

A systematic review and meta-analysis of pro-dopaminergic interventions for anhedonia - results from human studies

Jaycee Kennett, Claire Friedrich, Edoardo G. Ostinelli, Virginia Chiocchia

31 May 2024

- 1. Methods (brief)
- 2. Results
 - 2.1 Flow diagram
 - 2.2 Table of included studies
 - 2.3 Description of included studies
 - 2.4 Primary outcome: reduction in anhedonia scores at 8 weeks (from 4 to 12 weeks)
 - 2.4.1 Pairwise meta-analysis
 - 2.4.2 Risk of bias
 - 2.4.3 Reporting bias
 - 2.4.4 Meta-regression analyses
 - 2.4.5 Sensitivity analyses
 - 2.5 Secondary outcome: Reduction in mean anxiety score at 8 weeks (from 4 to 12 weeks)
 - 2.5.1 Pairwise meta-analysis
 - 2.5.2 Risk of Bias
 - 2.5.3 Meta-regression analyses
 - 2.6 Secondary outcome: Dropouts due to any reason
 - 2.6.1 Pairwise meta-analysis
 - 2.6.2 Risk of bias
 - 2.6.3 Meta-regression analyses
 - 2.7 Secondary outcome: dropouts due to side effects
 - 2.7.1 Pairwise meta-analysis
 - 2.7.2 Risk of bias
 - 2.7.3 Meta-regression analyses
 - 2.8 Secondary outcome: nausea
 - 2.8.1 Pairwise meta-analysis
 - 2.8.2 Risk of bias
 - 2.8.3 Meta-regression analyses
 - 2.9 Secondary outcome: headache
 - 2.9.1 Pairwise meta-analysis
 - 2.9.2 Risk of bias
 - 2.9.3 Meta-regression analyses
 - 2.10 Secondary outcome: insomnia
 - 2.10.1 Pairwise meta-analysis
 - 2.10.2 Risk of bias
 - 2.10.3 Meta-regression analyses
 - 2.11 Secondary outcome: constipation
 - 2.11.1 Pairwise meta-analysis
 - 2.11.2 Risk of bias
 - 2.11.3 Meta-regression analyses
 - 2.12 Secondary outcome: dizziness
 - 2.12.1 Pairwise meta-analysis
 - 2.12.2 Risk of bias
 - 2.12.3 Meta-regression analyses
 - 2.13 Secondary outcome: dry mouth
 - 2.13.1 Pairwise meta-analysis
 - 2.13.2 Risk of bias
 - 2.13.3 Meta-regression analyses
 - 2.14 Secondary outcome: vomiting
 - 2.14.1 Pairwise meta-analysis
 - 2.14.2 Risk of bias
 - 2.14.3 Meta-regression analyses
 - 2.15 Summary of evidence tables
- 3. Abbreviations
- 4. Software Used
- 5. References

1. Methods (brief)

In this first iteration of the living systematic review we searched for randomised controlled trials that compared pro-dopaminergic interventions to placebo in adults with unipolar depression (i.e. any standardised measure, above-threshold symptoms on any standardised measure, or a clinical diagnosis based on any operationalised criteria).

Eight databases were searched from inception up to the 9th of November, 2023 (see protocol (<https://wellcomeopenresearch.org/articles/8-425>) for full search strings). Database search results were imported into EPPI-Reviewer (<https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2914>) and de-duplicated prior to screening. All steps related to record screening and data extraction were completed in EPPI-Reviewer (<https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2914>).

Titles and abstracts of the identified records were screened by at least two reviewers (CF, MC, JK, JP). We retrieved the full-texts and any supporting documents for all records that were not excluded at the title and abstract screening stage. The full-text screening was conducted by at least two reviewers (CF, JK, JP, AK, EB). Conflicts at title and abstract, and full-text screening, were resolved through discussion between the two reviewers and involvement of a third reviewer (AC, EGO). Additional information on the full study eligibility criteria can be found in the pre-published protocol (<https://wellcomeopenresearch.org/articles/8-425>).

Relevant data was extracted using EPPI-Reviewer (<https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2914>) by at least two reviewers (CF, CA, EB, JK).

As specified in our protocol (<https://wellcomeopenresearch.org/articles/8-425>), we focused on the following outcomes:

- anhedonia symptom severity: using anhedonia-specific scales, anhedonia-specific sub-scales, or individual items focusing on anhedonia (observer-rated or self-rated). Continuous, primary outcome.
- anxiety symptom severity: as per observer or self-reported standardised scales. Continuous, secondary outcome.
- acceptability: proportion of participants dropping out for any reason. Binary, secondary outcome.
- tolerability: the proportion of participants dropping out due to an adverse event. Binary, secondary outcome.
- safety: the proportion of participants reporting specific adverse events (nausea, headache, insomnia, constipation, dizziness, dry mouth, vomiting). Binary, secondary outcome.

For anhedonia and anxiety symptom severity, we extracted outcome data reported at 8 weeks post-treatment or manipulation. If the information at 8 weeks was not available, we considered eligible data ranging between 4 and 12 weeks (with preference to the time point closest to 8 weeks and, if equidistant, the longer outcome). For acceptability, tolerability, safety and safety (specific adverse events), we extracted outcome data reported at the end of the studies.

When extracting continuous outcomes we extracted mean and standard deviation to two decimal places. Where standard error was reported instead, we converted the value to standard deviation. Baseline and endpoint values were extracted, where only change in score and baseline or endpoint was reported, the missing value was calculated by adding or subtracting the change score to the baseline or endpoint.

When extracting dichotomous outcomes we extracted natural numbers and where only percentages of participant groups were reported, a value was calculated and rounded up to the nearest natural number. Adverse events were extracted using the exact terms they were reported in the included studies.

We assessed risk of bias with the RoB2 tool (Higgins et al. 2019). All outcomes for all included studies were assessed by at least two reviewers (JK, CF, CA, AH) and conflicts were resolved by discussion between reviewers (Fleming et al. 2023). To evaluate biases due to missing evidence, the ROB-ME tool (Page et al. 2023) was used with the same double screening and conflict resolution process as described above. We took into account the usable data from the eligible studies identified in the search, the comprehensiveness of the search, and potential patterns of missingness and small study effects. We followed the algorithm to assign a low or high risk of reporting bias, or to express some concerns, by answering signalling questions related to the domains mentioned above.

Effect sizes were calculated as standardised mean differences (SMDs) for continuous outcomes (anhedonia and anxiety symptom severity) and odds ratios (ORs) for dichotomous outcomes (acceptability, tolerability, and specific-adverse events). We calculated the 95% confidence interval (CI) around the pooled effect size for each meta-analysis.

Meta-analyses were conducted using a random effects model with the inverse variance method, using the restricted maximum-likelihood estimator for τ^2 and the Hartung-Knapp correction method to adjust 95% confidence intervals, if there are at least five studies. Prediction intervals of the overall pooled effect were calculated to report the heterogeneity.

In terms of sensitivity analyses, we aggregated individual participant data (IPD) on the MADRS "inability to feel" item from 34 randomised controlled trials (14054 participants) on antidepressants in people with depression we had access to. We performed the following analyses to estimate the performance of bupropion versus placebo at the primary outcome (i.e. reduction in anhedonia scores): - aggregated IPD, all antidepressants and placebo, random effects network meta-analysis. - aggregated IPD, bupropion versus placebo, random effects pairwise meta-analysis. - combination of aggregated IPD and early studies identified in this living systematic review for which IPD were not available, random effects pairwise meta-analysis.

Meta-regressions were planned for the following variables: mean age of participants, mean anhedonia baseline score, mean anxiety baseline score, sex (proportion of female participants), and planned treatment duration. Meta-regressions were only conducted for outcomes where data was available from 10 or more studies.

Summary of evidence tables were constructed for all outcomes including a summary of the meta-analytic result, biases within-study, across-study, and due to indirectness.

Please refer to the protocol (<https://wellcomeopenresearch.org/articles/8-425>) and the extended data for more details.

A list of abbreviations can be found towards the end of the document.

2. Results

2.1 Flow diagram

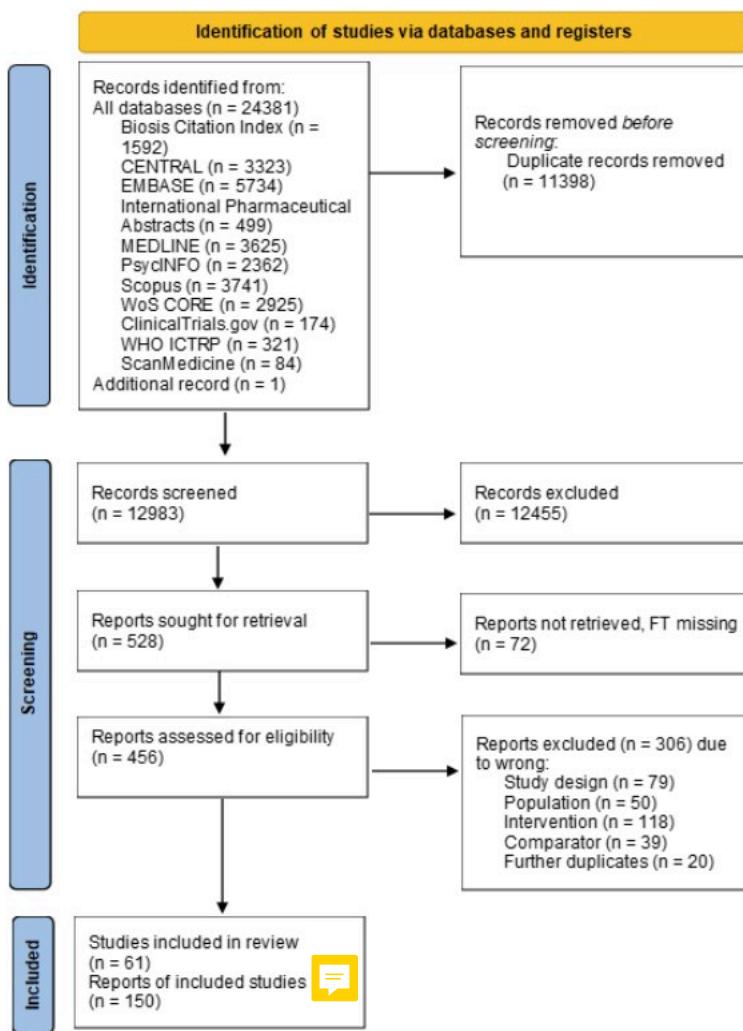


Figure 1. PRISMA 2020 flow diagram (Page et al. 2021).

2.2 Table of included studies

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Agosti (1991)	USA	NA	6 weeks	Phenelzine 60-90mg	10	NA	NA	Flexible	Oral
Agosti (1991)	USA	NA	6 weeks	Placebo	23	NA	NA	Flexible	Oral
Agosti (1991)	USA	NA	6 weeks	Selegiline 40mg	12	NA	NA	Fixed	Oral
Amsterdam (1989)	USA	Sanofi Research (partial grant)	4 weeks	Minaprine 100mg	34	12	41	Flexible	Oral
Amsterdam (1989)	USA	Sanofi Research (partial grant)	4 weeks	Minaprine 200mg	39	25	37	Flexible	Oral
Amsterdam (1989)	USA	Sanofi Research (partial grant)	4 weeks	Minaprine 300mg	43	22	40	Flexible	Oral
Amsterdam (1989)	USA	Sanofi Research (partial grant)	4 weeks	Minaprine 400mg	37	22	37	Flexible	Oral
Amsterdam (1989)	USA	Sanofi Research (partial grant)	4 weeks	Placebo	37	18	39	NA	Oral
Amsterdam (2003)	USA	Somerset Pharmaceuticals, Inc.	8 weeks	Selegiline 20mg	149	94	41.2	Fixed	Trans

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Amsterdam (2003)	USA	Somerset Pharmaceuticals, Inc.	8 weeks	Placebo	152	99	43.5	Fixed	Trans
Bakish (1992)	Canada	NA	6 weeks	Moclobemide up to 600mg	58	26	42	Flexible	Oral
Bakish (1992)	Canada	NA	6 weeks	Placebo	56	20	44	Flexible	Oral
Bellak (1966)	USA	*MH	4 weeks	Placebo	25	NA	NA	NA	NA
Bellak (1966)	USA	*MH	4 weeks	Phenelzine	25	NA	NA	NA	NA
Benes (2011)	Germany	GSK	12 weeks	Placebo	67	45	59.5	Flexible to week 7, then fixed	Oral
Benes (2011)	Germany	GSK	12 weeks	Ropinirole 0.5-4mg	198	144	58.2	Flexible to week 7, then fixed	Oral
Bodkin (2002)	NA	Somerset Pharmaceuticals	6 weeks	Placebo	88	53	43.2	Fixed	Trans
Bodkin (2002)	NA	Somerset Pharmaceuticals	6 weeks	Selegiline 20mg	89	53	41.4	Fixed	Trans
Botte (1992)	NA	NA	6 weeks	Placebo	24	16	43.33	NA	NA
Botte (1992)	NA	NA	6 weeks	Moclobemide 300-600mg	23	13	51.39	Flexible	Oral
Bymaster (2011)	Romania, Serbia, USA	DOV Pharmaceuticals, Euthymics Bioscience	6 weeks	Placebo	29	19	49.5	Fixed	Oral
Bymaster (2011)	Romania, Serbia, USA	DOV Pharmaceuticals, Euthymics Bioscience	6 weeks	Amitifadine 50mg	34	25	48.2	Fixed	Oral
Casacchia (1984)	Italy	NA	4 weeks	Moclobemide 150-450 mg	18	8	49.5	Flexible	Oral
Casacchia (1984)	Italy	NA	4 weeks	Placebo	16	11	49	Flexible	Oral
Chouinard (1993)	Canada, UK	NA	6 weeks	Placebo	109	66	40.200000000000003	Fixed	Oral
Chouinard (1993)	Canada, UK	NA	6 weeks	Brofaromine 75-100mg	111	57	41.2	Fixed	Oral
Clayton (2006a)	USA	Glaxo Wellcome Inc.	8 weeks	Bupropion	141	85	36.5	Flexible	Oral
Clayton (2006a)	USA	Glaxo Wellcome Inc.	8 weeks	Placebo	141	88	35.1	Flexible	Oral
Clayton (2006b)	USA	Glaxo Wellcome Inc.	8 weeks	Bupropion	138	76	37	Flexible	Oral
Clayton (2006b)	USA	Glaxo Wellcome Inc.	9 weeks	Placebo	137	76	37	Flexible	Oral
Coleman (1999)	USA	Glaxo Wellcome Inc.	8 weeks	Placebo	124	73	38.5	Flexible	Oral
Coleman (1999)	USA	Glaxo Wellcome Inc.	8 weeks	Bupropion SR 150-400mg	122	68	38.1	Flexible	Oral

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Coleman (1999)	USA	Glaxo Wellcome Inc.	8 weeks	Placebo	152	92	36.700000000000003	Flexible	Oral
Coleman (1999)	USA	Glaxo Wellcome Inc.	8 weeks	Bupropion 150-400mg	150	95	36.6	Flexible	Oral
Corrigan (2000)	USA	NA	8 weeks	Placebo	35	NA	NA	Fixed	Oral
Corrigan (2000)	USA	NA	8 weeks	Pramipexole 0.375mg	36	NA	NA	Fixed	Oral
Corrigan (2000)	USA	NA	8 weeks	Pramipexole 1mg	35	NA	NA	Fixed	Oral
Corrigan (2000)	USA	NA	8 weeks	Pramipexole 5mg	33	NA	NA	Fixed	Oral
Croft (1999)	NA	Glaxo Wellcome Inc.	8 weeks	Placebo	121	61	37.4	Flexible	Oral
Croft (1999)	NA	Glaxo Wellcome Inc.	8 weeks	Bupropion SR 150-400mg	120	61	35.9	Flexible	Oral
Davidson (1988)	NA	Hoffmann La Roche	6 weeks	Isocarboxazid	68	37	41.9	Flexible	Oral
Davidson (1988)	NA	Hoffmann La Roche	6 weeks	Placebo	62	35	41.9	Flexible	Oral
DelBello (2014)	USA	Somerset Pharmaceutical, Inc.	12 weeks	Placebo	156	104	14.7	Flexible	Trans
DelBello (2014)	USA	Somerset Pharmaceutical, Inc.	12 weeks	Selegiline 6-12mg	152	93	14.8	Flexible	Trans
Feiger (2006)	USA	Somerset Pharmaceutical, Inc.	8 weeks	Selegiline 6-12mg	132	81	42	Flexible	Trans
Feiger (2006)	USA	Somerset Pharmaceutical, Inc.	8 weeks	Placebo	133	71	42	Flexible	Trans
Feighner (1984)	NA	NA	4 weeks	Placebo	22	19	49	NA	Oral
Feighner (1984)	NA	NA	4 weeks	Bupropion up to 600mg	44	30	43.9	Flexible	Oral
Georgotas (1986)	USA	NAMH	7 weeks	Placebo	28	15	64.7	Flexible	Oral
Georgotas (1986)	USA	NAMH	7 weeks	Phenelzine	22	13	65.5	Flexible	Oral
Giller (1982)	USA	NAMH, Hoffman-LaRoche	6 weeks	Placebo	NA	NA	NA	Flexible	Oral
Giller (1982)	USA	NAMH, Hoffman-LaRoche	6 weeks	Isocarboxazid	NA	NA	NA	Flexible	Oral
GlaxoSmithKline (1980)	USA	GSK	6 weeks	Bupropion 150-450mg	52	35	36.4	Flexible	Oral
GlaxoSmithKline (1980)	USA	GSK	6 weeks	Bupropion 300-900mg	23	13	37.79999999999997	Flexible	NA
GlaxoSmithKline (1980)	USA	GSK	6 weeks	Placebo	47	31	37.4	Flexible	Oral
GlaxoSmithKline (1985)	USA, Canada	GSK	4 weeks	Placebo	43	20	51.9	Fixed	Oral

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
GlaxoSmithKline (1985)	USA, Canada	GSK	4 weeks	Bupropion 300mg	45	18	52.4	Fixed	Oral
GlaxoSmithKline (1985)	USA, Canada	GSK	4 weeks	Bupropion 450mg	40	18	47.5	Fixed	Oral
GlaxoSmithKline (1993)	USA	GSK	8 weeks	Placebo	124	80	40.700000000000003	NA	NA
GlaxoSmithKline (1993)	USA	GSK	8 weeks	Bupropion SR 100mg	119	77	39.6	Fixed	NA
GlaxoSmithKline (1993)	USA	GSK	8 weeks	Bupropion SR 200mg	120	65	39.6	Fixed	NA
GlaxoSmithKline (1993)	USA	GSK	8 weeks	Bupropion SR 300mg	120	70	39.9	Fixed	NA
GlaxoSmithKline (1993)	USA	GSK	8 weeks	Bupropion SR 400mg	119	66	38.79999999999997	Fixed	NA
GlaxoSmithKline (1994)	USA	GSK	8 weeks	Bupropion 50-150mg	152	90	39.1	Flexible	Oral
GlaxoSmithKline (1994)	USA	GSK	8 weeks	Placebo	154	99	38.20000000000003	NA	Oral
GlaxoSmithKline (1994)	USA	GSK	8 weeks	Bupropion 100-300mg	150	98	37.20000000000003	Flexible	Oral
Han (2012)	South Korea	Korea Research Foundation Grant	8 weeks	Placebo	28	0	18.10000000000001	NA	NA
Han (2012)	South Korea	Korea Research Foundation Grant	8 weeks	Bupropion 150-300mg	29	0	21.2	Fixed	Oral
Hewett (2009)	Austria, Belgium, Bulgaria, Croatia, Estonia, Finland, Greece, Ireland, Latvia, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden and Mexico	GSK	8 weeks	Placebo	199	142	41.8	Flexible	Oral
Hewett (2009)	Austria, Belgium, Bulgaria, Croatia, Estonia, Finland, Greece, Ireland, Latvia, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden and Mexico	GSK	8 weeks	Bupropion XR 150-300mg	188	138	41.8	Flexible	Oral

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Hewett (2010a)	Australia, France, Germany, the Netherlands, Norway, South Africa and Sweden	GSK	8 weeks	Placebo	189	125	44.5	Flexible	Oral
Hewett (2010a)	Australia, France, Germany, the Netherlands, Norway, South Africa and Sweden	GSK	8 weeks	Bupropion XR 150-300mg	204	127	45.6	Flexible	Oral
Hewett (2010b)	Australia, Belgium, Canada, Croatia, Finland, France, Germany, India, Latvia, Netherlands, Norway, Poland, Republic of South Africa, Russia and United States	GSK	10 weeks	Placebo	207	144	71.3	Flexible	Oral
Hewett (2010b)	Australia, Belgium, Canada, Croatia, Finland, France, Germany, India, Latvia, Netherlands, Norway, Poland, Republic of South Africa, Russia and United States	GSK	10 weeks	Bupropion XR 150-300mg	211	157	70.900000000000006	Flexible	Oral
Iosifescu (2022)	USA	Xsome Therapeutics	6 weeks	Dextromethorphan + Bupropion	156	95	42.1	NA	Oral
Iosifescu (2022)	USA	Xsome Therapeutics	6 weeks	Placebo	162	117	41.2	NA	Oral
Jarrett (1999)	NA	NA	10 weeks	Phenelzine 0.85-1mg/kg	36	25	38.700000000000003	NA	NA
Jarrett (1999)	NA	NA	10 weeks	Placebo	36	22	40.299999999999997	NA	NA
Jefferson (2006)	NA	GSK	8 weeks	Placebo	139	96	39.799999999999997	Flexible	Oral
Jefferson (2006)	NA	GSK	8 weeks	Bupropion XR 150-450mg	135	89	40	Flexible	Oral
Koshino (2013)	Japan, South Korea	GSK	10 weeks	Placebo	186	85	37.9	Fixed	Oral

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Koshino (2013)	Japan, South Korea	GSK	10 weeks	Bupropion 150mg	190	92	36	Fixed	Oral
Koshino (2013)	Japan, South Korea	GSK	10 weeks	Bupropion 300mg	188	83	37.5	Fixed	Oral
Kusalic (1993)	NA	NA	6 weeks	Placebo	9	NA	NA	Flexible	Oral
Kusalic (1993)	NA	NA	6 weeks	Moclobemide	11	NA	NA	Flexible	Oral
Larsen (1989)	Denmark	NA	6 weeks	Placebo	18	12	57	Flexible	Oral
Larsen (1989)	Denmark	NA	6 weeks	Moclobemide up to 300mg	22	15	51	Flexible	Oral
Learned (2012a)	Australia, Belgium, Bulgaria, Canada, Estonia, Finland, France, Germany, India, Poland, Slovakia, and South Africa	GSK	10 weeks	Placebo	126	46	41.9	Fixed	Oral
Learned (2012a)	Australia, Belgium, Bulgaria, Canada, Estonia, Finland, France, Germany, India, Poland, Slovakia, and South Africa	GSK	10 weeks	GSK372475 1.5-2mg	134	51	43	Fixed	Oral
Learned (2012b)	Bulgaria, Canada, Chile, Costa Rica, Croatia, France, Germany, India, Italy, and Poland	GSK	10 weeks	Placebo	156	39	41.8	Fixed	Oral
Learned (2012b)	Bulgaria, Canada, Chile, Costa Rica, Croatia, France, Germany, India, Italy, and Poland	GSK	10 weeks	GSK372475 1-1.5mg	171	54	42.4	Fixed	Oral
Liebowitz (1984)	NA	Public Health Service	6 weeks	Placebo	24	14	37.700000000000003	Flexible	Oral
Liebowitz (1984)	NA	Public Health Service	6 weeks	Phenelzine 15-90mg	15	7	33.79999999999997	Flexible	Oral
Mann (1989)	USA	Irma Hirsch and Mallinckrodt Foundations	6 weeks	Placebo	22	17	40.200000000000003	Flexible	NA

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Mann (1989)	USA	Irma Hirschl and Mallinckrodt Foundations	6 weeks	Selegiline up to 50mg	22	16	45.2	Flexible	Oral
Nair (1995)	Canada, Denmark, UK	NA	7 weeks	Moclobemide 400mg	36	25	67 (median)	Fixed	Oral
Nair (1995)	Canada, Denmark, UK	NA	7 weeks	Placebo	35	25	71 (median)	Fixed	Oral
Ose (1992)	NA	NA	4 weeks	Moclobemide 300-500mg	35	21	49 (median)	Fixed	Oral
Ose (1992)	NA	NA	4 weeks	Placebo	33	18	50 (median)	Fixed	Oral
Parnetti (1993)	Italy	Gruppo Sanofi	12 weeks	Minapramine 200mg	63	36	71.59999999999994	Fixed	Oral
Parnetti (1993)	Italy	Gruppo Sanofi	12 weeks	Placebo	67	47	71.3	Fixed	Oral
Quitkin (1990)	USA	*MH; NHCRC	6 weeks	Phenelzine 90mg	33	NA	38.9	Fixed	Oral
Quitkin (1990)	USA	*MH; NHCRC	6 weeks	Placebo	34	NA	30.1	Fixed	Oral
Raft (1981)	USA	*H	5 weeks	Phenelzine 90mg	NA	NA	NA	Fixed	Oral
Raft (1981)	USA	*H	5 weeks	Placebo	NA	NA	NA	Fixed	Oral
Rampello (1991)	Italy	NA	6 weeks	Minapramine 100mg	10	NA	NA	Fixed	Oral
Rampello (1991)	Italy	NA	6 weeks	Placebo	10	NA	NA	Fixed	Oral
Raskin (1972)	USA	*MH	5 weeks	Placebo	111	NA	NA	Fixed	Oral
Raskin (1972)	USA	*MH	5 weeks	Phenelzine 45mg	110	72	37 (median)	Fixed	Oral
Ravaris (1976)	NA	Public Health Service; Warner Lambert Research Institute	6 weeks	Phenelzine 60mg	21	NA	43.1	NA	Oral
Ravaris (1976)	NA	Public Health Service; Warner Lambert Research Institute	6 weeks	Phenelzine 30mg	21	NA	41.2	Fixed	Oral
Ravaris (1976)	NA	Public Health Service; Warner Lambert Research Institute	6 weeks	Placebo	21	NA	38.9	Fixed	Oral
Reimherr (1998)	USA	Glaxo Wellcome Inc.	8 weeks	Placebo	121	69	40.20000000000003	Fixed	Oral
Reimherr (1998)	USA	Glaxo Wellcome Inc.	8 weeks	Bupropion SR 150mg	121	86	38.29999999999997	Fixed	Oral
Reimherr (1998)	USA	Glaxo Wellcome Inc.	8 weeks	Bupropion SR 300mg	120	92	38.6	Fixed	Oral
Rickels (1970)	USA	Public Health Service	4 weeks	Methylphenidate 15mg	NA	NA	NA	Fixed	Oral
Rickels (1970)	USA	Public Health Service	4 weeks	Placebo	NA	NA	NA	Fixed	Oral
Riesenbergs (2010)	USA	Rexahn Pharmaceuticals	8 weeks	Placebo	21	11	42.5	Fixed	Oral

Author (Year)	Country	Sponsor	Treatment duration	Intervention group	Participants (n)	Females (n)	Age (mean)	Dosage fixed or flexible	Inter form:
Riesenbergs (2010)	USA	Rexahn Pharmaceuticals	8 weeks	RX-10100 5mg	21	11	44.8	Fixed	Oral
Riesenbergs (2010)	USA	Rexahn Pharmaceuticals	8 weeks	RX-10100 10mg	16	7	42.6	Fixed	Oral
Riesenbergs (2010)	USA	Rexahn Pharmaceuticals	8 weeks	RX-10100 15mg	17	9	39.4	Fixed	Oral
Robin (1958)	UK	NA	4 weeks	Placebo	23	13	39.5	Flexible	Oral
Robin (1958)	UK	NA	4 weeks	Methylphenidate 20-40mg	22	16	37.5	Flexible	Oral
Rowan (1980)	NA	NA	6 weeks	Phenelzine 45-75mg	NA	NA	NA	Flexible	Oral
Rowan (1980)	NA	NA	6 weeks	Placebo	NA	NA	NA	Fixed	Oral
Tomarken (2004)	USA	Glaxo Wellcome Inc.	6 weeks	Bupropion SR 300-400mg	10	6	39.4	Fixed	Oral
Tomarken (2004)	USA	Glaxo Wellcome Inc.	6 weeks	Placebo	9	6	37.5	Fixed	Oral
Ucha (1990)	NA	NA	6 weeks	Placebo	24	13	42.2	Flexible	Oral
Ucha (1990)	NA	NA	6 weeks	Moclobemide 300-600mg	24	16	40.5	Flexible	Oral
UK Moclobemide Study Group (1994)	UK	NA	6 weeks	Placebo	54	NA	NA	Fixed	Oral
UK Moclobemide Study Group (1994)	UK	NA	6 weeks	Moclobemide 450mg	56	NA	NA	Fixed	Oral
Versiani (1989)	NA	NA	6 weeks	Moclobemide 300-600mg	164	124	44	Flexible	Oral
Versiani (1989)	NA	NA	6 weeks	Placebo	162	123	42	Flexible	Oral
Versiani (1990)	Brazil	NA	6 weeks	Moclobemide 600mg	25	NA	NA	NA	Oral
Versiani (1990)	Brazil	NA	6 weeks	Placebo	25	NA	NA	NA	Oral
Versiani (1997)	NA	NA	6 weeks	Moclobemide 75-750mg	108	73	41	Flexible	Oral
Versiani (1997)	NA	NA	6 weeks	Placebo	104	71	40	Flexible	Oral
White (1984)	USA	NA	4 weeks	Tranylcypromine 30-60mg	63	14	38	Flexible	Oral
White (1984)	USA	NA	4 weeks	Placebo	59	21	39	Flexible	Oral
Zarate (2006)	NA	NA	8 weeks	Memantine 5-20mg	16	9	47.1	Flexible	Oral
Zarate (2006)	NA	NA	8 weeks	Placebo	16	7	46.1	Flexible	Oral
Zisook (1985)	NA	NA	6 weeks	Isocarboxazid up to 80mg	NA	NA	NA	Flexible	Oral
Zisook (1985)	NA	NA	6 weeks	Placebo	NA	NA	NA	NA	NA

Table 1. Characteristics of included studies that reported anhedonia scores. NA = not available.

2.1 Description of included studies

We identified 63 eligible studies. The characteristics of the identified studies can be found in **Table 1**. Data from studies contributed with at least one outcome with quantitative data (total of 10532 participants), which included adults from multiple countries. The mean age of participants was 42.2 years (range 15 to 72 years), with a mean proportion of 0.58 female participants (range 0 to 0.86). Included studies allocated the participants to treatment lasting between 4 to 12.9 weeks (median, 6 weeks).

2.4 Primary outcome: reduction in anhedonia scores at 8 weeks (from 4 to 12 weeks)

2.4.1 Pairwise meta-analysis

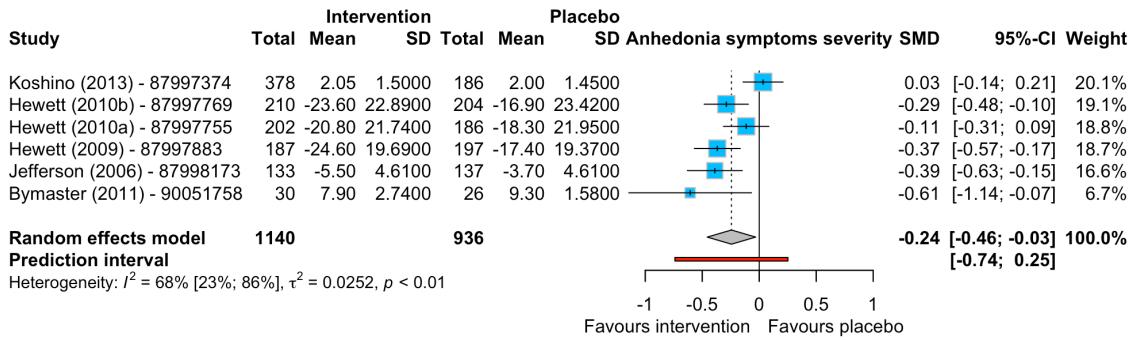


Figure 2. Forest plot for symptoms of anhedonia (primary outcome) comparing pro-dopaminergic interventions vs placebo for individuals with anhedonia at 4-12 weeks (primary timepoint). SMD: standardised mean difference, 95% CI: 95% confidence intervals, SD: standard deviation.

6 studies contributed with data to the meta-analysis with a total of 2076 participants (1140 allocated to pro-dopaminergic interventions, 936 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring pro-dopaminergic interventions with a SMD of -0.244 (95% CI from -0.456 to -0.031). There is some heterogeneity as shown by the 95% prediction interval from -0.74 to 0.252.

2.4.2 Risk of bias

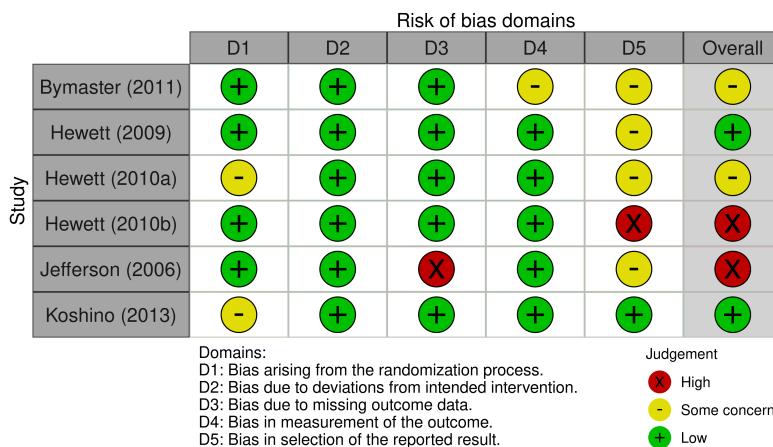


Figure 3. Risk of bias assessment.

Evidence for the efficacy of pro-dopaminergic interventions vs placebo were rated as having a range in their overall risk of bias. Two studies (33%) were assessed as having 'high' risk of bias due to having 'high' risk of bias in the missing outcome data domain and selection of the reported results domain. Two studies (33%) had an overall 'moderate' risk of bias rating as they had 'some concerns' in two domain ratings. The remaining two studies were rated as having a 'low' overall risk of bias. This result was judged to be at moderate risk of bias due to indirectness as while there was no clear indication of indirectness in terms of population, comparator, or outcomes, five of the six studies measured the same intervention, bupropion.

2.4.3 Reporting bias

The extent to which the result was affected by reporting biases was rated as low as per the RoB-ME assessment (Page et al. 2023). This was as the potential for missing studies across the review was judged to be low. In addition, none of the included studies were deemed to have generated an eligible result that was not reported, and no studies were judged to be unclear as to whether they generated an eligible result that was not reported. We made this decision based on the results matrix we generated in step 2 of the RoB-ME tool (Page et al. 2023).

2.4.4 Meta-regression analyses

We did not perform any meta-regressions as the total number of studies was below 10.

2.4.5 Sensitivity analyses

We performed a series of random effects network meta-analyses on the MADRS "inability to feel" item (aggregated IPD from 34 studies, 14054 participants). First, we included all the available studies and compared all the antidepressants against placebo.

2.4.5.1 Aggregated IPD, all antidepressants and placebo, random effects network meta-analysis

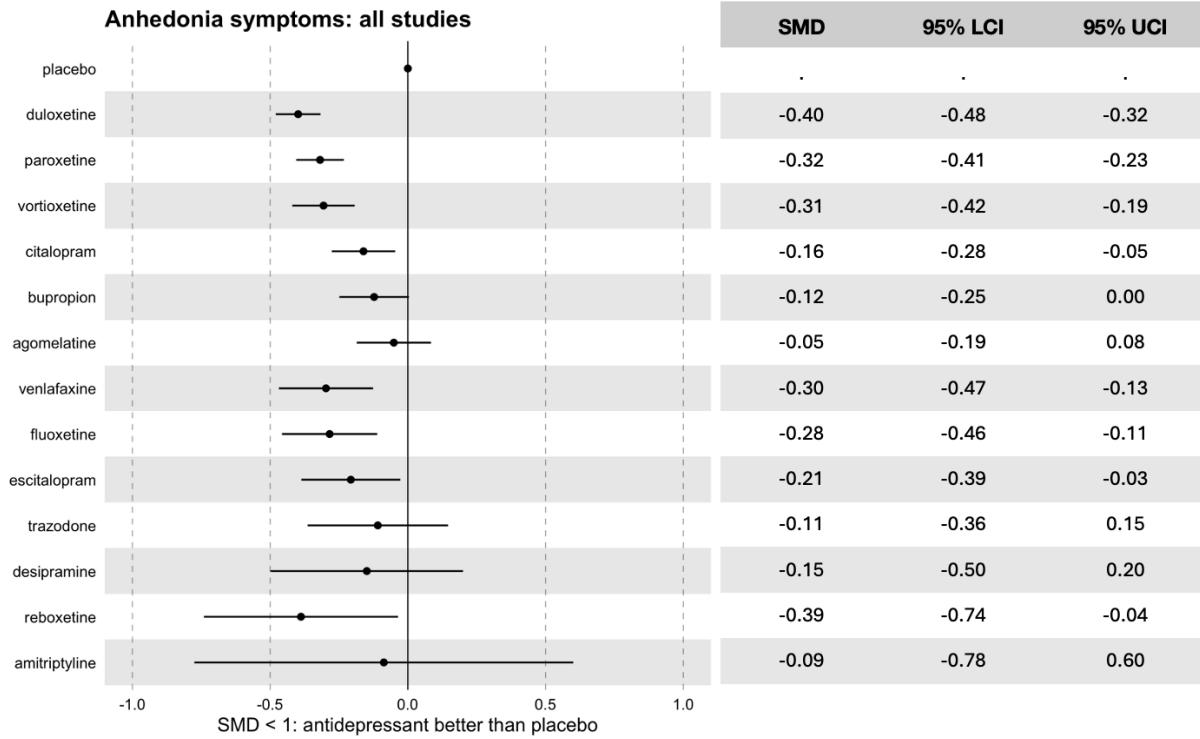


Figure 4. Comparative effect sizes of antidepressants versus placebo.

The comparative effect of bupropion versus placebo was -0.12 (SMD, 95% CI from -0.25 to 0.00; 34 studies, 14054 participants), lower than what we could observe from the retrieved data (random effects pairwise meta-analysis, bupropion versus placebo): -0.22 (SMD, 95% CI from -0.44 to 0.01; 5 studies, 2020 participants).

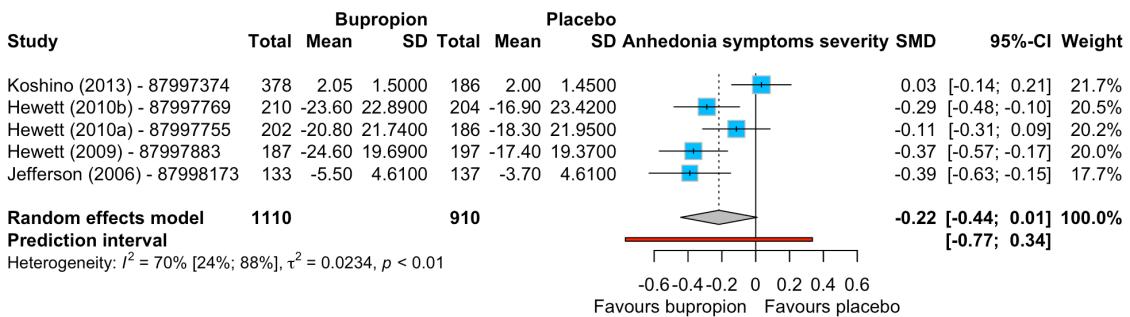


Figure 5. Forest plot for symptoms of anhedonia (primary outcome) comparing bupropion versus placebo for individuals with anhedonia at 4-12 weeks (primary timepoint). SMD: standardised mean difference, 95% CI: 95% confidence intervals, SD: standard deviation.

2.4.5.2 Aggregated IPD, bupropion versus placebo, random effects pairwise meta-analysis

We also performed a random effects pairwise meta-analysis of bupropion versus placebo based on the aggregated IPD, resulting in estimates comparable to the network meta-analytical model (SMD -0.12, 95% CI from -0.29 to 0.05; 4 studies, 1085 participants).

2.4.5.3 Aggregated IPD and early studies identified in this living systematic review, random effects pairwise meta-analysis

Finally, we performed a random effects pairwise meta-analysis including aggregate data from both sources (IPD and retrieved as aggregated). As three studies (Hewett 2009 - 87997883, Hewett 2010a - 87997755, Koshino 2013 - 87997374) were available in both sources, we prioritised aggregate IPD over data retrieved as aggregated. The comparative effect of bupropion versus placebo was -0.19 (SMD, 95% CI from -0.33 to 0.04; 6 studies, 2489 participants)

2.5 Secondary outcome: Reduction in mean anxiety score at 8

weeks (from 4 to 12 weeks)

2.5.1 Pairwise meta-analysis

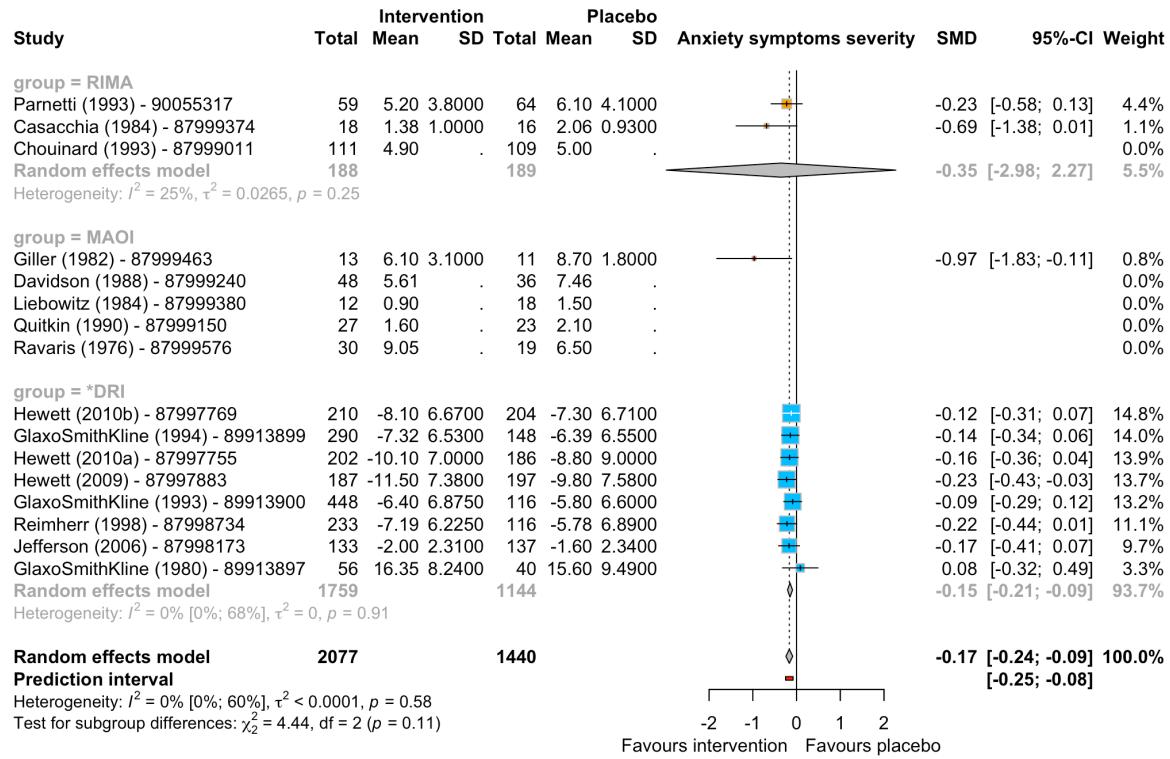


Figure 6 Forest plot for symptoms of anxiety (secondary outcome) comparing pro-dopaminergic interventions vs placebo for individuals with anxiety at 4-12 weeks (primary timepoint). SMD: standardised mean difference, 95% CI: 95% confidence intervals, SD: standard deviation.

11 studies contributed with data to the meta-analysis with a total of 3517 participants (2077 allocated to pro-dopaminergic interventions, 1440 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring pro-dopaminergic interventions with a SMD of -0.166 (95% CI from -0.243 to -0.088). The study results presented a τ^2 value of 0 indicating little to no heterogeneity (95% prediction interval: -0.251 to -0.08).

2.5.2 Risk of Bias

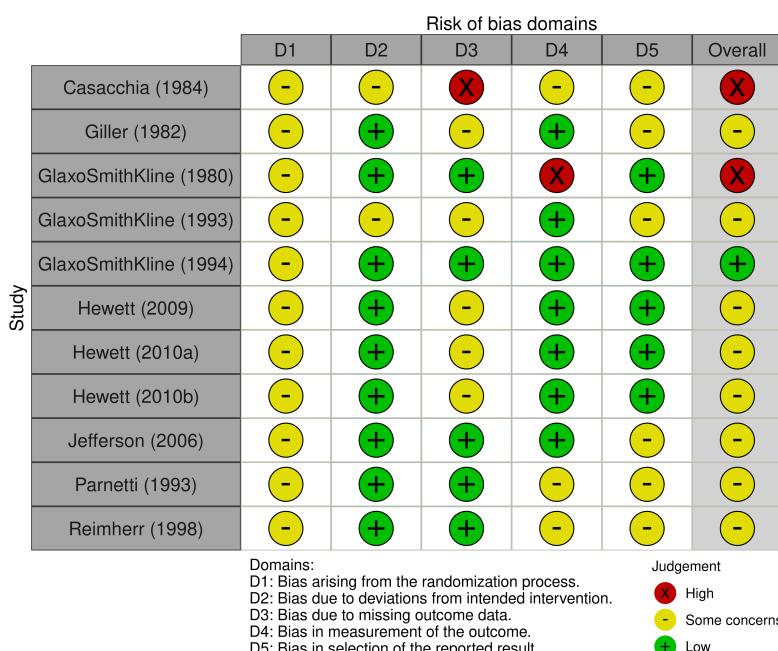


Figure 7. Risk of bias assessment.

2.5.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (r^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on anxiety symptom severity. For anxiety baseline, the regression coefficient (β) is intended per point increase. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia baseline score as the total number of studies was below 10.

Moderator	β	95% CI	r^2
Overall effect	-0.166	-0.243 to -0.088	0
Anxiety baseline	0.01	-0.01 to 0.03	0
Age	0	-0.01 to 0.01	0
Female proportion	-0.15	-1.85 to 1.55	0
Treatment duration	0.01	-0.05 to 0.08	0

The smaller r^2 value for anxiety baseline suggests that this predictor seems to explain some of the heterogeneity.

2.6 Secondary outcome: Dropouts due to any reason

2.6.1 Pairwise meta-analysis

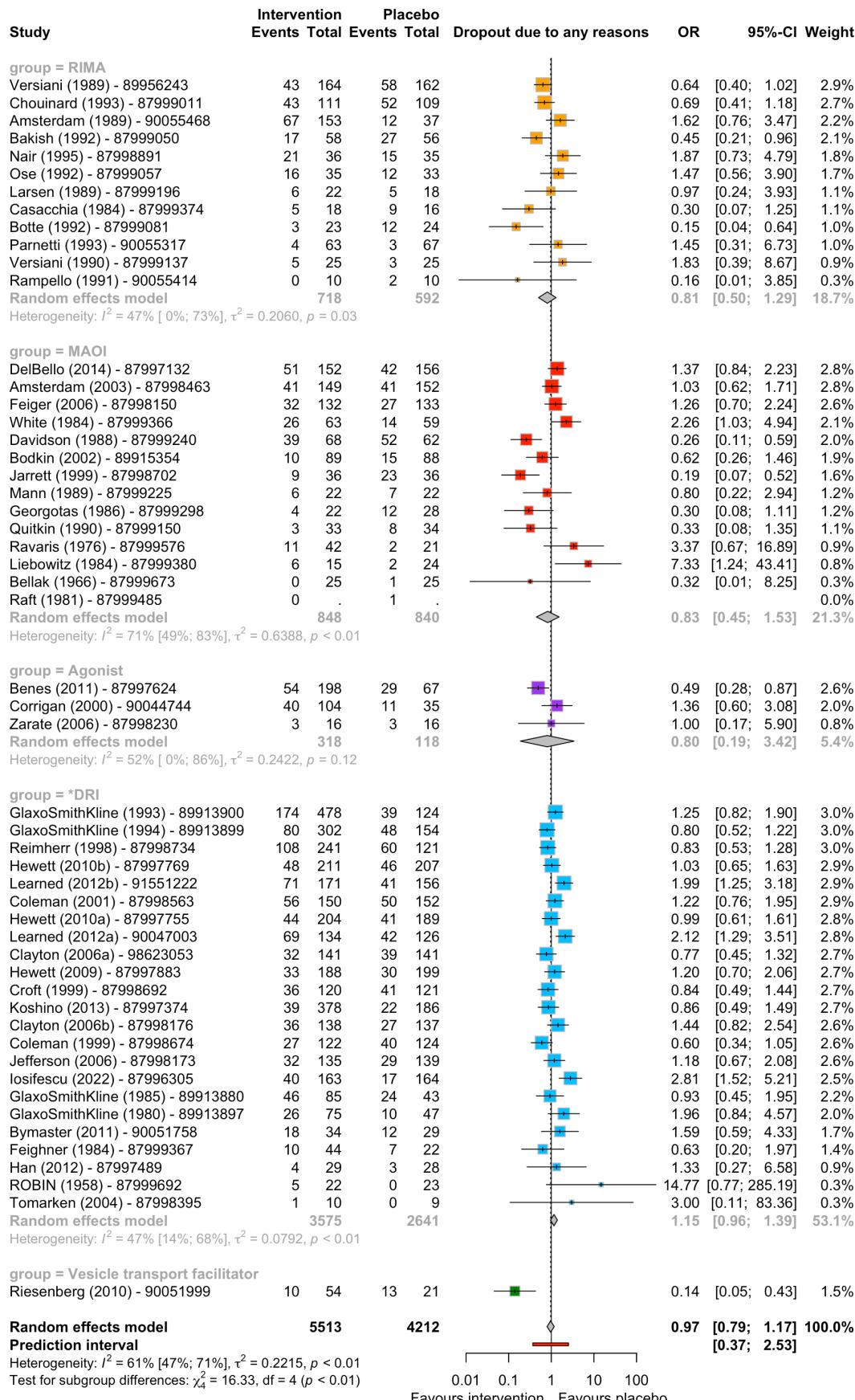


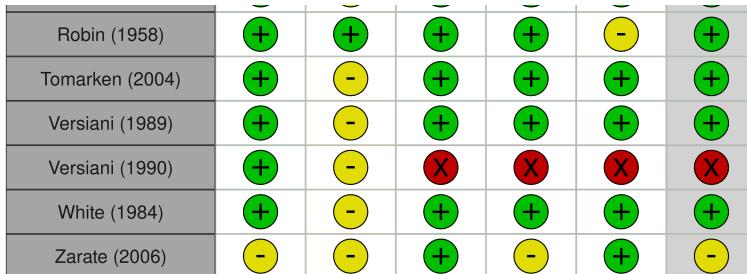
Figure 8 Forest plot for dropouts due to any reason for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

52 studies contributed with data to the meta-analysis with a total of 9725 participants (5513 allocated to pro-dopaminergic interventions, 4212 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed a comparable effect not excluding the null effect with an OR of 0.965 (95% CI from 0.794 to 1.172). The study results presented a r^2 value of 0.222. There is some heterogeneity as shown by the 95% prediction interval from 0.369 to 2.526.

2.6.2 Risk of bias

	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Amsterdam (1989)	X	+	+	+	+	X
Amsterdam (2003)	+	-	+	-	+	-
Bakish (1992)	+	+	+	X	+	X
Bellak (1996)	+	+	+	X	+	X
Benes (2011)	+	-	+	-	+	-
Bodkin (2002)	+	-	+	-	+	-
Botte (1992)	-	-	+	-	+	-
Bymaster (2011)	+	+	+	X	+	X
Cassachia (1984)	-	-	+	+	+	-
Chouinard (1993)	+	-	+	+	+	+
Clayton (2006a)	+	-	+	+	+	+
Clayton (2006b)	+	-	+	+	+	+
Coleman (1999)	+	-	+	+	+	+
Coleman (2001)	+	-	+	+	+	+
Corrigan (2000)	+	-	+	-	+	+
Croft (1999)	+	-	+	+	+	+
Davidson (1988)	+	-	+	+	+	+
DelBello (2014)	+	-	+	+	+	+
Feiger (2006)	+	-	+	-	+	-
Feighner (1984)	-	-	+	-	+	-
Georgotas (1986)	+	-	+	-	+	-
GlaxoSmithKline (1980)	-	-	+	+	+	-
GlaxoSmithKline (1985)	+	-	+	-	+	-
GlaxoSmithKline (1993)	+	-	+	-	+	-
GlaxoSmithKline (1994)	+	-	+	+	+	+
Han (2012)	-	-	+	+	+	-
Hewett (2009)	+	-	+	+	+	+
Hewett (2010a)	+	-	+	+	+	+
Hewett (2010b)	+	-	+	+	+	+
Iosifescu (2022)	+	+	+	+	+	+
Jarett (1999)	+	-	+	+	+	+
Jefferson (2006)	+	-	+	+	+	+
Koshino (2013)	+	-	+	+	+	+
Larsen (1989)	+	-	+	+	+	+
Learned (2012a)	+	-	+	+	+	+
Learned (2012b)	+	-	+	+	+	+
Liebowitz (1984)	+	-	+	+	+	+
Mann (1989)	+	-	+	+	+	+
Nair (1995)	+	-	+	+	+	+
Ose (1992)	+	-	-	+	+	-
Parnetti (1993)	+	-	+	+	+	+
Quitkin (1990)	-	-	+	+	+	-
Rampello (1981)	+	-	+	-	+	-
Ravaris (1976)	+	+	+	+	+	+
Reimherr (1998)	+	-	+	+	+	+
Riesenbergs (2010)	+	-	+	+	+	+



Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

X High

- Some concerns

+ Low

2.6.3 Meta-regression analyses

Figure 9. Risk of bias assessment.

The table below shows which of the covariates, if any, explain some of the heterogeneity (r^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on acceptability. For anxiety baseline, the regression coefficient (β) is intended per point increase. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia baseline score as the total number of studies was below 10.

Moderator	β	95% CI	r^2
Overall effect	0.965	0.794 to 1.172	0.22
Anxiety baseline	0.03	-0.01 to 0.07	0.01
Age	-0.01	-0.03 to 0.01	0.24
Female proportion	-0.82	-2.4 to 0.76	0.22
Treatment duration	-0.01	-0.11 to 0.09	0.25

The smaller r^2 values for anxiety baseline and female proportion suggest that these predictors seem to explain some of the heterogeneity.

2.7 Secondary outcome: dropouts due to side effects

2.7.1 Pairwise meta-analysis

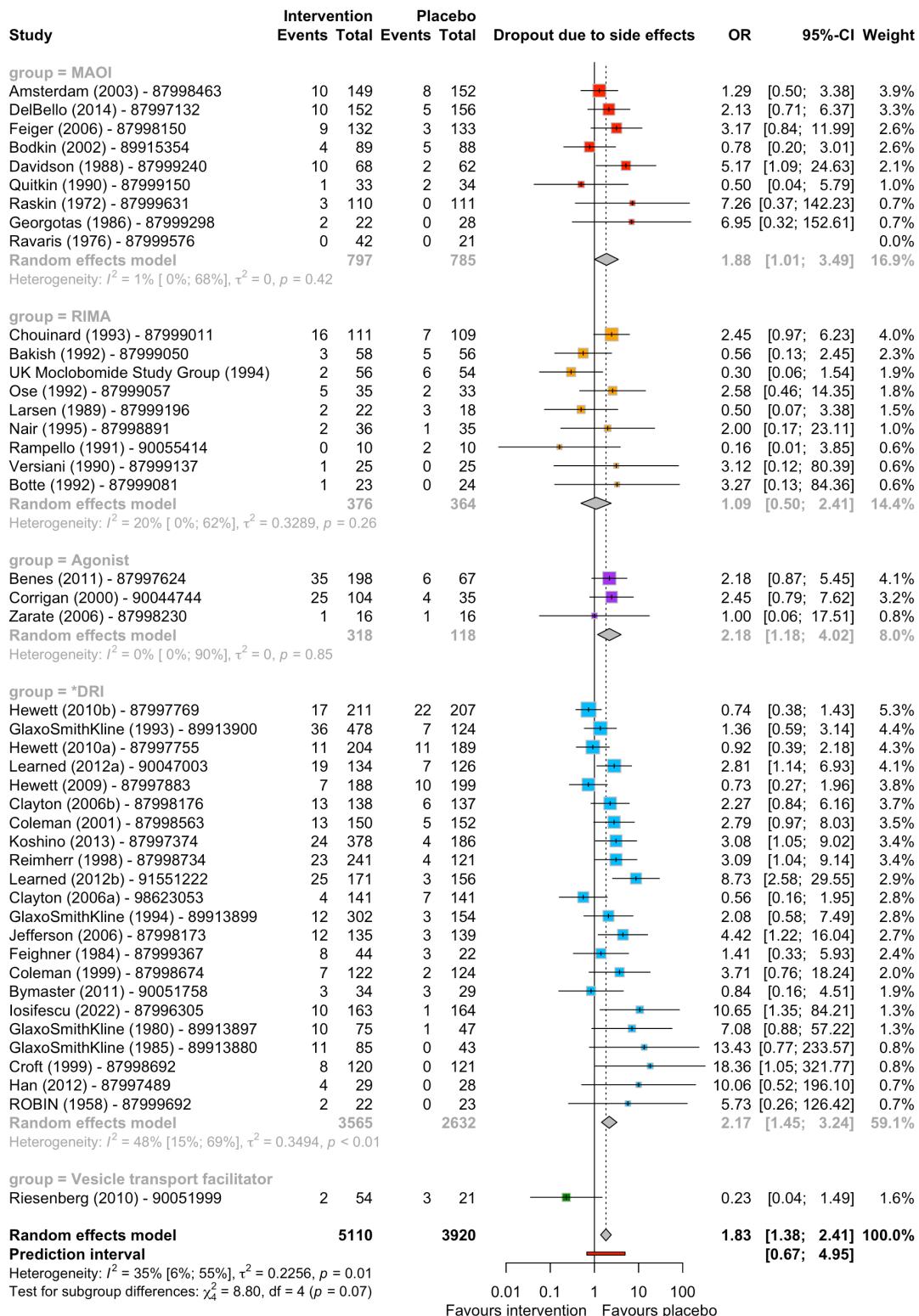


Figure 10 Forest plot for dropouts due to adverse events for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

43 studies contributed with data to the meta-analysis with a total of 9030 participants (5110 allocated to pro-dopaminergic interventions, 3920 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 1.825 (95% CI from 1.382 to 2.41). The study results presented a τ^2 value of 0.226 indicating the presence of some heterogeneity (95% prediction interval from 0.369 to 4.945).

2.7.2 Risk of bias



Figure 11. Risk of bias assessment.

2.7.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (τ^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on tolerability. For anxiety baseline, the regression coefficient (β) is intended per point increase. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia baseline score as the total number of studies was below 10.

Moderator	β	95% CI	τ^2
Overall effect	1.825	1.382 to 2.41	0.23
Anxiety baseline	-0.07	-0.15 to 0.01	0.01
Age	-0.02	-0.05 to 0.01	0.17
Female proportion	-2.82	-4.97 to -0.67	0.08
Treatment duration	0.03	-0.12 to 0.18	0.26

The tau² value for the overall effect indicates that there is some between-study variability in the effect of pro-dopaminergic interventions on discontinuation due to side effects not explained by these moderators. The predictor anxiety baseline score explained minimal between-study variance and its 95% CI included zero. While age and treatment duration both had tau² scores that suggested moderate between study variance due to these predictors, their 95% CIs also included zero. The predictor proportion of females had a negative beta and a 95% CI that did not include zero, indicating that in our model, for every 1% increase in proportion of females, there is a 5.9% ($\exp(2.82) = 0.059$) decrease in the OR of discontinuation due to size effects.

2.8 Secondary outcome: nausea

2.8.1 Pairwise meta-analysis

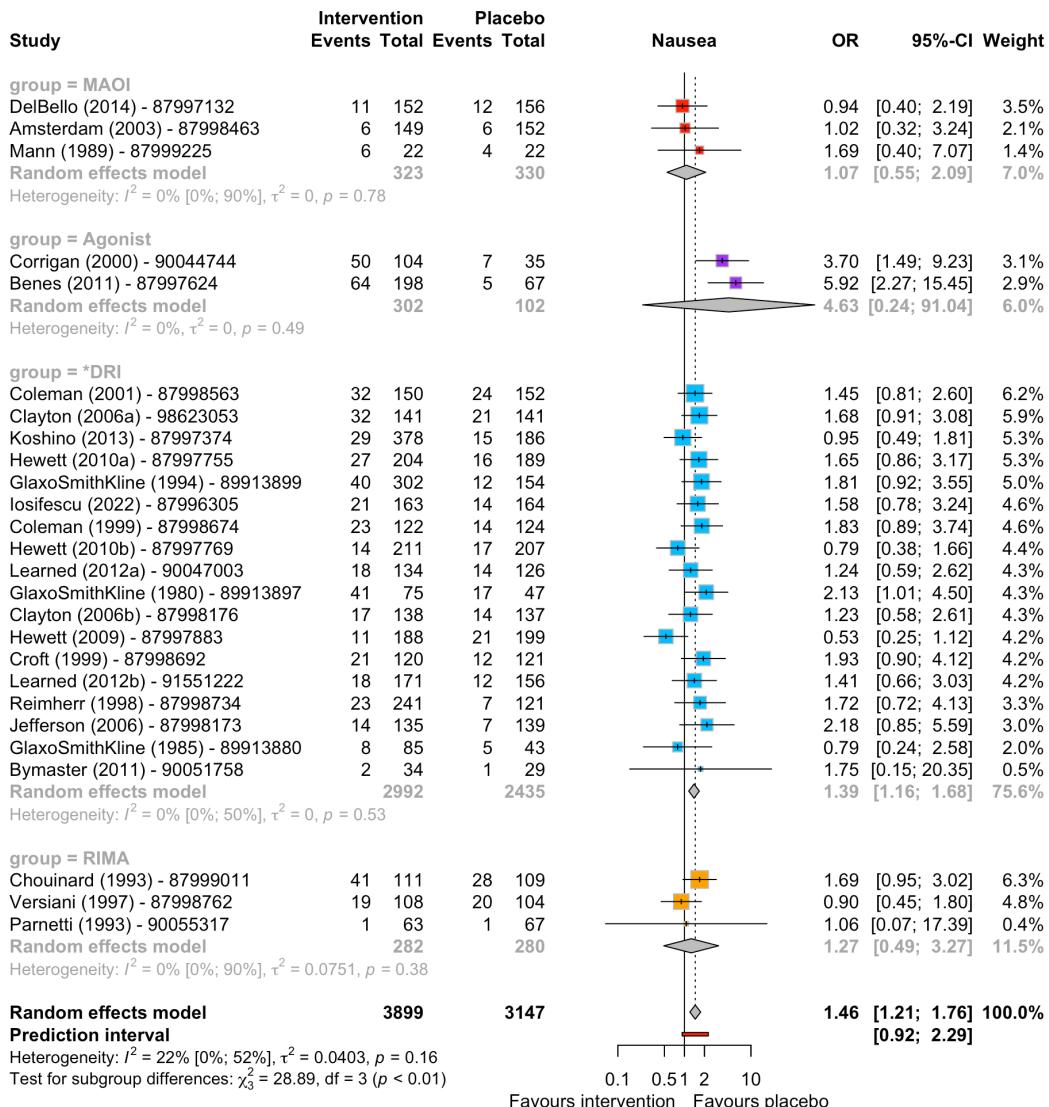


Figure 12 Forest plot for nausea for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

26 studies contributed with data to the meta-analysis with a total of 7046 participants (3899 allocated to pro-dopaminergic interventions, 3147 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 1.455 (95% CI from 1.206 to 1.756). The study results presented a τ^2 value of 0.04 indicating the presence of some heterogeneity (95% prediction interval from 0.925 to 2.291).

2.8.2 Risk of bias



Figure 13. Risk of bias assessment.

2.8.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (τ^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on nausea. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia and anxiety baseline scores as the total number of studies was below 10.

Moderator	β	95% CI	τ^2
Overall effect	1.455	1.206 to 1.756	0.04
Age	0	-0.02 to 0.02	0.03
Female proportion	0.11	-1.6 to 1.81	0.03
Treatment duration	0.01	-0.11 to 0.12	0.06

2.9 Secondary outcome: headache

2.9.1 Pairwise meta-analysis

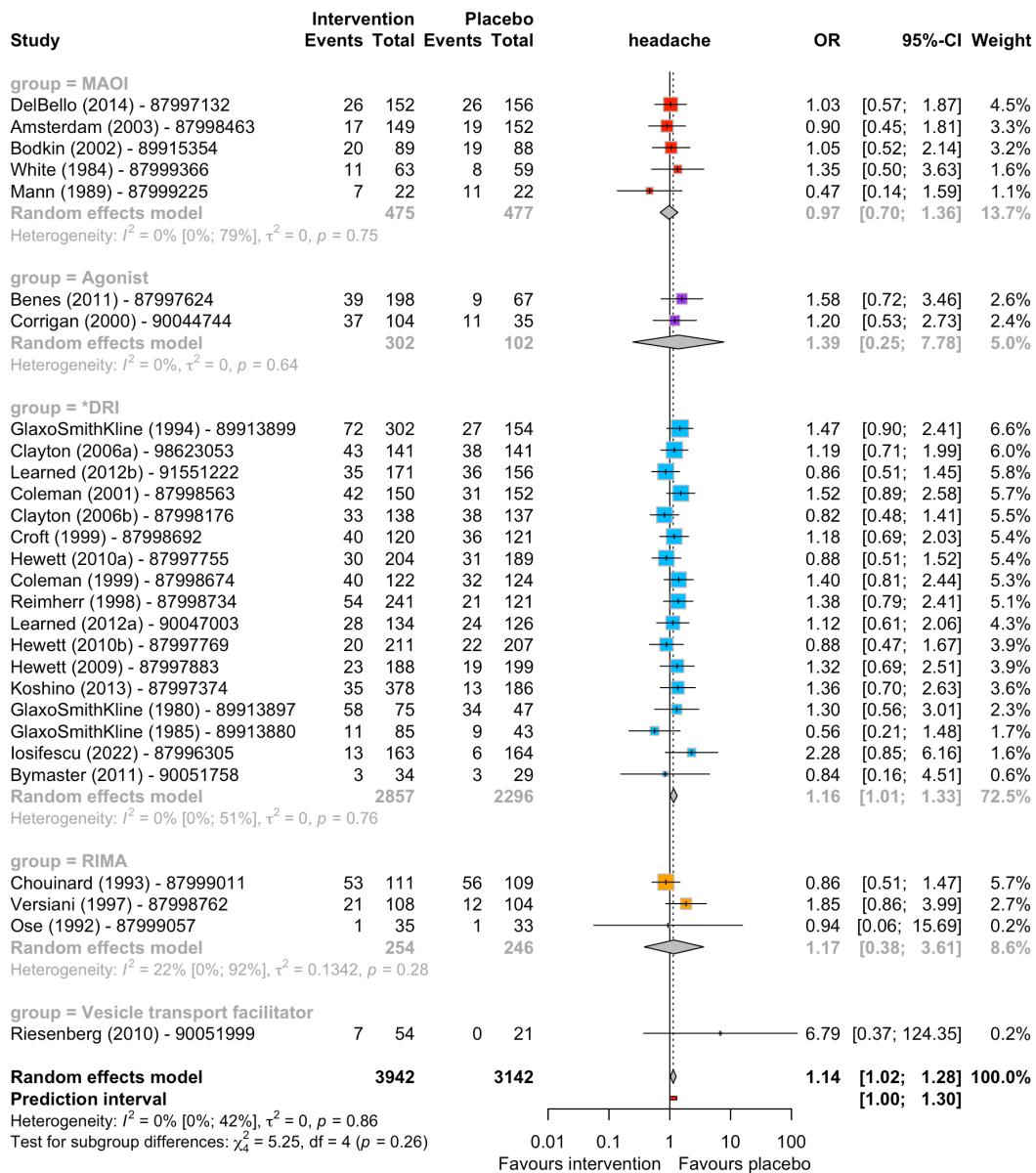


Figure 14 Forest plot for headaches for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

28 studies contributed with data to the meta-analysis with a total of 7084 participants (3942 allocated to pro-dopaminergic interventions, 3142 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 1.14 (95% CI from 1.019 to 1.275). The study results presented a τ^2 value of 0 indicating little to no heterogeneity (95% prediction interval from 0.998 to 1.302).

2.9.2 Risk of bias

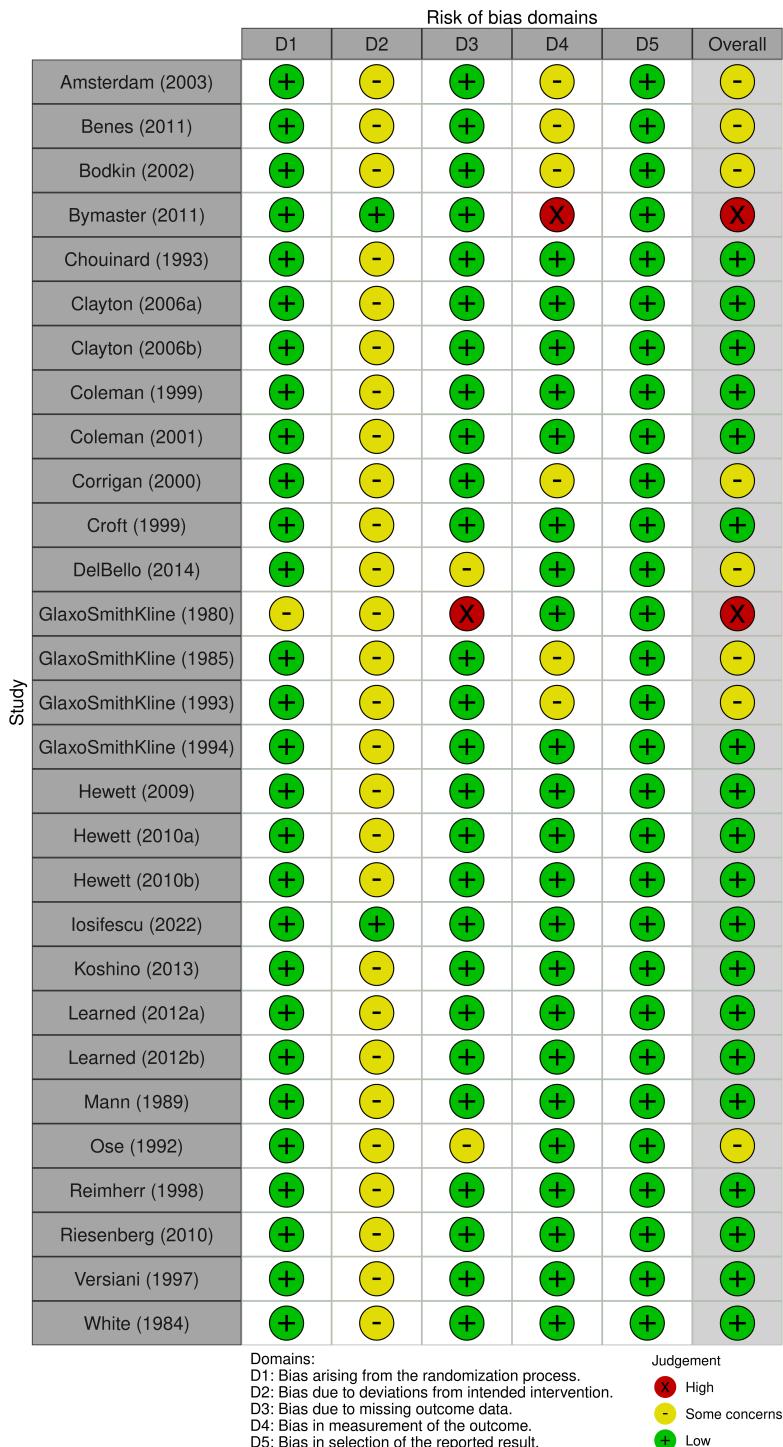


Figure 15. Risk of bias assessment.

2.9.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (r^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on headache. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia and anxiety baseline scores as the total number of studies was below 10.

Moderator	β	95% CI	r^2
Overall effect	1.14	1.019 to 1.275	0
Age	0	-0.02 to 0.01	0
Female proportion	0.53	-0.45 to 1.52	0
Treatment duration	0.01	-0.06 to 0.07	0

2.10 Secondary outcome: insomnia

2.10.1 Pairwise meta-analysis

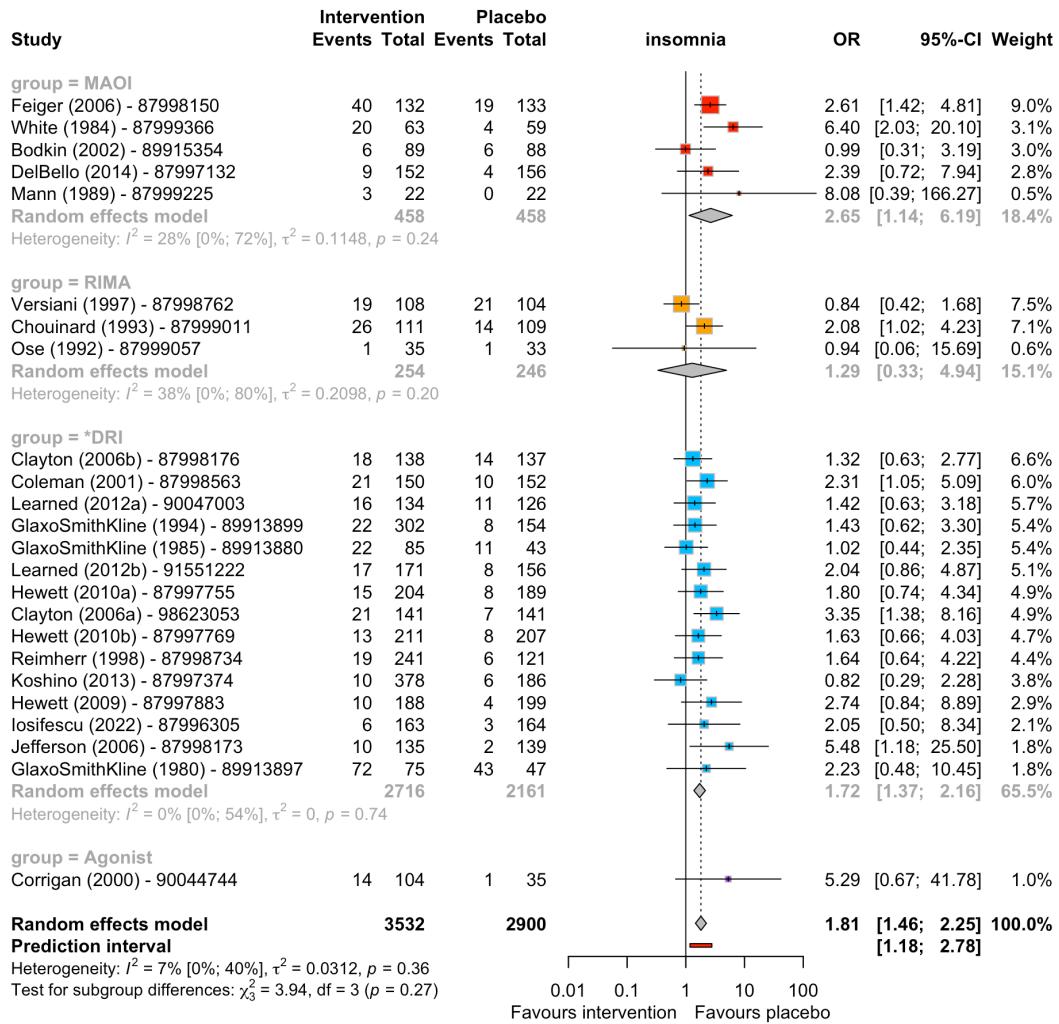


Figure 16 Forest plot for insomnia for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

24 studies contributed with data to the meta-analysis with a total of 6432 participants (3532 allocated to pro-dopaminergic interventions, 2900 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 1.809 (95% CI from 1.458 to 2.246). The study results presented a τ^2 value of 0.031 indicating some heterogeneity (95% prediction interval from 1.178 to 2.778).

2.10.2 Risk of bias



Figure 17. Risk of bias assessment.

2.10.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (τ^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on insomnia. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia and anxiety baseline scores as the total number of studies was below 10.

Moderator	β	95% CI	τ^2
Overall effect	1.809	1.458 to 2.246	0.03
Age	-0.01	-0.04 to 0.02	0.04
Female proportion	-0.18	-2.02 to 1.65	0.04
Treatment duration	0.01	-0.11 to 0.13	0.05

2.11 Secondary outcome: constipation

2.11.1 Pairwise meta-analysis

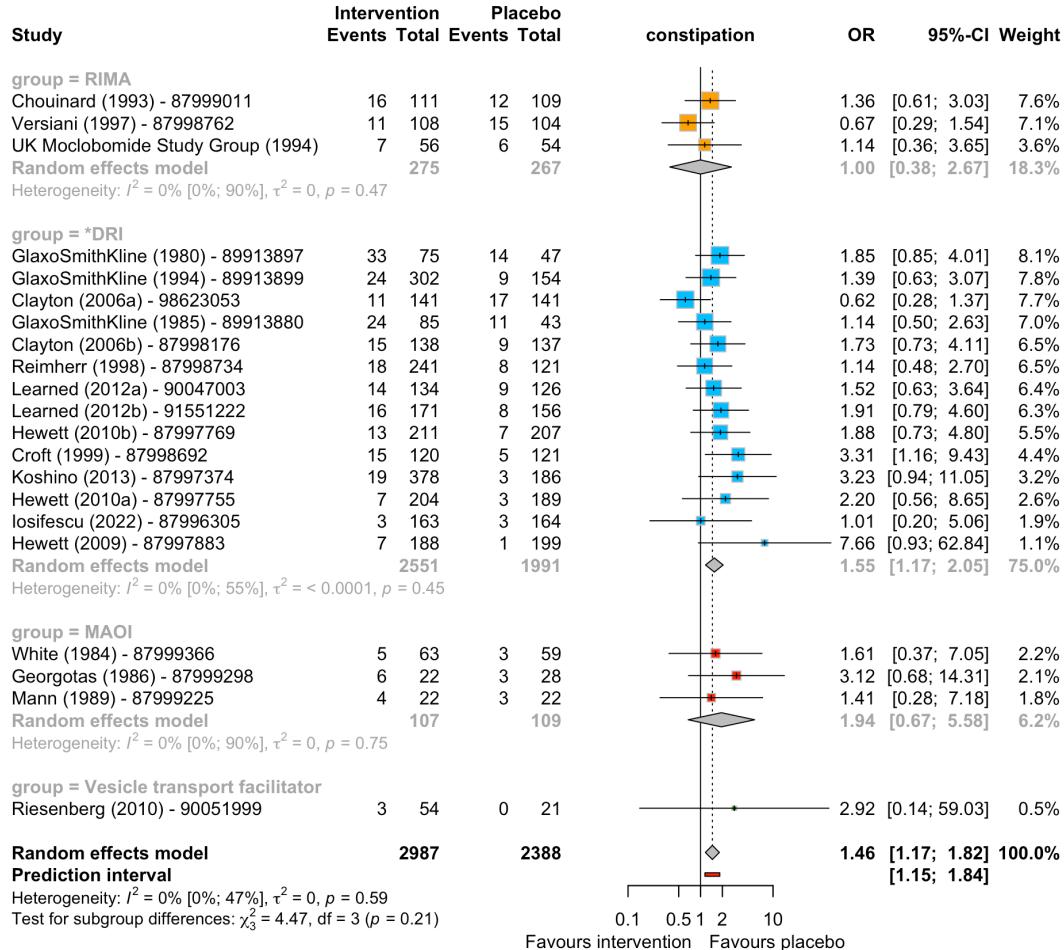


Figure 18 Forest plot for constipation for the comparison of pro-dopaminergic interventions vs placebo at 8 (4-12) weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

21 studies contributed with data to the meta-analysis with a total of 5375 participants (2987 allocated to pro-dopaminergic interventions, 2388 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 1.456 (95% CI from 1.166 to 1.818). The study results presented a τ^2 value of 0 indicating little to no heterogeneity (95% prediction interval from 1.15 to 1.842).

There were no important differences between participants assigned to different classes of drug.

2.11.2 Risk of bias

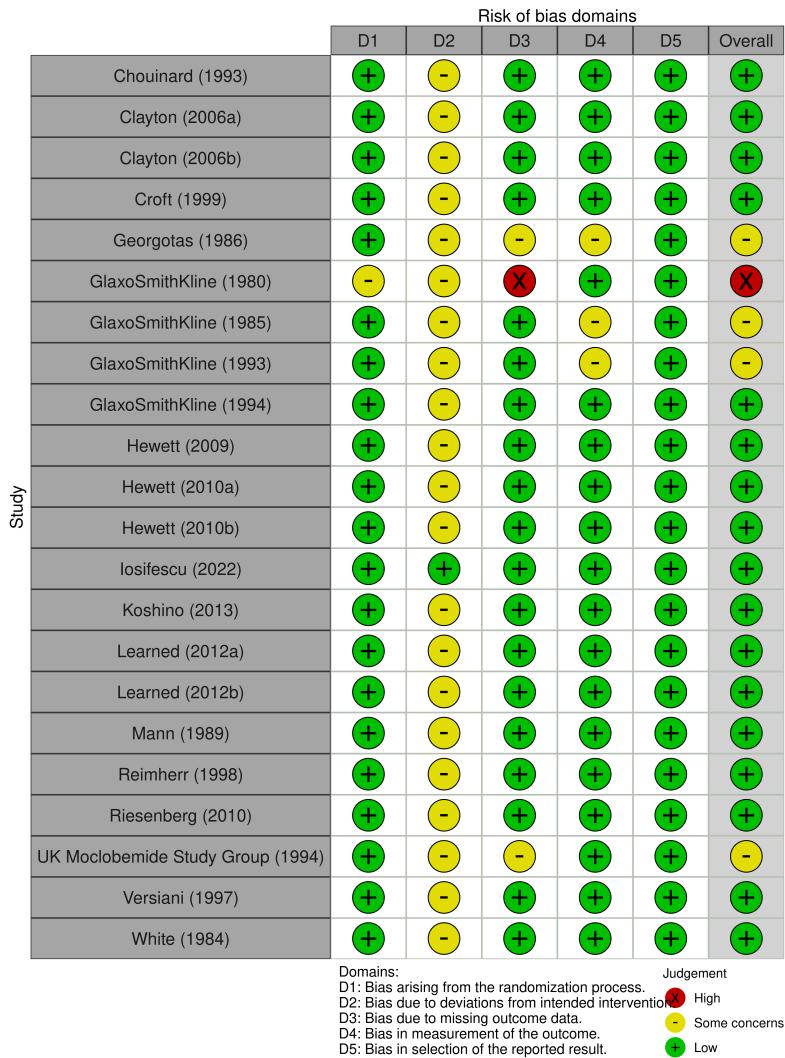


Figure 19. Risk of bias assessment.

2.11.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (τ^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on constipation. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia and anxiety baseline scores as the total number of studies was below 10.

Moderator	β	95% CI	τ^2
Overall effect	1.456	1.166 to 1.818	0
Age	0.01	-0.02 to 0.04	0.01
Female proportion	-0.87	-2.7 to 0.96	0
Treatment duration	0.09	-0.04 to 0.21	0.01

2.12 Secondary outcome: dizziness

2.12.1 Pairwise meta-analysis

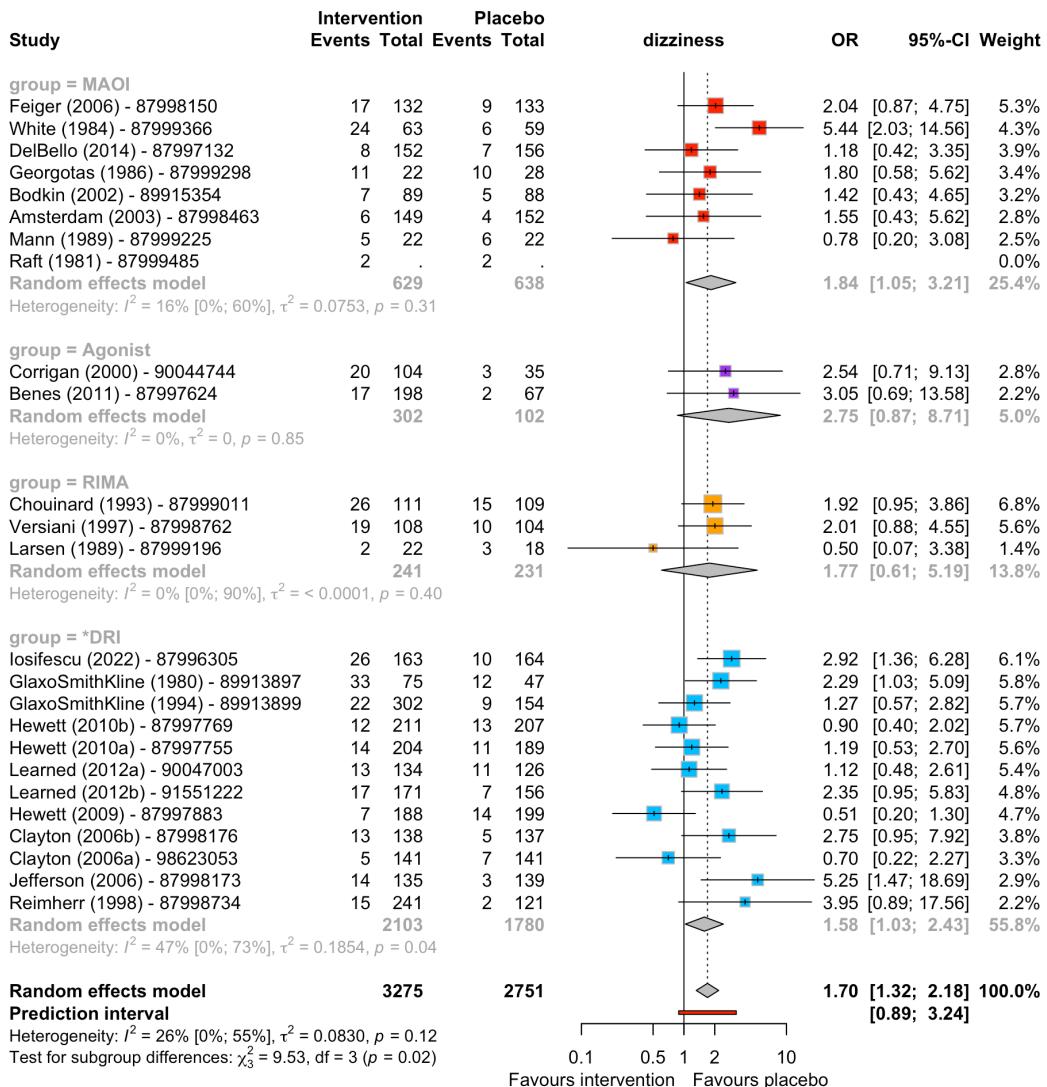


Figure 20 Forest plot for dizziness for the comparison of pro-dopaminergic interventions vs placebo at 8 (4-12) weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

24 studies contributed with data to the meta-analysis with a total of 6026 participants (3275 allocated to pro-dopaminergic interventions, 2751 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 1.697 (95% CI from 1.319 to 2.184). The study results presented a τ^2 value of 0.083. There is some heterogeneity as shown by the 95% prediction interval from 0.889 to 3.241.

2.12.2 Risk of bias

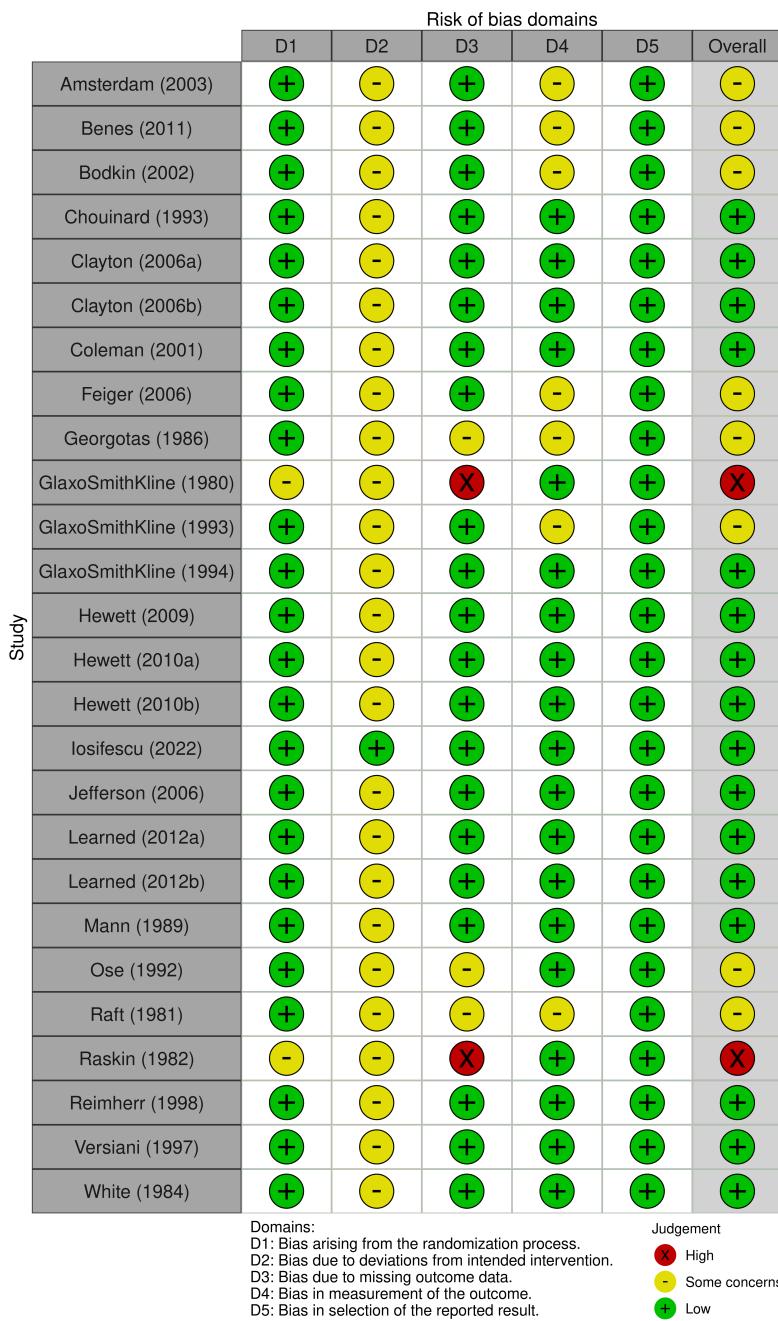


Figure 21. Risk of bias assessment.

2.12.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (τ^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on dizziness. For age, the regression coefficient (β) is intended per year of age. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week. We did not perform a meta-regression on mean anhedonia and anxiety baseline scores as the total number of studies was below 10.

Moderator	β	95% CI	τ^2
Overall effect	1.697	1.319 to 2.184	0.08
Age	-0.01	-0.03 to 0.02	0.09
Female proportion	-1.7	-3.65 to 0.26	0.06
Treatment duration	-0.1	-0.23 to 0.03	0.04

The smaller τ^2 values for female proportion and treatment duration suggest that these predictors may explain some of the heterogeneity.

2.13 Secondary outcome: dry mouth

2.13.1 Pairwise meta-analysis

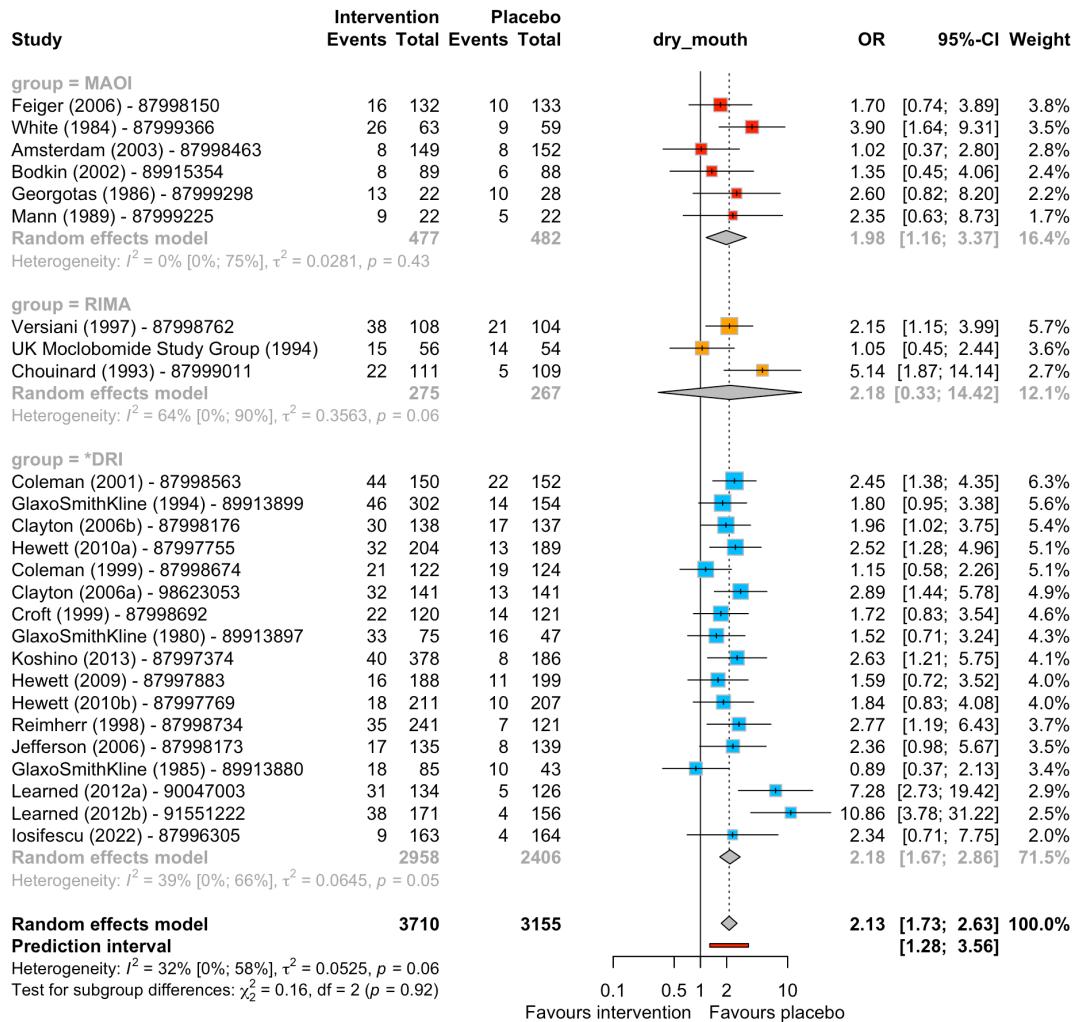


Figure 22 Forest plot for dry mouth for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

26 studies contributed with data to the meta-analysis with a total of 6865 participants (3710 allocated to pro-dopaminergic interventions, 3155 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed an effect favouring placebo with an OR of 2.134 (95% CI from 1.731 to 2.631). The study results presented a τ^2 value of 0.053 indicating some heterogeneity (95% prediction interval from 1.28 to 3.557).

2.13.2 Risk of bias



Figure 23. Risk of bias assessment.

2.13.3 Meta-regression analyses

The table below shows which of the covariates, if any, explain some of the heterogeneity (τ^2) observed in the effect sizes of the effect of pro-dopaminergic interventions on dry mouth. For age, the regression coefficient (β) is intended per year of age increase. For female proportion, the regression coefficient (β) is intended per percentage point increase. For treatment duration, the regression coefficient (β) is intended per week increase. We did not perform a meta-regression on mean anhedonia and anxiety baseline scores as the total number of studies was below 10.

Moderator	β	95% CI	τ^2
Overall effect	2.134	1.731 to 2.631	0.05
Age	-0.01	-0.03 to 0.02	0.05
Female proportion	-1.98	-3.68 to -0.27	0.02
Treatment duration	0.1	-0.03 to 0.24	0.06

The smaller τ^2 value for female proportion suggests that this predictor seems to explain some of the heterogeneity.

2.14 Secondary outcome: vomiting

2.14.1 Pairwise meta-analysis

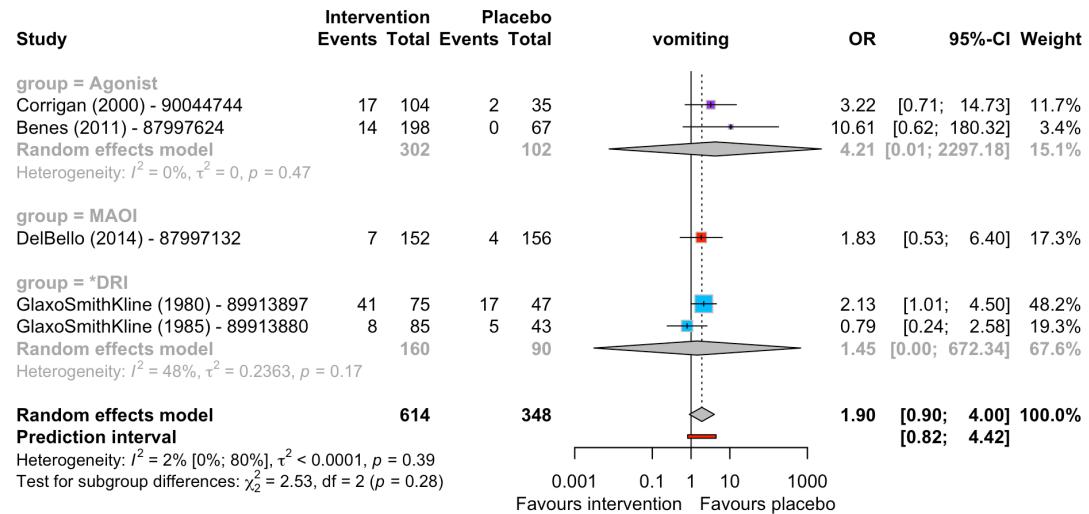


Figure 24 Forest plot for vomiting for the comparison of pro-dopaminergic interventions vs placebo at 4-12 weeks. OR: odds ratio, 95% CI: 95% confidence intervals.

5 studies contributed with data to the meta-analysis with a total of 962 participants (614 allocated to pro-dopaminergic interventions, 348 allocated to pill placebo).

The comparative effect of pro-dopaminergic interventions versus placebo showed a comparable effect not excluding the null effect with an OR of 1.898 (95% CI from 0.901 to 3.997). The study results presented a τ^2 value of 0 indicating little to no heterogeneity (95% prediction interval from 0.816 to 4.416).

2.14.2 Risk of bias

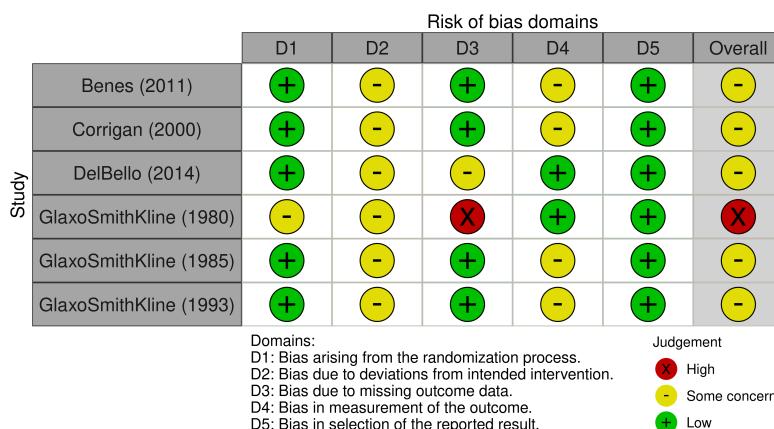


Figure 25. Risk of bias assessment.

2.14.3 Meta-regression analyses

We did not perform any meta-regressions as the total number of studies was below 10.

2.15 Summary of evidence tables

Source of evidence	Timepoint	Summary of the association	Bias due to study limitations (internal validity)	Bias due to reporting bias (external validity)	Bias due to indirectness	Bias due to other reasons
Pro-dopaminergic intervention. vs placebo in depressed patients with symptoms of anhedonia	4-12 weeks	N=6, n=2076; random effects: SMD= -0.24, 95%CI: -0.46, -0.03, 95%PI: -0.77, 0.34	Moderate risk: 33% of the studies had an overall high risk of bias (due to missing outcome data, and issues with outcome measurement and selective reporting of findings. 33% of studies had a moderate risk of bias.)	Moderate risk: 83% of studies were rated at least some concerns in RoB2 domain 5, selection of results. The impact of the bias on the magnitude and direction of the effects of pro-dopaminergic agonists is unclear.	Moderate risk: 83% of included studies examined the effects of the same pro-dopaminergic intervention, bupropion.	No clear indication of other biases.

Source of evidence	Timepoint	Summary of the association	Bias due to study limitations (internal validity)	Bias due to reporting bias (external validity)	Bias due to indirectness	Bias due to other reasons
Pro-dopaminergic interventions vs placebo in improving anxiety	4-12 weeks	N=11, n=3517; random effects: SMD=-0.17, 95%CI: -0.24, -0.09, 95%PI: -0.25, -0.08	Moderate risk: 73% of studies were rated moderate risk of bias while 18% were rated as high risk of bias. This was primarily due to domain 2- deviation from intended interventions.	Moderate risk: 55% of studies were rated moderate risk in domain 5 of RoB2. The impact of the bias on the magnitude and direction of the effects is unclear.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases.
Acceptability of pro-dopaminergic interventions vs placebo	8 weeks	N=52, n=9725; Random effects: OR=0.97, 95%CI: 0.79, 1.17, 95%PI: 0.37, 2.53	Low risk: 10% of studies had an overall high risk of bias, primarily due to concerns over outcome measurement, while 31% were rated moderate risk of bias.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases.
Tolerability of pro-dopaminergic interventions vs placebo	8 weeks	N=43, n=9030; Random effects: OR=1.83, 95%CI: 1.38, 2.41, 95%PI: 0.67, 4.95	Low risk: 12% of studies had an overall high risk of bias, primarily due to concerns over outcome measurement, while 35% were rated moderate risk of bias.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases.
Constipation reported for pro-dopaminergic interventions vs placebo	8 weeks	N=21, n=5375; random effects: OR=1.46, 95%CI: 1.17, 1.82, 95% PI: 1.15, 1.84	Low risk: 77% of studies were rated as low risk of bias and 5% were rated high risk of bias.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases
Dizziness reported for pro-dopaminergic interventions vs placebo	8 weeks	N=24, n=6026, random effects OR=1.70, 95%CI: 1.32, 2.18, 95%PI: 0.89, 3.24	Low risk: 59% of studies were rated low risk of bias and only 8% were rated high risk of bias.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases
Dry mouth reported for pro-dopaminergic interventions vs placebo	8 weeks	N=26, n=6865, random effects OR=2.13, 95%CI: 1.73, 2.63, 95%PI: 1.28, 3.56	Low risk: 67% of studies were rated low risk of bias for RoB2 while only 4% were rated high risk of bias.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases
Headache reported for pro-dopaminergic interventions vs placebo	8 weeks	N=28, n=7084, random effects, OR=1.14, 95%CI: 1.02, 1.28, 0	Low risk: 65% of studies were rated low risk for RoB2 while 31% were rated as moderate risk with scores of 'some concerns' spread out across domains in no clear pattern.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases
Nausea reported for pro-dopaminergic interventions vs placebo	8 weeks	N=26, n=6489, random effects OR=1.46, 95%CI: 1.21, 1.76, 95% PI: 0.92, 2.29	Low risk: 73% of studies were rated low risk for RoB2 while 23% were rated moderate.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases

Source of evidence	Timepoint	Summary of the association	Bias due to study limitations (internal validity)	Bias due to reporting bias (external validity)	Bias due to indirectness	Bias due to other reasons
Insomnia reported for pro-dopaminergic interventions vs placebo	8 weeks	N=24, n=6432, random effects OR=1.81, 95%CI: 1.46, 2.25, 95%PI: 1.18, 2.78	Low risk: 68% of studies were rated as low risk for RoB2 while 28% were rated as moderate risk.	Low risk: the impact of bias on the magnitude and direction of the effects of pro-dopaminergic agonists is low.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases.
Vomiting reported for pro-dopaminergic interventions vs placebo	8 weeks	N=5, n=962, random effects OR=1.90, 95%CI: 0.90, 4.00, 95%PI: 0.82, 4.42	Moderate risk: 80% of studies were rated as moderate risk and 20% as high risk due to concerns in RoB2 domains 3 (missing outcome data) and 4 (measuring the outcome)	Moderate risk: the impact of the bias on the magnitude and direction of the effects of pro-dopaminergic interventions is unclear.	Low risk: all studies included patients with depression receiving pro-dopaminergic interventions and assessed for anhedonia.	No clear indication of other biases.

Table 2. Summary of evidence table for the considered outcomes.

3. Abbreviations

- CI: Confidence Interval
- GALENOS: Global Alliance for Living Evidence on anxiety depression and psychosis
- IPD: Individual Participant Data
- OR: Odds Ratio
- N: number of studies
- n: number of participants
- NI: No Information
- SD: Standard Deviation
- SMD: Standard Mean Difference
- REML: Restricted Maximum Likelihood
- RoB2: Risk of Bias 2
- ROB-ME: Risk of Bias for Missing Evidence

4. Software Used

We used R version 4.3.1 (R Core Team 2023) and the following packages; meta (Balduzzi, Rucker, and Schwarzer, 2019); dplyr (Wickham et al. 2023); readxl (Wickham and Bryan, 2023); kableExtra (Zhu, 2024).

5. References

- Higgins, J. P., Savović, J., Page, M. J., Elbers, R. G., & Sterne, J. A. (2019). Assessing risk of bias in a randomized trial. *Cochrane handbook for systematic reviews of interventions*, 205-228.
- Flemming, E., Moore, T. H., Boutron, I., Higgins, J. P., Hróbjartsson, A., Nejstgaard, C. H., & Dwan, K. (2023). Using Risk of Bias 2 to assess results from randomised controlled trials: guidance from Cochrane. *BMJ Evidence-Based Medicine*, 28(4), 260-266.
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, 372.
- Page, M. J., Sterne, J. A., Boutron, I., Hróbjartsson, A., Kirkham, J. J., Li, T., ... & Higgins, J. P. (2023). ROB-ME: a tool for assessing risk of bias due to missing evidence in systematic reviews with meta-analysis. *bmj*, 383