1. Background

Headaches are one of the most common and debilitating disorders presenting to medical attention, affecting all ages and genders. Many headache sufferers turn to medication for relief from their headaches. Unfortunately, frequent use of some medications may lead to the development of medication overuse headache (MOH), which contributes to increasing headache frequency and resistance to future treatment (1). MOH is defined, as per the International Classification of Headache Disorders-3 beta (ICHD-3 beta), as headache occurring on 15 or more days per month in the context of 3 or more months of medication overuse (2). The worldwide prevalence of MOH is estimated at over 58 million, affecting up to 70% of patients with chronic daily headache, with a female preponderance of roughly 3:1 (1,3,4). Treatment of MOH typically involves withdrawal of overused medications, often with initiation of a prophylactic agent, although exact strategies vary by site, patient, and types of medications overused (5,6).

Adverse childhood experiences (ACE) are a known risk factor for the development of chronic migraine and chronic daily headache, possibly through the over-sensitization of brain pain pathways in early life (7,8). ACE is defined, in accordance with previous studies, as any of the following occurring before age 18: abuse (whether sexual, physical, or emotional), neglect (physical or emotional), or exposure to household dysfunction (parental violence or substance abuse, mental illness, criminal behaviour, and parental separation or divorce).

2. Study rationale

The risk factors for developing MOH are incompletely understood, although a history of migraine, smoking, a family history of substance abuse, and psychiatric disorders including depression, anxiety, and obsessive-compulsive disorder have been associated with MOH (9-12). The type of medication being overused is thought to influence the risk of developing MOH, with opioids and barbiturates carrying a higher risk than triptans or NSAIDs (13,14). Many patients with MOH meet DSM criteria for dependence on their overused medications, and indeed MOH has been posited to exist on a spectrum with substance abuse disorders (15).

Furthermore, while some patients are better able to successfully break a cycle of medication overuse than others, prognostic factors influencing successful medication withdrawal remain unclear. Although the type of overused medication may influence prognosis, a recent systematic review did not find a consistent correlation between overused medication and prognosis (6). Overall, the rate of successful medication withdrawal is estimated at 40-70%, with roughly 45% of these patients experiencing a reduction in their headache-related disability at 6 months (16-18). However, the relapse rate is high at 42% by 3 years in those treated with medications alone, vs 12.5% in those also receiving behavioural therapies (19), suggesting a possible behavioral component to ongoing medication overuse.

We aim to examine the frequency of ACE in patients with MOH, in particular in MOH related to narcotic use, and whether responsiveness to typical pharmacological methods of treating MOH is affected by the presence of ACE. Patients with ACE may require more intensive psychotherapy-based approaches to treating their MOH.

3. Research design and methods

We will perform a retrospective chart review of all patients newly assessed at the Women's College Hospital Centre for Headache between October 2015 and October 2016. Inclusion

criteria are 1) any age at time of assessment, 2) underlying diagnosis of chronic daily headache or migraine with or without aura, with superimposed MOH, 3) absence of another primary or secondary headache diagnosis, and 4) at least one follow-up visit within the first 6 months.

Data will be collected at the following time points: initial visit (T0), first follow-up visit at 0-3 months (T1), and second follow-up at 3-6 months (T2). We will record demographic data such as gender and age, disease information including diagnosis (presence of aura or other migraine subtypes), age at onset of headaches, headache frequency at time of assessment, presence of childhood migraine equivalents such as abdominal migraine, benign paroxysmal vertigo, benign paroxysmal torticollis, motion sickness, cyclic vomiting, infantile colic, and sleep walking/talking, smoking status, presence of alcohol use and age at first drink, presence of substance use, and duration of MOH if known. We will record whether patients attended an education session about lifestyle modifications and MOH prior to their first visit. We will document the presence or absence of ACE, including specifics as to type of ACE when available. At all visits we will record current medications including abortive and prophylactic agents as well as their doses and frequency (medication days per month). We will also document any complementary therapies such as psychotherapy. At all visits, we will document presence of psychiatric comorbidities and headache-related disability using well-validated scales including the Patient Health Questionnaire (PHQ-4) and Migraine Disability Assessment (MIDAS), respectively (20-22). We will document whether the patient and examiner feel that medication overuse has been successfully treated, and if so how long this process took.

The primary outcome will be to examine the frequency of ACE in patients with MOH. Our secondary outcomes will include an assessment of whether the presence of ACE affects responsiveness to typical pharmacological treatments for MOH, as measured by 1) reduction in MIDAS score, 2) change in MIDAS disability grade, 3) responder rate of 50% reduction in headache days per month, 4) change in PHQ-4 score, and 5) medication days per month.

4. Statistical analysis

We will first present a descriptive table of demographic and clinical information. Chi-square will be utilized to conduct two-proportion comparison. MIDAS scores will be analyzed as absolute values as well as by change in level of disability. PHQ-4 scores will be analyzed as absolute values. We will analyze ACE as binary (present or absent), multiple categories (types of ACE), and numerical data (number of different types of ACE). We will use ANOVA for continuous variables, and logistic regression for descriptive variables. Values will be expressed as mean ± standard deviation where applicable. A p-value of 0.05 will be deemed statistically significant.

5. Preliminary findings

Research Ethics Board approval for this study has been obtained (Women's College Hospital REB # 2016-0110-E), and a preliminary chart survey has identified 97 patients meeting inclusion criteria. Data collection is approximately two-thirds complete.

6. Study significance and future directions

This study aims to assess both the frequency of ACE in MOH and its effects on treatment responsiveness. Future work will include an extended follow-up period to examine relapse rates in patients with MOH and ACE. We hope to further the understanding of the most effective treatment methods for these complex patients, whose level of headache-related disability is high.

7. References

1. Kristoffersen E and Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. *Ther Adv Drug Saf* 2014;5(2):87-99.
2. International Classification of Headache Disorders-3 (beta version). Cephalalgia 2013;33:629–808.
3. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1545-1602.
4. Cheung V, Amoozegar F, and Dilli E. Medication overuse headache. *Current Neurology and Neuroscience Reports* 2015;15:509.
5. Kristoffersen E and Lundqvist C. Medication-overuse headache: a review. *Journal of Pain Research* 2014;7:367-378.
6. Chiang C, Schwedt T, Wang S, and Dodick D. Treatment of medication-overuse headache: a systematic review. *Cephalalgia* 2016;36(4):371-386.
7. Anda R, Tietjen G, Schulman E, Felitti V, and Croft J. Adverse childhood experiences and frequent headaches in adults. *Headache* 2010;50(9):1473-1481.
8. Tietjen G, Khubchandani J, Herial N, and Shah K. Adverse childhood experiences are associated with migraine and vascular biomarkers. *Headache* 2012;52(6):920-929.
9. Cevoli S, Sancisi E, Grimaldi D, Pierangeli G, Zanigni S, Nicodemo M, Cortelli P, and Montagna P. Family history for chronic headache and drug overuse as a risk factor for headache chronification. *Headache* 2009;49(3):412-418.
10. Hagen K, Linde M, Steiner T, Stovner L, and Zwart J. Risk factors for medication-overuse headache: an 11-year follow-up study. The Nord-Trondelag Health Studies. *Pain* 2012;153(1):56-61.
11. Munksgaard S and Jensen R. Medication overuse headache. *Headache* 2014;54(7):1251-1257.
12. Diener HC, Holle D, Solbach K, and Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. *Nat Rev Neurol* 2016;12:575-583.
13. Bigal M, Serrano D, Buse D, Scher A, Stewart W, and Lipton R. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008;48(8):1157-1168.
14. Starling A, Hoffman-Snyder C, Halker R, Wellik K, Vargas B, Dodick D, Demaerschalk B, and Wingerchuk D. Risk of development of medication overuse headache with nosteroidal anti-inflammatory drug therapy for migraine: a critically appraised topic. *Neurologist* 2011;17(5):297-299.
15. Radat F, Creac'h G, Guegan-Massardier E, Mick G, Guy N, Fare N, Giarud P, Nachit-Ouinekh F, and Lanteri-Minet M. Behavioral dependence in patients with medication overuse headache: a cross-sectional study in consulting patients using the DSM-IV criteria. *Headache* 2008;48(7):1026-1036.
16. Bigal M, Rapoport A, Sheftell F, et al. Transformed migraine and medication overuse in a tertiary headache centre – clinical characteristics and treatment outcomes. *Cephalalgia* 2004;24:483-490.
17. Zeeberg P, Olesen J, and Jensen R. Discontinuation of medication overuse in headache patients: Recovery of therapeutic responsiveness. *Cephalalgia* 2006;26:1192-1198.
18. Tassorelli C, Jensen R, Allena M, De Icco R, Sances G, Katsarava Z, Lainez M, Leston J, Fadic R, Spadafora S, Pgani M, Nappi G, and the COMOESTAS Consortium. A consensus protocol for the management of medication-overuse headache: evaluation in a multicentric, multinational study. *Cephalalgia* 2014;34(9):645-655.
19. Grazzi L, Andrasik F, D'Amico D, et al. Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. *Headache* 2002;42(6):483-490.
20. Stewart W, Lipton R, Kolodner K, Sawyer J, Lee C, and Liberman J. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. *Pain* 2000;88(1):41-52.
21. Stewart W, Lipton R, Dowson A, and Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology* 2001;56(6 Suppl 1):S20-28.
22. Seo J and Park S. Validation of the Patient Health Questionnaire-9 (PHQ-9) and PHQ-2 in patients with migraine. *J Headache Pain* 2015;16:65.