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**Epidemiology and qualitative aspects of  
medication overuse headache and non-  
adherence to prophylactic migraine treatment**

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**Institute of Medicine  
at Sahlgrenska Academy  
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### ABSTRACT

**Aim:** The aim was to analyze problematic medication use among persons with headache, focusing on overuse of acute medications, with subsequent medication overuse headache (MOH), and on underuse of prophylactic medication.

**Methods:** Data in Studies I and II came from a population survey in which 44 300 Swedes were interviewed by telephone about headache and medication use. In Study III, a questionnaire concerning adherence and beliefs about medicines was distributed to 174 consecutive migraine patients at a headache clinic. Study IV was a qualitative study, using grounded theory, in which 14 individual interviews were conducted with persons who fulfilled the diagnostic criteria for MOH.

**Results:** The prevalence of MOH in Sweden was 1.8% (95% C.I. 1.7–1.9). It was 2.8 times more common among women than among men and inversely associated with socioeconomic status. Fewer than half of those with MOH had made a headache-related visit to a physician during the previous year, and almost half used only over-the-counter (OTC) medications to treat their headaches. The proportion only using OTC medications was particularly high among the young. There were several differences indicating that the use of medications and the rate of health care contacts were unequal in relation to educational level. As for use of prophylactic medications, approximately one third of the migraineurs were considered non-adherent. The participants in the qualitative study perceived headaches as something that threatened to ruin their lives, and despite extensive efforts, they were unable to find any effective aid other than the acute medication. Because of this, the acute medication became indispensable to them.

**Conclusion:** Both overuse of acute medication and underuse of prophylactic medication are significant problems among persons with headache. Since both problems may lead to increased headaches, it is likely that many persons with headache carry an unnecessarily high disease burden.

**Keywords:** Headache, migraine, medication overuse headache, adherence, medication use, socioeconomic differences, beliefs about medicines, grounded theory

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# **SAMMANFATTNING PÅ SVENSKA**

## **Problematiske läkemedelsanvändning bland personer med huvudvärk**

Personer som har huvudvärk kan använda både förebyggande läkemedel och akutläkemedel för att behandla sin åkomma. Många använder inte sina läkemedel på det sätt som rekommenderas, vilket är problematiskt eftersom det kan leda till att huvudvärken börjar komma ännu oftare. Underanvändning av de förebyggande läkemedlen gör att den förebyggande effekten uteblir och överanvändning av akutläkemedlen kan leda till att man utvecklar en typ av kronisk daglig huvudvärk som kallas för läkemedelsöveranvändningshuvudvärk (LÖH).

Det övergripande syftet var att analysera problematisk läkemedelsanvändning bland personer med huvudvärk. I fyra olika delarbeten studerades 1) förekomsten av LÖH, 2) användning av läkemedel och hälso- och sjukvård bland personer med LÖH 3) följsamhet till ordinationer av förebyggande läkemedel bland personer med migrän, samt 4) tankar kring läkemedelsanvändning och huvudvärk bland personer som uppfyllde diagnoskriterierna för LÖH.

De första två frågeställningarna undersöktes genom en nationell telefonundersökning, där 44 300 slumpvis utvalda personer intervjuades. Den tredje frågeställningen undersöktes genom att dela ut en enkät bland personer med migrän på en svensk huvudvärksklinik. Frågeställning nummer fyra studerades genom kvalitativa intervjuer med 14 personer som med egna ord fick berätta om sina tankar kring huvudvärk och läkemedel.

Resultaten visade att 1.8% av Sveriges vuxna befolkning hade LÖH. Det motsvarar ca 140 000 svenskar. Sjukdomen var 2.8 gånger vanligare bland kvinnor än bland män och vanligare bland personer med lägre utbildning och inkomst än bland de med högre utbildning och inkomst. Ungefär hälften av de med LÖH uppgav att de alltid köpte sitt akutläkemedel receptfritt. När det gällde de förebyggande läkemedlen visade resultaten att ca 1/3 av migränpatienterna inte följde sin ordination. Deltagarna i den fjärde studien beskrev sin huvudvärk som något som hotade att förstöra deras liv. De hade lagt ner mycket kraft på att försöka hitta sätt att handskas med huvudvärken

men upplevde att det enda som verkligen hjälpte var deras akutläkemedel. Läkemedlet blev därför livsviktigt för dem.

Avhandlingen har genom de fyra delarbetena visat att både underanvändning av förebyggande läkemedel och överanvändning av akutläkemedel är betydande problem bland personer med huvudvärk.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. The articles have been printed in the thesis with kind permission of the publishers.

- I. Jonsson P, Hedenrud T, Linde M. Epidemiology of medication overuse headache in the general Swedish population. *Cephalalgia* (2011) 31(9):1015–22.
- II. Jonsson P, Linde M, Hensing G, Hedenrud T. Sociodemographic differences in medication use, health-care contacts and sickness absence among individuals with medication overuse headache. *The Journal of Headache and Pain* (2012) 13(4):281– 90.
- III. Hedenrud T, Jonsson P, Linde M. Beliefs about medicines and adherence among Swedish migraineurs. *The Annals of Pharmacotherapy* (2008) 42(1):39–45.
- IV. Jonsson P, Jakobsson A, Hensing G, Linde M, Moore C. D, Hedenrud T. Holding on to the indispensable medication – A grounded theory on medication use from the perspective of persons with medication overuse headache (submitted).

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# ABBREVIATIONS

ASA	Acetylsalicylic acid
BMQ	Beliefs about Medicines Questionnaire
CDH	Chronic daily headache
CI	Confidence interval
EFNS	European Federation of Neurological Societies
ICHD-II	International Classification of Headache Disorders, 2 <sup>nd</sup> edition
IHS	International Headache Society
MARS	Medication Adherence Report Scale
MOH	Medication overuse headache
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
OTC	Over-the-counter medication
TCA	Tricyclic antidepressant medication
TTH	Tension-type headache

# DEFINITIONS

Episodic headache	Headache that comes in distinct attacks fewer than 15 days per month, e.g. migraine or tension-type headache (1)
Chronic daily headache	Headache that is present on at least 15 days per month during the previous 3 months (2)
Medication overuse headache	A type of chronic daily headache that may develop in people with episodic headache who overuse acute medication. Overuse is defined as the use of ergotamine, triptans, opioids, or combination analgesic medication on $\geq 10$ days/month or use of simple analgesics or a combination of different medications on $\geq 15$ days/month, for $> 3$ months (3).
Acute headache medication	Medication that is used to treat headache symptoms when they occur
Prophylactic headache medication	Medication that is used to prevent headache attacks from occurring
Adherence	The extent to which a person's behavior—taking medications, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider (4)



# 1 INTRODUCTION

This thesis deals with medication use among people with headache. Headache is a burdensome disorder, and to manage the pain and the subsequent consequences on their daily lives, most people with headache use medications. They may use both preventive and acute medications. Some of the medications are obtained on prescription, whereas others are bought as over the counter (OTC) medication. Because of this diversity in medication use, a variety of issues may arise.

Many do not use their medications in the way it was prescribed (5). Adherence, that is, the extent to which a person's behavior corresponds with agreed recommendations from a health care provider (4), has probably been an issue for as long as medications have existed (6). As early as 440 BCE, Hippocrates noted that some patients did not take their medication as prescribed and that many later complained because the treatment did not help. Non-adherence to medical treatment is observed in all types of diseases, for example, acute and chronic, serious and non-serious, and in relation to both symptom alleviation and prophylactic treatment (4). It is a problem in headache as well as in other diseases (7).

In this thesis, I focus on two particular issues of medication use in headache, namely overuse of acute medications, with subsequent medication overuse headache (MOH), and underuse of prophylactic treatment. These issues are examples of medication use that cause problems because

- a) they differ from what was recommended and may thus lead to miscommunication and misunderstandings between patients and health care professionals, and
- b) assuming that the recommendations are sound and evidence based, any deviation from them may lead to problems in terms of negative health outcomes for the patients.

Both the overuse of acute treatment and the underuse of preventive therapy lead to increased headache frequency, and thus to negative consequences for the individual and increased costs for society (8, 9). The underlying reasons that people decide to use their medications in ways that, at least from a medical point of view, cause such negative effects are generally unknown.

## 1.1 Headache

Headache is a very common disorder. The lifetime prevalence has been estimated to be 99% among women and 93% among men (10). In Europe approximately 53% of the population are estimated to have had headache during the past year (11). In a Swedish study from 2008, 17% of the participants reported recurrent headaches during the past three months, and in an earlier study, 12% stated they had had this problem in the past two weeks (12, 13).

Headache is disabling and has consequences for the individual sufferers as well as for society. Persons with headache report negative effects on social activities as well as on relationships with family and friends (14). Headache also affects working ability. A large proportion of headache patients in primary care state that they have difficulties working full-time due to their condition (15). In an attempt to calculate the global burden of disease, headache disorders were included among the 10 most disabling conditions worldwide (16). In a recent estimation of the extent to which economic resources are lost to headache, the annual cost for headache among adults aged 18–65 years in the EU was estimated at € 173 billion (9).

There are many different types of headache. The International Headache Society (IHS) has developed a system of headache classification, the International Classification of Headache Disorders, 2<sup>nd</sup> edition (ICHD-II) (1). The system is an important guideline, used for classification of headache both in clinical practice and in research. All headache diagnoses in this thesis are based on this system and associated appendix criteria (1, 3).

The different types of headache may be divided into two categories, depending on how often the headaches occur, namely episodic headaches and chronic daily headaches. Episodic headaches are headaches that occur in distinct and recurrent attacks, as opposed to chronic daily headache (CDH), in which the headaches appear more frequently (3, 17). An overview of the headache disorders that are relevant for this thesis can be found in Table 1.

Table 1. *Overview of headache disorders*

<b>Primary episodic headaches</b>
Migraine
Tension-type headache
Other episodic headaches
<b>Chronic daily headaches</b>
Primary chronic daily headaches
Chronic migraine
Chronic tension-type headache
Other primary chronic daily headaches
Secondary chronic daily headaches
Medication overuse headache
Other secondary chronic daily headaches

### 1.1.1 Primary episodic headaches

Primary headaches are headaches that exist independent of other medical conditions, whereas secondary headaches are headaches caused by some underlying condition (1). Episodic headaches are headaches that occur in distinct and recurrent attacks. Primary episodic headaches are thus headaches that exist independent of other medical conditions and occur in recurrent attacks. The two most common types are migraine and tension-type headache (TTH) (11), and these two disorders will be described below.

#### **Migraine**

Migraine is a hereditary, chronic disorder with recurrent attacks of severe headache (18). The attacks are usually characterized by pulsating unilateral headache of medium to severe intensity, nausea, and increased sensitivity to sensory stimuli, such as light and sound (1). The pain is often aggravated by physical activity (1). A usual migraine attack lasts between 4 and 72 hours and the average migraineur has 1.3 attacks per month (19). Attacks may be triggered by factors such as stress, sleep disturbance, certain types of food, and so forth. (20).

The prevalence in the general, adult Swedish population is 13% (19). These figures are similar to what has been seen in other countries; a recent review concluded that the mean prevalence of migraine in Europe was 15% (11). Migraine is more common in women (12–25%) than in men (5–9%) (11, 21). Women's migraine attacks are generally longer than those of men, and women experience more nausea and vomiting associated with attacks (19, 22). Among both women and men, the prevalence is highest between the ages of 20 and 50 years (23). Migraine is more common among people with lower income and lower educational level than among the general population (24). It is under-diagnosed. A Swedish study showed that only 49% of those with migraine in Sweden had had their headache diagnosed by a physician (19).

A person with migraine is severely handicapped during the attacks, but between attacks, he or she is usually completely free of physical symptoms (25). However, because of the inability to predict the next attack, many people with migraine live under constant worry concerning the next attack (26). These fears often develop into anxiety, and many migraineurs are thus in fact living with a chronic disability (26). Migraine affects quality of life. Those with migraine have a reduced health-related quality of life compared to healthy controls (27, 28), as well as compared to individuals with other chronic diseases such as diabetes, hypertension, depression, and osteoarthritis (29). Migraine also leads to substantial costs for society, particularly indirect costs due to increased sickness absence and reduced productivity at work (9, 19, 30).

### **Tension-type headache**

Tension-type headache (TTH) is another type of primary episodic headache. It is characterized by bilateral, pressing, tightening pain of mild to moderate intensity. The headache is not associated with typical migraine features such as vomiting or sensitivity to both sound and light, and typically not aggravated by physical activity (1).

Tension-type headache is the most prevalent type of headache across all age groups worldwide (11, 31). The lifetime prevalence varies greatly, depending on study method, but is usually reported in the range of 60–90% (10, 11, 32–34). Tension-type headache is slightly more common among women than among men in all age groups, with a male-to-female ratio ranging between 1:1 and 3:1 (33). In both sexes, the prevalence peaks between the ages of 30 and 39 years and declines with increasing age (34, 35).

For the individual, the disease burden is less severe than in migraine, but due to the large number of people affected, the global burden of TTH is

presumably higher than that of migraine (16). However, a recent estimation of the cost of headache disorders in Europe concluded that the total economic costs of migraine were higher than those of TTH (9).

### **1.1.2 Chronic daily headaches**

Chronic daily headache (CDH) is a collective description of headaches that occur very frequently (2). The term was first mentioned by Mathew et al. and later defined by Silberstein et al. (36, 37). More recently, the term has been redefined and is usually interpreted as headaches occurring at least 15 days/month over the past 3 months (2). This definition is applied in this thesis. It should, however, be noted that CDH is not a formal diagnosis and does not appear in the ICHD-II (1).

Approximately 4% of the adult population has CDH (11, 38-41). The disorder is approximately twice as common among women as among men, and the prevalence appears to be relatively constant throughout the adult lifespan (35, 42). The relatively constant prevalence of CDH is in contrast with the pattern seen with episodic migraine, and to a lesser extent, TTH, both of which tend to become less prevalent with increasing age (23, 34). The prevalence of CDH is inversely associated with educational level (42).

Chronic daily headaches may be classified as primary or secondary (43), Table 1. Primary CDH exists independent of other medical conditions, and the two most prevalent types are chronic TTH and chronic migraine (38, 39, 41). Secondary CDH is caused by some other underlying condition, for example head trauma, cervical spine disorders, vascular disorders, or overuse of acute headache medication (43). Chronic daily headache associated with overuse of acute medication is called medication overuse headache (MOH) and will be discussed in the next section.

## **1.2 Medication use in headache**

Medications are the most common mode of treatment in health care today. Approximately two thirds of all Swedes purchase one or more prescription drugs at a pharmacy per year, with a higher proportion among women than among men (44-46). In 2011, the total sale of OTC medications from pharmacies was more than three billion Swedish kronor (€364 million) (47).

Headache is no exception; a majority of persons with headache use medications for treatment, either prescription or OTC preparations (13, 14, 48). People with headache may use acute as well as prophylactic medication

to manage their disorder. Headache may also be treated and prevented with non-pharmacological methods (49, 50), but these are beyond the scope of this thesis.

### **1.2.1 Acute medication**

According to clinical guidelines from the European Federation of Neurological Societies (EFNS) Task Force (51), oral analgesics (acetylsalicylic acid (ASA), ibuprofen, naproxen, diclofenac, and paracetamol), and triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are medications of first choice for acute treatment of migraine. Ergot alkaloids may also be used, but are considered less effective. The analgesic, but addictive, opioids are not recommended for treatment of migraine. In very severe attacks intravenous ASA or subcutaneous sumatriptan are medications of first choice (51).

The World Health Organisation (WHO)'s list of essential medications only includes analgesics (ASA, ibuprofen, and paracetamol) for acute treatment of migraine (52). It has been suggested that triptans should be included on this list (53). However, the WHO have declined to do so, referring to a meta-analysis of three randomized clinical trials that concluded that ASA is as effective as triptans in the treatment of migraine attacks (54). An even more recent meta-analysis of six randomized controlled trials also concluded that ASA should be regarded as first-choice treatment in both migraine and TTH, regardless of headache intensity (55). In line with this, a Finnish study of prescription patterns recently showed that analgesics were the most commonly prescribed acute medications for migraine in Finland (48).

For acute treatment of TTH, simple analgesics are the medications of first choice, and combination analgesics containing caffeine are medications of second choice (56). Triptans and ergot alkaloids are mainly used for the treatment of migraine headache and are not effective in TTH.

In Sweden many of the medications used to treat headaches are available as OTC medications. Most of the analgesics exemplified above may be purchased as OTC medications. Triptans are generally not available as OTC medication, but since 2008, sumatriptan tablets and zolmitriptan nasal spray may be purchased without prescription. In relation to similar decisions regarding triptans in the United Kingdom and in Germany, the risk of an increased medication overuse has been stressed (57). No ergot alkaloids or opioids are available as OTC medications in Sweden.

## 1.2.2 Overuse of acute medication

Some people with headache overuse the acute medications. Such overuse could lead to the development of a type of CDH called medication overuse headache (MOH) (3). Because of this, there are strict recommendations for how often acute treatment may be used (58):

- Triptans, ergot alkaloids, opioids, and combination analgesics should not be used more than 10 days/ month, and
- Simple analgesics should not be used more than 15 days/month.

Anything above these limitations (for more than 3 months) is regarded as overuse (3). Different types of medications have different limitations, since they have shown different potential in inducing MOH (59). In a prospective study by Limmroth et al. (59) the interval between first intake and daily headache was 1.7 years for triptans, 2.7 years for ergots, and 4.8 years for analgesics. Both the time until development of MOH and the amount of medication that was sufficient to induce MOH was higher for simple analgesics than for other types of acute medication.

For persons who have headache more often than 10–15 days per month, strategies other than acute medication must thus be used on headache days exceeding the recommended limitations for use of acute medication. Such strategies include non-pharmacological treatment or no acute treatment at all (58). Ideally, preventive measures (appropriate management of the primary episodic headache and patient information) should be taken, so that the patient is not faced with such a situation (58). However, as many as 3–4% of the population have headache on 15 days per month or more (11), and are thus faced with the problem of having to ration their use of acute medication.

Most likely, several different factors affect the vicious circle of headache and medication overuse, such as work-related pressure, social demands, and the perception of limited non-pharmacological options to control the headache. Results from a Danish qualitative study showed that young women with headache use analgesics as a tool when coping with performance pressures, but also to alleviate anxieties about missing out on social activities (60). More than half of those with CDH reported taking an analgesic and continuing to work if the headache occurred on a working day, but only 38% acted similarly on a day off (61).

## **Medication overuse as a cause of chronic daily headache**

Although most researchers regard the causal association between overuse of acute medication and subsequent development of MOH as an established fact, it is still a matter of debate (62-64). It is debated whether the overuse of acute medication is indeed a cause of CDH, or if the overuse occurs in individuals who are already developing CDH for other reasons.

A population-based longitudinal study conducted in Norway, on data from the Head-HUNT study, addresses this association (65). In this study, those who used analgesics daily or weekly at baseline had a higher risk of having developed CDH at the follow-up 11 years later. The authors thus concluded that overuse of acute medications predicted the development of CDH in the population. However, since information about the headache status was not collected at baseline, the possibility that frequent analgesic use was only a marker for frequent headache cannot be excluded. The association has, however, been replicated in several other studies (66-68). In 2004, Katsarava et al. (66) conducted a longitudinal headache clinic-based study in Germany and showed that among persons with episodic migraine, use of acute medications was associated with a frequency of use-dependent increased risk of developing CDH. In multivariate models, the frequencies of both headache and of acute medication use were independent predictors for the development of CDH. Among the medications overused, opioids were the strongest risk factor.

MOH is developed from primary episodic headache disorders, such as migraine or TTH (69, 70). Approximately two thirds of those with MOH have had migraine as primary headache, one third have had TTH, and only a small fraction have had other headaches (69-71). Acute medication overuse does not seem to cause headache in individuals without any pre-existing headache disorder. When analgesics were used daily for rheumatic pain, they did not cause CDH in individuals without pre-existing headache disorders. In contrast, analgesics were a strong risk factor for CDH in individuals with pre-existing migraine (72, 73). In another study, patients with a previous history of migraine who used opioids daily for treatments of bowel motility problems developed CDH, whereas patients without pre-existing primary headache did not (74). The fact that daily use of analgesics can lead to CDH in susceptible individuals, even when the medications are used for indications other than headache, strengthens the evidence for a causal association between medication overuse and subsequent CDH (63, 64).

Further, temporary worsening after withdrawal of the acute medication has been demonstrated in a placebo-controlled study, and this also points to the medication overuse being a causal factor (75). A majority of the patients who undergo withdrawal therapy experience significant improvement (75, 76).

The specificity of the findings is also of importance (64). The strengths of the associations between use of different classes of acute medications and subsequent development of MOH have been established. Use of opioids or barbiturates is the strongest risk factor, followed by triptans and NSAIDs (non-steroidal anti-inflammatory drugs) (67, 68). Further, the dose-response nature of the relationship has been established and found to be different for different classes of medications (5 days /month for barbiturates, 8 days /month for opioids, 10 days /month for triptans, and only in specific situations for NSAIDs) (67).

Not everyone with episodic headache and medication overuse develops CDH, and not all cases of CDH are caused by medication overuse, but neither fact negates the causal relationship (63). The data presented above suggest that there is indeed a causal relationship between the overuse of acute medication and the subsequent development of CDH.

### **1.2.3 Medication overuse headache**

#### **Classification**

Medication overuse headache (MOH) is a type of CDH that develops in individuals with primary headache disorders who overuse acute headache medications (3, 66). The idea that overuse of acute medication could lead to development of CDH was first presented by Peters and Horton in the 1950s, when describing chronic headache in patients with migraine who used ergotamine frequently (77, 78). They also noted that the CDH vanished when the patient stopped overusing acute medication. In these first studies, MOH was mainly associated with the overuse of ergotamine derivatives and therefore first called ergotamine headache. The first classification of the International Headache Society (IHS) came in 1988 and introduced the term drug-induced headache (79). It was defined as a chronic headache in patients with migraine or TTH following overuse (intake of analgesics or ergots on 15 days or more per month for at least 3 months) of headache medication, and vanishing within 1 month of withdrawal (79).

The introduction of triptans in the 1990s opened a new era in the treatment of migraine. They were widely used and rather soon it became evident that

many patients overused them (80, 81). Later, it was shown that intake of triptans, even on 10 days/month, could lead to MOH (59, 82). Today, the general view is that all medications for acute headache treatment have the potential to cause MOH in persons with a primary headache disorder (70, 83).

The second version of the IHS's classification (ICHD-II) introduced the term MOH and decreased the critical threshold for triptan intake to 10 days/month (1). These criteria, however, were criticized, because the MOH diagnosis could only be established retrospectively, after the patient had gone through withdrawal and shown significant improvement (84). In 2006, the IHS therefore published new appendix criteria, introducing a broader concept of MOH, which no longer required improvement of headache after withdrawal (3), Table 2. Thus, a person is by definition diagnosed with MOH if he or she has coexisting CDH and medication overuse. These are the criteria used in this thesis. It should be noted that in order to determine whether the overuse is truly the cause of the CDH in an individual person, improvement after withdrawal is needed. The proportion of patients who do improve after withdrawal varies greatly between studies, but is usually reported to be between 50% and 80% (76). From the criteria, it can also be noted that overuse is defined in terms of treatment days per month, and the quantity of medication used is not a criterion.

Table 2. *Appendix diagnostic criteria for medication overuse headache, as proposed by the International Headache Society 2006 (3)*

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**Appendix diagnostic criteria for Medication overuse headache (3)**

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- A. Headache present on  $\geq 15$  days/month;
  - B. Regular overuse for  $>3$  months of one or more symptomatic treatment drug such as
    - 1. ergotamine, triptans, opioids or combination analgesics on  $\geq 10$  days/month, or
    - 2. simple analgesics or any combination of ergotamine, triptans, analgesics or opioids on  $\geq 15$  days/month without overuse of any single class alone;and
  - C. Headache has developed or markedly worsened during medication overuse
-

## Epidemiology

Studies from different countries analyzing MOH in the adult population have reported prevalence of around 1–2% (35, 38, 39, 69, 85-89). The incidence of MOH is 0.72 per 1,000 person years (95% CI 0.62-0.81) (90), and it is the third most common headache diagnosis in clinical practice in the United States (91).

Medication overuse headache is more common in women than in men, with a male:female ratio ranging between 1.4 and 2.0 (39, 69, 85, 87). Medication overuse headache generally starts earlier in life than other types of CDH (69). It is most prevalent in the forties and thus is particularly prevalent in the productive age, thereby affecting productivity at work and work attendance (8, 92). A recent longitudinal study from Norway showed a 5-fold increased risk for developing MOH among individuals who reported regular use of tranquilizers or who had a combination of chronic musculoskeletal complaints, gastrointestinal complaints, and high scores of anxiety and depression (90). Smoking and physical inactivity more than doubled the risk of MOH.

Studies from Norway and Turkey have shown that CDH is more prevalent among those with a low socioeconomic status (93, 94). Atasoy et al. (93) showed that MOH patients generally had a lower level of education than migraine patients (93). Hagen et al. found that low socioeconomic status was associated with CDH. They also found that the risk of CDH decreased with increasing income, but only among men (94). Results from two German studies have indicated a higher prevalence among immigrants than among native Germans (86, 95). One of the studies showed that the prevalence of medication overuse was 16.5% in first-generation Turkish immigrants, but only 1.5% in second-generation Turkish immigrants and 1.1% in native Germans (95). The suggested explanation behind the difference was that first-generation immigrants did not seek medical help for their headache condition to the same extent as the other groups, but other explanations such as unequal access to health care and culturally different attitudes to headache and medication use are also possible.

## Burden of disease

Medication overuse headache is a public health problem that has implications for people's everyday lives, as well as an individual's and a nation's finances. In a recent estimation (2012) of how economic resources are lost to headache in Europe, the mean annual per-person cost for MOH was calculated to be €3,561 (9). This was higher than the calculated corresponding costs for

episodic headaches, such as migraine and TTH. For all three types of headaches, indirect costs such as sickness absence and reduced productivity at work were the dominating costs. People with MOH have a greater disease burden and higher sickness absence than those with migraine (8). They also report more days with reduced productivity at work and more missed social/family events than migraineurs (8). The general quality of life of individuals with MOH is poorer than for individuals with episodic headache, as measured by the General Health Questionnaire-28 (86). Further, results from a Spanish population study using the quality of life short-form 36 (SF-36) health survey indicated a decreased score in all health-related domains for individuals with MOH compared with healthy individuals, with the highest differences for bodily pain and physical activity (69). Within headache research, the migraine- and CDH-specific Migraine Disability Assessment (MIDAS) is often used to measure disability (96). This instrument shows scores, that are significantly higher in individuals with MOH than in those with episodic migraine (8).

Potential secondary physiological complications also emphasize MOH as an important health problem (71). These complications are mainly side effects caused by the overused medication, for example the risks of kidney failure (combination analgesics) or gastric ulcers (NSAIDs) (71, 97).

### **Treatment and prognosis**

Withdrawal is the recommended treatment for MOH, that is, a discontinuation of acute medication or reduction to less than 10 days per month (58, 70). The goal of the withdrawal treatment is primarily to detoxify the patient, but also to improve the responsiveness to acute and prophylactic treatment (75). There is conflicting evidence as to whether prophylactic treatment is effective when started before withdrawal (70, 98).

Several different strategies can be used for withdrawal (58). One study compared the outcome between three different procedures for withdrawal therapy and found that strong advice to withdraw the overused medication was just as effective as standard outpatient and inpatient detoxification programs (99). Symptoms caused by abrupt withdrawal (primarily worsening of the headache, nausea, and anxiety) usually abate after 2–10 days, but can persist for up to 4 weeks. A majority of the patients experience a significant reduction of their headache frequency thereafter (75, 76).

If withdrawal is successful, another common problem may arise, namely, relapse; the relapse rate one year after withdrawal is about 25–30%, regardless of which withdrawal procedure is used (70).

## Mechanisms

The pathophysiology of MOH is almost completely unknown (70). There are a number of theories, for example, neurophysiological changes, hereditary factors and variations in endocrine and neurotransmitter functions, as well as psychological factors (70, 100). Most of these theories emanate from biology, but it is probable that the initiation and sustaining dynamics of this condition involve factors beyond that (101). There are indeed some psychological issues that may help explain the vicious circle of headache and medication overuse, for example, anticipatory fear of pain, external pressures, psychological drug dependence, and psychiatric comorbidity (60, 102, 103).

## Addiction and dependence

Another way of regarding the overuse of acute medication in MOH is to focus on aspects of addiction and dependence. Some of the medications used in MOH (e.g., opioids and barbiturates) are indeed addictive, but there is no evidence for addiction to triptans or to simple analgesics (70). Despite this, two studies, using the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) criteria (104), have found that two thirds of MOH patients were considered dependent on acute headache treatment (105, 106). Another study showed that headache patients actually had higher scores of dependency than drug addicts (107). However, there is also research that has not found any difference in dependence-related behavior when comparing MOH patients to patients with episodic migraine and healthy individuals (108).

Critics argue that the use of the DSM-IV or International Classification of Diseases (ICD-10) criteria for substance-related disorders in MOH is unreflected (108, 109). Individuals with long-term medication use may easily fulfill some of the defining features of addiction, such as tolerance, withdrawal symptoms, use of medication in a larger amount or for a longer period than intended, unsuccessful efforts to cut down or control the use despite harmful consequences, and a high priority given to medication use. However, addiction is often characterized by a progressive neglect of alternative pleasures or interests because of drug use (109). This is usually not the case in MOH. Instead, research suggests that persons with MOH are overusing the medication to retain their functioning (107, 109). Ferrari et al. compared headache patients with drug addicts and found that, in contrast to the motivation of the drug addicts, it was the pain that controlled the headache patients' behaviour, with the aim of coping with everyday life (107). Further, even though the need for analgesics was stronger than the

analogous need for narcotic drugs, it was not the type of medication that was important but the effect (107).

It has also been suggested that persons with MOH could be divided into two separate groups, according to which those overusing psychotropic substances should be regarded as a specific, more severe subgroup of MOH than those overusing other medications (110-112).

## **1.2.4 Prophylactic medication**

Most people with headache use only acute medications, but additional prophylactic medication is recommended when the headache is frequent. Prophylactic medications are available for both migraine and TTH. There is no commonly accepted indication for when to start using a prophylactic medication. However, the EFNS Task Force guidelines recommend it when the quality of life, work, or school attendance are severely impaired, when frequency of migraine attacks is two per month or higher, when attacks do not respond to acute treatment, or when frequent very long or uncomfortable auras occur (51). Patients who are at a risk of overusing acute medication are a specific subgroup, in which use of prophylactic medication is particularly urgent in order to prevent overuse (58). In the US, 50% of patients with migraine meet the criteria for use of prophylactic treatment, but only 5–12% actually use it (113). In the Netherlands 12% of all patients with migraine use prophylactic treatment (114), and in Belgium the proportion is 8% among migraineurs with two or more attacks per month (115). A migraine prophylaxis is considered successful if the frequency of attacks per month is decreased by at least 50% within 3 months (51).

Several different types of medications may be used to prevent migraine. A recent Finnish study of prescription patterns found that the most commonly used prophylactics were beta blockers and antidepressants (48). The EFNS Task Force has evaluated the available evidence of efficacy and tolerability and their recommendations are summarized in Table 3 (51). The medications of first choice are beta blockers, calcium channel blockers, and antiepileptic medications (51). Medications of second choice include amitriptyline, pectasites, and bisprolol. The only prophylactic migraine medication included in the WHO List of Essential Medicines is propranolol (52).

Tension-type headache may also be treated with prophylactic medication, particularly when the headache is chronic (56). The tricyclic antidepressant amitriptyline is the medication of first choice, and mirtazapine and venlafaxine are medications of second choice (56).

Table 3. *Recommended substances for prophylactic headache treatment, the European Federation of Neurological Societies 2009 and 2010 (51, 56)*

Headache	Substances
Migraine	Beta blockers: Metoprolol Propranolol  Calcium channel blockers: Flunarizine  Antiepileptic medications: Valproic acid Topiramate
Tension-type headache	Tricyclic antidepressants: Amitriptyline

For the individual, the use of prophylactic medication means daily use of medications with potential adverse events or other inconveniences. Therefore, clinicians often find that their patients are reluctant to use prophylactic medication and in patients who do, the adherence may be poor (116, 117). A recent qualitative study showed that persons with migraine based their decision to start using a prophylactic medication on a combination of considerations (118). These considerations were grouped into five categories, namely the context of being active or passive in taking the initiative to start prophylactics, assessing the advantages and disadvantages of prophylactics, satisfaction with current migraine treatment, the relationship with the physician, the feeling of being heard, and previous steps taken to prevent migraine. The authors concluded that a number of these considerations had to be met before the patient agreed to initiate preventive therapy. A Spanish study showed that patients rated effectiveness as the most important factor when evaluating prophylactic treatment (119). They preferred the treatment options with higher effectiveness, even if side effects were present and a more frequent dosing schedule was necessary.

## 1.2.5 Non-adherence to prophylactic headache medication

A common problem in medication use is low adherence to treatment recommendations. Adherence has been defined by WHO as the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider (4). Low adherence is often the principal obstacle to successful pharmacotherapy, especially when under-recognized clinically, as often occurs (6). Non-adherence is highly prevalent, associated with increased morbidity and mortality, and costly to manage (4, 6). It has been found that about 30% of all prescriptions are never filled (120), and that only around one half of persons with chronic disorders are adherent to prescribed medication regimens (120, 121).

The problem is as prevalent in headache as in any other disorder (7). Among migraineurs, between one fourth and one half do not adhere to prescribed prophylactic treatment (7, 114, 122, 123). Mulleners et al. (122), evaluated adherence to prophylactic migraine medications by using covert tracking devices in pill bottles (medication event monitoring system, MEMS) and pill counts. Overall adherence was 66%, with a linear trend toward poorer adherence with multiple daily dosing regimens. Steiner et al. (123), demonstrated similar adherence rates with pizotifen migraine prophylaxis. In an analysis of a large prescription database in the Netherlands, more than half had terminated treatment with migraine prophylactic medication within 3 months (114). Since the main aim with prophylactic migraine medication is prevention of attacks, individuals who do not adhere to prophylactic treatment are likely to suffer from more frequent headache attacks. This may in turn lead to increased use of acute medications and increased risk of developing MOH.

A very large number of studies have been conducted, trying to identify predictive factors for low adherence (124). However, most of these factors, for example, demographical factors such as sex, ethnicity, and socioeconomic status, and factors related to the disease have shown no or limited effect (5, 124). In headache treatment, some variance in adherence is accounted for by the medication regimen itself. Adherence tends to decline with increasing obstacles. For example, the adherence becomes poorer as the dosing regimen becomes more complex and requires the patient to deviate from his/her routine, or if the user experiences disturbing side effects (5, 122). Other factors, such as psychiatric comorbidity, lack of social support or poor quality of the patient–physician relationship have also been associated with

lower adherence to headache treatment (5). Cognitive factors such as the patient's beliefs about medications and self-efficacy (confidence in one's ability to perform an action) are also important for adherence (125, 126).

## **1.3 Decision-making and beliefs about medicines**

In the previous section, two types of problematic medication use in headache were described, overuse of acute medication and non-adherence to prophylactic medication. Assuming that the prescriptions and recommendations given by the treating health care professionals were adequate, these types of problematic medication use will lead to worse health outcomes for the individual medication user, in these cases more frequent headache. This raises questions about how persons with headache make decisions about their medications and other strategies to handle headache. In this section, I attempt to explore this by presenting some theories concerning decision-making and beliefs about medications.

### **1.3.1 Decision-making in headache**

Studies analyzing the decision-making process concerning medication use among people with headache have shown results pointing in somewhat similar directions (127-129). Ivers et al. (127) found that patients employed a two-stage cognitive process. In the first stage, they tried to determine whether the emerging headache was indeed a migraine attack. In the second stage, they analyzed the situation to determine the costs and benefits of medication use in the current context, taking into account expectations and experience, the medication's burdens and benefits, alternatives to medication use, and their personal beliefs regarding use of medications. In a qualitative study from 2003, Peters et al. (128) found that persons with headache were often active decision-makers when choosing appropriate ways to manage their headache. In the decision-making process, headache severity and possible options perceived by the patient were weighed against personal attitudes and expectations. In a recent review, Katic et al. (129) presented a model attempting to explain underuse of acute medication in migraine patients. According to their model, patients base their decisions on a combination of headache and medication characteristics, as well as personal and interpersonal factors. The model predicts that patients will decide to medicate if they consider headache as an important disorder and if they perceive the medications as safe. All three studies suggest that headache patients somehow actively weigh costs and benefits of taking the medication before making a decision whether to medicate or not. This is in line with the beliefs-

about-medicines model for patients with chronic illness, presented by Horne and Weinman in 1999 (126), which will be described in the next section.

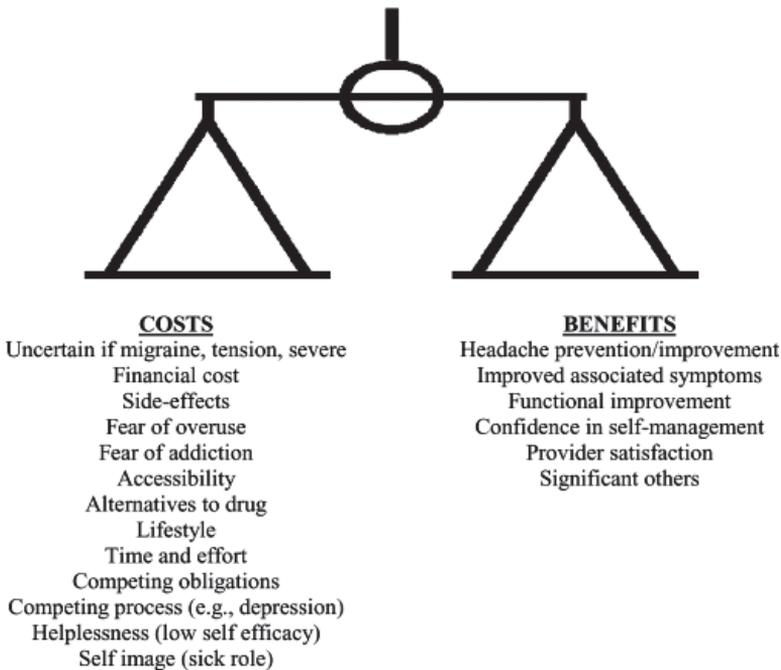
In the only study specifically investigating decision-making in MOH, Lauwerier et al. (109) explored the behavior from a functional coping perspective. They found that patients who framed the problem of pain as one that needed to be solved were at a higher risk of developing MOH than those who tried to disengage from the problem and focus on other areas of life instead. The authors thus suggest that an approach characterized by persistent attempts to solve the problem of pain may increase the need for medications, despite clear negative consequences. They propose two possible explanations that may both contribute to this behavioral pattern. First, the pain-relieving effect of the acute medication is more obvious to the patient than its long-term negative consequences. As such, it may provide a sense of control over the pain. Second, the on-going activities and goals that are interrupted by pain are of central importance in a patient's life. The authors suggest that the patient may then prefer to search for a solution, instead of giving up valued goals. Thus, a focus on solving pain may unintentionally heighten the attention to pain and thereby add to the problematic medication use. These suggested explanations are interesting and may indeed be valuable in explaining decision-making among those who have MOH, but research to test whether they are valid is needed.

### **1.3.2 Beliefs about medicines**

The beliefs-about-medicines model for patients with chronic illness was presented by Horne and Weinman in 1999 (126). They hypothesized that patients engage in an implicit risk–benefit analysis in which beliefs about the necessity of their medication are weighed against concerns about the potential adverse effects of taking it and that these beliefs are related to medication use.

In the case of headache, using prophylactic medication could seem less necessary and more risky to the patient than using acute medication, since the beneficial effects are less obvious. Taking the acute medication is beneficial, because the headache attack is aborted, but it also leads to costs in terms of fear of side effects and the potential development of MOH. When such negative effects prevail, Horne and Weinman's model would predict decreased medication use. However, this is not the case in headache, where people seem inclined to underuse prophylactic and overuse acute medication, despite being aware of the negative consequences (109). At a first glance, this model thus seems unable to fully account for the decision-making in patients

who develop MOH. It is, however, likely that we are not aware of all the factors included by patients in their possible cost–benefit analysis, and how they assess the weight of such factors. A hypothetical patient cost–benefit analysis was presented by Rains et al. in 2006 (125), Figure 1. The figure concerns persons with headache in general and the factors included are to be regarded as suggestions of factors that could influence the balance. Scientific knowledge about the actual factors involved in the processes is lacking, but the overall picture of the decision-making as a balance is helpful.



*Figure 1. Hypothetical patient cost–benefit analysis for headache treatment, Rains et al., 2006 (125).*

## 1.4 Summary of the problem area

There are several issues in problematic medications use among persons with headache. Lack of adherence in terms of both overuse of acute treatment and underuse of prophylactic treatment appears to be prevalent. This is problematic, since it may lead to unsuccessful treatment outcomes such as increased headache frequency. It is thus likely that some individuals with headache carry an unnecessarily high disease burden because of the problematic medication use. Since headache is a highly prevalent disorder, the misuse of medication may also lead to substantial costs for society in terms of reduced productivity and use of health care resources.

Overuse of acute medication may lead to increased headache frequency in the form of MOH. There is almost no previous Swedish research concerning this disorder. One clinical study evaluated the effect of withdrawal therapy (130), but there are no population-based studies, and the prevalence in Sweden is not previously known. Underuse of prophylactic medication may also lead to increased headache frequency. Little is known about the reasons behind such non-adherence, and beliefs about medicines have not been studied before among persons with headache. More knowledge about how persons with headache think and make decisions about their medication use is needed, particularly among those who develop MOH. There are few studies concerning medication use that are based on headache sufferers' own statements (60, 128, 131-133), and none has been identified concerning MOH. Qualitative research could fill this gap and has the possibility to provide explanations of the problematic medication use.

## 2 AIM

### 2.1 General aim

The overall aim was to study problematic medication use among persons with headache, from both an individual and a population perspective. Two types of problematic medication use were analyzed, namely overuse of acute medications with subsequent medication overuse headache (MOH), and non-adherence to prophylactic therapy.

### 2.2 Specific aims

- To estimate the prevalence of MOH in Sweden and to analyze the occurrence of the disorder in different population groups.
- To analyze medication use and health care contacts among individuals with MOH.
- To analyze adherence to prophylactic medications among individuals with migraine, and examine whether beliefs about medicines and medication-related variables are associated with adherence.
- To explore how individuals with MOH use medications and other strategies to manage headaches in their daily lives, and their thoughts and perceptions of their own use of acute medications; also to develop a theoretical model about the development of MOH, emanating from the perspective of those having MOH.



### 3 METHODS

The thesis is based on four studies, using different methodologies and addressing both qualitative and quantitative aspects of medication use in headache. Studies I–III are quantitative, whereas Study IV is qualitative. All studies were conducted in Sweden. Studies I–II include a national sample of participants from all over Sweden, Study III includes a clinical sample of migraine patients from Gothenburg, and Study IV, a qualitative sample of people from different parts of Sweden. The studies are listed in Table 4.

Table 4. *Overview of the four studies included in this thesis*

	Study I	Study II	Study III	Study IV
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Grounded theory
Study population	General population sample (n = 44 300)	Population sample of people with MOH (n = 799)	Clinical sample of migraineurs (n=174)	Purposive sample of people with MOH (n = 14)
Medications concerned	Acute medication	Acute medication	Prophylactic medication	Acute and prophylactic medication
Data collection	National telephone survey	National telephone survey	Questionnaire at headache clinic and medical records	Individual interviews
Outcomes	Prevalence of MOH	Medication use, healthcare contacts, and sickness absence	Adherence	An empirically grounded theory on medication use in MOH

## **3.1 Sampling and participants**

The sampling procedures used in Studies I-IV are described below.

### **Studies I and II**

Data for Studies I and II were collected through a national telephone survey conducted by TNS SIFO Research International Sweden AB, a Swedish opinion-polling agency. This survey has an omnibus design. It runs continuously, reaches approximately 1,000 individuals per week and provides a means for data collection for different research projects, companies, and organizations. Sampling for Studies I and II was performed between March 2009 and March 2010 and consisted of randomized sampling in two steps. In the first step, a household was selected, and in the second step, a member from that specific household was singled out.

The basis for selection was the national telephone directory. Households without telephones were not included and cell phones were not called. A computer program randomly chose numbers in the telephone directory. It also constructed new telephone numbers by adding digits to those already chosen. For every chosen number, nine additional numbers were generated by adding 1 through 9 to the last digit of the chosen number. This procedure ensured inclusion of numbers that were not listed in the directory. If the number led to a company or a public authority, or if there was an unobtainable tone, a new number was chosen. Numbers with no reply were called again later, and if there was still no reply after four attempts, these numbers were replaced with new numbers. When the interviewer came into contact with a household, he or she initially collected information on the number of Swedish-speaking household members aged  $\geq 15$  years, and the computer program randomly chose one of these individuals for the interview.

An initial power calculation indicated that 56,760 interviews would be required to identify at least 850 persons with MOH, based on an anticipated prevalence of 1.5% and an accepted error of 0.1%.

### **Study III**

Study III was a cross-sectional study conducted at a headache specialist clinic in Gothenburg, Sweden. A sample of adult migraineurs with a current prescription of prophylactic migraine medication responded to a questionnaire.

Patients were consecutively recruited between September 2004 and June 2006 at the clinic, which had funding from the public health care system. The

clinic received patients from different parts of the country on referral mainly from other neurologists, but also from other specialists and general practitioners. It was chosen for practical reasons, to collect data from diagnosed migraineurs who used prophylactic medication within a reasonable inclusion period. In June 2006, the clinic had 1,783 registered adult migraineurs.

Eligible patients were those aged 18 years and above, with a diagnosis of migraine according to the ICHD-II (1). Acute treatment and advice on avoiding trigger factors had been given according to common guidelines (18). Patients with MOH and patients considered unable to complete the questionnaire for reasons of language difficulties were not included.

The estimated requirement of 166 participants was the result of a power calculation, with 80% power to detect a difference of 1.45 in the BMQ subscale General Harm between adherent and non-adherent migraineurs at 5 % significance level. The difference in mean values was based on preliminary results from a study of pharmacy clients, in which General Harm was significantly associated with adherence (134).

#### **Study IV**

Study IV was a qualitative study. Grounded theory, as described by Corbin and Straus, 2008 (135), was chosen since it is a qualitative research method that is well suited for studying how people manage the problematic situations in their lives (135, 136). Grounded theory has been developed from symbolic interactionism, a theoretical perspective that requires the individual to develop through social interaction and the creation of meaning (135, 137). Our intention was to develop a theoretical model that could provide knowledge for clinical use. Grounded theory offers a systematic procedure for generating theories that are grounded in empirical data and describe how people's construction of reality is manifested in behaviors (135). The method is thus suitable for studying how thoughts about headache and medication use can lead to overuse and development of MOH. Grounded theory is suitable for exploring areas where little previous knowledge exists or when new approaches are needed to an issue studied earlier (135, 138).

By interviewing people with MOH, an attempt was made to explore behavioral patterns underlying the development of MOH. This approach was chosen to allow the participants to describe their thoughts and actions in their own words (138). An essential feature of grounded theory research is the continuous cycle of collecting and analyzing data (135). Thus, the analysis was started as soon as the first set of data was collected, and the research

question and the developing theory then guided the sampling and data collection.

Participants were recruited through a total of three advertisements, one in the national journal of an organisation for headache patients (September 2010), and two in a local daily newspaper (October 2011 and January 2012). Inclusion criteria were to be  $\geq 18$  years old and able to speak Swedish, and to have a diagnosis of MOH, according to the 2006 International Headache Society appendix criteria (3).

In total, 39 eligible participants reported interest in participating. This allowed us to make a purposive selection to obtain as much variation as possible with regard to age, sex, employment status, and headache history. Data were collected through individual qualitative interviews.

## **3.2 Data collection and procedure**

The procedures used for data collection in Studies I–IV are described below.

### **Studies I and II**

Data for Studies I and II were collected in a national telephone survey. Lay interviewers who had an average interviewing experience of 2 years administered the interview. They introduced the interview by explaining that it was a survey from SIFO covering several different areas, and lasting approximately 5–25 minutes. Verbal informed consent was obtained. All had a right to decline participation or to turn down specific questions without having to give an explanation. All respondents were asked background questions.

The interviewers introduced the part of the survey that was specifically related to headache and medications by explaining that the questions concerned headache and came from the University of Gothenburg. This section of the survey began with two screening questions, and only respondents who passed those were asked further questions about headache and medication use. Criteria to pass the screening were having headache present on  $\geq 15$  days/month and using medication for  $\geq 10$  days/month during the past 3 months.

The subsequent interview comprised questions about medication use, health care contacts, headache-related sickness absence, and primary headache.

### **Study III**

Each morning, a neurologist identified in the clinics database potential participants among the patients scheduled for a physician visit during that day. When the patient arrived in the waiting room, a research assistant invited him or her to participate in the study, before meeting the physician. It was explained that their physician would not know whether they participated or not. All data were coded and only the research assistant had access to the “key” that identified participants. If they agreed to participate, patients signed a consent form and then filled out the questionnaire. It was also possible to take the questionnaire home and send it to the research assistant in a stamped envelope.

The participants also consented to collection of data from their medical records. This included information on migraine characteristics and present and previous prescriptions of prophylactic medications.

### **Study IV**

Data were collected through individual qualitative interviews. Each interview was audio-recorded and later transcribed verbatim. All interviews were conducted in Swedish by the first author (PJ). The citations presented in the thesis have been translated into English by the first author (PJ). The accuracy of the translation was verified by two co-authors (TH and AJ). All interviews were held at the University of Gothenburg, except for one, that took place at the participant’s workplace (a hospital).

The first author (PJ) made a preliminary MOH diagnosis before each participant was included in the study. After the interview, all participants talked on the phone to a neurologist specialized in headache (ML), for verification of the diagnosis. This was also an opportunity for the participant to ask questions that may have arisen during the interview. Though it would have been convenient to have the diagnosis confirmed before the interview, this procedure was chosen to avoid the risk that the consultation would affect the interview. In total, 15 interviews were conducted, but one had to be excluded because the interviewee did not meet the diagnostic criteria for MOH.

The researchers involved in the study have different professional backgrounds. Two are pharmacists (PJ and TH), two have a background in social work (GH and CDM), one is a nurse (AJ), and one is a physician (ML). Only ML has clinical experience of working with headache patients.

TH, ML, and PJ have previous experience of headache research, and AJ, GH and CDM are experienced in using qualitative research methods.

### 3.3 Questionnaires and interview guide

Below, the telephone interview used in Studies I and II, the questionnaire used in Study III and the interview guide used in Study IV are described.

#### Studies I and II

The telephone interview included background questions that were answered by all participants, and subsequent questions on headache, medications use, health care contacts, and sickness absence that were only answered by those who had passed the screening questions.

*Background questions:* All participants were asked background questions concerning sex, age, educational level (elementary school, high school, or university), main occupation (blue-collar worker, white-collar worker, pensioner, student, sick-listed, unemployed, or other), household income, and Swedish citizenship.

*Headache diagnoses:* All headache diagnoses were established according to criteria of the International Headache Society (IHS) (1, 3). The 2006 IHS appendix criteria were used to diagnose MOH, Table 2 (3). Consequently, it was also possible to diagnose CDH, defined as  $\geq 15$  headache days/month during the past 3 months. The primary episodic headaches were diagnosed as “migraine” or “other headaches “according to the ICHD-II (1).

*Medication use:* The participants were first asked to name the medication that they most frequently used to treat their headache (the primary acute medication). They were then asked a series of follow-up questions regarding this medication, with respect to: frequency of use; form of dosage; and whether they bought it on prescription, as OTC medication, or both (this variable was dichotomized into “always OTC” and “sometimes or always on prescription”). For medications other than the primary one, participants were asked only for the name and the frequency of use. The medications reported were divided into five different groups corresponding to the diagnostic criteria of MOH, Table 2 (3). Addictive behavior has been discussed in relation to MOH (110-112). Therefore, in some analyses all medications containing psychotropic substances (alone or in combination with other active compounds) were analyzed as one group. There was also a question regarding the use of prophyllactic medication.

*Health care contacts:* The participants were asked how many times they had visited a physician due to headache during the past year. They were also asked what type of physician(s) they had visited (neurologist or other), how many prescribing physicians they saw and whether any physician had ever informed them that excessive use of headache medication could lead to an increased frequency of headache.

*Sickness absence:* The participants were asked how many days of headache-related sickness absence they had had during the past three months. Sickness absence was reported as mean number of days/month and person during the past three months and analysed only among those aged 18–65 years.

### **Study III**

The questionnaire included background questions concerning age, sex, and educational level (compulsory school only, high-school, or university education). There were also questions about migraine frequency and intensity, the migraine's effect on everyday life, use of herbal products for migraine, perceived effects and adverse effects of migraine medication, adherence, and beliefs about medications.

Adherence to prophylactic medications was self-reported with the Medication Adherence Report Scale (MARS) (139). The instrument includes five statements about the use of medications, concerning forgetfulness, altering the dosage, stopping to take the medication, missing a dose, and taking less than instructed. For each statement the participants marked their response on a five-point Likert scale (from always to never). The MARS had a coefficient of reliability (Cronbach's alpha) of 0.68. To further promote truthful reporting, an introductory part of the MARS encouraged the participants to answer according to their true medication behavior.

The questionnaire also included the Beliefs about Medicines Questionnaire (BMQ) (140), which measures beliefs about the risks and benefits of medication use. The instrument was developed in England and has been translated into Swedish, with the back translation accepted by the original author. The BMQ has two parts, one specific and one general (140, 141). The general part refers to beliefs about medicines in general, and the specific part refers to a specific medicine that the participant is using. The general BMQ has three subscales: General Harm, General Overuse, and General Benefit. The specific part has two subscales: Specific Necessity and Specific Concerns. For each statement in the general (12 items) and the specific (10 items) parts, participants marked their degree of agreement on a five-point Likert scale (from strongly disagree to strongly agree). The coefficients of

reliability (Cronbach's alpha) of the scales were 0.57 (Harm), 0.72 (Overuse), 0.64 (Benefit), 0.83 (Concern), and 0.80 (Necessity).

### **Study IV**

During the interview, the participants were asked the broad opening question "Could you tell me about your headaches?" They were then asked questions about headaches and daily life, strategies to manage headaches, use of medication, and thoughts about using less medication. They were encouraged to tell their stories as freely as possible, and probing questions were used to obtain as much detail as possible.

## **3.4 Data analysis**

Below, the data analysis in Studies I–IV is described.

### **Studies I and II**

In Study I, the SPSS version 17.0 for Windows was used for all statistical analyses, and in Study II, the IBM SPSS Statistics version 19.0 for Windows was used.

Prevalence was presented as percentage with 95% confidence intervals (95% CI). The overall prevalence was standardized according to age (nine age groups), sex, and working status (working/not working). The Swedish population aged  $\geq 15$  years in 2009 (7.8 million inhabitants) was used as the standard population. Both the crude and the standardized prevalence are presented. All other results are based on crude data.

Percentages were compared using the Pearson's chi-squared test or odds ratios (OR). All percentages are valid percentages, that is, calculated after the exclusion of missing values. Means were presented with standard deviations (SD) or 95% CI. Differences between means were tested using the independent samples t-test. When three or more means were compared, univariate analysis of variance (ANOVA) was used. When a difference was detected, the most appropriate post hoc range test was performed to determine which scores differed. The significance level was set to  $p < 0.05$ .

In Study I, a multivariate logistic regression was performed, with MOH diagnosis as the dependent variable, socioeconomic factors (educational level, employment status, occupation, household income, and Swedish citizenship) as independent variables, and background variables (age and sex) as potential confounders. In the regression analysis, the occupation variable

was split into two variables: employment status (working, pensioner, student, on sick leave, unemployed, and other) and occupation (blue-collar job, white-collar job, or other). The logistic regression was performed according to the procedures described by Hosmer and Lemeshow (142). First, separate logistic regressions were conducted for each independent variable to test for association between that variable and MOH diagnosis. Independent variables with  $p < 0.25$  were candidates for the multivariate model. For each independent variable, the background variables were tested for confounding effects in new separate regressions. Those background variables that caused a 15–20% change in the coefficient for any independent variable compared with the first, separate regression with that independent variable, and had  $p < 0.05$ , were included in the multivariate logistic model. The multivariate regression model was then tested with all significant independent variables and background variables. The least significant independent variable was then excluded and the regression rerun. This procedure was repeated until all included independent variables showed significance. Results are presented as odds ratios (OR) with 95% confidence intervals (CI).

### **Study III**

SPSS 14.0 for Windows was used for all statistical analysis.

Only participants who had answered all the five items of MARS were included in the analyses. A score for each participant was calculated for adherence (MARS), which ranged from 5 to 25. A participant was defined as adherent if his or her score was 23 or higher. Since previous studies using dichotomization of MARS showed no consensus regarding a cut-off point (143, 144), the levels for adherence and non-adherence were decided before any analysis, with the levels based on the answer alternatives for MARS. The cut-off point for a participant to be considered adherent was whether he or she responded "sometimes" for one or "rarely" for two of the statements.

Scores obtained for each BMQ statement were summed for each scale. A higher score indicated a stronger belief in the concept described. Non-response to one or more statements within a scale resulted in exclusion from that particular scale. For BMQ Specific, a necessity-concerns differential was calculated for each participant. The differential is the difference between the score for necessity and the score for concerns (140). It can range between -20 and 20, and a positive value indicates a stronger belief in the necessity than in the concerns. The differential may be regarded as each individual's assessment of the balance between concerns about the risks of medication use compared to perceived need for the medication (126).

The independent t-test and the chi-square-test were used to analyze adherence differences between groups. Differences in adherence and in the subscales of BMQ with regard to age groups and educational level were analyzed by ANOVA. When a difference was detected, the most appropriate post hoc range test was performed to determine which scores differed. A significance level of  $p < 0.05$  was chosen.

Logistic regression was performed to analyze possible associations between adherence and factors such as beliefs about medicines, medication-related variables and background variables. First, a backward stepwise analysis was conducted. In the second step, a manual logistic regression was carried out with adherence as the dependent variable. First, univariate analysis was conducted with each independent variable analyzed separately against adherence. Variables with p-values less than 0.25 were candidates for the multivariate model. Each of the background variables was then entered in separate analysis with the candidate variables to test for confounding effects. The final logistic regression was performed with significant independent and significant background variables included. Results are presented as odds ratios (OR) with 95% confidence intervals (CI).

## **Study IV**

Grounded theory analysis according to Corbin and Strauss (135), consists of three major steps; open coding, axial coding and selective coding. The open coding began as soon as the first interview was completed, through reading the text line by line and creating codes. The main author (PJ) conducted the open coding. Two co-authors (TH and AJ) read each interview and all three researchers discussed the coding and analysis in meetings between every subsequent interview. The discussions proceeded until consensus was reached. Throughout the analysis, constant comparison and asking questions about the data were important tools. Constant comparison is to compare each situation with other situations for similarities and differences (135), and useful questions to ask could be: “What is going on?” and “What is expressed here?” (138)

The codes were eventually clustered into categories. The next step, axial coding, included exploration of the connections between categories and subcategories to develop conceptual density. In this process, three main categories with several subcategories were defined. The core category developed in the selective coding process. The selective coding is the last step of the analysis, and aims at integrating and refining the categories to obtain a dense, saturated theory. The theory developed when linking the core category with the three main categories.

After 11 interviews, the preliminary categories and the emerging theory were discussed between all co-authors and at a seminar with researchers from different disciplines/professions. After 14 interviews and analyses, no more meaningful information was gained, indicating theoretical saturation. During the analysis, ideas and preliminary theoretical reflections were written down in memos to help with the generation of a theoretical model (135).

## **3.5 Ethical approvals and considerations**

### **Studies I and II**

The Regional Ethical Review Board in Gothenburg reviewed the study protocol and stated that ethical review was not necessary. In these studies, the participants were not at risk of any direct physical harm, but the telephone call might nevertheless have been perceived as an intrusion of their privacy, and it took up their time. However, for participants who did not have MOH themselves, the interview was very short. Those who did fulfill the diagnostic criteria for MOH had a longer interview, but they could also have indirect use of the results from the study. Verbal informed consent was obtained from the participants. All had a right to decline participation or to refuse to answer specific questions without having to give an explanation. The research group never knew the identity of the participants.

### **Study III**

The Regional Ethical Review Board in Gothenburg approved the study (year 2004, approval No 179-04). This study took place at a clinic, and as in all clinical studies, there was a risk that patients might feel obliged to participate because of their role as patients and their relation to their caregiver. In order to protect the autonomy of potential participants, a research assistant who was not involved in their treatment recruited them, and their treating physician did not know whether they participated or not. They received verbal and written information that participation was voluntary, that they could withdraw without further explanation, and that confidentiality was guaranteed. Written informed consent was obtained. Only the research assistant had the key to the identity of the participants.

### **Study IV**

The Regional Ethical Review Board in Gothenburg approved the study (year 2010, approval No 293-10). The participants received verbal and written information that participation was voluntary, that they could withdraw without further explanation, and that confidentiality was guaranteed. Written informed consent was obtained.

Not all participants were aware of the fact that they had MOH, or even that MOH existed. During the telephone call, after the interview, the neurologist diagnosed each participant and informed the participants that the study concerned a type of headache called MOH. Participants who asked further questions were given information about the diagnosis and recommendations to the contact health care service for further help. The co-authors had thorough discussions as to whether it was ethically preferable to give this information or not. On the one hand, the participants had not asked for a diagnosis when consenting to participate and the research group did not have access to any specific health care resources that could provide treatment for the condition. On the other hand, the participants were actively looking for solutions to their headache, and it seemed dishonest to conceal a possible reason behind the headache. Based on this discussion, the procedure described above was chosen.

## 4 RESULTS

### 4.1 Prevalence of medication overuse headache (Study I)

Results from Study I revealed that the prevalence of chronic daily headache (CDH) in the general Swedish population aged 15 years or above was 3.2% (95% CI 3.1–3.4,  $n = 1428$ ). Chronic daily headache was more common among women (4.4%) than among men (1.8%) ( $p < 0.001$ ).

Of those with CDH, 56.0% fulfilled the diagnostic criteria for medication overuse headache (MOH). A total of 799 individuals had MOH, and the prevalence in Sweden was thus 1.8% (95% CI 1.7–1.9) (Table 5). The corresponding figure using weighted numbers was 1.8%.

Table 5. *Prevalence of MOH in the general Swedish population aged 15 years and above*

		Total sample N	MOH n	Prevalence % (95%CI)
Total:	All	44 300	799	1.8 (1.7–1.9)
Sex:	Women	24 195	609	2.5 (2.3–2.7)
	Men	20 105	190	0.9 (0.8–1.1)
Age (years):	15–20	2195	23	1.0 (0.6–1.5)
	21–29	2516	46	1.8 (1.3–2.4)
	30–39	6316	114	1.8 (1.5–2.1)
	40–49	7641	192	2.5 (2.2–2.9)
	50–64	13 088	284	2.2 (1.9–2.4)
	65–74	7917	89	1.1 (0.9–1.4)
	75–	4553	50	1.1 (0.8–1.4)
	Missing	74	1	–

The MOH prevalence was higher among women (2.5%) than among men (0.9%), with a male–female ratio (2.5/0.9) of 1:2.8. The highest prevalence was seen in the 40–49 years age group (Table 5).

The prevalence of MOH was higher among those who had only attended elementary school (2.3%,  $n = 296$ ) than among those who had attended university (1.2%,  $n = 182$ ) (OR = 2.0, 95% CI 1.6–2.4). The prevalence was

lower among those with white-collar jobs than among those with blue-collar jobs (1.1%, n = 135 vs. 2.1%, n = 223, OR = 0.6, 95% CI 0.4–0.7).

Table 6. *Logistic regression model with MOH diagnosis as dependent variable, socioeconomic parameters as independent variables, and background variables (sex and age) as possible confounders (n = 35 416)*

Parameter	OR	95 % CI	p-value
Education			<0.01
University	1.0	ref.	
High school	1.6	1.3–2.0	
Elementary school	2.2	1.8–2.8	
Employment status			<0.01
Working	1.0	ref.	
Pensioner	3.3	2.5–4.4	
Student	1.2	0.7–2.0	
Sick-listed	6.2	4.5–8.7	
Unemployed	1.1	0.7–1.8	
Other	1.3	0.9–1.8	
Household income (\$/year)			<0.01
> 100 100	1.0	ref.	
71 500 – 100 099	1.5	1.1–2.1	
42 900 – 71 499	1.8	1.3–2.5	
25 025 – 42 899	2.3	1.6–3.2	
<25 024	2.1	1.4–3.1	
Sex			<0.01
Men	1.0	ref.	
Women	2.5	2.0–2.9	
Age (years)			<0.01
15–20	1.0	ref.	
21–29	1.5	0.5–4.0	
30–39	1.7	0.6–4.6	
40–49	2.2	0.8–5.9	
50–64	1.3	0.5–3.4	
65–74	0.3	0.1–0.7	
75–	0.2	0.1–0.6	

*Independent variables entered into the regression: education, employment status, household income, sex, age, occupation (blue-collar worker, white-collar worker, or other), and Swedish citizenship (yes or no). Only significant variables are shown in the table.*

The prevalence was higher among those who did not have Swedish citizenship (3.0%,  $n = 29$ ) compared to those who did (1.8%,  $n = 770$ ) (OR = 1.7, 95% CI 1.2–2.5). This difference was only observed among women. Among those who had MOH ( $n = 799$ ), a total of 88% reported being born in Sweden, 6.9% in another European country, and 3.8% in other parts of the world.

A multivariate logistic regression model, including 35 416 participants, showed statistically significant associations between MOH diagnosis and educational level, employment status, and household income (Table 6). Sex and age were potential confounders.

## 4.2 Overuse of acute medication (Study II)

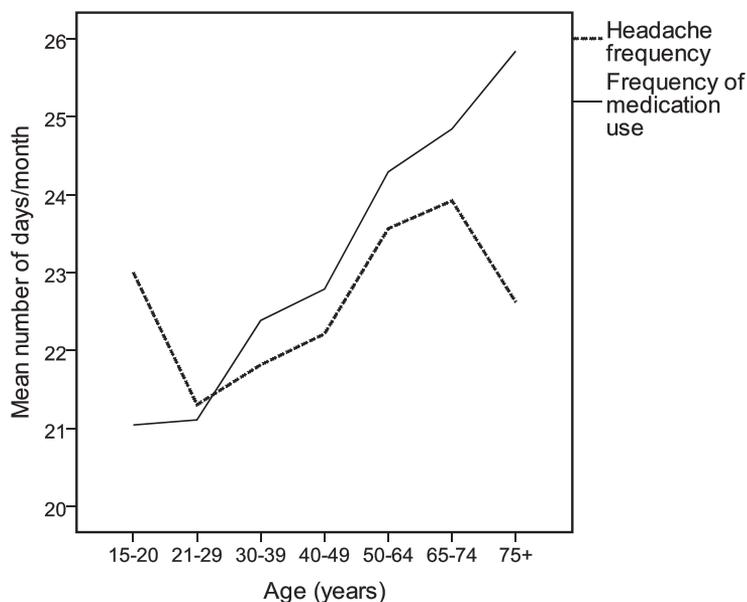
Results from Study II revealed that the mean frequency of headache among those with MOH was 22.8 days/month. Thirty-five percent ( $n = 276$ ) reported having headaches every day. Those who had only had elementary school education reported a higher frequency of headache (23.8 days/month) than those who had attended high school (22.4 days/month,  $p = 0.011$ ) or university (21.9 days/month  $p = 0.0021$ ).

Among those with MOH, daily medication use was reported by 46% ( $n = 366$ ). On average, they reported using acute medication 23.5 days/month. Among the youngest, the number of days/month with headache was greater than the number of days/month with medication use, whereas the opposite was true for those aged  $\geq 30$  years (Figure 2). The mean number of days/month with medication use was higher among those who had only attended elementary school (24.4 days/month) than among those with high school education (23.0 days/month,  $p = 0.018$ ).

The most commonly overused type of medication was simple analgesics. More than half ( $n = 508$ , 65%) of the participants reported simple analgesics as their main acute medication. The second largest group was combination analgesics ( $n = 173$ , 22%), followed by triptans ( $n = 65$ , 8%), opioids ( $n = 32$ , 4%), and ergotamine ( $n = 7$ , 1%). The most commonly used specific compound was paracetamol ( $n = 335$ , 42%), followed by the combination of ASA and caffeine ( $n = 119$ , 15%), and ibuprofen ( $n = 106$ , 13%).

Thirty-two individuals reported using an opioid as primary acute medication, and 51 used a combination analgesic containing opioids. Thus, 10% ( $n = 83$ ) used a psychotropic medication as primary acute medication. The proportion was higher among men (16%,  $n = 31$ ) than women (8.5%,  $n = 52$ ) ( $p =$

0.0022). The frequency both of headache and of medication use was higher among those using psychotropics (25.5 days/month, SD  $\pm$ 5.9 and 27.1 days/month, SD  $\pm$ 5.2, respectively) than among those using other medications (22.5 days/month, SD  $\pm$ 6.2 and 23.1 days/month, SD  $\pm$ 6.8) ( $p < 0.001$  in both cases). Those using psychotropic medications were older (mean age 55 years, SD  $\pm$ 14) than those using other medications (mean age 51 years, SD  $\pm$ 15) ( $p = 0.011$ ) and had made more visits to their physician ( $p = 0.0040$ ).



*Figure 2. Frequency of headache and of medication use in relation to age, among 799 individuals with medication overuse headache (MOH). The frequencies are reported as the mean number of days/month over the last 3 months.*

Almost half (47%,  $n = 370$ ) reported only using OTC medications. This proportion was higher among the young than the old ( $p < 0.001$ , OR 0.98, 95% CI 0.97–0.98), and lower among those who had only attended

elementary school compared to those with high school education ( $p = 0.0032$ ) or university education ( $p = 0.0081$ ).

Among those who used prescription medication, 82% ( $n = 311$ ) reported receiving all prescriptions from the same physician. This proportion did not differ according to the primary medication, for example, between those using psychotropics ( $n = 64$ , 81%) and those using other medications ( $n = 246$ , 82%) ( $p = 0.78$ ).

Use of prophylactic medication was reported by 11% ( $n = 83$ ). The proportion using prophylactics was smaller among those who only had elementary school education (8%,  $n = 22$ ) compared to those with university education (14%,  $n = 26$ ,  $p = 0.021$ ).

### **4.3 Health care contacts (Study II)**

During the previous year, fewer than half (44%,  $n = 343$ ) of the persons with MOH had visited their physician at all, and 14% ( $n = 102$ ) had seen a neurologist. The proportion having seen a neurologist was lower among those who had only attended elementary school (10%,  $n = 30$ ) than among those who had a high school education (15%,  $n = 48$ ,  $p = 0.046$ ).

Fewer than half (46%,  $n = 362$ ) reported ever having received information about MOH from a physician. This proportion was larger among those who used prescription medications compared to those who only used OTC medications ( $p < 0.001$ ).

### **4.4 Non-adherence to prophylactic medication (Study III)**

In Study III, 36% ( $n = 63$ ) of the 174 participants reported a MARS value  $< 23$  and were thus considered non-adherent to their prophylactic medication.

The most commonly used type of medication was tricyclic antidepressants ( $n = 63$ , 36%). The proportion with self-reported non-adherence was lower among those using beta blockers (22%) than among the rest (39%) ( $p = 0.032$ ), and the reverse was true for those using tricyclic antidepressants (44% vs. 29%,  $p = 0.036$ ).

Adherence did not differ in relation to sex, age, education level or beliefs about medicines.

## 4.5 Beliefs about medicines (Study III)

Results from Study III showed that persons with migraine believed that the necessity of their prophylactic medication outweighed the concerns. The necessity–concerns differential was 4.6, Table 7. The scores on the BMQ subparts did not differ among those who were considered adherent (MARS values >23) and those who were non-adherent, and there were no differences in relation to age or sex.

Table 7. *Beliefs about medicines among 174 Swedish migraineurs using prophylactic medication*

	Total	Compulsory school	Further education	Higher education	p-value*
BMQ subscales	Mean ± SD	mean ± SD	mean ± SD	mean ± SD	
Specific Necessity	18.9 ±3.9	19.5 ±3.4	18.9 ±3.8	18.8 ±4.1	0.83
Specific Concerns	14.2 ±4.7	10.9 <sup>a</sup> ± 5.3	14.4 <sup>a</sup> ±4.8	14.4 ±4.8	0.039
Necessity–concerns differential	4.6 ±5.7	8.5 <sup>b</sup> ± 5.5	4.2 <sup>b</sup> ±5.0	4.4 ±6.0	0.044
General Harm	12.2 ±3.1	11.6 ±3.8	12.7 ±2.7	11.9 ±3.2	0.21
General Benefit	16.7 ±2.2	16.9 ±2.4	16.3 ±2.3	17.1 ±2.0	0.067
General Overuse	8.6 ±2.3	6.5 <sup>c,d</sup> ±1.8	8.8 <sup>c</sup> ±2.1	8.7 <sup>d</sup> ±2.4	0.0039

\*The p-values indicate the results from an ANOVA analysis.

<sup>a,b,c,d</sup>Results from the post hoc range test (Fisher's LSD): Mean scores marked with the same letter are significantly different from each other.

Missing values are not included.

There was, however, a difference in relation to educational level. Mean scores for BMQ, by education, are shown in Table 7. Participants with the lowest level of education expressed less concern about medicines and had a higher necessity–concerns differential compared with those with a higher

educational level. The same analyses for the subgroups of BMQ General showed that, compared with those educated to a higher level, subjects with a lower level of education believed, to a lesser extent, that physicians overprescribed medications.

## 4.6 A grounded theory on medication overuse headache (Study IV)

The qualitative data in Study IV revealed three main categories: *headaches threaten to ruin one's life*, *medication as the only solution* and *shortsighted medication use*. The core category, labeled *holding on to the indispensable medication*, was central to the data and could pull all three main categories together into an explanatory whole, Figure 3.

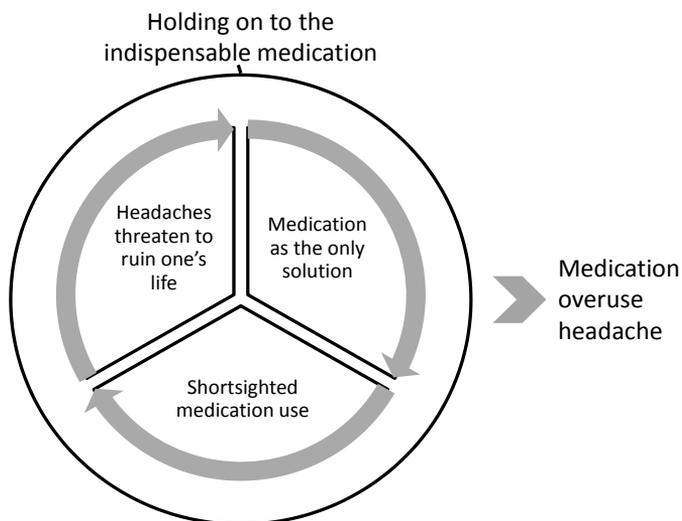
### Core category:

#### Holding on to the indispensable medication

The basic process leading to medication overuse was *holding on to the indispensable medication*, Figure 3. The participants viewed their medication as indispensable, because they perceived it to be the only thing that was effective against their headaches. They described that, without the medication, the negative consequences of headaches would ruin their lives. In that sense, they depended on the medication to maintain their current lifestyle.

The participants perceived headaches as something that threatened to ruin their lives (*headaches threaten to ruin one's life*), and despite extensive efforts, they had been unable find any other effective aid besides the acute medication. They thus regarded the medication as the only effective aid (*medication as the only solution*) and as a result, the medication became indispensable. They avoided questioning their medication use by focusing on the headaches, rather than keeping track of the amount of medication used (*shortsighted medication use*). One participant concluded:

*These triptans are the only thing I have found that really helps, so that I can live my life and do what I want to in the daytime, even during the bad days. So this is... if it stops, or if I am not allowed to take it anymore, because I have taken too much /.../ Just thinking about it makes me very nervous. Because my own assessment of the situation is pretty much that I would have to go on disability pension then. (No 4)*



*Figure 3. The process of holding on to the indispensable medication, which eventually leads to MOH, includes three subparts: headaches threaten to ruin one's life, medication as the only solution, and shortsighted medication use.*

## **Main categories:**

### **Headaches threaten to ruin one's life**

Headaches affected important areas in the participants' lives in ways that made life feel less worth living. This was partly because the disorder itself was unbearable, and partly because of its consequences for other parts of their lives. The headaches were an extra burden in their everyday lives. Because of the headaches, they had to make life adjustments and were unable to live their lives the way they wanted to. They struggled to keep working. The headaches were unpredictable, which meant that they often had to cancel things they had planned.

## **Medication as the only solution**

The participants went to great lengths to find ways to manage their headaches. They searched for explanations, tested numerous treatments, and made extensive lifestyle changes. In their experience, however, none of the efforts had led to significant improvement of the headaches. The only thing that had actually helped was the acute medication. Because of this, they eventually became resigned, accepting the acute medication as the only effective aid. The acute medication was thus perceived as indispensable, and they made sure to always have it on hand.

They were reluctant to use prophylactic medication, because they did not like the idea of having to medicate daily. They viewed the acute medication as indispensable, and because they already had to take so much of it, they were reluctant to add another medication (the prophylactic). They were also afraid of side effects from the prophylactic medication.

## **Shortsighted medication use**

Throughout the interviews, the participants described their use of medication as something they had to do, to manage their headaches, not as something they chose to do. They had a general intention to use as little medication as possible, but found themselves compelled to medicate frequently to cope with the headaches. They did not want to think about how much medication they used. Instead, they focused on the headaches. Decisions about when to medicate were based on the characteristics of the current headache attack. Despite years of experience, it was often perceived as difficult to determine the severity of an upcoming attack and the need to medicate. During periods in life with increased headache frequency, they viewed themselves as forced to increase their medication use. There was variation in the participants' awareness and acknowledgement of the link between the increasing headaches and the use of acute medication.



## 5 DISCUSSION

In the first part of this section, the results of the thesis are discussed, in the second part there is a discussion about the methodology used, and finally, there is a discussion about the relevance and potential implications of the results.

### 5.1 Discussion of results

Below, the results of Studies I–IV are discussed.

#### 5.1.1 Main findings

The overall aim of this thesis was to study problematic medication use among people with headache. Two types of problematic medication use were analyzed, namely overuse of acute medications in MOH, and non-adherence to prophylactic therapy in migraine.

The first Swedish population-based study of MOH showed that the prevalence was 1.8% in the general population, aged  $\geq 15$  years. The prevalence was 2.8 times higher among women than among men and inversely associated with socioeconomic status. Fewer than half of those with MOH had made a headache-related visit to a physician during the past year, and almost half used only OTC medications. The proportion using only OTC medications was particularly high among the young.

As for use of prophylactic medications, approximately one third of the migraine patients at a Swedish headache clinic were considered non-adherent, using the MARS questionnaire for measurement. The patients' beliefs about the necessity of their prophylactic medication were greater than their concerns, but there was no association between beliefs about medicines and adherence to prophylactic medication.

There were several socioeconomic differences in all the quantitative studies, indicating that MOH was not only more common among those with low socioeconomic status, but that there were also socioeconomic differences in terms of medication use and health care contacts. Beliefs about medicines also differed in relation to educational level. Migraineurs with lower level of education had fewer concerns about their prophylactic medications than those with a higher educational level.

The qualitative study showed that the participants perceived headaches as something that threatened to ruin their lives and despite extensive efforts, they had been unable find any effective aid other than the acute medication. Because of this, the acute medication became indispensable to them. Their medication use was shortsighted. They avoided questioning the medication use by focusing on the headaches, instead of keeping track of the amount of medication used. This process, eventually leading to MOH, was labeled “holding on to the indispensable medication.”

### **5.1.2 Prevalence of medication overuse headache**

Study I showed that the prevalence of MOH in Sweden was 1.8%. This represents approximately 140 000 Swedes, and overuse of acute medication in headache is thus a significant public health problem in Sweden. This was the first population-based Swedish study on MOH.

Several prevalence studies have been conducted in other countries and these are summarized in Table 8. The prevalence in Study I was similar to that found in a recent Norwegian population-based study (1.7%), which also applied the appendix diagnostic criteria (87). However, that study included only 30-44 year olds, a group in which the prevalence is rather high. An even more recent Norwegian study, which included all ages  $\geq 20$  years, found a prevalence of 1.0% (35). It is, however, likely that this study, as well as the Norwegian study from 2004 (85), underestimated the prevalence, since they did not include triptan-induced MOH (35). Other recent studies have shown a somewhat lower prevalence, for example, 0.9% in Georgia and 1% in Germany (88, 89). The Georgian study had a very small sample size, and the authors further suggested that the relatively low prevalence might be explained by fact that some Georgians are hindered from overusing acute headache medication because of poverty. In the German study (88), the researchers only asked about acute medications used to treat headaches, whereas in Study I, we asked for use of acute headache medication as well as use of analgesics for other indications, as recommended in the ICHD-II (1). This may possibly have caused a slight under-representation of MOH in the German study compared to Study I. The studies conducted before 2004 have used slightly different variations of diagnostic criteria and are thus difficult to compare.

All studies in Table 8 are population based and refer to roughly the same age group, except the Norwegian study from 2008 (87), which included only 30–44 year olds. Some studies used clinical interviews to diagnose MOH (38, 39, 69, 87), whereas others, including Study I, used standardized questionnaires

(35, 85, 88, 89). However, in two previous studies comparing structured interviews conducted by lay interviewers with headache specialist ratings, the agreement between the two was validated (88, 145). Both studies used the same diagnostic criteria for MOH as used in this thesis (3). The prevalence in Study I was slightly higher than in most other studies, and though there are no obvious methodological differences compared to the other studies, it is difficult to say whether it reflects a true difference in prevalence or if it has to do with the way the studies were conducted.

Table 8. *Prevalence of medication overuse headache in population-based studies of adults*

Study country	Data collection	Participants (n)	Prevalence		
			Men (%)	Women (%)	Overall (%)
Norway, 2011 (35)	Questionnaire	39 690	0.6	1.3	1.0
Georgia, 2009 (89)	Interview	1145	-	-	0.9
Germany, 2009 (88)	Interview	7417	-	-	1.0
Norway, 2008 (87)	Questionnaire Interview	20 598	1.1	2.3	1.7
Norway, 2004 (85)	Questionnaire	49 064	0.6	1.2	0.9
Spain, 2004 (69)	Questionnaire, Interview	4855	1.2	2.6	1.4
Taiwan, 2001 (39)	Questionnaire, Interview	3377	0.9	1.3	1.1
Spain, 1999 (38)	Questionnaire, Interview	1881	-	-	1.2

### 5.1.3 Overuse of acute medication

The use of headache medications varies between different parts of the world and is most likely influenced by cultural factors (83). In this thesis (Study I), simple analgesics (particularly paracetamol) were most often the primarily overused medication. This is in line with the current guidelines for acute treatment of headache, (51, 56), and with findings from other studies (92, 146). In Study II, nearly one half of the persons with MOH reported always buying their primarily used acute medication as OTC medication. Previous

research on the use of OTC medications in headache is rather limited, presumably because those who use only OTC medications cannot be identified via their prescribers, for example, in prescription databases or in clinical samples.

In Study II, it was shown that almost half (46%) of those with MOH used acute medications every day. The frequency of acute medication use differed with age, being lowest among the young, whereas the frequency of headache did not show the same age pattern. In fact, the frequency of headache was higher than the frequency of medication use among the youngest, whereas the opposite was seen in the older age groups. There was also an association between older age and a larger proportion using prescription medications. A similar relation was observed among migraineurs by Linet et al. (147), who found that the proportion using prescription medications was almost twice as high among young men aged 18–29 years as among boys aged 12–17 years old. A recent Danish study showed that medication use for headache follows a behavioral pattern that may track from adolescence into adulthood (148), thus underlining the need for early identification and more research on the strategies used by young persons to manage headache.

Choosing acute medication as the main strategy to master headache could be regarded as choosing an easy alternative. It requires less effort than many other strategies, for example, lifestyle changes and psychotherapy. However, the results of Study IV show that the use of acute medication was not the participants' first choice. They had gone through extensive efforts trying to find other strategies. The range of strategies used was similar to that found in a previous qualitative study (131). Some of the treatments they had tried lacked scientific evidence (e.g., homeopathic treatments and various naturopathic methods) but they had also tried treatments that are recommended in official headache treatment guidelines, such as prophylactic medication, psychotherapy, and physiotherapy (51, 56), without experiencing improvement. In this study, we did not go into clinical reasons as to why these strategies had not been effective. The participants perceived them as ineffective, and consequently, they eventually became resigned, accepting the acute medication as the only effective aid. The reliance on acute medication was thus not a convenient quick solution to the problem; it was rather the only remaining alternative after having tried everything else.

### **5.1.4 Limited health care contacts**

Less than one half (44%) of those with MOH in Study II had made a headache-related visit to a physician during the past year. Previous population-based figures in MOH are scarce, but in a recent Norwegian population-based study 16% of those with MOH reported having no contact at all with their physicians (149). Only 14% of the participants in Study II had consulted a neurologist during the previous year. In the Norwegian study the corresponding figure was 21% (149).

These findings suggest that many Swedes with MOH do not have regular contact with health care providers. It should be noted that, since there is neither a comparator group nor a gold standard for the amount of health care contacts persons with MOH ought to be having, it is a matter of judgement whether the rate of health care contacts presented in Study II is actually to be regarded as limited. However, considering the disease burden that is indicated by the reported frequencies of headache and medication use, I find it surprisingly low. A possible explanation for these low consultation rates may be found in a qualitative study of CDH by Peters et al. (131). They reported that some patients had low expectations, and that they questioned physicians' ability and interest in treating headaches, to the extent that they chose not to consult for headaches (131). The findings may also be a result of limited access to headache care. Increasing the contacts with health care seems important, in order to improve the situation of persons with MOH.

### **5.1.5 Awareness of medication overuse headache**

The results of Studies II and IV indicate that the awareness of MOH may be limited. Fewer than half of the participants in Study II reported having been informed by a physician about the fact that excessive use of acute medication could lead to increased headache frequency. This result could be interpreted in several ways. It is possible that the participants had found information some other way and were thus aware of MOH, despite never having been informed by a physician. It is also possible that the participants had indeed been informed, but that they did not remember so being, or that they had not understood the information. If no information had been given, this could be either because the physician had chosen not to do so, or because he or she was actually not aware of the problem of MOH. Either way, the results may be interpreted as an indicator that more information about MOH is needed, and it is likely that both health care professionals and persons at risk of developing MOH could benefit from more knowledge about MOH.

The question in Study II concerned information given by physicians, but the responsibility to inform about MOH does not rest only with physicians. Other health care professionals who meet with these patients, such as physiotherapists, psychologists, nurses and so on, also have opportunities to inform about MOH. Pharmacists play a potential key role, considering that the participants reported having such limited health care contacts and such a high use of OTC medications. In their role of dispensing prescriptions and OTC medications to persons at risk of MOH, they have both the opportunity and responsibility to inform about MOH. It is not known to what extent this opportunity is being used. Very little research concerning the role of pharmacists in the prevention of MOH is available (150, 151). A recent Belgian study showed that 24% of the clients at a community pharmacy, purchasing analgesics to treat headache, were overusing the medication (150). The authors emphasized the strategic position of pharmacists in early detection and prevention of MOH.

Considering the number of people at risk of developing MOH, the potential benefit of primary prevention is high. In fact, every one having some type of primary episodic headache disorder, such as migraine or TTH, may be at risk of developing MOH, if they overuse acute medication. The prevalence of these disorders in the general population is around 15% and 60–90% respectively (11), and a Swedish study has shown that the majority of people with recurrent headaches do use medications for treatment (152). The potential number of people who could develop MOH is thus very high. Informing persons with episodic headaches about the fact that overuse of acute headache medication can cause MOH seems to be an important first step in the preventive work. A Norwegian, population-based study recently showed that around 76% of those with MOH stopped overusing acute medication within 1.5 years after having received information about the possible role of medication overuse in their increased headache frequency (153). The authors concluded that brief interventions consisting of advice to stop overuse might be a useful and cost effective strategy in MOH.

Study IV showed a variation in awareness of MOH among the participants. A few participants said that they had never heard about the disorder. When this is the case, a first step to prevent or treat MOH must be to inform the person about the disorder, as discussed above. However, there were also participants who knew that MOH existed, but did not acknowledge it as the reason behind their own increasing headache. Indeed, since the participants were not detoxified, the possibility that there really was another reason underlying the headache for some cannot be excluded. Nevertheless, the results suggest that simply knowing that there is a disorder such as MOH may not necessarily

mean awareness of the fact that one's own increasing headache could have been caused by overuse of acute medication. This implies that the efforts required to prevent and treat MOH may, at least in some cases, be more complex than merely informing about MOH.

### **5.1.6 Medication overuse headache and addiction**

There is an ongoing discussion as to whether MOH should be considered an addictive disorder or not (105, 107, 108, 111, 154). Some studies indicate that many of those with MOH do fulfill criteria for addiction, whereas others have not found any difference concerning addiction between persons with MOH, migraineurs, and the general population (105-108).

The participants with MOH in Study IV expressed that they did not view themselves as addicts and that they felt offended if someone made them feel as if they were. An important difference between those with MOH and those with addiction seems to be the reason for the overuse. Addiction is often characterized by a progressive neglect of alternative pleasures or interests because of drug use and may result in a reduction of social, occupational, and recreational activities (107, 109). This is usually not the case in MOH. Instead, both Study IV and previous research suggest that the persons with MOH are, rather overusing the medication to be able to live their lives as normally as possible and to reduce the impact of their disorder on their daily lives (107, 109). The participants in Study IV held on to the medication to prevent the headaches from ruining their lives, not because they wanted the medication per se.

In Study II, 1 in 10 participants with MOH reported using a psychotropic medication as primary acute medication. Colas et al. (69) found a corresponding figure of 12.5% in their population-based study of MOH. Psychotropic medications are addictive and not recommended for headache treatment (58). It has been suggested that those with MOH who use psychotropic substances should be regarded as a specific subgroup (110-112). In Study II, there were indeed several differences between the two groups, for example, the frequencies of headache and of medication use, the proportion with headache-related sickness absence, and the number of physician visits were all higher among those overusing psychotropics than among those overusing other medications. The higher consultation rate may partly be explained by the fact that no psychotropic medications are available without prescription in Sweden. However, the differences suggest that MOH sufferers using psychotropic medications are more bothered by their disorder than those using other medications are. Since this was a cross-sectional study,

causality is unknown. The findings may however be interpreted as support for the suggestion that persons with MOH who overuse psychotropic substances should be regarded as a specific, more severe subgroup of MOH (110-112).

### **5.1.7 Non-adherence to prophylactic medication**

Thirty-six percent of the migraine patients in Study III were defined as non-adherent to their prescriptions of prophylactic migraine medication. This is lower than in an earlier study of mixed headache patients (155). In a longitudinal Dutch study, only 25% of the migraineurs continued their prophylactic treatment after one year (156). However, the proportion of non-adherers is difficult to compare between studies, since it depends on the case definition used in each study. A review concluded that the level of adherence in headache is similar to levels generally seen in other chronic diseases, that is, around 50% (5). In Study III, no differences were found in adherence for age, gender, or educational level, which confirms the earlier findings (155). Demographic factors are usually not strong predictors for adherence, since an individual's level of adherence may vary over time and across different aspects of treatment (5).

In Study III, the type of medication was associated with adherence in the univariate analysis, but not in the final logistic regression model. These relationships need further investigation. The univariate results suggested that the proportion of non-adherence was higher among those using tricyclic antidepressants (TCA) than among the rest, and lower among those using beta blockers than among the rest. Beta blockers are recommended as first-choice medications for prevention of migraine, whereas TCAs are recommended as second-choice, partly due to their more limited proof of effectiveness (51). Patients who do not have sufficient effect from other treatments are often the ones who are prescribed TCAs, with one possible reason being previous non-adherence. Other medication-related variables were not associated with adherence in Study III, contrary to suggestions in the literature (5, 122). The participants' beliefs about medicines were not associated to adherence either. Their scores on the BMQ are comparable to those of patients suffering from other chronic conditions (such as hypertension and asthma); however, in those patient populations there were significant relationships between specific beliefs and adherence (126, 157). The lack of association among the migraineurs in this study was thus somewhat surprising. It could reflect the possibility that other factors have a greater impact on the decision to use prophylactic migraine medication or

that some important component of the beliefs about medicines is lacking, or it could be a result of methodological limitations of the study.

In Study IV, which was a qualitative study, the participants expressed skepticism toward the idea of using prophylactic medication. They did not like the idea of having to medicate daily. The reluctance to use daily medication has been described in previous research, for example, among asthma patients (158). This notion is interesting, since the participants in Study IV had MOH and were already using acute medication more or less daily. When asked about this, they explained that the acute medication was indispensable to them. Since they were already using so much of that, they felt it was not a good idea to add yet another medication, that is, the prophylactic. This implies that the participants somehow viewed the prophylactic and the acute medication as the same thing, that is, a medication that was harmful and ought to be used as little as possible. Regarding it that way, it is not surprising that they held on to the acute medication rather than the prophylactic. The acute medication had a more obvious effect and only had to be taken when needed. This finding may provide a possible explanation to the non-adherence to prophylactic treatment found in Study III. It is also an example of how the perspectives of the individual medication user can differ from the traditional medical view. A first step to arriving at successful use of headache medication is probably to bridge the gap between the perspectives of patients and health care personnel.

### **5.1.8 Gender in headache and medication use**

In Study I, it was shown that MOH is almost three times more common among women than among men. The prevalence was higher among women in most sociodemographic groups, and women had an earlier age of onset than men. The main reason that MOH is more common among women than among men is probably that the primary episodic headaches from which it develops are also more common among women than men (22). The higher prevalence of headache in women is usually attributed to the effect of female sex hormones (22). From a gender perspective, however, several other possible factors could also contribute to the observed sex differences. Social factors such as women's and men's different living conditions is one example. Swedish women take part in the labor market almost to the same extent as men do (159). However, they more often work in sectors with lower salaries and have positions with lower status than men (160). In addition to this, women still take a larger responsibility for the family and domestic duties (161, 162). This is a potentially stressful situation, and stress is a

trigger factor for both TTH and migraine attacks (163). Work stress has been found to be associated with headache among both men and women (13).

Historically, headache has been regarded as a women's disease, and the cultural meaning of the word headache is still gendered feminine (164). In a content analysis of migraine advertisements, Kempner et al. (165) demonstrated that the pharmaceutical industry directs its marketing of migraine medications predominantly to women. As a part of this strategy, pharmaceutical advertisements portray women as the prototypical migraine sufferer, by bringing out familiar pictures of femininity and hegemonic feminine behavior, for example, women with headache are depicted as bad mothers, because they are not giving their children the care they need. The writer argues that the pharmaceutical gendering of the migraine medication market creates the false impression that migraine is exclusively a "woman's disorder," thus ignoring the men with migraine and reinforcing gender bias in help seeking and diagnosis (164).

### **5.1.9 Socioeconomic differences in headache and medication use**

Several differences in relation to socioeconomic status were found in the quantitative studies (I–III). In Study I, multivariate logistic regression showed that having a low level of education, and a low household income, and not working, were associated with MOH. This was a cross-sectional study, and therefore it is not possible to draw conclusions about causality. Longitudinal research is needed to find out whether low socioeconomic status is a risk factor for development of MOH, or if it is the other way around, that is, that having MOH somehow induces low socioeconomic status, for example, by hindering people from attaining education and pursuing a career. An association between MOH and low socioeconomic status has been suggested previously, by Atasoy et al. (93). They found that low education was more common among those with MOH than among migraineurs in Turkey (93). In a large Norwegian prospective study, Hagen et al. (94) showed that low socioeconomic status was indeed a risk factor for frequent headache, but this has yet to be confirmed for MOH specifically. Interpreting their results, Hagen et al. (94) suggested that other factors associated with low socioeconomic status, such as stress, poor diet, or poor medical care, may influence headache risk. It seems likely that similar factors may be involved in MOH.

In Study II, several differences relating to educational level were detected; for example, both the frequencies of headache and of medication use were

higher among those who only had elementary school education than among the more highly educated. Further, those with a lower educational level were less likely to use prophylactic medication or to have consulted a neurologist than those with a higher educational level. These findings suggest that the use of medications and health care is unequally distributed in relation to educational level among individuals with MOH in Sweden. Such differences are not in line with the Swedish health care act, which states that health care should be provided to everyone, on equal terms (166). There is a need for longitudinal research to evaluate the consequences of these differences and to analyze whether they are the result of health care actually being provided unequally or if help-seeking behaviors differ in relation to educational level. Similar differences have been found in a Swedish study on epilepsy patients, in which socioeconomic characteristics were important for access to neurologists and the prescriptions of individual antiepileptic medications (167). The authors suggested differences in help-seeking behaviour as a possible explanation.

Some of the socioeconomic differences found in Study II may contribute to the prevalence difference found in Study I. The fact that those with low socioeconomic status in Study II medicated more frequently could either be the result of their having more headaches to begin with, or it could be a factor actually contributing to their higher headache frequency and the higher prevalence of MOH in that group. One of the recommended ways to prevent development of MOH is to have good management of the primary headache, for example, with use of prophylactic medication (58). In Study II, it was shown that both the proportion using prophylactic medication and the proportion having seen a neurologist was lower among those with low educational level than among those with higher education. This could possibly contribute to the higher prevalence of MOH among those with low education level.

In Study III, it was shown that beliefs about medications differed in relation to educational level. Participants with the lowest level of education expressed less concerns about medicines and had a higher necessity–concerns differential compared with those with a higher educational level. The same analyses for the general part of BMQ showed that participants with a higher educational level had stronger beliefs than those with a lower education in the notion that doctors overprescribe medications. In Study III no association between beliefs about medicines and adherence was shown, but several other studies have shown relations between beliefs about medicines and medication behavior (126, 157). It is thus possible that the differences in beliefs are somehow related to the differences in medication use seen in Study II.

In Study I, the prevalence of MOH in Sweden was almost twice as high among women without Swedish citizenship as in women with Swedish citizenship. This difference could not be detected among men, possibly due to the limited sample size (only four of the men with MOH were without Swedish citizenship). In a previous German study, Kavuk et al. found that medication overuse was more frequent among first generation Turkish immigrants than among German natives (95). In Study I, the association between MOH and not having Swedish citizenship was not significant after controlling for other socioeconomic factors (education, employment status and household income). Furthermore, the proportion of those with MOH who reported that they were born outside of Sweden was 12%, which is notably below the 16% normally reported for the general Swedish population (168). Thus, it is difficult to draw firm conclusions regarding immigrant status and MOH from Study I.

### **5.1.10 Decision-making and beliefs about medicines**

Several studies have described the process in which persons with headache make decisions about medication use, showing somewhat similar results (127-129). The studies suggest that persons with headache actively weigh risks and benefits of taking the medication before making a decision about whether to medicate or not. This is in line with Horne and Weinman's beliefs-about-medicines model for patients with chronic illness, mentioned earlier (126). They hypothesized that patients engage in an implicit risk-benefit analysis in which beliefs about the necessity of their medication are weighed against concerns about the potential adverse effects of taking it, and that these beliefs are related to medication use. In the case of headache, taking acute medication is beneficial, because the attack is aborted, but it also leads to costs in terms of the potential development of MOH. If applying the model strictly, one would expect the risk-benefit analysis to lead to a decreased medication use, when such negative effects prevail. However, this is not the case in MOH, where the persons overuse acute medications despite the negative consequences (109). Even after successful withdrawal treatment, often consisting of thorough patient education, the relapse rate is around 30% (70, 169).

The model presented in Study IV provides possible explanations to this behavior. The perception that headaches are threatening to ruin one's life and that there are no available solutions other than the acute medication could likely tip the balance so that the benefits of taking acute medication outweigh the risks. Further, the fact that the participants avoided keeping track of their medication use and did not necessarily think about it as something that

contributed to increased headache probably made it more difficult for them to make the clear-sighted kind of risk–benefit analysis described by the decision-making models (126-129). Such analyses can only include factors that the person using the medication is aware of, and when there are important unknown aspects involved, such as the risk of MOH, the risk–benefit analysis becomes blurred. It is also possible that the beliefs-about-medicines model is missing some important aspects concerning the use of headache medication. For example, the balance between using prophylactic and acute medication may not be captured by the model. The data in Study IV indicated that thoughts about use of acute and prophylactic medication were closely interrelated. The BMQ’s specific part refers to one medication only, and its general part to medications in general. An instrument considering both acute and preventive medication would probably better reflect the situation of those with headache and could most likely be useful in other diseases as well, for example, asthma.

The beliefs about medicines reported by the migraineurs in Study III are similar to what has been reported in studies concerning other chronic conditions, such as hypertension and asthma (126, 157). The necessity–concerns differential represents the migraineurs’ risk–benefit assessment when they make the active decision whether or not to take the prophylactic medication. The differential had a positive mean value, which implies that the participants perceived that the benefits of taking the prophylactic migraine medication outweighed the costs. This is somewhat in contrast with the results of Study IV, where the participants expressed skepticism towards prophylactic medication. However, it should be kept in mind that the participants of Study IV were people with MOH, whereas those in Study III were migraineurs, specifically included because they did use prophylactic medication.

The participants in Study IV were skeptical about the use of prophylactic medication, but they conveyed a very different picture concerning use of acute medication. The acute medication was perceived as indispensable, and the participants held on to it as the only thing that could prevent the headaches from ruining their lives. It is not known whether this view of the acute medication is unique to those who develop MOH or if it could also be transferred to migraineurs, such as the participants of Study III, and persons with other headache disorders. This is a question for future research and could be analyzed as a possible key in identifying people at risk of developing MOH. Further, the fact that people with MOH have such different perceptions of acute and prophylactic medications should be taken into account in future research on headache and medication use.

## **5.2 Methodological considerations**

Below, some methodological considerations of Studies I-IV are discussed. Since the same data collection was used for Studies I and II, these are discussed under the same heading. The last section contains a discussion about the general methodological issues of combining the results of the four studies together in the thesis.

### **5.2.1 Studies I and II**

A major methodological strength of Studies I and II was the large sample size, which was based on the entire Swedish population aged  $\geq 15$  years. The sample was somewhat skewed towards a larger proportion of women and elderly compared to the general population. Therefore, an attempt was made to standardize the data according to age, sex, and work status. However, as the adjustment had no effect on the overall prevalence, it was assumed that the survey sample could be considered representative of the general population. Thus, only crude figures are presented for all other analyses.

The response rate in the survey is unknown. The fact that the survey contained questions from other organizations and surveys as well as the questions of Study I and II makes it less likely that potential non-response was specifically related to issues regarding headache or medication use. Having frequent headaches could affect the tendency to answer telephone surveys in two directions. On the one hand, one may spend more time at home and thus have more time by the phone, but on the other hand, one may be feeling too ill to answer the phone or be unable to leave bed. One can only speculate that this did not affect the conclusions. However, it is likely that people in general who spend more time at home and are often available to answer the telephone are over-represented in the study, and this could affect the generalizability of the results.

Another limitation is that only households with a regular phone were included in the survey. In 2009, 15% of Swedes reported living in a household without regular telephone (170). This proportion is increasing, as more and more households rely on cell phones only. Not having a regular phone is particularly common in households with young individuals. For example, in households where nobody is above 26 years old, 56% are without regular phone (170). This has probably contributed to the fact that young people were slightly under-represented in the study. It should also be noted that the young people that were included might not be entirely representative of their age group in the general population, since they were selected from the limited proportion that did have a regular phone.

All data in this survey are based on self-report, and the risk of recall bias is thus a potential limitation. However, previous studies comparing the self-reported use of health care resources and medications with registry data have shown high concordance between the two (171), even when patients were interviewed over the telephone (172). Care was taken to make the questions as clear and as easy to answer as possible. The risk of recall bias was minimized by asking for the shortest time periods possible. All questions concerning medication use and headache concerned the previous three months, since this is how the diagnostic criteria for MOH are formulated (3). The questions concerning health care contacts concerned the previous year, since it was anticipated that such events occurred less often and would be easier to remember.

In the multivariate regression analysis, there were interaction effects between some of the socioeconomic variables. This is not surprising, since they all illustrate socioeconomic status, albeit in slightly different ways. An attempt to include interaction variables in the model was made, but since most of the independent variables in the model were categorical, with multiple alternatives, the interaction variables made the model difficult to interpret and were thus excluded.

### **5.2.2 Study III**

The results from Study III are difficult to generalize to people with migraine in general, since the participants were sampled from a highly specialized headache clinic in Gothenburg, Sweden. The fact that they had been referred to the clinic most likely meant that their migraine was quite severe and/or difficult to treat. Further, the proportion of the participants with university education was approximately 50%. This is higher than in the general Swedish population, where less than 30% of the population has a higher education qualification (173).

Adherence to prophylactic medications was self-reported with the Medication Adherence Report Scale (MARS) (139). The questionnaire was developed in England and later translated to Swedish, with the back-translation accepted by the original author (personal communication, Tove Hedenrud). There are no validations published of the English or Swedish versions of MARS. However, there are validations of the German and the Danish version (174, 175). The German study actually published some data on internal consistency and reliability from the original English questionnaire that were supportive of its validity (174). However, another German study found MARS not valid for measuring adherence to medications against hypertension (176). The

instrument was chosen because it was the only questionnaire identified in which the participants were asked to rate their adherence on a scale, rather than just answering yes or no. We thought this would reduce the influence of social desirability—that is, that the participants would rather claim to be adherent, since that answer is presumably more socially desirable—and thus give a more accurate measurement of adherence. The instrument has not been used among headache patients before, but it has been used in a number of previous studies on patients with diagnoses, for example, asthma (139, 177, 178), cardiovascular disease (179), renal disease (180, 181), and bipolar disorder (143). The fact that MARS has been validated in other languages and used extensively in previous research strengthens its credibility; nonetheless, there is no formal validation of the Swedish version, and it has not previously been used among people with headache. This is a limitation to the study and because of this, the results must be interpreted with caution. The Cronbach's alpha, which measures internal consistency, was 0.68. There is no definition of an exact minimal acceptable limit for Cronbach's alpha (182, 183), but a value of 0.7 is often regarded as the lower limit for good internal consistency (182). The fact that some of the results were contrary to previous literature, for example, the lack of association between adherence and beliefs about medicines and medication related variables, raises questions about the validity. A possible factor causing problems when measuring adherence in this particular patient population could be the findings (in Study IV) that thoughts about the prophylactic medication seem to be entwined with thoughts about the acute medication, and the instrument did not take this into account.

### **5.2.3 Study IV**

Study IV was a qualitative study using grounded theory. There was a variation among the participants concerning how much experience and insight they had in the phenomenon of MOH. Some did not know that MOH existed; others knew about MOH but did not think that it was the reason behind their own increasing headache frequency and some were aware of the relationship between increasing headache and increasing medication use. Despite this variation, the theoretical pattern relating to the core category applied to all of the participants. Somehow, they all told the same story regarding their use of headache medication but owing to their varied range of experience, they told it from very different angles and added different perspectives. This added richness to the theory.

A limitation is that all the participants were recruited via advertisements and that the study thus only included persons who had taken the initiative to talk

about their situation. This may e.g. have led to a selection of MOH sufferers who were active and open and thus reinforced the impression that persons with MOH are actively searching for new treatments and new information about their disorder. Interviewing other persons with MOH may possibly have given another picture of the problem.

The participants had varied sociodemographic characteristics. The proportion with university education was higher than in the general Swedish population. However, the external validity in qualitative studies focuses on transferability rather than generalizability (184, 185), and even if some of the examples given in the data referred to the participants own specific contexts, they generally expressed the importance of the medication to prevent their disorder from disrupting their lives. This finding can easily be transferred to persons using headache medication in other settings and even to patients using medications for other disorders.

The model described in Study IV is novel and original, but the essences of several of the categories described are supported by other studies (see discussion of results), and this strengthens the credibility of the findings (138). Another factor that added to the credibility was the regular peer scrutiny applied (186). In between each interview, two of the co-authors (AJ and TH) read each interview, scrutinized the open coding and discussed the developing analysis. All major steps in the analysis were discussed in these meetings until consensus was reached. Researcher triangulation was used to increase the credibility and trustworthiness of the study (186), by discussions with the other co-investigators (GH, ML and CM) and in a multi-disciplinary research seminar.

## **5.2.4 General considerations**

The results of this thesis rest on data from three different research projects with different design, data collection, and research populations. This diversity means that the research problem has been approached from several different angles and as such, it adds strength to the thesis. However, when drawing general conclusions from the thesis, it is important to consider how the four studies relate to each other.

Studies I and II are based on a large population survey concerning the occurrence of MOH in the population. Study III is a smaller study concerning a sample of migraineurs at a headache clinic and their use of prophylactic medication. Study IV is a qualitative study about MOH. The third study concerned migraine patients, whereas the other studies concerned persons

with MOH. These are two different types of headache. However, MOH always develops from a primary episodic headache, such as migraine (or other episodic headaches) (70), and among persons with MOH who go through successful withdrawal therapy, the headache reverts to its original episodic pattern (e.g., migraine) (58). The relapse rate after withdrawal is high (70), and persons with an original episodic headache may in fact drift in and out of MOH several times during their lifetime. In order to gain the full picture of the medication use, it is thus important to study the primary headaches as well as MOH. In Study IV, the intention was to gain a picture of the development from primary episodic headache to MOH, and in that sense, it tied the previous studies together. Study IV was a qualitative study, thus adding another perspective to the thesis. By including the perspective of the individual persons with MOH, it added detail and important explanations to the overall results of the thesis.

In the thesis, both the overuse of acute medication and the underuse of prophylactic medication are studied. Studies I and II are mainly concerned with overuse of acute medications. Study IV is also mainly focused on the overuse of acute medications, even though the data also concern use of prophylactics as well as information about how the participants relate their use of acute medication to their use of prophylactic medication. Study III is the only study with a full focus on the use of prophylactic medication. Since this study concerned a selected group of migraineurs and had some methodological weaknesses concerning the use of non-validated instruments, the results in this thesis concerning underuse of prophylactic medication are less robust than the results about overuse of acute medication. However, the fact that scientific literature consistently show similar, or even worse, rates of non-adherence to prophylactic headache medication (5, 122, 123), adds strengths to the conclusion that underuse of prophylactic medication is indeed a problem. Considering that only a small proportion of persons with headache use prophylactic medications (113-115), whereas a majority use acute medication (152), the problem with overuse of acute medication may be ascribed a greater public health importance. However, since successful use of prophylactic medication is a possible way to prevent overuse of acute medication, the two problems are intertwined.

## 5.3 Relevance and implications

The results of this thesis will be important for future measures to improve the use of headache medication. Studies I and II are the first population-based studies of MOH in Sweden. As such, they shed light on an important public health problem whose distribution in Sweden was previously unknown. Now that the prevalence and the distribution of the disorder are known, preventive measures may be taken. How such measures should be designed is a matter for further research. In fact, there is very little research available concerning primary prevention of MOH (187, 188). Fritsche et al. (188) found that the use of an information brochure was helpful for the prevention of MOH in migraine patients. Clinical guidelines focus on preventing MOH by proper management of the primary headache disorder (51, 58). However, the results of this thesis indicate that many persons with MOH do not have regular contact with a physician and would thus not be reached by such attempts to optimize the treatment of primary headache. In addition, even those who are seeing a physician and using prophylactic medication may not be helped because of the low adherence to prophylactic treatment indicated by Study III.

It seems likely that preventive measures would be more effective if directed in a way that reaches as many persons at risk as possible. Given the results of this thesis, channels other than the health care service should also be included. Examples of such channels might be pharmacies, other traders that sell OTC medications, patient organizations, and so on. Considering the number of people at possible risk of developing MOH, the potential benefit of primary prevention is high. In fact, everyone having some type of primary episodic headache disorder may be at risk of developing MOH if they overuse acute medications. The issue of preventing medication overuse is thus important for a large proportion of the population.

The results of the qualitative study convey valuable information about the use of headache medications and the development of MOH from the perspective of the individual persons with headache. The knowledge about their thoughts and reasoning could increase the understanding between patients and health care professionals and may thus contribute to development of new strategies for prevention and care. A first step to arrive at successful use of headache medication is probably to bridge the gap between the perspectives of patients and health care personnel.

## 6 CONCLUSIONS

Problematic medication use is a significant problem among people with headache. Medication overuse headache occurs in 1.8% of the adult Swedish population. The problem is almost three times more common among women than men, and prevalence is inversely associated with socioeconomic status. There were also socioeconomic differences concerning medication use and health care contacts. The proportion using only OTC medication was high, particularly among the young. Approximately one third of the migraineurs in Study III were considered non-adherent to their prophylactic medication. Although this study had some methodological limitations and represents a selected group of migraineurs, it can be concluded that low adherence to prophylactic treatment is also a significant problem among people with headache. Because of the overuse of acute medication and the underuse of prophylactics, it is likely that many persons with headache suffer from an unnecessarily high disease burden.

The qualitative study showed that the participants' perceived headaches as something that threatened to ruin their lives. Because of this, they went to extensive efforts to find strategies to manage it. However, the only strategy actually perceived as effective was the acute medication, and they eventually became resigned, accepting it as the only effective aid. The acute medication thus became indispensable to them. They did not like to think about their medication use and avoided keeping track of the amount used. They had a general intention to use as little medication as possible, but found themselves compelled to medicate very frequently to cope with the headache.

In Sweden, there is a need for improved and increased information about medication overuse headache. Approximately one half of those with MOH in Study II had never been informed by a physician about the risk of MOH. More knowledge about MOH thus seems to be needed among people at risk of developing MOH and among health care professionals. Since the results of this thesis showed that people with MOH have limited contacts with health care, such preventive measures should also include other actors, such as pharmacies and other traders that sell OTC medications.

## 7 FUTURE PERSPECTIVES

The results of this thesis showed that people with headache have limited contacts with health care and that their use of OTC medications is high. Previous research on headache medication use has often been conducted from a clinical perspective, including only patients at headache clinics, or in large epidemiological studies, including only prescription medication identified via prescription databases. A large area of medication use in headache has thus been overlooked, namely the use of OTC medications among people who do not have regular contact with health care. Very little is known about the medication use in this group, and research questions that need to be approached concern, for example, how decisions about OTC medication use are made, how information about the medications is retrieved, and how potential risks are assessed by the individual user. Such knowledge is important in order to avoid problematic medication use, in headache as well as in other indications where the use of OTC medications is substantial.

Another area where there is a need for more research is the prevention of MOH. Few intervention studies have been conducted with the aim of preventing development of MOH, and little is known about suitable and effective methods.

Young individuals with MOH differed from older individuals in the sense that they medicated less frequently and also that they tended to use OTC medications rather than prescription medications. Many of these young individuals are most likely at the beginning of their disease career, and more research on this group and their coping strategies could shed valuable light on the development of MOH.

Finally, there is a need for a validated instrument to measure medication adherence among persons with headache. Considering the results of this thesis, such an instrument should take into account the use of both acute and prophylactic headache medication, and it should account for both under- and overuse of medication.



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