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What is the effectiveness of OnabotulinumtoxinA (Botox®) in reducing the number of chronic migraines (CM) in patients 18-65 years old?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Department of Physician Assistant Studies
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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not onabotulinumtoxinA (Botox®) is effective in reducing the number of chronic migraines (CM) in patients 18-65 years old?

Study Design: Review of three published, double blind randomized controlled trials were used for this review, which were found on PubMed; were selected based on their relevance to the clinical question and if they included patient oriented outcomes.

Outcomes Measured: The outcomes measured were headache/migraine free days measured by ≥50% responder rate analysis, the Treatment Responder Rate based on Physician Global Assessment, and total adverse events reported by the participants.

Results: In the study by Mathew et al, onabotulinumtoxinA reported ≥50% reduction in HA/migraine days at 3,6,9 months and was consistent if not better when compared to topiramate (TOPAMAX®). A study by Cady et al. showed the treatment responder rate based on Physician Global Assessment 9-point scale (+4= clearance of signs and symptoms and -4 =very marked worsening), that by 12 weeks onabotulinumtoxinA treatment when compared to topiramate had improved chronic migraines (CM) by 79.2% verses 70.8%. Dodick et al, illustrated that onabotulinumtoxinA against placebo showed a ≥50% responder rate starting at week 4 and including 24 weeks. Dodick et al, also looked at total adverse events (AE). Most adverse events (AE) were mild or moderate in severity and included neck pain, mild fatigue, nausea and muscular weakness, and resolved without sequelae.

Conclusions: The results of these three randomized controlled trials demonstrate that onabotulinumtoxinA is safe and effective at treating chronic migraines when compared to placebo and topiramate.

Key words: Chronic Migraine, OnabotulinumtoxinA

INTRODUCTION

Chronic migraines (CM) are a debilitating disorder that can be defined as ≥15 headache days per 30 days for 3 months or more[7]. CM impairs the quality of life for many patients, and due to the fact that there are no biological markers for migraines, diagnosis is made on the clinical history and exclusion of other headache disorders[6,7]. Acute pharmacologic and non-pharmacologic treatments have failed to date, so prophylactic treatments should be investigated as the best option for these patients.

Migraines: including both episodic and chronic, affect 14% of the population and 18% of women[6,2]. Migraines greatly affect family, work, and social life for many people. Stressful life events, contraceptive pill use, hypertension, mood changes, and the use or overuse of certain drugs can increase the frequency of headaches. Dietary changes, regular sleep, physical activities and relaxation can help to decrease the frequency of them[9,2]. The total annual US costs for treating migraines, based on 2010 US census data, was $3.2 billion for outpatient visits, $700 million for emergency room (ER) visits, and $375 million for inpatient hospitalizations for migraine; costs totaling near $4.3 billion annually[5]. Regarding health care visits each year, there is not an exact estimate, but based off of 2010 US Census data there were 22,758,044 outpatient visits, and 908,541 ER visits[5].

Migraines are generally an inherited condition, one of neuronal hyper-excitability that sends out impulses to blood vessels, initially causing constriction then vasodilation. The actual pain that comes with a migraine is caused from the release of prostaglandins, serotonin, and other inflammatory substances[9]. The definition of migraine (without aura) from the second edition of the International Classification of Headache Disorders (ICHD-2) requires all of the following symptoms: recurrent headaches (at least five lifetime attacks),

untreated or unsuccessfully treated headache duration of 4-72 hours, at least two of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. The migraine attacks are also associated with at least one of the following: nausea/vomiting, photophobia, or phonophobia[6].

For the acute treatment of CM, conventional therapies such as analgesics, non steroidal anti-inflammatory drugs (NSAIDS), or migraine specific agents (triptans and ergot derivatives) have been used[6]. Medication overuse with these acute therapies can be hazardous to patients with CM, and it is critical to limit and monitor the use of these when treating[6].

Preventative treatment for CM include: anti-hypertensives, anti-epileptics and anti-depressants. Beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are specific anti-hypertensive medications used to prevent CM[2]. Beta blockers, although having top level effectiveness and scientific evidence, they are contraindicated for many patients; specifically ones with hypotension, congestive heart failure, asthma, raynauds disease, depression and diabetes[2].

Types of anti-epileptic medications are topiramate, valproate, and gabapentin[6]. Valproate is often used, and has excellent evidence and clinical effectiveness; however the use of this medication comes with serious adverse events. Some of which are teratogenicity, with neural tube defects, polycystic ovarian syndrome, as well as hepatotoxicity when co-administered with other medications[2]. Many of these drugs have demonstrated efficacy and safety, however, tolerability issues often arise that attribute to poor adherence to the prescribed drugs[7].

The goal of chronic migraine prophylaxis is to reduce the frequency of migraines. With the appropriate prophylaxis treatment, patients should be able to perform daily activities, and health related quality of life should improve significantly. The MIDAS (Migraine Disability Assessment Scale) is used to assess the ability to perform daily activities. Preventative therapy is recommended to be used for periods of months, minimum of 2 to 3 months of daily administration[2]. OnabotulinumtoxinA is currently being proposed to treat CM because it has been shown to be safe, effective and tolerable. Evidence has shown that onabotulinumtoxinA is effective in reducing myogenic pain associated with cervical dystonia, chronic limb spasticity, hand dystonia, muscular stress as a migraine trigger, and pericranial painful muscular trigger points[7, 9]. Due to its long duration of action, and lacking the usual side effects caused by prophylaxis, onabotulinumtoxinA is highly recommended for patients with poor compliance[9].

OBJECTIVE

The objective of this selective evidence based medicine (EBM) review is to determine whether or not onabotulinumtoxinA is effective in reducing the number of chronic migraines (CM) in patients 18-65 years old.

METHODS

The studies that are included in this review are three randomized, double blind, placebo controlled clinical trials (RCTs). Two of these RCTs were an open label extension study. The population studied was males and females aged 18-65 years old, who are diagnosed with chronic migraines (CM) and are naive to onabotulinumtoxinA treatment. The interventions used were onabotulinumtoxinA 200 units (100 units fixed site, 100 units follow-the-pain), plus an oral placebo, compared to 4 week titration of topiramate to

100mg/day plus placebo saline injections[7]. Cady et al. also used onabotulinumtoxinA up to 200 units or placebo injected with 100 units into fixed sites; this was compared to topiramate 25mg daily which was increased to 100mg, plus placebo injections[1]. The last comparison was made using pivotal trials in the PREEMPT: phase 3 evaluating migraine prophylaxis therapy clinical program which included a 24 week randomized trial; onabotulinumtoxinA 155 units was administered as 31 fixed-site, fixed dose injections across 7 specific head, and neck muscle areas, compared to placebo injections in the same locations[3]. The outcomes measured were all based on patient oriented evidence that matters (POEMS). The reduction of headache days per month compared to baseline; the frequency of headache/migraine days compared to baseline, and the safety and tolerability of the onabotulinumtoxinA treatment.

Key words used in the searches were "onabotulinumtoxinA" and "chronic migraines." All articles were published in English, and in peer reviewed journals. The articles were selected based on their relevance to my clinical question and if they included patient oriented outcomes. The sources used were researched via Medline, PubMed, and OVID using key words: OnabotulinumtoxinA, Chronic Migraines.

The inclusion criteria included: Studies that were randomized, controlled, double blind, and subjects with CM between ages 18-65 years old. Exclusion criteria included: Subjects <18 years old, and >65 years old, who were pregnant/breast feeding or not using birth control methods; subjects who had recently used study medications, subjects who had other co-morbid conditions, articles with diseased oriented evidence (DOE), or articles published before 1996. Summary statistics were reported using: RBI, ABI, NNT, RRI, ARI and NNH.

OUTCOMES MEASURED

The outcomes measured the decrease in frequency of HA/Migraines by 50% responder rate analysis. Treatment responder rate assessed using the Physician Global Assessment 9 point scale (+4 = clearance of signs and symptoms and -4 = very marked worsening). Safety and tolerability was also measured by looking at the nature and frequency of adverse reactions by treatment related adverse reaction reports.

RESULTS

Two randomized control trials (Mathew, Cady) in this systematic review compared onabotulinumtoxinA to topiramate, and the third randomized control trial (Dodick) compared onabotulinumtoxinA to placebo. One of the studies (Cady) studied the two groups (onabotulinumtoxinA vs. topiramate) for 12 weeks, followed by an open label phase from week 14-26 for the patients who were considered non-responders. Mathew et al. made assessments at 1,3,6,9 months. The third study (Dodick) compared onabotulinumtoxinA to placebo for 24 weeks, followed by a 32 week open label phase including 3 injection cycles.

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Dodick[2] (2010)	Double blind RCT of the PREEMPT clinical program (Open label phase)	1384 adults	18-65 years old	-age 18-65 years with a history of chronic migraine meeting the diagnostic criteria	Subjects with continuous headaches, or if the subject had used any headache prophylaxis medication within 4 wks prior to the start of baseline, + urine preg test, or had previous exposure to Botox	0	Randomized to receive onabotulinumtoxinA (155-195U) or placebo injections across 31 fixed sites in two 12 week injection cycles, then open label with 3 injection cycles to 32 weeks
Cady[1] (2010)	Double blind RCT (Open label phase)	59 adults	18-65 years old	-age 18-65 years with criteria for CM	Females who were pregnant, breast feeding, or planning to become pregnant. Headache disorders other than CM, medical disorders, liver or renal impairment, ketogenic diets, previous exposure to Botox/topiramate, recent drug/ETOH abuse	15	Randomized to 200 U of onabotulinumtoxinA plus placebo tablets, or topiramate 25mg daily, escalated to 100mg plus placebo injections for 12 weeks. Open label phase for additional 12 weeks.
Mathew[6] (2009)	Double blind RCT	60 adults	18-65 years old	- age 18-65 years with criteria for CM non attributable to another cause	Females who were pregnant, breast feeding, or planning to become pregnant. Headache disorders other than CM, pts who previously used study medications for any reason	24	Randomized to onabotulinumtoxinA – max 200U dose plus oral placebo, compared to topiramate – 4 wk titration to 100mg/day, optional 200mg/day plus placebo saline injections

The study by Cady et al. was an open label extension study of 26 weeks from a 12 week experiment. There were 59 participants who began the study and 15 discontinued (8 topiramate and 7 botox subjects). Only 20 subjects (9 from topiramate group and 11 from onabotulinumtoxinA group) volunteered for the extension[1]. The comparison of topiramate (initiated at 25mg and escalated to 100mg) to onabotulinumtoxinA (up to 200 units) looked at the treatment responder rate based on the Physician Global Assessment 9-point scale (+4 = clearance of signs and symptoms and -4 = very marked worsening)[1]. At week 12, the topiramate group had 17/24 (70.8%) improved compared to 19/24 (79.2%) in the onabotulinumtoxinA group[1]. Table 2 shows relative benefit increase for treatment responder rate at 12 weeks. The relative benefit increase (RBI) was calculated to be 12% and absolute benefit increase was 8.4%. Numbers needed to treat (NNT) was calculated as 12, meaning that 12 patients need to be treated with onabotulintoxinA compared to topiramate, in order to have one person benefit from this type of treatment at 12 weeks.

Table 2: Benefit of onabotulinumtoxinA on treatment responder rate (improvement of signs/symptoms)

CER	EER	RBI	ABI	NNT
70.8%	**79.2%**	**12%**	**8.4%**	**12**

The study conducted by Mathew et al. started out with 60 subjects and in the end 24 withdrew from the study (40%). In the topiramate group 24.1% discontinued the study because of treatment related adverse events, and 7.7% discontinued the study in the

onabotulinumtoxinA group[7]. For the 36 who participated in the full length of the study; at six months of treatment, the onabotulinumtoxinA group (58.3%), and topiramate (31.8%) reported a ≥50% reduction in HA/Migraine days, as seen in table 3[7]. The relative risk benefit (RBI) was calculated to 83.3%, and absolute benefit increase (ABI) was 26.5%. NNT was calculated to be 4, which means 4 people must be treated with onabotulinumtoxinA for 6 months in order for 1 person to benefit from this treatment when compared to topiramate.

Table 3: Benefit of onabotulinumtoxinA with reduction in HA/Migraine days

CER	EER	RBI	ABI	NNT
31.8%	**58.3%**	**83.3%**	**26.5%**	**4**

The study by Dodick et al, had 1384 and all participants remained throughout this 24 week study. Of the 688 participants in the onabotulinumtoxinA group, 47.1% at week 24 had at least 50% decrease from baseline in frequency of headache days when compared to 35.1% of the 696 participants given placebo[3]. As shown in table 4, the RBI was 34%, and the ABI was 12%. The NNT came out to 8, meaning that 8 patients treated with onabotulinumtoxinA, one person would benefit from this treatment compared to placebo.

Safety and tolerability was looked at, and the nature and frequency of the adverse events (AE's) were similar for both groups[3]. Most AE's were mild to moderate; total adverse events occurred in 62.4% of patients in the onabotulinumtoxinA group, and 51.7% of the patients in placebo group, as shown in table 5[3]. The RRI was 20.7%, ARI was 10.7%. The numbers needed to harm (NNH) was calculated to be 9; this means that if 9 patients were treated with onabotulinumtoxinA for 24 weeks, one more person would be harmed by the treatment than control. Table 6 shows overall AEs reported in the 24 week, double bind

phase. Serious adverse events only occurred in 4.8% of the onabotulinumtoxinA group and 2.3% in the placebo group. No deaths were reported from this study[3].

Table 4: Benefit of onabotulinumtoxinA at frequency of headache days from baseline to all time points

CER	EER	RBI	ABI	NNT
35.1%	**47.1%**	**34%**	**12%**	**8**

Table 5: All AE's from the onabotulinumtoxinA injections when compared to placebo

CER	EER	RRI	ARI	NNH
51.7%	**62.4%**	**20.7%**	**10.7%**	**9**

Table 6: Summary of Overall AEs reported in 24 weeks[3]

	OnabotulinumtoxinA (687)	**Placebo (692)**
All adverse events	492 (62.4%)	358 (51.7%)
Treatment related AEs	202 (29.4%)	88 (12.7%)
Serious adverse events	33 (4.8%)	16 (2.3%)
Treatments related, serious AEs	1 (0.1%)	0 (0.0%)
Discontinuations related to AEs	26 (3.8%)	8 (1.2%)
Death	0 (0.0%)	0 (0.0%)

DISCUSSION

This systematic review investigated three RCTs for the effectiveness of onabotulinumtoxinA in reducing the number of chronic migraines (CM) in patients 18-65 years old. All of these studies demonstrated the effectiveness of onabotulinumtoxinA in reducing the frequency of CMs, and demonstrating a treatment response rate where signs and symptoms of CMs were reduced. The study by Dodick et al, demonstrated that this drug is also safe and tolerable when compared to placebo.

Until recently, patients with CM have been excluded from prophylaxis trials because the thought was that they are treatment resistant[3]. However, due to the amount of people who suffer from this terrible illness, it calls for some attention. OnabotulinumtoxinA is FDA approved for chronic migraines (≥15 days/month with ≥4 hours/day headache duration) in adults. Administration of the drug is by a 30 gauge needle to a total of 31 sites[8]. As of right now, if used chronically, the long term effects are unknown.

There are various limitations among the studies presented in this review. In the Cady et al. study, the use of an active comparator rather than placebo, may have made the study stronger. The investigators in this study were more sophisticated in the evaluation of migraine response than the broader population of physicians treating migraines; therefore, it does not reflect accurate clinical assessment. The sample size of 44 may not have been sufficient enough to represent the CM population. A small sample size of only 40 also occurred in the study done by Mathew et al. In addition, Dodick et al. did not include an active comparator, nor was there a notable placebo response in this study.

CONCLUSION

OnabotulinumtoxinA is a safe and effective treatment for chronic migraine prophylaxis and treatment. The treatment response rate and decrease in number of migraines was statistically significant in all three studies. Future studies need to incorporate cost of this treatment along with its effectiveness, compared to other treatments. If this treatment becomes popular and is widely used in the future, it would be important to examine the long term side effects of this drug. Continued research on onabotulinumtoxinA for prophylactic use for chronic migraines will be very beneficial to patients who do not have control with other medications.

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