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Research Submission

Triptans for Acute Migraine: Drug Class Review to Help Inform Policy Decisions

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Background/Objective.—In Ontario, triptans are publicly funded through the Ontario Drug Benefit's Exceptional Access Program, a prior authorization program. However, it was unclear whether this listing aligned with current evidence of safety and effectiveness for triptans in migraine. Using a comprehensive and novel drug class review framework, we describe our review of triptans for the management of acute migraine to evaluate the appropriateness of triptan listing on the public drug formulary in Ontario.

Methods.—This supplement in *Headache* highlights four key components of the triptan drug class review, including findings from a qualitative analysis of patient and clinician perspectives, a systematic review and network meta-analysis of clinical trial evidence, a pharmacoepidemiologic analysis comparing utilization trends across Canada, and a reimbursement-based economic analysis.

Results.—We found that triptans were efficacious and safe for the treatment of acute migraine. However, Ontario has among the lowest rates of publically funded triptan use in Canada, which may be due to the highly restrictive nature of access to triptans in Ontario. Expanding access to triptans via a less restrictive listing (eg, Limited Use) would potentially increase use by 20-fold, with increase in costs of approximately 220%.

Conclusion.—Based on findings from our multi-faceted review and after stakeholder review and input from the Citizens' Panel, two policy options for triptans were recommended for Ontario's publically funded drug program: Limited Use access or coverage via the Exceptional Access Program, both options including quantity limits of 12 units per month.

Key words: migraine, triptan, public drug coverage

Abbreviations: EAP Exceptional Access Program, OPDP Ontario Public Drug Programs, ODB Ontario Drug Benefit, ODPRN Ontario Drug Policy Research Network

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Triptans are selective 5-hydroxytryptamine receptor agonists that are recommended for use in the management of acute migraine.[1,2] Seven triptans are commercially available: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Triptans are available on the public health plans of all provinces and territories in Canada. In Ontario, triptans are available through the publicly funded drug program for eligible individuals via the EAP, a prior authorization program (Table 1). However, it is uncertain how this listing impacts patient access to these products and whether it aligns with current evidence of safety and effectiveness of triptans in the management of acute migraine.

Furthermore, a potential concern with frequent use of triptans (and other medications used in the treatment of acute migraine headaches) is development of medication overuse headache.[3] To avoid medication overuse headache, the newly released Canadian guidelines for treatment of acute migraine suggest avoidance of use of triptans, ergots, opioids, or combination analgesics on more than 9 days per month.[1] Similarly, the International Headache Classification defines triptan overuse headache as regular intake of 1 or more triptans on 10 or more days per month for more than 3 months.[4] However, Ontario's current criteria for access to these products do not include any limits to quantity dispensed.

In order to evaluate the efficacy and safety of triptans and to provide evidence-informed recommendations for reimbursement strategies for the Ontario Ministry of Health and Long-Term Care,[5] a comprehensive drug class review was undertaken. Although the focus for this review was for the Ontario public drug plan, the research findings from our drug class review provide contextualizing information for other provinces and jurisdictions.

This supplement in *Headache* highlights 4 key components of the triptan drug class review including findings from a qualitative analysis of patient and clinician perspectives, a systematic review and network meta-analysis of clinical trial evidence, a pharmacoepidemiologic analysis comparing utilization trends across Canada, and a reimbursement-based economic analysis. Using the findings from these studies, we summarize the evidence related to the use of triptans for migraines, and outline a set of policy options that could be considered by the Ontario Public Drug Programs (OPDP).

The OPDP is a division within the Ontario Ministry of Health and Long-Term Care that is responsible for the province's publicly funded drug benefit programs such as the Ontario Drug Benefit (ODB) Program. The ODB program provides drug coverage to individuals receiving social assistance, persons 65 years and older, residents of homes for special and long-term care as well as patients receiving home care services.[6] The OPDP, with the advice of the expert advisory committee, governs the approval process for drugs within program formularies.

Table 1.—Ontario Drug Benefit (ODB) Formulary: Listing Options

Type of Listing	Reimbursement of Drugs	Rationale
General Benefit	• No specific conditions for reimbursement	• Have been determined to be efficacious, safe, and cost-effective
Limited Use	• Specific clinical criteria/conditions must be met for reimbursement • Less restrictive than Exceptional Access Program; a specified code is entered at the pharmacy level and no prior authorization is required	• Have the potential for widespread use outside the indications for which benefit has been demonstrated • May be useful but are associated with predictable severe adverse effects and a less toxic alternative is available as a general benefit • May be very costly and a lower-cost alternative is available as a general benefit
Exceptional Access Program (EAP)	• Prior authorization program for drug/indication that has been approved for funding	• Strong clinical evidence is not available to support efficacy and/or cost-effectiveness, when compared with drugs on the ODB formulary

In order to provide the OPDP with pertinent and timely research, the Ontario Drug Policy Research Network (ODPRN) was developed as a collaboration between policymakers and researchers from across Ontario.[7] Although initially established to provide analyses for individual research requests, changes in the pharmaceutical environment and the emergence of novel expensive therapeutic agents required the need for more comprehensive analyses. In order to respond to these challenges, the ODPRN expanded its mandate to include formulary modernization through comprehensive drug class reviews.

A novel framework was developed by the ODPRN that expands on the structure of existing drug class reviews, in particular those developed by the National Health Service in the United Kingdom and the Canadian Agency for Drugs and Technologies in Health.[8,9] The ODPRN framework incorporates: (1) patient and healthcare professional perspectives; (2) contextualization of the available evidence and experience from other regions; (3) pharmacoepidemiologic analyses of prescribing patterns across Ontario and when applicable, across Canada; (4) rapid reviews and network meta-analysis of the literature on efficacy and safety; (5) reimbursement-based economics (ie, economic analyses designed to establish the impact of various reimbursement options); (6) identification of barriers to implementation, health equity, and accessibility; (7) stakeholder feedback; and (8) policy options of potential drug reimbursement models (see Table 1). This structure was designed to facilitate the identification of recommendations on policy-based approaches to optimize resource use, safety, effectiveness, and appropriateness of prescribing of medications to Ontarians.

Using the innovative 8-step approach for drug class reviews as outlined in Table 1, the results of each component of the review is summarized. Additional and more detailed information can be found as companion articles in this supplement of *Headache*.

Step 1: Patient and Healthcare Professional Perspectives.—Through 1-on-1 interviews, a qualitative study investigating the perspectives and experiences of patients, physicians, and pharmacists was conducted.[10] Migraineurs were found to experience significant productivity losses and may become socially isolated during repeated migraine episodes. For patients who used triptans, most patients stated that this drug class helped to restore daily functionality and the ability to work. However, challenges were identified, including finding the most effective triptan for an individual patient. Although many patients interviewed had access to these drugs through private insurance plans, coverage limitations (eg, quantity limits) were found to impact treatment adherence, as patients are anxious about exceeding the monthly coverage limit.

Step 2: Local and Historical Context, Including Environmental Scan.—Canadian and international guidelines were reviewed for the use of triptans for patients with moderate to severe acute migraine.[1,2,11] Triptans are available as insured benefits through all public drug programs in Canada, either as a general benefit or as a restricted benefit.[12] Triptans are listed as general benefits (without restrictions) in 3 publicly funded programs, general benefits (with quantity limits) in 1, and restricted access in 8 publicly funded programs, including Ontario where they are listed as part of EAP. Five provinces impose a quantity limit of 6 doses/month, whereas 4 jurisdictions have a quantity limit of 12 doses/month.

In order to help prevent medication overuse headaches, quantity limits for triptans have been used in various jurisdictions, both public and private. Another possible benefit with the use of quantity limits is resultant cost-savings for the payer.[13-15] However, a potential concern identified with imposition of severely restrictive quantity limits is that some patients with migraines may delay treatment until the pain is moderate or severe in order to conserve the limited number of tablets allotted per month; this is similar to the findings of the patient interviews that were conducted by the qualitative research team.[10,16,17] This strategy employed by some patients is in contrast to that recommended by most guidelines; in general, it is recommended that patients treat migraine headaches as early as possible during their migraine attacks, when pain is still mild.[1,2,11,18] Early treatment with triptans has been shown to result in increased efficacy, with superior pain-free relief.[1] However, for patients with frequent migraine attacks, the strategy of early treatment should be used

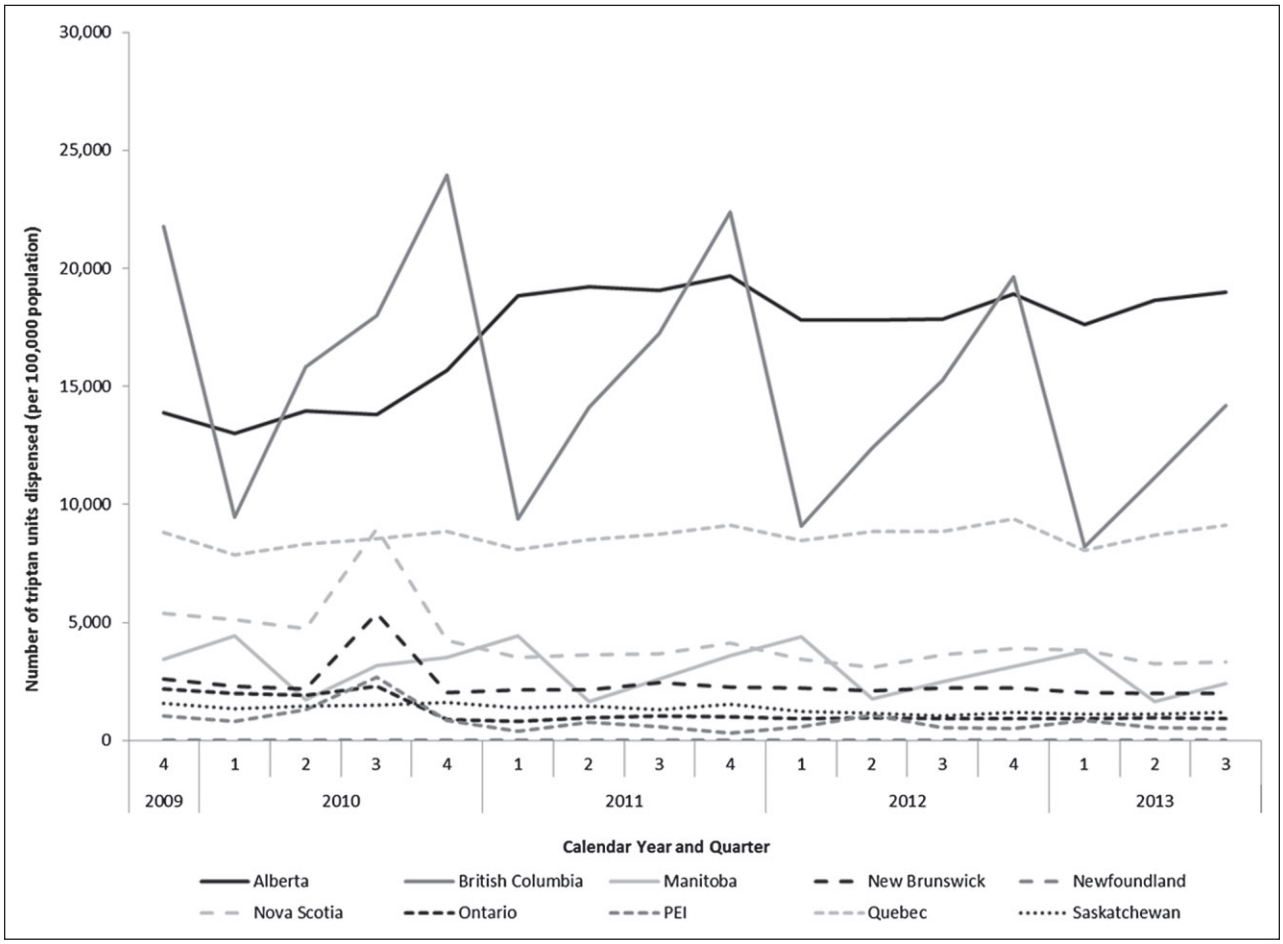

Figure.—Population-adjusted utilization of provincially funded triptans in Canada, by province.
Note: The cyclic trend in rates of publicly funded triptan use in British Columbia is likely driven by patterns of deductible payments and associated stockpiling of drugs near the end of the coverage period.

cautiously as indiscriminate use may potentially lead to the development of medication overuse headache. A quantity limit of 12 doses per month has been recommended by some clinicians in order to allow the patient flexibility to treat migraines early, provide cost savings, and not to lead to medication overuse headache.[16]

Step 3: Local Utilization Trends.—An important component of the Drug Class Review process is the use of claims data for determining utilization of triptans in Ontario as well as across Canada. In Ontario, health administrative data for the entire population of Ontario is linked and includes demographic information, physician claims, hospitalization, and drug data for ODB program recipients (approximately 2.5 million people).[6]

Triptan use (via public or private payers, or cash) in Canada has increased by 13% over the past 4 years. Ontario has among the lowest rates of publicly funded triptan use in Canada (Figure), which is balanced by having among the highest rates of triptan use paid by other means (eg, cash, private insurance).[19] This may be due to the highly restrictive nature of access to triptans in Ontario. However, for patients who do have access via the publicly funded program in Ontario, approximately 10% exceeded 18 units per month, placing them at risk of developing medication-overuse headache.[20]

Step 4: Rapid Reviews and Network Meta-Analyses for Efficacy and Safety.—Overall, the results of our systematic review and network meta-analysis found that triptans were efficacious for the

treatment of acute migraine, as compared with ergots, acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs).[21] For 2-hour headache relief, standard dose triptan achieved better outcomes (42-76% response) than ergots (38%), and equal or better outcomes than NSAIDs, aspirin, and acetaminophen (46-52%). When comparing triptans vs triptans, most triptans (except for frovatriptan) had a significant effect on pain relief, as measured by 2-hour headache relief. There was no high quality evidence of differences between the triptans in terms of safety (eg, cardiovascular events, risk of serotonin syndrome) and tolerability.

Step 5: Reimbursement Based Economics.—A systematic review of the cost-effectiveness literature identified a total of 21 published economic analyses of triptan use. Overall, the weight of evidence suggests that triptans are cost-effective relative to other acute migraine treatments, including ergots and aspirin (acetylsalicylic acid) in combination with an antiemetic.[22,23]

Several alternative reimbursement strategies were considered in the reimbursement-based economic analysis including maintaining triptans on EAP or changing the listing to general benefit or Limited Use (Table 2).[23] Limited Use is a much less restrictive option for reimbursement than EAP, and results in increased accessibility to applicable individuals under the ODB program. Although both Limited Use and EAP are associated with clinical criteria/conditions for reimbursement, for Limited Use, only a code (assigned by the prescriber) is required at the pharmacy level and no prior authorization is required. This is in contrast to drugscovered under the EAP

Table 2.—Framework for Ontario Drug Policy Research Network (ODPRN) Drug Class Reviews

Review Process	Description
Step 1: Patient and Healthcare Professional Perspectives	• Obtain relevant contextual information (eg, 1-on-1 interviews of patients, physicians, pharmacists)
Step 2: Local and historical context, including environmental scan	• Consolidate knowledge from guidelines, labeling information • Summarize funding policies in other jurisdictions both nationally and internationally
Step 3: Local utilization trends	• Access databases to understand historical prescribing trends in Ontario and Canada
Step 4: Rapid reviews and network meta-analyses (NMA) for efficacy and safety	• Systematic review and NMA (where applicable) of the published literature for efficacy and safety
Step 5: Reimbursement-based economics	• Develop drug reimbursement models to identify optimal, evidence-based price points and potential for innovative reimbursement (eg, price caps, risk-sharing)
Step 6: Health equity and accessibility	• Assess implications of policy changes on health equity • Include consideration of sex and gender-based analyses
Step 7: Stakeholder feedback	• Obtain feedback from stakeholders (eg, patients, healthcare providers, industry) throughout the drug class review process including workshops and review of research plans and report/ recommendations • Citizen's Panel recommendations
Step 8: Policy Options	• Options presented to the Ontario Ministry of Health and Long-Term Care based on all components of the review and may include: ○ Expansion of access to drugs on the formulary ○ Revision or restriction of access to drugs ○ No change to current listing status ○ Alternative drug reimbursement models ○ Education of prescribers regarding appropriate prescribing

program, which requires written requests for prior authorization for reimbursement.

In addition, each of the reimbursement strategies considered generic substitution and/or quantity limits of 6, 12, or 18 units/month. Proposed EAP strategies indicate a 16% to 84% reduction in total triptan costs from the current $1.8 million annual cost, and no change to the expected number of triptan users. Alternative Limited Use strategies suggest a 126% to 302% increase in total costs (to $3.9-$7.1 million annually), and an increase in the number of users by 1900% (from approximately 1200 users to 25,000 users).

Step 6: Health Equity and Accessibility.—Lack of accessibility to triptans, especially in terms of affordability, was a key finding that was highlighted by participants interviewed in the qualitative study.[10] Despite the availability of triptans through EAP, some physicians perceived that accessing triptans through this program was a significant and cumbersome barrier. As well, some physicians were unaware that triptans were available through EAP. Based on prevalence of use of triptans in Alberta (which has the highest number of triptan units dispensed per 100,000 eligible population in Canada and has no restrictions or quantity limits for those under 65 years of age), proposed general benefit or limited use reimbursement options would potentially expand triptan use by 1900% (from approximately 1200 current number of patients to 25,000 patients).

Step 7: Stakeholder Feedback.—Three main policy options were identified for stakeholder review. These included a general benefit listing for triptans (no quantity limits), a Limited Use listing with quantity limits of 12 doses/month, and continued listing of triptans through the EAP with a quantity limit of 12 doses/month. A quantity limit of 12 doses per month was chosen as this would not lead to medication overuse headache and permitted patient flexibility to treat migraines early. As well, oral triptans are most commonly packaged in blister packs of 6 tablets.

Stakeholder feedback on the research conducted and policy options proposed was sought from patients, healthcare providers, and industry representatives. As well, the ODPRN's Citizens' Panel, comprising 15 members of the general public, provided feedback on policy recommendations related to acceptability, accessibility, and affordability of the proposed recommendations from a societal perspective.[24] The members of the Citizens' Panel believed that placing quantity limits on triptans was an important consideration to ensure proper use and safety. In addition, the general benefit option was considered too liberal and did not consider physician accountability for limiting triptans. The Limited Use (with quantity limits) scenario was the most positively perceived option. The EAP option was considered a good alternative if improvements to the EAP process (eg, use of standardized forms) could be made to address some of the barriers to access that were identified in the qualitative study.

Step 8: Policy Options.—Our review of the evidence suggests that triptans are an effective and safe treatment for the management of acute migraine. However, under the current EAP in Ontario, only a fraction of potentially eligible patients are receiving this medication, likely due to considerable barriers to access through this program. A quantity limit of 12 was included for both recommendations to allow for patient flexibility to treat migraines early, provide cost savings, and not to lead to medication overuse headache.

Based on the results of the review, input from stakeholders, and feedback from the ODPRN Citizens' Panel, 2 primary reimbursement options for triptans were recommended as funding alternatives for the OPDP: Limited Use with quantity limit of 12 per month, or EAP with quantity limit of 12 per month (Table 3). Although both of these options recommend quantity limits, they have different implications from a cost and access perspective, and provide the OPDP options to balance cost against accessibility. The Limited Use option will potentially increase access 20-fold from the current 1200 users to 25,000 users. However, increased access will result in a threefold increase in cost (from $1.8 million to $5.6 million per annum). In contrast, listing of triptans through the EAP with quantity limits will not change accessibility of these agents, but may result in a reduction in expenditures of approximately 75% (from $1.8 million to $400,000 per annum).

Using the ODPRN framework, recommendations for policy changes for triptan reimbursement

Table 3.—Assessment of Reimbursement Options

	Limited Use with Quantity Limit (12 per month)	Exceptional Access Program with Quantity Limit (12 per month)
Accessibility	≈25,000 patients (20 × increase)	≈1200 patients (no change)
Budget impact (2014 expected cost)	221%↑ ($1.8 million to $5.6 million)	77%↓ (from $1.8 million to $400,000)
Safety concerns	Minimal risk of MOH	Minimal risk of MOH
Other considerations	Potential use in other headache disorders (eg, cluster headache)	Recommend improvements to the EAP process (eg, use of standardized forms) in order to increase accessibility

MOH = medication overuse headache.

were made to the OPDP. The recommendations incorporated all facets of the review including efficacy, safety, cost, utilization, accessibility, as well as input from all stakeholders and outlined the strengths and limitations of each option. Our unique framework provided valuable information that not only identified issues of safety, efficacy, and cost-effectiveness, but also provided contextualization regarding the listing of triptans in other jurisdictions, current utilization patterns, and perspectives of patients, providers, and other stakeholders.

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