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Nocebo in multiple sclerosis trials: A meta-analysis on oral and newer injectable disease-modifying treatments

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ABSTRACT

Background: Nocebo phenomena are linked to decreased adherence to treatments in clinical practice as well as difficulty in assessing the adverse effect profile in clinical trials.
Objective: To estimate the incidence and severity of nocebo responses in clinical trials of oral and newer injectable disease-modifying treatments (DMTs) for relapsing multiple sclerosis (MS).
Methods: Meta-analysis of the incidence of nocebo responses was performed by pooling the percentage of placebo-treated patients that exhibited adverse events (AEs) in randomized, placebo-controlled MS trials published between 2005 and 2018. Nocebo severity was estimated as a percentage of placebo-treated patients who discontinued the treatment due to drug-related AEs.
Results: The pooled incidence of nocebo was 89% (95% CI: 88%–90%) in trials for oral DMTs (cladribine, fingolimod, teriflunomide and dimethyl fumarate) and 66% (95% CI: 51%–80%) in trials of newer injectable DMTs (biosimilar glatiramer acetate 20 mg, innovator glatiramer acetate 40 mg and pegylated interferon beta). The pooled nocebo severity was 8% (95% CI: 5%–12%) for oral treatments and 2% (95% CI: 0–2%) for newer injectable DMTs.
Conclusions: Oral DMTs may be associated with a higher incidence and greater nocebo severity than newer injectables.

1. Introduction

In the early 1960s, Kennedy introduced the term nocebo, which refers to the adverse events (AEs) following the administration of an active or inert substance (Kennedy, 1961). Unlike placebo, nocebo is detrimental for clinical research and practice, complicating the assessment of the side effect profile of drugs (Reeves et al., 2007) and sometimes leading to drug discontinuation (Preston et al., 2000). Furthermore, it adversely affects drug adherence while also increasing the cost of care. Nocebo is thought to result from the negative psychological context surrounding the treatment including both pretrial expectations and previous negative treatment experience. Current data suggest that AEs are one of the most common reasons for non-adherence and discontinuation of disease-modifying treatments (DMTs) in multiple sclerosis (MS) (Cunningham et al., 2010). We have estimated the nocebo frequency and magnitude in trials with DMTs in remitting – relapsing multiple sclerosis (RRMS), previously and found that nocebo varies by the year of publication suggesting that the more recent the trial the greater the likelihood of nocebo responses leading to withdrawal from a trial (Papadopoulos and Mitsikostas, 2010). Since then however, several novel DMTs have been developed and are in use worldwide currently, administered either parenterally or orally.

The aim of the present study is to determine the magnitude and severity of nocebo responses and the factors associated in trials with the novel DMTs for RRMS, in order to develop strategies to minimize its consequences in clinical practice and improve the design of clinical trials (Barsky et al., 2002). The incidence of drug-related AEs (%AE) in placebo-treated MS patients was used as a measure of incidence of the nocebo phenomenon. The drop-out rate (%DO) of placebo-treated MS patients due to drug-related AEs was used as a measure of severity and strength of the nocebo phenomenon.

2. Methods

A computer-based literature search was conducted on PubMed using "multiple sclerosis", "treatment", "placebo", "clinical trial" and "phase 3" as key words and electronic publication date from 1 January 2005 to 31 December 2018, randomized controlled trials, clinical trial phase 3 and English language as limitations. The search followed the PRISMA recommendations (Moher et al., 2009). The following inclusion criteria were applied to the 86 articles retrieved by the search. Articles were eligible if they were: (i) randomized, double blind, inert placebo-controlled trials, (ii)

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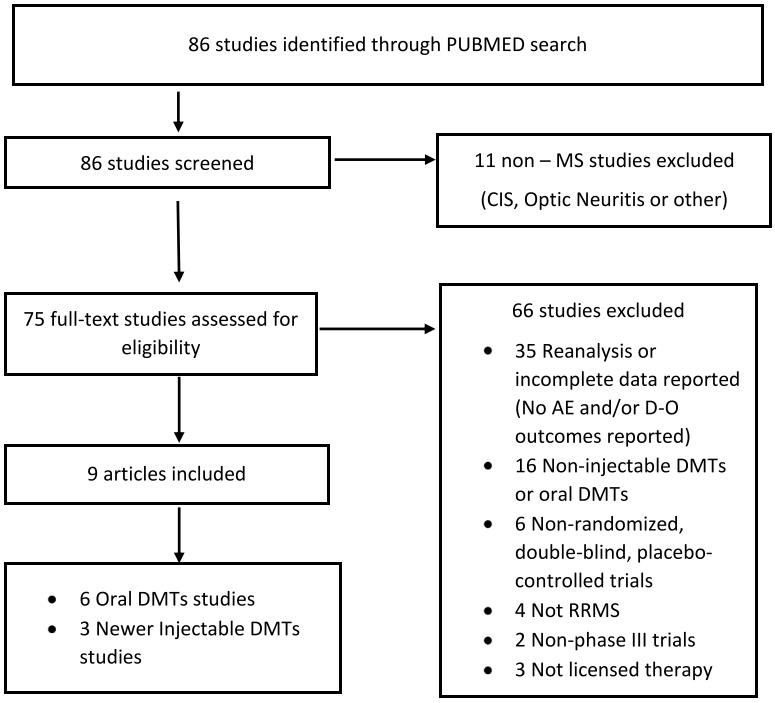

Fig. 1. Article selection flow diagram.

Table 1
Patients and medication characteristics of studies included in the meta-analysis.

	All trials (n = 9)	Trials for orals (n = 6)	Trials for injectables (n = 3)
Patient number (n)	3415	2370	1045
Mean (SD)	379.4 (119.9)	395 (32)	348.3 (229.7)
Age			
Mean (SD)	37.3 (2.1)	38.2 (1.1)	35.6 (2.8)
Females			
n(%)	2432 (71)	1704 (72)	728 (69)
Mean % (SD)	66 (10)	66 (12)	67 (2)
Disease Duration (years)			
Mean % (SD)	6.5 (2.7)	7.6 (2.1)	4.3 (2.9)
Population			
Europe + North America + South America + Asia + Oceania	4	4	0
Europe + North America + South America + Asia + Oceania + Africa	2	1	1
Europe + North America + South America + Asia + Africa	1	0	1
Europe + North America + Oceania + Asia	1	1	0
Europe + North America + South America + Asia + Africa	1	0	1
Route of administration Oral / parenteral	6/3		

trials of pharmacological agents only, (iii) reporting at least one of the following outcomes: the percentage of placebo-treated MS patients that exhibited drug-related AE or the percentage of placebo-treated MS patients that dropped out due to drug-related AEs (DO), (iv) studies of drugs for remitting – relapsing multiple sclerosis (RRMS) (v) reporting complete study data (preliminary data reporting studies and re-analyses were excluded), (vi) studies of licensed oral or injectable DMTs, (vii) phase 3 studies, (viii) if they reported the CONSORT chart. In case of trials with both open and blind phases only the double blind part was included. Other data extracted from the articles included: continent where the trial took place, percentage of females in each trial, mean patient age, mean disease duration, disease course and route of administration.

2.1. Quality assessment

Jadad scale was used to assess the quality of the included studies. Jadad scale scores three parameters: randomization, blindness (of the patients, caregivers, investigators) and adequate documentation of withdrawals and dropouts and is considered the most reliable (Olivo et al., 2008; Jadad et al., 1996).

2.2. Statistical analysis

Meta-analysis was carried out using the StatsDirect statistical software (www.statsdirect.com). Pooling was conducted using the DerSimonian Laird method (random effects model) due to heterogeneity (DerSimonian and Laird, 1986). The heterogeneity within trials was tested by Cochran's Q-test based on inverse variance weights (Deeks, 2001). The I^2 statistic was also used to quantify the extent of inconsistency in outcomes across studies. The effect of publication and selection bias on the summary estimates was tested by the Harbord–Egger bias indicator (Harbord and EggerMand Sterne, 2006) and by the Egger indicator (Egger et al., 1997).

Table 2
Most frequent adverse events in active and placebo groups in multiple sclerosis trials.

Study/Drug	Active group	Placebo group
Calabresi et al., 2014 *Fingolimod (Appendix)*	Infections 73% Gastrointestinal disorders 49% Muscosceletal disorders 44% Respiratory disorders 41% Headache 22%	Infections 72% Gastrointestinal disorders 40% Muscosceletal disorders 42% Respiratory disorders 38% Headache 22%
Confavreux., 2014 *Teriflunomide (Appendix)*	Infections 44% ALT increased 14% Hair thinning 13% Headache 12% Nausea 10%	Infections 51% Headache 11% Fatigue 11% Nausea 9% Back pain 9%
Gold et al., 2012 *Dimethyl Fumarate (Appendix)*	Flushing 32% Diarrhea 19% Nausea 13% Proteinuria 12% Abdominal Pain 12%	Diarrhea 13% Nausea 9% Abdominal Pain 8% Proteinuria 8% Vomiting 6%
Fox et al., 2012 *Dimethyl Fumarate (Appendix)*	Flushing 24% Nasopharyngitis 18% Diarrhea 15% Upper respiratory tract infection 14% Back pain 8%	Nasopharyngitis 16% Headache 13% Urinary tract infection 12% Upper respiratory tract infection 9% Back pain 9%
Kappos et al., 2010 *Fingolimod (Appendix)*	Headache 27% Nasopharyngitis 26% Lower respiratory tract infection 11% Back pain 11% Diarrhea 11%	Nasopharyngitis 27% Headache 23% Urinary tract infection 11% Fatigue 11% Nausea 9%
Giovannoni et al., 2010 *Cladribine (Appendix)*	Lymphopenia 31% Headache 21% Nasopharyngitis 13% Upper respiratory tract infection 12% Nausea 11%	Headache 17% Nasopharyngitis 14% Upper respiratory tract infection 10% Nausea 9% Lymphopenia 2%
Cohen et al., 2015 *Glatiramer Acetate (Appendix)*	Injection site reaction 16% Immediate post injection reaction 7% Headache 5% Injection site swelling 4% Nasopharyngitis 4%	Headache 8% Injection site reaction 7% Nasopharyngitis 7% Injection site swelling 4% Injection site pain 1%
Khan et al., 2013 *Glatiramer Acetate (Appendix)*	Injection site erythema 21% Nasopharyngitis 11% Injection site pain 10% Headache 10% Immediate post injection reaction 8%	Headache 12% Nasopharyngitis 9% Injection site pain 2% Injection site erythema 2% Immediate post injection reaction 2%
Calabresi et al., 2014 *Pegylated Interferon β−1a (Appendix)*	Injection site erythema 62% Influenza like illness 47% Pyrexia 45% Headache 44% Myalgia 19%	Headache 33% Pyrexia 15% Nasopharyngitis 15% Influenza like illness 13% Back pain 11%

3. Results

3.1. Literature search & study characteristics

The results of our MEDLINE search are summarized in Fig. 1. After repeated filtering, from the 86 articles retrieved, only nine were included in the meta-analysis (six studies for orals and three studies for injectable DMTs, Appendix). These studies published from 2005 to 2018 involved 3415 placebo-treated RRMS patients. The main study characteristics and the adverse events that occurred most frequently in placebo and active groups are summarized in Tables 1 and 2, respectively.

3.2. The magnitude of nocebo responses in MS trials

The pooled incidence of AE in placebo-treated MS patients that was used as a measure of nocebo incidence (%AE) was 83% (95% CI: 74%–91%) for all studies (Fig. 2A). In trials studying oral DMTs and injectable DMTs nocebo incidence was 89% (95% CI: 88%–90%) and 66% (95% CI: 51%–80%), respectively (Figs. 3A and 4A). The pooled drop-out rate (%DO) due to drug-related AE was 6% (95% CI: 3%–9%) for all trials, 8% (95% CI: 5%–12%) in trials for oral treatment and 2% (95% CI: 0–2%) in trials for injectable DMTs (Figs. 2B, 3B and 4B). Bias assessment funnel plots are provided in Fig. 5.

4. Discussion

This meta-analysis included nine randomized controlled phase-3 trials for oral or injectable DMTs for RRMS published from 2005 to 2018 and estimated the incidence and severity of the nocebo effect.

4.1. Nocebo phenomenon varies by year of study publication and route of administration

Our findings confirm that nocebo is increasing with time in RRMS. In our previous study, conducted with the same methodology showed that nocebo incidence was 74,4% (95% CI: 69.9%–88.3%) in DMT trials (Papadopoulos and Mitsikostas, 2010). In this meta-analysis the estimated incidence of non-specific AEs in MS patients receiving placebo reached a notable 83% (95% CI 74%–91%) in all DMT studies. Moreover, nocebo seems to be more frequent in oral than in injectable DMTs (89%, 95% CI: 88%–90% vs. 66%, 95% CI: 51%–80%) and more severe if we focus on the drop-out rates due to AEs (8%, 95% CI: 5%–12% vs. 2% (95% CI: 0–2%). Perhaps patients were more familiar with the newer injectable DMTs than with the orals, which had not been previously used in MS (cladribine, fingolimod, dimethyl fumarate and teriflunomide). Specifically, studies of newer injectables were testing new formulations, doses, biosimilars and administration frequencies of interferon-beta and glatiramer acetate, which have been licensed and marketed since 1993 and 1996, respectively. The different routes of administration may also at least partly account for the differences in nocebo incidence and severity between injectable and oral DMTs. The drop-out rate due to AEs in the placebo-treated group both in oral and in newer injectable DMTs was found increased (6%) compared to our previous estimate from DMTs published between 1999 and 2010 (2.16%) indicating that nocebo is more likely to lead to treatment discontinuation in recent years that it used to in the past. As noted previously by numerous studies, nocebo AEs largely mirror those of the active arm of the trial, indicating how pre-treatment information may influence nocebo responses (Papadopoulos and Mitsikostas, 2010; Stathis et al., 2013; Kravvariti et al., 2018).

4.2. Nocebo in biosimilar GA vs. innovator GA and in pegylated INFb1-a vs INFb1-a

In recent years there is an increasing interest in generic drugs, thus we compared the percentages of placebo treated patients who

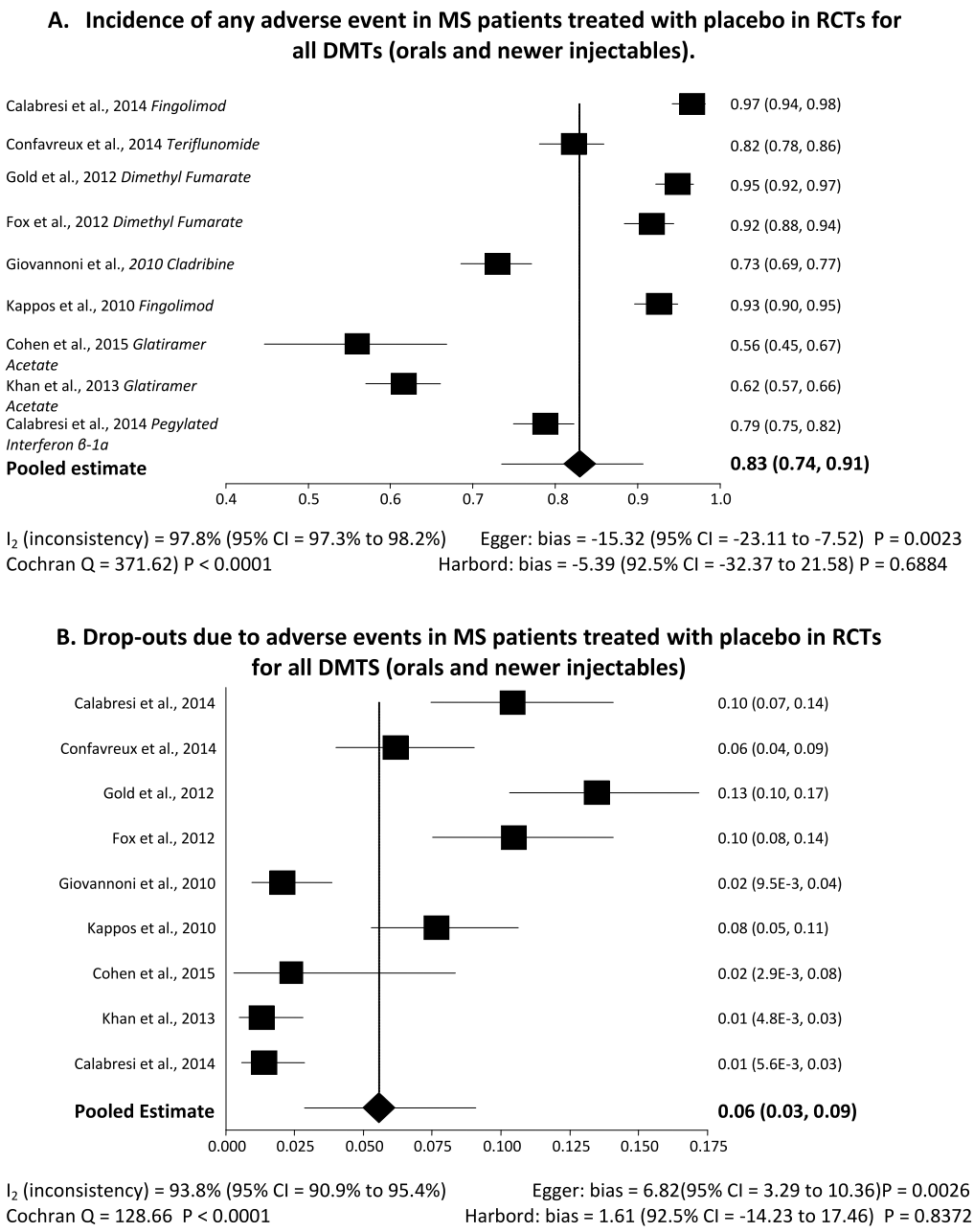

Fig. 2. Meta-analysis forest plots. A: Meta-analysis of incidence of any adverse event in all DMTs studies. B: Meta-analysis of drop-outs in all DMTs studies.

discontinued therapy due to AE in trials of the innovator drug (GA, INFβ-1a) with those in trials for biosimilars (GA, pegINFβ-1a). The pooled drop-out rate (%DO) due to AE was 1.6% (95%CI: 0.0069%–3%) in trials for the innovator INFβ-1a and 1.4% (95%CI: 0.0056%–3%) in trials of pegINFβ-1a (Fig. 6), showing the is no significant difference in nocebo severity between INFβ-1a and pegINFβ-1a. This finding is in contradiction with the higher drop-out rate of biosimilars compared to the innovator drugs, found in a study for drugs in rheumatology (Kravvariti et al., 2018). The drop-out rate of placebo treated patients was 13.5% in the trial for the innovator GA and 2.3% (95% CI: 0.0029%–8%) in the trial of the generic drug. However, a direct comparison between these two percentages cannot be made for several reasons. In the former trial the reason for discontinuation of therapy was not reported. Moreover, trials for innovator drugs were conducted nearly 20 years before those for the generic ones. MS patients had different profile, lower educational background regarding the condition they were suffering from, as well as higher expectations from the therapy that time. These features might affect nocebo severity leading to higher drop-out rates in the innovator drugs within the recent years.

4.3. Factors influencing nocebo responses

The exact mechanisms of nocebo effect are still not fully understood but a number of factors have been linked to its development. The neuropsychological profile of MS patients, often characterized by depression and anxiety (Beiske et al., 2008), is likely to predispose towards the development of non-specific AEs. Neuroimaging and pharmacological studies have provided insight into the physiological and biochemical basis of the nocebo phenomenon (Benedetti et al., 2006). Mental health disorder comorbidities also increase susceptibility to nocebo. In patients with mild cognitive impairment or dementia related to Alzheimer disease, a loss of prefrontal functional connectivity and executive control has been associated with an attenuated placebo response and a high rate of nocebo effects, such as nausea, dizziness, headache and depression (Kravvariti et al., 2018). Also, certain

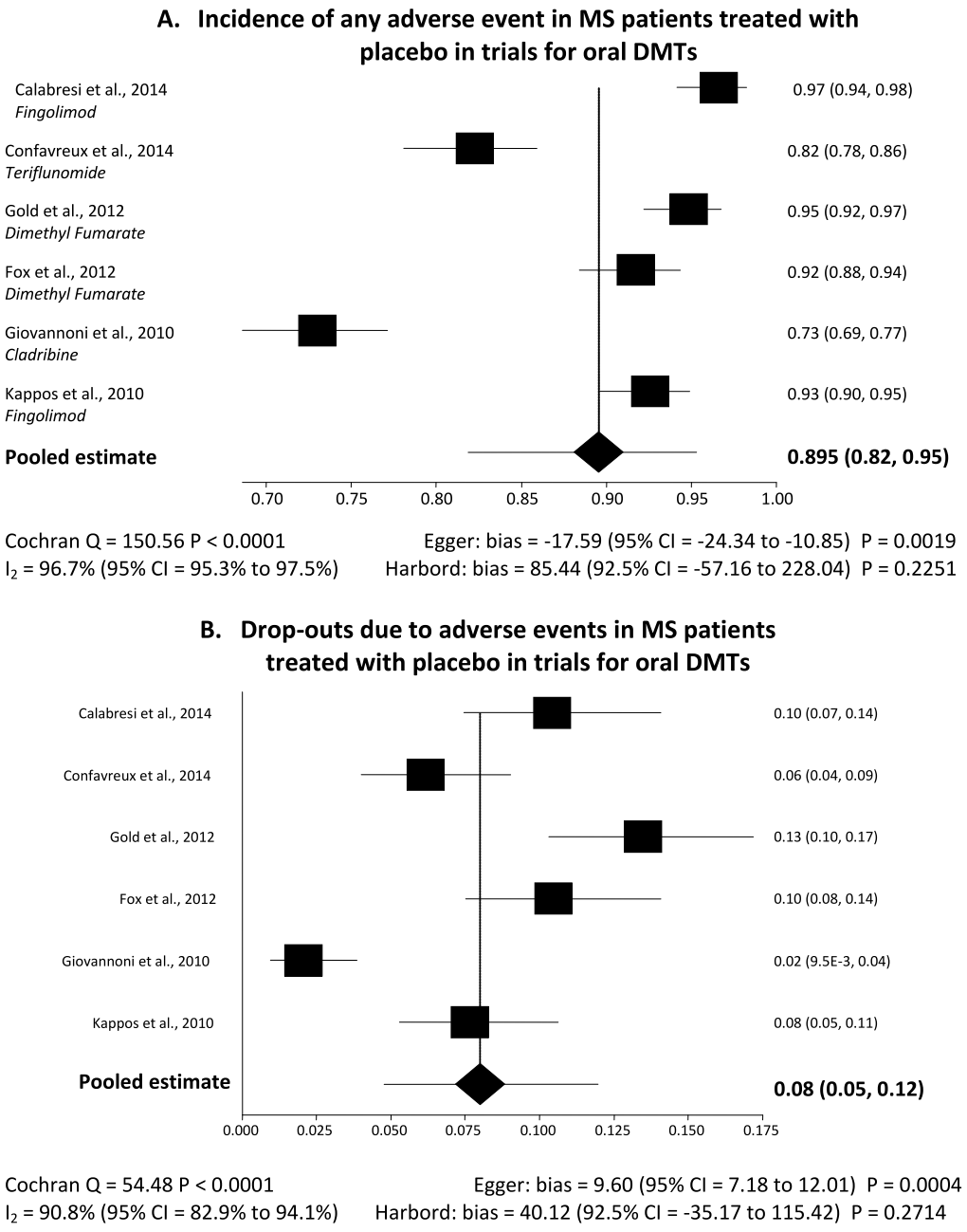

Fig. 3. Meta-analysis forest plots. A: Meta-analysis of the incidence of any adverse event in trials for oral DMTs. B: Meta-analysis of drop-outs in trials for oral DMTs.

personality traits are associated with a higher likelihood of experiencing nocebo effects; for example, a tendency toward somatization and high levels of anxiety, which can hinder effective communication and increase pain perception, are associated with susceptibility to nocebo effects such as hyperalgesia, fatigue and decreased motor strength (Kravvariti et al., 2018). In addition, negative publicity, a history of serious AEs associated with a particular medicine or a previous trial suspension may also contribute to the development of nocebo. Information regarding trial medications made increasingly available by the media and other sources including the internet may have contributed to MS patients discontinuing trial medications more easily today than 30 years ago (Tausczik et al., 2012). Physician-related factors may also enhance nocebo. Anxiety and uncertainty regarding patient management on the part of the physician might be a reason for conditioning and perpetuating nocebo effects both in daily practice and in RCTs. The process of informed consent to therapeutic interventions is the part of the encounter in which negative anticipation is frequently introduced. Acknowledging that information on medication safety is a potential nocebo gives the treating physician the additional responsibility of weighing the risks and benefits of sharing this information with the patient. The benefits of providing all relevant information concerning the adverse effects of treatment and prognosis need to be weighed against the risk of nocebo-driven treatment discontinuation (Kravvariti et al., 2018). Besides patient and physician related factors, drug factors unrelated to their main therapeutic action such as the route of administration, price and labeling or the even the color of capsules, tables and their packaging can influence patients expectations (Faasse et al., 2013; Planes et al., 2016; Kong and Benedetti, 2014).

Nocebo has been explored in randomized clinical trials of various neurological conditions. Nocebo drop-out frequencies vary greatly in these studies with 2% drop-out frequency in the placebo arm in multiple sclerosis (Papadopoulos and Mitsikostas, 2010), 2.1% in CIDP (Zis et al., 2018), 2.4% in myasthenia gravis (Varma and Zis, 2019), 4% in epilepsy (Zis et al., 2017), 4.75% in migraine (Mitsikostas et al., 2011), 4.8% in

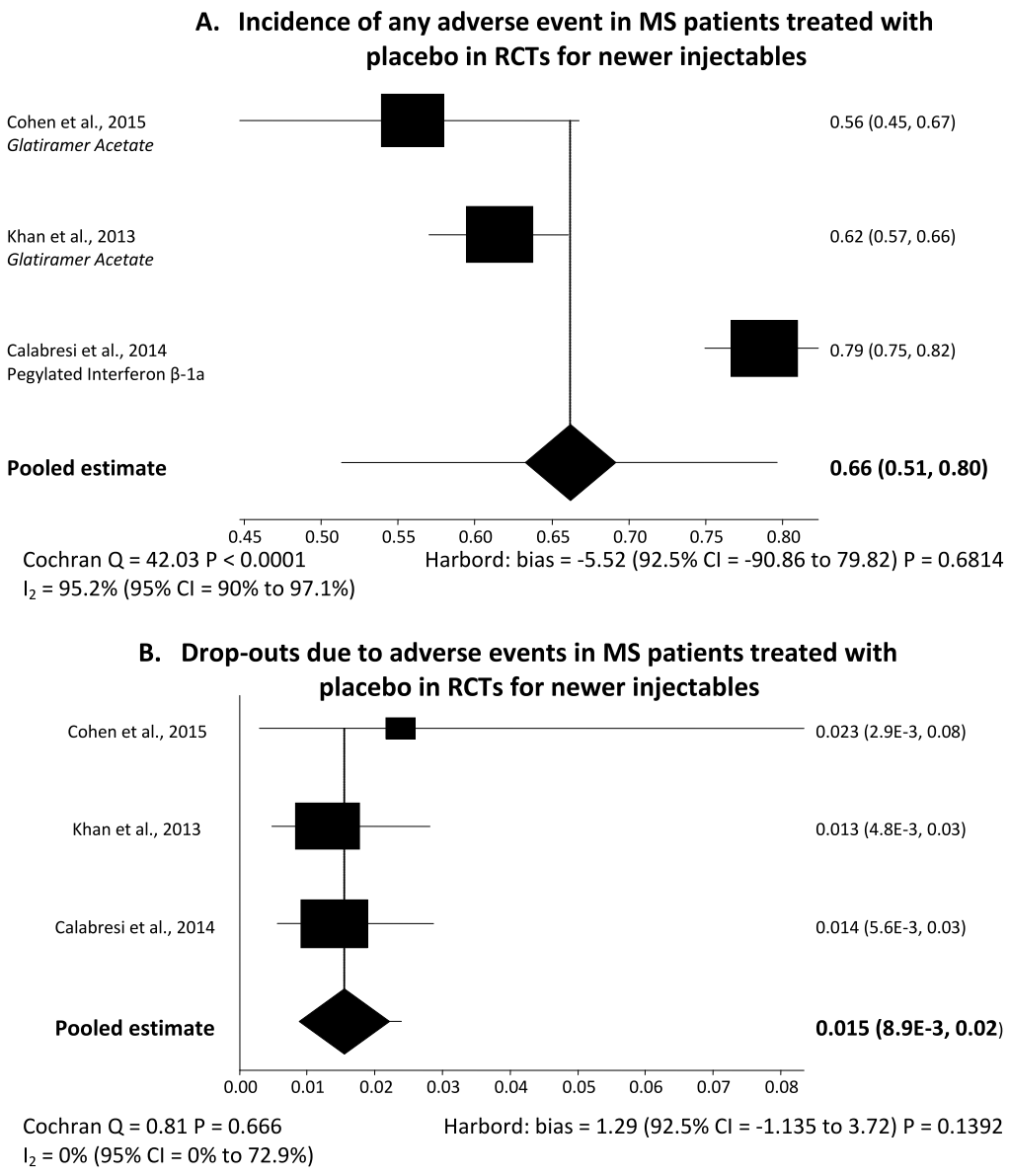

Fig. 4. Meta-analysis forest plots. A: Meta-analysis of incidence of any adverse event in trials for newer injectables. B: Meta-analysis of drop-outs in trials for newer injectables.

cerebellar ataxia (Alam et al., 2019), 5.4% in tension-type headache (Mitsikostas et al., 2011), 5.8% in diabetic neuropathy (Häuser et al., 2012), 6% in neuropathic pain (Papadopoulos and Mitsikostas, 2012), 6.6% in Alzheimer's disease (Zis and Mitsikostas, 2015), 8.4% in motor neuron disease (Shafiq et al., 2017), 8.8% in Parkinson's disease (Stathis et al., 2013) to 9.5% in fibromyalgia (Mitsikostas et al., 2012). A recent analysis of nocebo responses of anti-epileptic medications used to treat different conditions showed that nocebo rates strongly depend on the clinical condition (Zaccara et al., 2016). Disease pathology appears to influence the development of nocebo as conditions with central nervous system involvement exhibit greater nocebo rates in clinical trials compared to those with pathologies involving the peripheral nervous system (Zis et al., 2018; Zis and Mitsikostas, 2018). However, when the safety profile of oral naltrexone was examined no significant differences were observed in the prevalence of adverse events or serious adverse events in different diseases, indicating that nocebo responses may be largely treatment-specific (Bolton et al., 2019). Our finding of significantly stronger nocebo responses with oral disease-modifying treatments compared to injectables in multiple sclerosis supports the view that both treatment and disease-related factors influence the variation seen in nocebo responses in randomized clinical trials (Zis and Sykioti, 2019).

4.4. Implications for clinical trial design

Since nocebo may play an important role in clinical trial outcomes, new recruiting policies are essential to avoid biased selection, particularly in studies of behavior-modifying drugs. Nocebo should be taken into account in sample sizing, data safety reports and in the design of the informed consents (Colloca, 2017). Most importantly, in order to prevent high drop-out rates, researchers should consider the participant's predisposition to nocebo even before randomization. In addition, new methodologies to assess nocebo within trials are needed. To apply a proper comparator for determining nocebo, AEs could be compared with those observed in a 'no intervention' group (no drug or placebo). Furthermore, some placebos like saline injection are not truly inert and should be avoided. On the other hand investigators should obtain informed consent and reduce nocebo-like AEs by paying careful attention to the ways information about AEs is disclosed to patients (Colloca, 2017).

4.5. Nocebo effect in clinical practice

Our data clearly demonstrate that the nocebo effect is a confounding factor in clinical drug trials, but the prevalence of an analogous nocebo

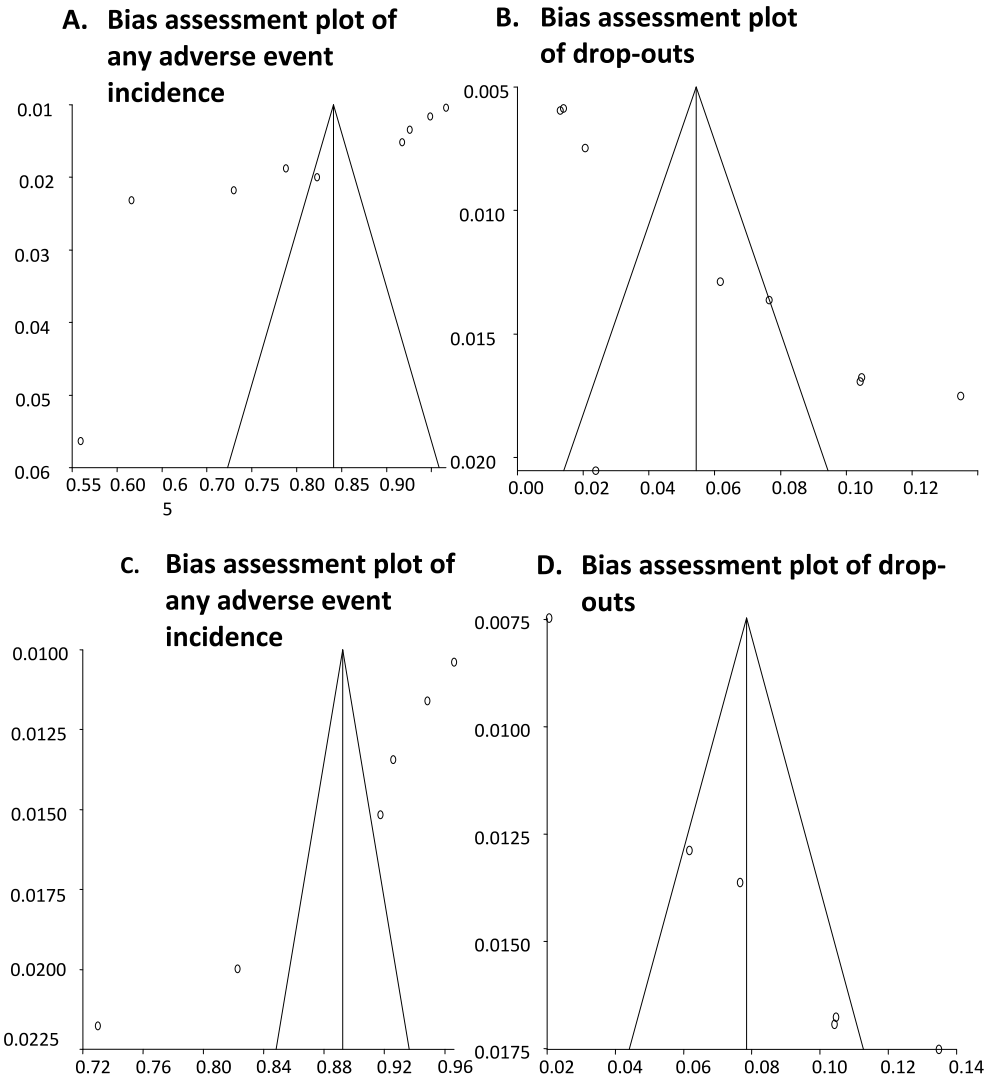

Fig. 5. Bias assessment plots. A: Funnel plot showing bias in meta-analysis of any adverse event incidence in all DMTs studies B: Funnel plot showing bias in meta-analysis of drop-outs in all DMTs studies. C: Funnel plot showing bias in meta-analysis of any adverse event incidence in trials for oral DMTs. D: Funnel plot showing bias in meta-analysis of drop-outs in trials for oral DMTs.

effect may be even greater in the clinical practice. Indeed, patients participating in clinical trials may not accurately reflect the patient population treated in daily clinical practice as they may differ in neuropsychological profile, cultural characteristics, comorbidities, disease course and severity. MS patients who are willing to participate in trials are likely to be less risk averse and more committed to adhere to the treatment regime. Furthermore, RCTs are characterized by highly regulated and standardized experimental conditions that can be largely reassuring to patients. Therefore, in our opinion, the actual nocebo effects of MS DMTs in clinical practice are likely to exceed the nocebo responses seen in clinical trials.

4.6. Study limitations

This study has a number of limitations that should be acknowledged. Firstly, although nocebo was estimated based on the drug-related trial drop-outs and adverse events there are inherent difficulties in attributing non-specific symptoms, hence this can prove a potential source of bias. Secondly, the heterogeneity observed in the frequency of adverse events and dropouts among the selected trials limits the accuracy of pooled estimates. Moreover, data from this meta-analysis are not representative of nocebo in all MS trials as only newer drugs were included. Finally, it must be recognized that our estimates of nocebo incidence and severity have been calculated in phase 3 clinical trials and they cannot be readily generalized to clinical practice.

5. Conclusions

Nocebo is prevalent in MS clinical trials and appears to have increased in the last 30 years. It is more frequent and more severe in oral DMTs than in newer injectables. Nocebo phenomena have serious implications for MS trial design and clinical practice. Clinicians should be aware that drug intolerance and treatment failure may at least be partly explained by nocebo effects. Further research is required to achieve a deeper understanding of the factors that contribute to the development of nocebo in order to develop strategies to minimize its consequences in clinical trials and practice.

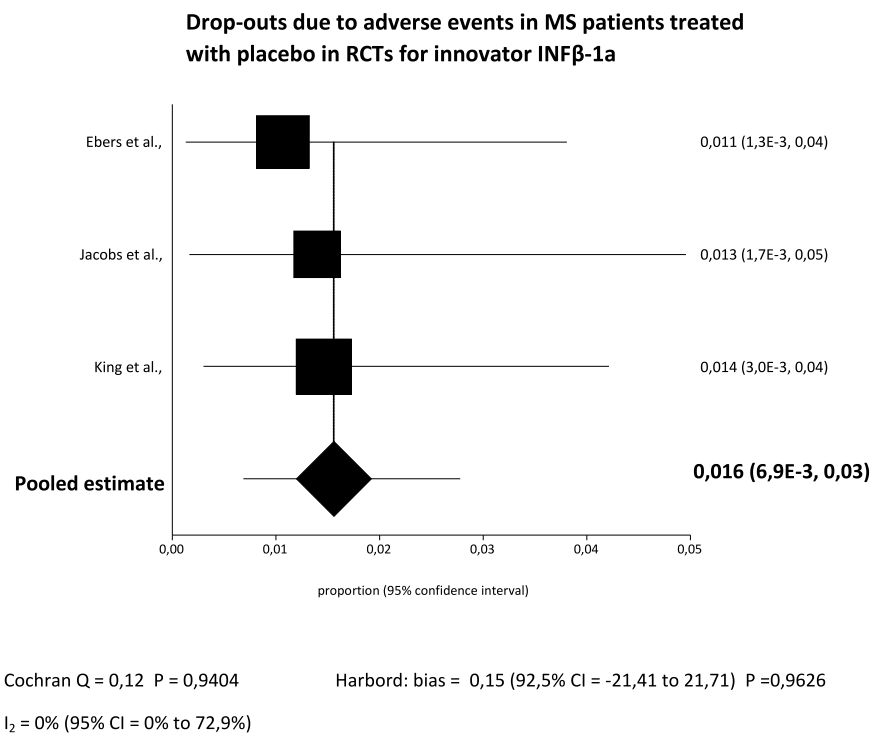

Fig. 6. Meta-analysis of drop-outs due to AE in trials for innovator INFβ-1a.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Appendix 1

Studies included in the meta-analysis

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