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CLINICAL TRIAL

Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial

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Botulinum toxin A (BTA) is widely used as treatment of chronic migraine. Efficacy in studies, however, was only modest and likely influenced by unblinding due to BTA-induced removal of forehead wrinkles. Moreover, most study participants were overusing acute headache medications and might have benefitted from withdrawal. We assessed in a double blind, placebo-controlled, randomized clinical trial whether add-on therapy with BTA enhances efficacy of acute withdrawal. Participants were enrolled between December 2012 and February 2015, with follow-up to January 2016, in a single academic hospital in the Netherlands. A total of 179 participants, male and female, aged 18–65, diagnosed with chronic migraine and overuse of acute headache medication were included. All participants were instructed to withdraw acutely from all medication for a 12-week period, in an outpatient setting. In addition, they were randomly assigned (1:1) to 31 injections with BTA (155 units) or placebo (saline); to prevent unblinding, placebo-treated participants received low doses of BTA (17.5 units in total) in the forehead, along with saline injections outside the forehead region. Primary endpoint was percentage change in monthly headache days from baseline to the last 4 weeks of double-blind treatment (Weeks 9–12). Among 179 randomized patients, 90 received BTA and 89 received placebo, and 175 (98%) completed the double-blind phase. All 179 patients were included in the intention-to-treat analyses. BTA did not reduce monthly headache days versus placebo (-26.9% versus -20.5%; difference -6.4%; 95% confidence interval: -15.2 to 2.4; $P = 0.15$). Absolute changes in migraine days at 12 weeks for BTA versus placebo were -6.2 versus -7.0 (difference: 0.8; 95% confidence interval: -1.0 to 2.7; $P = 0.38$). Other secondary endpoints, including measures for disability and quality of life, did also not differ. Withdrawal was well tolerated and blinding was successful. Thus, in patients with chronic migraine and medication overuse, BTA does not afford any additional benefit over acute withdrawal alone. Acute withdrawal should be tried first before initiating more expensive treatment with BTA.

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Introduction

Chronic migraine is a highly disabling and difficult to treat form of migraine (Headache Classification Committee of the International Headache Society, 2013; Schwedt, 2014; May and Schulte, 2016) affecting nearly 2% of the general population (Schwedt, 2014; May and Schulte, 2016). It is defined by occurrence of headaches on ⩾15 days per month for >3 months, of which ⩾8 days fulfil migraine criteria (Headache Classification Committee of the International Headache Society, 2013; Schwedt, 2014; May and Schulte, 2016). The majority of patients overuse acute headache medications including analgesics, triptans, and opioids (Schwedt, 2014; May and Schulte, 2016). 'Medication overuse' is a major risk factor for transformation from episodic (<15 headache days) to chronic migraine and an important factor in maintaining and aggravating chronification (Headache Classification Committee of the International Headache Society, 2013; Schwedt, 2014; May and Schulte, 2016).

Acute withdrawal may be a cost-effective therapy to reduce headache frequency, improve quality of life, halt medication overuse-induced adverse events, and prevent systemic toxicity (Zeeberg *et al.*, 2006*a*; Rossi *et al.*, 2006, 2011, 2013; Evers and Marziniak, 2010; Munksgaard *et al.*, 2012; Tassorelli *et al.*, 2014; Chiang *et al.*, 2016; May and Schulte, 2016; Pijpers *et al.*, 2016; Carlsen *et al.*, 2018). It might also improve efficacy of migraine prophylactics (Zeeberg *et al.*, 2006*b*; Chiang *et al.*, 2016; May and Schulte, 2016). Unfortunately, acute withdrawal is frequently hampered by acute withdrawal symptoms that may considerably disrupt patient's daily life, comfort, and mental state (Katsarava *et al.*, 2001; Diener, 2012). Because of these withdrawal symptoms, many physicians are reluctant to recommend withdrawal, despite the potential advantages (Diener, 2012; Olesen, 2012; Chiang *et al.*, 2016).

Recently, botulinum toxin A (BTA) (Pirazzini *et al.*, 2017) has emerged as therapy for chronic migraine (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Diener, 2012; Jackson *et al.*, 2012; Silberstein *et al.*, 2013; Dougherty and Silberstein, 2015; Simpson *et al.*, 2016). There is, however, controversy regarding its efficacy, particularly in patients with medication overuse (Olesen and Tfelt-Hansen, 2010; Olesen, 2012; May and Schulte, 2016). In the registration trials, the therapeutic gain of BTA versus placebo was only modest, with an additional reduction of 1.8 headache days from 19.9 at baseline (percentage change: 9%) (Dodick *et al.*, 2010). Moreover, unblinding might have influenced efficacy. Study medication was injected at 31 sites including the forehead, which will remove wrinkling and likely cause

unblinding versus placebo (Olesen and Tfelt-Hansen, 2010; Solomon, 2013). In trials using similar designs, 85% of BTA-treated participants correctly guessed their treatment (Australian Government, 2011; Solomon, 2013).

A second important issue is that ~65% of the participants in these studies were overusing medication, and might have benefitted from withdrawal (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Jackson *et al.*, 2012; Silberstein *et al.*, 2013). Direct, double-blind comparison of withdrawal versus BTA is technically hardly feasible. Placebo-matching for the various types and combinations of overused medications is virtually impossible, as well as controlling for the psychological effects of withdrawal. We compared acute withdrawal plus BTA administered according to standard protocols (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Jackson *et al.*, 2012; Silberstein *et al.*, 2013) versus acute withdrawal plus placebo in a double-blind, randomized clinical trial in patients with chronic migraine and medication overuse. To minimize risk of unblinding, injections in the forehead of participants allocated to placebo contained low masking doses of BTA, sufficient to remove forehead wrinkling, but unlikely to reduce headache frequency.

Materials and methods

Study design and participants

This was a randomized, double-blind, placebo-controlled, clinical trial done at Leiden University Medical Centre Headache Clinic: the Chronification and Reversibility of Migraine study (CHARM; www.trialregister.nl #3440). We enrolled consecutive patients with chronic migraine and medication overuse (Headache Classification Committee of the International Headache Society, 2013). Diagnoses were established in consultation with headache experts and confirmed by a 4-week baseline headache diary. Patients aged 18–65, who were able to comply with the study protocol, and provided written informed consent, were eligible. Exclusion criteria included: contraindications for BTA (Pirazzini *et al.*, 2017); other primary or secondary headaches or neurological disorders; moderate/severe chronic pain disorders; psychiatric disorders other than depression; cognitive, behavioural, or oncological disorders; use of ergots, opioids or barbiturates; and abuse of recreational soft or hard drugs.

The study was performed in accordance with the declaration of Helsinki and Good Clinical Practices and approved by the local ethics committee.

Randomization

Upon inclusion, patients were randomly assigned to receive BTA or placebo injections (1:1), according to a centralized randomization schedule using blocks of four to eight patients,

stratified for gender. The randomization schedule was prepared and kept concealed in the data management system by an independent trial statistician. An independent pharmacist and research nurse prepared the appropriate treatments. The study investigators who enrolled participants and administered treatment were not involved in these procedures.

Procedures

Participants started with a 4-week baseline-assessment period, followed by a 12-week randomized, double-blind, placebo-controlled phase with BTA injections immediately prior to medication withdrawal (Fig. 1). After this double-blind phase, participants who had withdrawn from medication but remained to have chronic migraine were offered open-label BTA injections (155 units, one treatment cycle) in addition to standard care regarding acute headache medication (open-label phase). Participants who were not eligible for BTA open label treatment received standard care with acute headache medication and, if needed, prophylactic treatment.

Study follow-up visits were planned at Weeks 12, 24 and 48, with additional clinical visits according to medical need. Participants kept 4-week paper diaries with daily registration of headache characteristics, accompanying symptoms, and use of acute headache medication during the baseline observation period and post treatment Weeks 9–12, 21–24, 33–36, and 45–48. The diaries had to be sent in every week to ensure an accurate status. Cross checking of data (entry) was performed both manually in a random manner and electronically with fixed algorithms. Determination of migraine and non-migraine headache on any given calendar day was calculated by an algorithm based on the International Classification of Headache Disorders criteria.

In addition, electronic questionnaires were filled out every 12 weeks regarding quality of life [SF-36 (Brazier et al., 1992)], headache impact and disability [HIT-6 (Kosinski et al., 2003), Migraine Disability Assessment (MIDAS; Stewart et al., 2001)], depression and anxiety [Hospital Anxiety and Depression Scale HADS (Bjelland et al., 2002)]. Adverse events were recorded based on spontaneous reports from participants and upon questioning by the study investigators at Day 3 and Week 12.

Treatments and masking

In accordance to our national guidelines (Werkgroep Migraine Richtlijn NVN, 2017) and other withdrawal studies (Rossi et al., 2006, 2011; Pijpers et al., 2016; Carlsen et al., 2018), participants were instructed to withdraw abruptly from all acute headache medications and caffeine in an outpatient setting for 12 weeks. Prophylactic treatment was tapered off and rescue medication to treat headaches of any kind was not allowed. Participants were explained what to expect after withdrawal, including the likely occurrence of sometimes severe withdrawal symptoms, and were informed about the possible practical, social and professional consequences.

BTA was administered at 31 predefined injection sites (5 units per injection; 155 units in total), in accordance with published protocols (Dodick et al., 2010). Placebo was administered at the same 31 injection sites. However, while the 24 injections outside the forehead region contained saline, the seven injections in the forehead contained low dose BTA (2.5 units per injection site; 17.5 units in total). Participants were explained that change in facial expression was not indicative of any particular treatment. Active and placebo treatment were indistinguishable. Participants and investigators were blinded for treatment.

Outcomes

There is no universally agreed primary endpoint for trials in chronic migraine. The differences, however, between the various recommended (Silberstein et al., 2008; Tassorelli et al., 2018) and used endpoints (Bigal et al., 2015a; Silberstein et al., 2017; Tepper et al., 2017; Detke et al., 2018; Deen et al., accepted for publication) are in fact only marginal. We choose as primary outcome the percentage change in 4-weekly headache days from baseline to the last 4 weeks of double-blind treatment (Weeks 9–12). As patients with chronic migraine have a high headache frequency at baseline, percentage change in headache days is considered a more meaningful endpoint than absolute change. Percentage change was calculated as change in number of headache days per 4 weeks, divided by the number of baseline headache days. A headache day was any calendar day on which a migraine or non-migraine headache of any duration was reported. We did not include a minimal duration of 4 h (as used in some trials), as most of our participants would usually use medication within 4 h after headache onset. For the same reason we decided not to specify that headache had to have a moderate or severe peak intensity.

Secondary outcomes were assessed 12, 24, 36 and 48 weeks after therapy onset. The main secondary outcome was change in quality of life (SF-36). Additional secondary outcomes were change from baseline in number of (i) headache days; (ii) migraine days (days with headache fulfilling migraine criteria or treated with acute migraine medication); (iii) moderate or severe headache days; (iv) hours with headache (cumulative); and (v) days with use of acute headache medication. We also assessed: (i) the proportion of participants with ≥50% or ≥25% reduction in headache days; (ii) the proportion of participants who persevered successfully with medication withdrawal (≤2 medication days per 4 weeks); (iii) the proportion of participants without medication overuse (<10 medication days per 4 weeks); and (iv) HIT-6 and MIDAS scores.

To assess satisfaction, participants were asked after 12 weeks to rate their treatment on a 0–10 satisfactory scale (0 = completely dissatisfied, 10 = completely satisfied), and whether they would recommended their therapy to family or friends ('no', 'yes' or 'I don't know'). To assess success of blinding, we asked participants and investigators 3 days and 12 weeks after therapy onset which treatment they believed they had received or given (BTA, placebo, or don't know).

Statistical analysis

We defined a 20-percentage point difference in mean percentage change in 4-weekly headache days from baseline to Weeks 9–12 of BTA versus placebo, as clinically meaningful. Based on a previous withdrawal study (Pijpers et al., 2016), we expected a standard deviation of 40 percentage points. Thus, 84 participants per group were required to detect a 20-percentage
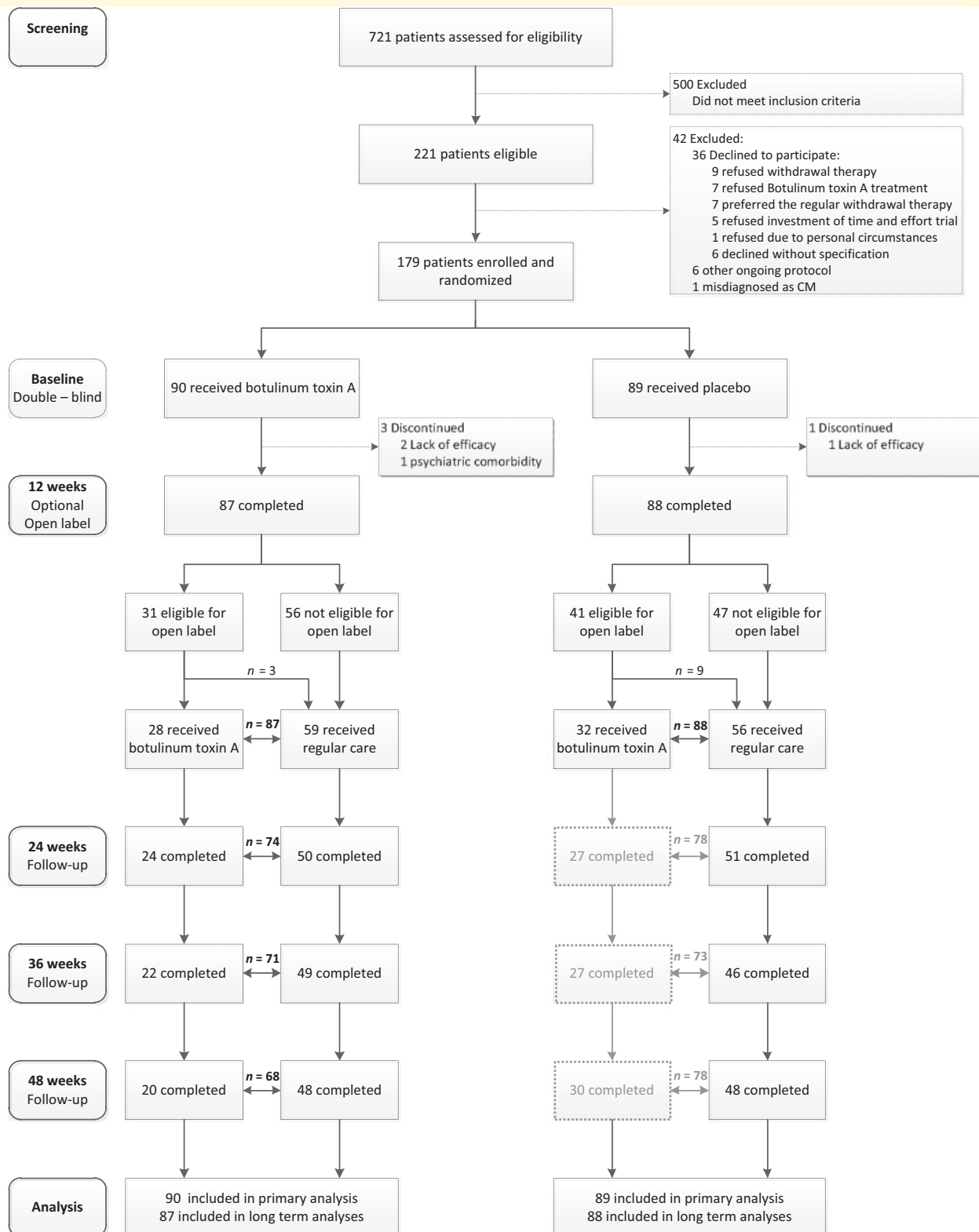
Figure 1 Trial profile. Primary analysis included all participants (intention-to-treat), using outcomes after 12 weeks. Of 90 participants receiving withdrawal and BTA during the double blind phase, 31 still had chronic migraine after 12 weeks, of whom 28 participants received one cycle open label BTA. Accordingly, of 89 participants receiving withdrawal and placebo during the double blind phase, 41 still had chronic migraine, of whom 32 received one cycle open label BTA. Long term analyses, comparing one or two cycles of BTA versus placebo after 12, 24, 36, and 48 weeks, included all participants providing at least one outcome measurement. The open-label results (i.e. outcomes after 24, 36, and 48 weeks) of placebo treated patients receiving open label BTA were set as missing (depicted in grey within dashed boxes). The boxes show the number of participants of whom data were available.

point difference with 90% power and a 0.05 type 1 error. To allow for dropouts, we aimed to include 90 participants per group.

The primary intention-to-treat analysis included all patients. We used a pre-specified analysis of covariance (ANCOVA) model to compare the percentage change in 4-weekly headache days between the two groups. Fixed factors were treatment, support by a headache nurse, gender, depression and anxiety. Covariates were age and number of baseline headache days. Similar models were used for the secondary outcomes after 12 weeks. Missing data on follow-up (<14 completed headache dairy days) was handled using multiple imputation. Ten imputed datasets on headache days, migraine days, moderate or severe headache days, headache duration, and SF-36 score were generated using automatic imputation. In case of 14–27 completed days, the existing data were extrapolated to a 28-days period.

To assess long-term efficacy, we included the open label and follow-up phases in the analysis. As some placebo-treated participants received BTA in the open label phase, including these patients in the analysis of 'placebo-treated participants' would potentially confound the comparison. To avoid this, the open-label results (outcomes after 24, 36 and 48 weeks) of placebo-treated participants receiving open-label BTA were set to missing (see grey numbers in Fig. 1). Thus, participants treated only with placebo were compared to participants who received one or two cycles of BTA. Participants providing at least one outcome measurement were included. We used linear mixed models with changes from baseline to follow-up as the dependent variable. Such models automatically handle missing outcomes, including those censored by us. Fixed effects were treatment, visit number, treatment × visit number interaction, headache nurse, gender, depression, and anxiety. Covariates were age and baseline value of the variable of interest. Unstructured covariance matrices were used. We report the adjusted means with 95% confidence intervals (CI). To facilitate objective assessment of the open-label long-term follow-up we present the results both as crude data, without any statistical modelling (Table 3), and by using the statistical model (Fig. 4).

Two-sided P-values < 0.05 were considered statistically significant. Analyses were performed in SPSS23.0 (SPSS Inc., Chicago, USA). The audit trial of the trial register captures protocol amendments: no changes were made after unblinding of study investigators or completion of the trial. Data entry and processing was performed before unblinding of study investigators.

Data availability

The trial is registered at the Netherlands trial registry, #3440, www.trialregister.nl. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Between December 2012 and February 2015, 721 patients with high frequent migraine were screened, of whom 221 were eligible and 179 included and randomly assigned to

Table 1 Baseline demographic and clinical characteristics

	BTA (n = 90)	Placebo (n = 89)
Gender, female	69 (76.7%)	67 (75.3%)
Age, years	43.7 ± 11.8	46.7 ± 9.5
Headache days	21.7 ± 4.7	21.0 ± 4.8
Moderate/severe headache days	16.1 ± 6.0	15.3 ± 4.9
Headache duration, cumulative hours	199.6 ± 156.6	196.0 ± 148.2
Migraine days	15.5 ± 6.0	14.9 ± 5.0
Duration of migraine, years	26.6 ± 13.5	28.6 ± 12.3
HIT 6[a]		
Mean score	65.0 ± 4.6	65.0 ± 3.9
% severe (⩾60)	81 (90.0%)	84 (94.4%)
Days using medication[b]	16.5 ± 5.8	16.4 ± 5.4
Type of overuse		
Isolated triptan	18 (20.0%)	15 (16.9%)
Isolated simple analgesics[c]	6 (6.7%)	1 (1.1%)
Combined medication[d]	66 (73.3%)	73 (82.0%)
Prophylaxis[e]		
Current use	30 (33.3%)	35 (39.3%)
History of use[f]	82 (91.1%)	81 (91.0%)
Number of used prophylactics	2.5 ± 1.8	2.2 ± 1.8
Anxiety, % present (HADS-A ⩾ 8)	28 (31.1%)	27 (30.3%)
Anxiety, mean HADS-A score	6.2 ± 4.0	6.3 ± 3.7
Depression, % present (HADS-D ⩾ 8)	32 (35.6%)	34 (38.2%)
Depression, mean HADS-D score	6.3 ± 4.2	6.5 ± 4.1

Values are means ± SD or n (%).
[a]BTA n = 87, placebo n = 87.
[b]Simple analgesics and/or triptans.
[c]Simple analgesics: paracetamol, NSAID's.
[d]Combined medication: combination of triptans, simple analgesics or combination drugs such as paracetamol and caffeine.
[e]Commonly used prophylaxis for migraine.
[f]History of use: current or past use of at least one type of prophylaxis.

either BTA (n = 90) or placebo (n = 89) (Fig. 1). The treatment groups were well balanced for age, gender, headache and migraine frequency, and psychiatric comorbidity (Table 1). Four participants discontinued the study in the double-blind phase, one in the placebo group because of lack of efficacy and three in the BTA group, because of lack of efficacy (n = 2) or exacerbation of pre-existing depression (n = 1). All 179 participants were included in the intention-to-treat analysis. Follow-up ended in January 2016. Discontinuation of participants until the end of follow-up is depicted in Fig. 1.

The primary outcome, mean percentage change in 4-weekly headache days from baseline to Weeks 9–12 after therapy onset, did not differ between withdrawal plus BTA (−26.9%; 95% CI: −19.9 to −34.0) versus withdrawal plus placebo (−20.5%; 95% CI: −13.5 to −27.6). The adjusted treatment difference was 6.4% (95% CI: −2.4 to 15.2; P = 0.15; Fig. 2).

Likewise, there were no treatment differences after 12 weeks for any of the secondary outcome measures, including headache days or hours, migraine days, 50% and 25% responder rates, and measures of quality of life and (Table 2). The change in headache days was −5.6 for BTA versus −4.4 for placebo (mean difference −1.3; 95% CI: −3.1 to 0.6) and in migraine days was −6.2 for

BTA versus −7.0 for placebo (mean difference 0.8; 95% CI: −1.0 to 2.7) (Table 2). Approximately 60% of participants had reverted back to episodic migraine, without any treatment differences (Table 2 and Fig. 3). BTA did also not increase the proportion of participants who managed to persevere with withdrawal. In both groups, 90% of participants withdrew successfully, defined as ⩽2 medication days, and the proportions of participants still meeting the criteria for medication overuse at week 12 were negligible (2.3%; Table 2).

After 12 weeks, 60 patients received open-label BTA treatment (Fig. 1). Preventatives that were started as part of standard care included topiramate (23%), candesartan (11%), valproate (4%), beta-blockers (3%), amitriptyline (2%) and flunarizine (1%).

We also assessed the long term effects of withdrawal plus one or two BTA treatments versus withdrawal without BTA. There were no differences after 12, 24, 36, or 48 weeks for any of the outcome measures: days with any headache or migraine (Fig. 4A and B), days with moderate or severe headache, cumulative number of hours with headache, or days with medication use (adjusted data not shown). These results were supported by comparisons of the unadjusted data of the four possible combinations for initial double-blind and subsequent open-label treatment, which did not show any relevant difference (Table 3).

Satisfaction with treatment after 12 weeks was 7/10 (median, interquartile range = 3). Treatment was rated as
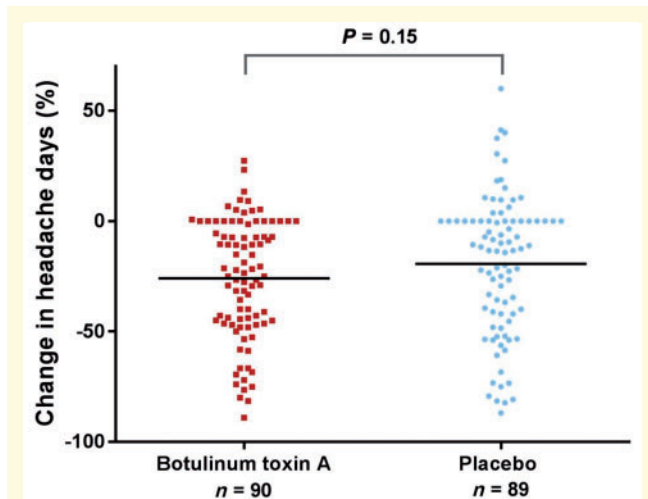

Figure 2 Percentage change in 4-weekly headache days from baseline to the last four weeks of double-blind treatment (Weeks 9–12). Depicted are unadjusted values and means.

Table 2 Secondary outcomes

	BTA (n = 90)	Placebo (n = 89)	Mean difference (95% CI)	P-value
Change in headache days[a]	−5.6 (0.8)	−4.4 (0.7)	−1.3 (−3.1 to 0.6)	0.17
Change in migraine days[b]	−6.2 (0.8)	−7.0 (0.7)	0.8 (−1.0 to 2.7)	0.38
Change in moderate / severe headache days[c]	−4.9 (0.7)	−5.4 (0.7)	0.5 (−1.2 to 2.2)	0.55
Change in hours of headache (cumulative)[d]	−20.8 (13.5)	−13.3 (13.5)	−7.5 (−41.0 to 25.9)	0.66
Transformation from chronic migraine to episodic migraine	65.2%	57.0%	8.2 (−6.0 to 22.4)	0.29
25% responder rate[e]	48.3%	37.8%	10.5 (−3.9 to 24.9)	0.16
50% responder rate[e]	18.1%	20.4%	−2.5 (−13.8 to 9.2)	0.69
Succeeded to withdraw from medication (yes)[f,m]	89.7%	89.8%	−0.1 (−9.3 to 9.1)	0.98
Medication overuse status (no overuse)[g,m]	97.7%	97.7%	0.0 (−4.4 to 4.4)	0.99
Change in SF-36 physical health[h]	−1.0 (1.9)	1.8 (1.8)	−2.8 (−7.1 to 1.4)	0.19
Change in SF-36 mental health[h]	0.0 (2.0)	0.6 (2.0)	−0.6 (−5.4 to 4.1)	0.79
Change in HIT-6[i,l]	−0.8 (0.7)	−0.8 (0.6)	0.0 (−1.5 to 1.6)	0.96
Change in MIDAS[j,k]	18.7 (10.2)	24.0 (9.8)	−5.3 (−19.0 to 29.6)	0.67

Data are least squares means (standard error) or proportions. Note that some scores do not add up because of rounding.
[a]Day with a migraine or non-migraine headache of any duration.
[b]Day with headache fulfilling migraine criteria or treated with acute anti-migraine medication.
[c]Day with headache of moderate or severe intensity of any duration.
[d]Cumulative duration in hours of any headache of any severity.
[e]Proportion of participants with ⩾25% or ⩾50% reduction in headache days.
[f]Proportion of participants who persevered successfully with medication withdrawal, defined as no more than two medication days per month.
[g]Proportion of participants without medication overuse, i.e. <10 medication days per month.
[h]Physical and mental health sum scores, range 0–100, a higher score corresponds to a higher quality of life.
[i]Headache impact sum score, range 36–78, a higher score corresponds to a higher headache impact.
[j]Sum of days with disability due to migraine, a higher score corresponds to a higher migraine disability.
[k]BTA n = 76; placebo n = 77.
[l]BTA n = = 76; placebo n = 79.
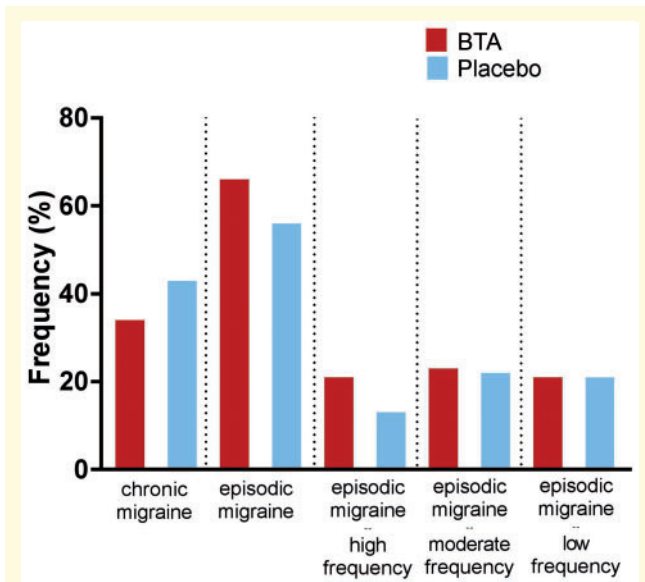[m]BTA n = = 87; placebo n = 88.

Figure 3 Migraine status after 12 weeks. Proportion of participants who remained to have chronic migraine, or who transformed to episodic migraine. Episodic migraine was subcategorized in high frequent, moderate frequent and low frequent episodic migraine. Chronic migraine: $\geq$15 headache days of which $\geq$8 are migraine days; episodic migraine: = not fulfilling chronic migraine criteria; episodic migraine–high frequency: = >15 headache days, but <8 are migraine days; episodic migraine–moderate frequency: = 10–14 headache days; episodic migraine–low frequency: <10 headache days.

very good ($\geq$8/10) by 44.7% of BTA and 47.5% of placebo treated participants. Furthermore, 61.8% of BTA and 72.5% of placebo-treated patients would recommend their treatment to friends or family, 25% and 17.5% did not know, and 13.2% and 10% would not.

In total 59 presumably treatment-related adverse events were reported in the double blind phase by 52 participants: 25 on BTA and 27 on placebo (Supplementary Table 1). Adverse events were mild (92%) or moderate (8%). Most frequently reported adverse events were pain (37%) and small haematoma (31%) at injection sites. Ptosis was reported by six participants (BTA $n = 2$, placebo $n = 4$).

Blinding appeared successful (Table 4). Assumptions about received (participants) or given (investigators) treatments were equally distributed, and neither participants nor investigators guessed the correct treatment significantly more often. At 12 weeks, investigators correctly identified treatment in 54.3% of BTA-treated patients and 55.0% of placebo-treated patients. For participants these proportions were 38.2% and 44.0%.

Discussion

We assessed whether double-blind add-on therapy of BTA increased efficacy of acute withdrawal in chronic migraine

with medication overuse. Efficacy was evaluated primarily after 12 weeks, as this period comprises the acute withdrawal phase. Low doses of BTA in the forehead of placebo-treated participants successfully prevented unblinding. Acute withdrawal was well-accepted and associated with meaningful improvement. BTA did not afford any additional benefit over withdrawal alone.

Most patients with chronic migraine overuse acute headache medications (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Louter *et al.*, 2013; Silberstein *et al.*, 2013; Schwedt, 2014; May and Schulte, 2016) and withdrawal may significantly reduce headache (Rossi *et al.*, 2009; Munksgaard *et al.*, 2012; Olesen, 2012; Chiang *et al.*, 2016; May and Schulte, 2016; Pijpers *et al.*, 2016; Carlsen *et al.*, 2018). Yet, many patients and physicians are reluctant to initiate withdrawal fearing acute withdrawal symptoms (Katsarava *et al.*, 2001; Diener, 2012; Headache Classification Committee of the International Headache Society, 2013; Schwedt, 2014; Chiang *et al.*, 2016; May and Schulte, 2016). In our study, 90% of the study population completed withdrawal, almost 50% evaluated their therapy as very good, and 70% would recommend their therapy to friends and family. After withdrawal, mean number of headache days had decreased by ~5 days ($\approx$25%) and of migraine days by 6–7 days ($\approx$45%; Table 2). In total 60% of patients had reverted back to episodic migraine, which was mainly due to the large drop in migraine days below the threshold of 8 days required to fulfil the criteria for chronic migraine (Fig. 3). Over 30% of participants (29% in the BTA group and 34% in the placebo group) did not need preventive medication anymore as their number of migraine days had dropped below four per month. These results confirm that withdrawal is well-tolerated and associated with meaningful improvement.

Comparison with results from other studies is difficult because of different study designs and populations. For instance, many studies (Rossi *et al.*, 2006, 2011, 2013; Zeeberg *et al.*, 2006*a*; Evers and Marziniak, 2010; Munksgaard *et al.*, 2012; Tassorelli *et al.*, 2014; Chiang *et al.*, 2016; May and Schulte, 2016; Pijpers *et al.*, 2016) were conducted in patients who had medication overuse headache, but not necessarily chronic migraine. In a study in patients with medication overuse of whom 60% fulfilled the criteria for chronic migraine (Carlsen *et al.*, 2018), acute withdrawal resulted in a reduction in mean monthly migraine days and a reversion to episodic migraine very similar to what we found in our study.

In the PREEMPT studies, patients with daily headaches and/or comorbid depression were excluded because they are more treatment-resistant. In our trial, such patients were included as, in clinical practice, daily headaches and comorbid depression are common features of patients with chronic migraine. The inclusion of these difficult-to-treat patients certainly makes our study population more representative for the general chronic migraine population, but may also have contributed to lower response rates for BTA
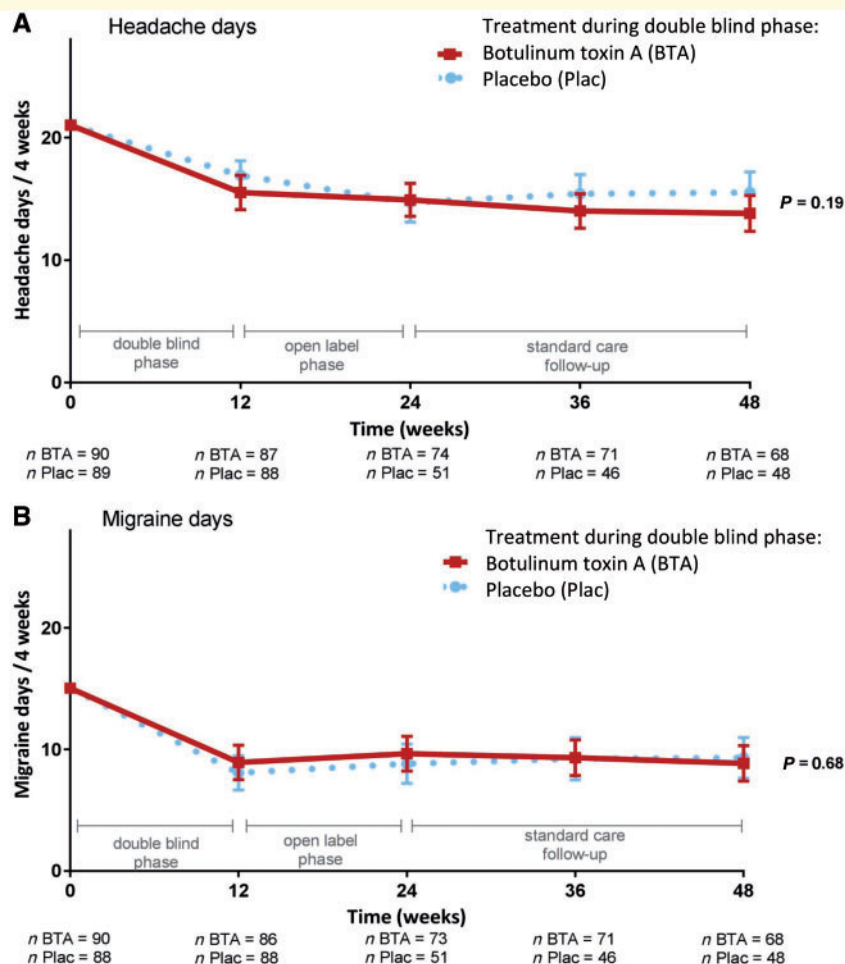
Figure 4 Change from baseline of the 4-weekly number of days with headache (A) and migraine (B) over 48 weeks. To compare the long-term effects of withdrawal plus BTA versus withdrawal plus placebo, the open label phase and follow-up phase were included in the analysis. As some placebo-treated participants received BTA in the open label phase, including the outcomes of these patients in the analysis of 'placebo-treated participants' would potentially influence the comparison. To avoid this, the open-label results (i.e. outcomes after 24, 36 and 48 weeks) of placebo-treated participants receiving open-label BTA were set to missing. In this way, participants treated only with placebo were compared to participants who had received one or two cycles of BTA. Depicted are adjusted means with 95% CI; headache and migraine days at baseline are derived from the model. A headache day is a day with a migraine or non-migraine headache of any duration; a migraine day is a day with headache fulfilling migraine criteria or treated with acute anti-migraine medication.

(−5.6 headache days from a baseline of 21.7 = 26%) and placebo (4.4 headache days from a baseline of 21 days = 21%). Likewise, in the PREEMPT studies, exclusion of patients with daily headaches and/or comorbid depression might have contributed to higher response rates for BTA but also placebo. In fact, placebo response rate in the PREEMPT studies was remarkably high (−6.6 headache days per 4 weeks from a baseline of 19 days = 35%) as emphasized by authoritative reports such as from the British National Institute for Health and Care Excellence (NICE guidance TA260, 2012) and from the European Headache Federation (Bendtsen *et al.*, 2018). As a result, the therapeutic gain in the PREEMPT studies of BTA over placebo was only modest: −8.4 versus −6.6 headache days, i.e. <2 days gain per 4 weeks (Dodick *et al.*, 2010).

Comparison with recent trials testing anti-CGRP (receptor) antibodies in chronic migraine is similarly complicated by remarkable differences in study design, inclusion and exclusion criteria, and even definitions for primary and secondary endpoints. Placebo response rates for the primary endpoints in these trials were considerably lower compared to the PREEMPT trials: −4.6 monthly headache days (versus 12.8 at baseline = 36%) for fremanezumab versus −2.5 headache days for placebo (versus 13.3 at baseline = 19%) (Silberstein *et al.*, 2017); −6.6 monthly migraine days for erenumab (versus 17.9 at baseline = 37%) versus −4.2 for placebo (versus 17.8 at baseline = 24%) (Tepper *et al.*, 2017); −4.8 monthly migraine days (versus 19.2 at baseline = 25%) for galcanezumab versus −2.7 migraine headache days for placebo (versus 19.6 at

Table 3 Unadjusted changes from baseline over 48 weeks, on most important secondary outcomes

Treatment: double blind phase	Baseline	12 weeks Mean (95%CI)	Treatment: open label phase	12 weeks[a] Mean (95%CI)	24 weeks Mean (95%CI)	36 weeks Mean (95%CI)	48 weeks Mean (95% CI)
Headache days							
BTA	21.7	−5.4 (−6.6 to −4.2)	BTA	−1.5 (−3.1 to 0.1)	−1.9 (−4.0 to 0.2)	−2.5 (−4.0 to −1.1)	−4.6 (−7.3 to −1.8)
			Standard care	−7.3 (−8.7 to −5.8)	−7.6 (−9.1 to −6.1)	−8.9 (−10.6 to −7.2)	−8.2 (−9.9 to −6.5)
Placebo	21.0	−3.9 (−5.3 to −2.5)	BTA	0.0 (−1.4, 1.4)	−3.2 (−5.7 to −0.8)	−2.2 (−4.3 to −0.1)	−5.9 (−8.4 to −3.4)
			Standard care	−6.1 (−7.9 to −4.3)	−7.4 (−8.9 to −6.0)	−6.6 (−8.1 to −5.2)	−6.6 (−8.3 to −5.0)
Migraine days							
BTA	15.5	−6.5 (−8.1 to −5.0)	BTA	−0.5 (−2.2 to 1.3)	−2.0 (−4.7 to 0.8)	−4.8 (−8.1 to −1.6)	−3.6 (−6.4 to −0.7)
			Standard care	−9.4 (−11.1 to −7.7)	−7.6 (−9.4 to −5.7)	−7.1 (−8.8 to −5.4)	−7.9 (−9.7 to −6.0)
Placebo	14.9	−6.9 (−8.3 to −5.6)	BTA	−3.5 (−5.4 to −1.7)	−3.1 (−5.7 to −0.6)	−2.7 (−5.7 to 0.2)	−4.5 (−7.0 to −2.0)
			Standard care	−8.9 (−9.1 to −7.2)	−7.5 (−9.1 to −5.8)	−6.5 (−8.2 to −4.7)	−6.3 (−7.6 to −4.9)
Moderate/severe headache days							
BTA	16.1	−4.7 (−5.9 to −3.5)	BTA	−0.5 (−2.4 to 1.4)	−2.4 (−5.4 to 0.6)	−4.3 (−6.9 to −1.7)	−4.2 (−7.1 to −1.4)
			Standard care	−6.7 (−7.9 to −5.5)	−5.9 (−7.6 to −4.2)	−6.1 (−7.7 to −4.4)	−7.4 (−9.2 to −5.6)
Placebo	15.3	−4.9 (−6.2 to −3.6)	BTA	−2.2 (−4.1 to −0.3)	−3.6 (−5.7 to −1.5)	−2.8 (−5.2 to −0.3)	−5.2 (−7.4 to −3.1)
			Standard care	−6.4 (−8.0 to −4.8)	−6.6 (−8.3 to −4.9)	−5.8 (−7.3 to −4.4)	−6.2 (−7.7 to −4.7)
Medication days							
BTA	16.1	−15.7 (−16.9 to 14.5)	BTA	−17.1 (−19.6 to −14.6)	−12.4 (−15.9 to −8.9)	−12.4 (−16.5 to −8.2)	−12.6 (−16.3 to −8.8)
			Standard care	−15.0 (−16.5 to −13.6)	−10.4 (−12.1 to −8.7)	−9.5 (−11.4 to −7.6)	−9.3 (−11.2 to −7.5)
Placebo	15.3	−15.3 (−16.6 to 13.9)	BTA	−16.5 (−18.6 to −14.4)	−9.4 (−12.2 to −6.7)	−9.4 (−12.1 to −6.6)	−10.3 (−12.9 to −7.8)
			Standard care	−14.5 (−16.3 to −12.8)	−9.0 (−10.7 to −7.3)	−7.1 (−8.8 to −5.4)	−8.0 (−9.4 to −6.5)

Shown are the crude data, derived without any modelling. The outcomes are subdivided in the four possible combinations for initial double-blind and subsequent open-label treatment (i.e. BTA + BTA, BTA + standard care, Placebo + BTA, Placebo + Standard care).

[a]Outcomes after 12 weeks are subdivided in the four treatment groups as well, to enable comparison for the open label and follow up phases.

Table 4 Blinding results: assumptions of participants on the received treatment

Assumption	Actually received BTA			Actually received placebo			P-value
	BTA	Placebo	Don't know	BTA	Placebo	Don't know	
At 3 days[a]	29 (33.0)	59 (67.0)	0 (0.0)	29 (33.7)	56 (65.1)	1 (1.2)	0.81
At 12 weeks[b]	29 (38.2)	35 (46.1)	12 (15.8)	30 (37.0)	36 (44.0)	15 (18.8)	0.90

Values are *n* (%).
[a]BTA *n* = 88, placebo *n* = 86.
[b]BTA *n* = 76, placebo *n* = 81.

baseline = 14%) (Detke *et al.*, 2018). In the latter two trials, patients with daily headaches were excluded.

Our study was triggered by the controversy of whether or not BTA is superior to withdrawal and might save patients from experiencing acute withdrawal symptoms (Katsarava *et al.*, 2001; Diener, 2012; Olesen, 2012; Silberstein *et al.*, 2013; Schwedt, 2014; Dougherty and Silberstein, 2015; Chiang *et al.*, 2016; May and Schulte, 2016). Direct double-blind placebo-controlled comparison for all (over)-used medications versus withdrawal is technically impossible. Therefore, we assessed whether add-on therapy BTA would enhance efficacy of acute withdrawal and improve quality of life during withdrawal. However, we failed to find any evidence for additional benefit from BTA on the primary (Fig. 2) or any of secondary endpoints (Table 2 and Fig. 3). Insufficient study power seems an unlikely explanation. The 95% CIs for the treatment differences versus placebo are for nearly all endpoints very narrow. The interval for the primary endpoint (−2.5 to 15.2 percentage point change) does not include our predefined clinically meaningful treatment effect of 20-percentage points (corresponding with four headache days). Of note, our study was powered for detecting even smaller differences than the 30-percentage point treatment effect generally considered the smallest meaningful effect in chronic pain and migraine studies (Ostelo *et al.*, 2008; Silberstein *et al.*, 2008).

Compared to previous studies suggesting efficacy of BTA in chronic migraine (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Jackson *et al.*, 2012; Silberstein *et al.*, 2013), our study shows three important methodological differences that potentially might explain the disparate outcome. First, while in earlier studies participants received two BTA treatment cycles 3 months apart (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Silberstein *et al.*, 2013), in our study participants received only one. We therefore cannot exclude that some participants might have benefitted from a second BTA treatment at 12 weeks. However, considering the only marginal improvement in the 28 BTA non-responders who received open label BTA at 12 weeks (0.9 days; 95% CI: −0.9 to 2.7), we doubt that omission of a second treatment of BTA has materially affected the results.

Second, in our study, unblinding was successfully prevented. This was most likely because of the injection of

low masking doses of BTA in the forehead of placebo-treated participants. As a result, removal of forehead wrinkling was similar in both the placebo and BTA-treated group. Some might argue that doses even as low as 17.5 units BTA might have been effective, thereby nullifying a potential treatment difference from placebo. There is, however, no documented, double-blind, placebo-controlled, evidence for any effect of BTA at doses considerably lower than 155 units, and certainly not with a total dose of as little as 17.5 units (Herd *et al.*, 2018). This dose is even lower than doses used for cosmetic purposes. The therapeutic gain of 155 units BTA versus placebo in the PREEMPT studies was only modest at best (reduction of 1.9 headache days from a baseline of 19 days, i.e. only a 10% better improvement with BTA than with placebo) (Herd *et al.*, 2018). It therefore seems extremely unlikely that a dose of only 17.5 units would have produced any clinically relevant effect. Moreover, the effect of only seven injections of only 2.5 units of BTA each in the forehead (17.5 units) was not inferior compared to currently recommended treatment protocols using 31 injections of 5 units of BTA each (155 units) (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Jackson *et al.*, 2012; Silberstein *et al.*, 2013). If the low dose treatment protocol was indeed effective, the high dose treatment protocol could easily be simplified by drastically reducing the doses and number of injection sites.

Finally, unlike in the PREEMPT and other studies (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; Silberstein *et al.*, 2013), we did not exclude patients with moderate to severe depression or who had no headache-free days as these characteristics are common in chronic migraine (Louter *et al.*, 2014; May and Schulte, 2016; Pijpers *et al.*, 2016). This, combined with the fact that many patients included in the study were directly referred from general practitioners or general neurologists throughout the country, leads us to believe that our study population is more representative for the average patient with chronic migraine and medication overuse.

In conclusion, withdrawal is an efficacious and well-tolerated treatment for patients with chronic migraine and medication overuse. Add-on therapy with BTA did not afford any additional benefit whatsoever, neither on headache frequency nor on quality of life, disability or a range of other outcome measures. The therapeutic gain in

previous BTA trials was only modest and likely positively influenced by unblinding. In the present study, low masking doses of BTA in the forehead successfully prevented unblinding. Before prescribing medications such as BTA, withdrawal should be tried first in patients with chronic migraine and medication overuse. Similarly, emerging and likely expensive new antimigraine medications such as antibodies against CGRP or its receptor (Bigal *et al.*, 2015*b*; Tepper *et al.*, 2017; Detke *et al.*, 2018) should also first be compared against withdrawal. As traditional designs are impossible, a similar add-on design as the one used in the present study might prove useful.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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