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REVIEW

# Placebo response in degenerative cerebellar ataxias: a descriptive review of randomized, placebo-controlled trials

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## Abstract

Placebo response in degenerative cerebellar ataxias (CAs) has never been studied despite the large number of randomized controlled trials (RCTs) that have been conducted. In this descriptive review, we aimed to examine the placebo response in patients with CAs. We performed a literature search on PubMed for RCTs on CAs that were published from 1977 to January 2020 and collected data on the changes from the baseline to the endpoint on various objective ataxia-associated clinical rating scales. We reviewed 56 clinical trials, finally including 35 parallel-group studies and excluding 21 cross-over studies. The included studies were categorized as follows: (1) studies showing significant improvements in one or more ataxia scales in the placebo groups ($n=3$); (2) studies reporting individual placebo responders with improvements in one or more ataxia scales in the placebo groups ($n=5$)—the overall proportion of placebo responders was 31.9%; (3) studies showing mean changes in the direction of improvement in at least one ataxia scale in the placebo groups, though not statistically significant ($n=19$); (4) studies showing no placebo response in any of the ataxia scales in the placebo groups ($n=4$); (5) studies where data on the placebo groups were unavailable ($n=9$). This review demonstrated the placebo response in patients with CAs on various objective ataxia scales. Our study emphasizes that the placebo response should be considered when designing, analyzing, and interpreting clinical trials and in clinical practice in CA patients.

**Keywords** Placebo response · Degenerative · Cerebellar ataxia · Randomized controlled trials

## Introduction

The placebo response, a phenomenon of benefits from inactive substances or sham treatments [1], has been observed in patients with movement disorders in clinical trials and clinical practice; many randomized controlled trials (RCTs) on Parkinson's disease have documented placebo responses [2, 3]. However, placebo responses in patients with degenerative cerebellar ataxias (CAs) have not been studied despite the large number of RCTs that have been performed [4–6]. The main reasons for the lack of studies on placebo responses in CAs include: the heterogeneity of CA, i.e. the etiology, disease progression, and associated non-cerebellar symptoms are heterogeneous between studies and within the same study; the differences in clinical scoring systems and treatment modalities used in each study; the relatively small number of studies, and the small sample size in the studies [4–7].

Nevertheless, it is crucial to evaluate placebo responses in CAs to acknowledge its presence and its extent, given that there is currently no effective treatment for CAs. Moreover,

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considering placebo responses in CAs is necessary when designing clinical trials and interpreting results in clinical practice. In the present study, we aimed to investigate placebo responses in patients with CAs by conducting a descriptive review of the outcomes of various objective ataxia scales in placebo-controlled trials on CAs.

## Methods

### Search strategy and selection criteria

The online database, PubMed, was searched for RCTs on CAs that were published from 1977 to January 2020 during the period from November 2019 to February 2020, using the search terms "ataxia AND placebo." All titles and abstracts of the retrieved publications and full-texts of potentially relevant studies were reviewed. Review articles were also searched to identify further relevant studies. Studies were eligible for inclusion if they met the following criteria: they reported randomized, double-blinded, placebo-controlled trials—parallel-group design studies were mainly included in our study, and we also included cross-over design studies to evaluate whether placebo responses also existed in such studies; they included only human subjects with idiopathic or genetic CAs; the texts were published in English; and the full-text articles were available. We excluded studies on acquired CAs. We did not limit the number of subjects or the route of administration, such as oral, intramuscular, intravenous, or subcutaneous administration, in the different study settings.

### Outcomes

We extracted the following outcomes for the ataxia scales from the included clinical trials. The outcomes are objective measuring tools to assess ataxia [8]: clinical ataxic rating scales—the International Cooperative Ataxia Rating Scale [ICARS] [9]; the Scale for the Assessment and rating of Ataxia [SARA] [10]; the Friedreich Ataxia Rating Scale [FARS] [11]; the Neurological Examination Score for Spino-CA [NESSCA] [12]—and ataxia-associated functional performance tests—he SCA Functional Index [SCAFI] that is composed of a timed 8-m walk [8MW], 9-hole pegboard test [9HPT], and speech test [PATA repetition rate] [13]; the Composite Cerebellar Functional Severity Score [CCFS] that combines the 9HPT and the click test [14]; post-urography [15]; oculomotor measures; other ataxia-related quantitative performance tests. Measurements that were not specific for ataxia, such as from general physical examinations, neuropsychiatric tests, neuroimaging, electrophysiology, laboratory tests for biomaterials, and participant-derived subjective assessments were not included in this study [8]. In addition, we examined the changes in ataxia scales in the active treatment groups to compare with the changes in the placebo groups. The following characteristics were also collected from each study: authors, year of publication, design, patient demographics, and treatment interventions.

### Categorization and narrative review of the studies

Due to the heterogeneity of the study populations, intervention modalities, and ataxia scales used in each study and the incompleteness or absence of quantitative data in some of the studies, we evaluated placebo responses by changes in the objective ataxia scales (clinical ataxic rating scales or ataxia-associated functional performance tests as mentioned above) from the baseline to the endpoint in each clinical trial and classified the studies showing placebo responses into: (1) studies showing statistically significant improvements in one or more ataxia scales in the placebo groups (Group 1), and (2) studies reporting individual responders with improvements in one or more ataxia scales in the placebo groups (Group 2). Furthermore, because not all the studies compared the outcomes between the baseline and the endpoint in the placebo groups or reported the placebo responders even when there was trend for improvement at the group level, both of which might lead to an underestimation of the placebo response when ignored, we investigated mean changes in the objective ataxia scales of the placebo groups and added additional groups: studies showing mean changes in the direction of improvement in at least one ataxia scale in the placebo groups, even though the changes were not statistically significant (Group 3) and studies showing no placebo response in any of the ataxia scales in the placebo groups (Group 4). When classifying a study into Group 2 or 3, we considered any change in the direction of improvement (i.e., greater than 0) regardless of its statistical significance because currently there is no consensus on the minimal difference of clinical importance on various ataxia scales and all types of CAs are progressively deteriorating disorders. The studies with limited information on placebo responses, due to the absence of baseline or endpoint data of the placebo groups, were classified as Group 5.

## Results

The initial search identified 324 publications, of which 275 were excluded after assessing the eligibility criteria. Forty-nine clinical trials and additional 7 identified by reviewing the searched review articles [4–6, 16–31] met the inclusion criteria. Therefore, a total of 56 clinical trials (study no. 1–56) [32–87], were reviewed in this study. Thirty-five studies (study no. 1–35) [32–66] were parallel-group trials (Fig. 1); 26 of 35 studies were categorized into Groups 1–4,

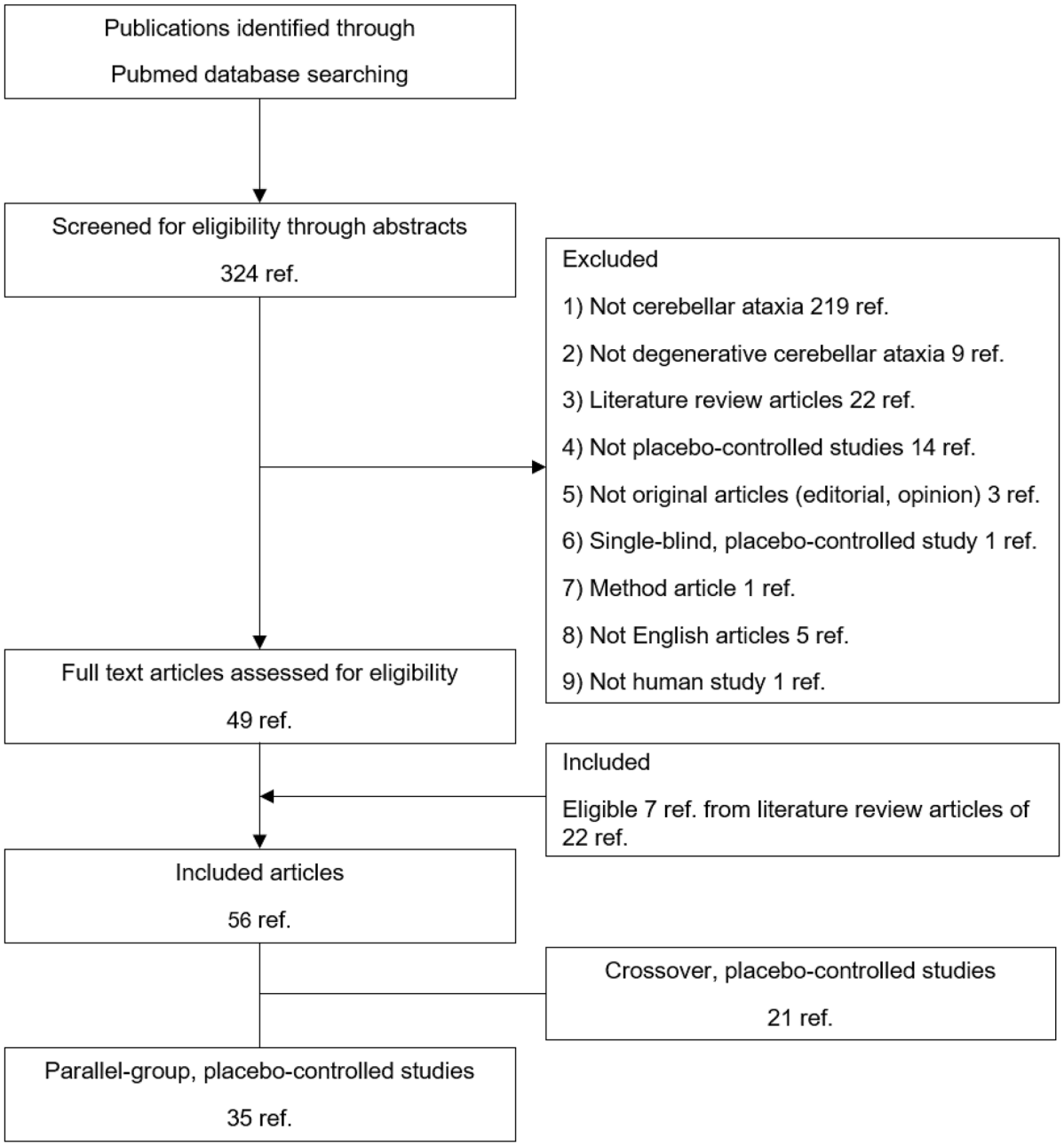


**Fig. 1** Flow diagram of this study

and 9 into Group 5 (Supplementary Table 1). Detailed data regarding the placebo treatments of the reviewed 56 studies are provided in Supplementary Table 2.

Of the 26 studies in Groups 1–4, 3 (11.5%) studies (study no. 1–3) [32–34] were categorized as Group 1 (Table 1). Study no. 1 on patients with mixed ataxia showed significant improvement compared to the baseline in 3 out of 5 functional performance tests associated with gait and balance control after sham transcranial magnetic stimulation. In study no. 2 on SCA type 2, the SARA total score significantly improved while the oculomotor function did not improve with the placebo medication. Study no. 3 on SCA3 patients also showed significant improvement in the SARA total score and subscale scores for gait and stance with placebo medication, however, the subscale scores for speech and hand movement coordination did not improve. In the active treatment groups of the studies, study no. 1 showed significant improvement compared to the placebo group while studies no. 2 and 3 showed no difference between the two groups (detailed

**Table 1** Group 1: studies showing statistically significant improvements in one or more ataxia scales in the placebo treated groups

| Study no. | Authors (year of study publication) | Study population (total no. of patient) | Interventions | Intervention period (month) | Ataxia scales | Baseline data (mean [± SD]) | Endpoint data (mean [±SD]) |
|---|---|---|---|---|---|---|---|
| 1 | Shiga et al. (2002) [31] | Mixed: SCA1/3/6; OPCA (73) | (1) Transcranial magnetic stimulation<br>(2) Sham stimulation | 0.7 | Functional performance tests:<br>(1) Time to 10 m walk test<br>(2) No. of steps for 10 m walk<br>(3) Standing capacities scale | (1) Time to 10 m walk test (13.78 [1.23] s)<br>(2) No. of steps for 10 m walk (25.19 [1.71] no.)<br>(3) No. of steps for tandem (2.26 [0.67] no.)<br>(4) Standing capacities scale (2.43 [0.21])<br>(5) Walking capacities scale (2.11 [0.20]) | Significant improvements in a group:<br>(1) Time to 10 m walk test (12.65 [1.20] s)<br>(2) No. of steps for 10m walk (23.49 [1.69] no.)<br>(3) Standing capacities scale (2.11 [0.17])<br>Mean improvements (without significance) in a group:<br>(1) No. of steps for tandem (3.25 [1.38] no.)<br>(2) Walking capacities scale (2.07 [0.20]) |
| 2 | Velazquez-Perez et al. (2011) [32] | SCA2 (36) | (1) Zinc Sulphate PO<br>(2) Placebo | 6 | Ataxia rating scale:<br>(1) SARA total score | (1) SARA total score (about 15.5 [2]) | Significant improvement in a group:<br>(1) SARA total score (about 11.5 [3]) |
| 3 | Lei et al. (2016) [33] | SCA3 (34) | (1) Valproic acid PO<br>(2) Placebo | 3 | Ataxia rating scale:<br>(1) SARA total score and subitems scores for gait, stance, heel to shin | (1) SARA: total score (10.88 [4.29]); subitems scores for gait (3.00 [1.76]); stance (2.25 [1.22]); sitting (0.00 [0.00]; speech (1.67 [1.15]); finger chase (1.17 [0.39]); finger to nose (0.33 [0.49]); rapid alternation (1.33 [0.89]); heel to shin (1.25 [0.75]) | Significant improvements in a group:<br>(1) SARA: total score (9.00 [3.62]); subitems scores for gait 2.08 [1.24]); stance (1.67 [0.89]); heel to shin (0.92 [0.51]) |

*SD* standard deviation, *SCA1/2/3/6* spinocerebellar ataxia type 1/type 2/type 3/type 6, *OPCA* olivopontocerebellar atrophy, *PO* per oral, *SARA* Scale for the assessment and rating of ataxia

data regarding the active treatments are shown in Supplementary Table 3).

Five (19.2%) of 26 studies (study no. 4–8) [35–39] were included in Group 2 (Table 2). The overall proportion of placebo responders ranged from 9.5 to 57.1%, the average being 31.9%. The highest responder rate was reported in study no. 5 in the ataxia-associated functional performance test on patients with mixed ataxia. The lowest rate (9.5%) was in study no. 8 on Friedreich ataxia (FA); however, in that study, the placebo responders showed substantial reductions in the FARS-Neuro scores (estimated mean reductions were by 34 points). In study no. 6 on FA, there were substantial

**Table 2** Group 2: Studies reporting individual placebo responders in one or more ataxia scales

| Study no. | Authors (year of study publication) | Study population (total no. of patient) | Interventions | Intervention period (month) | Ataxia scales | Proportion of placebo responders |
|---|---|---|---|---|---|---|
| 4 | Sobue et al. (1983) [34] | Mixed: ILOCA; OPCA; SCA (256) | (1) Thyrotropin releasing hormone IM<br>(2) Placebo | 0.5 | Functional performance test:<br>(1) Ataxia improvement rating scale | (1) 48.7% |
| 5 | Filla et al. (1993) [35] | Mixed: FA; SCA (14) | (1) Amantadine PO<br>(2) Placebo | 0.5 | Functional performance test:<br>(1) Functional ataxia scoring scale | (1) 57.1% |
| 6 | Lynch et al. (2010) [36] | FA (70) | (1) Idebenone PO<br>(2) Placebo | 6 | Ataxia rating scale:<br>(1) ICARS total score | (1) 33% with reduction by − 2.5; 25% with reduction by -5 |
| 7 | Romano et al. (2015) [37] | Mixed: SCA; FA (55) | (1) Riluzole PO<br>(2) Placebo | 12 | Ataxia rating scale:<br>(1) SARA total score | (1) 11.1% |
| 8 | Zesiewicz et al. (2018) [38] | FA (63) | (1) α-tocotrienolol quinone; vatiquinone PO<br>(2) Placebo | 6 | Ataxia rating scale:<br>(1) FARS total score | (1) 9.5% |

*FA* Friedreich ataxia, *OPCA* olivopontocerebellar atrophy, *CA* cerebellar ataxia, *PO* per oral, *ILOCA* idiopathic late-onset cerebellar ataxia, *SCA1*/2/3 spinocerebellar ataxia type 1/type 2/type 3, *ICARS* International cooperative ataxia rating scale, *SARA* scale for the assessment and rating of ataxia, *FARS* Friedreich ataxia rating scale

improvements in the ICARS scores in the placebo group; 33% of the placebo-treated patients improved by 2.5 points and 25% by 5 points. Nineteen (73.1%) of 26 studies (study no. 5, 6, and 8–24) [36, 37, 39–55] were included in Group 3, and 4 studies (study no. 4, 7, 25, and 26) [35, 38, 56, 57] were included in Group 4. The effect of treatment duration on a placebo response was unknown and we hypothesized that a shorter treatment duration resulted in a greater placebo response. Therefore, we compared treatment durations between Group 1 and/or 3 versus Group 4, but there was no difference between the groups.

The mean changes in the three most commonly used and validated ataxic rating scales (the ICARS, SARA, or FARS) [8] from 16 studies (study no. 2, 3, 6, 8, and 13–24) [33, 34, 37, 39, 44–55] were studied: mean reductions in the ICARS scores from 4 studies (study no. 6, 13, 18, and 23) ranged from 0.2 to 2.8; mean reductions in the SARA scores from 7 studies (study no. 2, 3, 15–17, 19, and 24) ranged from 0.1 to 4; mean reductions in the FARS, FARS-Neuro, and modified FARS scores from 8 studies (study no. 8, 13, 14, 16, 18, and 20–22) ranged from 0.8 to 2.5 (Fig. 2). In studies using ataxia-associated functional performance tests, we found 11 studies (study no. 1, 2, 8, 9, 15, 17, 18, 22, 26, 29, and 49) [32, 33, 39, 40, 46, 48, 49, 53, 57, 60, 80] that used measurement indices: timed walk tests, such as 8 MW in 6 studies (study no. 1, 8, 15, 17, 18, and 22); coordination of hand movement tests, such as 9HPT in 6 studies (study no. 8, 15, 17, 18, 26, and 49); speech tests, such as PATA repetition in 2 studies (study no. 9 and 17); oculomotor measures in 2 studies (study no. 2 and 9); post-urography in 1 study (study no. 49). Among the evaluated measurements, the timed walk test in study no. 1 showed a significant placebo response.

We also investigated placebo responses in cross-over trials (study no. 36–56) [67–87] and classified them into 5 groups, corresponding to those of the parallel-group studies (Supplementary Table 4). Among the 21 cross-over studies, no studies showed statistically significant improvements in any ataxia scale with placebo treatment. Eight studies (study no. 36–43) reported placebo responders in one or more ataxia scales. Eight studies (study no. 44–51) showed mean changes in the direction of improvement in at least one ataxia scale in the placebo groups, although the changes were statistically insignificant.

## Discussion

In this study, we assessed placebo responses in patients with CAs by reviewing changes in various objective ataxia scales from the baseline to the endpoint in RCTs. We found that of the included 35 parallel-group studies in our review (26 when including studies that provided data for the placebo groups), 3 (11.5%) studies showed statistically significant improvements in objective ataxia scales in the placebo groups, and 21 (80.8%) studies showed placebo responders or some degree of improvement, though not significant, in at least one ataxia measure with placebo treatments. However, in most of the studies, the data

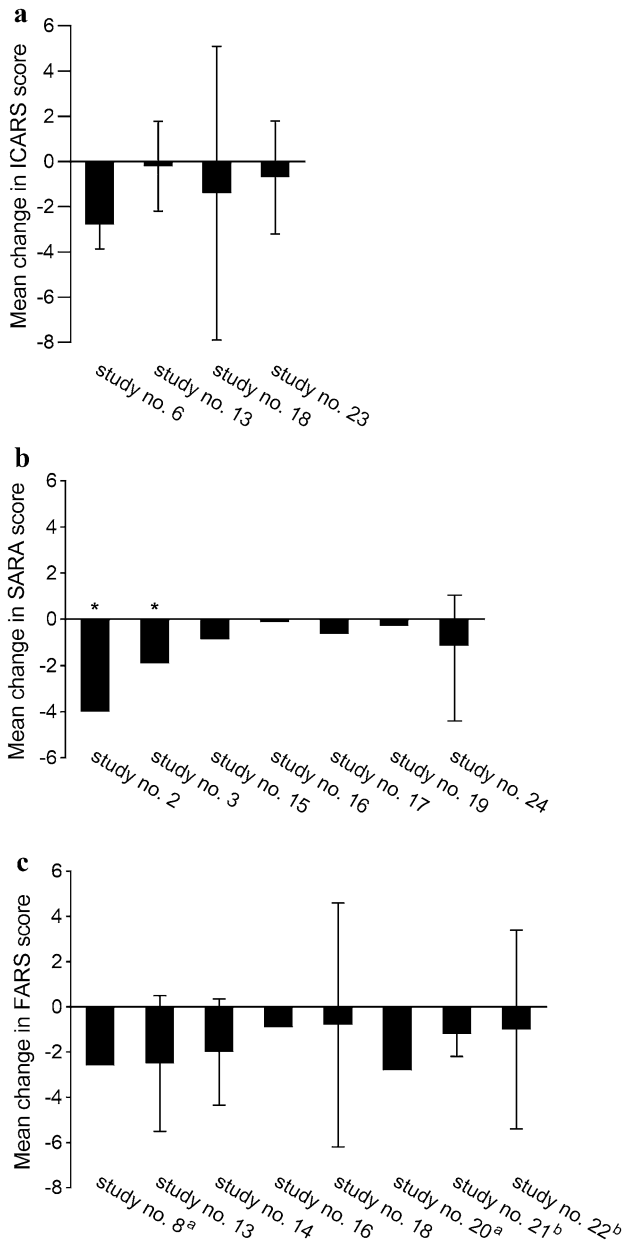


**Fig. 2** Mean change from the baseline to the endpoint on objective ataxia scales. **a** ICARS score, **b** SARA score, **c** FARS score. [a]FARS-Neuro; [b]Modified FARS; *significant changes ($p < 0.05$) from the baseline to the endpoint; Error bar, the standard deviation of the mean if provided in the study. *ICARS* International cooperative ataxia rating scale, *SARA* scale for the assessment and rating of ataxia, *FARS* Friedreich ataxia rating scale

presentation and analysis were focused on comparing the active treatment and the placebo groups at the endpoint and statistical analyses on changes in ataxia scales in the placebo groups were rarely provided. Therefore, it cannot be ruled out that some studies that actually showed statistically significant improvement in the placebo groups (which then should be included in Group 1) were classified into Group 3 in our review, which then might have led to an underestimation of placebo responses.

It may be argued that non-significant changes in ataxia scales between the baseline and the endpoint in many of the studies are non-substantial changes, which are nothing more than a variation inherent to each ataxia scale. However, considering the relentlessly progressive nature of CAs and the absence of proven symptomatic therapies, let alone disease-modifying therapies, even small improvements with placebos should not be ignored. Otherwise, the efficacy of a new treatment might be overestimated and misinterpreted. Our results suggest that even 'no change over several months' should not be interpreted as a symptomatic or protective effect.

The mechanism of anticipation-driven neural modulation that improves ataxia-associated motor functions, as shown in our results, remains poorly understood. Expectation and overestimation of a response to treatment by raters who are blinded to the treatment may contribute to placebo responses. However, increasing evidence has shown that the cerebellum is involved in the regulation of cognition and emotion through complex connections with the frontal cortex and limbic areas [88–90], and a dysfunctional cerebellum may result in hypersensitivity to anticipated rewards. Previous studies have shown that in the "gambling" task, preferring a large gain with a larger loss rather than a small gain with a small loss has been observed in patients with cerebellar hemispheric lesions [91, 92]. It has been proposed that the cerebellar hemispheres modulate higher cognition, i.e. prospective thinking and planning, while the cerebellar vermis is responsible for primitive emotions for survival, i.e. fear of potentially harmful stimuli [93]. These results and our findings support that cerebellar pathology may be related to placebo responses in patients with CAs. Interestingly, in a previous study, the nocebo effect, which is a negative placebo effect, was reported in 13.8% of CA patients and approximately 1 in 20 (4.8%) patients withdrew due to adverse events related to placebo treatments [29]. Further studies are warranted to elucidate the mechanisms of the placebo and nocebo effects in CA patients.

There are limitations to this review. In most studies on CAs, the sample size was small, and data on placebo groups were not fully addressed. In addition, the heterogeneity of the study populations and evaluated measurements made the comparison of studies infeasible. A standardized consensus-based rating scale that can be applied to various types of CAs is required to allow the comparison between studies in the future.

To the best of our knowledge, this study is the first to assess placebo responses in CA patients. Considering that there are currently no proven treatments effective for CAs and that a large number of clinical trials are underway or being planned, our study emphasizes that placebo responses

should be taken into consideration when designing, analyzing, and interpreting clinical trials and for clinical practice. Moreover, it suggested that placebo responses could also influence the outcomes of active treatment groups in RCTs on CAs.

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**Data access and responsibility statement** HJ. Kim and JH. Choi had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Compliance with ethical standards

**Conflicts of interest** There is no conflict of interest from all authors relative to this study.

**Ethical standards** The manuscript does not contain clinical studies or patient data.

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