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Botulinum Toxin and Other New Approaches to Migraine Therapy

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Abstract

The number of migraine treatments and our understanding of migraine pathophysiology are both increasing. Newer treatments are focusing on migraine prevention. Botulinum toxin (BTX) is a potent neurotoxin that has been used primarily for diseases associated with increased muscle activity. Recently the toxin was found to have antinociceptive effects that are probably independent of its muscle-relaxant action. Recent clinical trials support the efficacy of BTX type-A (and possibly also type-B) in the treatment of migraine. The anticonvulsant topiramate was recently shown to be effective for migraine prevention. With the low doses used for this indication, cognitive side effects are less of a concern. Angiotensin (AT) II receptor blockade is a new approach to migraine prevention that was recently examined. The high tolerability of the AT₁ receptor blocker candesartan warrants further studies to assess its role in migraine prevention.

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Introduction (*first heading*)

Migraine is an episodic neurovascular disorder characterized by repeated attacks of headache, autonomic dysfunction, and gastrointestinal symptoms (1). Some patients experience an aura, manifesting as transient neurological symptoms that usually last less than 60 minutes, preceding attacks. Migraine is a common disorder, with a prevalence of 12% in the adult population (6% in men and 18% in women) and 4% in children. It has a strong impact on quality of life. The World Health Organization has ranked migraine as one of the most disabling of the chronic diseases (2).

Significant progress has been made in our understanding of migraine pathophysiology. Migraine is now considered a primary CNS disorder with secondary effects on meningeal blood vessels (1). The treatment of acute migraine attacks has improved dramatically with the introduction of the 5-HT_{1B/1D} agonists, known as the triptans. The preventive treatment of migraine has been neglected and, due to the relatively low efficacy and high adverse event (AE) rates of previously available preventive medicines, not satisfactory for many patients.

In this review we describe recent advances in the treatment of migraine, including neurotoxins as a novel approach to migraine prevention.

Botulinum toxin (*first heading*)

Botulinum toxin (BTX) is a potent neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*. (3, 4). It causes a dose-dependent muscle relaxation by blocking acetylcholine release at the neuromuscular junction. Human intoxication by BTX results

in botulism – an acute, potentially fatal muscle paralysis (5). Over the last two decades, BTX has been used to treat various disorders associated with increased muscle tone (6, 7). Recently, its efficacy in the treatment of headaches and other pain syndromes has been demonstrated.

Structure and Preparations (*second heading*)

BTX belongs to the clostridial neurotoxin family and exists as seven antigenically-distinct serotypes (A-G) (3). The toxin is non-covalently associated with non-toxic proteins. In its purified form, it is a ~150 kDa polypeptide that consists of two subunits, a light chain and a heavy chain, linked by a disulfide bond. The light chain acts as a zinc-dependent endopeptidase. The heavy chain contains two domains. One, in the C-terminal (H_C), is the ganglioside-binding domain, which has a key role in binding of the toxin to the target cell membrane and its internalization. The other, in the N-terminal (H_N), is the translocation domain that promotes penetration of the light chain through the endosomal membrane into the cytosol.

BTX type A (BTX-A) is the most widely used serotype in clinical practice. It is available in the US as Botox[®] (Allergan, CA) and in Europe as Dysport[®] (Ipsen, UK). Although these two preparations contain the same serotype, they differ in potency and in antigenicity (4, 8). BTX type B has recently become available for clinical use in the US (Myobloc[®], Elan Pharmaceuticals, CA), and in Europe (NeuroBloc[®], Elan Pharmaceuticals, CA). Clinical experience with this serotype, however, is still limited.

Immunology (*second heading*)

Since BTX is a protein of non-human origin, it may evoke antibody formation (4, 9). Once neutralizing antibodies are present, the efficacy of the toxin is lost (10). The reported prevalence of treatment resistance due to antibody formation is variable and depends on the assay used for antibody detection, the patient population, and the treatment protocol. Using an older formulation, it was estimated to occur in at least 5%-10% of patients with cervical dystonia (11). Factors that increase the risk for antibody formation include higher doses and short intervals between doses (12-14). With the new formulation and the relatively low doses used in migraine treatment (see below), this complication is unlikely to occur. Recommendations for minimizing immunoresistance include using the lowest effective dose at the longest possible intervals and avoiding booster injections (4). When resistance to one BTX serotype develops, switching to a different serotype may restore the therapeutic response (10). This response, however, may be only temporary. In a recent study, ten patients with antibody-mediated therapeutic failure to BTX-A were given BTX-B (NeuroBloc[®]). After an initial response, six patients developed secondary therapeutic failure with documented antibodies to BTX-B (15). A new low-molecular-weight BTX-A has recently been developed and shown to be effective in an animal model (16). This novel toxin may be less immunogenic than the conventional BTX-A.

Mechanism of Action (*second heading*)

BTX affects the nervous system through a multi-stage process that results in blocking neurotransmitter release (3, 4, 17). The toxin binds to the target nerve terminal through its

H_C domain, and is subsequently internalized into an intracellular vesicle. The disulfide bond is then cleaved, and the light chain undergoes translocation to the cytosol. This stage is facilitated by the H_N domain of the heavy chain. In the final stage, the light chain cleaves one or more proteins involved in neurotransmitter release. The type of protein cleaved depends on the toxin serotype. BTX-A cleaves a synaptosomal-associated protein of 25 kDa (SNAP-25), whereas BTX-B attacks a vesicle-associated membrane protein (VAMP), also called synaptobrevin. In both cases, the result is prevention of synaptic vesicle fusion with the plasma membrane and thus, of neurotransmitter release.

Effect at the Neuromuscular Junction (*third heading*)

The main site of action of BTX is the neuromuscular junction. By interfering with acetylcholine release from the pre-synaptic axon terminal at this site, BTX causes a dose-dependent and reversible muscle relaxation. Axonal sprouting, which occurs following BTX entrance into the cell, causes termination of the toxin effect in 2 to 6 months.

Effect on the Autonomic Nervous System (*third heading*)

Botulism is known to be associated with autonomic nervous system dysfunction (5). BTX affects cholinergic synapses in both sympathetic and parasympathetic pathways. By acting at these sites, the toxin was shown to reduce sweat secretion in patients with hyperhidrosis and to improve bladder function in patients with detrusor sphincter dyssynergia (18, 19).

Effect on Afferent Pathways (*third heading*)

BTX may also act via afferent mechanisms (20). In animal models BTX was shown to reduce spindle afferent discharges, suggesting a direct effect on gamma motor nerve endings (21). It also caused atrophy of both intrafusal and extrafusal muscle fibers when injected into rats (22).

Effects on the Central Nervous System (*third heading*)

There is increasing evidence that BTX affects the CNS (23). In earlier animal studies, retrograde transport of the toxin into the CNS was suggested (24). More recently, however, it was shown that only breakdown products of the toxin were transported in a retrograde manner (25). Janicki & Habermann found that BTX inhibits the release of methionine-enkephalin-like material in the rat striatum in vitro (26). However, little evidence currently exists for the penetration of functional toxin into the CNS in humans. The central effects of BTX are more likely to result from CNS neuroplasticity, induced by alterations in afferent input. Several studies support this hypothesis. Byrnes et al found that BTX can reverse changes in cortical motor representation of the upper limb in patients with writer's cramp (27). More recently, Gilio et al. have shown that BTX-A normalizes intracortical circuits in patients with dystonia (28).

Antinociceptive Effects (*third heading*)

The analgesic effect of BTX has long been recognized, while used for the treatment of dystonia and other disorders associated with increased muscle tone (29-31). In many patients, the toxin's analgesic effect occurs earlier and lasts longer than its effect on muscular hyperactivity (4). Pain reduction may also be observed in the absence of weakness. Cui & Aoki examined the effect of BTX-A on the pain behavior of rats after formalin injection (32). Five and twelve days before formalin injection, rats were treated with BTX-A injected subcutaneously to the hind-paw. BTX-A inhibited the delayed nociceptive response, as assessed by reduced pain behavior, at both time points. This effect was achieved at doses that did not cause muscle weakness. Lew et al. studied the analgesic effect of BTX-B, given in three different doses, in 122 patients with idiopathic cervical dystonia (33). Using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) pain score, 61% to 83% of patients treated with BTX-B were responders, and the response was dose-dependent. In contrast, a study of healthy volunteers showed that BTX-A, injected intradermally, reduced neurogenic flare induced by electrical stimulation, but had little effect on acute pain and allodynia (34). This model is of acute, rather than chronic, pain and may have little relevance to disorders associated with sensitization.

The analgesic effect of BTX cannot be explained solely by the reduction of muscle tone induced by the toxin. Moreover, several studies showed little or no direct effect of BTX on cutaneous nociception (34, 35). Other mechanisms must be involved, but their exact nature remains speculative. Several theories have been proposed (31): 1. By decreasing prolonged muscle contraction, BTX may reduce the release of various substances that sensitize muscle nociceptors; 2. Through its effect on muscle spindle activity, BTX can

indirectly disrupt muscle pain associated with abnormal muscle contraction. Since the spindle afferents have important supraspinal projections, the change in their firing pattern caused by BTX may also cause changes in sensory processing at higher levels of the nervous system; 3. BTX may suppress neurogenic inflammation, which has been implicated in the pathogenesis of migraine and other pain syndromes; 4. BTX may affect the release of neurotransmitters other than acetylcholine. There is evidence that it inhibits the release of substance P in vitro (36, 37). More evidence for this theory comes from an in vivo study by Cui et al, who showed that the effect of BTX on pain behavior in the rat formalin model is associated with reduced glutamate release (38).

Clinical Uses – General (*second heading*)

Botulinum toxin was shown to be effective in the treatment of a variety of disorders (6, 7, 39). Its first clinical use was for the treatment of strabismus (40). It has also been used extensively for various forms of dystonia and other conditions associated with increased muscle tone (7, 41). Other conditions responsive to treatment with BTX include achalasia, spastic bladder, and hyperhidrosis (18, 42).

Data shows that BTX is effective in the treatment of various pain syndromes, including neuropathic pain, low back pain, and whiplash-associated disorders (43-45). Its use in migraine and other types of chronic headaches was recently studied and showed positive results (29, 46-49).

The Clinical Use of Botulinum Toxin for the Treatment of Migraine (*second heading*)

The beneficial effect of BTX-A in migraine treatment was first noted in patients who were given the toxin for the treatment of facial wrinkles (50). Since then, an increasing number of studies have been conducted to examine the efficacy of BTX-A, and more recently BTX-B, as a migraine preventive drug (Table).

Botulinum Toxin Type A (BTX-A) (*third heading*)

Efficacy and Tolerability (*fourth heading*)

Binder et al conducted an open-label study to examine the efficacy of BTX-A for acute and preventive treatment of migraine (50). Treatment protocols were individualized. Of 77 migraine patients who were treated prophylactically, 51% reported complete relief from migraine symptoms for a mean duration of 4.1 months. Thirty eight percent reported partial response (more than 50% reduction in headache frequency or severity), with a mean response duration of 2.7 months. Of ten migraine patients who were treated acutely, 70% reported complete response, with improvement occurring 1 to 2 hours after treatment.

Silberstein et al examined the efficacy of BTX-A for migraine prevention in a double-blind vehicle-controlled study (51). The study included 123 patients with International Headache Society (IHS)- defined migraine with or without aura. Patients were randomized to receive a single administration of either BTX-A (at a dose of 25 units or 75 units) or vehicle. BTX-A was given into the frontalis, temporalis, and glabellar muscles. BTX-A, at the 25 unit dose, caused a reduction in migraine frequency of 1.88 attacks/month (compared with 0.98 attacks/month for placebo) three months following treatment. BTX-A at this dose also reduced migraine severity and migraine-associated

vomiting. The 75 unit dose was not significantly more effective than placebo. This has been attributed to the lower baseline headache frequency of patients who received this dose. BTX was well tolerated, with transient side effects that included blepharoptosis, diplopia, and injection site weakness.

In another double-blind, placebo-controlled study, Brin et al examined the effect of BTX-A on 56 migraine patients (52). BTX was injected into the frontalis and temporalis muscles; the outcome measures were attack frequency, attack duration, and pain intensity. The maximal effect was found at week 12 following treatment. BTX reduced migraine frequency by 1.8 attacks/month (compared with a reduction of 0.2 attack/month for placebo). It also reduced mean headache severity by 4.0 points, on a scale of 0-10, compared with a decrease of 0.2 points for placebo. Headache duration was reduced in the BTX group by an average of 15.2 h, compared with a mean reduction of 5.6 h for placebo.

Barrientos & Chana examined prospectively the efficacy and safety of BTX-A in the prophylactic treatment of migraine (53). Thirty patients with IHS-defined migraine were randomized to receive either placebo or BTX-A at a dose of 50 units, injected to six sites. BTX-A treatment resulted in a significant decrease in the number of monthly days with headache, from 5.7 at baseline to 2.5 at 90 days post-treatment. It also reduced migraine frequency, duration of migraine attacks and consumption of acute pain-medications.

BTX-A therapy was safe and well-tolerated.

Behmand et al evaluated prospectively the efficacy of BTX-A on migraine, when injected to the corrugator muscle (54). Twenty nine patients were given 25 units at each side to a total of 50 units. At two months following treatment, 16 (55%) patients had complete

elimination of headaches and 8 (28%) had significant improvement (decreased migraine frequency from 6.4 to 2.1 per month and decreased pain intensity from 8.6 to 6.1 points on a scale of 0-10).

In a recent double-blind placebo-controlled study, Relja & Klepac evaluated the effect of BTX-A treatment on 32 migraineurs (55). Two treatments, at a dose of 100 units each, were given at three-month intervals. BTX-A treatment reduced the use of triptans.

Although total number of days with headache was not reduced, the character of the pain changed to a moderate, non-throbbing headache responsive to standard analgesics.

Several other retrospective studies have shown efficacy for BTX-A in migraine prevention (56-58). Other studies of patients with chronic daily headache, many of whom have chronic migraine, showed only a mild or no response to BTX (59, 60).

Safety Considerations (*fourth heading*)

With clinical experience for over two decades, BTX-A has proved to be a remarkably safe drug. Based on animal studies, the lethal dose in humans is estimated at approximately 3000 units (4). The doses used for migraine treatment (25-100 units) are unlikely to be toxic. An antitoxin is available in the event of accidental overdose (61).

BTX should be used with caution in patients with neuromuscular junction diseases (e.g. myasthenia gravis). It is contraindicated in patients who take aminoglycosides, which interfere with neuromuscular transmission (62). Since there is little data on the safety of BTX in pregnant and lactating women, it is not recommended for use in these circumstances.

Evidence for the efficacy of BTX-A in the treatment of migraine is growing. Compared with conventional migraine-preventing drugs, it offers several unique advantages: 1. It has a long duration of action of up to four months; 2. It is safe and well-tolerated, with almost no systemic side effects. These properties make BTX-A particularly appealing to patients who do not comply with daily drug treatments or cannot tolerate them. Several questions regarding BTX-A use for migraine remain to be answered: 1. What sub-group of migraine patients will benefit the most from treatment? 2. What is the optimal therapeutic dose? 3. Should the treatment program (dose and injection sites) be standardized or tailored individually for each patient? Large controlled studies, which are underway, may resolve these questions.

Botulinum Toxin type B (BTX-B) (*third heading*)

Clinical experience with BTX-B is far less extensive than that with BTX-A. Few preliminary studies assessing its efficacy in headache treatment exist. Lake & Saper conducted an open-label study on the efficacy of BTX-B in the treatment of 21 patients with IHS-defined migraine (63). Patients were given a total of 5000 units of BTX-B, injected into 11 sites. Evaluation was done at baseline and four months following treatment. Mean monthly headache frequency declined from 7.7 pre-injection to 4.6 at four months following treatment. Significant improvement also occurred on visual analog scales of headache, sleep, MIDAS scores, and overall treatment satisfaction. Adverse events were transient and rated as mild in five of six patients who experienced them. In an open-label study, Opida examined the efficacy of BTX-B for the treatment of transformed migraine (64). The study included 36 patients with at least four migraine

episodes in a four-week period. Patients were given a dose of 5000 units of BTX-B, injected to three or more muscles. The sites of injection were chosen according to pain distribution, trigger points, and frown lines. Twenty four patients (66%) reported improvement in headache severity as assessed by the numeric rating scale. Headache frequency was also reduced. Adverse events were mild, and included dry mouth and transient pain at the injection site.

Another study, evaluating the efficacy of BTX-B in a randomized, double-blind, placebo-controlled fashion on patients with chronic headaches, including migraine, is underway (65).

BTX-B may be effective for migraine treatment, but clinical experience is still limited. Currently, it may be considered for patients who develop antibody-mediated resistance to BTX-A. Larger clinical trials may better define the role of BTX-B in migraine prevention.

Other New Approaches to Migraine Treatment (*first heading*)

Recent advances in the research of migraine pathophysiology have led to new concepts in migraine prevention (1, 66). Migraine is currently viewed as a neurovascular disorder with a CNS generator (1). Therefore, the current focus in migraine prevention is on attempting to modulate central neurotransmitter systems.

Topiramate (*second heading*)

Anticonvulsants are being increasingly used for migraine prevention. Topiramate is a structurally-unique anticonvulsant derived from D-fructose (67). In addition to seizure

prevention, it is used to treat mood disorders and essential tremor (68, 69). Its role in migraine treatment was recently evaluated (70). Topiramate acts via several mechanisms that may be relevant in the context of migraine treatment (71). 1. It has a state-dependent blocking effect on voltage-sensitive sodium and L-type calcium channels. 2. It acts on the γ -amino butyric acid (GABA) type-A receptor to enhance GABA transmission. 3. It reduces excitatory glutamatergic neurotransmission by binding to the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor. 4. It is a weak inhibitor of carbonic anhydrase. These effects of the drug are probably mediated by modulation of receptor and channel phosphorylation. Activation of neurons within the trigeminocervical complex is probably the biological substrate for pain in migraine.

Migraine preventive action is most likely within the nervous system. Storer studied the effect of topiramate on trigeminocervical activation in the cat (72). The superior sagittal sinus (SSS) of anesthetized cats was isolated and electrically stimulated to produce a model of trigeminocervical nociceptive activation. Topiramate reduced SSS-evoked firing of neurons in the trigeminocervical complex in a dose-dependant fashion, with the maximum effect seen at 30 minutes. At this time point, topiramate at 5 mg/kg reduced neuronal firing by $48 \pm 5\%$. Topiramate may directly inhibit the trigeminocervical complex or influence the neural network that controls sensory input.

In several recent clinical studies, topiramate was shown to be effective in migraine treatment (73-75). Silberstein et al evaluated the effect of topiramate on migraine in a placebo-controlled trial of 487 patients (the MIGR-001 study) (75). Topiramate, at a daily dose of 100 mg, reduced the average migraine frequency by 2.1 episodes/month (from 5.4 to 3.3) compared with a corresponding reduction of 0.8 episodes/month by placebo.

Significantly more patients treated with topiramate 100 mg/day had $\geq 50\%$ reduction in migraine frequency (responders) compared with placebo-treated patients (54% vs 23%). Topiramate treatment was also associated with a reduction in the mean monthly migraine days and a decrease in the consumption of acute pain medications. The 200 mg dose was not significantly more effective than the 100 mg dose. The onset of drug effect was observed by the end of the first month of treatment. Topiramate was well tolerated. The most common adverse events were paresthesias, taste change, anorexia, fatigue, and nausea. Cognitive adverse events occurred in 19% of patients taking the 100 mg dose, but led to withdrawal in only 4%. In contrast to many other migraine preventive drugs, that cause weight gain, topiramate treatment was associated with an average of 3.8% weight loss.

A similarly-designed study that included 483 migraine patients (the MIGR-002 study) was recently completed (76). Patients were randomized to receive either topiramate (50, 100 or 200 mg/day) or placebo. Patients treated with topiramate 100 mg/day had a mean decrease of 2.3 episodes/month in migraine frequency, compared with a decrease of 1.1 episodes/month for patients receiving placebo. Responder rates (as defined above) were significantly higher in the topiramate 100 mg group (49%) compared with placebo (23%). As in the MIGR-001 study, the 100 mg dose had the most favorable efficacy/tolerability profile. Topiramate was safe and generally well-tolerated. Side effects were similar to those found in the previous study. There was an average weight loss of 3.3% of body weight in the topiramate 100 mg group. The third trial (MIGR-003 study), which compared topiramate to propranolol and placebo, has recently been completed but results are still not available.

Young et al evaluated the outcome of 74 migraine patients treated with topiramate in a case series study (73). Twenty four patients had episodic migraine and fifty had chronic migraine. The mean dose was 208 mg/day and treatment was given for at least six weeks. Topiramate treatment resulted in a mean decrease of seven days/month with headache (from 21.6 to 13.6). The responder rate to topiramate (as defined above) was 44.6% (58.3% for episodic migraine and 38.0% for chronic migraine). Headache severity was also significantly reduced. Adverse events were usually mild to moderate and included paresthesias, cognitive difficulties, dizziness, and nausea. Patients with comorbid depression had a similar outcome to those who were not depressed.

Another retrospective study was conducted by Mathew et al to evaluate the efficacy of topiramate in the treatment of migraine (74). Topiramate was given as add-on therapy for chronic migraine patients and as monotherapy for episodic migraine patients. The mean daily dose of topiramate was 87.5 mg and the mean duration of treatment was 8.4 months. In patients with chronic migraine, mean days with migraine per 28 days decreased from 6.3 to 3.7. Headache severity, consumption of acute pain medications, and MIDAS scale values also decreased significantly in this group. Patients with episodic migraine also had a significant decrease in headache severity and in monthly migraine days (from 5.8 to 1.9 per 28 days). In this study, which also included cluster headache patients, topiramate was well tolerated, with only 8/178 patients discontinuing treatment. Several other studies have demonstrated topiramate's efficacy in migraine treatment (77, 78). These results show that topiramate is effective for migraine prevention. The doses needed for this indication (100-200 mg/day) are significantly lower than those used for

epilepsy, making cognitive side effects less of a concern. Weight loss, rather than the weight gain seen with many other preventive treatments, is a major benefit.

Angiotensin II Receptor Blockade (*second heading*)

Several reports on the efficacy of angiotensin converting enzyme (ACE) inhibitors for migraine prevention have been published (79, 80). Angiotensin receptor antagonists block the renin-angiotensin system without the common side effects caused by ACE inhibitors (e.g. coughing and angioneurotic edema). Recently, the efficacy of candesartan, an angiotensin II type 1 (AT₁) receptor blocker, in migraine prevention was evaluated in a placebo-controlled study that included sixty patients (81). Patients were given candesartan 16 mg/day or placebo for two 12-week periods in a cross-over design. The mean number of days with headache during a 12-week period was significantly lower with candesartan than with placebo (13.6 vs 18.5). Candesartan also lowered headache severity, level of disability, and days of sick leave. Candesartan was very well tolerated, with a tolerability profile similar to that of placebo. The mechanism of action of this drug in migraine prevention is currently unknown. Angiotensin II affects cerebral blood flow through AT₁ receptors (82). It was also shown to modulate the activity of various neurotransmitters, including serotonin, dopamine, and melatonin (83, 84). Finally, angiotensin may be an indirect activator of nitric oxide (NO) synthase, thereby increasing levels of NO, a molecule that affects nociceptive pathways (85). Blocking angiotensin II activity at any of these sites may result in migraine prevention. The high tolerability of candesartan compared with many other migraine-preventive drugs is an advantage, warranting further studies of this drug for this indication.

Conclusion (*first heading*)

The number of drugs available for migraine preventive treatment is increasing. More data are available regarding the efficacy of various drugs, enabling a more rational, rather than the previously-used empiric, therapeutic approach.

There is increasing evidence for the efficacy of BTX-A in the treatment of migraine. Its long duration of action and high tolerability make it especially appealing for patients whose compliance to orally-administered drugs is poor. The anticonvulsant topiramate is effective for migraine prevention at relatively low doses, making cognitive side-effects less of a concern. It has the beneficial added result of weight loss. Angiotensin II receptor blockade is a new approach to migraine prevention that needs to be further tested.

Legend

Table: Studies of BTX for migraine prevention

(*n* = number of patients)

Study design	<i>n</i>	BTX serotype and total dose	Results	Reference
Prospective, double blind, placebo-controlled	123	Type A, 25 U or 75 U	25 U: significant reduction in migraine frequency 75 U: no significant efficacy	(51)
Prospective, double blind, placebo-controlled	56	Type A, dose variable	Significant reduction in migraine frequency, severity and duration	(52)
Prospective, placebo-controlled	30	Type A, 50 U	Significant reduction in migraine frequency and duration	(53)
Prospective, open label	29	Type A, 50 U	Complete elimination of headaches in 55% of patients, significant improvement in additional 28%	(54)
Prospective, double blind, placebo-controlled	32	Type A, 200 U	Significant reduction in migraine-related disability and in consumption of acute-pain medications; no change in number of days with headache	(55)
Prospective, open label	77	Type A, dose variable	Complete elimination of headaches in 51% of patients, significant improvement in additional 38%	(50)
Prospective, open label	21	Type B, 5000 U	Significant reduction in headache frequency and severity	(63)

Prospective, open label	36	Type B, 5000 U	Improvement in 66% of patients	(64)
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