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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Botulinum Toxin A for Chronic Migraines: Clinical Effectiveness

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Research Questions

1. What is the clinical effectiveness of botulinum toxin A for patients with chronic migraines?
2. What is the clinical effectiveness of botulinum toxin A plus opioid derivatives for patients with chronic migraines?

Key Findings

Two systematic reviews, six randomized controlled trials, and two non-randomized studies were identified regarding the clinical effectiveness of botulinum toxin A for patients with chronic migraines.

Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2013 and December 12, 2017. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with chronic migraines
Interventions	Q1: Botulinum toxin A: • OnabotulinumtoxinA (Botox); • IncobotulinumtoxinA (Xeomin); • AbobotulinumtoxinA (Dysport Therapeutic) Q2: Botulinum toxin A + an opioid derivative (e.g., codeine)
Comparators	• Pharmacotherapy interventions, including: ○ Tricyclic antidepressants ○ Beta blockers ○ Anticonvulsants ○ Calcium channel blockers ○ Serotonin-norepinephrine reuptake inhibitors • Non-pharmacological interventions, including: ○ Behavioural therapies ○ Physical therapy ○ Lifestyle modifications ○ Natural products • Placebo
Outcomes	Q1: Clinical effectiveness (benefit/harm), reduction in headache/migraine episodes, safety

	Q2: Opioid usage outcomes (e.g., number of patients who cease opioid usage, reduction in opioid usage), clinical effectiveness (benefit/harm), safety
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

Two systematic reviews, six randomized controlled trials, and two non-randomized studies were identified regarding the clinical effectiveness of botulinum toxin A for patients with chronic migraines. No relevant health technology assessments or meta-analyses were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Two systematic reviews (SRs),[1-2] six randomized controlled trials,[3-8] and two non-randomized studies[9-10] were identified regarding the clinical effectiveness of botulinum toxin A (BTX-A) for patients with chronic migraines (CM). Detailed study characteristics are provided in Table 2.

Conclusions from most of the identified studies[2,5-6,9-10] (and pooled analyses of the PREEMPT trial[3,-7-8]) indicated that BTX-A provided some relief for patients with CM; however, it was observed to be associated with increased risks of adverse events and withdrawals due to adverse events in one SR.[2] Conversely, the authors of the other identified SR that met the inclusion criteria concluded that there was uncertainty associated with whether BTX-A reduced the frequency of headache days and acute headache pain medication or was associated with any impact on functioning when compared to placebo.[1]

Table 2: Description of the Included Studies and Their Conclusions

Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Conclusions
Systematic Reviews					
Kim et al.,[1] 2014	• Comparing BTX injection to PL (saline) in patients with CM • 6 publications describing 3 PL-controlled RCTs included • N=1444	• BTX-A	• Placebo (saline injections)	• Frequency of headache days • Reduction in acute headache pain medication • Impact on functioning	• Uncertain whether BTX reduces frequency of headache days, acute headache pain medication, or has any impact on functioning when compared to saline • BTX may results in little/no difference in headache hours,

Table 2: Description of the Included Studies and Their Conclusions

Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Conclusions
					episodes, or QoL • Effects of repeated BTX during ≥ 1 year follow-up are unknown
Shamliyan et al, 2013[2]	• Assessing comparative effectiveness and safety for community-dwelling adults with CM or episodic migraines[a] • 245 publications of RCTs and 76 NRS included • BTX formulations examined in N=4,237 (20 RCTs)	• BTX formulations	• Inactive controls (PL) • Non-pharmacologic interventions • Other drugs	• Prevention of CM or episodic migraines[a]	• BoNTA more effective at reducing month CM attacks (≥ 50%) compared with PL (low strength evidence from 3 RCTs, n=459) • BoNTA produced inconsistent improvements in QoL • Per 1000 treated adults: ○ 170 (95% CI 82 – 258) would experience ≥50% reduction in migraine frequency ○ 155 (95% CI 90 to 220) would experience adverse effects ○ 26 (95% CI 10-43) would WDAE • No differences in CM prevention were identified when comparing BoNTA with topiramate and divalproex • ***Major conclusion:*** BoNTA reduced migraine attacks in patients with CM but increased the risk of AEs and WDAEs
Randomized Controlled Trials					
Matharu et al. 2017[3]	• Determine whether BoNTA has impact on headache-day severity in non-responding patients with CM • Pooled analysis of data from PREEMPT • 24-week, 2-treatment cycle,	• BoNTA	• PL	• Reduction in number of severe headache days • Average daily headache severity	• Patients with CM deemed non-responders (based on analysis of headache frequency alone) appear to achieve clinical meaningful relief from headache intensity upon receiving BoNTA when compared to PL after 24 weeks • Between group differences were

Table 2: Description of the Included Studies and Their Conclusions

Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Conclusions
	parallel, DB PL-controlled trial followed by 32-week, 3-treatment cycle OL phase)				reduced or non-significant at week 56
Lipton et al, 2016[4]	• Patients with CM from PREEMPT • N=1,236 • DB RCT phase (24 weeks) followed by 36 week OL phase	• BoNTA (DB phase) • O/O (OL phase; n=607)	• PL (DB phase) • P/O (OL phase; n=629)	• HRQoL endpoints (over 56 weeks); including HIT-1 and MSQ	• Benefits of BoNTA on HRQoL versus baseline were evident through the OL phase • *"Statistical superiority in favor of O/O was demonstrated for HIT-6 through 48 weeks and for MSQ (role restrictive) at 56 weeks."*[4]
Shehata et al., 2016[5]	• Pilot RCT comparing rTMS vs BTX-A • N=29	• BTX-A (n=15)	• rTMS (n=14)	• Primary outcomes were headache frequency and severity • Secondary outcomes were 25-item HDI, HIT-1, and number of acute medications	• Reduction of all outcomes measures observed in both treatment groups • The reductions in all outcome measures were more sustained in the BTX-A group • Both therapies were well tolerated
Hou et al, 2015[6]	• Compared the fixed (muscle) – site and acupoint-site injections with BoNTA and PL • Patients had either CM or episodic migraines[a]	• BoNTA (2.5 U each site, 25 U per subject) injection at fixed-sites (n = 41); including occipitofrontalis, corrugator supercilii, temporalis and trapeziue • BoNTA acupoint-sites (n = 42); including Yintang (EX-HN3), Taiyang (EX-HN5), Baihui (GV20), Shuaigu (GB8), Fengchi	• PL (n=19)	• Efficacy of fixed-versus acupoint injection at reducing frequency, intensity, and duration	• BoNTA administration for migraines is effective • Acupoint injections of BoNTA appear to show more efficacy than fixed-site injections

Table 2: Description of the Included Studies and Their Conclusions

Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Conclusions
		(GB20) and Tianzhu (BL10).			
Silberstein et al., 2015[7]	• To assess whether treatment non-responders (from cycle 1) will respond in cycle 2 and whether treatment non-responders (from cycles 1 and 2) will respond in cycle 3 • Used pooled data from the PREEMPT trial	• BoNTA (n=688)	• PL	• Non-responders response to subsequent cycles of treatment with BoNTA • Cumulative hours of headache and HRQoL outcomes	• A meaningful proportion of patients with CM that were non-responders to cycle 1 were responders in cycles 2 or 3
Aurora, et al., 2014[8]	• Patients with CM were part of the PREEMPT trial • This is a secondary assessment of patients receiving 5 treatment cycles • N=1,005	• BoNTA (O/O; n=513)	• PL (n=492; 2 cycles of PL and 3 cycles of BoNTA [P/O])	• Multiple headache symptom measures	• This subgroup analysis demonstrated improvements in O/O with the multiple headache outcomes compared to the P/O group • These results suggest that better outcomes were achieved in those patients on BoNTA earlier (with outcomes assessed at 56 weeks)
Non-Randomized Studies					
Dodick et al., 2015[9]	• Assessed results from the PREEMPT trial and a topiramate trial • Patients with CM	• BoNTA	• Topiramate	• Headache prophylaxis in CM (frequency headache days and migraine days) • Responder rates, HRQoL, safety, tolerability, and discontinuation	• Statistically significant and clinically relevant treatment benefits were evident from the clinical data for both BoNTA and topiramate • The results support the use of both agents for meaningful headache prophylaxis in CM
Diener et al., 2014[10]	• Pooled analysis from 4 DB PL-	• BoNTA	• PL	• Safety and tolerability	• Multiple treatments with BoNTA doses of 75-260 U

Table 2: Description of the Included Studies and Their Conclusions

Author, Year	Study Characteristics	Interventions	Comparators	Outcomes	Conclusions
	controlled RCTs (two phase II and two phase III) • N=2,436 (n=1,997 received ≥ 1 dose of BoNTA)				administered every 12 weeks were tolerated well in patients with CM

AE – adverse event; BTX = botulinum toxin; BTX-A = botulinum toxin A; BoNTA = Onabotulinumtoxin A; CI = confidence interval; CM = chronic migraine; DB = double blind; HDI = Henry Ford Hospital Headache Disability Inventory; HIT-1 = Headache Impact Test; HRQoL = health-related quality of life; MSQ = Migraine-Specific Quality of Life Questionnaire; NRS = non-randomized studies; OL = open label; PL = O/O = BoNTA/BoNTA; placebo; P/O = placebo/BoNTA; PREEMPT = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy; QoL = quality of life; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; WDAE = withdraw due to adverse events.

[a] Information regarding episodic migraines is not provided; only for CM.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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Randomized Controlled Trials

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Non-Randomized Studies

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Appendix — Further Information

Previous CADTH Reports

11. CADTH Canadian Drug Expert Committee (CDEC) clinical review report: onabotulinumtoxinA (Botox — Allergan Inc.)[Internet]. Ottawa: CADTH; 2015 July [cited 2018 Jan 2]. Available from: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0345_Botox_Migraine_CL_Report_e.pdf
12. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: onabotulinumtoxinA (Botox — Allergan Inc.)[Internet]. Ottawa: CADTH; 2014 May 28 [cited 2018 Jan 2]. Available from: https://www.cadth.ca/media/cdr/complete/SR0345_complete_Botox-May-30-14.pdf
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Randomized Controlled Trials

Currently Recruiting

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Alternative Population – Patients with Chronic Migraines and Co-Morbidities

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Alternative Intervention – Combined Intervention

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Non-Randomized Studies

No Comparator

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PubMed: PM28458982

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No Comparator - Patients with Chronic Migraine and Acute Headache Medication Overuse

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No Comparator - Refractory/Resistant Migraines

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Alternative Outcome

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Non-Completed Studies

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Qualitative Studies

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