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REVIEW

Nocebo response in dentistry: A systematic review and meta-analysis of adverse events in analgesic trials of third molar removal

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Abstract

Background: The nocebo response refers to the phenomenon where non-specific factors, including negative verbal suggestion and treatment expectations, cause adverse events (AE) following a placebo treatment. Non-specific factors are also likely to influence AE occurrence following administration of active pharmacological treatments.

Objective: This meta-analysis aimed to estimate the nocebo response in dentistry by assessing the AEs prevalence in placebo- and active arms of randomised controlled trials (RCTs) assessing analgesic treatment following third molar (M3) surgery.

Methods: A systematic search was performed in PubMed, Embase, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials. Eligible studies had to report the number of patients experiencing at least one drug-related AE (patients with AE ≥ 1) separately for the active and placebo arms. The proportion of patients with AE ≥ 1 and drug-related dropouts were pooled, and risk differences (RDs) between patients in the placebo- and active arm were calculated.

Results: In 50 independent RCTs of 47 identified articles, the pooled rates of patients with AE ≥ 1 were 22.8% in the placebo arm and 20.6% in the active arm. The pooled rates of drug-related dropout were 0.24% in the placebo arm and 0.08% in the active arm. There were no significant RDs in patients with AE ≥ 1 and drug-related dropouts.

Conclusion: These results show that patients in the placebo arm reported AEs to the same extent as patients receiving active treatment, suggesting that most AEs in analgesic medication following M3 surgery may be attributed to the nocebo phenomenon.

KEYWORDS
analgesics, long term adverse effects, nocebo effect, oral surgery, pain, third molar

Takeshi Watanabe and Mette Sieg should be considered joint first author.

1 | INTRODUCTION

In randomised controlled trials (RCTs), adverse events (AEs) often occur following the administration of an active pharmacological agent. However, AEs may also occur following the administration of a placebo (inactive agent).[1] An overview of systematic reviews, including 1271 RCTs that investigated a variety of different treatments, identified that 49% of patients in placebo groups experienced AEs.[1] A placebo, by definition, is inert and has no pharmacological effect.[2] AEs experienced by placebo-treated patients must, therefore, result from non-pharmacological, non-specific factors.[3] These non-specific factors may be context-related. For example, the information patients receive about potential AEs during the informed consent process has been shown to increase the risk of AEs.[4] In addition, the natural history of the disease, unrelated to the treatment context, may cause symptom fluctuations and thereby contribute to the AE profile.[5]

Thus, non-specific factors explain the occurrence of AEs following the administration of a placebo treatment, which is sometimes called a *nocebo response*.[5] Of relevance to clinical practice, a large proportion of AEs following the administration of an active pharmacological agent may similarly be caused by non-specific factors, rather than by the active drug component(s).[3] A recent meta-analysis, investigating AE occurrences in placebo- and active treatment arms of 231 RCTs covering a large range of medical conditions, reported that more than 70% of AEs from pharmacological treatments may be non-specific.[3] It is vital to understand the influence of non-specific factors on the occurrence of AEs, as it may lead to new ways of minimising unnecessary AEs following pharmacological treatments. For example, evidence shows that withholding information about potential AEs during the informed consent process decreases the patient's risk of experiencing AEs.[4] While non-disclosure is ethically problematic in relation to informed consent, other methods such as positive reframing of the AE information have also shown potential for mitigating nocebo effects.[6] Hence, these types of evidence reflect that learning more about nocebo and nocebo-like responses, and finding ways to reduce non-specific AEs, has great potential for treatment optimisation in clinical practice.

Although the nocebo phenomenon and role of non-specific factors have been investigated and identified across a wide range of medical conditions and treatments,[1] there is a dearth of knowledge about these factors within the field of dentistry. The latter despite an increase in papers highlighting the importance of recognising the possible nocebo phenomenon within this field.[7–11] As experimental research inducing nocebo effects is often complicated by ethics,[12] systematically assessing the nocebo response in placebo arms of RCTs provides a good platform to understand the influence of non-specific factors. The third molar (M3) extraction model has been used to investigate the efficacy and safety of analgesics[13] and, therefore, provides a good model to explore the nocebo response within the field of dentistry. Thus, the aim of this systematic review and meta-analysis was to estimate and compare (i) the pooled rates of AE occurrence and (ii) dropout rates in the placebo arms and active arms of RCTs investigating the efficacy and safety of analgesics following M3 surgery, in order to estimate the nocebo response, that is the contribution of non-specific factors, in dentistry.

2 | METHODS

The methodology and reporting of the review follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA 2020] guidelines.[14] The review protocol was registered with the international prospective register of systematic reviews (PROSPERO; CRD42021242203).

2.1 | Search strategy

A systematic search was conducted in PubMed, Embase, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL), on the 22 May 2021. In collaboration with dentists (LBH, MPi, PT, TW) and a skilled librarian, search strings containing free-text words and subject headings were adapted for each database. All search strings followed the same basic structure combining the following concepts: 'analgesics' AND 'third molar surgery' AND 'randomised controlled trial' AND 'adverse event'. The detailed search strings are shown in Appendix S1. Following removal of duplicates, identified articles were imported to the web-based systematic review software 'Covidence' (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.)

2.2 | Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: (1) Randomised, double-blind, parallel-group, placebo-controlled trials; (2) assessing analgesics for post-operative pain following M3 surgery in patients without significant systemic diseases; (3) reporting number of patients who experienced at least one drug-related AE (patients with AE ≥ 1). Studies were excluded for the following reasons in line with these criteria: (1) Not randomised, double-blind, parallel group, placebo-controlled trial. (2) Not pain treatment in relation to -M3 surgery. (3-1) No report of drug-related adverse events in the placebo arm. (3-2) No report of number of patients reporting at least one adverse event. (3-3) No clear distinction between drug-related and non-drug-related adverse events. Moreover, articles with no full-text available ($k = 9$) or not published in English ($k = 4$) were excluded in the title and abstract screening.

2.3 | Outcome measures

The nocebo response and primary outcome measure of the review was assessed as the proportion of patients with at least one

drug-related AE. The secondary outcome was proportion of drug-related study dropout, as an estimate of AE severity. 'Drug-related' AEs were defined based on previous studies investigating AEs in the placebo arms of analgesic trials.[1,15] AEs were considered to be non-drug-related (surgery-related) if terms included those listed in the Appendix S2.

2.4 | Study selection

Two reviewers (MPe and TW) independently screened all identified articles against the eligibility criteria, first based on titles and abstracts followed by full-text screening. Disagreements were resolved through discussion with a third reviewer (MS).

2.5 | Quality assessment

Quality assessment was performed by two independent reviewers (MPe and TW) using the Cochrane Risk of Bias Tool 2 (RoB2). Disagreements were resolved through discussion with a third reviewer (MS).

2.6 | Data extraction

The data extraction process was conducted by two independent reviewers (MPe and TW), and any disagreements were resolved through discussion with a third reviewer (MS). In addition to authors, year and country of publication, and name and type of the analgesic, the following data were extracted from the included articles, both for the placebo and active arm: number of subjects, proportion of females, mean age, number of patients with AE ≥ 1, drug-related dropout rate.

2.7 | Data synthesis and statistical methods

Pooled rates of patients experiencing AE ≥ 1 were calculated for the placebo arms and active arms. Risk differences (RDs) between the proportion of patients with AE ≥ 1 in the placebo- and active arms were calculated.[16] RDs were calculated using both fixed and random-effects model to account for between- and within-study variability, with associated 95% confidence intervals, and the random-effects model was accepted for the main analysis and fixed-effects model was applied to the sensitivity analysis. Pooled rates and RDs were similarly calculated for drug-related dropout rates. The available data did not allow for comparisons between specific AE profiles in placebo arms of different types of analgesia. Statistical heterogeneity was quantified using the I^2 statistic and Cochran's Q tests.[17,18] An I^2 value of 0%, 50% and 75% indicated low, moderate or high heterogeneity, respectively.[19] Potential publication bias and small study effects for RDs were assessed using funnel plots and Egger's linear regression asymmetry test.[20] All analyses were conducted using R (version 4.0.4).[21] We used meta-analysis of binary outcome data (metabin) functions for the main analyses and influence analysis in meta-analysis using leave-one-out method (metainf) functions for leave-one-out analysis from the meta package (version 4.18-0).

3 | RESULTS

3.1 | Search results

The systematic search identified 581 articles. After removing duplicates, 283 articles were screened based on titles and abstracts. The basic inter-rater agreement on the title-abstract screening was 85.5%, and Cohen's Kappa statistic was 0.70, indicating moderate agreement. Based on full-text screening of 162 articles, 115 were excluded. The main reasons for exclusion were (3-3) no report of number of patients reporting at least one adverse event ($k = 40$), (3-2) no clear distinction between drug-related and non-drug-related adverse events ($k = 31$), and (3-1) no report of drug-related adverse events in the placebo arm ($k = 30$). Forty-seven articles thus fulfilled the eligibility criteria and were included in the analyses. A PRISMA flowchart of the study selection is presented in Figure 1. The reasons for exclusion of full-text screened articles are provided in Appendix S3.

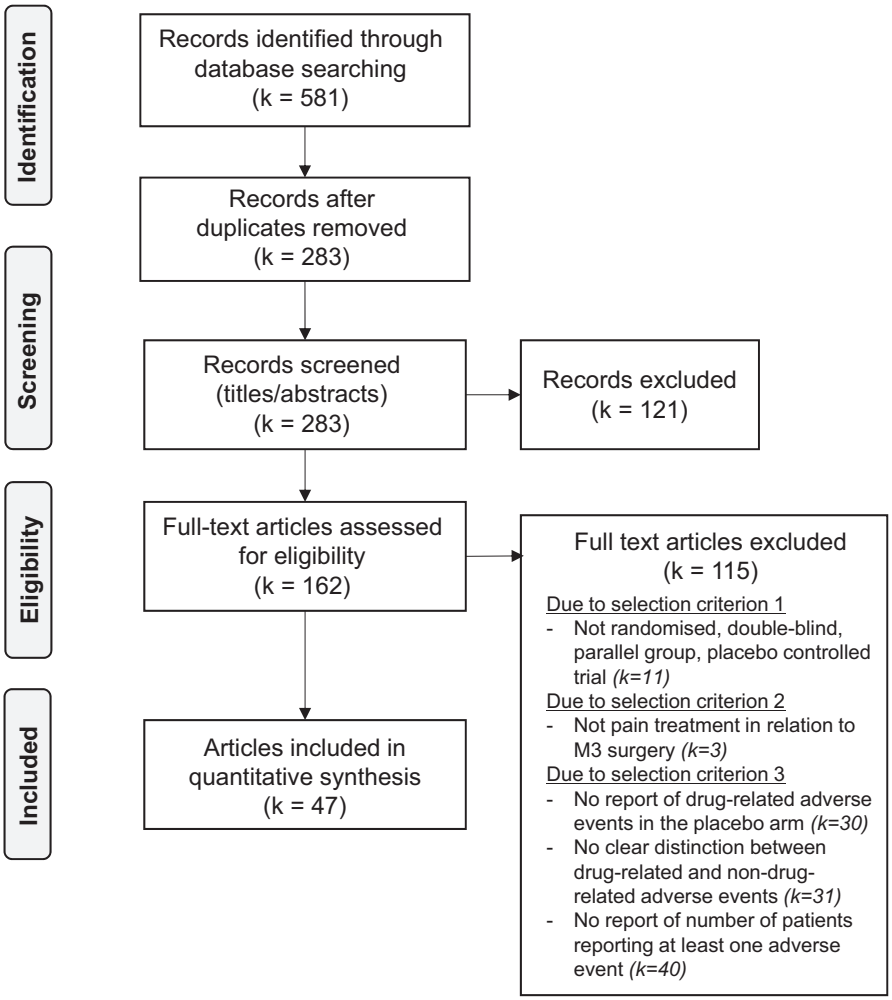
3.2 | Included studies

The characteristics of included studies are presented in Table 1. None of these studies were classified as high risk of bias (result of quality assessment are shown in Appendix S4). The 47 included studies covered 10 909 patients across 50 trials, of which 2471 patients were randomised to the placebo arms and 8438 patients to the active arms. Mean age and proportion of females in the included trials were 23.7 years ± 2.6 (SD) and 55.8% ± 8.7, respectively, and the majority of the trials were conducted in North America ($k = 30$) and Europe ($k = 16$), with one study conducted in Asia. Types and frequencies of AEs in the placebo arms are listed in Table 2, with nausea/vomiting and headache most frequently reported. A detailed list of types and frequencies of AEs across the placebo arms and active arms of each of the included trials can be found in Appendix S5.

3.3 | Pooled rate of drug-related AEs and drug-related dropout rates

The pooled rates of patients experiencing at least one drug-related AE in the placebo arms and active arms were 22.8% [95% CI: 21.1, 24.5] and 20.6% [95% CI: 19.8, 21.5], respectively. The pooled drug-related dropout rates in the placebo arms and active arms were 0.24% [95% CI: 0.09, 0.52] and 0.08% [95% CI: 0.03, 0.17], respectively. There were no significant differences in the proportion

FIGURE 1 PRISMA flowchart



of patients experiencing at least one drug-related AE between the placebo arms and the active arms (RD −0.84% [95% CI: −4.06, 2.38], $p = .61$; Figure 2), nor were there significant differences in drug-related dropout rates (RD −0.01% [95% CI: −0.37, 0.34], $p = .94$; Figure 3). There was evidence of high statistical heterogeneity between studies for the proportion of patients experiencing AE ≥ 1 ($I^2 = 79.7\%$, Q (d.f. = 49) = 241.63, $p < .001$) (Figure 2), but not for drug-related dropout rates ($I^2 = 0\%$, Q (d.f. = 49) = 5.93, $p = 1.00$) (Figure 3). Sensitivity analysis showed little change in the overall effect when using a fixed-effects model (RD −0.42% [95% CI: −2.10, 1.25]; $p = .62$), and the leave-one-out analysis had minimal effect (min = −1.35%, max = 0.14%, all p-values >.40) on the analysis of the proportion of patients experiencing AE ≥ 1. An assessment of publication bias found no significant asymmetries in the funnel plots ($p = .21$, Appendix S6A; and $p = .08$, Appendix S6B, respectively).

4 | DISCUSSION

This is the first systematic review and meta-analysis to show the nocebo response within the field of dentistry. Pooled across 50 dental RCTs, patients treated with a placebo analgesic following M3 surgery experienced similar levels of AEs compared to those treated with an active analgesic (23% vs. 21%). This suggests that a large proportion of AEs from analgesic medication following M3 surgery may not be attributed to the pharmacological agent, but rather to a nocebo-like response, and that the nocebo phenomenon may play a role in dental surgery similarly to other clinical fields.[1,3]

While AE reports from 23% of placebo-treated patients in the present meta-analysis is relatively low, compared to an average of 49% across 20 different treatment trials (e.g., treatment of migraine, cardiovascular disease and psychiatric diseases),[1] similar proportions of AE reports by placebo-treated patients were found in knee osteoarthritis trials (27%),[22] trials of symptomatic treatment for headache (18%)[23] and symptomatic treatment for multiple sclerosis (25%).[24] Furthermore, the results of the present meta-analysis are in line with observations made in similar studies, in which the proportions of drug-related AEs in the placebo and active treatment groups were 19% and 26%, respectively.[3]

In line with previous meta-analyses, the current study assesses the nocebo *response*, which is the occurrence of AE in a placebo group.[5] The nocebo *effect* is the difference in AE occurrence between a placebo group and a no-treatment group controlling for natural symptom occurrence.[25] As the majority of RCTs do not include a third no-treatment control group,[1] only the nocebo *response* can be investigated in this type of meta-analysis. However,

TABLE 1 Summary of adverse events and dropout rates within placebo arms and active arms of included trials

		Placebo arm			Active arm		
First author (year)	*N* total (placebo + active)	Patients experiencing drug-related AE ≥1, *n* (%)	Drug-related dropout rate, *n* (%)	*N*	Patients experiencing drug-related AE ≥ 1, *n* (%)	Drug-related dropout rate, *n* (%)	*N*
Cheung (2007)	171	39 (68)	3 (3)	57	64 (56)	1 (1)	114
Christensen (2017)[a]							
Trial 1	196	8 (28)	0 (0)	29	11 (7)	0 (0)	167
Trial 2	106	23 (44)	3 (3)	52	8 (15)	0 (0)	54
Cooper (1998)	177	4 (15)	0 (0)	26	63 (42)	0 (0)	151
Daniels (2002)	406	53 (51)	0 (0)	103	133 (44)	0 (0)	303
Daniels (2006)[a]							
Trial 1	450	12 (24)	0 (0)	49	40 (10)	0 (0)	401
Trial 2	125	24 (38)	0 (0)	24	14 (14)	0 (0)	101
Daniels (2009)	322	24 (30)	0 (0)	81	68 (28)	0 (0)	241
Daniels (2011)	491	6 (13)	0 (0)	46	81 (18)	5 (1)	445
Desjardins (1983)	139	6 (18)	0 (0)	34	15 (14)	0 (0)	105
Desjardins (2000)	151	6 (19)	0 (0)	31	100 (83)	0 (0)	120
Desjardins (2001)	224	22 (39)	0 (0)	56	50 (30)	0 (0)	168
Desjardins (2002)	284	33 (58)	0 (0)	57	15 (42)	0 (0)	227
Dionne (1998)	78	4 (14)	0 (0)	28	7 (14)	0 (0)	50
Forbes (1981)	133	6 (18)	0 (0)	34	7 (8)	0 (0)	99
Forbes (1990)	401	6 (7)	0 (0)	86	30 (10)	0 (0)	315
Forbes (1991a)	269	3 (6)	0 (0)	47	27 (12)	0 (0)	222
Forbes (1991b)	80	0 (0)	0 (0)	15	7 (11)	0 (0)	65
Forbes (1992)	317	2 (4)	0 (0)	46	33 (12)	0 (0)	271
Forbes (1994)	286	10 (15)	0 (0)	65	49 (22)	0 (0)	221
Frame (1989)	148	3 (6)	0 (0)	50	3 (3)	0 (0)	98
Fricke (2002)	200	24 (48)	0 (0)	50	60 (40)	0 (0)	150
Fricke (2004)	456	24 (39)	0 (0)	151	179 (59)	1 (0)	305
Gay-Escoda (2019)	653	2 (2)	0 (0)	131	51 (10)	0 (0)	522
Gorecki (2018)	75	0 (0)	0 (0)	16	16 (27)	0 (0)	59
Grant (2010)	80	8 (20)	0 (0)	40	16 (40)	0 (0)	40
Henrikson (1979)	550	17 (9)	0	184	30 (8)	0 (0)	366
Hersh (1993)	254	9 (18)	0 (0)	51	17 (8)	0 (0)	203

TABLE 1 (Continued)

First author (year)	*N* total (placebo + active)	Placebo arm			Active arm		
		Patients experiencing drug-related AE ≥1, *n* (%)	Drug-related dropout rate, *n* (%)	*N*	Patients experiencing drug-related AE ≥ 1, *n* (%)	Drug-related dropout rate, *n* (%)	*N*
Hersh (1998)	123	5 (24)	0 (0)	21	24 (24)	0 (0)	102
Hill (2001)	198	1 (2)	0 (0)	50	27 (18)	0 (0)	148
Hutton (1983)	168	4 (9)	0 (0)	43	24 (19)	0 (0)	125
Hyrkäs (1992)	151	30 (61)	0 (0)	49	51 (50)	0 (0)	102
Juhl (2006)	297	1 (3)	0 (0)	33	4 (2)	0 (0)	264
Kempf (1987)	98	1 (4)	0 (0)	24	5 (7)	0 (0)	74
Matthew (2000)	70	4 (25)	0 (0)	16	13 (24)	0 (0)	54
McQuay (1996)	161	1 (9)	0 (0)	11	9 (6)	0 (0)	150
Mishra (2012)	74	1 (4)	0 (0)	24	12 (24)	0 (0)	50
Møller (2005)	152	14 (8)	0 (0)	50	45 (44)	0 (0)	102
Møller (2008)	200	2 (5)	0 (0)	40	10 (6)	0 (0)	160
Morrison (1999)	151	12 (24)	0 (0)	50	10 (10)	0 (0)	101
Ostenfeld (2011)	123	19 (61)	0 (0)	31	64 (70)	0 (0)	92
Petersen (1975)	50	4 (16)	0 (0)	25	7 (28)	0 (0)	25
Petersen (1978)	90	9 (30)	0 (0)	30	21 (35)	0 (0)	60
Rood (2002)	93	7 (22)	0 (0)	32	7 (11)	0 (0)	61
Seymour (2003)	153	28 (88)	0 (0)	32	90 (74)	0 (0)	121
Sunshine (1983)	203	1 (3)	0 (0)	40	4 (2)	0 (0)	163
Sunshine (1986)	182	1 (3)	0 (0)	30	4 (3)	0 (0)	152
Yue (2013)[a]							
Trial 1	300	4 (7)	0 (0)	60	15 (6)	0 (0)	240
Trial 2	401	10 (13)	0 (0)	80	14 (4)	0 (0)	321
Zuniga (2010)	249	7 (11)	0 (0)	61	17 (9)	0 (0)	188

[a]Study includes two independent trials.

Abbreviations: AE, adverse event; *N*, the number of patients.

TABLE 2 Types and frequencies of adverse events observed in the placebo arms across the included studies

Type of AEs	Patients with the AE
Nausea/vomiting	266
Headache	172
Dizziness/lightheadedness/dizzy/lightheaded/giddy	71
Sleepiness/drowsiness/somnolence/sleepy/drowsy	27
Flushing/hot, flushed (feverish)/hot flushes/fever/elevated temperature/pyrexia	13
Tiredness/fatigue	9
Abdominal pain/stomachache/stomach pain/stomach cramps/diarrhoea	7
Tachycardia	4
Insomnia	3
Chills/shivering	3
Dyskinesia	2
Hyperhidrosis/sweating	2
Nosebleed	1
Syncope	1
Eyes tearing	1
Depression	1
Nervousness	1
Rash	1
Restlessness	1
Excessive salivation	1
Xerostomia	1
Urticaria	1
Tingling sensation	1
Flu-like symptoms	1

Abbreviation: AE, adverse event.

another method of showing the potential negative influence of patients' expectations on AE occurrence is to investigate differences in types of AEs between placebo groups of RCTs testing medications with different AE profiles. A systematic review of anti-migraine trials showed that AE profiles in the placebo arms for three different types of anti-migraine medicines differed, matching those observed in the active treatment group of the same trials.[15] For example, placebo-treated patients in anticonvulsant trials reported AEs typically associated with anticonvulsants (such as anorexia, memory difficulties, paraesthesia and upper respiratory tract infection), but these AEs were not reported by placebo-treated patients in other anti-migraine trials. Since AE information disclosed during the informed consent process is specific to the medication tested, these findings suggest that information about AE risks may increase expectations and risk of experiencing those specific AEs. Many of the included studies in the present meta-analysis tested both cyclooxygenase inhibitors and opioids within the same trials,[26–35] and participants in these trials would have received AE risk information concerning both of these analgesics. Thus, while we originally planned to compare AE profiles in placebo arms of RCTs with different active comparators, the data did not allow for such comparisons to be made.

To assess the severity of AEs in placebo groups, previous meta-analyses have investigated the pooled proportion of dropouts due to AEs, with a median dropout ratio of 5% (interquartile range 2.3%–8.4%).[1] The pooled dropout ratio in the current meta-analysis for the placebo groups was comparatively low (0.24%) and did not significantly differ from the active treatment groups. Subjects included in the present meta-analysis were healthy, except for their impacted M3, which might be one explanation for the comparatively low dropout rate. Therefore, dropout rates may not be an ideal factor for investigating the AE severity in healthy individuals.

It should be noted that heterogeneity was relatively high; however, this is commonly observed in meta-analyses assessing AE occurrence in placebo-controlled trials.[3,18] One of the reasons for the high heterogeneity in these types of meta-analyses might be explained by the large variation in how data on AEs are collected.[36] Furthermore, other factors like study population, blinding success, and timing of outcome measurement might also moderate the nocebo response and add to heterogeneity. The available data did not allow for such assessments; however, this would be a valuable addition to future research.

Nonetheless, the finding that nearly one quarter of participants experienced AEs in the placebo arms of RCTs assessing analgesics

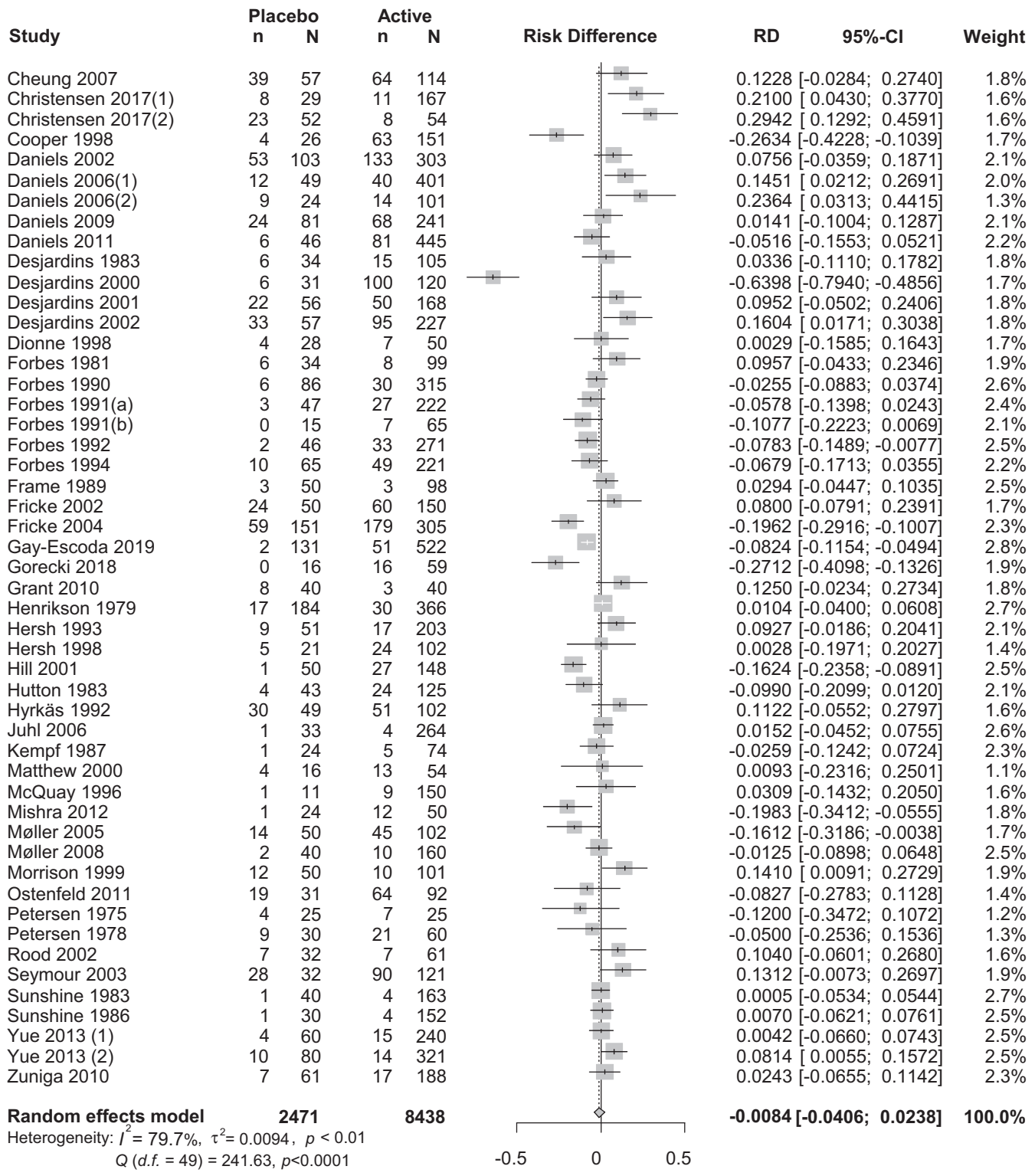


FIGURE 2 Forest plot displaying risk differences between the placebo arm and active arm of patients reporting at least one drug-related adverse event. CI, confidence interval; *N*, the number of patients; *n*, the number of patients reporting at least one adverse event; RD, risk difference.

following M3 surgery supports the existence of nocebo responses in dentistry. Furthermore, the observation that AE proportions are similar across placebo- and active groups, may indicate that non-pharmacological, non-specific factors could play a relatively large role in dentistry. This highlights the importance of further investigations into the nocebo phenomenon and potential implications to dental clinical practice. Experimental studies investigating the influence of non-specific treatment-related factors, such as nocebo

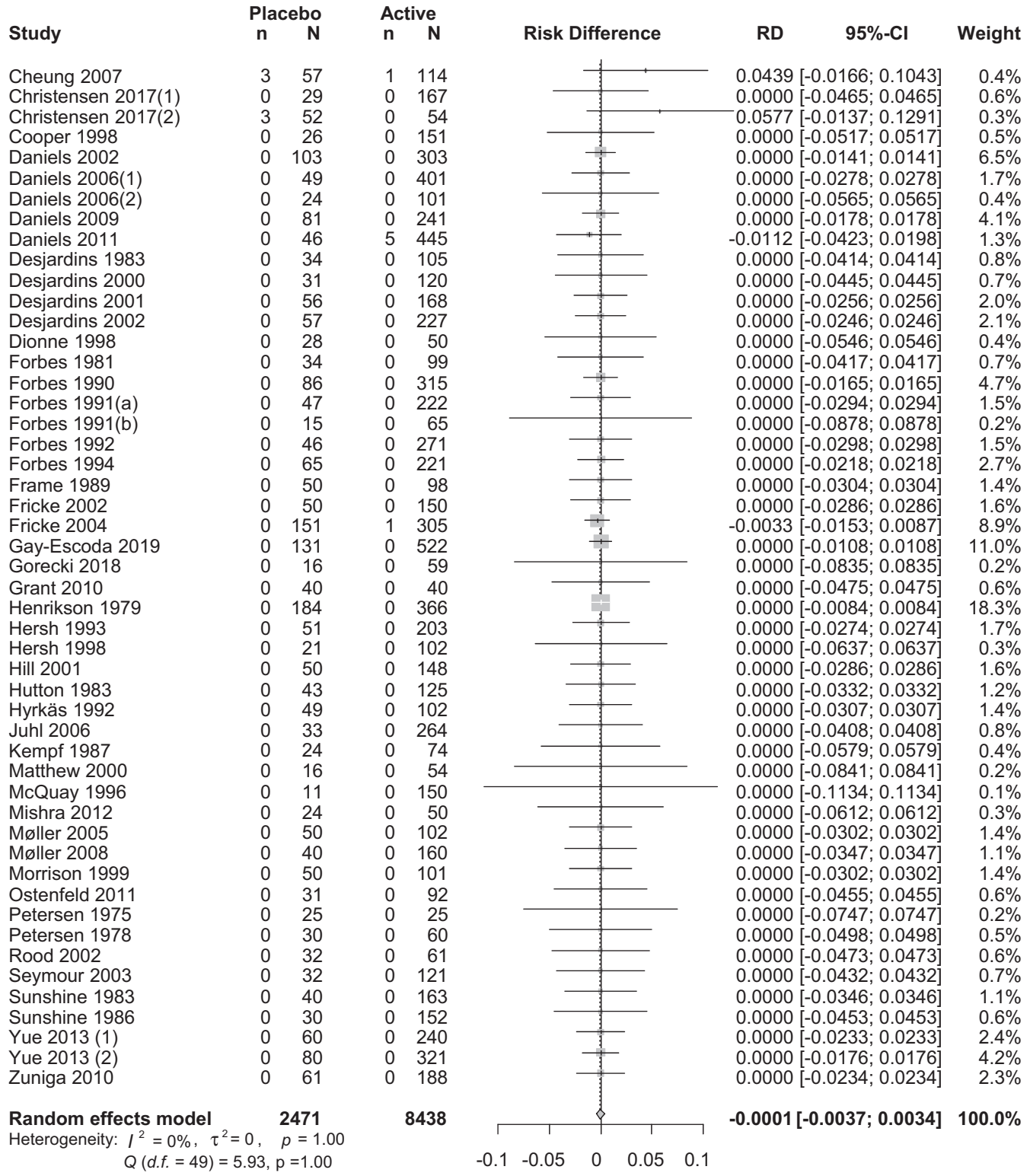


FIGURE 3 Forest plot displaying risk differences between the placebo arm and active arm of drug-related dropout rates. CI, confidence interval, *N*, the number of patients; *n*, the number of dropouts; RD, risk difference.

effects, within a dental setting are needed to better understand the role of these factors in dentistry. Promising strategies for mitigating nocebo effects, such as positive framing of AE information,[6] a strong patient-clinician relationship,[37,38] educating patients about the nocebo effect[39,40] and optimising treatment expectations[41] are being investigated, and such strategies could eventually be implemented to mitigate the negative influence of the nocebo phenomenon and optimise treatment outcome in daily dental practice.

AUTHOR CONTRIBUTIONS

All authors contributed to conception, preparation of the manuscript and gave final approval and agree to be accountable for all aspects of the article. Takeshi Watanabe, Mette Sieg and Mads Persson performed screening, quality assessment of identified articles and data extraction under the supervision of Lene Vase. Takeshi Watanabe performed statistical analysis. Takeshi Watanabe and Mette Sieg drafted the first version of the manuscript. Sigrid Juhl Lunde, Pankaj Taneja, Lene Baad-Hansen and Lene Vase critically revised the manuscript.

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CONFLICT OF INTEREST

All authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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