Lessons learned from nocebo effects in clinical trials for pain conditions and neurodegenerative disorders

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Lessons Learned From Nocebo Effects in Clinical Trials for Pain Conditions and Neurodegenerative Disorders

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Abstract: It has been demonstrated that patients in the placebo arm of a clinical trial may experience adverse events (AEs), which may lead to nonadherence and dropout. However, so far, it is unknown to which extent this phenomenon is observed consistently across different diseases such as pain and neurodegenerative disorders.

The current review shows for the first time that different diseases share a common risk for patients in terms of a negative outcome: a large percentage of placebo-treated patients experience AEs in pain conditions (up to 59%) and neurodegenerative disorders (up to 66%). In addition, the rate of patients who discontinue because of AEs is up to 10% and 11% in pain conditions and neurodegenerative disorders, respectively.

We highlight methodological shortcomings with the aim of suggesting how the detection and reporting of AEs can be improved in future trials. The insights from the current review should be taken into consideration when designing clinical trials to tailor individualized treatments.

Key Words: randomized controlled trials, placebo groups, adverse events in clinical trials, expectancy theory, nocebo effect

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The placebo arm of randomized controlled trials (RCTs) provides researchers with the opportunity to study the effect of the psychosocial context surrounding a treatment.[1–3] In RCTs, patients receive either active medication or inactive placebo treatment in a double-blind fashion. Accordingly, patients in both the active treatment arm and the placebo arm are informed not only about the positive therapeutic action of the active medication but also about the possible negative adverse events (AEs) that medication may cause. Informing patients about possible AEs may have a significant influence on their expectations. Interestingly, it has been demonstrated that patients in the placebo group experience AEs similar to the ones reported by the active drug group. In particular, the AE profile of the placebo groups matched the AE profile of the group receiving the active agent being tested in RCTs of antimigraine and antidepressant drugs,[1,3] and these effects were defined in terms of nocebo effects.[4–6] As no active medication is administered in the placebo arm in RCTs, the observed AEs are not caused by the pharmacodynamic processes but rather by the psychosocial factors surrounding treatments and patients. Indeed, verbal suggestions given via the informed consent may influence patients' expectations and subsequent experiences. In this way, the psychosocial context surrounding the treatment and, in particular, the information given to a patient may contribute to the observed AEs in the placebo-treated groups in RCTs.[1,3,7,8]

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The extent of nocebo-related AEs in placebo-treated groups has been investigated in patients having neurological diseases such as Alzheimer disease (AD),[2] Parkinson disease,[9] and multiple sclerosis[10] and in pain disorders such as neuropathic pain,[11] fibromyalgia, and migraine.[1,12–16] Each study demonstrated that the experience of AEs and, consequently, the dropout rate during placebo treatments are common in these types of patients.

The current review aims to describe and interpret the overall results obtained from the literature investigating the frequency of AEs and/or the severity of AEs (ie, dropout rate) in placebo-treated patients who participated in RCTs and experienced neurodegenerative disorders or pain conditions. Up to now, the nature of AEs has been poorly understood, and existing theories require further empirical testing. In particular, the findings have not been systematically compared across the various neurological diseases. Furthermore, although a brief report of AEs in placebo-treated patients in chronic pain conditions, mainly considering headache sufferer patients, has been published,[17] the current review will allow for a systematical list of major methodological shortcomings with the aim of improving future trials.

MATERIALS AND METHODS

Search Strategy and Selection Criteria for the Descriptive Review

We selectively searched the PubMed database for articles published up to January 31, 2016, containing the following search term: nocebo effect in RCTs. No limits were applied, and 53 publications were found. Our aim was to describe nocebo-related AEs in terms of the percentage of placebo-treated patients who (1) reported AEs and (2) dropped out because of AEs across various neurodegenerative disorders and pain conditions. The following selection criteria were applied:

1. The study should be either a meta-analysis or a systematic review examining nocebo effects and/or discontinuation due to AEs in RCTs of pain conditions or neurodegenerative disorders.
2. The study should estimate the percentage of placebo-treated patients and report at least 1 AE and/or the percentage of placebo-treated patients who dropped out because of AEs.

Twelve articles were excluded as they referred to healthy subjects, and 18 studies were excluded as they did not include neurodegenerative disorders or pain conditions. The remaining studies were examined in more detail. Seventeen studies were excluded as they did not fulfill additional selection criteria (see Supplementary Content of Excluded Studies, Supplemental Digital Content 1, http://links.lww.com/JCP/A383). Six studies met the inclusion criteria and were included in the review (cf. Fig. 1). F1

RESULTS

Description of the Selected Studies

Four of the selected meta-analyses concern different pain conditions, whereas the remaining are focused on neurodegenerative disorders (cf. Tables 1 and 2). A large percentage of T1 T2

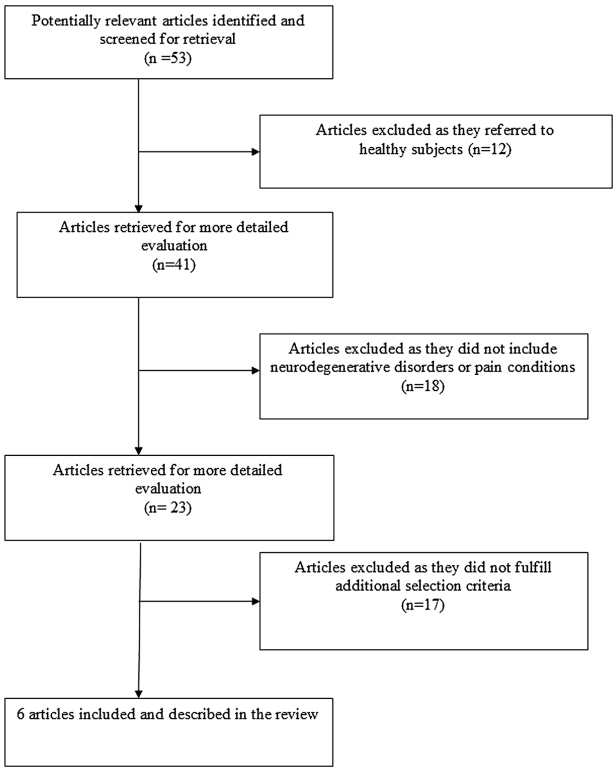

FIGURE 1. Article selection flow chart.

placebo-treated patients experience AEs in pain conditions and in neurodegenerative disorders (up to 59% and 66%, respectively). In addition, the highest range value of patients who discontinue because of AEs is approximately 11% and 12% in pain conditions and neurodegenerative disorders, respectively. T3 In Table 3, the characteristics of the selected studies are shown, taking into account the design of the RCTs. Any shortcomings in the selected meta-analyses are reported, considering the assessment strategy of AEs, the neuropsychological characteristics of T4 patients, and the contextual factors assessed (cf. Table 4).

Nocebo Effects in Clinical Trials for Pain Conditions

In 2011, Mitsikostas et al[16] carried out a systematic literature review on RCTs for primary headache disorders published between 1998 and 2009. The trials were concerned with the treatment of migraine, tension-type headache, and cluster headache and documented noxious AEs and dropouts due to AEs in the placebo-treated control groups. In particular, the frequency of nocebo-related AEs was estimated on the basis of the percentage of placebo-treated patients who reported at least 1 AE. The dropout frequency was estimated by the percentage of placebo-treated patients who discontinued the treatment because of AE intolerance. The authors reported that patients participating in preventive treatment studies experienced higher AE rates than patients enrolled in symptomatic treatment trials. In particular, approximately 20% of migraineurs assigned to the placebo group in symptomatic drug trials experienced AEs, but less than 1% dropped out of the study. Patients experiencing cluster headache showed similar results (approximately 19% of placebo-treated patients experienced AEs). The nocebo-related AEs were in fact much more prevalent and stronger in preventive treatment studies; almost half of the headache sufferers, be it from migraine or tension-type headache, reported nocebo-related AEs, and approximately 5% dropped out of the study. Moreover, in the stratified analysis, the nocebo-related AE frequency varied significantly by year of publication in trials for symptomatic treatment of migraine, decreasing from 22.05% for trials published between 1998 and 2004 to 14.39% for trials published between 2005 and 2009. Finally, nocebo-related AEs did not change with route of drug administration, and no differences were found among studies carried out in North America and Europe.

Methodological shortcomings (selected study, Mitsikostas et al[16]):
- -Studies with either crossover or parallel design were included.
- -Absence of an observation (no treatment) arm.
- -No indication about the methodology used in the selected studies to assess AEs, that is, structured or unstructured, not standardized strategies.
- -Meta-regression and stratified analyses may uncover some potential sources of bias as the unit of analysis is represented by the placebo-treated group and not by the individual patient.
- -Absence of a systematic assessment of psychological characteristics of patients including somatization, anxiety, and depression.
- -No indication of the mean age of the patients included in the meta-analysis.
- -Absence of patients' treatment expectation assessment and of quality of verbal suggestions by health care providers.

TABLE 1. Selected Studies on Pain Conditions

Disease	No. Trials	Total No. Patients Reporting AEs and/or Percentages	Total No. Patients who Dropped Out Because of AEs	Selected Studies
Migraine (preventive treatment)	N = 31	42.78%	4.75%	Mitsikostas et al[16]
Tension-type headache (preventive treatment)	N = 4	23.99%	5.44%	
Migraine (symptomatic treatment)	N = 59	18.45%	0.33%	
Cluster headache (symptomatic treatment)	N = 3	18.67%	Not applicable*	
Neuropathic pain	N = 12	n = 491, 52.0%	n = 57, 6.0%	Papadopoulos and Mitsikostas[11]
Painful diabetic peripheral neuropathy	N = 62	n = 2354, 46.2%	n = 296, 5.8%	Häuser et al[12]
Fibromyalgia	N = 58	59.9%	9.6%	
Fibromyalgia	N = 18	Not calculated	10.9%	Häuser et al[13]

*Because of insufficient data, the calculation of nocebo dropout was not possible.

TABLE 2. Selected Studies on Neurodegenerative Disorders

Disease	No. Trials	Total No. Patients Reporting AEs and/or Percentages	Total No. Patients who Dropped Out Because of AEs	Selected Studies
AD	N = 16	n = 1373, 66.7%	n = 221,* 11.7%	Amanzio et al[2]
MCI	N = 3	n = 180, 23.0%	n = 43,* 8.2%	
Parkinson disease	N = 41	n = 2292, 64.7%	n = 312, 8.8%	Stathis et al[9]

*Calculations based on 2 of 3 original included studies.

In 2012, Papadopoulos and Mitsikostas[11] proposed a meta-analytic approach aiming to estimate the frequency of AEs and dropout rates due to AEs in the placebo-treated groups of RCTs dealing with pharmacological treatment for neuropathic pain and published between 2001 and 2010. The frequency analysis of nocebo-related AEs was performed by pooling the percentage of placebo-treated patients experiencing AEs. Dropout rates were estimated as the percentage of placebo-treated patients who dropped out because of AEs. When examining crossover or parallel designs, the authors found a significant inverse association between the frequency of developing AEs and the percentage of women in the placebo-treated groups, suggesting that nocebo-related AEs are more common in male than female neuropathic pain sufferers. Furthermore, nocebo severity (percentage of dropout rate) also displayed a significant association with the study population, indicating that dropout due to nocebo-related AEs is weaker in American than in European and Australian placebo-treated neuropathic pain sufferers participating in clinical trials.

Methodological shortcomings (selected study, Papadopoulos and Mitsikostas[11]):
- -Studies with either crossover or parallel design were included.
- -Absence of an observation (no treatment) arm.
- -No indication of the methodology used in the selected studies to assess AEs, that is, structured or unstructured, not standardized strategies.
- -Meta-regression and stratified analyses may uncover some potential sources of bias as the unit of analysis is represented by the placebo-treated group and not by the individual patient.
- -Absence of a systematic assessment of psychological characteristics of patients including somatization, anxiety, and depression.
- -Absence of a systematic assessment of possible cognitive dysfunctions (ie, mild cognitive impairment [MCI]) considering the mean age of the patient population (59.1 y).
- -Absence of patients' treatment expectation assessment and of quality of verbal suggestions by health care providers.

The impact of nocebo-related AEs in drug trials of painful diabetic peripheral neuropathy was investigated in a systematic review of RCTs designed by Häuser et al,[12] where drug therapies were compared with placebos using a parallel design (the search for study selection was conducted up to December 31, 2010). Pooled estimates of AEs and dropout rates due to AEs were calculated by the authors for the placebo groups. In the same study,[12] the authors also analyzed the impact of nocebo-related AEs on patients with fibromyalgia syndrome, using the same criteria as the ones used in drug trials for diabetic peripheral neuropathy. Regarding patients with fibromyalgia syndrome, the results obtained were in line with those found in diabetic peripheral neuropathy subjects. In particular, the magnitude of nocebo-related AEs was associated with a higher incremental year of study initiation and with longer duration of the study in both diseases. The authors also found a positive association of women among the dropouts due to AEs. Moreover, regression coefficients for mean age on the logit of event rates of patients with at least 1 AE (on the one hand) and the number of dropouts due to AEs (on the other hand) were significant, indicating a strong linear correlation both in fibromyalgia syndrome and diabetic peripheral neuropathy trials. Finally, the quality of reporting the assessment strategy of AEs was poor in most trials. In particular, the authors found that only 22.6% and 37.9% of the diabetic peripheral neuropathy and fibromyalgia syndrome trials, respectively, reported details of the assessment strategy. These findings did not permit the authors to perform subgroup analyses of the different assessment strategies.

Methodological shortcomings (selected study, Häuser et al[12]):
- -Absence of an observation (no treatment) arm.
- -Assessment strategy of AEs: only few trials of the diabetic peripheral neuropathy and fibromyalgia syndrome reported details of the assessment strategy. The authors reported that, as a result of the lacking or insufficient data, they were unable to test for the impact of the assessment strategy on the incidence of nocebo effects.

TABLE 3. Characteristics of the Selected Studies Taking Into Consideration the Publication Year (From the Newest to the Oldest)

Selected Studies	Randomized	Placebo Controlled	Double Blind	Crossover Design*	Parallel Design
Stathis et al[9]	✓	✓		✓	✓
Häuser et al[13]	✓	✓	✓		✓
Häuser et al[12]	✓	✓	✓		✓
Amanzio et al[2]	✓	✓	✓		✓
Papadopoulos and Mitsikostas[11]	✓	✓	✓	✓	✓
Mitsikostas et al[16]	✓	✓	✓	✓	✓

*Note the criticality to insert this design while considering nocebo effect in the placebo group. In particular, if placebo is given as the initial treatment, only the effects of suggestion are measured, whereas if placebo is given as a second treatment, the effects of both suggestion and conditioning are measured.[1]

TABLE 4. Characteristics of the Selected Studies Taking Into Consideration the Publication Year (From the Newest to the Oldest)

Selected Studies	Assessment Strategy of AEs	Neuropsychological Assessment	Contextual Factor Assessment
Stathis et al[9]	Not reported	Not reported	Not reported
Häuser et al[13]	Not reported	Not reported	Not reported
Häuser et al[12]	Unstructured: 24 studies (FMS), structured: 1 study (FMS), unstructured: 13 studies (DPN), structured: 1 study (DPN)	Not reported	Not reported
Amanzio et al[2]	Unstructured: MCI studies (all), structured: 1 study (AD), unstructured: 15 studies (AD)	MMSE	Not reported
Papadopoulos and Mitsikostas[11]	Not reported	Not reported	Not reported
Mitsikostas et al[16]	Not reported	Not reported	Not reported

DPN indicates painful diabetic peripheral neuropathy; FMS, fibromyalgia syndrome.

-Meta-regression and stratified analyses may uncover some potential sources of bias as the unit of analysis is represented by the placebo-treated group and not by the individual patient.
-Absence of a systematic assessment of psychological characteristics of patients including somatization, anxiety, and depression. The authors underlined that they could not assess putative patient-related predictors of nocebo response such as anxiety and somatization.
-Absence of a systematic assessment of possible cognitive dysfunctions (ie, MCI) considering the mean age of the patient population (52 and 54 y of fibromyalgia and painful diabetic polyneuropathy trials, respectively).
-Absence of patients' treatment expectation assessment and of quality of verbal suggestions by health care providers.

In a further study, Häuser et al[13] analyzed the magnitude of nocebo-related AEs in another sample of 3546 patients with fibromyalgia syndrome, determined by the pooled estimate of dropout rates due to AEs in placebo groups in RCTs with a parallel design. The authors expanded the study analysis to include the magnitude of placebo and nocebo effects in drug trials of patients with fibromyalgia syndrome up to June 30, 2012.[12,14,15] Nocebo-related AEs were not significantly associated with study- and patient-related characteristics. Importantly, the authors emphasized that they may have underestimated the impact of nocebo-related AEs as they only analyzed the nocebo dropout rates and not the frequency of specific AEs in placebo groups (eg, dizziness). Finally, they could not assess the potential impact of the patients' treatment expectations and of the quality of verbal suggestions manifested by health care providers because these contextual factors affecting placebo and, possibly, nocebo effects were not assessed in the studies analyzed.

Methodological shortcomings (selected study, Häuser et al[13]):
-Absence of an observation (no treatment) arm.
-Assessment strategy of AEs: no indication of the methodology used in the selected studies to assess AEs, that is, structured or unstructured, not standardized strategies.
-Meta-regression and stratified analyses may uncover some potential sources of bias as the unit of analysis is represented by the placebo-treated group and not by the individual patient.
-Absence of a systematic assessment of psychological characteristics of patients including somatization, anxiety, and depression.
-Absence of a systematic assessment of possible cognitive dysfunctions (ie, MCI). The mean age of the participants in the placebo arm was not reported; only the coefficient β of the mean age of participants in the placebo arm was reported.
-Absence of patients' treatment expectation assessment and of quality of verbal suggestions by health care providers.

Nocebo Effects in Clinical Trials for Neurodegenerative Disorders

On the basis of RCTs of the acetylcholinesterase inhibitor donepezil with parallel design, published between January 1989 and December 2010, a systematic review analyzed the level of cognitive impairment as a crucial aspect for the AEs reported by placebo-control group patients with MCI and AD.[2] To test whether trials involving patients with AD and MCI were comparable, the authors first compared these 2 types of trials with respect to year of publication, duration of study, quality of study (Jadad score), assessment strategy (structured vs spontaneous recording of AEs), age, sex, race, Mini Mental State Examination (MMSE) scores, general withdrawal, and withdrawal due to AEs. There were no significant differences between MCI and AD trials with respect to the variables considered. However, the ratio of women was significantly higher in the AD studies as compared with the MCI studies.

As expected, trials involving patients with MCI and AD had significantly different MMSE scores showing that patients with AD had a higher level of cognitive impairment (27.38 vs 15.50, respectively). As far as the assessment strategy is concerned, all of the MCI studies and 15 of 16 AD studies were unstructured. Interestingly, a significantly higher number of AEs in the placebo groups were reported in trials involving patients with AD compared with trials involving patients with MCI. Further findings indicated that placebo-treated patients with AD experienced depression, dizziness, headache, and nausea/vomiting much more frequently than patients with MCI did. These kinds of AEs are similar to those observed in the active group.[18] In particular, active treatment with donepezil induces cholinergic AEs such as nausea, vomiting, diarrhea, muscle cramps, and dizziness,[18] and these are in line with those found in the placebo groups.

Methodological shortcomings (selected study, Amanzio et al[2]):
-Absence of an observation (no treatment) arm.
-The relationship between the level of cognitive impairment and the report of AEs deals with clinical trials and not with individual patients.
-Absence of a systematic assessment of psychological characteristics of patients including somatization, anxiety, and depression.
-Absence of patients' treatment expectation assessment and of quality of verbal suggestions by health care providers.

A meta-analysis of RCTs of Parkinson disease pharmacologic treatments published between 2000 and 2010 assessed

percentages of placebo-treated patients who had reported at least 1 AE or dropped out because of AEs.[9] The study also searched for factors that influenced the extent of nocebo-related AEs. The study population size, the year of study publication, and the Jadad score were significantly and negatively correlated with the nocebo dropout rate on metaregression analysis. In particular, the Jadad score refers to the quality assessment of reports of randomized clinical trials considering the description and sequence of randomization, the double-blind procedure, its appropriateness, and the description of withdrawals and dropouts (range, 0–5).[19]

Methodological shortcomings (selected study, Stathis et al[9]):
- -Studies with either crossover or parallel design were included.
- -Absence of an observation (no treatment) arm.
- -No indication of the methodology used in the selected studies to assess AEs, that is, structured or unstructured, not standardized strategies.
- -Meta-regression and stratified analyses may uncover some potential sources of bias as the unit of analysis is represented by the placebo-treated group and not by the individual patient.
- -Absence of a systematic assessment of psychological characteristics of patients including somatization, anxiety, and depression.
- -Absence of a systematic assessment of possible cognitive dysfunctions (ie, MCI) considering the mean age of the patient population (62.6 y).
- -Absence of patients' treatment expectation assessment and of quality of verbal suggestions by health care providers.

DISCUSSION

The current review highlights the need for high-quality evidence on the AEs in RCTs to inform policy, practice, and research: meta-analyses carried out in recent years suggest that up to 59.9% of placebo-treated patients experience an AE in pain conditions, whereas up to 66.7% of placebo-treated patients experience an AE in neurodegenerative disorders. In addition, discontinuation occurs in approximately 10.9% of cases in the former and in 11.7% of cases in the latter. Taking into account the previously highlighted methodological shortcomings, the results found in the different neurological diseases are similar. A possible explanation is that they may underline a common risk for patients in terms of a negative outcome possibly related with the presence of a chronic disease.

In particular, the current review is the first attempt to formalize the results obtained from the literature through methodological shortcomings, which may contribute to revise data collection in RCTs to set in future specific strategies for patients having chronic diseases to reduce nocebo effects in clinical trials and practice.

An important recognized feature of meta-analyses is that their results are critically dependent on the quality and homogeneity of the individual studies analyzed. On the basis of the general nocebo effect literature of specific neurological diseases, it will be possible to hypothesize standardization of procedure in clinical trial designs through methodological shortcomings, which may contribute to tailoring individualized treatment in patients having chronic diseases. Three points will be discussed as critical issues accounting for nocebo-related AEs in RCTs: (1) appropriate assessment strategy of AEs, (2) putative patient-related psychological factors and baseline characteristics, and (3) verbal suggestions and behaviors manifested by health care providers.

Methodological Shortcomings

Appropriate Assessment Strategy of AEs

First, it is critical how AEs in double-blind, placebo-controlled RCTs of drug efficacy were defined or recorded and the selection criterion used by authors when reporting them.[20] The use of validated methods of collection and standardization of procedures would increase the validity and comparability of AEs across trials,[21] not only in the drug groups but also in the placebo groups. Greater attention to these aspects could lead to the development of treatment strategies that will ameliorate their effects in clinical practice and improve clinical trial design.[22,23] In particular, a combination of sophisticated approaches that combine expected AEs, systematic screening for general adverse effects, and patient and observer ratings for the most valid and reliable results should be preferred.[24,25] When a participant reports an AE, the event can be classified with the aid of a dictionary such as the Medical Dictionary for Regulatory Activities and World Health Organization Adverse Reactions. Given that AEs will be strongly dependent upon the drug and not only the condition, it would seem appropriate to develop core AE outcomes by therapeutic class.

Baseline Characteristics and Patients' Related Psychological Factors

Second, we noted the absence of an observation (no treatment) arm in all the included studies. Using an additional natural history group as the trial's so-called third arm is an important factor that should be considered in RCTs. As to the third group, it would be possible to study the AEs because of the nocebo effects as the difference between the symptoms collected in the natural history group and the AEs presented in the placebo group.[5] Indeed, natural course conditions should be incorporated more frequently in RCTs, such as in Zelen design. This allows the natural history of the disease to be monitored without randomizing patients to a no-treatment control group to overcome ethical issues.[26] As suggested by Rothwell,[27] it is important to pay attention on patients' baseline clinical characteristics, severity and stage in the natural history of their disease, comorbidity, and AEs of treatment when planning RTCs.

Rief et al[3] underlined the importance that drug trials consider more rigorously the base rates of preexisting general complaints to distinguish drug-associated AEs from the general base rates of symptoms. In particular, AE recording in trials may frequently include unfavorable outcomes that arise from disease progression or concomitant comorbidity and are unrelated to drug treatment.[20] It would be important, when designing RCTs of chronic diseases (such as those analyzed in the current review), to assess patient baseline characteristics before the study or even as a part of the recruitment procedure, given that patient characteristics may influence the development of nocebo-related AEs. Indeed, the clinical factors characterizing neurodegenerative diseases and chronic pain, such as those analyzed in this review, may potentiate nocebo-related AEs. In particular, the nocebo literature suggests how somatization, tendency to catastrophizing, comorbid anxiety, and depression, as well as previous experiences with AEs, may also influence the "reservoir of bodily symptoms available for misattribution"[6] and possibly the nocebo-related AEs and dropout rates in the placebo groups. Interestingly, baseline anxiety and depression have been found to be the main predictors of the presence of AEs in the placebo groups in RCTs of patients with cancer-related fatigue.[28]

A thorough anamnesis to identify patients with a history of medically unexplained complaints is also a crucial issue because previous treatments may influence the experience of later nocebo-related AEs. Moreover, although the patients' neuropsychosocial profile is little analyzed, it is likely to be operating in nocebo response.[2] The implications of these clinical suggestions are important because patients who are most at risk of developing

nocebo-related AEs should have a poor adherence to treatment.[29] Indeed, it would be important to further test the extent to which these psychological variables are related to the presence/absence of AEs in prospective RCTs. Importantly, a complex and not yet developed integrated approach to the study of these combining factors would be required to clarify the presence of psychological distress predisposing patients to report nocebo-related AEs to an even greater extent.

Verbal and Nonverbal Suggestions Manifested by the Health Care Providers

Third, the shortcomings included the methodology to assess contextual factors. This represents another important critical point because verbal suggestions and behaviors manifested by health care providers are likely to vary greatly across research contexts and may consequently generate considerable variability in nocebo-related AEs measured by the included studies.

A study by Amanzio and colleagues[1] has shown that AEs are frequently experienced in the placebo arm of antimigraine trials and that the frequency and type of AEs correspond to the AE experience in the active arm. For example, AEs in the placebo arm of anticonvulsant trials are more frequent and related to a higher dropout rate than AEs in the placebo arm of nonsteroidal anti-inflammatory trials and triptan trials, respectively. These findings suggest that the information given to patients about AE as part of the informed consent procedure influences the development of specific adverse reactions. Other authors have also suggested an association between contextual factors such as negative suggestions on the part of the physician and nocebo-related AEs,[6,22] but to the best of our knowledge, this association has not yet been prospectively evaluated by empirical studies.

How Chronic Patients May Develop AEs

Clinical Trials for Pain Conditions

As Mitsikostas et al[16] demonstrated, nocebo effects are prevalent in clinical trials for primary headaches, particularly in preventive treatment studies. They found that nocebo-related AEs with concomitant trial dropout were common in preventive drug trials whereas dropout due to AEs was relatively rare in symptomatic trials. Although the possibly longer duration of preventive studies may play a role or be an important factor, the difference observed may also be related to the psychological profile of chronic headache sufferers, as preventive or prophylactic trials focus on chronic sufferers.[16] In this particular case, comorbidity with anxiety disorders, neuroticism, somatization, hypochondria, and depression increases the negative expectation of possible AEs,[30] and these traits are common in chronic headache sufferers.[31,32] Hence, it is likely that a serious illness, possibly associated with comorbid disorders, makes headache sufferers more susceptible to negative expectations and consequently to AEs. Unfortunately, as we have previously underlined, these important variables were not assessed in this included study.

Studies on patients with neuropathic pain and fibromyalgia syndrome[11–13] have found that approximately half of the patients in the placebo group reported nocebo-related AEs. This relevant nocebo effect in neuropathic pain trials may be influenced by population-related factors. Neuropathic pain is a common distressing condition that affects 7% to 8% of the general population[33–35] and, in most cases, runs a chronic course. Neuropathic pain affects patients' mood, daily activities, and sleep, and it has a strong negative impact on their quality of life.[36,37] As we observed in studies on preventive headache treatments, anxiety and depression, known to be associated with chronic pain,[38–40] may be contributing factors to the robust nocebo effect seen in neuropathic pain and fibromyalgia syndrome trials. In particular, the possible mechanisms underlying the presence of anxiety and/or depression, in terms of comorbidity in neuropathic pain and chronic widespread pain (fibromyalgia), may be explained by shared morphological and functional alterations observed in both chronic pain and mood disorders.[41] Unfortunately, in this case as well, it is not possible to demonstrate the role of mood changes on the occurrence of nocebo-related AEs.

Neurodegenerative Disorders

The finding that patients with AD and Parkinson disease reported a higher level of AEs than patients with MCI may be explained by several factors related to disease duration, comorbidities, and biases in research designs. Longer disease duration is likely to be associated with a higher level of comorbidity, including anxiety and depression, as well as with multiple pharmacological treatments that have potential toxic effects.[42] Barsky et al[6] have also provided a theoretical framework for interpreting the data obtained. They pointed out that misattribution of symptoms is most likely to occur when patients expect to experience AEs, have previously been conditioned to experience AEs, or have specific psychological predispositions, particularly anxiety, depression, or somatization. They noted that patients experiencing anxiety and depression have a "reservoir of bodily symptoms available for misattribution." Specifically, it has been hypothesized that, where patients with AD are concerned, the comorbidity with anxiety and depression may give rise to patients expressing emotional distress as bodily symptoms and this may be the reason for reporting AEs in the placebo arm in RCTs.[2] Although most of the studies considered by Amanzio et al[2] did not include a systematic assessment of somatization and mood changes, previous results have shown that, in patients with dementia of the Alzheimer type, there is a strong association between cognitive status and somatic comorbidity.[43] Interestingly, the relation between pain increase–related nocebo responses and opioid release in Parkinson disease patients was associated with a deactivation of the dopamine system.[44] Nocebo-related AEs may be important in brain diseases in which damage or dysregulation of brain networks controlling expectations may alter responses to active and dummy treatments.[44] Although it is not known whether dopamine reduction and mood changes are related to a higher frequency of AEs, it has been suggested that the high level of AEs seen in patients having Parkinson disease may be explained by comorbid depression and anxiety as these patients frequently show changes in mood.[9] Moreover, a frailty syndrome,[45] characterized by specific symptoms such as confusion, sarcopenia, falls, fractures, and urinary incontinence, is often present in the elderly population, which could also explain why these patients are more susceptible to AEs.[42] Finally, the presence of a possible cognitive impairment may cause patients with AD and Parkinson disease to have decreased capacity for expectation mechanisms and to increase the risk of misattribution of symptoms; this is not the case with patients having an MCI.

Although factors related to changes in mood, severity, and duration of the disease are likely to be the reason why patients with AD and Parkinson disease experienced more AEs than patients with MCI, other factors should however be taken into account. For example, only 1 systematic review has been conducted in relation to patients with MCI,[2] and it only included 3 trials with a total of 783 patients. Thus, the number of patients in this study is much lower than those in the other analyses involving RCTs of AD and Parkinson disease. Additional studies are needed to further understand the phenomenon in neurological diseases, and they should take into account the previously mentioned factors.

TABLE 5. Guiding Principles for Nocebo-Related AEs in RCTs

	Guiding Principle	Implications for Clinical Practice and RCTs
Assessment of nocebo-related AEs	• Definition • Selection and recording • Duration • Standardization of procedures	• External validity of RCT improvement • Development of enhanced treatment strategies • Development of better tailored prevention programs • Patients' outcome improvement • Treatment dropout reduction
Patients' baseline characteristics	Depression, anxiety, and somatization influence AEs and dropout rates.	A brief neuropsychiatric assessment should be part of routine screening and intake procedures.
	Catastrophic thinking is an important marker for the development of AEs as well as for poor treatment outcomes.	Catastrophic thoughts should be recognized and replaced with less-exaggerated beliefs as an alternative.
	Neuropsychosocial factors and MCI that may influence AE experience are not routinely assessed.	Better strategies of screening and intervention are needed.
	History of medically unexplained complaints may affect the experience of later AEs.	A thorough anamnesis should be part of routine screening procedures.
	Expectations about the course of AEs, AE recovery, and treatment benefits are associated with AE outcome.	An assessment of the expectancies related to treatment should be better improved.
Contextual factors	Verbal suggestions and behaviors manifested by health care providers are likely to vary greatly across research contexts and may consequently generate considerable variability in nocebo-related AEs.	Standardized procedures for collecting relevant information in randomized double-blind placebo-controlled trials of drug efficacy are needed.

Conclusions and Implications

This review of the placebo arm of RCTs of different pain conditions and neurodegenerative disorders indicates that nocebo-related AEs may be substantial. Unfortunately, being possible sources of bias, some methodological shortcomings may have played an important role in the results observed. Because an important recognized feature of meta-analyses is that their results are critically dependent on the quality and homogeneity of the individual studies analyzed, based on the general nocebo effect literature of specific neurological diseases, it is possible to suggest the inclusion of methodological assessment in clinical trial designs, which may contribute to the homogeneity of the population, and to tailor individualized treatment in T5 patients having chronic diseases (cf. Table 5).

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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