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# Prospective real-world analysis of OnabotulinumtoxinA in chronic migraine post-National Institute for Health and Care Excellence UK technology appraisal

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chronic migraine, headache, medication overuse headache, OnabotulinumtoxinA

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**Background and purpose:** The National Institute for Health and Care Excellence (NICE) in the UK recommends the use of OnabotulinumtoxinA (BoNTA, Botox<sup>®</sup>) in the management of chronic migraine (CM) following specific guidelines within the National Health Service. In view of the lack of data on the efficacy of this therapy following implementation of these guidelines in clinical practice and on the evaluation of guidance compliance, we aimed to evaluate the effectiveness and safety of BoNTA in patients with CM following the NICE guidelines.

**Methods:** This was a prospective real-life audit study.

**Results:** After two treatments, 127 of 200 patients (63.5%) obtained at least a 30% reduction in headache days. Those who continued the treatment up to 3 years reported a stable beneficial effect compared with baseline. Amongst responders, 68 patients (53.5%) were reclassified as episodic migraineurs. A total of 57 of these patients (83.8%) converted to an episodic migraine pattern at 6-month follow-up. The majority of those whose migraine became episodic after BoNTA extended the treatment intervals beyond 3 months (range 4–8 months) before noticing any worsening of headache. We observed no significant differences in the efficacy measures in patients treated with 155 U BoNTA compared with those treated with >155 U BoNTA.

**Conclusions:** When administered according to the NICE guidance, BoNTA produced a clinically meaningful effect in the long-term management of CM with and without medication overuse headache. Treatment discontinuation when CM becomes episodic may be useful in clinical practice to identify those who may benefit from extended treatment intervals. Our clinical experience indicates a lack of additional benefit from using the 'follow-the-pain' paradigm.

## Introduction

Chronic migraine (CM) affects 1.4–2.2% of the general population and is ranked amongst the most disabling medical conditions [1–3]. It significantly affects the patient's quality of life and is associated with a

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substantial socioeconomic burden [4]. A broad arsenal of non-specific pharmacological prophylactic treatments is available in clinical practice, although robust evidence exists only for topiramate and OnabotulinumtoxinA (BoNTA) [5,6]. The adherence to oral preventive medicines is often poor, mainly due to side effects, leading to high rates of drug discontinuation [7,8]. CM sufferers often rely on excessive consumption of abortive medicines, leading to the development of medication overuse headache (MOH) [9], a very

common chronification factor in migraine sufferers, which interferes with the full potential effect of concomitant prophylactic treatments [10].

The management of CM has advanced since the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) programme that demonstrated evidence of efficacy, improvement of quality of life, safety and tolerability of BoNTA (Botox®) as a preventive treatment in adults with CM for up to 52 weeks [11–13]. Additionally, patients with CM with MOH benefited from the BoNTA therapy, similarly to those patients without MOH [14]. The PREEMPT administration protocol of BoNTA recommends a fixed-site, fixed-dose (155 U) paradigm of 31 intramuscular injections given across seven specific head/neck muscle areas. Additional injections of up to 40 U of BoNTA can be administered into additional sites according to the ‘follow-the-pain’ protocol [15].

Based on this evidence, the National Institute for Health and Care Excellence (NICE) in the UK produced guidance to regulate the use of BoNTA on the National Health Service for the prevention of CM in adult subjects. The guidance recommends BoNTA for subjects with CM who have failed at least three different established preventives and have undergone appropriate medication overuse management when required. Two courses of BoNTA (3 months apart) is the recommended cut-off number of treatments before assessing outcomes. The NICE Committee also recommended that the therapy should be discontinued if patients do not achieve at least a 30% reduction in headache days (negative stopping criterion) after two treatments or if their CM pattern reverts into episodic for three consecutive months (positive stopping criterion) [16]. In any other cases the treatment could be continued at 3-monthly intervals.

OnabotulinumtoxinA is currently the only NICE-recommended treatment for the management of CM. No studies have hitherto assessed the outcome of implementing this guidance in a ‘real-world’ clinical setting. We report here the outcomes of a clinical audit that was designed to prospectively document the clinical outcomes of adopting NICE guidelines for the use of BoNTA in a tertiary headache centre.

## Methods

The full methodological description can be found online (Data S1 [17]). In summary, this was a prospective audit of outcome at the Headache Centre of the Guy’s and St Thomas’ NHS Foundation Trust, London, UK between May 2013 and December 2016. Patients with CM with and without MOH who failed to respond to or tolerate at least three trials of

pharmacological preventive medications given for a sufficient period of time and at therapeutic dosages were considered for this audit. Completion of our headache diary and Headache Impact Test-6 (HIT-6) score at baseline and through the treatment period was a requirement for audit inclusion. This audit did not require ethics approval. All patients gave written informed consent for the treatment. As per NICE guidance, the change in headache days from baseline was the primary efficacy measure of the audit. A patient was classified as a responder if they demonstrated a minimum of a 30% reduction of the number of headache days after two treatments with BoNTA.

## Results

### Demographic and baseline headache characteristics

A total of 243 patients with CM received at least two treatments of BoNTA injections. A total of 200 patients with CM [158 females; mean age ( $\pm$ SD), 46 ( $\pm$ 12) years] who received at least two treatments of BoNTA injections (total number of treatments, 1176) were included in the subsequent analysis. We could not identify full data in the form of diaries and HIT-6 questionnaires in 43 patients and hence we excluded them from this analysis. Baseline demographic and clinical characteristics of our patients are shown in Table 1.

### Outcomes of OnabotulinumtoxinA treatment after two treatments

A total of 127 of the 200 patients (63.5%) treated with two BoNTA treatments obtained at least a 30% reduction in headache days at 6 months follow-up. After two treatments, a median reduction of headache

**Table 1** Demographic and clinical characteristics at baseline of 200 patients with chronic migraine (CM) treated with OnabotulinumtoxinA

	Total no. of patients
Sex (M/F)	42/158
Age (years)	46 $\pm$ 11.9
CM duration (years)	5.9 $\pm$ 5.0
Aura	56 (29%)
Medication overuse	89 (46%)
	Median (IQR)
Headache days	24 (18–30)
Migraine days	13 (9–19)
Headache-free days	0 (0–6)
Abortive treatment intake days	9 (2–16)
HIT-6 score	70 (65–72)

F, female; HIT-6, Headache Impact Test-6; IQR, interquartile range; M, male. Data are given as mean  $\pm$  SD or *n* (%).

days from 24 to 11.3 ( $P < 0.001$ ,  $Z = -10.2$ ), a median reduction of migraine days from 13 to 5.7 ( $P < 0.001$ ,  $Z = -9.1$ ) and a median increase of headache-free days to 11 ( $P < 0.001$ ,  $Z = -9.7$ ) was observed (Table 2). Abortive treatment intake days were reduced from 9 to 5 ( $P < 0.001$ ,  $Z = -6.7$ ). Additionally, the HIT-6 score was significantly reduced from 70 to 65 ( $P < 0.001$ ,  $Z = -9.7$ ) compared with baseline (Table 2). All responders agreed to continue receiving BoNTA treatment.

### Comparison between first (3 months) and second (6 months) OnabotulinumtoxinA treatments

Changes in the efficacy outcomes considered after the first (3 months follow-up) and second (6 months follow-up) treatments are outlined in Table 2. We observed a statistically significant improvement in all outcomes after the first treatment compared with baseline. There were no statistically significant differences in the efficacy outcomes between the first and second BoNTA treatment. The 30% response rate after the first treatment was 62% ( $n = 124/200$  patients). Three patients (1.5%) who were not responders at 3 months became responders after the second treatment.

### Comparison of patients with and without medication overuse headache at 6 months

Patients with CM and MOH ( $n = 89$ , 44.5%) displayed a significantly higher number of migraine days [median, 13; interquartile range (IQR), 8–18] compared with patients with CM without MOH ( $n = 111$ ; median, 9; IQR, 8–15;  $P < 0.025$ ,  $Z = -2.8$ ) and, as expected, a higher number of abortive treatment intake days (median, 16; IQR, 12–26) compared with patients with CM without MOH (median, 5.5; IQR, 0–9;  $P < 0.001$ ,

**Table 2** Clinical characteristics at baseline, 3 and 6 months of 200 patients with chronic migraine treated with OnabotulinumtoxinA

	Baseline	3 months (1 <sup>st</sup> treatment)	6 months (2 <sup>nd</sup> treatment)
Headache days	24.0 (18–30)	12.0 (7–19)*	11.3 (6.3–18)*
Migraine days	13.0 (9–19)	5.7 (1.3–10.7)*	5.0 (1.3–9.42)*
Headache-free days	0 (0–6)	11.0 (0–18)*	12.8 (0.6–20)*
Abortive treatment intake days	9.0 (2–16)	5.3 (2–10)*	5.0 (1–9.7)*
HIT-6 score	70 (65–72)	66 (60–69)*	64 (60–68)*
No. of responders	–	124 (62%)	127 (63.5%)

HIT-6, Headache Impact Test-6; IQR, interquartile range. \* $P < 0.025$  compared with baseline. Data are given as median (interquartile range) and  $n$  (%).

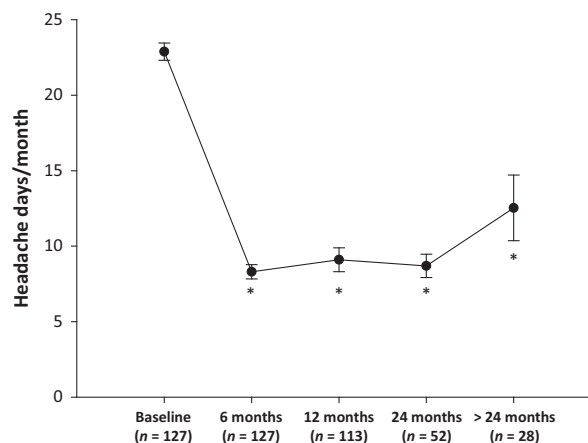
$Z = -9.1$ ). No significant difference was found in the number of headache days ( $P = 0.1$ ,  $Z = -1.6$ ), number of headache-free days ( $P = 0.77$ ,  $Z = -0.3$ ) and HIT-6 score ( $P = 0.7$ ,  $Z = -0.4$ ) at baseline between the two groups. At 6 months follow-up (after two BoNTA treatments), both groups demonstrated a statistically significant reduction for all efficacy outcomes examined (Fig. S1). A total of 72 patients with CM without MOH (64.9%), compared with 50 patients with CM with MOH (56.2%), obtained at least a 30% reduction in headache days after two BoNTA treatments. Of the 89 patients with MOH, 37 (41.6%) continued to overuse medications after two BoNTA treatments.

### Negative stopping criterion at 6 months: treatment discontinuation

At the 6-month assessment, 73 of 200 patients (36.5%) obtained <30% reduction in headache days (median reduction to 20.8 headache days; IQR, 11.3–28) and hence treatment was discontinued. Moreover, non-responders demonstrated no significant reduction in migraine days (median, 8; IQR, 4–13.5) from baseline.

### Long-term outcomes of OnabotulinumtoxinA

Of the 127 patients who responded to BoNTA treatment after two treatments, 113 patients received at least five treatments (1 year follow-up), 52 received at least eight treatments (2 years follow-up) and 28 patients completed at least 13 treatments (>3 years follow-up) at the time of the data analysis. Figure 1 shows the long-term changes in headache days from baseline for those who continued the treatment over two treatments. Table 3 summarizes the change in all



**Figure 1** Long-term outcomes of OnabotulinumtoxinA treatment at 6, 12, 24 and >24 months (mean  $\pm$  SD). \* $P < 0.025$  compared with baseline.

**Table 3** Clinical characteristics of patients with chronic migraine at baseline, 6, 12, 24 and >36 months of patients with chronic migraine who responded to and received long-term treatment with OnabotulinumtoxinA

	Baseline (n = 127)	6 months (n = 127)	12 months (n = 113)	24 months (n = 52)	36 months (n = 28)
Headache days	23 (17–30)	8 (5–11)	8 (2–12)	8 (5–11.3)	11 (9–16)
Migraine days	13 (9–18)	4 (0.5–7.75)	3 (0–8)	4 (0–8)	8 (4–9)
Abortive treatment intake days	10 (4–16)	4 (0–7.3)	4 (0–9)	3 (3.3–18.8)	5 (2–7)
Headache-free days	0 (0–5)	17.3 (7.5–22)	16.5 (3.8–22)	20.3 (10.7–22)	18.8 (12.3–22.3)
HIT-6 score	70 (66–72)	64 (57.3–68)	63 (54–67.8)	62 (56.5–66)	66 (60–69.5)

HIT-6, Headache Impact Test-6. Data are given as median (interquartile range).

efficacy measures from baseline to the last treatment for those who continued the treatment over 6 months. There was a sustained significant decrease in number of headache days, migraine days, abortive treatment intake days and HIT-6 score, and a sustained increase in headache-free days at 12 and 24 months. The overall effectiveness of the therapy was maintained at least up to 36 months compared with baseline.

#### Positive stopping criterion: conversion to episodic migraine pattern

At 6-month follow-up or at any later stage of the treatment, patients whose headache reverted into an episodic migraine pattern were asked to delay the subsequent BoNTA treatment until they documented at least 15 moderate to severe headache days on the headache diary. Figure 2 summarizes the outcome of patients in whom the positive stopping criterion was applied. A total of 34% of patients (68/200) were reclassified as episodic migraineurs following BoNTA treatment. In the vast majority of these patients (83.8%), the conversion from chronic to episodic migraine occurred after two BoNTA treatments. Treatment was temporarily discontinued in 54 of 68 patients who reverted to episodic pattern (79.4%). The remaining 14 patients were not willing to discontinue the treatment mainly due to an initial worsening towards the end of the third month and they were concerned about further headache worsening if treatment was delayed. Of those in whom the treatment was temporarily discontinued, 20.3% relapsed into a chronic pattern after 6 months and hence subsequent treatments were scheduled at 3-month intervals. Five patients (9.3%) discontinued the treatment after they remained episodic for 12 months without receiving any BoNTA injections and 70.3% maintained an episodic pattern with BoNTA treatment performed every 4–8 months.

#### Dose–response analysis

Of the 200 patients included in this analysis, 97 patients received 155 U (fixed-site, fixed-dose paradigm) and

103 patients received >155 U (follow-the-pain protocol) BoNTA per treatment; the latter group received an average of 177 U per treatment. We observed no significant difference between the two groups in terms of responder rates, i.e. 67% of patients treated with 155 U obtained at least a 30% reduction in headache days compared with 59% of those treated with >155 U ( $P > 0.025$ ). Furthermore, no significant differences were observed between the two groups in any of the other efficacy outcomes examined at 6 months (Fig. S2) and at the last follow-up treatment.

#### Safety and tolerability

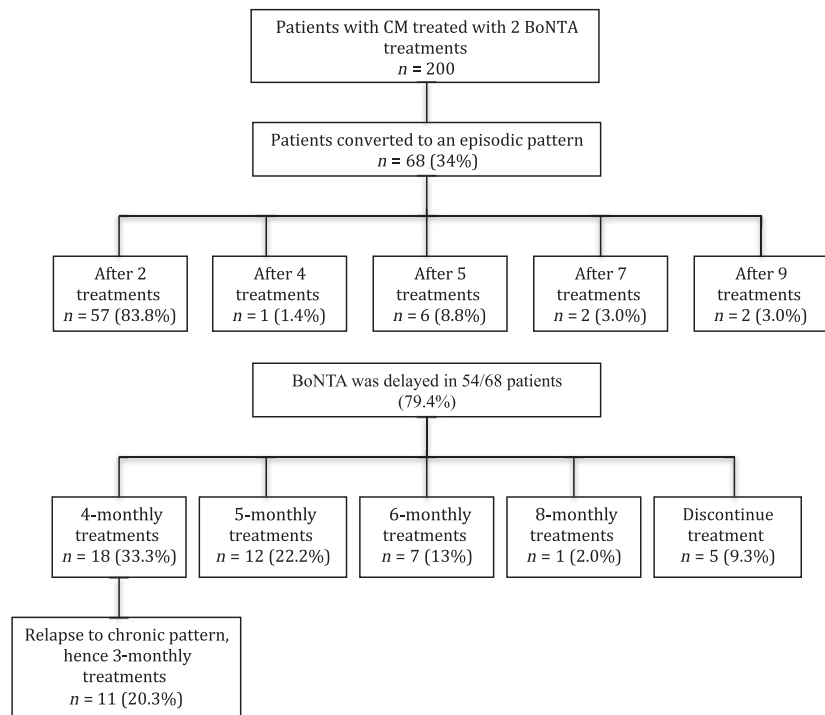
The adverse events shown in Table 4 were observed in the whole cohort of our BoNTA-treated patients (Table 4). All of the adverse effects were transient and described as mild or moderate in severity by patients. None of the patients who responded to BoNTA treatment discontinued due to side effects.

### Discussion

This is the first large prospective study on patients with CM treated with BoNTA following the NICE guidelines in a real-world setting. These findings are relevant for specialist headache clinics in the UK but also for headache clinics in European countries that administer BoNTA following recommendations similar to the NICE guidance. Given the nature of the audit, its limitations include the open-label design and the fact that other acute and preventive therapies may have changed over time, potentially interfering with the outcome of BoNTA. However, given that randomized controlled trials had already been published, our aim was to produce real-world evidence within a National Health Service setting.

#### Outcome measures

Two-thirds of patients who received two BoNTA treatments 3 months apart obtained at least a 30% reduction in headache days per month. Most responders



**Figure 2** Chronic to episodic migraine conversion pattern and rate of delayed treatments in patients with episodic migraine.

benefit from the first BoNTA treatment, but a small number of patients may still respond after the second treatment. Although a 50% reduction in headache days is a common definition for responders to a headache treatment in clinical trials, the choice of the cut-off of 30% in headache day reduction as per NICE guidelines seems to be a clinically relevant outcome measure that allows the majority of patients treated to benefit from treatment continuation. Importantly, a cut-off of 30%, rather than 50%, reduces the proportion of patients who, having failed four classes of medications, could be left with no further treatment options, in view of the paucity of effective evidence-based treatments for refractory CM at present. However, recent evidence coming from a multicentre prospective study showed an increased proportion of patients reporting a 50% improvement in migraine after 12 months of treatment compared with the first treatment, particularly in those with a disorder duration of <12 months. These findings suggest that starting treatment with BoNTA in the early phase of the disorder and continuing the treatment for 1 year before assessing its outcome may ensure that as many as 80% of patients obtain meaningful benefits [18]. It is therefore conceivable that, by applying the NICE guidance, a small proportion of patients who otherwise would have benefited from a prolonged treatment with BoNTA have been precluded from achieving a relevant response to therapy.

Change in 'headache days' as the sole efficacy outcome by NICE has been challenged in an open-label

pre-NICE technology appraisal study where 455 treatments were given to 254 patients. The authors reported at least a 30% reduction in headache days in only 46.5% of their patients and suggested that using other outcomes, such as change in migraine days and headache-free days, may be more appropriate [19]. However, the internationally accepted definition of a headache day as a moderate headache ( $\geq 4$  on a numerical rating scale) lasting for at least 4 h if not treated incorporates migraine or probable migraine days in patients with CM. In this audit, responders according to the NICE criteria also displayed a meaningful reduction in migraine days and an increase in headache-free days, suggesting that the use of change in 'headache days' is a clinically relevant outcome measure for BoNTA treatment.

The reduction in headache days after BoNTA treatment led to a clinically relevant improvement of headache-related quality of life according to the HIT-6 score. According to the PREEMPT data, at the end of a 1-year treatment with BoNTA, despite 70% of participants obtaining a 50% reduction in headache days, 63% of them displayed a lower HIT-6 score, which was still within the category of severe disability ( $\geq 60$ ). Similarly, in our audit, the reduction in headache days of at least 30% showed by two-thirds of patients corresponded to an average reduction in the HIT-6 score that still fell within the category of severe disability. The high headache-related disability score of our patients at baseline may explain the discrepancy

**Table 4** Adverse events following any treatment with OnabotulinumtoxinA

Adverse event observed	No. of patients (%)
Ptosis (mild/moderate)	14 (7.0)
Neck weakness or pain	2 (1.0)
Swallowing difficulties	1 (0.5)
Allergic reaction	1 (0.5)
Vaso-vagal episode during injection	1 (0.5)
Others	8 (4.0)

between the reduction in headache days and HIT-6 score, highlighting the complexity of assessing meaningful changes in headache-related quality of life in patients with CM. Although the NICE guidelines do not suggest assessing patients' quality of life, headache disability questionnaires remain a valuable clinical tool for identifying patients in whom improvements in clinical measures do not translate into improvement in their headache-related disability. These patients may benefit from a reappraisal of their management options.

#### OnabotulinumtoxinA and medication overuse

The NICE guidelines recommend that medication overuse should be managed before offering BoNTA treatment, despite the PREEMPT studies demonstrating similar efficacy of BoNTA in patients with CM and in CM with acute medication overuse. In line with other studies, our results showed that, in some cases, BoNTA therapy facilitates medication reduction in patients with MOH who were previously unable or unwilling to reduce their analgesic medications and BoNTA is equally effective in patients with and without MOH [9,20]. Our study further supports its role as a treatment option in CM with MOH.

#### Long-term effect of OnabotulinumtoxinA

To date, no other data are available on the long-term outcome of patients with CM who become episodic after BoNTA treatment administered according to the NICE guidelines. In this audit, approximately one-third of patients' CM reverted into an episodic pattern mostly after two BoNTA treatments. Of those in whom the treatment was discontinued, 9% remained episodic for 12 months without receiving any further BoNTA treatment. A total of 20% of patients in whom treatment was discontinued relapsed into a chronic pattern after 4 months and hence BoNTA treatment was resumed, with subsequent treatments maintained every 3 months. The remaining patients maintained an episodic pattern with BoNTA treatment performed every 4–8 months. These outcomes suggest

the importance of temporarily discontinuing BoNTA treatment in patients who become episodic and may not need 3-monthly treatments in the long term. However, applying the positive stopping criterion in clinical practice can be challenging and may not be best practice in every case given the difficulty of restarting the treatment promptly after recurrence of a CM pattern.

Regardless of the length of the treatment intervals, patients who continued BoNTA therapy were followed up for over 3 years, providing the first data on long-term efficacy and safety of BoNTA following the NICE guidelines. Our long-term analysis displayed a pattern characterized by an initial dramatic improvement in the headache efficacy measures, followed by a plateau and a subsequent mild headache worsening, the latter possibly caused by the delayed subsequent treatments imposed by our guidelines in those who became episodic during BoNTA treatment. This fluctuating response over time is in contrast to the long-term outcome of most of the real-life studies. However, in these studies, BoNTA was never temporarily discontinued, meaning that all patients received 3-monthly BoNTA for the duration of the studies [18,20,21]. Although the latter approach may lead to a more homogeneous improvement over time, it prevents the identification of those patients who may benefit from longer treatment intervals, requiring fewer treatments overall per annum.

#### 'Fixed-site, fixed-dose' and 'follow-the-pain' injection paradigms

The NICE guidelines do not provide any indication on the number of BoNTA units. Our audit showed that the 'follow-the-pain' paradigm might not offer additional benefits compared with the standard dose paradigm. However, given that our patients were treated by more than one practitioner and that the injection dose was based on their clinical judgement, it is difficult to draw robust conclusion from our data. It should be noted, however, that one study suggested that the use of 195 U is more efficacious than 155 U in MOH [21]. It is possible that consistent use of 195 U may produce better outcomes compared with our average dose of 177 U.

### Conclusions

This audit demonstrated that using the 30% reduction in headache days outcome after two BoNTA treatments is a meaningful efficacy measure in patients with CM and patients with CM with MOH. The application of the positive stopping criterion revealed that approximately one-third of patients become episodic at some stage of their treatment with BoNTA

and that the vast majority of those whose migraine reverts into an episodic pattern can extend the treatment intervals over the established 3 months. Furthermore, we observed the long-lasting safety and efficacy of BoNTA over a 3-year follow-up period. Finally, our data seem not to support any additional benefit from using the 'follow-the-pain' paradigm, suggesting that injection of 155 U may be sufficient to achieve meaningful outcomes in clinical practice.

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### Disclosure of conflicts of interest

All authors have completed the ICMJE uniform disclosure and declare financial support for the purpose of developing the electronic BoNTA database for data collection and analysis from Allergan. A.P.A. has received honoraria from Allergan for consultancies and for delivering educational presentations, and a research grant from eNeura. M.T., A.A.-K., M.M., S.P., C.F.

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### Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Comparison following two OnabotulinumtoxinA treatments (6 months follow-up) for patients with and without medication overuse headache for (a) headache days per month; (b) migraine days per month; (c) Headache Impact Test-6 score; (d) Headache-free days per month and (e) number of days per month that patients consumed any abortive treatment.

**Figure S2.** Comparison between patients who received the standard treatment protocol (155 U) and follow-the-pain protocol (average dose 177 U) after two treatments of OnabotulinumtoxinA (6 months follow-up). (a) Headache days per month; (b) migraine days per month; (c) Headache Impact Test-6 score; (d) headache-free days; (e) number of days per month that patients consumed any abortive treatment.

**Data S1.** Methods



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