAOI, treatement within on month of pre-inclusion with a non-reversible MAOI, uncotrolled somatic disease, closed angle glaucoma, prostate adenoma, women with effective contraception, pregnant or lactating women, patients with a history of drug or alcohol abuse or dependence.	Imipramine	Mean: 154.5	Placebo	Yes	42 days	64	29	31.4	31.0	No
Cassano 1996 - tianeptine	No	Yes	Patients of both sexes, aged between 18 and 60 years, had to fulfil DSM-III-R criteria for MDD (single episode or recurrent) or bipolar disorder (depressed), without psychotic features or melancholia. Initial severity of the depression was controlled by a MADRS score greater than or equal to 25.	Other types of depression, acute or chronic psychosis, non-responders to two different antidepressants for the current episode, necessity of ECT, treatement within seven days of pre-inclusion with non MAOI, treatement withing 14 days of pre-inclusion with a reverseible MAOI, treatement within on month of pre-inclusion with a non-reversible MAOI, uncotrolled somatic disease, closed angle glaucoma, prostate adenoma, women with effective contraception, pregnant or lactating women, patients with a history of drug or alcohol abuse or dependence.	Tianeptine	Mean: 39	Placebo	Yes	42 days	64	30	31.2	31.0	No

Claghorn 1983	No	Yes	Patients considered for entry were males and females aged 18-65 years, with a diagnosis of Major Depressive Disorder as defined by the Research Diagnostic Criteria of Spitzer et al. (7). All patients had dysphoric mood and at least four of the following symptoms; poor appetite or weight loss, sleep difficulty, loss of interest or pleasure in usual activities including social contact or sex, feelings of self-reproach or guilt, difficulty concentrating, and recurrent thoughts of death or suicide. They also had to have no evidence of other pre-existing psychiatric disorders and their current episode of illness had to be of at least 2 weeks' duration. A minimum total score of 18 on the 21-item Hamilton Depression (HAM-D) scale (8) modified according to the Early Clinical Drug Evaluation programme (ECDEU) manual (9) was required at entry as well as at the end of a placebo washout period of 3-7 days.	Females of childbearing potential were excluded from entry if the possibility of pregnancy could not be definitely excluded during the study. Patients with somatic illness, pre-existing psychiatric conditions such as schizophrenia, schizoaffective disorders, epilepsy, and alcohol or drug dependence were also excluded, as were lactating and pregnant women.	Amitriptyline	75-300	Placebo	Yes	4 weeks	127	139	26	27.25	No
Claghorn 1996	No	Yes	Patients fulfilled the DSM-III-R criteria for major depressive disorder (single or recurrent episode without psychotic features or only mood-congruent psychotic features) and who had given informed consent, were enrolled in the trial. The procedures and possible side effects were explained to the subjects, who were obtained through self-referral or health care professionals; informed consent was obtained according to federal regulations before the performance of any study-related procedures. All subjects were free of any significant health problems, as determined by a physical examination and clinical laboratory tests (blood chemistry, hematology, urinalysis, serum pregnancy test) and electrocardiograms (ECGs). Subjects also had to be free of psychoactive medications for at least 7 days before study start.	-	Imipramine	80-240	Placebo	Yes	6 weeks	50	50	25.93	26.42	No
Cohn 1984	No	Yes	Individuals aged 60 or older were selected from outpa-tient populations at two centers. To participate in the study, subjects were required to have diagnoses of primary affec-tive disorder-depression, based on the Primary Affective Disorders Checklist (adapted from Feighner et al.), which resembles the criteria for major depressive epi-sode. Duration of the present episode was to be between 1 and 6 months. Patients were also required to have minimum total scores of 20 on the Hamilton Depression Rating Scale (HDRS) and 14 on the Beck Depression Inventory; additional baseline ratings included the Raskin Depression Scale and Covi Anxiety Scale.	Potential subjects who had past or present significant abnormal clinical findings, or medical conditions that might affect drug metabolism, were excluded. Other exclusion criteria were sensitivity to tricyclic antidepressants, requirement of ECT or any psychotro- pic medication other than chloral hydrate, and chronic alcohol or drug abuse.	Imipramine	75-200	Placebo	Yes	4 weeks	Unclear	Unclear	27	28	No
Cohn 1985	No	Yes	Patients eligible for inclusion were outpatients diagnosed as having major depressive illness according to DSM-III criteria, except that our patients had to have had the illness for at least 1 month rather than 2 weeks. The HAM-D total score of each patient had to be equal to or greater than 20.	Patients were excluded because of concomitant physical conditions or histories of conditions that would interfere with therapy or evaluation.	Imipramine	Maximum: 300	Placebo	Yes	6 weeks	54	58	25.9	25.14	No
Cohn 1990	No	Yes	Recurrent or single episode, 18+ years old, 18 or more om HAMD-17, no more than 20% decrease between screen and baseline, RDS of at least 8 and higher than Covi Anxiety scale.	Schizophrenia, atypical type, anxiety, bipolar, drug or alcohol abuse, medical conditions.	Imipramine	65-275	Placebo	Yes	6 weeks	Unclear	Unclear	24.5	25.6	No
Cohn 1996	No	Yes	HAMD-17 of at least 20, 18+ years	-	Imipramine	Unclear	Placebo	No	8 weeks	11	13	23.6	23.4	No
Costa e Silva 1997	No	Yes	18- to 60-year-old patients, eligible for the study, had to fulfil DSM-III-R criteria for Major Depression or Bipolar Disorder. De-pressed, of moderate or severe intensity without psychotic features, with or without criteria for melancholic type and with a total Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 25 [22], The patients were in- or out-patients.	Patients could not be included if they were defined as treatment resistant after prescription of two different antidepressants, each antidepressant having been prescribed for at least 4 weeks, with daily dose regarded as being in the therapeutic range. Patients with a severe or uncontrolled disease, with a history of drug abuse or depen-dence, or with excessive drinking habits, women of child-bearing potential without effective contraception, or those pregnant or breast-feeding had to be excluded.	Tianeptine	25-50	Placebo	Yes	6 weeks	Unclear	Unclear	35.2	35.6	No
Dominguez 1985	No	Yes	Patients between the ages of 21 and 65 who meet DSM-III criteria of MDD (single or recurrent). All had establishes primary depressive symptoms of at least 2 weeks duration, with a minimum score of 15 on the HAM-D17	Patients were excluded if their depression was secondary to any other psychiatric illness, if they had any significant physical condition, or had a history of recent or continued substance abuse. Patients were also excluded of they were pregnant or of childbearing potential. Other exclusion criteria were exposure to antidepressants within 3 days, lithium within a week and/or MAO inhibitors, ECT, or investigational drugs within 1 month of the washout phase.	Imipramine	100-300	Placebo	Yes	4 weeks	35	31	22.0	20.9	No
Doogan 1994	No	Yes	Patients were eligible for inclusion if they were attending a general practitioner for treatment of a primary major depressive episode that met DSM-III-R criteria (American Psychiatric Association, 1987), were aged over 18 years, and gave informed consent. They also had to have a score on the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) of 22 or more, and a severity score of 4 or more on the Clinical Global Impression (CGI) scale (Guy, 1976).	Exclusion criteria were: (l) severe depression (a score over 35 on the MADRS); (2) risk of suicide (MAD RS item 10 rated over 2); (3) current pregnancy, lactation, or risk of pregnancy; (4) significant concomitant physical disease (including recent myocardial infarction or cardiac arrhythmias); (5) history of mania or hypomania; (6) benign prostatic hyperplasia; (7) history of hypotension; (8) concurrent antihypertensive therapy with bethanidine, debrisoquine, or guanethidine; (9) concurrent therapy with sympathomimetics or antihistamines; (10) lithium therapy within the preceding 3 months; (11) a history of intolerance, resistance, or sensitivity to either tricyclic antidepressants or 5-HT reuptake inhibitors; (12) resistant depression (8 or more weeks' treatment with antidepressants for the current episode or a duration of the current episode of over l year); (13) narrow-angle glaucoma; (14) depression secondary to other psychiatric disease (e.g. schizophrenia, dementia) or to organic disease; (15) history of epilepsy; (16) current use of other psychotropic medication (apart from a short-acting nonbarbiturate hypnotic).	Dothiepin	75-150	Placebo	Yes	6 weeks	108	101	27.3	27.4	No
Dunbar 1991	No	Yes	Outpatients who fulfilled the DSM-III criteria for major depression and had a score of 18 or more on HAMD-17. Their baseline Raskin depression score had to be higher than their Covi anxiety score.	Exclusion from the study occurred if patients had any other primary psychiatric diagnosis or progressive/ unstable physical illness. Women of childbearing potential were excluded for the initial part of the study (FDA requirement). During the latter stages of the trial, women not using adequate contraception or who were lactating were excluded. Therapy lasted 6 weeks following a 4-14 day placebo run-in period. Any patients who had a 2 20% reduction in the HAMD score over this period were excluded, the remaining subjects being randomised to either paroxetine, imipramine or placebo.	Imipramine	65-275	Placebo	Yes	6 weeks	241	244	26.2	26.6	No
Edwards 1983	No	Yes	Outpatients of both sexes between the ages of 18 and 66 years were selected from those referred to the Psychiatric Division of the Royal South Hants Hospital, Southampton. To be included in the study patients must have had a unipolar depressive illnes which had become established as an 'autonomous' process and whose course was largely independent of environmental influences even though stressful events might have been involved in its aetiology (Edwards & Ollerenshaw, 1974). Patients included met the Medical Research Council criteria for primary depressive illnes (Medical Research Council, 1965)and the criteria of Feighner and his colleagues (Feighner et al., 1972). They corresponded to the DSM-III category of 'major depression' and no patients had a score of less than 17 on the Hamilton Rating Scale for Depression (Hamilton, 1960).	Patients who had received treatment with a therapeutic dose of mianserin or maprotiline at any time during the course of their present illness were excluded. Patients were also excluded if they had a serious physical illness, organic brain syndrome, epilepsy, mental subnormality, a history of alcohol or illegal drug abuse or had been given ECT during the preceding six months.Pregnant women or women likely to become pregnant during treatment were also excluded.	Maprotiline	75-225	Placebo	No	6 weeks	20	19	22.1	24.1	No
Emsley 2018	Yes	Yes	Outpatients, at least 65 year, moderate to severe episodes of recurrent MDD.	MDD single epidose, bipolar I and II, dysthymic disorder, depression superimposed or dysthymic disorder, Alzheimers, dementia, mild cognitive impairment, panic disorder, agoraphobia, specific fobia, social phobia, OCD, PTSD, acute stress disorder, psychotic disorder according til DSM-IV-TR. Unstable medical conditions, alcohol or drug abuse. Not responded to 2 drugs, has ECT or structured psychoterapy.	Tianeptine	25-50	Placebo	Yes	8 weeks	105	107	26.7	26.6	No
Escobar 1980	No	Yes	(1) diagnosis of endogenous major depressive disorder according to the Research Diagnostic Criteria (RDC) 8 of the New York State Psychiatric Institute; (2) no history of other psychiatric disorder or major physical illness; (3) baseline total scores in the Hamilton Depression Scale (HAM-D) of 18 or higher; (4) seven of 21 symptoms of depression as listed in Table I distributed in at least three of the five symptom clusters; and (5) signed informed consent.	By the end of the washout period, total scores in the Hamilton Depression Scale had to be 18 or higher for the patient to go into the double-blind portion of the study.	Imipramine	100-300	Placebo	Yes	4 weeks	15	12	31.3	30.9	No
Fabre 1996	No	Yes	Females (using a medically acceptable method of birth control) and males aged 18 to 65 years who met DSM-111-R criteria for major depressive disorder were recruited on an outpatient basis. All subjects had a minimum score of 20 on the 21-item Hamilton Depression Rating Scale for Depression (HAM-D) and a minimum score of 2 on the "depressed mood" item at screening and baseline. A minimum Raskin Depression Scale score of 8 and a Covi Anxiety Scale score less than the Raskin Score were also required at the screening and baseline visits.	Exclusion criteria included any other primary psychiatric diagnosis, an unstable medical condition, clinically significant abnormal laboratory findings and patients who demonstrated a placebo response (defined as <':20% improvement in HAM-D total score) during the washout phase.	Imipramine	40-240	Placebo	Yes	6 weeks	50	50	26.5	26.0	No
Feiger 1996	No	Yes	Male and female subject ages 18 or older with the diagnosis off either single or recurrent episodes of major depression were eligible for this study. At least a 4-day baseline period and to be free of clinically relevant amounts of psychotropic agents for an appropriate time. A 3-week washout period was required for patients who had been treated for more than 3 months with antidepressants or anxiolytic drugs. Patients could not have been treated with another investigational drug within 2 months of the baseline period. Subjects were required to have a score of at least 20 on the HAMD-17 at the end of the baseline period.	Subject were excluded if they were pregnant or lactating or were sexually active and able to bear children but were not using adequate contraception. Other exclusion criteria included Axis 1 psychiatric diagnosis; delusions or hallucinations during current episode of depression, high probability of needing other treatments during the course of study (except chloral hydrate for sleep), significant current medical conditions, meeting DSM-III-R criteria for psychoactive substance use disorder within the prior 12 months, allergy or hypersensitivity to azaperones or tricyclic antidepressants, significant suicide risk, electroconvulsive therapy within 6 months of the study, and a history of glaucoma, urinary retention, or seizure disorders.	Imipramine	50-300	Placebo	Yes	8 weeks	41	40	24	24	No
Feighner 1980	No	Yes	Patients considered for this study were males and females, 18 to 65 years of age, with a psychiatric diag- nosis of primary depression according to the criteria of Feighner et al. 14 In addition, these patients were required to have at least seven of the 21 signs comprising the Symptom Profile for Depression or to exhibit symptoms distributed among at least three of the five categories encompassed by the Profile (manifest or reported depression, somatic disturbance, depressive ideation, re- tarded thought, psychomotor disturbance). In addition, a total score of 18 or more on the Hamilton Psychiatric Rating Scale for Depression was required.	Females at risk of conception were not permitted to enter the study. Also excluded were patients with other psychotic disease or neurosis, poor physical health or a history of brain trauma, alcoholism, drug addiction, seizure disorder, mental deficiency or electroshock therapy in the preceding six months.	Imipramine	100-300	Placebo	Yes	4 weeks	20	12	36.6	36.0	No

Feighner 1983	No	Yes	Outpatients suffering from moderate to severe symptoms of a Unipolar Major Depressive Disorder for at least 1 month were selected for the study. They met the Feighner Diagnostic Criteria for primary depression (13), which are essentially interchangeable with the DSM-I11 criteria for Major Depressive Episode (14). The Feighner criteria include dysphoric mood and at least five of the following symptoms: poor appetite or weight loss, sleep difficulty, loss of energy, agitation or retardation, loss of interest in usual activities or decrease in sexual drive, feelings of guilt, complaints of diminished ability, and thoughts of death or suicide. Additionally, participants were required to have minimum baseline baseline scores as follows: 18 or more on the 21-item Hamilton Psychiatric Depression Rating Scale; 8 or more on the Raskin Depression Scale; Covi Anxiety Scale less than or equal to the Raskin Score. Patients considered for participation were males or nonpregnant females using contraceptives or not of childbearing potential; 18 to 70 years of age; and outpatients suffering from moderate to severe symptoms of a Unipolar Major Depressive Disorder of at least 1 month's duration.	Patients were excluded who suffered from bipolar major affective disorders, predominantly psychomotor retarded depression, or depression secondary to other non-affective psychiatric illness. Patients with clinically unstable medical disorders were excluded as were any patients known to be hypersensitive to benzodiazepines or TCA's. In addition, patients who required anticholinergics, CNS active anti-hypertensives, or other psychotropic medications, except chlorohydrate, were excluded.	Imipramine	50-225	Placebo	Yes	6 weeks	Unclear	Unclear	30.4	30.0	No
Feighner 1989a	No	Yes	Inclusion criteria: 18-70, an intial 21-item HAMD score of at least 20, a minimum Raskin Depression Scale score of 8, and a Covi Anxiety Scale score less than or equal to the Raskin.	Patients were excluded if they were pregnant, not practicing medically acceptable contraception, or if they posed a serious suicide risk. Organic brain syndrome, schizophrenia, a history of seizures, drug or alcohol abuse within the past year, or a contraindication to imiprimine, such as glaucoma or chronic urinary retention. Also excluded after wash-out if their HAMD score was less than 20 or had decreased by 20% or more.	Imipramine	Unclear	Placebo	Yes	6 weeks	Unclear	Unclear	25.96	25.9	No
Feighner 1989b	No	Yes	DSM-III major depression	-	Imipramine	150-300	Placebo	Yes	6 weeks	36	19	27	25	No
Feighner 1989c	No	Yes	MDD according to DSM-III for at least 4 weeks. Minimum score of 18 on HAMD-17. Age 18-70	-	Imipramine	25-250	Placebo	Yes	6 weeks	15	15	Unclear	Unclear	No
Ferguson 1994 - dothiepin	No	Yes	Outpatients aged 18 to 75 years with a diagnosis of major depression without psychotic features (DSM-III-R) criteria) were screened at 15 centers. Patients were required to have a total score of at least 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D), a score of at least 9 on the Raskin Depression Scale, a score on the Covi Anxiety Scale 10 less than the Raskin score, and a moderate or greater severity of illness on the Clinical Global Impressions (CGI) scale.	Exclusion criteria included active suicidal ideation or suicide attempts in the last 12 months; schizophrenia, organic mental syndromes, or seizure disorders; failure to respond to an adequate course of antidepressant therapy; recent history of alcohol or drug abuse; electroconvulsive therapy within 30 days of the study; monoamine oxidase inhibitors or neuroleptics within 14 days of active drug treatment; and use of other antidepressants or anxiolytics within 7 days of baseline.	Dothiepin	50-150	Placebo	Yes	10 weeks	194	96	23.9	23.6	No
Ferguson 1994 - doxepin	No	Yes	Outpatients aged 18 to 75 years with a diagnosis of major depression without psychotic features (DSM-III-R) criteria) were screened at 15 centers. Patients were required to have a total score of at least 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D), a score of at least 9 on the Raskin Depression Scale, a score on the Covi Anxiety Scale 10 less than the Raskin score, and a moderate or greater severity of illness on the Clinical Global Impressions (CGI) scale.	Exclusion criteria included active suicidal ideation or suicide attempts in the last 12 months; schizophrenia, organic mental syndromes, or seizure disorders; failure to respond to an adequate course of antidepressant therapy; recent history of alcohol or drug abuse; electroconvulsive therapy within 30 days of the study; monoamine oxidase inhibitors or neuroleptics within 14 days of active drug treatment; and use of other antidepressants or anxiolytics within 7 days of baseline.	Doxepin	50-150	Placebo	Yes	9 weeks	193	96	23.8	23.6	No
Fontaine 1994	No	Yes	Inclusion criteria included age between 18 and 65 years, diagnosis of MDD (modified to require dysphoric features of at least 4 weeks' duration), minimum pretreatment score of 22 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D- 17), and written informed consent.	Patients were excluded from entry into the study for any of the following reasons: primary psychiatric diagnosis other than depression; history of bipolar disorder, organic mental disorder, or schizophrenia; symptoms of urinary retention or prostatic hypertrophy, or glaucoma; DSM-III-defined diagnosis of alcoholism or substance abuse within the past year; significant medical disorder (except mild hypertension controlled with drugs other than betablockers); hypersensitivity to trazodone or tricyclic antidepressants; need for concomitant medication affecting the central nervous system, except occasional chloral hydrate for sleep; serious risk of suicide; previous participation in an investigational drug trial; women breast-feeding or not using an approved method of contraception; use of a monoamine oxidase inhibitor within 14 days or any other psychotropic medications within 7 days before baseline; or electroconvulsive therapy within 28 days before baseline.	Imipramine	50-250	Placebo	Yes	6 weeks	45	45	25.8	25.9	No
Gelenberg 1990a	No	Yes	For inclusion patients had to meet DSM-III criteria for major depression and Feighner criteria for primary depression. They also had to score at least 16 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) at the end of a "washout" period.	We excluded women who were or who might become pregnant, patients with other psychiatric or serious medical illnesses, or patients with chemical dependencies. Further, patients must have been free of lithium for at least 7 days, MAO inhibitors for at least 2 weeks, tricyclic or other antidepressants for at least 3 days, and any other investigational drug for at least 4 weeks, and must not have had electroconvulsive therapy within at least 4 weeks.	Amitriptyline	50-350	Placebo	Yes	6 weeks	19	22	24.8	23.6	No
Gelenberg 1990b	No	Yes	Men and women (without childbearing potential) outpatients, ages 18 to 75 years, with a definite diagnosis of major depressive disorder per Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) and an entry score of >/= 20 on a modified Hamilton Depression Rating Scale (HAM-D), adapted to include symptoms of hypersomnia, hyperphagia, and weight gain (see Appendix).	We excluded patients with a history of mania, symptoms of psychosis or a diagnosis of schizophrenia, those unable to give informed consent, or patients with a current diagnosis of al- coholism, other drug addiction, epilepsy or clinical evidence of serious suicidal risk with poor past response to antidepressant therapy or with medical illnesses that might interfere with treatment.	Imipramine	Unclear	Placebo	No	4 weeks	Unclear	Unclear	24.3	24.5	No
Georgotas 1982	No	Yes	Patients were selected for the study on the basis of the following criteria: l) evidence of major depressive disorder according to Research Diagnostic Criteria (RDC) (9) , 2) age between 18 and 65 years, and 3) minimum baseline total score of 18 on the Hamilton Rating Scale for Depression .	Exclusion criteria were intercurrent medical illness, childbearing potential, and the need to take other medications. The patients were predominantly middle aged. For two-thirds of them the current depressive episode had lasted 6 months or more. All patients provided informed consent.	Amitriptyline	150-300	Placebo	Yes	4 weeks	Unclear	Unclear	28.5	28.6	No
Georgotas 1986	No	Yes	Men and women, 55 years of age and older, complaining of depressive symptoms, were evaluated for entry into this outpatient study. Patients incluaed in the study were independently diagnosed by two psychiatrists as suffering from a major depressive disorder as defined by the Research Diagnostic Criteria (Spitzer et al. 1978). A score of 16 or greater on the Hamilton Rating Scale for Depression was also required for inclusion. The depressive subtype (endogenous/nonendogenous) according to RDC was also ascertained.	Patients were excluded if they showed evidence of moderate to severe dementia, drug or alcohol dependence as defined by DSM-III, mental retardation, serious neurologicai disorders, other preexisting major psychiatric disorders, serious medicaf illness, urinary retention, narrow-angle glaucoma, or supersensitivity to TCAs or MAOIs. The severityof the depression or its resistance to previous treatment was not a deterrent to inclusion, provided that patients were not actively suicidal and that they had a responsible friend or family member who was in frequent contact with our research team.	Nortriptyline	Mean: 79	Placebo	Yes	7 weeks	Unclear	Unclear	23.6	23.1	No
Gerner 1980	No	Yes	60 years of age and older with a diagnosis of unipolar depression by the Research Diagnostic Criteria (48) and with a Hamilton Depression Score of at least 18 were included in this study.	Patients were excluded because of significant hepatic, renal, cardiovascular, peurological, or other medical problems, or use of prescribed or other drugs (including alcohol).	Imipramine	50-200	Placebo	Yes	4 weeks	21	20	25	25	No
Gershon 1980	No	Yes	Admission criteria were primary depressive disor-der of the endogenous type, a minimum score of 18 on the Hamilton Rating Scale for Depression and a score of at least 7 of the 21 symptoms in at least three of the five categories of the Symptom Profile for Depression (Table 1). The Diagnostic and Statistical Manual (DSM-III) criteria for a major depressive disorder were met by 261 of the 263 patients included in the analysis of efficacy. Patients with other psychotic or neurotic disorders, im-paired physical health, a history of brain trauma, alco-holism, drug addiction, seizure disorders, mental defi-ciency, and risk of pregnancy were excluded from the trial. All patients gave written informed consent for the study after an explanation of the possible risks and benefits was provided.	-	Imipramine	100-300	Placebo	Yes	4 weeks	Unclear	Unclear	31	30	No
Ginestet 1997 - 37.5 mg	No	Yes	The patients included were in-or outpatients, 18–65 years. They had to meet DSM-III-R criteria for major depression. Depression was of moderate or severe intensity, without psychotic features, meeting or not criteria for melancholic type. MADRS score had to be of at least 25 (Montgomery and Asberg, 1979) at the end of the placebo period and provided that, in case of a score decrease, this reduction was less than 30% of the initial score.	Patients who could not be included were: patients defined as nonresponders after prescription of an antidepressant for at least 4 weeks for the current episode with daily doses regarded as being within the therapeutic range; patients with severe or uncontrolled somatic diseases, patients with a history of drug or alcohol abuse, pregnant women or women of childbearing potential without effec- tive contraception	Tianeptine	37.5	Placebo	Yes	6 weeks	84	38	31.6	31.7	No
Ginestet 1997 - 75 mg	No	Yes	The patients included were in-or outpatients, 18–65 years. They had to meet DSM-III-R criteria for major depression. Depression was of moderate or severe intensity, without psychotic features, meeting or not criteria for melancholic type. MADRS score had to be of at least 25 (Montgomery and Asberg, 1979) at the end of the placebo period and provided that, in case of a score decrease, this reduction was less than 30% of the initial score.	Patients who could not be included were: patients defined as nonresponders after prescription of an antidepressant for at least 4 weeks for the current episode with daily doses regarded as being within the therapeutic range; patients with severe or uncontrolled somatic diseases, patients with a history of drug or alcohol abuse, pregnant women or women of childbearing potential without effec- tive contraception	Tianeptine	75	Placebo	Yes	6 weeks	84	38	31.6	31.7	No
Hicks 1988	No	Yes	Forty-eight patients, aged 18 to 59 years, entered the study by physician referral or in response to a newspaper advertisement. They were included in the study if their primary prychiatric diagnosis met DSM-III criteria for major depression with melancholia (American Psychiatric Association, 1980). Also required were a minimum score of 26 on the Hamilton Rating Scale for Depression (Hamilton, 1960) and 10 on the Raskin Depression Scale (Raskin et al., 1967), and a Covi Anxiety Scale score (Covi et al., 1979) below the Raskin score.	Patients were excluded from the study if they were pregnant, had major medical illness, epilepsy, glaucoma, hypothyroidism, or active alcohol or drug abuse. Also excluded were those who had received electroconvulsive therapy, monoamine oxidase inhibitors, or an investigational drug in the previous 2 weeks. Psychotropic medications were tapered and discontinued 7 days before hospitalization. Patients were admitted as inpatients to the Clinical Research Center, where they remained for 10-14 days.	Amitriptyline	25-300	Placebo	Yes	6 weeks	16	15	30.8	29.4	No
Itil 1983	No	Yes	Patients were selected who reported an episode of primary depression of at least 2 weeks duration, in which the alteration of mood exceeded customary sadness and could not be relieved by social contact. Patients all attained a minimum of 15 points on the first 17 items of the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967). All patients had a minimum of four overt symptoms, thus complying with the Research Diagnostic Criteria for depressive disorders (DSM, 1980). All patients met the criteria for major affective disorder; three were classified as bipolar depressed; the remainder were divided between single episode (n = 20) and recurrent major depressive disorder (n = 46).	Pregnant women and women of childbearing potential were excluded, as were patients whose depression was secondary to another illness. Patients receiving the following therapy were also excluded: imipramine, MAO inhibitors within 2 weeks of study commencement, electroconvulsive therapy within 4 weeks of study commencement, lithium carbonate, or any short- or long-term medication which might interact with either study drug.	Imipramine	50-300	Placebo	Yes	4 weeks	25	22	21.9	19.7	No
Itil 1993 - dothiepin	No	Yes	Diagnosis of Major Depressive Episode (DSM-III-R 296.2, 296.3)	Psychotic features	Dothiepin	50-150	Placebo	Yes	9 weeks	Unclear	Unclear	24.9	22.8	No
Itil 1993 - doxepin	No	Yes	Diagnosis of Major Depressive Episode (DSM-III-R 296.2, 296.3)	Psychotic features	Doxepin	50-150	Placebo	Yes	9 weeks	Unclear	Unclear	23.4	22.8	No
Jacobson 1990	No	Yes	Psychiatric outpatients meeting DSM-III criteria for a major depressive episode (single or recurrent), baseline 17-item HAM-D >= 18	>25% decrease in total HAM-D score during the placebo wash-out period, history of schizophrenia or other psychoses, atypical depression, adjustment disorder, drug or alcohol abuse, drug overdose in the previous 4 months, active suicidal tendencies; patients with clinically relevant renal, cardiovascular, respiratory or cerebrovascular diseases, prostatic hypertrophy, narrow-angle glaucoma, urinary retention, unstable diabetes, seizure disorder or clinically relevant EEG changes; no ECT in the previous 3 months, adequate dose of an antidepressant (>150 mg amitriptyline or equivalent for at least 6 weeks) in the month preceding the trial; women of childbearing potential without adequate contraception, mothers either breastfeeding or 6 months post partum	Amitriptyline	Mean: 115.1	Placebo	Yes	4-6 weeks (unclear)	Unclear	Unclear	21.6	21.4	No
Javors 2000	No	Yes	Patients meeting DSM-IV criteria for unipolar major depression	-	Desipramine	50-250	Placebo	No	6 weeks	5	4	Unclear	Unclear	No
Katz 1990	No	No	Consenting, medically stable subjects with persistent symptoms of major depression, a score on the 21-item Hamilton Rating Scale for Depression of at least 18, and no medical contraindications to the use of nortriptyline	-	Nortriptyline	Unclear	Placebo	Yes	7 weeks	Unclear	Unclear	21.7	23.7	No

Katz 1993b	No	Yes	For both protocols, patients were required to satisfy then-current DSM criteria for major depressive episode. For protocol 03, DSM-III criteria were to be satisfied, and for protocol 01, DSM-III-R criteria were to be satisfied. However, protocol 01 also specifically excluded patients with atypicality and double depressions. Thus, for both protocols the inclusion criteria for affective disorder were close. In addition, for both protocols patients were required to satisfy a severity criterion of 18 or greater on the Hamilton Depression Rating Scale. Patients were required to be 18-65 years old. Protocol 01 also allowed entry of patients 66-70 years old following medical consultation.	Patients were excluded on standard medical grounds including clinically significant hepatic disease, glaucoma, seizure disorder, hypertension, endocrine disorder, prostatic hypertrophy, renal disease, cerebral vascular disease, cardiovascular disease (including significant electrocardiogram [ECG] findings), clinical laboratory findings, bone marrow depression, blood dyscrasia, hypersensitivity to tricyclic or tetracyclic antidepressants. Women of childbearing potential, pregnant, and nursing women were not to be entered. Patients who were judged at risk for suicide were excluded. All patients provided written informed consent, and conduct of the protocol was approved at each site by an institutional review board.	Amitriptyline	75-225	Placebo	Yes	4 weeks	93	104	23.6	23.2	No
Katz 2004	No	Yes	Patients with a diagnosis of primary major depression, unipolar type, single, or recurrent episode were identified from newly admitted in-patients at two Texas Veterans Administration (VA) hospitals. All subjects provided written informed consent and the study was carried out as approved by the University of Texas Health Center at San Antonio's Institutional Review Board (IRB) and the Dallas VA Medical Center's IRB. Diagnostic interviews were conducted using the Structured Clinical Interview for DSM-III (SCID; Spitzer and Williams, 1983). Patients were required to score o18 on the HAMD (21-item version) (Hamilton, 1960).	-	Desipramine	50-350	Placebo	Yes	6 weeks	29	25	26	25.47	No
Klieser 1988	No	Yes	The patients all suffered from severe vitalized depression corresponding to the DSM-III classification "major depressive disorder". The severity of the disease was so pronounced that the treatment had to be carried out on a closed ward.	-	Amitriptyline	150	Placebo	No	3 weeks	12	14	34	31	Cognitive behavioural therapy, group therapy, occupational therapy
Klieser 1989	No	Yes	Severe vitalized depressions or acute schizophrenia, and for whom locked ward-based treatment was indicated.	-	Amitriptyline	150	Placebo	No	21 days	10	14	Unclear	Unclear	No
Kocsis 1985	No	Yes	Subjects were included if they (1) fulfilled DSM-III criteria for dysthymic disorder, ie, depressed or dysphoric mood for at least two continuous years plus at least three associated symptoms; (2) had a Global Assessment Scale (GAS) score of 70 or less; (3) had a score on the 24-item version of the Hamilton Depression Scale (HAM-D)10 of greater than 13; and (4) had given signed informed consent.	Patients were excluded if they had a history of bipolar disorder, ie,mania or hypomania, or "secondary depression" as indicated by a history of psychosis, alcohol or substance abuse, or severe or chronic medical illness. Also excluded were patients having a contraindication to imipramine or an apparently adequate trial of antidepressant medication within the past six months. The presence of Axis I and Axis II disorders other than those already stated was systematically assessed but was not used to exclude patients from the study.	Imipramine	100-300	Placebo	Yes	6 weeks	29	25	25.6	22.1	No
Kupfer 1979	No	No	All forty-seven patients were hospitalized on the Clinical Research Unit (CRU) at Western Psychiatric Institute and Clinic (WPIC). At the time of admission, all patients had a traditional psychiatric interview and a physical examination. In addition, collateral information was obtained from their families and from case records of previous hospitalizations. During a two-week drug-free-period, they underwent a series of routine laboratory tests, including thyroid function tests, an electroencephalogram, and any other tests that, based on their history or physical examination, were indicated. All patients thus underwent an "entrainment period" during this time with respect to their sleep-wake cycle, meal schedule, etc. Following the two-week drug-free period, the Schedule for Affective Disorders and Schizophrenia (SADS) was filled out by their psychiatrist. The SADS, a structured research interview, which collects data necessary to make diagnoses using the Research Diagnostic Criteria (RDC) (2), was completed using information obtained from the initial interview, the case record, collateral history from relatives, observation on the CRU, and, if necessary, a second interview with the patient. After diagnoses were made using the RDC information obtained in the SADS, all cases were reviewed to obviate any problems regarding reliability among interviewers. If the level of severity of depression remained sufficiently high at the end of the drug-free period (a minimum score of 30 on the 17-item Hamilton Rating Scale using the sum of two raters), patients then entered the actual protocol and were subsequently evaluated twice weekly for severity of depression using the HRS throughout the investigation.	-	Amitriptyline	50-200	Placebo	Yes	4 weeks	30	17	40.3	45.5	No
Langlois 1985	No	Yes	Patients were diagnosed by two psychiatrists as suffering from a major depressive disorder according to RDC and DSM-III criteria [9, 10]. A minimum total score of 20 on the Hamilton Rating Scale for Depression [11] was required to enter the study. None of the patients had received an antidepressant or an antipsychotic drug for at least 2 weeks prior to entering the study.	-	Amitriptyline	150-225	Placebo	No	4 weeks	15	15	Unclear	Unclear	No
Lapierre 1987	No	Yes	Minimum 15 on HAMD-17	Other psychiatric diagnoses, significant organic disease, dependent on licit or illicit drugs, recieving ECT within 4 weeks, lithium carbonate within one week, MAO inhibitors within 2 weeks, other antidepressants during wash-out, any drug which could not be discontinued and might interact with study drug	Imipramine	Maximum: 300	Placebo	Yes	6 weeks	21	20	24	22	No
Larsen 1989	No	Yes	In- and outpatients of either sex, above 17 years of age, suffering from major depressive disorder (DSM-111) (2) classified as reactive depression according to the Newcastle li scale (3) were eligible for this double-blind trial. At 2 successive examinations 1 week apart the patients scored at least 15 on the first 17 items of the Hamilton Rating Scale for Depression (HRSD) (4)	Exclusion criteria were: previous manic episodes, adequate treatment already instituted, need for ECT, obvious suicide risk, history of drug or alcohol abuse, noncooperation or unreliability, pregnancy, lactation, abnormal hepatic or renal function and known haematopoietic, metabolic or hormonal disorders, diastolic blood pressure above 100 mmHg and any contraindication for tricyclic antidepressants.	Clomipramine	75-150	Placebo	No	6 weeks	20	18	Unclear	Unclear	No
Lydiard 1989	No	Yes	Subjects were male and female, 18 years or above, who were not on psychotropic medications (no lithium within 6 months of study entry) and who met the DSM-III (American Psychiatric Association 1980) criteria for major depressive disorder. Patients had a score of at least 22 on the Hamilton Depression Rating Scale (HAM-D).	Exclusions included psychotic disorders, organic brain syndrome, bipolar affective disorder, current depressive symptoms of < 1 month or > ! 8 months duration, a current substance use disorder, or clear suicidal intent.	Imipramine	100-300	Placebo	Yes	6 weeks	18	18	26.4	26.0	No
Lydiard 1997	No	Yes	At least 18 years old, outpatients with DSM-III-R primary axis 1 of major depression (single or recurrent), current episode not less than 4 weeks. HAMD-17 score 18 or more. No more than slight improvement during placebo washout, max 3 points on CGI-I	DSM-III-R criteria for: acute/chronic organic mental disorder, organic brain syndrome, dysthymia, bipolar disorder, severe generalised anxiety disorder, OCD, psychotic disorders, severe personality disorder. Significant medical illness, recent history of substance abuse or depence, current suicide risk, history of neurologic disease, narrow-angle glaucoma or significant prostate symptoms. Additiona psychotropic drugs during study, previously receivedsertraline, within 1 month in other study, failed to respond to adequate trials of two or more antidepressants, received any depot neuroleptic, any daily psychotropic medication within 2 weeks, received MAOIs within 3 weeks. Significant laboratory or ECG abnormalities, women of childbearing potential were required contraception and negative pregnancy test prior	Amitriptyline	50-200	Placebo	Yes	8 weeks	131	129	22.1	22.1	No
Mann 1981	No	Yes	Admission criteria included a diagnosis of a major depressive disorder, endogenous subtype, according to research diagnostic criteria 25 of sufficient severity to score at least 18 on the Hamilton depression scale	Patients with other significant neurotic or psychotic disorders, alcohol or drug abuse, seizure disorders, mental retardation, brain trauma, significant physical disease, or females in whom the possibility of pregnancy could not be reasonably excluded were not admitted to the study.	Imipramine	100-300	Placebo	Yes	4 weeks	Unclear	Unclear	24	22.5	No
March 1990	No	Yes	Admission criteria included an illness duration between 1 and 18 months (mean±SD=7.9±4.5; range, 1-17 months) and a minimum score of 22 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D).	The following subjects were excluded from participation: pregnant women, lactating women, or women of childbearing potential who were taking inadequate contraceptive measures; patients with schizophrenia, psychotic symptoms, organic dementias, or a diagnosis within 1 year of substance abuse or alcoholism; patients with cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, or other systemic diseases that could interfere with the diagnosis, treatmeut, or assessment of depression; patients who required treatment with any concurrent medication that might interact with or obscure the action of the study medications; patients with clinically significant abnormalities in electrocardiographic or laboratory results; patients with multiple drug allergies; patients who had received monoamine oxidase inhibitors or lithium in the 2 weeks preceding study entry or who had received any other antidepressant drugs in the preceding 1 week; and patients who had received any investigational drug or electroconvulsive therapy (ECT) in the previous 4 weeks	Imipramine	50-300	Placebo	Yes	6 weeks	18	18	25.5	26.5	No
McGrath 2000	No	Yes	Subjects were men and women, age 18 to 65 years, who met DSM-IV criteria for a major depressive episode for at least 1 month and also met the Columbia criteria for atypical depression (9). Unlike DSM-IV, which requires two associated symptoms together with mood reactivity for a diagnosis of atypical depression, the Columbia criteria require only one associated symptom among the following four: overeating, oversleeping, severe anergy, and pathological sensitivity to interpersonal rejection. The requirement for only one symptom is based on treatment outcome studies showing that the presence of one associated symptom appears sufficient to observe the advantage of MAOIs over tricyclics (3, 4) and evidence indicating that all associated symptoms were equivalent in predicting MAOI advantage (23). In addition, biologic, course-of-illness, and family study data indicate that patients with a single associated symptom more closely resemble those with more associated features than those with none (9)	The exclusions criteria were 1) significant suicidal risk, 2) pregnancy, lactation, or unwillingness to use effective birth control in women, 3) unstable and serious physical illness, 4) a history of seizures, 5) psychosis or organic mental syndrome, 6) substance use disorders active within 6 months, except for nicotine dependence, 7) history of mania, 8) antisocial personality disorder, 9) history of nonresponse to an adequate trial of fluoxetine (defined as 40 mg/day for at least 6 weeks) or imipramine (defined as greater than 150 mg/ day for 2 consecutive weeks and 4 weeks total treatment), 10) history of nonresponse to any other SSRI, and 11) laboratory evidence of hypothyroidism.	Imipramine	50-300	Placebo	Yes	10 weeks	53	52	Unclear	Unclear	No
Merideth 1983	No	Yes	Patients with a diagnosis of MDD as defined by RDC, 18+ on HAM-D21	Patients with somatic diseases, drug allergy, schizophrenia, epilepsy or a history of drug or alcohol abuse were excluded from the trial, as were women of child-bearing potential and lactating or pregnant women.	Imipramine	Mean: 134-215	Placebo	Yes	6weeks	Unclear	Unclear	26	26	No
Merideth 1984	No	Yes	Patients who participated in this study were at least 60 years old and met criteria for primary affective disorder- depression, based on the Primary Affective Disorders-Depression Checklist adapted from Feighner et al. These criteria resemble those for major depressive episode in Patients were also required to have, at baseline, moderate or severe symptoms of depression that produced a total score of at least 18 on the 21-item Hamilton Depression Rating Scale (HDRS), including a score of 2 or more for the item depressed mood. Efforts were made to enroll patients whose current episode of illness had lasted at least 1 month, but not more than 6 months.	Patients who met any one of the following criteria were excluded from the study: 1) significant abnormal findings on physical examination or clinical laboratory study; 2) a medical or surgical condition that could interfere with the absorption, metabolism, distribution, or excretion of either test drug; 3) history of significant clinical illness in the pre-ceding 4 weeks; 4) history of hypersensitivity to psychotro- pic drugs chemically similar to nomifensine or imipramine; 5) use in the preceding 30 days of any investigational drug or of any marketed drug with a clear potential for toxicity to a major organ; 6) requirement of any psychotropic medica-tion other than chloral hydrate; 7) a need for electroconvul-sive therapy; and 8) chronic abuse of alcohol or other drugs.	Imipramine	50-200	Placebo	Yes	5 weeks	Unclear	Unclear	26	29	No
Miller 2001	No	Yes	All subjects gave oral and written informed consent before entry in the study. Patients meeting DSM-III-R criteria for Major Depression were randomly assigned to receive treatment.	-	Imipramine	Unclear	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Minelli 2010	No	Yes	MDD as diagnosed on the basis of DSM-IV criteria. All were judged treatment-resistant depressed patients. Treatment resistance to ADs was defined as two or more unsuccessful trials of ADs at an adequate dose for at least 4 weeks.	No patient presented psychotic symptoms or comorbility disorders in Axis II and Axis III of DSM-IV	Clomipramine	25	Placebo	No	1 hour	Unclear	Unclear	Unclear	Unclear	No

Murphy 1984 - vs CT	No	Yes	Unipolar, 18-60 years old, 20 or higher on BDI, 14 or higher on HAMD-17.	Free of psychotropic medication, neurologic disorders, medical disorders requiring medication other than diuretic.	Nortriptyline	Unclear	No intervention	No	12 weeks	Unclear	Unclear	20.55	18.83	Cognitive therapy
Murphy 1984 - vs CT + placebo	No	Yes	Unipolar, 18-60 years old, 20 or higher on BDI, 14 or higher on HAMD-17.	Free of psychotropic medication, neurologic disorders, medical disorders requiring medication other than diuretic.	Nortriptyline	Unclear	Active placebo	No	12 weeks	Unclear	Unclear	20.55	21.35	Cognitive therapy
Mynors-Wallis 1995	No	Yes	The main criterion for inclusion was that patients met the research diagnostic criteria for major depression-namely, that they had experienced low mood accompanied by at least four key symptoms of depression, such as appetite disturbance, sleep difficulty, loss of energy, poor concentration, guilt, suicidal thoughts, loss of interest or pleasure in usual activities, and psychomotor retardation, for at least two weeks. In addition, patients had to score 13 or more on the Hamilton rating scale for depression (17 items), which measures the severity of depression.	Criteria for exclusion included having another psychiatric disorder (other than anxiety disorder) before the onset of the depression, receiving current psychological or antidepressant drug treatment, having current psychotic symptoms, having serious suicidal intent, having a history of schizophrenia, recent drug or alcohol misuse, or physical problems that would preclude being able to take amitriptyline.	Amitriptyline	50-150	Placebo	No	12 weeks	31	30	19.1	18.4	Problem solving
Nair 1995	No	Yes	In- and out-patients of 60-90 years of age, meeting the DSM-III-R criteria for major depressive episode, were eligible. At randomization (baseline), the total score on the first 17 items of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960; Beth, 1981) was at least 18. The duration of the current episode was a minimum of 4 weeks and the severity at least moderate as rated on a Clinician's Global Impression of Severity Scale (CGIS) which covers the following categories: very severely ill, severely ill, moderately ill, mildly ill, minimally ill, or not ill.	Exclusion criteria were any other psychiatric or neurological diagnosis, known severe systemic diseases, acute infections, clinically significant abnormal laboratory findings, including ECG, sitting blood pressure of 2 170/l 00 mm Hg and heart rate of < 50 or > 100 bpm, orthostatic systolic fall in blood pressure of > 30 mm Hg after lying for 5 min and, finally, any contraindications to the trial drugs. Patients who were uncooperative, those with a history of drug or alcohol abuse or having received cyclic antidepressants in the preceding week, MAOIs and neuroleptics in the 2 preceding weeks and sleep deprivation or electroconvulsive therapy during the last month were also excluded.	Nortriptyline	25-100	Placebo	Yes	7 weeks	38	35	23.5	24.0	No
Niklson 1997	No	Yes	MDD according to DSM-III-R, age 18-70 years, HAMD-17 of 18 or greater, duration of present episode at least 2 weeks, but not longer than 12 months since diagnosis was made.	Any other primary psychiatric diagnosis, if they had received relevant antidepressants within 5 half-lives or ECT within 1 year. Patients with clinically relevant renal, hepatic, cardiovascular or cerebrovascular disease, diabetic or epileptic, women not adequately protected against pregnancy	Imipramine	Maximum: 150	Placebo	No	6 weeks	142	108	22.7	24.0	No
NIMH trial 1989	Yes	No	To be included in the study, patients had to meet Research Diagnostic Criteria for a current episode of definite major depressive disorder (with the additional criterion that the required symptoms had to be present for at least the previous 2 weeks) and had to have a score of 14 or greater on an amended version of the 17-item Hamilton Rating Scale for Depression (HRSD).	Exclusion criteria included specific additional psychiatric disorders (definite bipolar II and probable or definite bipolar I, panic disorder, alcoholism, drug use disorder, antisocial personality disorder, Briquet's syndrome, and Research Diagnostic Criteria diagnosis ofmajor depressive disorder, psychotic subtype), two or more schizotypal features, history of schizophrenia, organic brain syndrome, mental retardation, concurrent treatment, presence of specific physical illness or other medical contraindications for the use ofimipramine, and presence of a clinical state inconsistent with participating in the research protocol, eg, current active suicide potential or need for immediate treatment.	Imipramine	Mean: 185	Placebo	No	16 weeks	63	62	Unclear	Unclear	Minimal supportive therapy
Organon 3-020	No	Yes	Psychiatric outpatients meeting DSM-III criteria for a major depressive episode (single or recurrent), baseline 17-item HAM-D >= 18	>25% decrease in total HAM-D score during the placebo wash-out period, history of schizophrenia or other psychoses, atypical depression, adjustment disorder, drug or alcohol abuse, drug overdose in the previous 4 months, active suicidal tendencies; patients with clinically relevant renal, cardiovascular, respiratory or cerebrovascular diseases, prostatic hypertrophy, narrow-angle glaucoma, urinary retention, unstable diabetes, seizure disorder or clinically relevant EEG changes; no ECT in the previous 3 months, adequate dose of an antidepressant (>150 mg amitriptyline or equivalent for at least 6 weeks) in the month preceding the trial; women of childbearing potential without adequate contraception, mothers either breastfeeding or 6 months post partum	Amitriptyline	Mean: 133.7	Placebo	Yes	6 weeks	Unclear	Unclear	24.9	25.2	No
Organon 84062	No	Yes	Psychiatric outpatients meeting DSM-III criteria for a major depressive episode (single or recurrent), baseline 17-item HAM-D >= 18	-	Amitriptyline	Unclear	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Peselow 1989	No	Yes	All patients who gave consent were treated as out-patients at the Foundation for Depression-Manic Depression. All patients involved in the trial met DSM-III criteria for major depression, were 18 years of age or older, and had a minimum score of 18 on the first 17 items of the 21-item Hamilton depression scale	All patients who participated in the trial were free from active medical illness, endocrinopathy and current substance abuse	Imipramine	65-275	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Philipp 1999	No	Yes	Inclusion: · Men and women aged 18-65 · Diagnosis of a moderate depressive episode according to ICD-10 (international classification of diseases, 10th revision) codes F32.1 and F33.1 · Minimum total score of 18 on the 17 item version of the Hamilton depression rating scale · A clinical global impressions rating of severity (item 1) of moderately, markedly, or severely ill · Depression duration a minimum of four weeks and a maximum of two years	Exclusion · Mild and severe depressive disorders according to ICD-10 codes F32.0, F33.0, F32.2, F33.2, F32.3, and F33.3 · Bipolar disorders according to ICD-10 codes F 31.x · Comorbidity from alcohol or drug dependence according to ICD-10 codes F10-F19 · Suicidal risk (assessed by item 10 of the Montgomery Asberg depression rating scale) · Long term prophylaxis with lithium or carbamazepine · Non-sufficient washout phase of previous psychotropic drug · Any interfering psychotropic drug taken concurrently · Any previous long term (> 3 months) treatment with benzodiazepines · Patients at general and specific risk (imipramine contraindications)	Imipramine	50-100	Placebo	No	8 weeks	110	47	22.2	22.7	No
Pomara 2001	No	No	Participation was open to males and females between the ages of 18 and 85 with a psychiatric diagnosis of major depressive episode (American Psychiatric Association, 1987) (DSM-III-R) and a baseline score of 18 on the 21-item Hamilton Depression Rating Scale (HDRS). Patients were also diagnosed as having definite, primary, unipolar depression using Research Diagnostic Criteria (RDC) (Spitzer et al., 1977) based on the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott, 1979).	Patients using other psychotropic medications within 14 days of entry into the study were also excluded.	Nortriptyline	50-150	Placebo	Yes	6 weeks	Unclear	Unclear	20.3	21.3	No
Prasko 2002	No	No	1) Age 20–60 years. 2) Meeting the DSM-III-R diagnostic criteria for recurrent major depressive disorder of moderate or severe type (296.32 and 296.33) without seasonal pattern. 3) At least 2 episodes of major depression in life time, and at least one episode of major depression during the last 2 years previous the current episode; at least one episode in another season than the current one. 4) Total score of the 21-item Hamilton Psychiatric Rating Scale for Depression [10] higher than 20. 5) Written informed consent.	1) The presence of any of the following mental conditions: a. Bipolar depression b. Panic disorder. c. Alcoholism or drug abuse. d. Antisocial personality disorder. e. Histrionic personality disorder. f. History of schizophrenia. g. Organic brain impairment. h. Mental retardation. 2) Presence of speciic physical illness or medical contraindications for using imipramine; endocrine disease in history. 3) Pregnancy. 4) Treatment by drugs causing depression in the last month. 5) Eye diseases (such as the aphakic condition, retinal diseases, inlammatory diseases, glaucoma, cataracts and optic nerve disease).	Imipramine	150	Placebo	Yes	3 weeks	13	11	23	23.1	Bright light therapy
Raft 1981	No	No	Patients attending the N.C. Memorial Hospital Pain Clinical in 1974 were screened for the presence of definite primary depression, according to the criteria of Feighner et al. (4). If they were judged to require antidepressant therapy and gave informed consent, they were assigned to receive on a double-blind basis	-	Amitriptyline	100-300	Placebo	No	5 weeks	12	7	29	27	No
Raisi 2007	No	No	All subjects met the Diagnostic and Statistical Manual of Mental Disorders, Forth edition (22) (DSM-IV) criteria for MDD, based on the Structured Clinical Interview for DSM-IV and had a baseline Hamilton Rating Scale for Depression (HAM-D, 17 item) (23) score of at least 20.	Patients with history of other psychiatric disorders such as bipolar disorder, personality disorder, anxiety disorder, substance abuse and alcoholism, as well as those with history of organic brain disorders, were excluded. Also, patients were excluded if they were psychotic or posed a significant risk of suicide at any time during the trial. Pregnant or lactating women were excluded as well. All patients were free of unstable medical disorders including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine or hematological illnesses. All patients gave a complete medical and psychiatric history and were physically examined before entring the study.	Nortriptyline	50	Placebo	No	8 weeks	23	22	32	31	Citalopram
Ravindran 1995	No	Yes	18-65, DSM-III-R, minimum score of 15 on HAMD-17	No other axis I disorder, free of physical or organic disorders	Desipramine	50-225	Placebo	Yes	8 weeks	37	26	20.7	21.0	No
Reimherr 1990	No	Yes	Male or female patients between the ages of 18 and 65 years who met the DSM-III criteria for major depression were considered eligible. After a single-blind, placebo-washout period of 7 to 14 days, patients were required to have both a minimum baseline score of 18 on the first 18 items of the Hamilton Rating Scale for Depression (HAM-D)16 with less than a 25% decrease in HAM-D score compared with their screening value to exclude placebo responders, and a higher score on the Raskin Depression Scale than on the Covi Anxiety Scale.	Patients excluded from the study included those not meeting DSM-III criteria for major depression, pregnant or lactating females, and females of childbearing potential not presently using an adequate method of contraception. Also excluded were patients receiving concurrent psychotherapeutic medication or concomitant medications other than estrogens, progesterone, and diuretics; patients with other significant medical conditions; pa-tients receiving another investigational drug within 4 weeks of enrolling in this study; patients with a history of serious intolerance or resistance to antidepressant medications; patients with an alcohol or drug abuse condition; and patients with schizophrenia or schizoaffective disorder.	Amitriptyline	50-150	Placebo	Yes	8 weeks	149	150	23.18	23.43	No
Reynolds 1999 - nortriptyline	No	No	To be included in the study, potential subjects were required to meet the criteria of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (15) and the Research Diagnostic Criteria (RDC) (16) for a definite current major depressive episode (nonpsychotic and nonbipolar, with no history of chronic intermittent depression or dysthymia). Forty-eight subjects were diagnosed with the SADS-L and 32 with the Structured Clinical Interview for DSM-IV (17), which replaced the SADS-L as our primary diagnostic instrument in 1996. The onset of the episode was required to fall in the period between 6 months before the death of the spouse and 12 months after the death. Episodes could be either single or recurrent. No other diagnoses, with the exception of generalized anxiety disorder, panic disorder, and posttraumatic stress disorder, were allowed. Diagnostic reliability was ensured through the use of a structured diagnostic assessment together with independent clinical confirmation by a senior psychiatrist (M.D.M., R.E.P.). A bereavement intensity score of 45 or more on the Texas Revised Inventory of Grief (18) was required as an indication of active grieving. Finally, to be eligible for the study, subjects were required to provide written informed consent.	-	Nortriptyline	Unclear	Placebo	Yes	8 weeks	25	22	19.0	20.1	No
Reynolds 1999 - nortriptyline + IP	No	No	To be included in the study, potential subjects were required to meet the criteria of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (15) and the Research Diagnostic Criteria (RDC) (16) for a definite current major depressive episode (nonpsychotic and nonbipolar, with no history of chronic intermittent depression or dysthymia). Forty-eight subjects were diagnosed with the SADS-L and 32 with the Structured Clinical Interview for DSM-IV (17), which replaced the SADS-L as our primary diagnostic instrument in 1996. The onset of the episode was required to fall in the period between 6 months before the death of the spouse and 12 months after the death. Episodes could be either single or recurrent. No other diagnoses, with the exception of generalized anxiety disorder, panic disorder, and posttraumatic stress disorder, were allowed. Diagnostic reliability was ensured through the use of a structured diagnostic assessment together with independent clinical confirmation by a senior psychiatrist (M.D.M., R.E.P.). A bereavement intensity score of 45 or more on the Texas Revised Inventory of Grief (18) was required as an indication of active grieving. Finally, to be eligible for the study, subjects were required to provide written informed consent.	-	Nortriptyline	Unclear	Placebo	Yes	8 weeks	16	17	20.5	19.9	Interpersonal psychotherapy

Rickels 1982a	No	No	The subjects for the study were 202 nonpsychotic unipolar depressed outpatients; 120 patients were treated in private family practice and 82 patients in psychiatric practice. All participating physicians were trained by our research group in clinical research and were closely supervised (8).	-	Amitriptyline	100-200	Placebo	No	6 weeks	68	68	Unclear	Unclear	No
Rickels 1982b	No	Yes	To enter the trial, patients had to suffer from at least a moderate degree of depression (>/= one month), have a score of >/= 5 on the Feighner Depression Scale, a score of >/=8 on the Raskin Depression Scale and a score of >/= 18 on the Hamilton Depression Scale.	Patients were excluded if they were pregnant, lactating or planned to become pregnant. Also excluded from the study were patients suffering from schizophrenia, organic brain syndrome, mental retardation, alcoholism, sociopathy, schizo-affective disorder or bipolar depression and melancholia. Patients with serious impairment of hepatic and renal functions, cardiovascular or metabolic disease, and those with known hypersensitivity to the study drugs were also excluded. Concomitant therapy with other psychotropic drugs or anticholinergic agents was not permitted. Patients had to be willing and able to understand and sign a written consent form.	Imipramine	50-225	Placebo	No	6 weeks	60	57	Unclear	Unclear	No
Rickels 1982c - imipramine	No	Yes	To enter the trial, patients had to suffer from moderate to severe depression for which antidepressant medication was considered the treatment of choice and had to be free of all psychotropic medications for at least 1 week, and for 2 weeks if they were taking MAO inhibitors. Patients had to be depressed for at least 1 month, had to have a score of >/= 5 on the Feighner Depression Scale (Feighner et al. (1972)), a score of >/= 8 on the Raskin Depression Scale (Raskin et al. (1970)), and a score of >/= 18 on the 21-item Hamilton Depression Scale (HDS) (Hamil-ton (1960)).	Patients were excluded if they were pregnant, lactating, or planned to become pregnant. Also excluded were patients with schizophrenia, organic brain syndrome, or mental retardation, as well as patients suffering from serious impair- ment of hepatic or renal functions, or cardiovascular or metabolic disease, and those with known hypersensitivity to the study drugs. Concomitant therapy with other psychotropic drugs was not permitted. Patients had to be willing and able to understand and sign a written informed consent form.	Imipramine	75-150	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Rickels 1982c - lofepramine	No	Yes	To enter the trial, patients had to suffer from moderate to severe depression for which antidepressant medication was considered the treatment of choice and had to be free of all psychotropic medications for at least 1 week, and for 2 weeks if they were taking MAO inhibitors. Patients had to be depressed for at least 1 month, had to have a score of >/= 5 on the Feighner Depression Scale (Feighner et al. (1972)), a score of >/= 8 on the Raskin Depression Scale (Raskin et al. (1970)), and a score of >/= 18 on the 21-item Hamilton Depression Scale (HDS) (Hamil-ton (1960)).	Patients were excluded if they were pregnant, lactating, or planned to become pregnant. Also excluded were patients with schizophrenia, organic brain syndrome, or mental retardation, as well as patients suffering from serious impair- ment of hepatic or renal functions, or cardiovascular or metabolic disease, and those with known hypersensitivity to the study drugs. Concomitant therapy with other psychotropic drugs was not permitted. Patients had to be willing and able to understand and sign a written informed consent form.	Lofepramine	105-210	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Rickels 1982d	No	Yes	In order to enter the drug trial, patients had to suffer from at least a moderate degree of depression for which antidepressant medication was considered the treatment of choice. Patients had to be depressed for at least 1 month, have a minimum baseline score of 20 on the 21-item Hamilton Depression Scale (HDS), have a minimum score of 8 on the Raskin Depression Scale, and on the Feighner Depression Checklist they had to exhibit dysphoric mood plus at least five additional items. These intake criteria thus identified each patient as suffering from a major depressive disorder as specified in the DSM III.	Excluded from the study were patients under the age of 18 and over the age of 60, patients with strong sociopathic trends, alcoholism, organic brain syndrome, or evidence of schizophrenia. Patients with serious cardiac, hepatic, renal or thyroid disease, with a positive history of urinary retention, prostate hypertrophy or glaucoma, requiring guanethidine, and pregnant or lactating women were also excluded. Patients had to be free from psychotropic medication for at least 7 days and free from MAO inhibitors for at least 2 weeks prior to study participation. No psychotropic or hypnotic medication other than an occasional chloral hydrate was allowed during the study. Finally, patients whose laboratory data were not within normal range were excluded.	Imipramine	100-200	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Rickels 1985 - amitriptyline	No	Yes	Patients voluntarily participated in the study and signed an informed consent form before enrolling. To qualify for inclusion, patients had to meet the Feighner Diagnostic Criteria for primary depression, which have since been determined to be concordant with the DSM-III criteria for major depressive episode. The Feighner criteria include dysphoric mood and at least five of the following symptoms: poor appetite or weight loss, sleep difficulty, loss of energy, agitation or retardation, loss of interest in usual activities or decrease in sexual drive, feelings of guilt, complaints of diminished ability, and thoughts of death or suicide. In addition, patients were required to have a score on the Raskin Depression Scale of 8 or more, five items or more endorsed on the Feighner Depression Checklist, a HAM-D (21-item) score of 18 or more, and a Covi Anxiety Scale score less than or equal to the Raskin score.	-	Amitriptyline	50-225	Placebo	Yes	6 weeks	124	65	25.48	26.38	No
Rickels 1985 - doxepin	No	Yes	Patients voluntarily participated in the study and signed an informed consent form before enrolling. To qualify for inclusion, patients had to meet the Feighner Diagnostic Criteria for primary depression, which have since been determined to be concordant with the DSM-III criteria for major depressive episode. The Feighner criteria include dysphoric mood and at least five of the following symptoms: poor appetite or weight loss, sleep difficulty, loss of energy, agitation or retardation, loss of interest in usual activities or decrease in sexual drive, feelings of guilt, complaints of diminished ability, and thoughts of death or suicide. In addition, patients were required to have a score on the Raskin Depression Scale of 8 or more, five items or more endorsed on the Feighner Depression Checklist, a HAM-D (21-item) score of 18 or more, and a Covi Anxiety Scale score less than or equal to the Raskin score.	-	Doxepin	50-225	Placebo	Yes	6 weeks	122	65	25.85	26.38	No
Rickels 1987	No	Yes	To qualify for inclusion in the trial, patients had to fulfill DSM-III criteria for MDD, single or recurrent subtype, and had to have a score of 18 or higher on the HAM-D-21 and a score of 8 or more on the Raskin Depression Scale, with the Covi Anxiety Scale score being less than or equal to the Raskin score. Arrival at the DSM-III diagnosis was facilitated by a physician checklist that also allowed subtyping of patients as to whether or not they belonged to the melancholic subtype. Female patients, if sexually active, used medically accepted contraceptive methods. Duration of present illness had to be one month or longer, a slightly stricter criterion than used by the DSM-III.	Study exclusions included the following: psychopathy or psychosis; bipolar, involutional, schizoaffective, or secondary depression; severe liver or kidney disease; uncontrolled cardiovascular, pulmonary, endocrinological, or collagen diseases; glaucoma; history of urinary retention; paralytic illness; convulsive disorders; and any disorder contraindicating the use of tricyclic medication. Patients known to be sensitive to benzodiazepines or antidepressants, actively abusing alcohol or other drugs, or requiring other psychotropic medications, anticholinergics, guanethidine, propranolol, methyldopa, or thyroid medications were also excluded. the use of any psychotropic medication other than study medication was prohibited.	Imipramine	75-225	Placebo	Yes	6 weeks	63	61	24.4	24.5	No
Rickels 1994	No	Yes	Moderate to severe major depressive disorder or bipolar disorder, depressed type but without rapid cycling. Patients had to be 18 years of age and had to have a total score of 20 or above on the HRSD at baseline. Female patients, if sexually active, had to use medically accepted contraceptive methods.	Standard medical and psychiatric exclusions were utilised.	Imipramine	50-300	Placebo	No	8 weeks	92	95	24.3	23.5	No
Roffman 1982	No	Yes	Depressed outpatients 18 to 65 years of age with a diagnosis of a major depressive disorder according to the Diagnostic Statistical Manual (296.2, 296.3) of the American Psychiatric Association and with a score of at least 18 on the Hamilton Depression Rating Scale (HORS) were used in this study.	Exclusion criteria consisted of history or evidence of clinically significant: renal disease, BUN or creatinine elevations, hepatic disease, SGOT, SGPT, or alkaline phosphatase elevations, cardiovascular diseases, metabolic diseases, seizure disorders, hypersensitivity to tricyclic antidepressants or related compounds, cerebrovascular disease, drug abuse, alcoholism or endocrine disease. Also patients with adjustment disorders, manicdepressive illness, recurrent type schizophrenia and primary anxiety disorder were excluded. In addition, ingestion of caffeine was limited to 40 oz. of caffeinated beverages per day. Informed consent for participation in the study was obtained from each patient.	Amitriptyline	75-150	Placebo	Yes	4 weeks	Unclear	Unclear	24.3	25.0	No
Roth 1990	No	Yes	To quality for inclusion in the trial, patients had to fulfill DSM-III criteria for Major Depressive Episode (Spitrer, 1980). A current episode duration of at least one month, a score of 22 on the first 17 items of the Hamilton Depression Scale, and signed informed consent were required. The complete structured clintcal interview for DSM-III (SCID-P) 2/85 (Spitzer et al., 3985) was used during screening to ensure diagnostic accuracy and the homogeneity of the sample at the USF site. Eligible patients were outpatients of either sex, age 18 and older.	Women who were pregnant, lactating, or not using reliable contraception were excluded. Atso excluded were patients with a history of any other major Axis 1 psychiatric disorder, including mania or hypomania. Patients with any significant medical illness which could interfere with the diagnosis, treatment or assessment of depression as well as patients with any clinically important abnormalities in EGG or in laboratory tests were excluded. Patients with multiple drug allergies, those who had received any investigational drug or ECT within four weeks, MAOI's or lithium within two weeks, or any antidepressant drugs within one week of study baseline were also exchded.	Desipramine	50-300	Placebo	Yes	6 weeks	30	30	29.5	28.9	No
Rothblum 1982	No	Yes	Male and female outpatients between the ages of 60 and 85 years, with a DSM-III diagnosis of moderate to severe major depression, were included. The diagnoses were made following an assessment on the Schedule for Affective Disorders and Schizophrenia. Severity of depression was measured by the Raskin Depression Scale, and a score of at least 7 of a total of 15 was required for admission. The initial telephone screening interview attempted to rule out serious medical and psychiatric disorders. Patients could not be receiving other psychiatric treatment while participating and were required to be ambulatory, living in Connecticut, and able to read and understand English.	Exclusion criteria included diagnosed schizophrenia; addiction to alcohol or other drugs; significant dementia; uncontrolled liver, kidney, gastrointestinal or pulmonary disease; glaucoma; epilepsy or seizures as determined by physical examination, laboratory tests, and/or history; and allergies to benzodiazepines or tricyclic antidepressants. Also excluded were patients receiving concomitant therapy with psychotropic medications or thyroid medication with the exception of conjugated estrogens, nonnarcotic mild analgesics, antimigraine medications and diuretics; or patients who had received tranquilizers or benzodiazepines in the preceding 7 days, or lithium carbonate or antidepressants (including monoamine oxidase inhibitors) in any regular daily dose during the preceding month. All participation was by informed written consent.	Imipramine	25-225	Placebo	No	6 weeks	13	12	20.5	22.5	No
Schweizer 1994	No	Yes	Patients aged 18 years or older were recruited who met DSM-III-R criteria for major depression for a minimum of 4 weeks. The 21-item Hamilton Rating Scale for Depression (HAM-D) total score had to be at least 20 at both the initial screen evaluation and the pretreatment baseline. The score should not have decreased by more than 20% during the screening period.	Patients were excluded if their affective illness was bipolar, required hospitalization, or was primarily psychotic. Patients also were excluded if they reported marked suicidal ideation, recent (in the past 2 years) alcohol or drug dependence or abuse, any acute or unstable medical problem, or a history of seizures. Women capable of becoming pregnant were required to use a medically approved form of birth control and were admitted to the study only if a human chorionic gonadotropin test was negative. Concomitant psychotropic medication (other than chloral hydrate as needed) was excluded during the study, and for at least 7 days before double-blind treatment began (14 days for MAO inhibitors and 30 days for neuroleptics).	Imipramine	25-225	Placebo	Yes	6 weeks	73	78	24.2	24.6	No
Schweizer 1998	No	Yes	At least 65 of age, live in community setting and not a nursing home, DSM-III-R criteria for major depressive episode, unipolar type with minimum duration of illness of 3 months, minimum severity score of 18 on HAMD-17.	Alzheimers disease or other dementia, current or past history of psychosis, schizophrenia, shizoaffective disorder, bipolar disorder, seizures or glaucoma, any acute or unstable medical codition, including parkinsons disease, unstable endocrine dysfuntions, or cancer in past 5 years. Concomitant psychotropic medication was not permitted and use of alcohol was discouraged. History in past year of alcoholism or drug deprendence including daily use of benzodiazepines for more than 6 continuous weeks was also reason for exclusion.	Imipramine	50-150	Placebo	No	8 weeks	60	60	23.9	24.1	No
Shipley 1981	No	Yes	The 76 subjects studied were inpatients on the Clinical Research Unit at Western Psychiatric Institute and Clinic. When admitted, a psychiatric interview and physical examination were completed, routine laboratory data including thyroid function tests were obtained, and an EEG and any other tests deemed necessary were completed. After a 2-week drug-free period, the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer et al., 1978) was completed by the psychiatrists and used together with collateral information from previous hospitalizations, case records, and interviews, with family members to establish the diagnosis according to the RDC. If the severity of depressive symptoms at the end of the 2-week drug-free period was still marked (17-item HRS scores of at least 30 using the sum of two raters), then patients were entered into the protocol.	-	Amitriptyline	Maximum: 200	Placebo	Yes	Unclear	Unclear	Unclear	38.5	44.2	No

Silverstone 1994	No	Yes	Patients aged 18-65 with a diagnosis of a major depressive episode as defined by DSM-III-R criteria entered the study. At entry participants were required to have a minimum score of 16 on the 17-item Hamilton Depression Rating Scale (HDRS).	Patients at risk of suicide, with mood-incongruent symptoms, confusional states or whose depression was due to another psychiatric illness or organic factor were excluded from the trial. Patients with any significant physical disease, or a history of increased intraocular pressure, glaucoma or micturition disturbances were also excluded. Patients who had received electroconvulsive therapy (ECT) or an investigational drug within the last 4 weeks, an MAOI within the last 2 weeks or other marketed antidepressants, lithium or carbamazepine within the last 7 days were excluded. With the exception of benzodiazepines, all other antidepressant medication, ECT and psychoactive drugs (including anticonvulsants, barbiturates and phenothiazine derivatives) were prohibited. Patients established on a single benzodiazepine prior to entering the study were allowed to continue with the same treatment; the use of temazepam was permitted for night sedation. No dietary restrictions were imposed.	Imipramine	75-150	Placebo	No	6 weeks	83	83	25.4	24.4	No
Smith 1990	No	Yes	The study population consisted of 150 outpatients with a diagnosis of major depressive illness, DSM-III 296.2 or 296.3 (American Psychiatric Association 1980) and a minimum baseline score of 18 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960). Patients who had a 20 percent or greater reduction in total HAM-D score during the placebo washout period were considered placebo responders and were not randomized into the study. Additionally, patients were required to be at least 18 years of age; free of significant renal, hepatic, respiratory, cardiovascular, or cerebrovascular disease; free of narrow angle glaucoma, prostatic hypertrophy, and seizure disorders; and with no clinically relevant abnormal laboratory values or significantly abnormal electrocardiogram (EKG) findings.	Furthermore, patients were excluded if their primary diagnosis was schizophrenia, atypical depression, anxiety, adjustment, or bipolar disorder, or if they were known drug or alcohol abusers or had known active suicidal tendencies or known cognitive deficiencies.	Amitriptyline	80-280	Placebo	Yes	6 weeks	50	50	23.7	23.3	No
Stark 1985	No	Yes	Patients eligible for inclusion were outpatients diagnosed as having major depressive illness according to DSM-ill criteria, except that our patients had to have had the illness for at least 1 month rather than 2 weeks. The HAM-D total score of each patient had to be equal to or greater than 20.	Patients were excluded because of concomitant phy sical conditions or histories of conditions that would interfere with therapy or evaluation.	Imipramine	Maximum: 300	Placebo	Yes	6 weeks	Unclear	Unclear	28.2	28.1	No
Stewart 1981	No	Yes	HAMD below 19, 18-65 years.	-	Desipramine	Mean: 279	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Stratas 1984 - dothiepin	No	Yes	Candidates for this study, evaluated in a psychiatric outpatient clinic, were required to fulfill the following diagnostic criteria at a prestudy visit: RDC diagnosis of major depressive disorder; score of 18 or more on the 21-item Hamilton Depression Rating Scale (HDRS) and rating of 2 or more for the items "depressed mood" and "work activities;" rating of at least "moderately ill" (>/= 3 on a global severity scale of 0-6, where O = normal); and presence of depressive symptoms for at least 2 weeks prior to study entrance.	Patients were excluded for those physical and psychiatric disorders which are standard contraindications for tricyclics. All patients who fulfilled the inclusion criteria gave written informed consent to participate in the study.	Dothiepin	50-300	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Stratas 1984 - amitriptyline	No	Yes	Candidates for this study, evaluated in a psychiatric outpatient clinic, were required to fulfill the following diagnostic criteria at a prestudy visit: RDC diagnosis of major depressive disorder; score of 18 or more on the 21-item Hamilton Depression Rating Scale (HDRS) and rating of 2 or more for the items "depressed mood" and "work activities;" rating of at least "moderately ill" (>/= 3 on a global severity scale of 0-6, where O = normal); and presence of depressive symptoms for at least 2 weeks prior to study entrance.	Patients were excluded for those physical and psychiatric disorders which are standard contraindications for tricyclics. All patients who fulfilled the inclusion criteria gave written informed consent to participate in the study.	Amitriptyline	50-300	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Thomson 1982	No	Yes	The general practitioners selected a group of patients complaining of depression of at least 2 weeks' duration, who were considered by their practitioner to require antidepressant drug treatment but not to need psychiatric referral. The patients were aged 18-65 years, and were required to have a total Hamilton Depression Rating Scale (HDS) (Hamilton, 1960) score of 12 or more on entry into the study. Patients who had received antidepressants in the previous 2 weeks, or in whom the use of tricyclic antidepressants was contraindicated, were excluded. Patients were allowed to take diazepam 5 mg/day or nitrazepam as a hypnotic, but if started this was continued throughout the study.	-	Amitriptyline	75-150	Placebo	Yes	12 weeks	31	28	17.4	19.4	No
Van De Merwe 1984	No	Yes	Patients included in the study were of either sex, between ages 18 and 60 years and in good physical health without disease in any organ system. Patients with any cardiovascular or other psychiatric illness were excluded (this included organic brain disease, alcoholism, addiction or mental handicap).	Patients who had been treated in adequate dosage and time with antidepressants or with electroconvulsive therapy in the period prior to referral were excluded, as were patients with depression severe enough to war- rant electroconvulsive therapy. Individuals receiving known enzyme-inducing or enzyme-inhibiting drugs or psycho-active medication other than the trial medication were excluded. Individuals unable to comprehend the purpose of the study or unable to comply with the program were excluded. Women of childbearing age had to ensure that adequate contraceptive measures were taken. Patients were withdrawn from the trial if not responding to treatment or if considered in the best interest of the patient or if specifically requested.	Amitriptyline	Mean: 95.3	Placebo	Yes	28 days	Unclear	Unclear	Unclear	Unclear	No
Versiani 1989	No	Yes	Male and female, 18-65, diagnosis of major depressive episode according to DSM-III, minimum score of 17 on HAMD-21	High suicide risk, concomitant psychiatric diseases, drug or alcohol dependence, significant organic disease, pregnancy, allergy	Imipramine	33-200	Placebo	No	6 weeks	Unclear	Unclear	25.8	23.3	No
White 1984	No	Yes	Subjects were patients at the Adult Psychiatric Clinic of the Los Angeles County-University of Southern California Medical Center. For inclusion, such patients were required to meet Research Diagnostic Criteria (Spitzer et al. 1977) for major depressive disorder, confirmed in independent interviews by two clinicians, generally a psychologist and a psychiatrist. All patients were between the ages of 18 and 60, and all signed informed consent to participate. At the point of starting treatment with study medications, all patients were free of other psychotherapeutic drugs for at least 1 week; only hypnotics, analgesics, or antihistamines could be concurrently administered during the trial.	Exclusion criteria included history of schizophrenia, cerebral dysfunction, glaucoma, urinary retention, hyperthyroidism, diabetes, asthma, cardiovascular disease, hypertension, pheochromocytoma, or liver disease.	Nortriptyline	75-150	Placebo	No	4 weeks	61	59	25.2	27.0	No
Wilcox 1994	No	Yes	Outpatients: • Diagnosis of major depressive illness (DSM-III 296.2 or 296.3) • HAM-D-17 score at baseline >/= 18 • Age >/= 18 years • Abilility to complete the Zung Self-Rating Depression Scale	Exclusion criteria Any of the following histories: • Clinically significant renal, hepatic, respiratory, cardiovascular, or cerebrovascular disease • Narrow-angle glaucoma • Clinically significant prostatic hypertrophy • Seizure disorders • Drug allergies or other hypersensitivity reactions to tricyclic antidepressants or related compounds • Hyperthyroidism • History of blood dyscrasias from the use of tricyclics for prior episodes of depression • Primary psychiatric diagnoses of schizophrenia, anxiety, adjustment disorder or bipolar disorder Patients who: • Required concomitant treatment with other psychotropic drugs • Abused alcohol or drugs within the previous 6 months • Were treated with either ECT within 3 months of baseline, monoamine oxidase inhibitors within 14 days of baseline, or other psychotropic drugs within 7 days of baseline • Had clinically significant abnormal laboratory, ECG or physical examination findings at the screening visit • Had known active suicidal tendencies • Had known cognitive deficiencies • Had a total HAM-D-21 score decrease of 20% or more during the 1 week placebo washout period • Were females of childbearing potential not practicing a method of birth control acceptable to the investigator • Were pregnant or who intended to become pregnant during the study • Were nursing mothers	Amitriptyline	60-300	Placebo	Yes	6 weeks	50	49	24.2	23.5	No

Serious adverse events in the included trials.

Trial ID	Experimental Intervention	TCA participants assessed for serious adverse events		Control group participants assessed for serious adverse events	
		Numbers and types of serious adverse events	Proportion of participants with a serious adverse event	Numbers and types of serious adverse events	Proportion of participants with a serious adverse event
Amin 1984	Imipramine	reaction, 4 anorexia, 4 hyperkinesia, 2 hypokinesia	* out of 153	4 hyperkinesia, 4 anorexia, 3 hypotension, 2 manic reaction, 1 hypokinesia	* out of 149
Bakish 1992	Amitriptyline	1 kidney infection	1 out of 57	-	0 out of 55
Ban 1998	Desipramine	7 hypotension	7 out of 89	4 hypotension	4 out of 85
Bremner 1996	Amitriptyline	4 impotence, 4 amblyopia	* out of 50	-	0 out of 50
Carman 1991	Amitriptyline	16 amblyopia, 6 urinary retention	* out of 50	5 amblyopia	5 out of 50
Cassano 1996 - imipramine	Imipramine	4 hepatitis, 1 delirium, 1 suicide attempt	* out of 64	-	0 out of 29
Cassano 1996 - tianeptine	Tianeptine	1 suicide attempt	1 out of 64	1 suicide attempt	1 out of 30
Claghorn 1983	Amitriptyline	21 hypotension postural, 11 hypokinesia, 9 hyperkinesia	* out of 85	11 hypokinesia, 10 hyperkinesia, 3 hypotension postural	* out of 87
Claghorn 1996	Imipramine	hostility, 1 anorexia, 1 anxiety	* out of 45	4 hypertonia, 2 hostility, 1 anxiety	* out of 46
Dominguez 1985	Imipramine	7 syncope/dizziness, 3 anorexia	7 out of 35	-	0 out of 31
Dunbar 1991	Imipramine	9 taste alteration, 9 drugged feeling, 7 libido decreased, 5 tinnitus, 5 abnormal ejaculation	* out of 237	-	0 out of 240
Emsley 2018	Tianeptine	2 anxiety, 1 breast cancer, 1 arthritis, 1 dysgeusia	2 out of 105	2 fall, 1 paraesthesia, 1 panic attack, 1 anxiety	2 out of 107
Fabre 1996	Imipramine	5 anorexia, 1 abnormal ejaculation	* out of 48	1 ruptured ectopic pregnancy, 1 hernia repair	* out of 44
Feiger 1996	Imipramine	5 orthostatic dizziness, 6 tinnitus, 1 loss of libido	* out of 41	3 tinnitus	3 out of 40
Feighner 1989a	Imipramine	5 anxiety	5 out of 58	8 anxiety	8 out of 59
Ferguson 1994 - dothiepin	Dothiepin	16 amblyopia	16 out of 188	3 amblyopia	3 out of 95
Ferguson 1994 - doxepin	Doxepin	18 amblyopia	18 out of 186	3 amblyopia	3 out of 94
Fontaine 1994	Imipramine	23 orthostatic symptoms	23 out of 45	3 orthostatic symptoms	3 out of 45
Georgotas 1986	Nortriptyline	15 orthostatic effects, 15 syncope	* out of 25	10 syncope, 6 orthostatic effects	* out of 28
Gerner 1980	Imipramine	1 atrial fibrillation	1 out of 21	-	0 out of 20
Itil 1983	Imipramine	-	0 out of 25	1 suicide attempt	1 out of 22
Lapierre 1987	Imipramine	5 dizziness/syncope, 2 manic episodes, 1 depressive stupor, 1 overdose of fluvazepam	* out of 21	2 dizziness/syncope, 1 manic episodes, hypomania and hyperactivity	* out of 20
March 1990	Imipramine	-	0 out of 15	1 suicide attempt	1 out of 12
Nair 1995	Nortriptyline	events	16 out of 37	events	9 out of 35
Philipp 1999	Imipramine	-	0 out of 110	1 suicide attempt	1 out of 47
Prasko 2002	Imipramine	1 hypomania	1 out of 11	1 hypomania	1 out of 9
Raft 1981	Amitriptyline	-	0 out of 7	2 forgetfulnuess	2 out of 6
Raisi 2007	Nortriptyline	3 urinary retention, 3 decrease of libido, 3 anorexia, 3 orthostatic hypotension, 1 anorgasmia	* out of 19	5 anorexia, 3 urinary retention, 3 decrease of libido, 2 anorgasmia, 1 orthostatic hypotension	* out of 19
Ravindran 1995	Desipramine	-	9 out of 37	-	2 out of 26
Reimherr 1990	Amitriptyline	6 amnesia, 6 taste alteration, 5 sexual dysfunction, 1 anorexia	* out of 149	5 anorexia, 1 taste alteration, 1 amnesia, 1 sexual dysfunction	* out of 150
Rickels 1987	Imipramine	5 cognitive deficite	5 out of 63	4 cognitive deficite	4 out of 61
Rickels 1994	Imipramine	7 urinary retention, 7 postural hypotension	* out of 92	-	0 out of 95
Schweizer 1998	Imipramine	13 urinary retention	* out of 60	1 urinary retention	* out of 60
Silverstone 1994	Imipramine	1 suicide	1 out of 83	suicide	* out of 83
Smith 1990	Amitriptyline	hypotension, 6 dyscoordination, 6 hypertension	* out of 50	3 hypertension, 2 hypotension, 2 amblyopia, 1 dyscoordination	* out of 50
Stark 1985	Imipramine	9 anxiety, 7 taste change, 4 sexual dysfunction, 2 anorexia	* out of 186	12 anxiety, 3 taste change, 2 anorexia	* out of 169

Wilcox 1994	Amitriptyline	9 amblyopia	9 out of 50	3 amblyopia	3 out of 49

*** The overall proportion of serious adverse events was unclear.**

Number needed to harm for serious adverse events.								
Events	Number of trials reporting the event	TCA events	TCA analysed	Control events	Control analysed	Relative risk (95% CI)	P-value	NNH
Hypotension	10	111	636	31	633	3.31 (1.93, 5.68)	< 0.01	7
Urinary retention	5	36	266	4	270	6.07 (1.66, 22.19)	0.01	8
Amblyopia	5	73	574	16	388	3.32 (1.94, 5.66)	< 0.01	11
Sexual dysfunction	8	25	651	4	650	3.50 (1.29, 9.48)	0.01	31
Taste alteration	4	23	677	4	666	4.04 (1.23, 13.24)	0.02	35
Amnesia	2	6	150	3	153	1.20 (0.04, 32.84)	0.92	
Anorexia	7	19	616	16	592	1.15 (0.39, 3.37)	0.80	
Anxiety	4	17	377	22	359	0.74 (0.38, 1.46)	0.39	
Dyscoordination	2	6	107	1	110	3.74 (0.46, 30.20)	0.22	
Hyperkinesia	2	13	225	14	222	0.94 (0.45, 1.93)	0.86	
Hypertension	2	6	149	3	154	1.86 (0.52, 6.65)	0.34	
Hypokinesia	2	13	225	12	224	1.10 (0.50, 2.41)	0.82	
Mania	4	7	261	5	256	1.29 (0.39, 4.31)	0.68	
Syncope	3	27	54	12	67	2.42 (0.80, 7.34)	0.12	
Tinnitus	2	11	267	3	277	3.12 (0.58, 16.75)	0.18	

Number needed to treat for non-serious adverse events.

Events	Number of trials reporting the event	TCA events	TCA analysed	Control events	Control analysed	Relative risk (95% CI)	P-value	NNT
Diarrhoea	13	35	895	82	886	0.46 (0.29, 0.	< 0.01	19
Infection	3	9	279	21	259	0.41 (0.19, 0.	0.02	21

Number needed to harm for non-serious adverse events.

Events	Number of trials reporting the event	TCA events	TCA analysed	Control events	Control analysed	Relative risk (95% CI)	P-value	NNH
Dry mouth	45	1863	3399	452	3066	3.43 (2.87, 4.10)	< 0.01	2
Anticholinergic symptoms	5	184	297	74	257	2.35 (1.46, 3.78)	< 0.01	3
Somnolence	33	919	2616	300	2393	2.65 (2.20, 3.21)	< 0.01	4
Sedation	5	98	301	54	272	1.67 (1.08, 2.58)	0.02	7
Dizziness	34	584	2753	209	2472	2.37 (1.87, 3.01)	< 0.01	7
Constipation	38	617	3082	196	2795	2.81 (2.16, 3.65)	< 0.01	7
Sweating	21	239	1563	54	1531	3.64 (2.41, 5.50)	< 0.01	8
Tremor	28	305	2321	47	2010	4.70 (3.02, 7.30)	< 0.01	9
Blurred vision	20	216	1485	66	1419	2.96 (2.21, 3.96)	< 0.01	10
Flushing	2	26	231	4	214	5.86 (1.33, 25.72)	0.02	10
Weight gain	8	78	671	16	469	2.98 (1.31, 6.77)	0.01	12
Abnormal dreams	2	8	86	1	86	5.55 (1.00, 30.71)	0.049	12
Nervousness	14	153	886	83	872	2.07 (1.19, 3.59)	0.01	12
Increased appetite	5	76	650	19	463	2.97 (1.70, 5.18)	< 0.01	13
Micturition disorder	3	25	259	6	265	3.97 (1.40, 11.22)	0.01	13
Asthenia	20	252	1937	119	1732	1.91 (1.47, 2.47)	< 0.01	16
Impaired urination	2	23	422	0	409	23.07 (3.14, 169.75)	< 0.01	18
Tachycardia	14	85	1095	25	1019	2.89 (1.63, 5.13)	< 0.01	18
Confusion	7	59	806	13	626	3.44 (1.86, 6.35)	< 0.01	19
Dyspepsia	11	127	1283	50	1073	2.20 (1.21, 4.00)	0.01	19
Urinary hesitancy	2	11	183	2	135	4.46 (1.00, 19.83)	0.0495	22
Appetite decreased	4	32	465	13	476	2.39 (1.10, 5.16)	0.03	24
Paraesthesia	7	52	872	16	688	2.55 (1.17, 5.56)	0.02	27
Agitation	10	62	771	49	757	1.10 (0.57, 2.11)	0.77	
CNS	2	24	115	19	79	1.05 (0.59, 1.87)	0.88	
Headache	33	466	2586	389	2289	0.97 (0.79, 1.20)	0.79	
Insomnia	26	163	2188	174	1966	0.85 (0.62, 1.16)	0.30	
Nausea	32	337	2604	234	2319	1.31 (0.99, 1.73)	0.06	
Pharyngitis	2	49	482	29	290	0.85 (0.50, 1.47)	0.57	
Rash	5	21	377	12	360	1.59 (0.50, 5.00)	0.43	
Rhinitis	2	58	419	31	235	1.04 (0.69, 1.57)	0.87	
Upper respiratory tract infection	2	12	291	11	276	1.00 (0.45, 2.22)	1.00	
Vasodilatation	3	28	330	4	330	4.64 (0.92, 23.32)	0.06	
Yawning	2	0	342	0	347	1.02 (0.06, 16.16)	0.99	