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Botulinum toxin in the management of chronic migraine: clinical evidence and experience

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Abstract: Chronic migraine (CM) is a severely disabling neurological condition characterized by episodes of pulsating unilateral or bilateral headache. The United States Food and Drug Administration (FDA) approved onabotulinumtoxinA (Botox®) for the prophylactic treatment of CM in 2010. It has been shown that onabotulinumtoxinA is effective in the reduction of headache frequency and severity in patients with CM. Treatment is well tolerated by the patients. This review reports on the history of botulinum neurotoxin (BoNT) in CM and presents the current clinical evidence for the use of onabotulinumtoxinA in the treatment of CM.

Keywords: Botox®, botulinum neurotoxin, chronic daily headache, chronic migraine, onabotulinumtoxinA

Introduction

Migraine is a common neurological disorder featuring recurrent attacks of headache. Typical migraine attacks last for 4–72 h and involve headaches of the following characteristics: pulsating quality, unilateral location, moderate or severe intensity and aggravation by routine physical activity. Attacks can be accompanied with nausea, vomiting, photophobia and phonophobia [Headache Classification Committee of the International Headache Society, 2013].

As stated by the International Headache Society (IHS) classification, migraine has two major subtypes: migraine without aura and migraine with aura. Aura symptoms are focal, neurological symptoms usually occurring prior to or sometimes during a migraine attack. They are fully reversible and last for 5–60 min. It is possible that patients suffer from migraine attacks both without and with aura.

More relevant to clinical practice is the distinction between episodic migraine (EM) and chronic migraine (CM). Although not mentioned in the IHS Classification, the term EM is quite common in scientific literature and among clinicians. It refers to patients, who suffer from migraine attacks, but miss the criteria for CM.

CM originally described a migraine headache present on at least 15 days per month for more than 3 months. According to the 2nd edition of the IHS classification, the diagnosis of CM could only be applied in patients without medication overuse [Headache Classification Subcommittee of the IHS, 2004]. Because only very few patients met these strict criteria, the IHS revised its definition for CM. The new definition was published in 2006 [Olesen *et al.* 2006] and finally incorporated in the 3rd edition of the International Classification of Headache disorders in 2013. According to the revised criteria CM is currently defined as a headache occurring on at least 15 days per month for more than 3 months, with typical features of migraine on at least 8 days per month. Medication overuse no longer excludes the diagnosis of CM [Headache Classification Committee of the IHS, 2013].

Epidemiology

A review of international studies on the epidemiology of CM presents a wide range of prevalence figures [Natoli *et al.* 2010]. Depending on the definition used and the population studied these numbers range from 0% [Rasmussen *et al.* 1991] to 5.1% [Queiroz *et al.* 2006]. More recent studies using the current IHS definition report a

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prevalence of 0.91% in the US population [Buse *et al.* 2012] and 0.5% in the German population [Katsarava *et al.* 2011]. Several studies in the general population and in patients with CM show that women are more likely to be affected by CM than men [Aurora *et al.* 2011; Blumenfeld *et al.* 2010; Diener *et al.* 2007]. Adjusted prevalence increases for both women and men from adolescence to midlife and declines after the fifth decade of life. In the population subgroup with the highest adjusted prevalence of CM (women between age 40–49) 1.89% are affected by CM [Buse *et al.* 2012].

In recent years, various studies investigated differences between episodic and chronic migraineurs. Compared with episodic migraineurs, patients with CM are at risk of a wide range of comorbid conditions such as asthma, chronic obstructive pulmonary disease, obesity, heart disease, stroke, depression and anxiety [Buse, 2010]. Due to the high frequency of migraine attacks, medication overuse is highly common among chronic migraineurs. Interventional studies in patients with CM found rates of 40.9% [Cernuda-Morollón *et al.* 2014] to 50.4% [Khalil *et al.* 2014] for medication overuse.

Socioeconomic status is reduced in patients with CM compared with those with less frequent headache. They have a lower annual income, are less likely to be employed part or full time and more likely to be occupationally disabled [Adams *et al.* 2015; Buse *et al.* 2010]. Patients with CM require more primary care visits, specialist visits, emergency room visits and are hospitalized more often. Unsurprisingly, CM has an enormous negative impact on quality of life [Blumenfeld *et al.* 2011; Wang *et al.* 2013].

Management and pharmacologic treatment

Diagnosis of CM is based on the patient's history (including a headache diary) and neurological examination. In some patients, cerebral magnetic resonance imaging and lumbar puncture might be necessary in order to rule out secondary causes for headaches [Diener *et al.* 2015].

The main goal in the treatment of CM is to reduce the impact of migraine on patients' lives. Therefore, it is necessary to keep migraine attacks as rare, short and as less-impairing as possible. Various nonpharmacological measures are useful to prevent migraine attacks: trigger avoidance (caffeine, alcohol, stress), dealing with risk factors (losing weight, modify response to stressors, getting sufficient sleep) [Schwedt, 2014].

Pharmacological treatment of CM is based on two pillars: abortive treatment of acute migraine attacks and prophylactic treatment. The substances most commonly used for the abortion of migraine attacks are nonsteroidal anti-inflammatory drugs (NSAIDs) and triptanes. There is good clinical evidence, that both substance groups are effective in the abortive treatment of acute migraine attacks. On the other hand, it has been shown, that both NSAIDs and triptanes may lead to medication overuse headaches. Therefore, the challenge is to restrict migraine-abortive substances to the least amount necessary. This observation highlights the special importance of prophylactic treatment in patients with CM. Generally, prophylactic medication can be given as soon as the diagnosis of CM is established. The choice of which substance is applied should be made with regard to the patient's comorbidities [Straube *et al.* 2012].

Because most clinical studies focused on EM, studies on prophylactic treatment of CM are scarce. The substances, which have been studied in patients with CM specifically, are: valproate [Yurekli *et al.* 2008], amitriptyline [Couch and Amitriptyline *versus* Placebo Study Group, 2011], gabapentin [Spira *et al.* 2003], topiramate [Diener *et al.* 2007; Silberstein *et al.* 2007; Silvestrini *et al.* 2003] and onabotulinumtoxinA. The latter one is the only substance approved by the United States Food and Drug Administration (FDA) for prophylactic treatment of CM. Guidelines of the American Academy of Neurology state that onabotulinumtoxinA is effective and should be offered to patients with CM [Simpson *et al.* 2016].

In the UK the National Institute for Health and Care Excellence (NICE) recommends onabotulinumtoxinA as a prophylactic treatment for CM in patients who did not respond to at least three prior pharmacologic prophylaxis therapies and whose condition is appropriately managed for medication overuse. According to NICE criteria, treatment with onabotulinumtoxinA should be stopped when patients do not respond to treatment adequately (defined as a reduction of monthly headache days of $<30\%$) or when the patient's condition changes to EM (defined as a

headache on <15 days per month in three consecutive months) [NICE, 2012].

Mode of action of botulinum neurotoxin

Botulinum neurotoxin (BoNT) is a protein complex produced by the Gram-positive, anaerobic bacterium *Clostridium botulinum*. There are at least seven different BoNT serotypes, of which only two are currently in clinical use: BoNT serotype A and BoNT serotype B [Bigalke, 2013].

After intramuscular or subcutaneous injection BoNT is internalized into peripheral motor neurons *via* SV2 binding protein [Mahrhold *et al.* 2006]. Once translocated into the cytosol, BoNT enzymatically cleaves the 25 kDa synaptosomal-associated protein (SNAP-25), a protein, which mediates the fusion of neurotransmitter-containing vesicles with the cell membrane. Through this mechanism, BoNT inhibits the release of neurotransmitters from presynaptic nerve endings [Rummel, 2015]. This effect has been best studied for the suppression of acetylcholine release at the neuromuscular junction. However, more recent studies show that BoNT also modifies the release of neurotransmitters, which are relevant in the transduction of pain such as substance P [Purkiss *et al.* 2000; Welch *et al.* 2000] or calcitonin gene-related peptide (GCRP) [Durham *et al.* 2004]. It is supposed that the inhibition of peripheral sensitization leads to an indirect inhibition of central sensitization and thus is a possible mechanism for the efficacy of BoNT in chronic pain [Aoki, 2003]. On the contrary, animal-model studies support the view, that there is a site for BoNT in the central nervous system, although the mechanisms of a central antinociceptive action of BoNT remain unclear [Matak and Lacković, 2014]. Research in this field is complicated by the absence of a widely accepted pathophysiological model for CM.

Clinical evidence

OnabotulinumtoxinA (Botox®)

The analgesic effects of BoNT were observed 30 years ago in patients with *Torticollis spasmodicus* [Tsui *et al.* 1986]. This observation was attributed to the myorelaxant effects of BoNT. The first evidence for an effect of BoNT on migraine was found in patients who were treated with BoNT for hyperfunctional lines of the face. The first open-label, nonrandomized study enrolled a total of 106 patients. Of these 106 patients, 77 patients were classified as true migraineurs according to IHS criteria and received prophylactic treatment with onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, California, USA). Therapeutic benefit was measured by patients' self-reports. A total of 51% of the patients classified as having true migraine reported a complete response and 28%, a partial response [Binder *et al.* 2000].

The first placebo-controlled, double-blind study in migraine patients (2–8 migraine attacks per month) was carried out in the year 2000 with 123 patients. Participants were randomized into three groups and treated with either placebo, 25 or 75 mouse units (MU) onabotulinumtoxinA. The treatment with 25 MU onabotulinumtoxinA was found to be superior to placebo in the reduction of the number of monthly migraine attacks, whereas no differences could be identified between the 75 MU group and the placebo group [Silberstein *et al.* 2000].

In the following years, several subsequent studies failed to demonstrate positive effects on EM [Jackson *et al.* 2012] and tension headaches [Gaul *et al.* 2016]. For CM the results from controlled clinical trials were inconsistent.

In a placebo-controlled study conducted in 58 patients with chronic daily headache (CDH), onabotulinumtoxinA tended to improve the number of headache days in a 12-week period after injection, but missed the criteria for statistical significance [Ondo *et al.* 2004]. A multicentre study with 279 patients with CDH (three injection cycles) showed, that onabotulinumtoxinA increased the number of headache-free days in a 30-day period, but again differences between placebo and *verum* group were not statistically significant [Mathew *et al.* 2005]. A subgroup analysis of 228 patients without prophylactic medication at the date of study enrolment found a statistically significant difference in the number of headaches in a 30-day period. So the authors concluded that onabotulinumtoxinA was effective in the treatment of patients with CDH who do not receive other prophylactic medication [Dodick *et al.* 2005]. In another multicentre study 702 patients with CDH received three injection cycles with placebo or 75,175 or 225 MU onabotulinumtoxinA for 9 months. All groups responded to treatment, but the response was not superior to placebo [Silberstein *et al.* 2005]. In 2007, a small, but

double-blinded and placebo-controlled study with 32 participants failed to demonstrate a benefit for onabotulinumtoxinA in the prophylactic treatment of CM [Vo *et al.* 2007]. Freitag and colleagues treated 86 CM patients without medication overuse and found a statistically significant effect for onabotulinumtoxinA in the reduction of migraine episodes [Freitag *et al.* 2007]. An Italian double-blind study with 68 patients with CM found no difference between onabotulinumtoxinA and placebo in the reduction of headache days, but was able to show, that treatment with onabotulinumtoxinA reduced the consumption of acute pain medication [Sandrini *et al.* 2011].

The breakthrough of onabotulinumtoxinA in the treatment of CM came in 2010, when the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study group published the results of the PREEMPT I and PREEMPT II trial, in which a total of 1384 Patients were enrolled into both trials (PREEMPT I: 679, PREEMPT II: 705). Both studies consisted of a 28-day baseline screening period, a 24-week double-blind, parallel-group, placebo-controlled phase (two injection cycles) and a 32-week open-label phase (three injection cycles). This pair of two multicentre randomized, placebo-controlled studies had an identical study design, but different endpoints.

In the PREEMPT I trial the primary endpoint reduction of migraine episodes was missed, but significant differences between the *verum* group and the placebo group were seen in the reduction of headache days and migraine days [Aurora *et al.* 2010]. The PREEMPT II trial confirmed the efficacy of onabotulinumtoxinA in the reduction of headache days as a primary endpoint [Diener *et al.* 2010].

Until now there were only two studies comparing onabotulinumtoxinA with other drugs effective in the prophylactic treatment of CM. Magalhães and colleagues showed, that onabotulinumtoxinA was as effective as amitriptyline in the prophylactic treatment of CM [Magalhães *et al.* 2010], Cady and colleagues compared onabotulinumtoxinA with topiramate and found similar efficacy for the prophylactic treatment of CM [Cady *et al.* 2011]. Taking all evidence into consideration a meta-analysis stated in 2012, that Botulinum toxin A compared with placebo was associated with a small-to-moderate benefit for CM and CDH [Jackson *et al.* 2012].

The positive results of the two PREEMPT trials led to the approval of onabotulinumtoxinA for the treatment of CM in September 2011 by the US FDA and subsequently many other registration authorities worldwide. After approval, various studies in real-life settings have been published on the use of onabotulinumtoxinA in CM. The results of these studies confirm the efficacy of onabotulinumtoxinA in CM [Cernuda-Morollón *et al.* 2014; Khalil *et al.* 2014; Negro *et al.* 2015; Russo *et al.* 2016].

Because medication overuse is a major problem in CM patients, a separate view on this subgroup of patients might be helpful. Pooled data of both PREEMPT studies reveal that onabotulinumtoxinA is effective in the reduction of headache days in CM patients with concomitant medication overuse [Silberstein *et al.* 2013]. In a prospective study no difference between CM patients with medication overuse and CM patients without medication overuse could be found in terms of efficacy of onabotulinumtoxinA [Ahmed *et al.* 2015]. There might be indications that in CM patients with concomitant medication overuse, treatment with 195 MU is superior to treatment with 155 MU in the reduction of headache days, migraine days and days with medication intake [Negro *et al.* 2015].

Beside its effects on headache frequency and severity treatment with onabotulinumtoxinA also improves quality of life in Patients with CM. In the PREEMPT studies patients treated with onabotulinumtoxinA had a significant higher quality of life throughout the double-blind phase [Lipton *et al.* 2011] and the open-label phase [Lipton *et al.* 2016].

Recently, a study from our centre confirmed these findings in a long-term real-life setting [Kollewe *et al.* 2016]. In this open-label study, 27 patients with CM received at least four injection cycles of onabotulinumtoxinA according to the PREEMPT injection paradigm. Monthly headache days, migraine days, days with nausea/vomiting and days with intake of pain medication were significantly reduced after the first treatment and this effect was stable throughout the entire study period. Furthermore, health-related quality of life and migraine-related quality of life improved after treatment with onabotulinumtoxinA. Patients were also screened for depression before the beginning of treatment and six weeks after every injection. Over the course of treatment patients had a significant decrease in depressive

symptoms. In contrast with most of the studies mentioned previously, patients with severe depression were allowed to participate in this study. Theoretically the improvement of depression might be caused by the additional antidepressive action of BoNT [Finzi and Rosenthal, 2014; Magid *et al.* 2014; Wollmer *et al.* 2012].

In all of these studies a certain number of patients did not respond to treatment with onabotulinumtoxinA. Up to 10% of patients might be concerned with treatment failure during long-term treatment [Cernuda-Morollón *et al.* 2014]. Currently the development of antibodies, an intrinsic worsening of migraine or an initial placebo effect are discussed as reasons for the development of resistance to treatment with onabotulinumtoxinA [Cernuda-Morollón *et al.* 2014].

In some studies, shorter duration of disease [Eross *et al.* 2005; Sandrini *et al.* 2011; Lee *et al.* 2016], predominantly unilateral location of pain, presence of scalp allodynia, and pericranial muscle tenderness [Mathew *et al.* 2007] and increased interictal calcitonin gene-related peptide (CGRP) levels [Cernuda-Morollón *et al.* 2014] for a favourable outcome were observed. In a Korean study patients were screened with transcranial Doppler sonography. Patients with a higher ratio of the mean blood flow velocity in the middle cerebral artery to that of ipsilateral internal carotid artery were more likely to respond to treatment with onabotulinumtoxinA [Lee *et al.* 2016]. However, reliable predictors and biomarkers for treatment response applicable in a real-world setting are lacking to date.

IncobotulinumtoxinA (Xeomin®) and abobotulinumtoxinA (Dysport®)

OnabotulinumtoxinA is the only BoNT preparation, which has been approved for the treatment of CM. Until now no prospective trials using other BoNT preparations in patients with CM have been published. There is only one retrospective case series of 21 CM patients treated with incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt/M, Germany) [Kazerooni *et al.* 2015]. In this case series significant improvements in headache frequency and severity were observed under treatment with incobotulinumtoxinA.

AbobotulinumtoxinA (Dysport®, Beaufour Ipsen, Boulogne-Billancourt, France) has been investigated in patients with EM, but no significant effects on the frequency and severity of headache were found [Petri *et al.* 2009]. To the best of our knowledge to date no data are available for the use of abobotulinumtoxinA in patients with CM.

Doses and injection sites

The first studies with BoNT injections in headache and migraine used a variety of different dosages, concentrations and injection sites for BoNT. In 2010 the PREEMPT study group developed an injection paradigm based on various studies conducted in patients with EM, CM and tension-type headaches. The PREEMPT injection paradigm combines two different approaches for the injection of BoNT in migraine: fixed injections sites and follow the pain injection sites. Fifty MU of onabotulinumtoxinA are diluted with 2.0 ml of saline, yielding a concentration of 5 MU/0.1 ml. Each intramuscular injection site is injected with 5 MU onabotulinumtoxinA. The injection paradigm consists of 31 fixed sites in the following muscles: *mm. frontalis* 20 MU (four sites), *mm. corrugatores* 10 MU (two sites), *m. procerus* 5 MU (1 site), *mm. occipitalis* 30 MU (six sites), *mm. temporalis* 40 MU (eight sites), *mm. trapezii* 30 MU (in six sites), cervical paraspinal muscle group 20 MU (four sites). In these fixed sites a total dose of 155 MU onabotulinumtoxinA is applied. Additional 40 MU can be administered into temporalis (two sites), occipitalis (two sites) or trapezius muscles (four sites), receiving a maximum of 195 MU [Blumenfeld *et al.* 2010].

Little is known about the duration of analgesic effects of onabotulinumtoxinA. It is supposed, that it is similar to the duration of its myorelaxant effects. Therefore most studies used a fixed treatment interval of 12 weeks for onabotulinumtoxinA injections. Clinical experience in the use of BoNT for other neurologic indications shows, that it might be useful to adapt treatment intervals individually to the patients' needs [Dressler *et al.* 2015]. However shorter treatment intervals go along with an increased risk of antibody formation against BoNT resulting in treatment failure [Lange *et al.* 2009].

Safety and tolerability

Adverse effects (AEs) of BoNT are usually related to the injection, systemic AEs are very rare [Silberstein, 2016]. Injection-related AEs are usually mild and transient and rarely lead to

abortion of therapy. Among the reported AEs in the PREEMPT studies, neck pain (4.3%), injection site pain (2.1%), eyelid ptosis (1.9%), muscular weakness (1.6%) were most common [Aurora *et al*. 2014]. Data from various clinical studies document that treatment with onabotulinumtoxinA is tolerable [Cernuda-Morollón *et al*. 2014; Kollewe *et al*. 2016; Silberstein *et al*. 2005].

Conclusion

OnabotulinumtoxinA is the substance that has been best studied in the prophylactic treatment of CM. There is good clinical evidence that treatment with onabotulinumtoxinA leads to a reduction of monthly headache days and improves quality of life. Treatment with onabotulinumtoxinA is well tolerated by the patients. Further research is needed to elucidate the analgesic mechanism of onabotulinumtoxinA in CM.

Conflict of interest statement

CE states that he has no conflict of interest. LP received travel grants from Ipsen (Boulogne-Billancourt, France) and Merz (Frankfurt/M, Germany). DD received honoraria for consultations from Allergan (Irvine, California, USA), Bayer (Leverkusen, Germany), Eisai (Tokio, Japan), IAB-Interdisciplinary Working Group for Movement Disorders (Hamburg, Germany), Ipsen, Merz and UCB (Monheim, Germany). He is shareholder of Allergan and holds several patents on botulinum toxins.
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References

Adams, A.M., Serrano, D., Buse, D.C., Reed, M.L., Marske, V., Fanning, K.M. *et al.* (2015) The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. *Cephalalgia* 35: 563–578.

Ahmed, F., Zafar, H., Buture, A. and Khalil, M. (2015) Does analgesic overuse matter? Response to OnabotulinumtoxinA in patients with chronic migraine with or without medication overuse. *Springerplus* 4: 589.

Aoki, K. (2003) Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache* 43(Suppl. 1): S9–15.

Aurora, S., Dodick, D., Diener, H., DeGryse, R., Turkel, C., Lipton, R. *et al.* (2014) OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. *Acta Neurol Scand* 129: 61–70.

Aurora, S., Dodick, D., Turkel, C., DeGryse, R., Silberstein, S., Lipton, R. *et al.* (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalgia* 30: 793–803.

Aurora, S., Winner, P., Freeman, M., Spierings, E., Heiring, J., DeGryse, R. *et al.* (2011) OnabotulinumtoxinA for Treatment of Chronic Migraine: pooled Analyses of the 56-Week PREEMPT Clinical Program. *Headache* 51: 1358–1373.

Bigalke, H. (2013) Botulinum toxin: application, safety, and limitations. *Curr Top Microbiol Immunol* 364: 307–317.

Binder, W., Brin, M., Blitzer, A., Schoenrock, L. and Pogoda, J. (2000) Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. *Otolaryng Head Neck* 123: 669–676.

Blumenfeld, A., Silberstein, S., Dodick, D., Aurora, S., Turkel, C. and Binder, W. (2010) Method of injection of OnabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache* 50: 1406–1418.

Blumenfeld, A., Varon, S., Wilcox, T., Buse, D., Kawata, A., Manack, A. *et al.* (2011) Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia* 31: 301–315.

Buse, D., Manack, A., Fanning, K., Serrano, D., Reed, M., Turkel, C. *et al.* (2012) Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache* 52: 1456–1470.

Buse, D., Manack, A., Serrano, D., Turkel, C. and Lipton, R. (2010) Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosur Ps* 81: 428–432.

Cady, R., Schreiber, C., Porter, J., Blumenfeld, A. and Farmer, K. (2011) A multicenter double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. *Headache* 51: 21–32.

Cernuda-Morollón, E., Martínez-Camblor, P., Ramón, C., Larrosa, D., Serrano-Pertierra, E. and Pascual, J. (2014) CGRP and VIP levels as predictors of efficacy of onabotulinumtoxin type A in Chronic Migraine. *Headache* 54: 987–995.

Cernuda-Morollón, E., Ramón, C., Larrosa, D., Alvarez, R., Riesco, N. and Pascual, J. (2015) Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: what happens after one year? *Cephalalgia* 35: 864–868.

Couch, J. and Amitriptyline *versus* Placebo Study Group (2011) Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache* 51: 33–51.

Diener, H., Bussone, G., Van Oene, J., Lahaye, M., Schwalen, S. and Goadsby, P. (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 27: 814–823.

Diener, H., Dodick, D., Aurora, S., Turkel, C., DeGryse, R. and Lipton, R. (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 30: 804–814.

Diener, H., Solbach, K., Holle, D. and Gaul, C. (2015) Integrated care for chronic migraine patients: epidemiology, burden, diagnosis and treatment options. *Clin Med* 15: 344–350.

Dodick, D., Mauskop, A., Elkind, A., DeGryse, R., Brin, M. and Silberstein, S. (2005) Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. *Headache* 45: 315–324.

Dressler, D., Tacik, P. and Saberi, F. (2015) Botulinum toxin therapy of cervical dystonia: duration of therapeutic effects, *J Neural Transm* 122: 297–300.

Durham, P., Cady, R. and Cady, R. (2004) Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. *Headache* 35–44.

Eross, E., Gladstone, J., Lewis, S., Rogers, R. and Dodick, D. (2005) Duration of migraine is a predictor for response to botulinum toxin type A. *Headache* 45: 308–314.

Finzi, E. and Rosenthal, N. (2014) Treatment of depression with onabotulinumtoxinA: a randomized, double-blind, placebo-controlled trial. *J Psychiatr Res* 52: 1–6.

Freitag, F., Diamond, S., Diamond, M. and Urban, G. (2007) Botulinum toxin type A in the treatment of chronic migraine without medication overuse. *Headache* 48: 201–209.

Gaul, C., Holle-Lee, D. and Straube, A. (2016) Botulinum toxin type A in headache treatment : established and experimental indications. *Nervenarzt* 87: 853.

Headache Classification Committee of the International Headache Society (2013) The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 33: 629–808.

Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders: 2nd edition. *Cephalalgia* 24(Suppl. 1): 9–160.

Jackson, J., Kuriyama, A. and Hayashino, Y. (2012) Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. *J Amer Med Assoc* 307: 1736–1745.

Katsarava, Z., Manack, A., Yoon, M., Obermann, M., Becker, H., Dommes, P. *et al.* (2011) Chronic migraine: classification and comparisons. *Cephalalgia* 31: 520–529.

Kazerooni, R., Lim, J., Blake, A. and Lessig, S. (2015) IncobotulinumtoxinA for migraine: a retrospective case series. *Clin Ther* 37: 1860–1864.

Khalil, M., Zafar, H., Quarshie, V. and Ahmed, F. (2014) Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, UK *J Headache Pain* 15: 54.

Kollewe, K., Escher, C., Wulff, D., Fathi, D., Paracka, L., Mohammadi, B. *et al.* (2016) Long-term treatment of chronic migraine with onabotulinumtoxinA: efficacy, quality of life and tolerability in a real-life setting. *J Neural Transm* 123: 533–540.

Lange, O., Bigalke, H., Dengler, R., Wegner, F., deGroot, M. and Wohlfarth, K. (2009) Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: much ado about nothing? *Clin Neuropharmacol* 32: 213–218.

Lee, M., Lee, C., Choi, H. and Chung, C. (2016) Factors associated with favorable outcome in botulinum toxin A treatment for chronic migraine: a clinic-based prospective study. *J Neurol Sci* 363: 51–54.

Lipton, R., Rosen, N., Ailani, J., DeGryse, R., Gillard, P. and Varon, S. (2016) OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: pooled results from the PREEMPT randomized clinical trial program. *Cephalalgia* 36: 899–908.

Lipton, R., Varon, S., Grosberg, B., McAllister, P., Freitag, F., Aurora, S. *et al.* (2011) OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology* 77: 1465–1472.

Magalhães, E., Menezes, C., Cardeal, M. and Melo, A. (2010) Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. *Clin Neurol Neurosur* 112: 463–466.

Magid, M., Reichenberg, J., Poth, P., Robertson, H., LaViolette, A., Kruger, T. *et al.* (2014) Treatment of major depressive disorder using botulinum toxin A: a 24-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 75: 837–844.

Mahrhold, S., Rummel, A., Bigalke, H., Davletov, B. and Binz, T. (2006) The synaptic vesicle protein 2C mediates the uptake of botulinum neurotoxin A into phrenic nerves. *FEBS Lett* 580: 2011–2014.

Matak, I. and Lacković, Z. (2014) Botulinum toxin A, brain and pain. *Prog Neurobiol* 119–120: 39–59.

Mathew, N., Frishberg, B., Gawel, M., Dimitrova, R., Gibson, J. and Turkel, C. (2005) Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache* 45: 293–307.

Mathew, N., Kailasam, J. and Meadors, L. (2007) Predictors of Response to Botulinum Toxin Type A (BoNTA) in chronic daily headache. *Headache* 48: 194–200.

Natoli, J., Manack, A., Dean, B., Butler, Q., Turkel, C., Stovner, L. *et al.* (2010) Global prevalence of chronic migraine: a systematic review. *Cephalalgia* 30: 599–609.

Negro, A., Curto, M., Lionetto, L., Crialesi, D. and Martelletti, P. (2015) OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. *Springerplus* 4: 826.

Negro, A., Curto, M., Lionetto, L. and Martelletti, P. (2015) A two years open-label prospective study of OnabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. *J Headache Pain* 17: 1.

NICE (2012) Technology appraisal guidance [TA260]. *Botulinum Toxin Type A for the Prevention of Headaches in Adults with Chronic Migraine*. Available at: https://www.nice.org.uk/Guidance/ta260.

Olesen, J., Bousser, M., Diener, H., Dodick, D., First, M., Goadsby, P. *et al.* (2006) New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 26: 742–746.

Ondo, W., Vuong, K. and Derman, H. (2004) Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia* 24: 60–65.

Petri, S., Tölle, T., Straube, A., Pfaffenrath, V., Stefenelli, U. and Ceballos-Baumann, A. (2009) Botulinum toxin as preventive treatment for migraine: a randomized double-blind study. *Eur Neurol* 62: 204–211.

Purkiss, J., Welch, M., Doward, S. and Foster, K. (2000) Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms. *Biochem Pharmacol* 59: 1403–1406.

Queiroz, L., Barea, L. and Blank, N. (2006) An epidemiological study of headache in Florianopolis, Brazil. *Cephalalgia* 26: 122–127.

Rasmussen, B., Jensen, R., Schroll, M. and Olesen, J. (1991) Epidemiology of headache in a general population–a prevalence study. *J Clin Epidemiol* 44: 1147–1157.

Rummel, A. (2015) The long journey of botulinum neurotoxins into the synapse. *Toxicon* 107: 9–24.

Russo, M., Manzoni, G., Taga, A., Genovese, A., Veronesi, L. and Pasquarella, C. (2016) The use of onabotulinum toxin A (Botox®) in the treatment of chronic migraine at the Parma Headache Centre: a prospective observational study. *Neurol Sci* 37: 1127–1131.

Sandrini, G., Perrotta, A., Tassorelli, C., Torelli, P., Brighina, F., Sances, G. *et al.* (2011) Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. *J Headache Pain* 12: 427–433.

Schwedt, T. (2014) Chronic migraine. *Brit Med J* 348: g1416.

Silberstein, S. (2016) The use of botulinum toxin in the management of headache disorders. *Semin Neurol* 36: 92–98.

Silberstein, S., Blumenfeld, A., Cady, R., Turner, I., Lipton, R., Diener, H. *et al.* (2013) OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. *J Neurol Sci* 331: 48–56.

Silberstein, S., Lipton, R., Dodick, D., Freitag, F., Ramadan, N., Mathew, N. *et al.* (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 47: 170–180.

Silberstein, S., Mathew, N., Saper, J. and Jenkins, S. (2000) Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. *Headache* 40: 445–450.

Silberstein, S., Stark, S., Lucas, S., Christie, S., DeGryse, R. and Turkel, C. (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 80: 1126–1137.

Silvestrini, M., Bartolini, M., Coccia, M., Baruffaldi, R., Taffi, R. and Provinciali, L. (2003) Topiramate in the treatment of chronic migraine. *Cephalalgia* 23: 820–824.

Simpson, D., Hallett, M., Ashman, E., Comella, C., Green, M., Gronseth, G. *et al.* (2016) Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 86: 1818–1826.

Spira, P. and Beran, R. and Australian Gabapentin Chronic Daily Headache Group. (2003) Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 61: 1753–1759.

Straube, A., Gaul, C., Förderreuther, S., Kropp, P., Marziniak, M., Evers, S. *et al.* (2012) Therapy and care of patients with chronic migraine: expert recommendations of the German Migraine and Headache Society/German Society for Neurology as well as the Austrian Headache Society/Swiss Headache Society. *Nervenarzt* 83: 1600–1608.

Tsui, J., Eisen, A., Stoessl, A., Calne, S. and Calne, D. (1986) Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 2: 245–247.

Vo, A., Satori, R., Jabbari, B., Green, J., Killgore, W., Labutta, R. *et al.* (2007) Botulinum toxin type-A in the prevention of migraine: a double-blind controlled trial. *Aviat Space Envir Med* 78: B113–B118.

Wang, S., Wang, P., Fuh, J., Peng, K. and Ng, K. (2013) Comparisons of disability, quality of life, and resource use between chronic and episodic migraineurs: a clinic-based study in Taiwan. *Cephalalgia* 33 171–181.

Welch, M., Purkiss, J. and Foster, K. (2000) Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. *Toxicon* 38: 245–258.

Wollmer, M., de Boer, C., Kalak, N., Beck, J., Götz, T., Schmidt, T. *et al.* (2012) Facing depression with botulinum toxin: a randomized controlled trial. *J Psychiatr Res* 46: 574–581.

Yurekli, V., Akhan, G., Kutluhan, S., Uzar, E., Koyuncuoglu, H. and Gultekin, F. (2008) The effect of sodium valproate on chronic daily headache and its subgroups. *J Headache Pain* 9: 37–41.