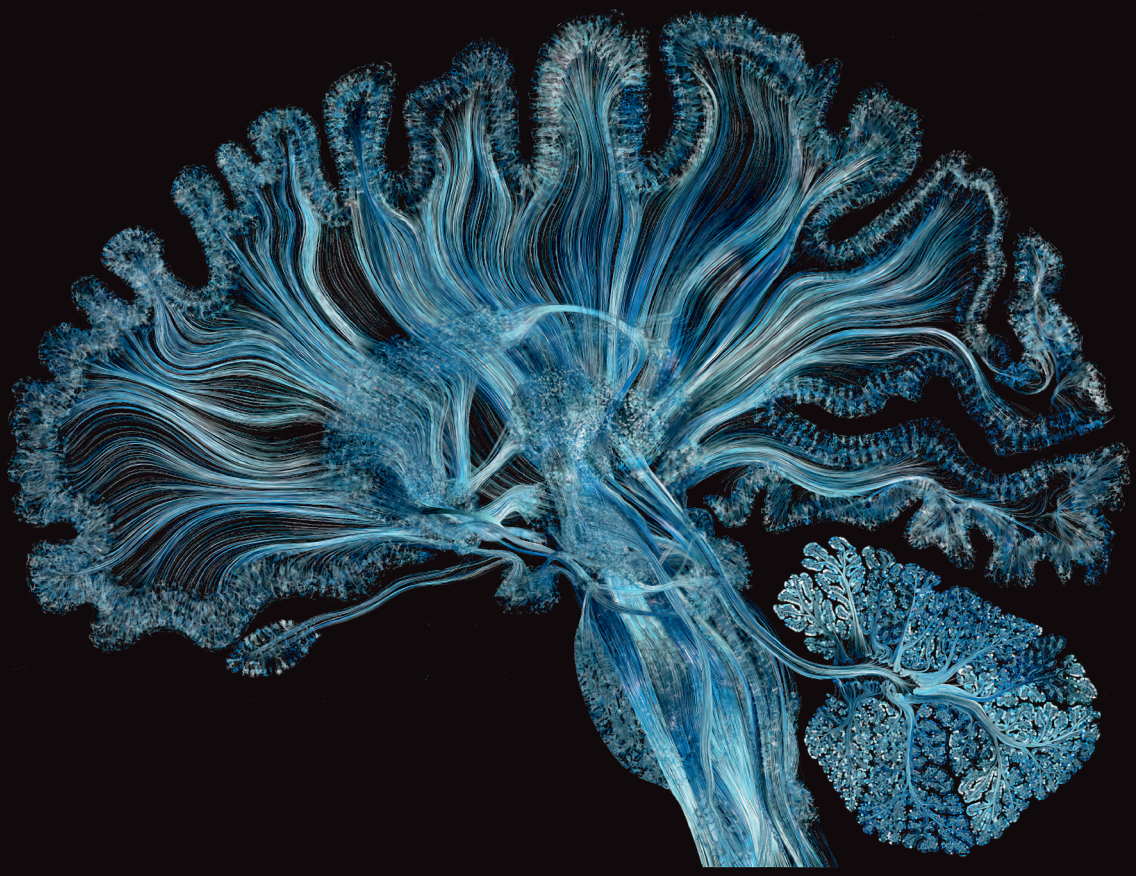
The clinical aspects and management of chronic migraine



Judith Anne Pijpers

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PhD thesis, Leiden University, Leiden, The Netherlands, 2022

ISBN/EAN: 978-94-6332-823-4

Cover design: Image by Greg Dunn (www.gregadunn.com)
Lay-out: Ferdinand van Nispen tot Pannerden. *my*-thesis.nl
Printing: GVO drukkers & vormgevers B.V., Ede

The research presented in this thesis was performed at the Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands.
This work is funded by grants of the Leiden University Medical Center (MD-PhD grant, J.A.P.), the Netherlands Organization for Scientific Research (NWO) (VIDI 917-11-319, G.M.T.), the Dutch Brain Foundation (2013(1)-247, G.M.T.) and the European Community (EC) [FP7-EUROHEADPAIN-no.602633]. They had no role in the design or conduct of any of the studies.

Funding for publication of this thesis has been provided by the Nederlandse Hoofdpijn Vereniging, and was gratefully accepted.

The clinical aspects and management of chronic migraine

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 22 februari 2022
klokke 13.45 uur

door

Judith Anne Pijpers

geboren te Alphen a/d Rijn

in 1989

Promotores
Prof.dr. G.M. Terwindt
Prof.dr. M.D. Ferrari

Promotiecommissie
Prof. dr. A. Dahan
Prof. dr. A.W.M. Evers
Prof. dr. R.H. Jensen, Faculty of Health and Medical Sciences, University of Copenhagen
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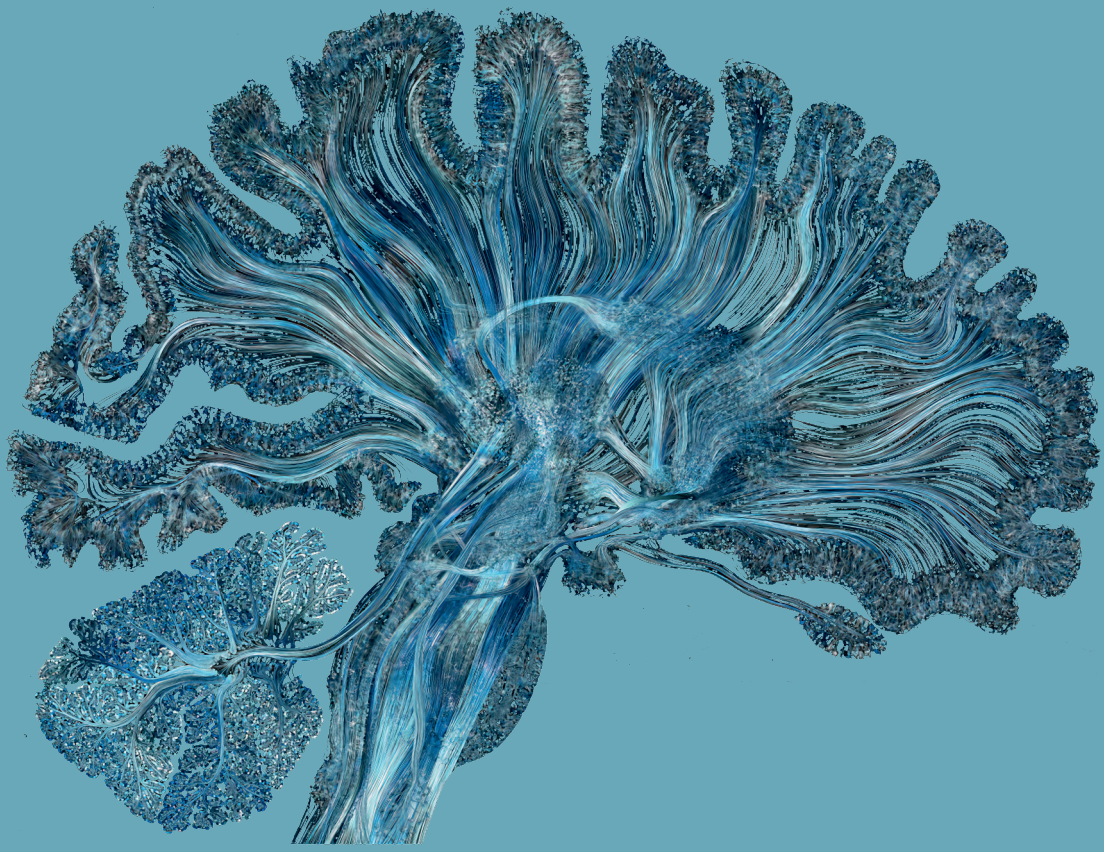
Contents



Chapter 1

General introduction

J.A. Pijpers

Adapted from:

Hoofdpijn door overgebruik van pijnmedicatie
J.A. Pijpers, N.J. Wiendels, H. Koppen, M.D. Ferrari, J. Haan, G.M. Terwindt
Nederlands Tijdschrift voor Geneeskunde 2018; 162: 27–33

Medicatieovergebruikshoofdpijn
J.A. Pijpers. N.J.Wiendels, G.M. Terwindt
Nervus Nascholing, 2017; 2:21-29

Migraine and migraine chronification

Migraine is a complex, multifactorial brain disorder, characterized by recurrent attacks of moderate to severe headache, typically accompanied by nausea, vomiting and hypersensitivity to movement, light and sound.[1–3] In one-third of patients, these headache attacks are preceded by transient focal neurological symptoms, called migraine aura. Migraine aura usually comprises visual symptoms, such as scintillating scotomas, but may occur as paresthesia, motor weakness or dysphasia. These symptoms are gradually developing over several minutes, lasting for 5-60 minutes.[4,5] Furthermore, most patients experience premonitory symptoms in the preceding days, such as mood and cognitive changes, food craving or neck stiffness.[6,7]

Migraine is a common disorder with a lifetime prevalence of 13.3%-33%, and most prevalent at the age of 35-50 years;[8] a socially and economically demanding period. As such, migraine is the second leading cause of Years Lived with Disability worldwide.[9] Most migraine patients have episodic migraine (< 15 headache days per month), with a median attack frequency of one per month.[8] However, every year 3% of these patients transform into chronic migraine, a high frequent variant of migraine with ≥ 15 headache days per month, of which at least 8 migraine days (box 1).[3,10] This transformation process is called migraine chronification. As a consequence of the high attack frequency, chronic migraine patients experience even more impairment on socioeconomic functioning and quality of life,[11] and the direct and indirect costs of chronic migraine are estimated to be fourfold higher compared to episodic migraine.[10]

Box 1. Chronic migraine criteria. Aggregation of the criteria on migraine and chronic migraine according to the International Classification of Headache Disorders (ICHD-3β criteria)3.

Chronic migraine

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for ≥3 months
B. Headache occurring in a patient who has had at least five attacks fulfilling criteria of migraine with or without aura

C. Headache on ≥8 days per month for >3 months, fulfilling any of the following:
1. Criteria for migraine:
   a) 4-72 hours
   b) At least two out of the four following characteristics: i) unilateral location; ii) pulsating quality; iii) moderate or severe pain intensity; iv) aggravation by or avoidance of routine physical activity (e.g. walking or climbing stairs)
   c) During the headache at least one of the following: i) nausea and/or vomiting ii) photophobia and phonophobia.
2. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

D. Not better accounted for by another ICHD-3 diagnosis.

Although migraine might be considered as a well-known, prevalent disorder, it remains underdiagnosed and undertreated.[12] Many migraine patients use non-specific 'over the counter' pain medication such as paracetamol (acetaminophen) of NSAIDs, instead of acute anti-migraine drugs.[12] Even the available acute anti-migraine drugs, triptans and to a lesser extent ergots, generally have a moderate effect, providing initial pain relief in 60% of patients, and sustained pain free rates of approximately 30%.[13] Also preventatives, daily medication in order to prevent headache attacks, have a moderate effect, both in episodic migraine as chronic migraine,[10] and knowledge in the prevention of chronic migraine is limited.[2,10]

To enhance treatment of chronic migraine, and ultimately prevent migraine chronification, better understanding of its pathophysiology and trials studying potential treatments are of uttermost importance. Hitherto some hypothesis on the pathophysiology and risk factor have been established.

Pathophysiology of chronic migraine

Migraine headache is caused by activation of the trigeminovascular system, consisting of trigeminal afferents surrounding meningeal blood vessels. The trigeminal afferents connect the meningeal blood vessels to the sensory cortex via the brain stem nucleus (Trigeminal Nucleus Caudatus, TNC) and the thalamus

(Figure 1). Upon activation, Calcitonin gene-related peptide (CGRP) is released, causing vasodilation of the meningeal arteries and signal transmission from the trigeminal afferents to the TNC.[1,14] The activation of the trigeminovascular system corresponds to the intracranial hypersensitivity experienced by patients (i.e. pulsating or throbbing type of pain, aggravated by pressure or physical activity).[1,15] The cause of activation, and thereby the origin of a migraine attack remains largely unknown, but changes in the brainstem and hypothalamus seem important factors.[1,10,16] Furthermore, the meninges can be stimulated by cortical events, such as 'cortical spreading depression', a depolarisation wave spreading over the cortex, which is regarded as the neurophysiological substrate of migraine aura.[2]

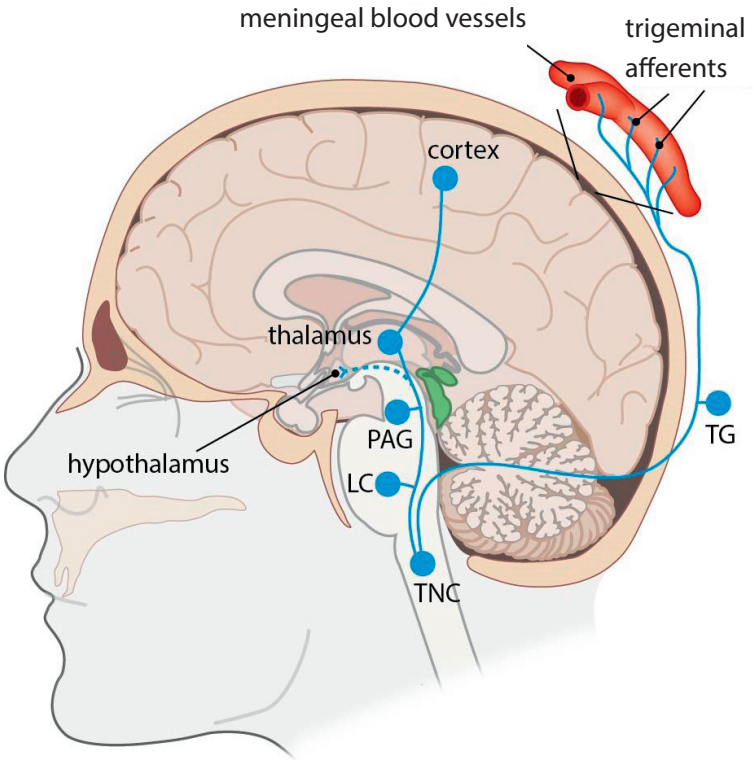


Figure 1. Migraine pathophysiology

Migraine headache is caused by activation of the trigeminovascular system, resulting in activation of the trigeminal afferents, trigeminal ganglion (TG) and trigeminal nucleus caudalis (TNC). Subsequently, sensory input is transmitted to the thalamus. This ascending nociceptive system is influenced by the descending pain modulation network, including the hypothalamus, periaqueductal grey (PAG) and locus coeruleus (LC).

LC = locus coeruleus; PAG = periaqueductal grey; TG = Trigeminal Ganglion; TNC = Trigeminal Nucleus Caudalis.

Image from Nervus Nascholing June 2017

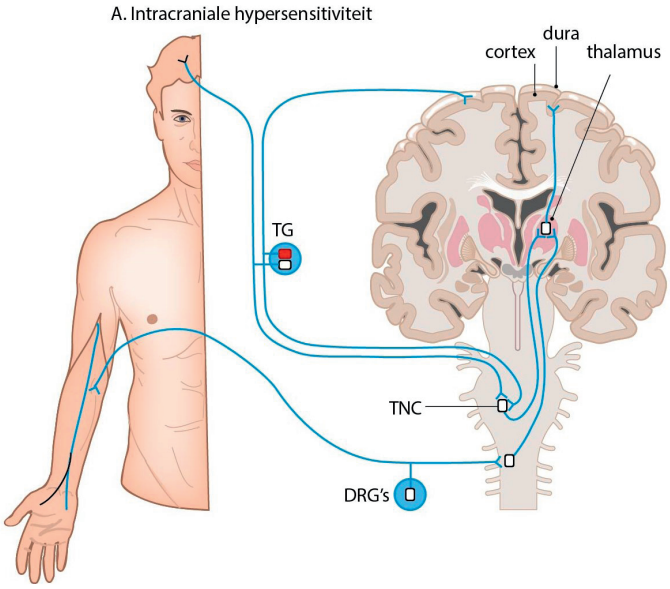
Chronification of migraine may be considered as a threshold problem, in which patients have an increased susceptibility for migraine attacks.[10] This increased susceptibility might be a consequence of specific factors, such as medication overuse or depression,[10] stable intrinsic factors such as genetics susceptibility,[17] and fluctuating intrinsic (eg. hormonal changes) and extrinsic factors (eg sleep deprivation), leading to enhanced pain facilitation (pro-nociception) or lack of pain inhibition (anti-nociception). [1,10,15,18–20]

Central sensitisation: enhanced pain facilitation

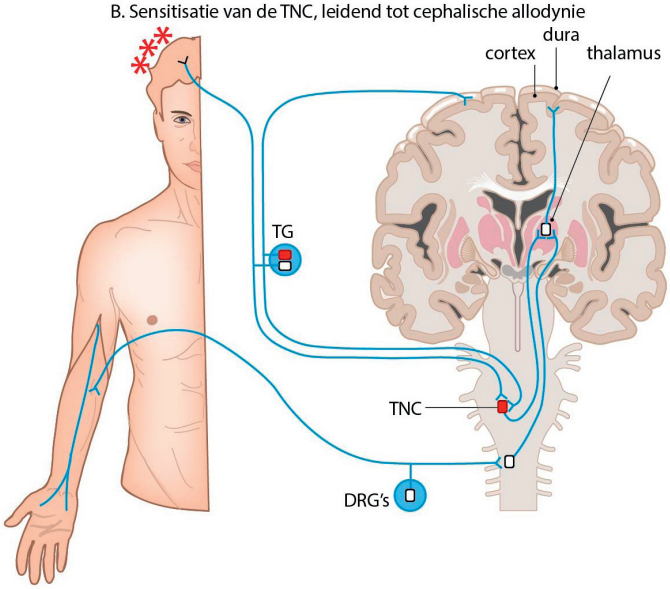
Enhanced pain facilitation, also known as central sensitization, is a state of ongoing excitability and hyper-responsiveness of central regions in the brain, even in the absence of the initial stimulation from peripheral neurons. In migraine, the initial peripheral stimulation is the activation of the trigeminal vascular system (elaborated on previously, see also figure 1), causing intracranial hypersensitivity. This is experienced by patients as pulsating pain in the head, aggravating by activity (Figure 2A).[1,14,15]

Activation of the trigeminovascular system results into stimulation trigeminal nucleus caudalis (TNC) and subsequently the thalamus (Figure 1). Recurrent activation induces sensitisation of the TNC, in which CGRP might play an important role.[1,14] Due to convergence of sensory input from both the meninges and the periorbital skin, sensitisation of the TNC results into referred ipsilateral cephalic cutaneous allodynia, i.e. the perception of pain due to a normally non-painful stimulus (Figure 2B).[15,20] Subsequently, thalamic neurons become sensitised by stimulation from the TNC, resulting into extended cephalic and extracephalic cutaneous allodynia (Figure 2C).[15,20]

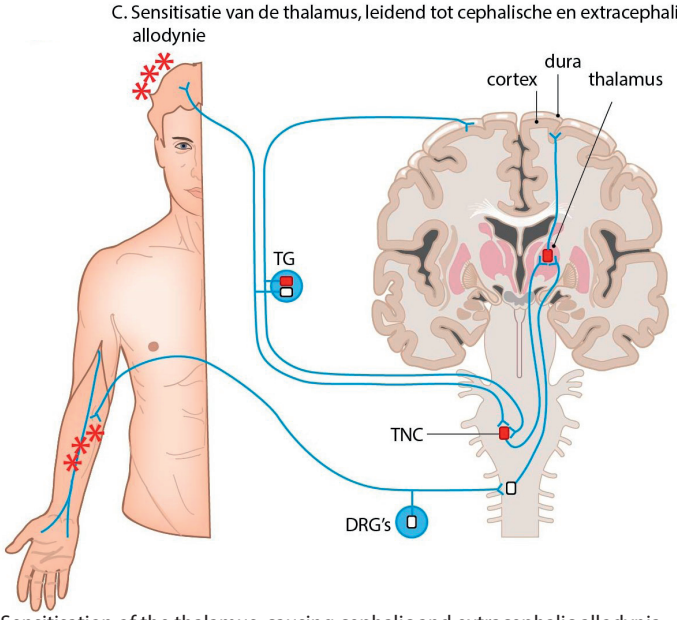
Figure 2. Central sensitisation and cutaneous allodynia



A: Sensitisation of trigeminal afferents, causing intracranial hypersensitivity
Activation and sensitisation of trigeminal afferents causes intracranial hypersensitivity



B: Sensitisation of the TNC, causing cephalic allodynia
Recurrent stimulation by trigeminal afferents induces sensitisation of the TNC, causing cutaneous allodynia in the referred sensory area (ipsilateral, cephalic allodynia)



C: Sensitisation of the thalamus, causing cephalic and extracephalic allodynia

Recurrent stimulation by the trigeminal afferents, TNC of pain modulating pathways, induces sensitisation of the thalamus. Due to convergence of all sensory input of the skin, this causes extended cutaneous allodynia (extended cephalic and extracephalic allodynia)

DRG = dorsal root ganglia; TG = Trigeminal Ganglion; TNC = Trigeminal Nucleus Caudalis.
Image from Nervus Nascholing June 2017

Hence, cutaneous allodynia is a clinical marker of these central sensitisation processes. Cutaneous allodynia can be assessed in detail by elaborate sensory testing,[15,21] but also by means of clinical information provided by patients with questions regarding hypersensitivity of head and extremities.[22–24] Cutaneous allodynia symptoms appear to be more often present, and more severe in migraine patients with a high attack frequency as compared to a low attack frequency.[23,25] Moreover cutaneous allodynia is an independent risk factor for migraine chronification.[24] These findings signify the importance of central sensitisation in the process of migraine chronification.

Descending pain modulating pathways: lack of pain inhibition

The ascending nociceptive system described above (i.e. activation of the peripheral trigeminal afferents, signalling to the brainstem, thalamus and sensory cortex) is modulated by descending pain modulating pathways. This descending system can either facilitate or inhibit nociceptive transmission. Important structures of this system include the hypothalamus, the periaqueductal grey

and the locus coeruleus (Figure 1).[1] The involvement of the descending pain modulating pathway specifically in migraine chronification has been suggested by functional-MRI studies. Differences in functional connectivity within this network have been found between allodynic and non-allodynic patients. In this study, allodynia patients had a higher attack frequency compared to non-allodynia patients, so the comparison might be extended to chronic migraine versus episodic migraine.[26] Moreover, a study in chronic and episodic migraine patients suggests that the posterior part of the hypothalamus might be involved in experiencing migraine pain in general, and the anterior part in migraine attack generation, and consequently chronicity.[27] Therefore, migraine chronification could be further enhanced by alterations in the descending pain modulating pathways, resulting in a lack of pain inhibition.

Risk factors for chronic migraine

Over the years, many factors for migraine chronification have been studied, resulting in several factors that consistently increase the risk for chronic migraine. Besides a high baseline headache frequency (which assumedly indicates that the transformation progress has already been initiated), overuse of acute headache medication, depression, and allodynia are important independent risk factors.[10,24,28–30] Genetic factors have also been suggestive to increase susceptibility for migraine chronification.[31]

Medication overuse

Overuse, or high-frequent use, of acute pain medication is a major risk factor for chronic migraine.[10,29,30] Medication overuse is defined as use of analgesics on at least 15 days per month, or use of either triptans or combinations of acute pain medication on at least 10 days per month (box 2).[3] The relation between medication overuse and chronic migraine gives rise to questions on the direction of the association: does medication overuse really lead to more migraine, or do patients simply use a lot of medication because of the increasing frequency of headache? A number of studies suggest the first option, that frequent medication overuse in itself causes migraine chronification. Firstly, the relationship has been suggested by the temporal relationship in the longitudinal studies identifying medication overuse as a risk factor, adjusting

for potential confounders. Secondly, frequent medication use seems to enhance the process of central sensitisation, both in human and animal studies. Patients with medication overuse were hypersensitive for mechanical pain compared to healthy controls, which reverted after withdrawal. In animal studies, recurrent administration of triptans resulted in cutaneous allodynia.[32,33]

Box 2. Medication overuse criteria. Synopsis of criteria on medication overuse according to the International Classification of Headache Disorders (ICHD-3β criteria)3 .

Medication overuse

Regular overuse for >3 months of one or more drugs that can be taken for acute treatment of headache. Regular overuse is use of:

1. triptans, ergots, opioids, combination-analgesics on ≥ 10 days per month
2. simple-analgesics (such as paracetamol, NSAID), on ≥ 15 days per month
3. combinations of multiple drug classes on ≥ 10 days per month

Psychiatric and psychological factors

Depression, a psychiatric disorder characterized by symptoms of anhedonia, low or sad mood, difficulties with eating, sleeping and concentrations, is highly prevalent disorder.[34] As is the case for others neurological disorders, such as dementia,[35] Parkinson disease[36] and multiple sclerosis,[37] and chronic pain conditions,[38] depression is even more prevalent in migraine patients, than would be expected based on prevalence in the general population.[39] This might lead to the reasoning that depression is caused by the somatic disorders, sometimes referred to in terms like 'chronic-pain induced depression'. However, migraine and depression don't have a purely unidirectional, causal relationship, but seem to have a bidirectional relationship: patients with migraine have higher risk on first-onset depression (OR = 5.8), and patients with depression have a higher risk on first onset migraine (OR = 3.4).[39]

This appearance of a bidirectional relationship leads to the hypothesis that migraine and depression have shared risk factors with a partial common pathway, which might be genetic factors.[40,41] A recent study measuring

correlation of genome-wide common variant risk for common psychiatric and neurological disorders, strikingly showed a shared heritability between depression and migraine, but no correlation between depression and other neurological disorders (amongst others Alzheimers disease, multiple sclerosis and epilepsy).[42] Furthermore, depression is a strong independent risk factor for chronic migraine and medication overuse, and a predictor for a poorer prognosis in therapy of headache with medication overuse.[28,29,43] The relationship between migraine and anxiety has also been established,[44,45] but is less well studied, especially in the context of migraine progression.

Furthermore, psychological factors have been studied in light of medication overuse and chronic headache. In the light of operant conditioning, medication intake would be both a negative as a positive reinforcement by the avoidance of pain and the psychotropic action of pain medication itself. This theory is supported by changes in reward-related systems in imaging studies at patients with medication overuse.[33,46,47] Taking into account pain coping methods, patient with (chronic) headache or high burden of disease seem to use unhealthy pain copings mechanism, score low on pain acceptance, high on catastrophizing, and experience a low rate of control on their diseases.[46,48–50] One could imagine that these psychologic factors aggravate or at least maintain migraine chronification processes, but this has not been formally studied.

Genetic factors

Migraine is a complex disease, which has a strong, but not exclusive genetic component. Multiple studies showed an increased familial risk of migraine,[51–53] but the inheritance pattern for the common types of migraine is not one of a monogenetic disease. As is the case in multifactorial diseases, genetic factors are increasing the susceptibility of the disease, but the effect size of one genetic factor by itself is too small and insufficient too cause the disease. As such, association studies did not result in a reproducible genetic association between a gene and migraine.[51] A relatively new technique, Genome Wide Association Studies (GWAS), can be used to identify genetic variants, underlying complex multifactorial diseases. These studies investigated in a non-hypothesis driven manner the association between migraine and an extremely large number of single nucleotide polymorphisms (SNPs), so far identifying 38 SNPs associated with migraine.[54] However, as a large number of patients and healthy controls is needed for GWAS (>350.000 participants), this method is hardly feasible yet

to study genetic variants underlying chronic migraine. In a limited number of chronic migraine patients, several pre-defined SNPs were not significantly associated with chronic migraine.[17] A recent study did find an association between positive family history of migraine and a higher attack frequency, but only in males, and of a small effect size.[31]

Treatment of chronic migraine

Withdrawal therapy for chronic migraine an medication overuse

The majority of chronic migraine patients (65-80%)[55,56] has medication overuse, which is the major risk factor for chronic migraine, and an important factor in maintaining and aggravating chronification.[3,10,30] As such, withdrawal of the acute headache medication has traditionally been the first step in the treatment of chronic migraine with medication overuse.

Withdrawal therapy is a low cost treatment to reduce headache frequency, improve quality of live, halt medication overuse-induced adverse events, and prevent systemic toxicity.[10,57–59] After withdrawal therapy most patients experience a reduction in headache frequency, and approximately 50% of patients reverts from chronic to episodic migraine.[33,57,58,60] Furthermore, only half of the patients are in need of preventatives after withdrawal therapy, and withdrawal therapy might also improve responsiveness to preventatives in the other half.[60] Besides these objective effects, it might help to reduce the feelings of dependency on the medication and lack of control patients experience whilst overusing medication.[46]

Many withdrawal strategies are being performed internationally. A recent randomized controlled open label trial shows that complete detoxification (no analgesics or acute migraine medication at all) during 2 months is more effective compared to a reduction of medication intake (intake of analgesics or acute migraine medication with a maximum of 2 days a week).[59] Outpatient withdrawal therapy by a simple advice to stop the medication is as effective as inpatient withdrawal therapy in uncomplicated medication overuse patients (amongst other things no overuse of opioids and barbiturates)[61] and also effective in medication overuse patients with some comorbidity (for instance mild depression) or more complex overuse (for instance daily intake of medication, and previous withdrawal attempt).[62] Outpatient withdrawal did

have a slightly higher drop-out percentage in some studies.[63] This might be prevented by additional outpatient support during the withdrawal period, as some studies show effectiveness of education or multidisciplinary involvement during withdrawal therapy.[64–67] Withdrawal strategies can also be applied in first care by a general practitioner, as a brief intervention comprising of education and personal feedback seems effective.[68]

Unfortunately, acute withdrawal is frequently complicated by acute withdrawal symptoms, as patients suffer temporarily aggravation of headache, before experiencing the beneficial effect of withdrawal.[69] Supportive medication during this period to endure withdrawal has been studied, such as oral prednisone, amitriptyline and ibudilast, but didn't have any effect on the endpoints.[70–72] Support by non-pharmalogical interventions such as behavioral interventions has not been studied, but could be helpful as it does have effect after withdrawal therapy.[73] Nevertheless, most patients manage to endure withdrawal in an outpatient setting, and in observational studies, success rates of 73-85% are observed.[57,59] However, due to the disruption of patient's socio-economic functioning due to these withdrawal symptoms and untreated headaches, many physicians are reluctant to recommend withdrawal,[74] despite the potential advantages.[58,74,75]

Preventatives for chronic migraine

In the past decade, botulinum toxin A (BTA)[55,74,76–82] and topiramate[56,83] have emerged as therapy for chronic migraine, further stirring up the debate on the necessity of withdrawal therapy as initial step in the treatment of chronic migraine[74,75] and leading to a tendency to initiate preventatives before patients are withdrawn from medication. Although these preventatives did show a significant difference in reduction in headache or migraine days in patients with chronic migraine with and without medication overuse compared to placebo, the efficacy remains questionable, as the therapeutic gain was only modest.[10] A small RCT (n=59) in chronic migraine (almost 80% with medication overuse), showed a therapeutic gain of topiramate vs placebo of 3.7 migraine days per month (baseline 16 migraine days per month), with a remarkable absence of a placebo effect (increase of 0.2 migraine days per month in the placebo group).[56] A second RCT resulted in an additional reduction of 1.7 days per month compared to placebo.[83] The follow-op rate in this RCT was only 55% due to discontinuation because of lack of efficacy and adverse events, [83] corresponding to a high adverse event rate in the first trial (75% in the topiramate group).[56]

RCTs studying BTA show similar small effects sizes: In the registration the trials, the therapeutic gain of BTA versus placebo was an additional reduction of 1.8 headache days per month. As the baseline number of headache days was 19.9 the percentage change was only 9%.[81] Another important issue in the BTA studies is potential bias by unblinding of participants. As study medication was injected at 31 sites including the forehead, removal of wrinkling in the BTA group would likely cause unblinding versus placebo.[84,85] Reports on blinding of participants were not provided in these studies, but in trials using similar designs, 85% of BTA-treated participants correctly guessed their treatment.[85,86] Phenomena as placebo and nocebo effect might have increased the difference between BTA and placebo.[85,87,88] With these remarks on RCTs at preventatives in chronic migraine and medication overuse, and the beneficial effect of withdrawal therapy in mind, both the Dutch national guidelines[89] and international literature[10,58] do recommend withdrawal therapy in case of medication overuse.
The small effect sizes of the preventatives studied in chronic migraine patients also stresses the need of effective therapy for these patients, especially the subpopulation who still suffer chronic migraine after withdrawal therapy.

Outline of the thesis

In this thesis, the clinical aspects and management of chronic migraine are investigated in order to enhance treatment of chronic migraine, and ultimately prevent migraine chronification. As described in this introduction, migraine chronification is a multifactorial phenomenon, with numerous related factors. Due to the complexity of the process, and limitations of scientific work in proving causality, it is not always clear which factor occurs first and causes the other. Therefore, it is important to analyse and interpret these factors concurrently, preferably using longitudinal study designs.
This thesis pays attention to risk factors for chronic migraine; depression, anxiety, medication overuse (**chapters 2 and 3**) and allodynia (**chapters 2, 3 and 6**), and treatment of chronic migraine by means of withdrawal therapy, botulinum toxin A and care by a specialized headache nurse (**chapters 3, 4 and 5**), in order to reverse chronic migraine to episodic migraine. Finally, it aims to study predictors of response and enhance insight in pathophysiology

of migraine chronification and reversibility by studying cutaneous allodynia characteristics related to response to therapy (**chapter 6**).

In **chapter 2** we elaborate on risk factors for migraine chronification, describing symptom patterns of affective disorders in participants with migraine, current or past affective disorders and healthy controls. Moreover the possible association between these symptom patterns, allodynia and migraine attack frequency is studied. **Chapter 3** describes a withdrawal study, relating to both medication overuse as a risk factor for headache chronification, and its treatment. In a controlled manner, the effect of the support by a headache nurse during withdrawal therapy is studied. **Chapters 4 and 5** are randomised controlled trials including participants with chronic migraine patients with medication overuse, both using unique designs to ensure blinding of patients. **Chapter 4** studies the effect of botulinum toxin A versus placebo concomitant to withdrawal therapy, **chapter 5** describes the effect of a behavioural therapy by a headache nurse concomitant to withdrawal therapy.
Chapter 6 studies the predictive value of cutaneous allodynia for response to withdrawal therapy. Furthermore it provides some insight into the pathophysiology of migraine chronification and reversibility, by differentiating different subtypes of cutaneous allodynia.
Finally, **chapter 7** provides a summary, general discussion and future perspectives on the different aspects and management of chronic migraine.

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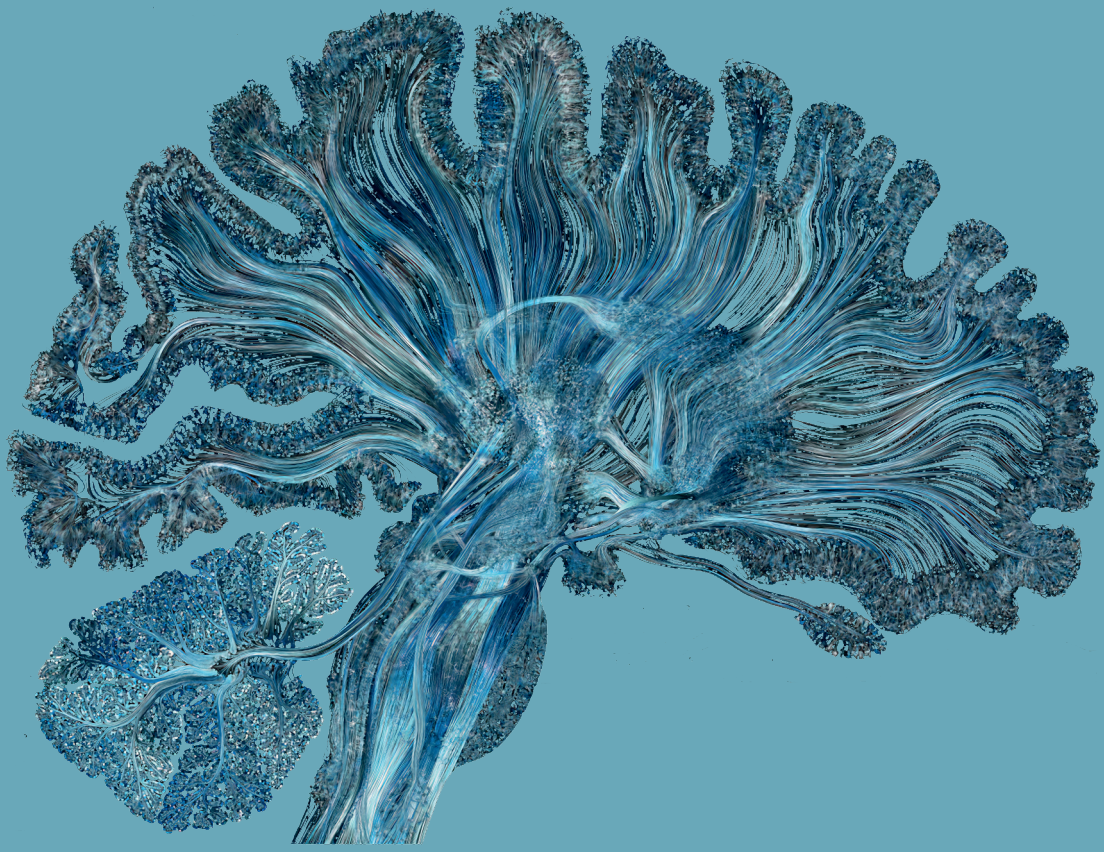

Chapter 2

Symptom dimensions of affective disorders in migraine patients

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Journal of Psychosomatic Research 2015; 79: 458-463

Abstract

Objective A strong association has been established between migraine and depression. However, this is the first study to differentiate in a large sample of migraine patients for symptom dimensions of the affective disorder spectrum.

Methods Migraine patients (n = 3174) from the LUMINA (Leiden University Medical Centre Migraine Neuro-analysis Program) study and patients with current psychopathology (n = 1129), past psychopathology (n = 477), and healthy controls (n = 561) from the NESDA (Netherlands Study of Depression and Anxiety) study, were compared for three symptom dimensions of depression and anxiety. The dimensions —lack of positive affect (depression specific); negative affect (nonspecific); and somatic arousal (anxiety specific)— were assessed by a shortened adaptation of the Mood and Anxiety Symptom Questionnaire (MASQ-D30). Within the migraine group, the association with migraine specific determinants was established. Multivariate regression analyses were conducted.

Results Migraine patients differed significantly ($p<0.001$) from healthy controls for all three dimensions: Cohen's *d* effect sizes were 0.37 for lack of positive affect, 0.68 for negative affect, and 0.75 for somatic arousal. For the lack of positive affect and negative affect dimensions, migraine patients were predominantly similar to the past psychopathology group. For the somatic arousal dimension, migraine patients scores were more comparable with the current psychopathology group. Migraine specific determinants for high scores on all dimensions were high frequency of attacks and cutaneous allodynia during attacks.

Conclusion This study shows that affective symptoms in migraine patients are especially associated with the somatic arousal component.

Introduction

Migraine and depression are both rated among the top 20 of most disabling disorders by the World Health Organisation.[1] Previous studies showed that persons with migraine have a fivefold higher risk of first-onset major depression than persons without migraine. In addition, persons with a lifetime depressive disorder have a threefold higher risk of first-onset migraine than persons without a depression diagnosis.[2;3] This bidirectional association suggests a shared aetiology, which is supported by several studies indicating shared genetic factors in migraine and depression.[4;5] Besides depression, there is an association between anxiety disorders and migraine as well.[6] The economic impact of migraine is significantly compounded in patients with comorbid psychiatric conditions.[7] Understanding the mechanisms underlying the comorbidity is important in order to gain more insight into the mechanism of both migraine and depression/anxiety and to develop specific preventive treatments.

Previous studies in migraine defined depression using either categorical DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) diagnoses or self-reported questionnaires. However, although DSM-IV categories are of great use in clinical practice, they have arbitrary boundaries, and show much overlap and comorbidity. Moreover, high heterogeneity of symptoms and severity within one diagnostic category is possible.[8] Depression and anxiety severity scales based on self-reported questionnaires also have limitations: two similar scores may indicate different clinical subtypes due to the heterogeneity of the covered range of symptoms as multidimensionality of symptomatology is not taken into account. Consequently, measuring affective disorders with these tools may provide suboptimal phenotyping for clinical and biological (e.g. genetic) research. Thus, in a research setting, it may be more appropriate to study dimensions of depressive and anxiety symptoms in migraine patients as these seem to reflect more homogeneous disease entities.

Several attempts have been made to develop a dimensional model for depression. Within a dimensional approach, a patient is described in terms of scores on a range of coexisting different symptom domains, and not in terms of presence or absence of psychopathology.[9] A well-known model is the tripartite model that accounts for the overlap between depression and anxiety.[10] In this model the broad symptom dimension of negative affect covers symptoms of general psychological distress (e.g. lack of concentration or pessimism). High

negative affect has often been indicated as a central clinical feature of both anxiety and depression, accounting for the high rates of comorbidity. The lack of positive affect covers anhedonic symptoms, which are mainly specific for depression.[11-14] The somatic arousal dimension comprises symptoms of hyperarousal which are anxiety specific.

The aim of the present study is to investigate whether migraine patients are characterized by different symptom patterns of depressive and anxiety symptomatology compared with healthy controls, and persons with a current or past depression and/or anxiety disorder. Furthermore, we investigate which migraine specific characteristics are associated with the affective symptom dimensions of the tripartite model.

Methods

Study design and population

Four groups were differentiated for comparison: i) migraine patients, ii) healthy controls without psychopathology and without migraine, iii) persons with 'current psychopathology', a 6-month diagnosis of major depressive disorder, dysthymia or anxiety disorder and without migraine, and iv) persons with 'past psychopathology', a lifetime (but no current) diagnosis of major depressive disorder, dysthymia or anxiety disorder and without migraine.

Migraine patients were collected as a part of the Leiden University Medical Centre Migraine Neuro-analysis Programme (LUMINA) project, a well defined web-based migraine population, the details of which are reported elsewhere.[15] The LUMINA project is an ongoing cohort study, designed to investigate migraine, its comorbidities, and its long-term course. Participants were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders (ICHD-III beta) criteria.[16] The LUMINA study population recruitment is still ongoing, but we included participants recruited between 2008 and 2011. Participants were recruited via nationwide public announcement, advertising in lay press and via the research website, inviting migraine patients to participate in migraine research. In addition, patients attending our dedicated headache clinic were also invited to participate in this survey. This latter group, however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out

a screening questionnaire that has been validated priorly.[17] Firstly, if patients fulfilled the screening criteria, they received a web-based extended migraine questionnaire, based on the ICHD-III beta criteria.[15;16] This questionnaire was previously validated by a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire.[15] The specificity of the questionnaire was 0.95. Participants without the needed internet skills could fill out the questionnaires on paper. Secondly, all applicable migraine patients were selected for a web-based questionnaire on symptoms of depression. Patients were enrolled in this study after completion of the depression questionnaire. The response rate to the depression questionnaire was 80%.

Healthy controls and patients with psychopathology were derived from the Netherlands Study of Depression and Anxiety (NESDA), which is an ongoing cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders. Participants were adults aged 18-65 recruited from community (19%), general practice (54%), and secondary mental health (27%) facilities. A total of 2981 participants, including persons with current or past depressive and/or anxiety disorders and healthy controls, were assessed at baseline between 2004 and 2007. Exclusion criteria for the NESDA study were inability to speak Dutch and a known clinical diagnosis of other psychiatric conditions, such as bipolar disorder, obsessive-compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. A detailed description of the NESDA study design can be found elsewhere.[18] In summary, the baseline assessment was comprised of a face-to-face interview, including a standardized diagnostic psychiatric interview, a medical assessment, computer tasks, written questionnaires, and biological measurement. For the current study, migraine patients, identified through a screening migraine questionnaire largely in accordance to the ICHD-III beta criteria for migraine (described in detail elsewhere)[19], were excluded from the NESDA population.

The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. The NESDA research protocol was approved by the Ethical Committee of participating universities. All respondents provided written informed consent.

Measurements

In the NESDA study, the presence of psychiatric disorders was determined by using the Composite International Diagnostic Interview (CIDI, version 2.1).

The CIDI is a standardized psychiatric diagnostic interview that follows the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria to establish diagnoses. The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders[20] and was administered by specially trained research staff. Psychopathology (major depressive disorder, dysthymia, anxiety disorder) status was categorized as follows: current diagnosis (i.e., past 6 months), past diagnosis (i.e., lifetime diagnosis but not in the past 6 months), controls (no lifetime diagnosis). In both the LUMINA and NESDA studies, a 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30) was used to measure the tripartite dimensions of depression. On the MASQ-D30, participants were asked to rate to what extent in the past week they had experienced 'feelings, sensations, problems and experiences that people sometimes have' on a 5-point scale, with 1 being 'not at all' and 5 being 'extremely'. The three 10-item subscales are 'general distress' (lack of positive affect), 'anhedonic depression' (negative affect) and 'anxious arousal' (somatic arousal). The MASQ-D30 scales showed adequate psychometric characteristics and showed good reliability and validity within the NESDA study.[21]

In the LUMINA population, we predefined migraine specific characteristics to be examined: migraine subtype (migraine with or without aura), frequency (migraine days per year), and cutaneous allodynia. Cutaneous allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. A significant part of migraine patients experience an increased sensitivity of the skin for common daily activities during attacks, such as combing of hair, taking a shower, touching the periorbital skin, shaving, or wearing earrings during migraine attacks. Cutaneous allodynia was measured using a validated questionnaire.[22] These migraine specific characteristics are shown to be associated with depression.[23;24]

Data analysis and statistics

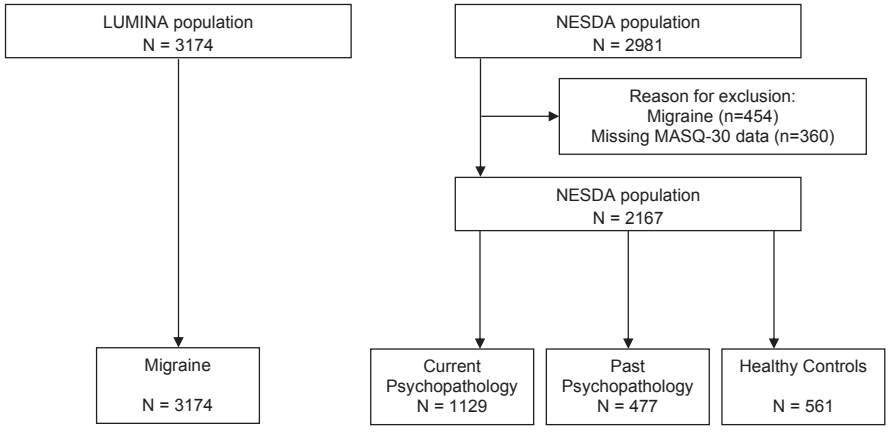
Baseline characteristics were reported as mean ± standard deviations (SD) or percentages. Analysis of covariance (ANCOVA) models were used to test the association between the four different groups and MASQ-D30 symptom profiles, adjusting for gender and age. Post-hoc analyses were run in case of significant findings, performing ANCOVA analysis to test for differences between the migraine group and the three remaining groups. Results were presented as p-values with Cohen's d (the difference between the means, divided by the pooled standard deviation) as a measure of effect size. Secondary

analyses were performed in the migraine population, using multivariate linear regression, testing for the association between general and migraine specific determinants and the three dimensions of affective disorders. Results were presented as p-values and B-values with 95% confidence intervals. For the primary analyses, we measured three outcomes (the three subscales of the MASQ-D30 questionnaire). Therefore, using Bonferoni correction for multiple testing, p-values <0.017 (0.05/3) were considered as statistically significant. Secondary, hypothesis generating analyses, were performed without correction for multiple testing. All analyses were performed using SPSS 20.0 (SPSS Inc., IBM, USA).

Results

Of 2981 NESDA participants, 454 fulfilled the criteria for migraine, and 360 lacked MASQ-D30 data and were excluded for analysis. As a result, the total amounts of participants were 1129 with current psychopathology, 477 with past psychopathology, and 561 healthy controls. A total of 3174 migraine patients with sufficient data on migraine characteristics and MASQ-D30 data were extracted from the LUMINA database. The total study flow is depicted in figure 1.

Figure 1: Study flow



LUMINA = Leiden University Medical Centre Migraine Neuro-analysis Program; NESDA = Netherlands Study of Depression and Anxiety; MASQ-D30 = Mood and Anxiety Symptoms Questionnaire

Baseline characteristics for the four groups are shown in table 1. Because of differences in gender distribution and age distribution between the four groups ($p < 0.001$), all analyses were corrected for gender and age. As the LUMINA and NESDA cohorts had different assessments of educational level the analyses were not corrected for that socio-demographic characteristic.

Table 1 Descriptive characteristics of the LUMINA and NESDA sample

	LUMINA	NESDA		
	Migraine patients N = 3174	Current psychopathology patients N = 1129	Past psychopathology patients N = 477	Healthy controls N = 561
Gender (% female)	85.6%	64.0%	68.1%	59.7%
Age (years± SD)	43.2 ± 11.7	42.7 ± 12.6	44.6 ± 13.2	41.5 ± 14.9
NESDA population characteristics				
Current MDD (without anxiety disorder)	.	25.4%	0%	0%.
Current anxiety disorder (without MDD)	.	33.1%	0%	0%
Current MDD & anxiety disorder	.	41.5%	0%	0%
Lifetime MDD (without anxiety disorder)	.	17.4%	45.7%	0%
Lifetime anxiety disorder (without MDD)	.	16.7%	18.9%	0%
Lifetime MDD & anxiety disorder	.	65.9%	35.4%	0%
LUMINA population characteristics				
Migraine with aura	38.2%	.	.	.
Migraine without aura	61.8%	.	.	.
Mean age at onset (years ± SD)	19.3 ± 10.7	.	.	.
Migraine attack frequency (migraine days/year)				
1-2	5.1%	.	.	.
3-6	10.1%	.	.	.
7-12	16.7%	.	.	.
13-54	46.1%	.	.	.
54+	22.0%	.	.	.
Cutaneous allodynia	70.0%	.	.	.

MDD = Major depressive disorder

In the first analysis (table 2) the four groups (migraine patients, healthy controls, persons with past psychopathology, and persons with current psychopathology) were compared using a multivariate linear regression analysis with adjustment for age and gender. There was a significant difference ($p<0.001$) between the four subgroups for the three symptoms dimensions (lack of positive affect (depression specific); negative affect (nonspecific); and somatic arousal (anxiety specific)).

Table 2 - Mean MASQ-D30 scores in the 4 study cohorts.

	LUMINA	NESDA			
	Migraine patients	Current psychopathology patients	Past psychopathology patients	Healthy controls	P-value (ANCOVA)
	N = 3174	N = 1129	N = 477	N = 561	
MASQ-PA	30.3 ± 9.0	37.5 ± 9.0	29.6 ± 8.9	26.6 ± 9.0	<0.001
MASQ-NA	18.4 ± 7.2	23.6 ± 7.1	16.2 ± 7.1	13.6 ± 7.1	<0.001
MASQ-SA	16.3 ± 5.4	17.8 ± 5.4	13.3 ± 5.3	12.1 ± 5.4	<0.001

Adjusted for age and gender.
MASQ-PA= positive affect subscale; MASQ-NA = negative affect subscale; MASQ-SA = somatic arousal subscale

Further pairwise comparison with migraine as reference group is depicted in figure 2. Migraine patients were significantly different ($p<0.001$) for all comparisons to the two psychopathology groups and healthy controls, except for the lack of positive affect compared with the past psychopathology group. In figure 2, differences between the groups are displayed as Cohen's d, a measure of effect size, showing that scores on the lack of positive affect (Cohen's d=0.07) and negative affect (Cohen's d=0.30) dimensions for migraine patients are most closely related to the past psychopathology group. For the somatic arousal subscale scores migraine patients are closer related to current psychopathology (Cohen's d=0.25).

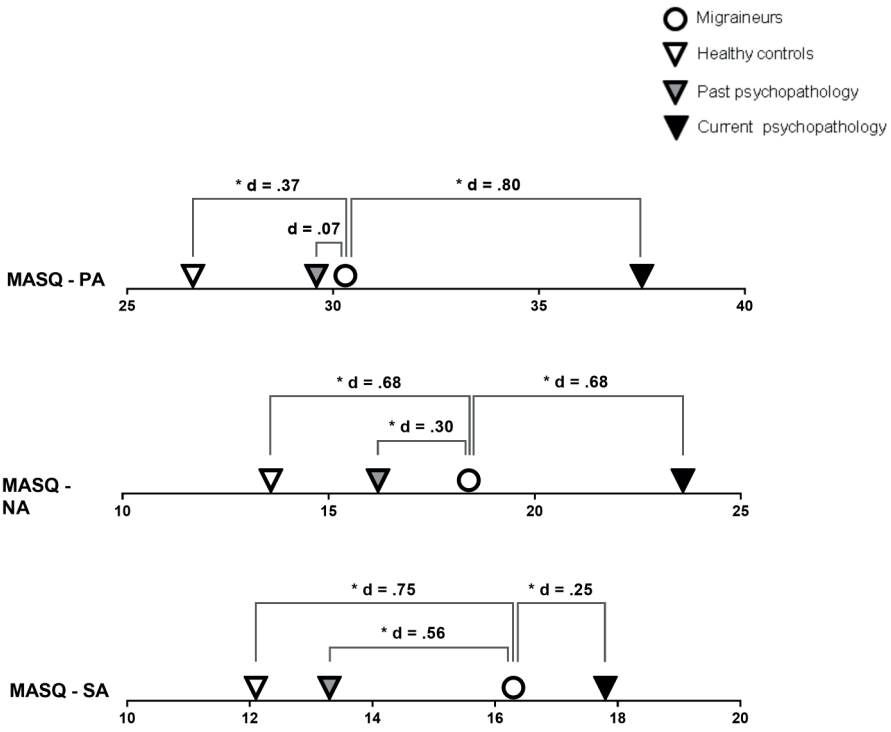


Figure 2: effect sizes of the difference between migraine patients compared with healthy controls, past psychopathology and current psychopathology.

Cohen's d indicates a small effect if it is around 0.2, a moderate effect if it is around 0.5 and a large effect if it is greater than 0.8. * indicates p<0.001
MASQ-PA= positive affect subscale; MASQ-NA = negative affect subscale; MASQ-SA = somatic arousal subscale

Within the group of migraine patients (n=3174), general and migraine specific determinants for the three subscales of affective disorders were analyzed using multivariate linear regression (table 3). Age was significantly associated with lack of positive affect and negative affect. Gender was significantly associated with somatic arousal. Migraine frequency and cutaneous allodynia, but not migraine subtype, were associated with all three symptom dimensions of the affective disorder questionnaire.

Table 3 – Determinants of MASQ-D30 subscales in a migraine population (n=3174).

	MASQ-PA		MASQ-NA		MASQ-SA	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
General determinants						
Age	0.05 (0.02 – 0.08)	<0.001	-0.06 (-0.08 - -0.04)	<0.001	0.01 (-0.002 – 0.03)	0.08
Gender (Female vs Male)	0.24 (-0.70 – 1.18)	0.62	0.35 (-0.37 – 1.07)	0.34	0.83 (0.29 – 1.38)	0.003
Migraine specific determinants						
Migraine subtype (without aura vs with aura)	0.19 (-0.48 – 0.86)	0.58	0.27 (-0.24 – 0.78)	0.30	-0.33 (-0.72 – 0.05)	0.09
Migraine frequency (migraine days/year)	0.04 (-1.69 – 1.78)	0.96	0.41 (-0.92 – 1.73)	0.55	1.03 (0.03 – 2.03)	0.04
3-6 vs 1-2	1.40 (-0.21 – 3.02)	0.09	0.55 (-0.68 – 1.78)	0.38	1.49 (0.56 – 2.42)	0.002
7-12 vs 1-2	1.65 (0.15 – 3.15)	0.03	0.92 (-0.22 – 2.06)	0.11	1.74 (0.88 – 2.60)	<0.001
13-54 vs 1-2	4.18 (2.60 – 5.75)	<0.001	2.64 (1.44 – 3.85)	<0.001	3.30 (2.39 – 4.21)	<0.001
54+ vs 1-2	2.00 (1.29 – 2.72)	<0.001	1.80 (1.26 – 2.35)	<0.001	2.04 (1.63 – 2.45)	<0.001
Cutaneous allodynia (yes vs no)						

MASQ-PA= positive affect subscale; MASQ-NA = negative affect subscale; MASQ-SA = somatic arousal subscale

Discussion

This is the first study differentiating in a large sample of migraine patients for symptom dimensions of depression and anxiety. In comparison with healthy controls and persons with past or current psychopathology, affective disorder symptoms in migraine are specifically associated with higher scores on the dimension somatic arousal which covers symptoms of hyperarousal. Furthermore, the association between MASQ-D30 scores and migraine frequency, which can be considered as an indication of migraine severity, is the strongest on the somatic arousal subscale. Besides migraine frequency, we show that cutaneous allodynia is associated with higher scores on all three symptom dimensions as well.

Our finding that migraine is particularly associated with the somatic arousal dimension, is in accordance with that of several other somatic disorders. Association studies investigating the relationship of depression with chronic diseases like diabetes, obesity, and cardio-vascular disease often show that somatic-affective symptoms of depression rather than cognitive-affective symptoms are related to somatic disease.[25-28] Therefore, it is often hypothesized that the association between a somatic disease and depression is primarily through the somatic-affective dimension of depression, the so-called somatic depression.[29;30]

One might also argue that part of the comorbidity between migraine and affective disorders could be due to overlapping symptomatology. Some of the characteristic features of migraine attacks, such as nausea, loss of energy, anhedonia, and sleep disturbances, could lead to misclassification of depressive disorder in migraine patients. However, the association of migraine and depression is still present when questionnaires focusing on the non-somatic aspects of depression are applied, such as the Hospital Anxiety and Depression Scale).[24] Furthermore, the current study clearly shows that the symptom profile of affective disorders in migraine patients differs from healthy controls for all three dimensions of the MASQ-D30 questionnaire, not only for the somatic arousal dimension. Therefore, our study shows that affective disorders in migraine patients cannot be fully explained by somatic depression or overlapping symptomatology.

However, our study does suggest an even stronger comorbidity between migraine and symptoms of anxiety, than between migraine and symptoms of depression per se. This is particularly interesting, since most studies hitherto focused on the comorbidity between migraine and depression, whilst the comorbidity of migraine and anxiety is a largely unexplored area. Larger and prospective studies on the comorbidity of migraine and anxiety disorders are necessary to establish the exact magnitude of this comorbidity. Our study shows that anxiety arousal might be the corresponding component, but the underlying mechanism should be further investigated.

Because the co-occurrence between migraine and affective disorders is not fully explained by mechanisms such as somatic depression or overlapping symptomatology we argue that there is a true comorbidity between migraine and depression. Additionally, previous studies showed a bidirectional relationship, in which the risk for depression is five times increased in migraine patients, and vice versa, the risk for migraine is three times increased in patients with depressio.[2;3] This bidirectional association suggests shared underlying mechanisms, presumably shared genetic factors.[4;5] However, further genetic research did not yet result in clues which exact genes are involved in this association. The current study stresses the importance of a dimensional approach for depression in migraine in a research setting, as the current concept of depression probably is too heterogeneous for detecting genetic variants involved in this association. Using subgroups of migraine patients, based on the tripartite model of depression and anxiety, may be warranted in further genetic research on the comorbidity of migraine and affective disorders.

Comorbid depression in migraine is an important predictor of substance dependence and is common in chronic migraine patients, in particular in those with overuse of acute headache medication.[31] Thus a triad between migraine chronification, depression and medication overuse has been suggested.[32-34] In this triad, cutaneous allodynia plays a role. Allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. Previously, we showed that depression and high migraine attack frequency (as a marker of chronification) are independently associated with cutaneous allodynia.[23] The present study supports this finding and shows that both cutaneous allodynia and high migraine frequency, are

associated with all three symptom dimensions of affective disorders, covering general distress as well as anxiety and depression specific symptoms.

The strengths of this study are the large sample size, the well-defined migraine status in the LUMINA population, the well-defined psychopathology status in the NESDA population, and the well-defined healthy control population from NESDA. Most importantly, this is the first study focusing on the different symptom dimensions of affective disorders in migraine patients. Possible limitations include the fact that we compare two different cohorts, in which data was collected in different ways and time periods.

In conclusion, we found that migraine patients, without taking their history of psychopathology into account, differ significantly from healthy controls on all three dimensions of affective disorders. The strongest difference is seen on the somatic-affective component which is suggestive of increased anxiety. Using subgroups of migraine patients, based on the tripartite model of affective disorders, may be warranted in further biological research on the comorbidity of migraine, anxiety and depression.

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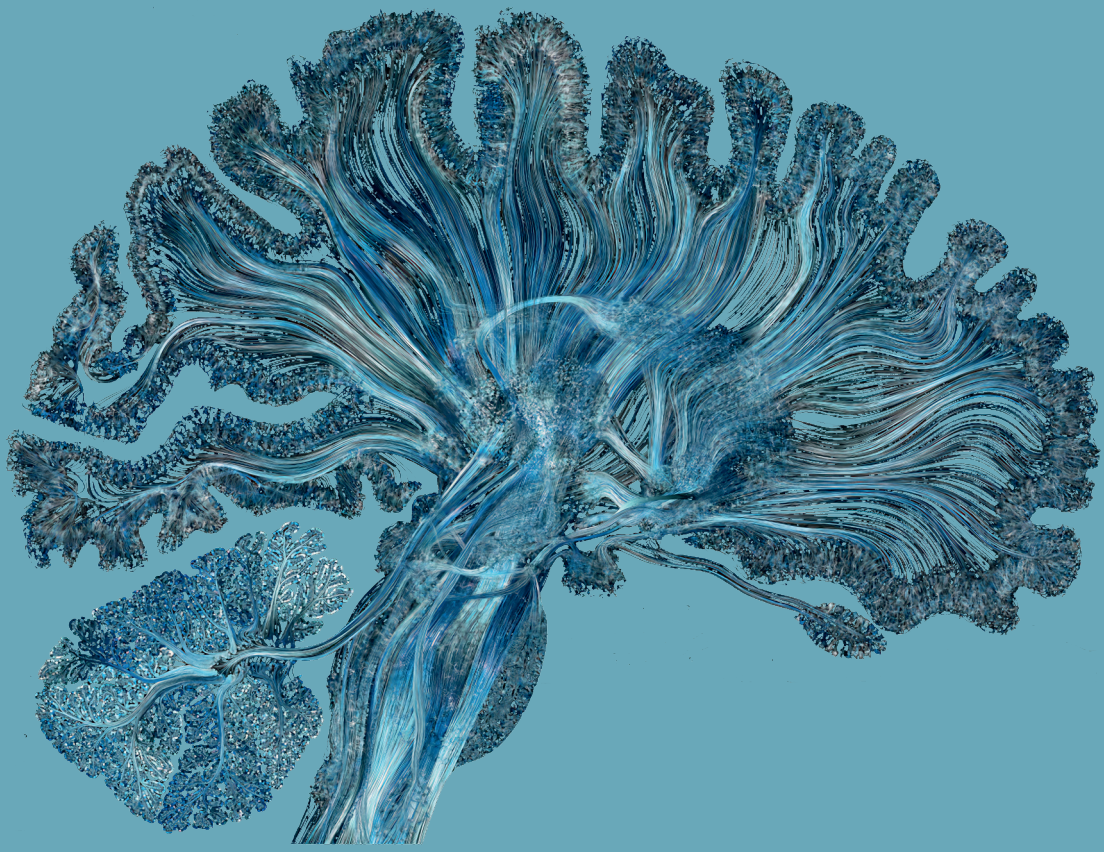

Chapter 3

Detoxification in medication overuse headache: does care by a headache nurse lead to cure?

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Cephalalgia 2016; 36(2): 122-130

Abstract

Aim To determine whether support of a headache nurse in the treatment of Medication Overuse Headache (MOH) increases successful withdrawal, and to study determinants of response to withdrawal therapy.

Methods A retrospective controlled follow-up study was performed with 416 MOH patients. All patients were treated with outpatient withdrawal therapy, with two treatment arms: with or without the support of a specialized headache nurse. The outcome measures were: i) successful withdrawal, defined as discontinuation of all headache medication according to the study protocol; and ii) the responder rate, defined as the percentage of patients with ≥ 50% reduction in headache days after successful withdrawal and iii) relative reduction in headache days after successful withdrawal.

Results Successful withdrawal percentages were significantly higher in the group supported by the headache nurse than in the group without support (73.1% vs. 60.7%; p=0.008), which was confirmed in multivariate analysis (OR 1.73, 95% CI 1.11-2.71, p=0.016). Support by a headache nurse was not associated with response. The underlying headache primary headache diagnosis, determined after withdrawal, was significantly correlated with response.

Conclusion The support by a headache nurse results in an increased adherence to detoxification.

Introduction

Medication Overuse Headache (MOH) is a highly disabling headache disorder, with a population based prevalence of 0.7 - 1.7% and a preponderance in women.[1–3] The prevalence in headache clinics ranges from 30% in Europe to more than 50% in the USA.[1,2] MOH is defined in the ICHD-III-beta criteria as headache occurring on half or more days per month as a consequence of regular overuse of acute headache medication (on ≥10 or ≥15 days per month, depending on the type of medication) for more than 3 months.[4] Although consensus about the optimal treatment for MOH is not yet reached, withdrawal of the overused medication is strongly suggested as an essential component in the management of MOH, to reduce headache frequency and improve responsiveness to both acute and prophylactic therapy.[1,2,5,6] Several studies have compared different treatment strategies[2,7] and some suggested that a simple withdrawal advice is effective.[8,9] In compliance with those studies, acute withdrawal without any concomitant therapy is advised in the national headache guidelines of the Netherlands, and common practice. However, a well-defined selection of patients prone to benefit from simple withdrawal advice, has not been established. Withdrawal programmes are increasingly multidisciplinary coordinated, with implementation of patient education and motivational or cognitive behavioural therapy, often realized by a headache nurse.[10–14] Despite of this, the effectiveness of a headache nurse in withdrawal therapy has never been studied in a controlled follow up study. Therefore, the objectives of this study are (i) to determine whether support of a headache nurse in the treatment of MOH increases successful withdrawal, and (ii) to investigate intrinsic patient factors associated with response to withdrawal therapy.

Methods

Study design and population

The current study used a retrospective controlled follow-up approach. Participants were recruited during a period of four years (1 April 2006 - 31 March 2010) among all new patients at the specialized outpatient headache clinic of the Leiden University Medical Centre (LUMC), functioning both as a primary and secondary referral centre with referrals from general practitioners

and from colleague neurologists. Inclusion criteria for participants were: (i) age ≥ 18 years; (ii) diagnosis of MOH, defined by the ICHD-II criteria[15], which are similar to the ICHD-III-b criteria on MOH[4] (supervised by an experienced headache neurologist (MDF, GMT)); and (iii) receiving an advice to withdraw all acute headache medication (triptans, analgesics, combination of both, other medication comprising opioids, ergots or combinations of those medications with analgesics or triptans), prophylactic medication and caffeine (-containing liquids) during two or three months. Follow up occurred after withdrawal, to determine the final underlying primary headache diagnosis and start further treatment. At the first visit patients were instructed that because of lack of therapeutic options whilst overusing medication, no follow-up visit was offered if they did not succeed to withdraw. Therefore, patients who were lost to follow-up were considered as 'not successfully withdrawn'. Patients were excluded when the final diagnosis was not migraine, tension-type headache or a combination of both. The treatment protocol for patients included between 1 April 2006 and 31 March 2008 (group A) comprised a withdrawal advice by a resident-in-neurology/neurologist. All physicians involved during the total inclusion period, gave the same instructions and maintained the same conditions of withdrawal, according to the standardised protocol at the LUMC. This encompassed an outpatient detoxification with the advice to instantly stop acute headache medication. The duration of the withdrawal period was two months in case of triptan overuse, three months for other types of medication or combinations of medication, and/or caffeine use of ≥ 5 units/day. If patients were on preventive treatment this was tapered off, since the present medication was not effective, and preventive medication regains effectiveness after withdrawal.[6] New preventive treatment was postponed until successful withdrawal was accomplished. Use of escape medication or caffeine(-containing liquids) was not permitted. During the withdrawal period no facility was provided for additional contacts or support. Due to the employment of specialized headache nurse ever since 1 April 2008, patients included between 1 April 2008 and 31 March 2010 (group B), were advised exactly the same withdrawal protocol, but additionally received support during the withdrawal period by a specialized headache nurse. The headache nurse was trained and experienced in headache care, and received additional training on cognitive behavioural therapy. The support by the headache nurse started immediately during the first visit with a 15-30 minutes consultation consisting of a reprise

of the withdrawal advice and elaboration on questions of the patient. The consequences for daily professional and social life were discussed and a plan of approach was assembled. Furthermore, strategies for pain management (other than medication treatment) were discussed. Subsequently, the headache nurse contacted all patients two weeks after initiation of the withdrawal period. Depending on the need for support of patients, the headache nurse had additional interaction during the withdrawal period, varying from one to six contacts (median three contacts) by telephone.

Measurement

Two trained examiners obtained medical information from the outpatient clinic administration, patient letters and medical files, using the same methods and criteria to select patients and classify data. The outcome measures were: i) successful withdrawal, defined as a completed medication- and caffeine-free period; ii) response, defined as ≥ 50% reduction in headache days after successful withdrawal; and iii) relative reduction in headache days after successful withdrawal, since a reduction <50% may be considered clinically relevant as well.[16] The number of headache days at baseline and at follow up were collected to calculate outcomes measures. In case of missing data on response (n=25 patients), patients reporting 'strong improvement', 'nearly no headache' or 'no headache' at follow-up were considered as a ≥ 50% reduction in headache days(responder), and patients reporting 'aggravation', 'no improvement' or 'some to moderate improvement' at follow-up were considered as a < 50% reduction in headache days (non-responder). This subjective classification and the classification based on absolute change in headache days were highly correlated (n=75, $r = 0.80$, $p<0.001$). To be able to find associations between potential intrinsic determinants and our outcome measures, we collected data on gender, age, pre-existing headache type, final primary headache after successful withdrawal, number of headache days at baseline, number of medication days at baseline, type of overused medication, and caffeine units per day. Pre-existing headache and final primary headache at follow-up were classified according to ICHD-II/ICHD-III-b criteria[4,15] as: i) migraine; ii) tension-type headache; and iii) combination of both migraine and tension-type headache. Because of the typical blurred presentation of primary headache at baseline, which is often the case during a period of medication overuse, the pre-existing headache was in some cases impossible to determine

(n=85). Therefore, final primary headache diagnosis was used in the analysis. In any case, pre-existing and final headache diagnoses were fairly correlated (n=182, r=0.62, p<0.001). Type of acute medication was classified as: i) triptans, ii) analgesics (paracetamol/acetaminophen and/or NSAIDs), iii) combination of triptans and analgesics, and iv) other medication, comprising opioids, ergots or combinations of those medications with analgesics or triptans. No approval of the local ethics committee was necessary as the study was a retrospective follow-up study and all data were analysed anonymously.

Data analysis and statistics

Baseline characteristics were reported as mean ± SD or absolute numbers with percentages. The number of headache days and medication days at baseline were grouped into daily (30.4 days/month) and non-daily (<30.4 days/month), because of the non-parametric distribution of the data. Differences in means between groups were tested with independent samples *t*-tests and one-way ANOVAs. Differences in proportions were tested using χ^2 tests. Patients were stratified into 'successfully withdrawn' and 'not successfully withdrawn', the latter including patient who were lost to follow-up. All patients were included in the analysis of the first outcome (successful withdrawal). Successfully withdrawn patients were included in the analysis of the second and third outcomes (response respectively relative reduction). Univariate logistic regression models were used to test crude associations. Analyses were rerun as a multivariate model, adjusting for the potential confounding effects of all variables that were tested in the univariate model. For all analyses, two-tailed *p*-values < 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA).

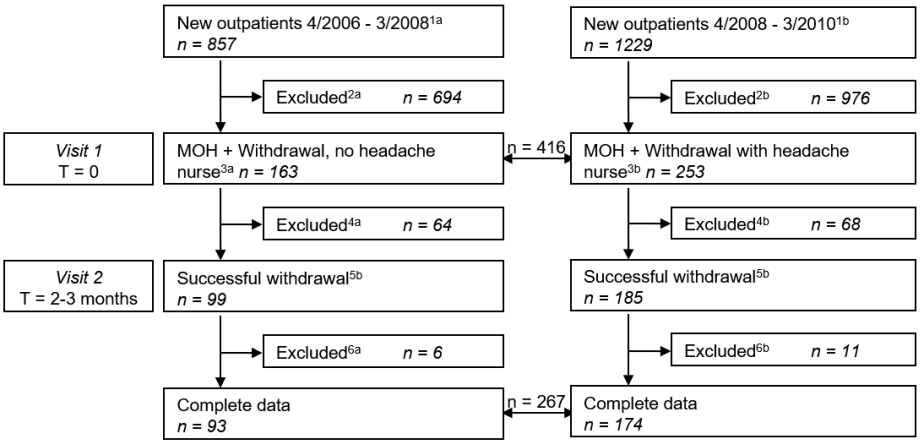
Results

Participants and descriptives

The total study flow is shown in Figure 1. Of 2086 new outpatients, 416 patients were diagnosed with MOH and advised to withdraw medication, 163 without (group A) and 253 with support of a headache nurse (group B). Both groups differed significantly in gender, age, type of medication and daily use of medication (Table 1). Although the absolute number of new headache

patients visiting the outpatient headache clinic raised in the last two years of the inclusion period, the proportion of patients who met inclusion criteria remained the same (19.0% in group A and 20.6% in group B). To detect shifts in population composition due to exclusion of patients, lost to follow-up or missing data, differences between the total included population (n=416) and the population that had successfully withdrawn (n=267) were explored. No major differences in composition occurred.

Figure 1. Study population flowchart



MOH: Medication Overuse Headache; TTH: Tension-Type Headache; LUMC: Leiden University Medical Centre.

[1] N*ew outpatients*: New patients at the LUMC outpatient headache clinic
[2] *Excluded*: No medication overuse ([2a] n=645 [2b] n=893); Age < 18 years ([2a] n=1 [2b] n=3); No withdrawal therapy ([2a] n=21 [2b] n=35); Withdrawal therapy elsewhere ([2a] n=27 [2b] n=45)
[3] *Diagnosis MOH and advice is to withdraw medication*: [3a] without support by a headache nurse; 3b with support by a headache nurse
[4] *Excluded*: Patient is not willing to start withdrawal ([4a] n=5 [4b] n=13); Unsuccessful withdrawal (4a n=15 [4b] n=24); Lost to follow-up ([4a] n=44 [4b] n=31)
[5] *Successful withdrawal*: 2-3 months medication- and caffeine-free period.
[6] *Excluded*: No migraine, TTH or combination ([6a] n=1 [6b] n=2); Missing data on primary headache, number of headache days or caffeine use ([6a] n=5 [6b] n=9)

Table 1. Baseline characteristics of patients with medication overuse headache, included for primary analysis, without (group A) and with (group B) support by a headache nurse (n = 416).

	A. No headache nurse (n=163)	B. Headache nurse (n=253)	*p*
Gender, % female	102 (63%)	196 (78%)	**0.001**[a]
Age at time of diagnosis	47.5 ± 10.7	44.4 ± 14.6	**0.014**[b]
Headache days			
% daily	93 (57%)	151 (60%)	0.60[a]
median (interquartile)	30.4 (17.4-30.4)	30.4 (19.1-30.4)	0.41[c]
Medication			**0.040**[a]
Analgesics only	83 (51%)	126 (50%)	
Triptans only	20 (12%)	13 (5%)	
Analgesics + triptans	51 (31%)	93 (37%)	
Other medication	9 (6%)	21 (8%)	
Caffeine units/day	5.7 ± 4.2	5.3 ± 3.6	0.55[b]
Medication days			
% daily	73 (45%)	95 (38%)	0.14[a]
median (interquartile)	21.7 (15.0-30.4)	20 (14.3-30.4)	0.37[c]

Values are the absolute numbers with corresponding % or means ± SD. Significant p values are depicted in bold. [a] χ^2 test

[b] Two-tailed independent samples t-test c Independent Samples Mann-Whitney U test

Effectiveness of support by a headache nurse in successful withdrawal in MOH

As shown in Table 2, the percentage of patients with successful withdrawal was significantly higher in the group with support of the headache nurse than the group without support (73.1% vs. 60.7%, p = 0.008, Absolute risk reduction = 12.4%, Number Needed to Treat = 8). As a consequence of the instructions at the first visit (not to come for a second visit if withdrawal was not successful) a larger proportion of patients of group A did not visit for a second time, and were lost to follow up (27.0% vs. 12.3%). However, the results were similar when lost to follow-up patients were analysed as a separate group. The support by a headache nurse was significantly associated with the odds for successful withdrawal in multivariate regression (Odds Ratio [OR] 1.73; 95% CI, 1.11 – 2.71; p=0.016)(Table 3), indicating that the support by a headache nurse enhances successful withdrawal, independent of age, the number of headache days, medication days and type of medication overuse at baseline. Daily use of headache medication and a higher ager were associated with lower odds for successful withdrawal (OR 0.50; 95% CI 0.30 – 0.83; p=0.008 resp. OR 0.98; 95% CI 0.96 – 0.99; p=0.017).

Table 2. Successful medication withdrawal, defined as a two- to three-month medication- and caffeine-free period, in patients with medication-overuse headache following withdrawal therapy without (group A) and with (group B) support by a headache nurse (n = 416).

	A. No headache nurse (n=163)	B. Headache nurse (n=253)	p
Medication withdrawal			
Successful	99 (60.7%)	185 (73.1%)	**0.008**[b]
Not successfula	64 (39.3%)	68 (26.9%)	

Values are the absolute numbers with corresponding %.
[a] Including patients who are lost to follow-up and therefore considered not successfully withdrawn 44 (27.0%) resp. 31 (12.3%). [b] χ^2 test

Table 3: Odds Ratios (1. univariate; 2. multivariate, adjusted for all mentioned covariates) for successful withdrawal, defined as a two- to three-month medication- and caffeine-free period (n = 416).

Variable	1. Univariate OR (95% CI)	p	2. Multivariate OR (95% CI) a	p
Gender				
Male	1.00	.	1.00	.
Female	1.09 [0.69 – 1.72]	0.72	0.88 [0.53 – 1.44]	0.60
Age	**0.98 [0.96 – 0.99]**	**0.002**	**0.98 [0.96 – 0.99]**	**0.017**
Headache nurse				
No support	1.00	.	**1.00**	.
Support	1.76 [1.16 – 2.68]	**0.008**	**1.73 [1.11 – 2.71]**	**0.016**
Headache days (baseline)				
Non-daily	**1.00**	.	1.00	.
Daily	**0.97 [0.64 – 1.48]**	0.90	1.36 [0.82 – 2.25]	0.24
Medication				
Analgesics	1.00	.	1.00	.
Triptans	0.97 [0.44 – 2.16]	0.94	1.22 [0.52 – 2.25]	0.65
Analgesics/triptans	0.87 [0.55 – 1.38]	0.55	0.80 [0.50 – 1.30]	0.37
Other	0.55 [0.25 – 1.20]	0.14	0.68 [0.29 – 1.61]	0.38
Caffeine usea	0.99 [0.94 – 1.05]	0.84	1.00 [0.94 – 1.06]	0.93
Medication days (baseline)				
Non-daily	**1.00**	.	**1.00**	.
Daily	**0.54 [0.35 – 0.81]**	**0.003**	**0.50 [0.30 – 0.83]**	**0.008**

[a] n=409, due to missing data. OR: odds ratio; CI: confidence interval

Variables associated with response and relative reduction to withdrawal therapy

The support by a headache nurse was not associated with response (OR: 1.42; 95% CI, 0.78–2.60; p=0.25) (Table 4). The responder rate, defined as the percentage of patients with ≥50% reduction in headache days, was not significantly different in both groups (no support 35.5%, with support 46.0%, p=0.098, Figure 2). The relative reduction in headache frequency, also showed no significant association with support by a headache nurse (B: 1.92; 95% CI, -7.75–11.60; p=0.70) This indicates that there is no effect of the support by the headache nurse on reduction of headache days when successfully withdrawn. The underlying primary headache disorder, that remained after the withdrawal,

was significantly associated with relative reduction and response, with a three times increased odds for response in case of migraine when compared to tension type headache (OR 0.31, 95% CI 0.16-0.63; p<0.001), and a nine times increased odds in case of migraine when compared to migraine with tension type headache (OR 0.11; 95% CI 0.05-0.24; p<0.01)(Table 4). This gives a clear indication that the reduction in headache frequency was highest in the migraine group and lowest in the migraine with tension type headache group (Table 4, also depicted in Figure 2). The relative reduction in headache days, was 34.2% ± 38.9 for the total group and was significantly different between persons with migraine, tension type headache, and combined migraine and tension type headache (resp. 56.1% ± 32.1, 26.0% ± 39.6 and 16.0% ± 31.9) (Figure 3). As shown in Table 4, gender and age were not associated with response, nor was the number of headache days or number of medication days at baseline. Furthermore, neither the type of medication that was overused (simple analgesics, triptans, combination of both, or other medication) nor caffeine use was associated with response. These covariates were not associated with relative reduction as well.

Table 4: Odds Ratios (1. univariate; 2. multivariate, adjusted for all mentioned covariates) for response, defined as a ≥ 50% reduction in headache days, following medication withdrawal (n = 267).

Variable	1. Univariate OR (95% CI)	p	2. Multivariate OR (95% CI)	p
Gender				
Male	1.00	.	1.00	.
Female	1.43 [0.82 – 2.49]	0.21	1.14 [0.59 – 2.18]	0.70
Age	1.00 [0.98 – 1.02]	0.87	1.00 [0.98 – 1.02]	0.78
Headache nurse				
No support	1.00	.	1.00	.
Support	1.55 [0.92 – 2.60]	0.10	1.42 [0.78 – 2.60]	0.25
Diagnosis				
Migraine	**1.00**	**.**	**1.00**	.
TTH	**0.26 [0.14 – 0.46]**	**< 0.001**	**0.31 [0.16 – 0.63]**	**< 0.001**
TTH and migraine	**0.10 [0.05 – 0.22]**	**< 0.001**	**0.11 [0.05 – 0.24]**	**< 0.001**
Headache days (baseline)				
Non-daily	**1.00**	**.**	1.00	.
Daily	**0.47 [0.28 – 0.77]**	**0.003**	0.84 [0.45 – 1.57]	0.58
Medication				
Analgesics	1.00	.	1.00	.
Triptans	1.00 [0.41 – 2.47]	1.00	0.54 [0.18 – 1.61]	0.27
Analgesics / triptans	1.63 [0.95 – 2.78]	0.08	1.24 [0.64 – 2.41]	0.52
Other	0.52 [0.16 – 1.69]	0.28	0.38 [0.11 – 1.33]	0.13
Caffeine use	1.01 [0.94 – 1.08]	0.79	1.02 [0.94 – 1.11]	0.61
Medication days (baseline)				
Non-daily	**1.00**	**.**	1.00	.
Daily	**0.45 [0.27 – 0.77]**	**0.003**	0.63 [0.33 – 1.22]	0.17

TTH: Tension-type headache; OR: odds ratio; CI: confidence interval

Figure 2. The responder rate, defined as the percentage of patients with a ≥ 50% reduction in headache days, following medication withdrawal with and without support by a headache nurse, subdivided by diagnosis (N = 267).

Responder rate group A (no headache nurse) = 35.5%, responder rate group B (headache nurse) = 46.0% (χ^2 test, p = 0.098). TTH: tension-type headache

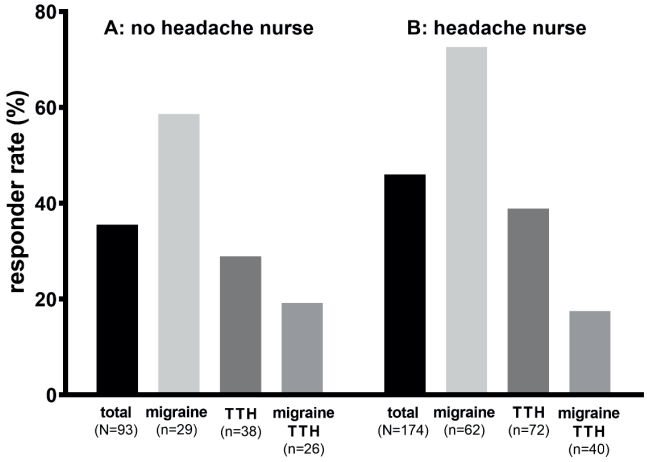
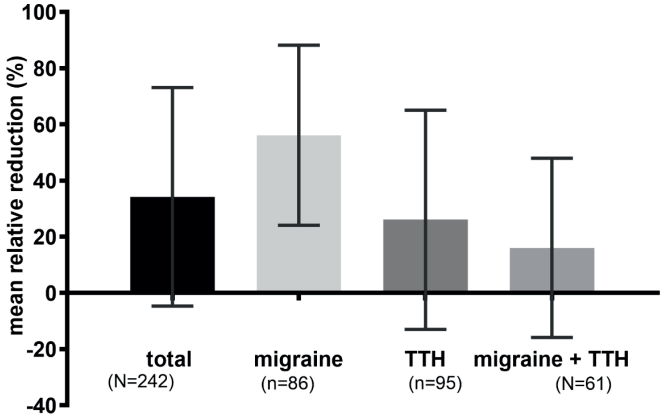


Figure 3. The mean relative reduction in headache days of successfully withdrawn patients and subdivided by diagnosis. (n = 242, due to missing data in 25 patients, one-way ANOVA:

p < 0.001). Error bars display standard deviations. TTH: Tension-Type Headache; ANOVA: analysis of variance.



Discussion

Being the first controlled follow-up study, this study shows that support of a headache nurse during simple withdrawal therapy increases the chance that a patient with Medication Overuse Headache (MOH) successfully withdraws from overused medication. In this manner, the high drop-out percentage seen in outpatient withdrawal therapy can be reduced.[7] As expected, the reduction in headache days during withdrawal therapy is independent of the support of a headache nurse, as this is more likely to be influenced by intrinsic, patient related factors. The current study shows that patients with migraine as the solely underlying headache disorder have a higher chance at response to withdrawal therapy.

The strengths of this study include the controlled design in a large, representative study population of MOH patients. Although randomisation was not achievable, the retrospective design is particularly suited to determine the effect of the headache nurse, since we studied the insulated effect of the nurse and there were no ethical issues or risk of blinding failure. We changed our treatment protocol of patients with MOH during our inclusion period by the employment of a headache nurse in April 2008, but no other changes regarding to treatment protocol or referral strategies were introduced. In a prospective controlled study, the recruitment procedure would lead to a highly motivated population, and it would be extremely difficult to blind patients for receiving or not receiving support by a nurse, since patients must be informed about the nature of a study. One group of patients would thus be instructed not to contact the outpatient clinic at any moment, whilst they know about the availability of support to the other group. This will definitely introduce disappointment and other expectations and will bias the results in favour of the intervention. The results of our retrospective study are not influenced by this kind of bias.
There are also some limitations of our study design. Firstly and most importantly, there was no ability to collect data of patients who did not return for a second visit and were, therefore, stated as lost to follow-up. Since patients were explicitly instructed that they were not allowed to revisit in case of unsuccessful withdrawal, and they were informed that no additional treatment would be supplied, we consider the majority of the lost to follow up patients as unsuccessfully withdrawn. We believe the possibility that loss to follow-up is caused by economic reasons negligible due to the health care system in our country, and

the visit could be changed to a 15-30 minute telephonic appointment in case patients definitely could not miss work. Analysis considering lost to follow-up as unsuccessfully withdrawn shows similar result as analysis with lost to follow-up patients as a separate group. Secondly, for the reason of uncertainty about diagnoses before withdrawal, we diagnosed the primary headache disorder only after successful withdrawal, and used this diagnosis. Still, the pre-existing primary headache diagnosis was fairly correlated with final diagnosis. Thirdly, long-term effects of withdrawal were not investigated in this study.

Considering the high recidivism rate, it would be interesting in future research to study the long term effect of a headache nurse in patients with MOH after withdrawal. However, the long term effect of a headache nurse on medication overuse was beyond the scope of this study as we specifically wanted to investigate the response to the initial withdrawal period. In many countries patients with MOH are usually unwilling to endure acute withdrawal therapy. Patients in these countries refuse to discontinue their medication on the grounds that the withdrawal symptoms will be too serious or they are afraid to lose their jobs if they will be ill for a longer period because of the withdrawal symptoms. There is usually a drug treatment started with prophylactics although it is recognized that it often fails if the patient continues to overuse acute headache medication. Therefore, it was of our main interest to show the high success rate of acute withdrawal with the support of a headache nurse.

In literature, several withdrawal therapies, sometimes with the support by a headache nurse for MOH patients have been described, but no other study investigated the insulated effect of a headache nurse and uniform endpoints are lacking, hampering direct comparison between studies.[11–14,16]

Possible explanations and implications

The headache nurse has an unmistakable effect on succeeding withdrawal therapy. Previous studies suggest that patients with (chronic) headache or high headache related disability, are more prone to use unsuitable coping mechanisms,[17] score low on pain acceptance[18] and high on catastrophizing scales, and experience a low internal pain control.[19] In patients with migraine, pain control and self-management can be improved by behavioural therapy.[20] We hypothesize that contact with a headache nurse influences the above mentioned factors and thus will help patients to endure the withdrawal period. Patients with tension-type headache and the combination of migraine and tension-type headache seem to benefit less from withdrawal therapy than

patients with migraine alone, which may suggest that the pathophysiological mechanism of medication overuse differs between different underlying primary headache syndromes.

Nowadays the view on treatment of MOH shifts from the traditional 'withdrawal therapy first' towards an approach in which prophylactic therapies are started before patients are withdrawn from the overused medication. Randomised trials in chronic migraineurs with topiramate and onabotulinum toxin A,[21–23] contributed significantly to the debate whether, and when, detoxification is necessary in the treatment of MOH.[24] From these trials the question remains, however, whether the effect is clinically relevant. Moreover, the studies lack adequate reporting of plausible blinding failure, and most importantly, in these trials withdrawal was not advocated. To illustrate, the responder rate of migraineurs in our study is comparable to the responder rate in the pooled results of the onabotulinum toxin A trials. We realize that in our population not many patients overuse barbiturates or opiates, which enables acute medication withdrawal, in accordance with our national guidelines. Nevertheless, our study shows that with the support of a headache nurse, comprising only one face-to-face contact and a median of three contacts by telephone, 75% of MOH patients succeed to undergo a highly cost-effective outpatient withdrawal therapy, which is easily implemented in general neurology practice.

Withdrawal therapy is an effective treatment for Medication Overuse Headache especially for patients with migraine. Support by a headache nurse provides a substantial increase of treatment adherence and can be applied in an outpatient setting.

Acknowledgements

The authors thank Mrs. J. Trouerbach, headache nurse, for supporting MOH patients during withdrawal therapy.

Clinical implications

- With support of a headache nurse, almost 75% of Medication Overuse Headache patients succeed to withdraw from overused medication.
- Withdrawal therapy with support of a headache nurse is applicable in an outpatient setting in general neurology practice
- Medication Overuse Headache patients with migraine as the solely underlying primary headache disorder benefit the most by simple withdrawal therapy.

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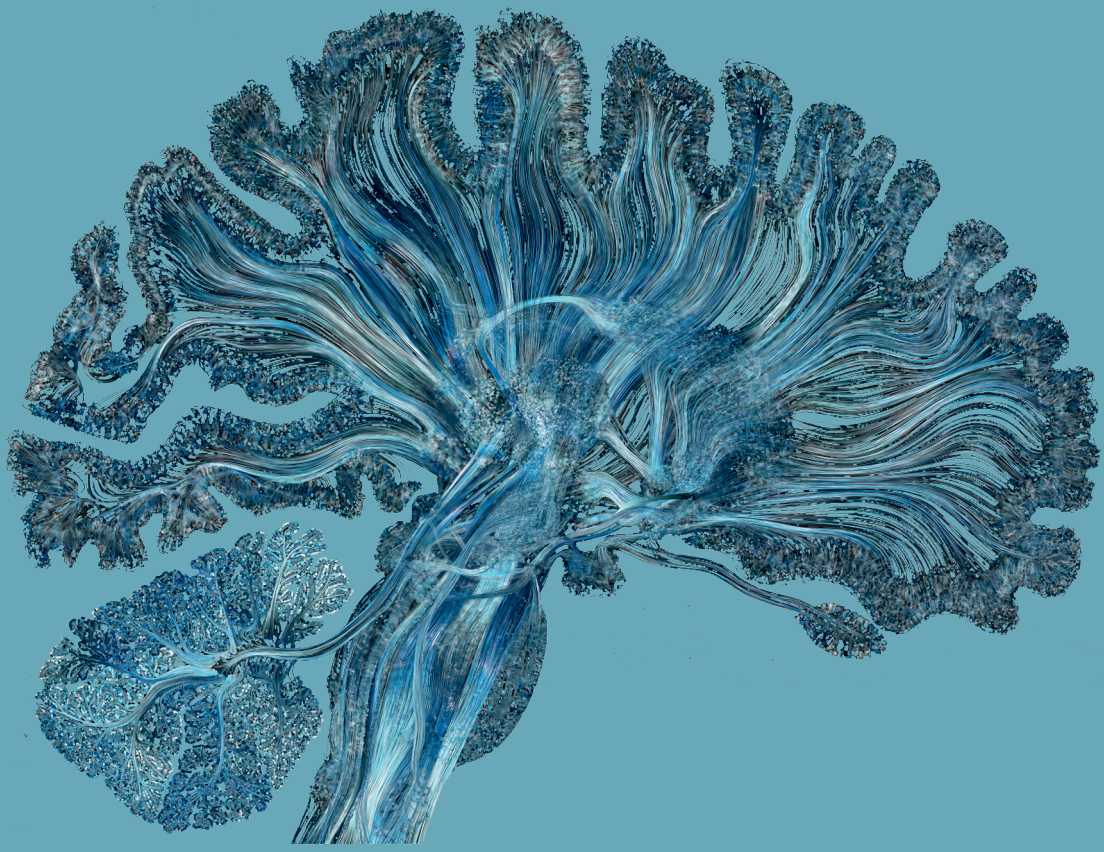

Chapter 4

Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial

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Brain 2019; 142 (5): 1203-1214

Abstract

Botulinum toxin A (BTA) is widely used as treatment of chronic migraine. Efficacy in studies, however, was only modest and likely influenced by unblinding due to BTA-induced removal of forehead wrinkles. Moreover, most study participants were overusing acute headache medications and might have benefitted from withdrawal. We assessed in a double blind, placebo-controlled, randomised clinical trial whether add-on therapy with BTA enhances efficacy of acute withdrawal. Participants were enrolled between December 2012 and February 2015, with follow-up to January 2016, in a single academic hospital in the Netherlands. A total of 179 participants, male and female, aged 18-65, diagnosed with chronic migraine and overuse of acute headache medication were included. All participants were instructed to withdraw acutely from all medication for a 12-week period, in an outpatient setting. In addition, they were randomly assigned (1:1) to 31 injections with BTA (155 units) or placebo (saline); to prevent unblinding, placebo-treated participants received low doses BTA (17.5 units in total) in the forehead, along with saline injections outside the forehead region. Primary endpoint was percentage change in monthly headache days from baseline to the last four weeks of double-blind treatment (weeks 9-12). Among 179 randomised patients, 90 received BTA and 89 received placebo, and 175 (98%) completed the double-blind phase. All 179 patients were included in the intention-to-treat analyses. BTA did not reduce monthly headache days versus placebo (-26.9% vs - 20.5%; difference -6.4%; 95% CI -15.2 to 2.4; p=.15). Absolute changes in migraine days at 12 weeks for BTA vs placebo were -6.2 [0.8] vs -7.0 [0.7] (difference: 0.8; 95% CI -1.0 to 2.7; p=.38). Other secondary endpoints, including measures for disability and quality of life, did also not differ. Withdrawal was well tolerated and blinding was successful. Thus, in patients with chronic migraine and medication overuse, BTA does not afford any additional benefit over acute withdrawal alone. Acute withdrawal should be tried first before initiating more expensive treatment with BTA.

Trial register identifier www.trialregister.nl; NTR3440

Introduction

Chronic migraine is a highly disabling and difficult to treat form of migraine,[1–3] affecting nearly 2% of the general population.[1,2] It is defined by occurrence of headaches on ≥ 15 days per month for > 3 months, of which ≥ 8 days fulfil migraine criteria.[1–3] The majority of patients overuse acute headache medications including analgesics , triptans, and opioids.[1,2] "Medication overuse" is a major risk factor for transformation from episodic (< 15 headache days) to chronic migraine and an important factor in maintaining and aggravating chronification.[1–3] Acute withdrawal may be a cost-effective therapy to reduce headache frequency, improve quality of life, halt medication overuse-induced adverse events, and prevent systemic toxicity.[1,4–13] It might also improve efficacy of migraine prophylactics.[1,7,14] Unfortunately, acute withdrawal is frequently hampered by acute withdrawal symptoms, which may considerably disrupt patient's daily life, comfort, and mental state.[15,16] Because of these withdrawal symptoms, many physicians are reluctant to recommend withdrawal, despite the potential advantages.[7,16,17]

Recently, botulinum toxin A (BTA)[18] has emerged as therapy for chronic migraine.[16,19–25] There is, however, controversy regarding its efficacy, in particular in patients with medication overuse.[1,17,26] In the registration trials, the therapeutic gain of BTA versus placebo was only modest, with an additional reduction of 1.8 headache days from 19.9 at baseline (percentage change: 9%).[23] Moreover, unblinding might have influenced efficacy. Study medication was injected at 31 sites including the forehead, that will remove wrinkling and likely cause unblinding versus placebo.[26,27] In trials using similar designs, 85% of BTA-treated participants correctly guessed their treatment.[27,28]

A second important issue is that approximately 65% of the participants in these studies were overusing medication, and might have benefitted from withdrawal.[20–24] Direct, double-blind comparison of withdrawal versus BTA is technically hardly feasible. Placebo-matching for the various types and combinations of overused medications is virtually impossible, as well as controlling for the psychological effects of withdrawal. We compared acute withdrawal plus BTA administered according to standard protocols[20–24] versus acute withdrawal plus placebo in a double-blind, randomised clinical trial in

patients with chronic migraine and medication overuse. To minimise risk of unblinding, injections in the forehead of participants allocated to placebo contained low masking doses of BTA, sufficient to remove forehead wrinkling, but unlikely to reduce headache frequency.

Methods

Study design and participants

This was a randomised, double-blind, placebo-controlled, clinical trial done at Leiden University Medical Centre Headache Clinic: the Chronification and reversibility of migraine study (CHARM; www.trialregister.nl # 3440). We enrolled consecutive patients with chronic migraine and medication overuse.[3] Diagnoses were established in consultation with headache experts and confirmed by a 4-week baseline headache diary. Patients aged 18-65, who were able to comply with the study protocol, and provided written informed consent, were eligible. Exclusion criteria included: contraindications for BTA;[18] other primary or secondary headaches or neurological disorders; moderate/severe chronic pain disorders; psychiatric disorders other than depression; cognitive, behavioural, or oncologic disorders; use of ergots, opioids or barbiturates; and abuse of recreational soft or hard drugs.

The study was performed in accordance with the declaration of Helsinki and Good Clinical Practices and approved by the local ethics committee.

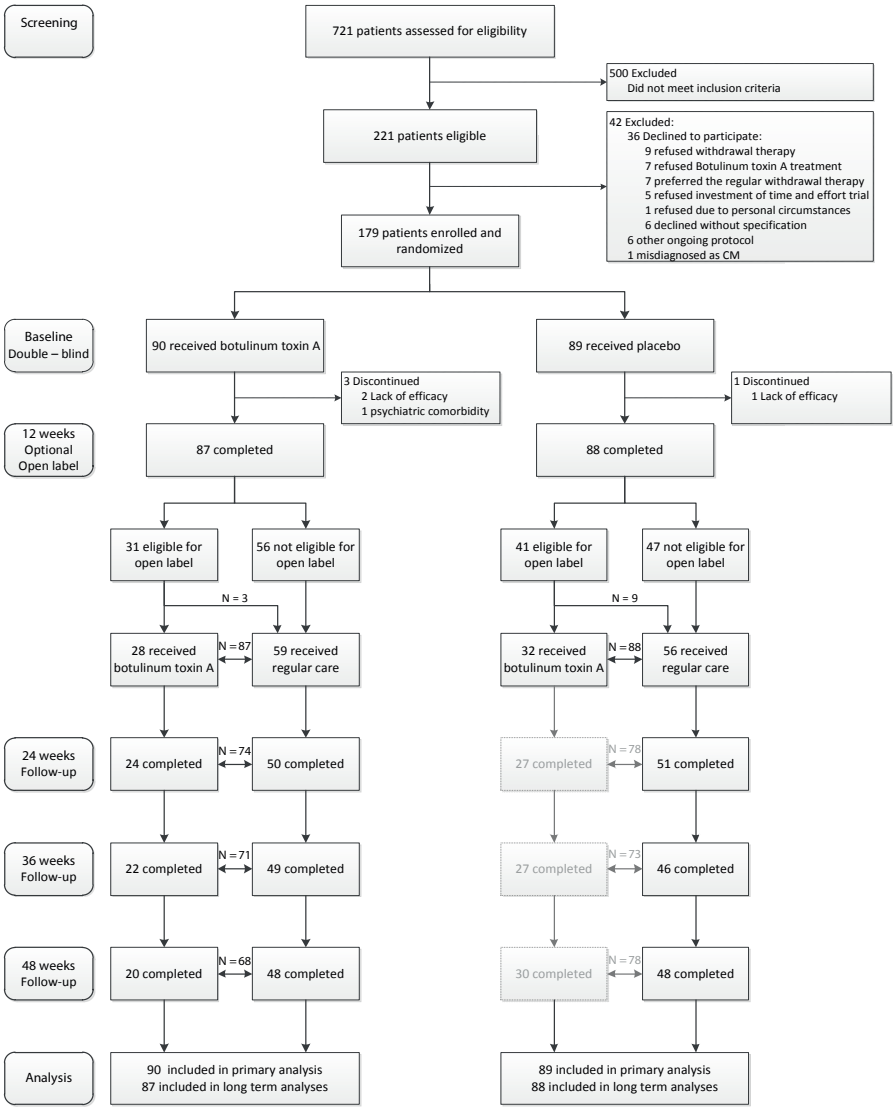
Randomization

Upon inclusion, patients were randomly assigned to receive BTA or placebo injections (1:1), according to a centralised randomisation schedule using blocks of four to eight patients, stratified for gender. The randomization schedule was prepared and kept concealed in the data management system by an independent trial statistician. An independent pharmacist and research nurse prepared the appropriate treatments. The study investigators who enrolled participants and administered treatment were not involved in these procedures.

Procedures

Participants started with a 4-week baseline-assessment period, followed by a 12-week randomised, double-blind, placebo-controlled phase with BTA injections immediately prior to medication withdrawal (Figure 1). After this double-blind phase, patients who had withdrawn from medication but remained to have chronic migraine were offered open-label BTA injections (155 units, one treatment cycle) in addition to standard care regarding acute headache medication (open-label phase). Participants who were not eligible for BTA open label treatment received standard care with acute headache medication and, if needed, prophylactic treatment. Study follow-up visits were planned at weeks 12, 24, 48, with additional clinical visits according to medical need. Participants kept 4-week paper diaries with daily registration of headache characteristics, accompanying symptoms, and use of acute headache medication during the baseline observation period and post treatment weeks 9-12, 21-24, 33-36, and 45-48. The diaries had to be send in every week, to ensure an accurate status. Cross checking of data (entry) was performed both manually in a random manner and electronically with fixed algorithms. Determination of migraine and non-migraine headache on any given calendar day was calculated by an algorithm based on the ICHD criteria. In addition, electronic questionnaires were filled out every 12 weeks regarding quality of life (SF-36 [29]), headache impact and disability (HIT-6 [30], MIDAS [31]), depression and anxiety (HADS [32]). Adverse events were recorded based on spontaneous reports from participants and upon questioning by the study investigators at day 3 and week 12.

Figure 1: Trial profile



Primary analysis included all participants (intention-to-treat), using outcomes after 12 weeks. Of 90 participants receiving withdrawal and BTA during the double blind phase, 31 still had chronic migraine after 12 weeks, of whom 28 participants received one cycle open label BTA. Accordingly, of 89 participants receiving withdrawal and placebo during the double blind phase, 41 still had chronic migraine, of whom 32 received one cycle open label BTA. Long term analyses, comparing one or two cycles of BTA versus placebo after 12, 24, 36, and 48 weeks, included all participants providing at least one outcome measurement. The open-label results (i.e. outcomes after 24, 36, and 48 weeks) of placebo treated patients receiving open label BTA were set as missing (depicted in grey within dashed boxes). The boxes show the number of participants of whom data was available.

Treatments and masking

In accordance to our national guidelines[33] and other withdrawal studies,[6,8,11,12] participants were instructed to withdraw abruptly from all acute headache medications and caffeine in an outpatient setting for 12 weeks. Prophylactic treatment was tapered off and rescue medication to treat headaches of any kind was not allowed. Patients were explained what to expect after withdrawal, including the likely occurrence of sometimes severe withdrawal symptoms, and were informed about the possible practical, social and professional consequences.

BTA was administered at 31 predefined injection sites (5 units per injection; in total 155 units), in accordance with published protocols.[23] Placebo was administered at the same 31 injection sites. However, while the 24 injections outside the forehead region contained saline, the seven injections in the forehead contained low dose BTA (2.5 units per injection site; 17.5 units in total). Participants were explained that change in facial expression was not indicative of any particular treatment. Active and placebo treatment were indistinguishable. Patients and investigators were blinded for treatment.

Outcomes

There is no universally agreed primary endpoint for trials in chronic migraine. The differences, however, between the various recommended[34,35] and used endpoints[36–40] are in fact only marginal. We choose as primary outcome the percentage change in 4-weekly headache days from baseline to the last four weeks of double-blind treatment (weeks 9-12). As chronic migraine patients have a high headache frequency at baseline, percentage change in headache days is considered a more meaningful endpoint than absolute change. Percentage change was calculated as change in number of headache days per 4 weeks, divided by the number of baseline headache days. A headache day was any calendar day on which a migraine or non-migraine headache of any duration was reported. We did not include a minimal duration of 4 hours (as used in some trials), as most of our participants would usually use medication within 4 hours after headache onset. For the same reason we decided not to specify that headache had to have a moderate or severe peak intensity.

Secondary outcomes were assessed 12, 24, 36 and 48 weeks after therapy onset. The main secondary outcome was change in quality of life (SF-36). Additional

secondary outcomes were change from baseline in number of (i) headache days; (ii) migraine days (days with headache fulfilling migraine criteria or treated with acute migraine medication); (iii) moderate or severe headache days; (iv) hours with headache (cumulative); and (v) days with use of acute headache medication. We also assessed: (i) proportion of participants with ≥ 50% or ≥ 25% reduction in headache days; (ii) proportion of participants who persevered successfully with medication withdrawal (≤ 2 medication days per 4 weeks); (iii) proportion of participants without medication overuse (< 10 medication days per 4 weeks); and (iv) HIT-6 and MIDAS scores.

To assess satisfaction, participants were asked after 12 weeks to rate their treatment on a 0 - 10 satisfactory scale (0 = completely dissatisfied, 10 = completely satisfied), and whether they would recommended their therapy to family or friends ('no', 'yes' or 'I don't know'). To assess success of blinding, we asked participants and investigators three days and 12 weeks after therapy onset which treatment they believed they had received or given (BTA, placebo, or don't know).

Statistical analysis

We defined a 20-percentage point difference in mean percentage change in 4-weekly headache days from baseline to weeks 9-12 of BTA versus placebo, as clinically meaningful. Based on a previous withdrawal study,[6] we expected a standard deviation of 40 percentage points. Thus, 84 participants per group were required to detect a 20-percentage point difference with 90% power and a 0.05 type 1 error. To allow for dropouts, we aimed to include 90 participants per group.

The primary intention-to-treat analysis included all patients. We used a pre-specified analysis of covariance (ANCOVA) model to compare the percentage change in 4-weekly headache days between the two groups. Fixed factors were treatment, support by a headache nurse, gender, depression and anxiety. Covariates were age and number of baseline headache days. Similar models were used for the secondary outcomes after 12 weeks. Missing data on follow-up (< 14 completed headache dairy days) was handled using multiple imputation. Ten imputed datasets on headache days, migraine days, moderate or severe headache days, headache duration, and SF-36 score were generated using

automatic imputation. In case of 14-27 completed days, the existing data were extrapolated to a 28-days period.

To assess long-term efficacy, we included the open label and follow-up phases in the analysis. As some placebo-treated patients received BTA in the open label phase, including these patients in the analysis of 'placebo-treated patients' would potentially confound the comparison. To avoid this, the open-label results (outcomes after 24, 36 and 48 weeks) of placebo-treated participants receiving open-label BTA were set to missing (see grey numbers in Figure 1). Thus, participants treated only with placebo were compared to participants who received one or two cycles of BTA. Participants providing at least one outcome measurement were included. We used Linear Mixed Models with changes from baseline to follow-up as the dependent variable. Such models automatically handle missing outcomes, including those censored by us. Fixed effects were treatment, visit number, treatment-by-visit number interaction, headache nurse, gender, depression, and anxiety. Covariates were age and baseline value of the variable of interest. Unstructured covariance matrices were used. We report the adjusted means with 95% confidence intervals. To facilitate objective assessment of the open-label longterm follow-up we present the results both as crude data, without any statistical modelling (Table 3), and by using the statistical model (Figure 4).

Two-sided p values <0.05 were considered statistically significant. Analyses were performed in SPSS23.0 (SPSS Inc., Chicago, USA). The audit trial of the trial register captures protocol amendments: no changes were made after unblinding of study investigators or completion of the trial. Data entry and processing was performed before unblinding of study investigators.

Role of the funding source

The study was funded by grants from the Netherlands Organization for Scientific Research and the Dutch Brain Foundation. They had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JAP, DAK, EWZ and GMT had access to all data in the study and JAP, DAK, MDF, and GMT had final responsibility for the decision to submit for publication.

Results

Between December 2012 and February 2015, 721 patients with high frequent migraine were screened, of whom 221 were eligible and 179 included and randomly assigned to either BTA (n=90) or placebo (n=89) (Figure 1). The treatment groups were well balanced for age, gender, headache and migraine frequency, and psychiatric comorbidity (Table 1). Four participants discontinued the study in the double-blind phase, one in the placebo group because of lack of efficacy and three in the BTA group, because of lack of efficacy (n=2) or exacerbation of pre-existing depression (n=1). All 179 participants were included in the intention-to-treat analysis. Follow-up ended in January 2016. Discontinuation of participants until the end of follow-up is depicted in Figure 1.

Table 1: Baseline demographic and clinical characteristics

	Botulinum toxin A (n=90)	Placebo (n=89)
Gender, female	69 (76.7%)	67 (75.3%)
Age (years)	43.7 ± 11.8	46.7 ± 9.5
Headache days	21.7 ± 4.7	21.0 ± 4.8
Moderate / severe headache days	16.1 ± 6.0	15.3 ± 4.9
Headache duration (cumulative hours)	199.6 ± 156.6	196.0 ± 148.2
Migraine days	15.5 ± 6.0	14.9 ± 5.0
Age of onset migraine (years)	17.1 ± 9.7	18.1 ± 9.5
HIT 6[1]		
Mean score	65.0 ± 4.6	65.0 ± 3.9
% severe (≥60)	81 (90.0%)	84 (94.4%)
Days using medication[2]	16.5 ± 5.8	16.4 ± 5.4
Prophylaxis[3]		
Current use	30 (33.3%)	35 (39.3%)
History of use[4]	82 (91.1%)	81 (91.0%)
Anxiety, % present (HADS-A ≥ 8)	28 (31.1%)	27 (30.3%)
Depression, % present (HADS-D ≥ 8)	32 (35.6%)	34 (38.2%)

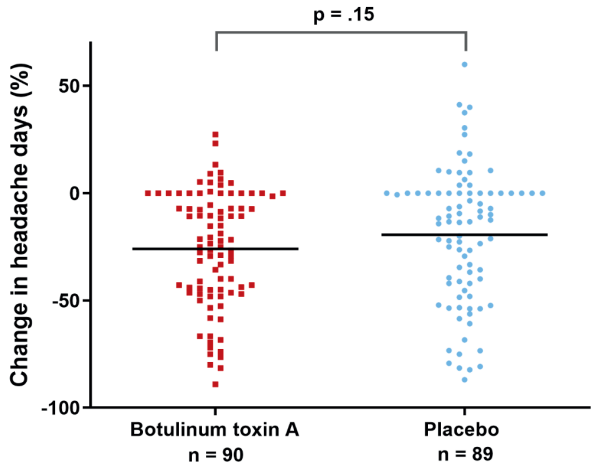
Values are means ± SD or n (%).

[1] N botulinum toxin A = 87, N placebo = 87; [2] Simple analgesics and/or triptans. [3]Commonly used prophylaxis for migraine [4]History of use: current or past use of at least one type of prophylaxis.

The primary outcome, mean percentage change in 4-weekly headache days from baseline to weeks 9-12 after therapy onset, did not differ between withdrawal

plus BTA (-26.9%; 95% CI -19.9 to -34.0) versus withdrawal plus placebo (-20.5%; 95% CI: -13.5 to -27.6). The adjusted treatment difference was 6.4% (95% CI -2.4 to 15.2; p=.15; Figure 2).

Figure 2: Percentage change in 4-weekly headache days from baseline to the last four weeks of double-blind treatment (weeks 9-12) Depicted are unadjusted values and means.



Likewise, there were no treatment differences after 12 weeks for any of the secondary outcome measures, including headache days or hours, migraine days, 50% and 25% responder rates, and measures of quality of life and (Table 2). The change in headache days was -5.6 for BTA versus -4.4 for placebo (mean difference -1.3; 95% CI: -3.1 to 0.6) and in migraine days was -6.2 for BTA versus -7.0 for placebo (mean difference 0.8; 95% CI: -1.0 to 2.7) (Table 2). Approximately 60% of participants had reverted back to episodic migraine, without any treatment differences (Table 2 and Fig. 3). BTA did also not increase the proportion of participants who managed to persevere with withdrawal. In both groups, 90% of participants withdrew successfully, defined as ≤2 medication days, and the proportions of participants still meeting the criteria for medication overuse at week 12 were negligible (2.3%; Table 2)

Table 2. Secondary outcomes.

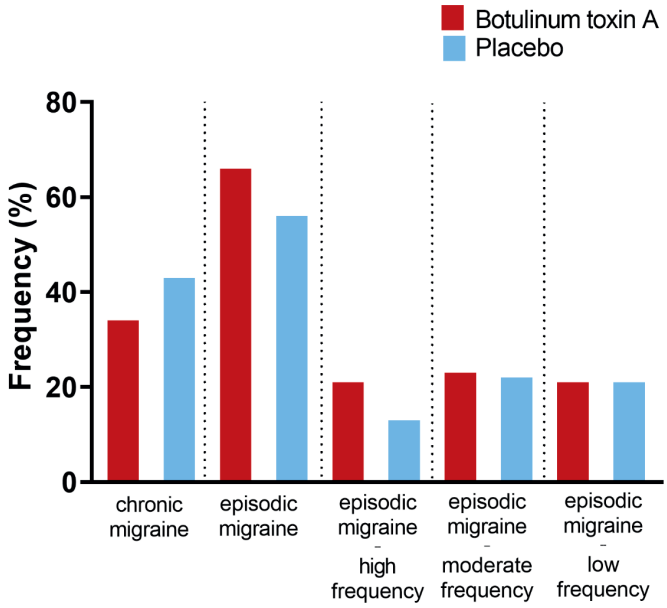
	Botulinum toxin A (n=90)	Placebo (n= 89)	Mean difference (95% CI)	P value
Change in headache days[1]	-5.6 (0.8)	-4.4 (0.7)	-1.3 (-3.1 to 0.6)	.17
Change in migraine days[2]	-6.2 (0.8)	-7.0 (0.7)	0.8 (-1.0 to 2.7)	.38
Change in moderate / severe headache days[3]	-4.9 (0.7)	-5.4 (0.7)	0.5 (-1.2 to 2.2)	.55
Change in hours of headache (cumulative)[4]	-20.8 (13.5)	-13.3 (13.5)	-7.5 (-41.0 to 25.9)	.66
25% responder rate[5]	48.3%	37.8%	10.5 (-3.9 to 24.9)	.16
50% responder rate[5]	18.1%	20.4%	-2.5 (-13.8 to 9.2)	.69
Succeeded to withdraw from medication (yes)[6] *	89.7%	89.8%	-0.1 (-9.3 to 9.1)	.98
Medication overuse status (no overuse) [7] *	97.7%	97.7%	0.0 (-4.4 to 4.4)	.99
Change in SF-36 physical health[8]	-1.0 (1.9)	1.8 (1.8)	-2.8 (-7.1 to 1.4)	.19
Change in SF-36 mental health[8]	0.0 (2.0)	0.6 (2.0)	-0.6 (-5.4 to 4.1)	.79
Change in HIT-6 [9] **	-0.8 (0.7)	-0.8 (0.6)	0.0 (-1.5 to 1.6)	.96
Change in MIDAS[10] ***	18.7 (10.2)	24.0 (9.8)	-5.3 (-19.0 to 29.6)	.67

Data are least squares means (SE) or proportions. (*Some scores do not add up due to rounding*)

*N botulinum toxin A = 87; N placebo = 88; ** N botulinum toxin A = 76; N placebo = 79; *** N botulinum toxin A = 76; N placebo = 77

[1] Day with a migraine or non-migraine headache of any duration; [2] Day with headache fulfilling migraine criteria or treated with acute anti-migraine medication; [3] Day with headache of moderate or severe intensity of any duration; [4] Cumulative duration in hours of any headache of any severity; [5] Proportion of participants with ≥ 25% or ≥ 50% reduction in headache days; [6] Proportion of participants who persevered successfully with medication withdrawal, defined as no more than two medication days per month; [7]Proportion of participants without medication overuse, i.e. < 10 medication days per month; [8] Physical and mental health sum scores, range 0 - 100, a higher score corresponds to a higher quality of life; [9] Headache impact sum score, range 36 - 78, a higher score corresponds to a higher headache impact; [10] Sum of days with disability due to migraine, a higher score corresponds to a higher migraine disability.

Figure 3. Migraine status after 12 weeks



Proportion of participants who remained to have chronic migraine, or who transformed to episodic migraine. Episodic migraine was subcategorized in high frequent, moderate frequent and low frequent episodic migraine.
Chronic migraine: ≥ 15 headache days of which ≥ 8 migraine days; episodic migraine: not fulfilling chronic migraine criteria; episodic migraine - high frequency: > 15 headache days, but < 8 migraine days; episodic migraine - moderate frequency: 10-14 headache days; episodic migraine - low frequency: < 10 headache days

After 12 weeks, 60 patients received open-label BTA treatment (see Figure 1). Preventatives that were started as part of standard care included topiramate (23%), candesartan (11%), valproate (4%), beta-blockers (3%), amitriptyline (2%) and flunarizine (1%).

We also assessed the long term effects of withdrawal plus one or two BTA treatments versus withdrawal without BTA. There were no differences after 12, 24, 36, or 48 weeks for any of the outcome measures: days with any headache or migraine (Figure 4A and 4B), days with moderate or severe headache, cumulative number of hours with headache, or days with medication use (adjusted data not shown). These results were supported by comparisons of the unadjusted data of the four possible combinations for initial double-blind and subsequent open-label treatment which did not show any relevant difference (Table 3).

Table 3. Unadjusted changes from baseline over 48 weeks, on most important secondary outcomes.

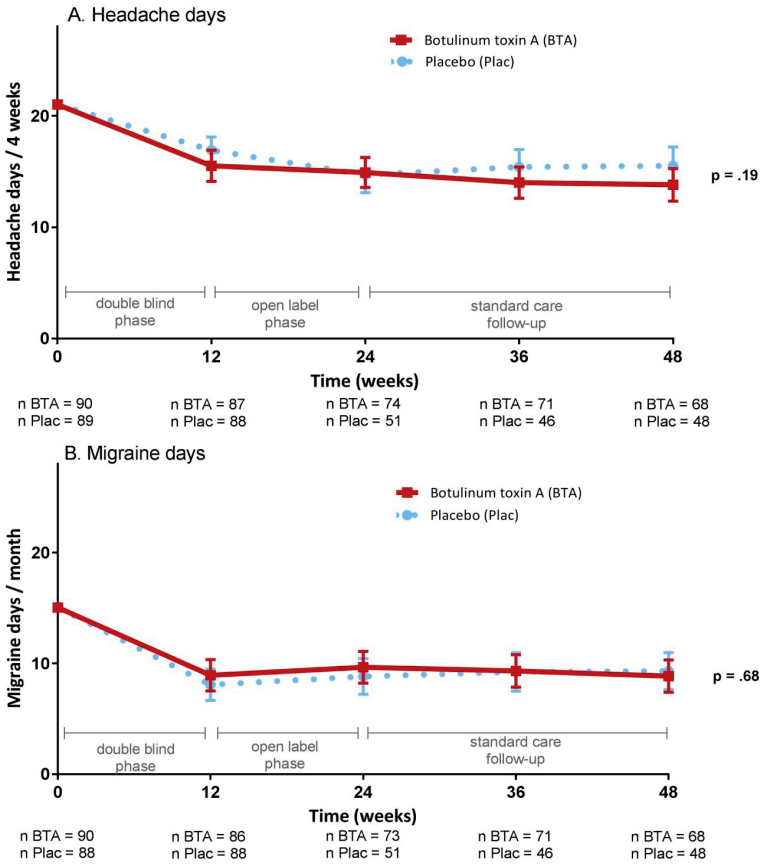
	Treatment Double blind phase	**Baseline**	**12 weeks** Mean (95%CI)	**Treatment** Open label phase
Headache days	Botulinum toxin A	21.7	-5.4 (-6.6 to -4.2)	Botulinum toxin A
				Standard Care
	Placebo	21.0	-3.9 (-5.3 to -2.5)	Botulinum toxin A
				Standard Care
Migraine days	Botulinum toxin A	15.5	-6.5 (-8.1 to -5.0)	Botulinum toxin A
				Standard Care
	Placebo	14.9	-6.9 (-8.3 to -5.6)	Botulinum toxin A
				Standard Care
Moderate / severe headache days	Botulinum toxin A	16.1	-4.7 (-5.9 to -3.5)	Botulinum toxin A
				Standard Care
	Placebo	15.3	-4.9 (-6.2 to -3.6)	Botulinum toxin A
				Standard Care
Headache duration (cumulative hours)	Botulinum toxin A	199.6	-11.5 (-37.9 to 14.9)	Botulinum toxin A
				Standard Care
	Placebo	196.0	-0.3 (-24.7 to 24.1)	Botulinum toxin A
				Standard Care
Medication days	Botulinum toxin A	16.1	-15.7 (-16.9 to 14.5)	Botulinum toxin A
				Standard Care
	Placebo	15.3	-15.3 (-16.6 to 13.9)	Botulinum toxin A
				Standard Care

Shown are the crude data, derived without any modelling. The outcomes are subdivided in the four possible combinations for initial double-blind and subsequent open-label treatment (i.e. Botulinum toxin A + Botulinum toxin A, Botulinum toxin A + Standard Care, Placebo Botulinum toxin A, Placebo + Standard Care)

* Outcomes after 12 weeks are subdivided in the four treatment groups as well, to enable comparison for the open label and follow up phases.

12 weeks* Mean (95%CI)	**24 weeks** Mean (95%CI)	**36 weeks** Mean (95%CI)	**48 weeks** Mean (95% CI)
-1.5 (-3.1 to 0.1)	-1.9 (-4.0 to 0.2)	-2.5 (-4.0 to -1.1)	-4.6 (-7.3 to -1.8)
-7.3 (-8.7 to -5.8)	-7.6 (-9.1 to -6.1)	-8.9 (-10.6 to -7.2)	-8.2 (-9.9 to -6.5)
0.0 (-1.4 ; 1.4)	-3.2 (-5.7 to -0.8)	-2.2 (-4.3 to -0.1)	-5.9 (-8.4 to -3.4)
-6.1 (-7.9 to -4.3)	-7.4 (-8.9 to -6.0)	-6.6 (-8.1 to -5.2)	-6.6 (-8.3 to -5.0)
-0.5 (-2.2 to 1.3)	-2.0 (-4.7 to 0.8)	-4.8 (-8.1 to -1.6)	-3.6 (-6.4 to -0.7)
-9.4 (-11.1 to -7.7)	-7.6 (-9.4 to -5.7)	-7.1 (-8.8 to -5.4)	-7.9 (-9.7 to -6.0)
-3.5 (-5.4 to -1.7)	-3.1 (-5.7 to -0.6)	-2.7 (-5.7 to 0.2)	-4.5 (-7.0 to -2.0)
-8.9 (-9.1 to -7.2)	-7.5 (-9.1 to -5.8)	-6.5 (-8.2 to -4.7)	-6.3 (-7.6 to -4.9)
-0.5 (-2.4 to 1.4)	-2.4 (-5.4 to 0.6)	-4.3 (-6.9 to -1.7)	-4.2 (-7.1 to -1.4)
-6.7 (-7.9 to -5.5)	-5.9 (-7.6 to -4.2)	-6.1 (-7.7 to -4.4)	-7.4 (-9.2 to -5.6)
-2.2 (-4.1 to -0.3)	-3.6 (-5.7 to -1.5)	-2.8 (- 5.2 to -0.3)	-5.2 (-7.4 to -3.1)
-6.4 (-8.0 to -4.8)	-6.6 (-8.3 to -4.9)	-5.8 (-7.3 to -4.4)	-6.2 (-7.7 to -4.7)
55.1 (6.1 to 104.1)	22.2 (-48.1 to 92.4)	4.0 (-31.8 to 39.9)	1.2 (-45.1 to 47.6)
40.8 (-69.8 to -11.7)	-24.4 (-52.8 to 4.1)	-48.2 (-64.5 to -11.9)	-47.8 (-84.3 to -11.3)
21.0 (11.7 to 53.6)	-30.8 (-86.9 to 25.2)	-2.1 (-66.4 to 62.2)	-53.1 (-114.4 to 8.2)
-12.3 (-46.1 to 21.5)	-29.6 (-59.1 to 0.0)	-38.1 (-58.9 to -17.4)	-28.6 (-58.4 to 1.2)
-17.1 (-19.6 to -14.6)	-12.4 (-15.9 to -8.9)	-12.4 (-16.5 to -8.2)	-12.6 (-16.3 to -8.8)
-15.0 (-16.5 to -13.6)	-10.4 (-12.1 to -8.7)	-9.5 (-11.4 to -7.6)	-9.3 (-11.2 to -7.5)
-16.5 (-18.6 to -14.4)	-9.4 (-12.2 to -6.7)	-9.4 (-12.1 to -6.6)	-10.3 (-12.9 to -7.8)
-14.5 (-16.3 to -12.8)	-9.0 (-10.7 to -7.3)	-7.1 (-8.8 to -5.4)	-8.0 (-9.4 to -6.5)

Figure 4: Change from baseline of the 4-weekly number of days with headache (A) and migraine (B) over 48 weeks.



To compare the long-term effects of withdrawal plus BTA versus withdrawal plus placebo, the open label phase and follow-up phase were included in the analysis. As some placebo-treated patients received BTA in the open label phase, including the outcomes of these patients in the analysis of 'placebo-treated patients' would potentially influence the comparison. To avoid this, the open-label results (i.e. outcomes after 24, 36 and 48 weeks) of placebo-treated participants receiving open-label BTA were set to missing. In this way, participants treated only with placebo were compared to participants who had received one or two cycles of BTA.
Depicted are adjusted means with 95% CI; headache and migraine days at baseline are derived from the model. A headache day is a day with a migraine or non-migraine headache of any duration; A migraine day is a day with headache fulfilling migraine criteria or treated with acute anti-migraine medication.

Satisfaction with treatment after 12-weeks was 7/10 (median, interquartile range=3). Treatment was rated as very good (≥8/10) by 44.7% of BTA and 47.5% of placebo treated participants. Furthermore, 61.8% of BTA and 72.5% of placebo treated patients would recommend their treatment to friends or family, 25% and 17.5% didn't know, and 13.2% and 10% would not.

In total 59, presumably treatment-related adverse events were reported in the double blind phase by 52 participants: 25 on BTA and 27 on placebo (Supplementary Table 1). Adverse events were mild (92%) or moderate (8%). Most frequently reported adverse events were pain (37%) and small hematoma (31%) at injection sites. Ptosis was reported by six participants (BTA n=2, placebo n=4).

Blinding appeared successful (Table 4). Assumptions about received (participants) or given (investigators) treatments were equally distributed and participants nor investigators significantly more often guessed the correct treatment. At 12 weeks, investigators correctly identified treatment in 54.3% of BTA-treated patients and 55.0% of placebo-treated patients. For participants these proportions were 38.2% and 44.0%.

Table 4. Blinding results: assumptions of participants on the received treatment.

	Actually received BTA			Actually received placebo			P value
Assumption	BTA	Placebo	Don't know	BTA	Placebo	Don't know	
At 3 days*	29 (33.0%)	59 (67.0%)	0 (0.0%)	29 (33.7%)	56 (65.1%)	1 (1.2%)	.81
At 12 weeks**	29 (38.2%)	35 (46.1%)	12 (15.8%)	30 (37.0%)	36 (44.0%)	15 (18.8%)	.90

Values are n (%)
* N BTA = 88, N Placebo = 86
** N BTA = 76, N Placebo = 81

Discussion

We assessed whether double-blind add-on therapy of Botulinum toxin A (BTA) increased efficacy of acute withdrawal in chronic migraine with medication overuse. Efficacy was evaluated primarily after 12 weeks, as this period comprises the acute withdrawal phase. Low doses of BTA in the forehead of placebo-treated participants successfully prevented unblinding. Acute withdrawal was well-accepted and associated with meaningful improvement. BTA did not afford any additional benefit over withdrawal alone.

Most patients with chronic migraine overuse acute headache medications[1,2,21–24,42] and withdrawal may significantly reduce headache.[1,4,6–8,17,43] Yet, many patients and physicians are reluctant to initiate withdrawal fearing acute withdrawal symptoms.[1–3,7,15,16] In our study, 90% of the study population completed withdrawal, almost 50% evaluated their therapy as very good, and 70% would recommend their therapy to friends and family. After withdrawal, mean number of headache days had decreased by approximately 5 days (≈ 25%) and of migraine days by 6-7 days (≈ 45%; Table 2). In total 60% of patients had reverted back to episodic migraine, which was mainly due to the large drop in migraine days below the threshold of 8 days required to fulfill the criteria for chronic migraine (Figure 3). Over 30% of participants (29% in the Botulinum toxin A group and 34% in the placebo group) did not need preventive medication anymore as their number of migraine days had dropped below 4 per month. These results confirm that withdrawal is well-tolerated and associated with meaningful improvement.

Comparison with results from other studies is difficult because of different study designs and populations. For instance, many studies[1,4–7,9–13] were conducted in patients who had medication overuse headache, but not necessarily chronic migraine. In a study in patients with medication overuse of whom 60% fulfilled the criteria for chronic migraine,[8] acute withdrawal resulted in a reduction in mean monthly migraine days and a reversion to episodic migraine very similar to what we found in our study.

In the PREEMPT studies, patients with daily headaches and/or comorbid depression were excluded because they are more treatment-resistant. In our

trial, such patients were included as, in clinical practice, daily headaches and comorbid depression are common features of patients with chronic migraine. The inclusion of these difficult-to-treat patients certainly makes our study population more representative for the general chronic migraine population, but may also have contributed to lower response rates for BTA (-5.6 headache days from a baseline of 21.7 = 26%) and placebo (4.4. headache days from a baseline of 21 days = 21%). Likewise, in the PREEMPT studies, exclusion of patients with daily headaches and/or comorbid depression might have contributed to higher response rates for BTA but also placebo. In fact, placebo response rate in the PREEMPT studies was remarkably high (-6.6 headache days per 4 weeks from a baseline of 19 days = 35%) as empathized by authoritative reports such as from the British National Institute for Health and Care Excellence[44] and from the European Headache Federation.[45] As a result, the therapeutic gain in the PREEMPT studies of BTA over placebo was only modest: −8.4 versus -6.6 headache days, i.e. less than two days gain per 4 weeks.[23]

Comparison with recent trials testing anti CGRP (receptor) antibodies in chronic migraine is similarly complicated by remarkable differences in study design, inclusion and exclusion criteria, and even definitions for primary and secondary endpoints. Placebo response rates for the primary endpoints in these trials were considerably lower compared to the PREEMPT trials: -4.6 monthly headache days (versus 12.8 at baseline = 36%) for Fremanezumab versus -2.5 headache days for placebo (versus 13.3 at baseline = 19%);[37] -6.6 monthly migraine days for Erenumab (versus 17.9 at baseline = 37 %) versus -4.2 for placebo (versus 17.8 at baseline = 24%);[38] -4.8 monthly migraine days (versus 19.2 at baseline = 25%) for Galcanezumab versus -2.7 migraine headache days for placebo (versus 19.6 at baseline = 14%).[41] In the last two trials, patients with daily headaches were excluded.

Our study was triggered by the controversy whether or not BTA is superior to withdrawal and might save patients from experiencing acute withdrawal symptoms.[1,2,7,15–17,24,25] Direct double-blind placebo-controlled comparison for all (over)used medications versus withdrawal is technically impossible. Therefore, we assessed whether add-on therapy BTA would enhance efficacy of acute withdrawal and improve quality of life during withdrawal. However, we failed to find any evidence for additional benefit from BTA on the primary (Figure 2) or any of secondary endpoints (Table 2 / Figure 3). Insufficient study

power seems an unlikely explanation. The 95% CIs for the treatment differences versus placebo are for nearly all endpoints very narrow. The interval for the primary endpoint (-2.5 to 15.2 percentage point change) does not include our predefined clinically meaningful treatment effect of 20-percentage points (corresponding with 4 headache days). Of note, our study was powered for detecting even smaller differences than the 30-percentage point treatment effect generally considered the smallest meaningful effect in chronic pain and migraine studies.[34,46]

Compared to previous studies suggesting efficacy of BTA in chronic migraine,[20–24] our study shows three important methodological differences which potentially might explain the disparate outcome. First, while in earlier studies participants received two BTA treatment cycles three months apart,[21–24] in our study participants received only one. We therefore cannot exclude that some participants might have benefitted from a second BTA treatment at 12 weeks. However, considering the only marginal improvement in the 28 BTA non-responders who received open label BTA at 12 weeks (0.9 days; 95% CI -0.9 to 2.7), we doubt that omission of a second treatment of BTA has materially affected the results.

Second, in our study, unblinding was successfully prevented. This was most likely due to the injection of low masking doses of BTA in the forehead of placebo-treated participants. As a result, removal of forehead wrinkling was similar in both the placebo and BTA-treated group. Some might argue that doses even as low as 17.5 units BTA might have been effective, thereby nullifying a potential treatment difference from placebo. There is however no documented, double-blind, placebo-controlled, evidence for any effect of BTA at doses considerably lower than 155 units, and certainly not with a total dose of as little as 17.5 units.[47] This dose is even lower than doses used for cosmetic purposes. The therapeutic gain of 155 units BTA versus placebo in the PREEMPT studies was only modest at best (reduction of 1.9 headache days from a baseline of 19 days, i.e. only a mere 10% better improvement with BTA than with placebo).[47] It therefore seems extremely unlikely that a dose of only 17.5 units would have produced any clinically relevant effect. Moreover, the effect of only 7 injections of only 2.5 units of BTA each in the forehead (17.5 units) was not inferior compared to currently recommended treatment protocols using 31 injections of 5 units of BTA

each (155 units).[20–24] If the low dose treatment protocol was indeed effective, the high dose treatment protocol could easily be simplified by drastically reducing the doses and number of injection sites.
Finally, unlike in the PREEMPT and other studies,[21–24] we did not exclude patients with moderate to severe depression or who had no headache-free days as these characteristics are common in chronic migraine.[1,6,48] This, combined with the fact that many patients included in the study were directly referred from general practitioners or general neurologists throughout the country, makes us believe that our study population is more representative for the average patient with chronic migraine and medication overuse.

In conclusion, withdrawal is an efficacious and well-tolerated treatment for patients with chronic migraine and medication overuse. Add-on therapy with BTA did not afford any additional benefit whatsoever, neither on headache frequency nor on quality of life, disability or a range of other outcome measures. The therapeutic gain in previous BTA trials was only modest and likely positively influenced by unblinding. In the present study, low masking doses of BTA in the forehead successfully prevented unblinding. Before prescribing medications such as BTA, withdrawal should be tried first in patients with chronic migraine and medication overuse. Similarly, emerging and likely expensive new antimigraine medications such as antibodies against CGRP or its receptor[38,41,49] should also first be compared against withdrawal. As traditional designs are impossible, a similar add-on design as the one used in the present study might prove useful.

Acknowledgements
We thank all participants for their time and effort. We thank Mrs. J. Trouerbach, headache nurse, for supporting patients during withdrawal, and Mrs. G. Hendriks, research nurse, for preparing randomised medication. Furthermore, we would like to thank the neurologists, who participated in the CHARM study by referring chronic migraine patients. Lastly, we thank prof. dr. F. Dekker and prof. dr. T. Stijnen for their statistical advice.

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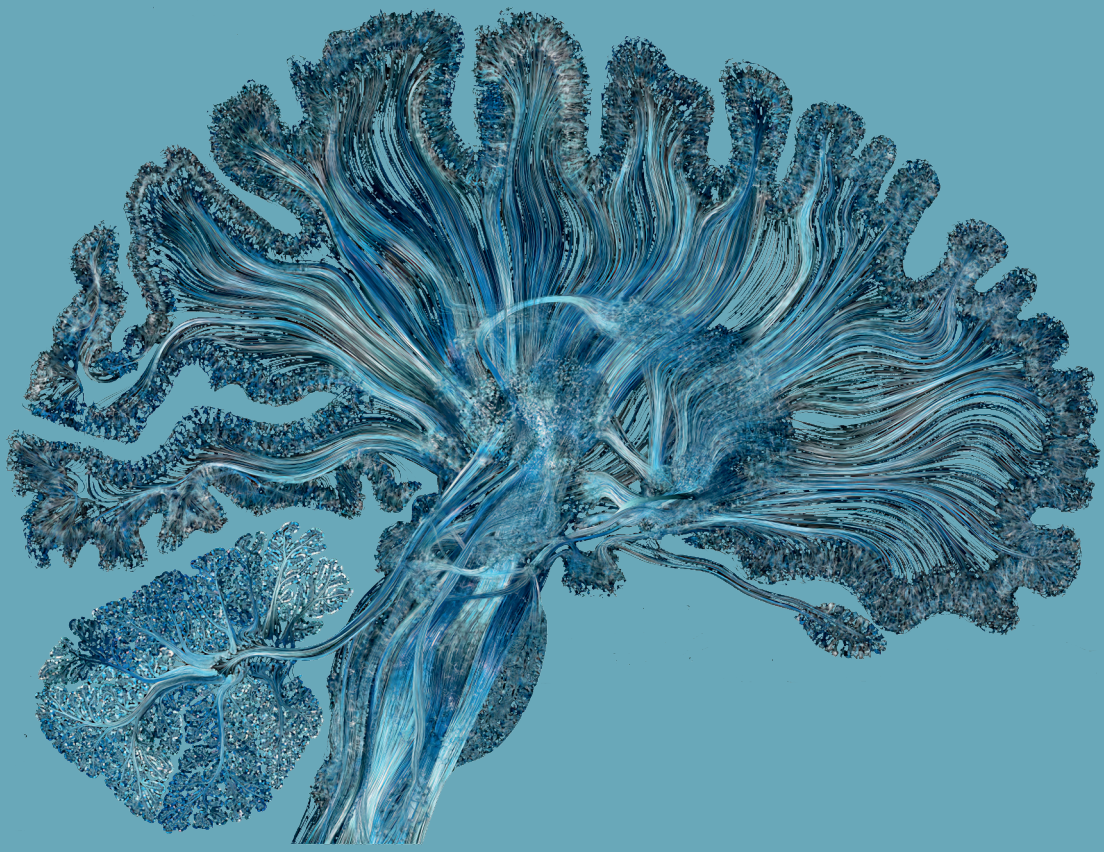
Supplementary Table 1. Adverse events during the double blind phase (weeks 0-12).

	Placebo	Botulinum toxin A
Type AE	3	
Muscle weakness	4	2
Ptosis	1	2
Rash	11	0
Pain at injection side	1	11
Oedema	10	2
Haematoma	1	8
Unknown AE	31	3
Total		28

59 adverse events, in 52 patients (placebo n =27, botulinum toxin A n = 25)



Chapter 5

Behavioural intervention in medication overuse headache: a double-blind, randomized controlled trial

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Submitted

Abstract

Objective To assess efficacy of behavioural intervention in Medication Overuse Headache (MOH) with underlying migraine.

Methods In this concealed, double-blind, randomised controlled trial in MOH patients with underlying migraine we compared the effect of maximal versus minimal behavioural intervention by a headache nurse, during withdrawal therapy at the outpatient Headache Clinic of the Leiden University Medical Center. Maximal intervention consisted of an intensive contact schedule, comprising of education, motivational interviewing and value-based activity planning during the 12 weeks of acute withdrawal. Minimal intervention consisted of one short contact only. Patients were unaware of the existence of these treatment arms, as the trial was concealed in another trial investigating the added value of botulinum toxin A to withdrawal therapy. Endpoints were successful withdrawal and monthly days of acute medication use after the withdrawal period.

Results We enrolled 179 patients (90 maximal intervention; 89 minimal intervention). At week 12, most patients achieved withdrawal in both groups (82/90 (93%) maximal intervention versus 75/89 (86%) minimal intervention, OR 2.44 (95%CI 0.83;7.23), p=0.107). At week 24, patients in the maximal intervention group had fewer acute medication days per month (mean difference -2.23, 95%CI: -3.76;-0.70, p=0.005). This difference receded over time.

Conclusion Intensive behavioural intervention by a headache nurse during withdrawal therapy for MOH patients is beneficial to reduce acute medication use during and shortly after the intervention, but extension of guidance seems warranted for a prolonged effect. A concealed study design may also be useful to investigate non-pharmacological therapies in other central nervous system disorders.

Trial register identifier www.trialregister.nl; NTR3440

Introduction

To reduce the burden of chronic disorders, many non-pharmacological interventions, such as behavioral therapy, lifestyle intervention and mindfulness are being studied and suggested to be effective.[1–3] Similarly, in headache disorders psychological treatment seems beneficial, although recommendations on these therapies are hampered due to the quality of available research.[3] A major concern about research in this field is the risk of bias by awareness of the received treatment, as it is difficult to perform blinded trials due to the nature of the intervention.[3] As such, evidence is mainly based on observational or non-blinded randomized controlled trials. Therefore, it remains difficult to distinguish the specific effect of therapy itself from that of other factors, such as underlying expectations and receiving attention,[4] which is especially important in trials on various disorders of the central nervous system.[5]

Implementation of behavioral interventions might be particularly relevant in care of headache patients with medication overuse headache (MOH). Medication overuse, the use of acute headache medication on 10 or more days per month[6], aggravates and maintains chronic headache.[7,8] Epidemiological data suggest that up to 4% of the population overuse analgesics and other drugs for the treatment of pain conditions such as migraine, and about 1% of the general population in Europe, North America, and Asia suffers from Medication Overuse Headache (MOH).[9] Medication overuse is a major risk factor for transformation from episodic migraine to chronic migraine (CM) (i.e. headache on 15 or more days per month, of which at least 8 days fulfilling migraine criteria).[6,7,10] Withdrawal of the overused medication is an important step in medical care, with possibly added effect of preventive medication during the withdrawal process.[7,8,11] Overuse of pain medication has a strong biobehavioral component,[12] and withdrawal therapy in itself requires significant adjustments in behavior and lifestyle. As such, behavioral and educational interventions during withdrawal therapy are likely beneficial, but have only been studied in observational trials.[13,14] We report a concealed double-blinded randomized trial to study the efficacy of a behavioral intervention during acute medication withdrawal, with and without BTX, in MOH patients with underlying migraine using a new study design that ensures blinding.

Methods

Study design and patients

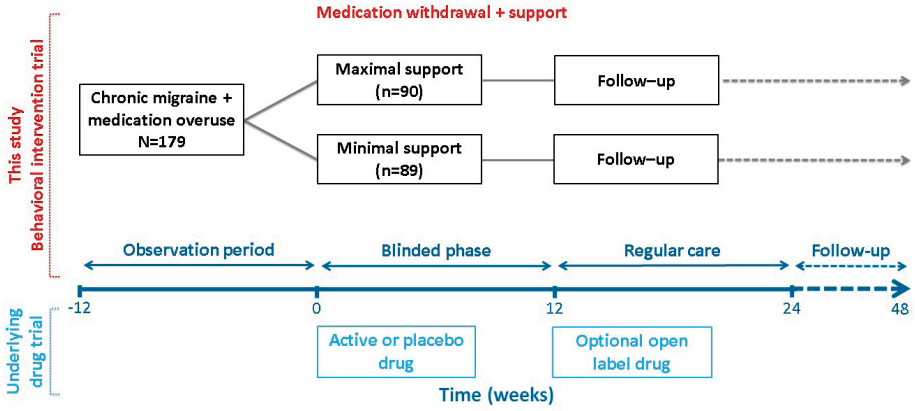
This was a concealed randomized, double-blind controlled clinical trial conducted at the Leiden University Medical Center, as part of the Chronification and Reversibility of Migraine study[15] (CHARM study[15]; www.trialregister.nl, NTR3440). Patients aged 18-65 years, diagnosed with MOH and CM according to the International Classification of Headache Disorders (ICHD-3) criteria[6] were enrolled between December 2012 and February 2015. Main exclusion criteria were: (i) other neurological disorders; (ii) other major comorbidity (chronic pain, psychiatric disorders, apart from depression and/or anxiety, cognitive, behavioral or oncologic disorders); (iii) regular use of ergots, opioids or barbiturates; (iv) abuse of illicit drugs in the past 12 months. The study was performed in accordance with the declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the local and national ethics committees.

Procedures and intervention

Patients started with a 4-week baseline assessment period, followed by the 12-week withdrawal period. Medication withdrawal was implemented according to the national guidelines and other withdrawal studies,[13,16–19] comprising abrupt cessation of any acute headache medication and no allowance for escape medication. In case of use of prophylactic drugs, these were tapered off. During this withdrawal period, patients were randomized to receive either maximal or minimal intervention by a headache nurse. A headache nurse is specifically educated for headache care with additional training on cognitive behavioral therapy and motivational interviewing, with at least some years of experience. Maximal intervention by a headache nurse consisted of a 30 minutes consult immediately after the neurologist's interview, examination and advice to withdraw, with at least three follow-up telephonic contacts (every 2-4 weeks) during withdrawal. These consults were used to reiterate the withdrawal advice, educate patients on the risks of medication overuse and expected course of the withdrawal period, and increase intrinsic motivation to initiate medication withdrawal using motivational interviewing techniques. Furthermore, an individualized plan of approach was developed, acknowledging the influence of chronic migraine and withdrawal on professional and social life and enhancing acceptance. Alternative behavioral strategies to cope with the untreated pain were discussed, and a value-based approach was used to establish activities

during the withdrawal period. Minimal intervention consisted of a single consult of ≤15 minutes and no offer of follow-up contacts by the nurse, mainly focusing on the reprise of the withdrawal advice and education on medication overuse. Patients of both treatment groups were provided with contact details to reach the hospital at any time if needed. Patients were unaware of the existence of these two treatment arms since the study was concealed within a drug trial, studying the added effect of Botulinum toxin A (BTX) to acute withdrawal therapy in a randomized placebo controlled manner (see Figure 1, reported in detail elsewhere).[15] In short, at the initiation of withdrawal, patients received either BTX (31 injections; 155 units) or placebo injections plus a low dose BTX in the forehead region to ensure blinding (24 injections with saline plus 7 injections with BTX 17.5 units). Subsequent to the 12-week withdrawal period, restricted use of acute medication was advised, and prophylactic treatment was initiated if necessary. In both treatment groups, behavioral intervention by a headache nurse was not continued after the 12-week period but regular care was provided by the treating physician. Patients who remained to have CM after successful withdrawal were offered to receive one treatment with open-label BTX. There were no differences between groups of patients treated with BTX and placebo on any of the outcome measurements in both the double blind phase (after 12 weeks) or long term, open-label phase (after 24, 36, 48 weeks).[15] Study follow-up visits were planned after 12, 24 and 48 weeks. Patients kept 4-weeks diaries with daily registration of headache characteristics and use of acute headache medication during the baseline assessment period and at weeks 9-12, 21-24, 33-36 and 45-48.

Figure 1. Study design



Blinded phase (weeks 0 - 12): Medication withdrawal therapy plus maximal or minimal intervention, randomized by a centralized schedule using a design with blocks of four to eight patients, stratified for gender and treatment allocation in the drug trial. Hence, in both groups, half of the patients received active drug Botulinum toxin A (BTA) and half of the patients received placebo drug (saline + low dose BTA).[15]

Regular care (weeks 12 - 48): Advice to restrict use of acute medication (on ≤ 4-8 days per month) to prevent relapse into medication overuse, and, if necessary, initiation of prophylactic treatment. Patients who succeeded to withdraw, but still suffered from chronic migraine, could receive open label drug (BTA) as prophylactic treatment. Regular care typically comprises 4-8 outpatient contacts per year by the treating physician.

Randomization and masking of intervention

According to a centralized randomization schedule, patients were randomized 1:1 to receive either maximal or minimal behavioral intervention by a headache nurse, using blocks of four to eight patients, stratified for sex and the allocated treatment in the drug trial, ensuring that half of the patients in each group received BTA. Patients were unaware of the existence of the two treatment arms, as this study was concealed within this drug trial studying BTA, guaranteeing blinding of patients. As both maximal and minimal behavioral intervention are interventions without any risk of harm, both fulfilling standard care for medication withdrawal, and patients were informed that the data of the CHARM study was supposed to be analyzed for a variety of research questions, this construction was approved by the local and national ethical committees. Treating physicians and observers were blinded to treatment allocation and did not have access to the randomization schedule.

Outcome measures and analysis

The predefined outcome measures were successful withdrawal after 12 weeks and monthly days with use of acute headache medication after the withdrawal period. Successful withdrawal was defined as intake of acute medication on ≤2 days/month. Change in monthly days of acute medication use was assessed at timepoints 12, 24, 36 and 48 weeks. Since the intervention aims to enhance medication withdrawal and focusses on medication-related behavior, all outcomes of this study were medication-use related. A previous retrospective study by our group indicated that intervention by a headache nurse increases withdrawal adherence, but does not directly influences migraine attack frequency.[13] Descriptives are reported as means ± standard deviations or numbers with proportions, and differences between groups are shown with 95% confidence intervals. Multivariate regression models were fit adjusting for age, gender, baseline medication days, drug treatment allocation, depression and anxiety (based on the Hospital Anxiety and Depression Scale (HADS))[20]. For the repeated measures model unstructured covariance matrixes were used. Analyses were (modified) intention-to-treat, including patients who provided at least one outcome measurement, performed in SPSS 23.0 (SPSS Inc., Chicago, Ill).

Data availability

Anonymized data can be made available upon request to the corresponding author.

Results

Of 179 MOH patients, 90 were allocated to receive maximal intensive behavioral intervention and 89 patients to minimal intervention during the first 12 weeks of withdrawal therapy. Patients in the two treatment arms did not differ in sex, age, headache characteristics, medication use, and psychiatric comorbidity (Table 1). Follow-up was complete for 98% (n=175) after 12 weeks and 82% (n=147) after 48 weeks, with similar numbers of dropouts in both groups (Figure 2). Most patients (88%) were accurately treated according to the protocol of the allocated treatment (maximal intervention n=82 (91%), minimal intervention n=75 (84%)).

Table 1. Baseline demographic and clinical characteristics

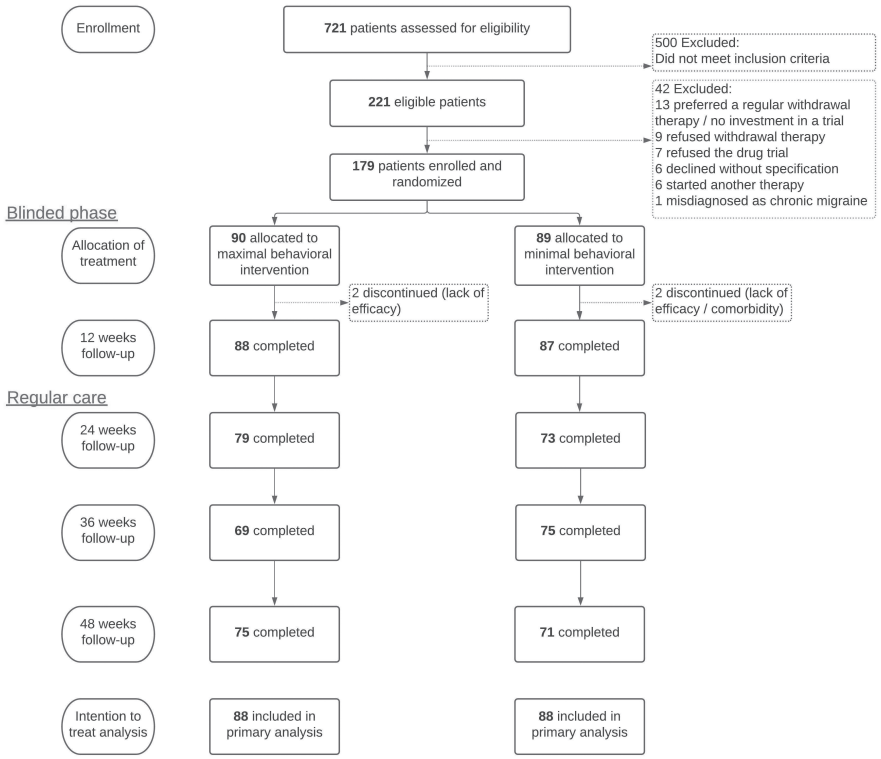
	Maximal intervention (n=90)	Minimal intervention (n=89)
Gender, female	67 (74.4%)	69 (77.5%)
Age (years)	45.3 ± 10.9	45.1 ± 10.7
Monthly Headache days (MHD)	21.3 ± 4.6	21.5 ± 4.9
Monthly Migraine days (MMD)	15.3 ± 5.5	14.9 ± 5.5
Duration of migraine (years)	27.3 ± 13.0	27.9 ± 12.9
HIT 6 score [a]	65.3 ± 4.4	64.7 ± 4.1
Treatment within drug trial		
Botulinum toxin A	45 (50%)	45 (50.6%)
Placebo	45 (50%)	44 (49.4%)
Monthly days with acute headache medication	16.7 ± 5.6	16.2 ± 5.6
Type of overuse		
Triptans	18 (20.0%)	15 (16.9%)
Simple analgesics [b]	2 (2.2%)	5 (5.6%)
Combination of acute medication [c]	70 (77.8%)	69 (77.5%)
Prophylaxis [d]		
Current use	29 (32.2%)	36 (40.4%)
History of use [e]	84 (93.3%)	79 (88.8%)
Number of used prophylactics	2.5 ± 1.8	2.2 ± 1.8
Anxiety, % present (HADS-A ≥ 8)	31 (34.4%)	24 (27.0%)
Anxiety, mean HADS-A score	6.4 ± 4.0	6.0 ± 3.7
Depression, % present (HADS-D ≥ 8)	35 (38.9%)	31 (34.8%)
Depression, mean HADS-D score	6.5 ± 4.4	6.3 ± 3.9

Values are absolute numbers with corresponding %, or means ± SD

[a] N maximal intervention = 85, N minimal intervention= 89; [b] Simple analgesics: paracetamol, NSAID's; [c] Combined medication: combination of triptan, simple analgesics or combination drugs such as paracetamol and caffeine;

[d] Commonly used prophylaxis for migraine; [e] History of use: current or past use of at least one type of prophylaxis.

Figure 2. COHORT flow diagram

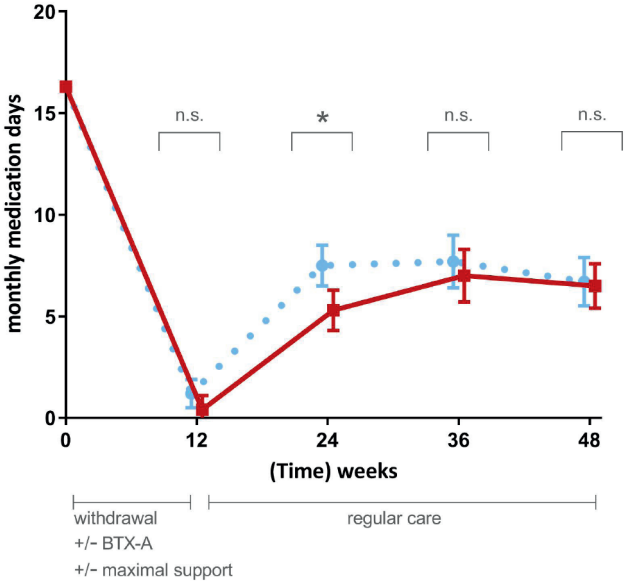


Patient flow including the double blind randimized phase (weeks 0 – 12) and regular care follow up (weeks 24, 36, 48). Not all numbers add up, as some patients decided to continue participation after one missed visit.

Successful withdrawal, defined as ≤ 2 days/month escape use of acute headache medication in the first 12 weeks of the study, was achieved in 82 (93%) of patients in the maximal intervention group, and 75 (86%) of those who received minimal intervention. The odds ratio for success was 2.44 (95%CI: 0.83 to 7.23, p=0.107) for maximal versus minimal intervention. The days with use of acute headache medication in this period was low in both groups, with no difference between groups (mean difference -0.76, 95%CI: -0.22 to 1.74, p=0.128) (Figure 3).

Patients in the maximal intervention group did have fewer monthly days with use of acute headache medication after 24 weeks (5.26 versus 7.49; mean difference: -2.23, 95%CI: -3.76 to -0.70, p=0.005) (Figure 3). The difference between the two groups disappeared over time (mean differences after 36 weeks: -0.77, 95%CI: -2.66 to 1.12, p=0.423 and after 48 weeks: -0.20, 95%CI: -1.90 to 1.49, p=0.812) (Figure 3).

Figure 3. Effect of maximal versus minimal behavioural intervention (for the first period of 12 weeks) on acute medication use during and after the withdrawal period.



In the first 12 weeks all patients had to withdraw from acute headache medication and were double-blinded randomized for BTX and placebo. A concealed double-blinded randomization was performed for maximal and minimal behavioral intervention in this 12 weeks period. After these 12 weeks, patients that remained CM were offered open label BTX, otherwise usual care was provided by the treating physician without further behavioral intervention of the headache nurse. A detailed explanation of maximal and minimal intervention is in the method section.

Depicted are adjusted means with standard errors derived from the linear mixed model analysis.
Monthly Medication days = Monthly days with use of acute headache medication
BTX = botulinum toxin A
n.s.: non-significant; *: p <0,01

Discussion

This double-blind randomized controlled trial suggests benefit of behavioral intervention for withdrawal therapy in medication overuse headache (MOH) with reduced use of headache medication in the period after acute withdrawal. As the behavioral therapy was only provided during the withdrawal period itself (first 12 weeks), this effect gradually diminished during the long term follow up period of almost one year.

Hitherto, evidence for non-pharmacological interventions in the treatment of MOH is mainly based on observational studies.[13,14,21] For headache disorders in general, contradictory conclusions have been drawn on existing data. A recent Cochrane review indicated a lack of good-quality research on the efficacy of psychological interventions in migraine. A potentially higher response rate was suggested (risk rate for response 2.21, 95% CI 1.63-2.98), but based on trials with a high risk of bias.[22] Meta-analyses using broader inclusion criteria, for instance a population with both migraine and tension-type headache, suggest efficacy of psychological treatment.[3,23] Nevertheless, common ground in these studies is an urgency for high quality clinical trials, minimizing risk of bias.

Our study has the big advantage that it conceals the behavioral intervention within another trial, which is a new and unique design in headache trials and provided an adequately blinded control group. A potential risk of unblinding can be social interactions among trial patients, which may affect clinical and biological variables.[5] Due to the intensive versus minimal behavioral intervention principle, the two treatment arms were unlikely to be revealed by incidental contact between patients. Furthermore, the patients were not even aware of the existence of this part of the study. Therefore, blinding was guaranteed, reducing bias by psychological mechanisms such as expectations and classical conditioning.[4]

Still, the concurrent drug trial might have influenced the results. The rates of successful withdrawal in our study are relatively high in both our groups (86 and 93%) as previous studies showed rates of 62-85%.[13,14,19,24] As patients would only receive subsequent open label BTA in case of successful withdrawal, the drug trial may have contributed to the high withdrawal success rates in both groups during the first 12 weeks, narrowing the differences between groups. This likely explains that the groups after 12 weeks did not differ. However, the main problem with MOH is relapse into overuse of acute medication. Therefore, our aim was to restrict patients on acute medication after the acute withdrawal period. Our study clearly shows benefit of behavioral intervention with reduced use of headache medication in the period after the acute withdrawal period. As the behavioral therapy was only provided during the withdrawal period itself (first 12 weeks), this effect gradually diminished during the long term follow up period of almost one year, which we also expected as only limited care was provided by the treating physician with only once per three months a visit at our headache clinic.

During the behavioral intervention, the consults were not only used to educate on medication overuse and to increase intrinsic motivation to initiate medication withdrawal using motivational interviewing techniques, but also aimed to enhance acknowledgement and acceptance of the influence of migraine on the various aspects of life in general. Furthermore, alternative behavioral strategies to cope with the untreated pain were discussed, and a value-based approach was introduced to establish activities. We hypothesize that these latter aspects of the consults induced the effect of the intervention beyond the withdrawal therapy itself, with significant lowering on use of headache medication after 24 weeks. As we stopped the behavioral intervention with the nurse after 12 weeks, this explains the diminishing effect during the long term follow up of 1 year. Underlying biological factors and comorbidities such as depressive symptoms and anxiety, e.g. factors that may influence relapse into chronification of migraine, might have played an important role for this diminishing effect as well.[7,10,28] In the first year after withdrawal therapy, high rates of relapse into medication overuse up to 40% are reported,[29] posing a challenge to maintain the effect of withdrawal therapy. Prolonged intensified intervention by a headache nurse after withdrawal might reduce relapse rates.[30,31]

Our findings in this randomized and blinded trial affirm previous results on benefit of multidisciplinary care during withdrawal in observational studies. Our previous retrospective study on behavioral intervention by a headache nurse showed an increased rate of successful withdrawal as well, but did not comprise a long term follow-up.[13] A Danish observational study suggested that multidisciplinary approaches during withdrawal therapy are effective. In that study, a structured schedule with both group and individual therapy by a nurse, psychologist and physiotherapist, was compared and found not to be superior to a structured schedule with a headache nurse alone. Interpretation from this comparison has to be done with caution though, since both groups also differed in withdrawal strategy.[14] In primary care, a cluster-randomized controlled trial amongst general practitioner practices showed effectiveness of an intervention in MOH patients. Feedback on their dependency behavior resulted in reduced medication use.[27] This study suggests that behavioral interventions can be implemented in GP practices as well.

Our unique large concealed double-blind randomized controlled trial study suggests benefit of implementation of a behavioral intervention for withdrawal therapy in medication overuse headache (MOH) with reduced use of headache medication in the period after withdrawal. Future studies may aim at investigating long-term behavioral intervention which can be provided by a trained nurse. The principles of a concealed study design can also be useful in the research field of behavioral interventions in other central nerve system disorders.

Acknowledgements
We thank all patients for their time and effort. We thank Mrs. J. Trouerbach-Kraan, headache nurse, for supporting patients during withdrawal.

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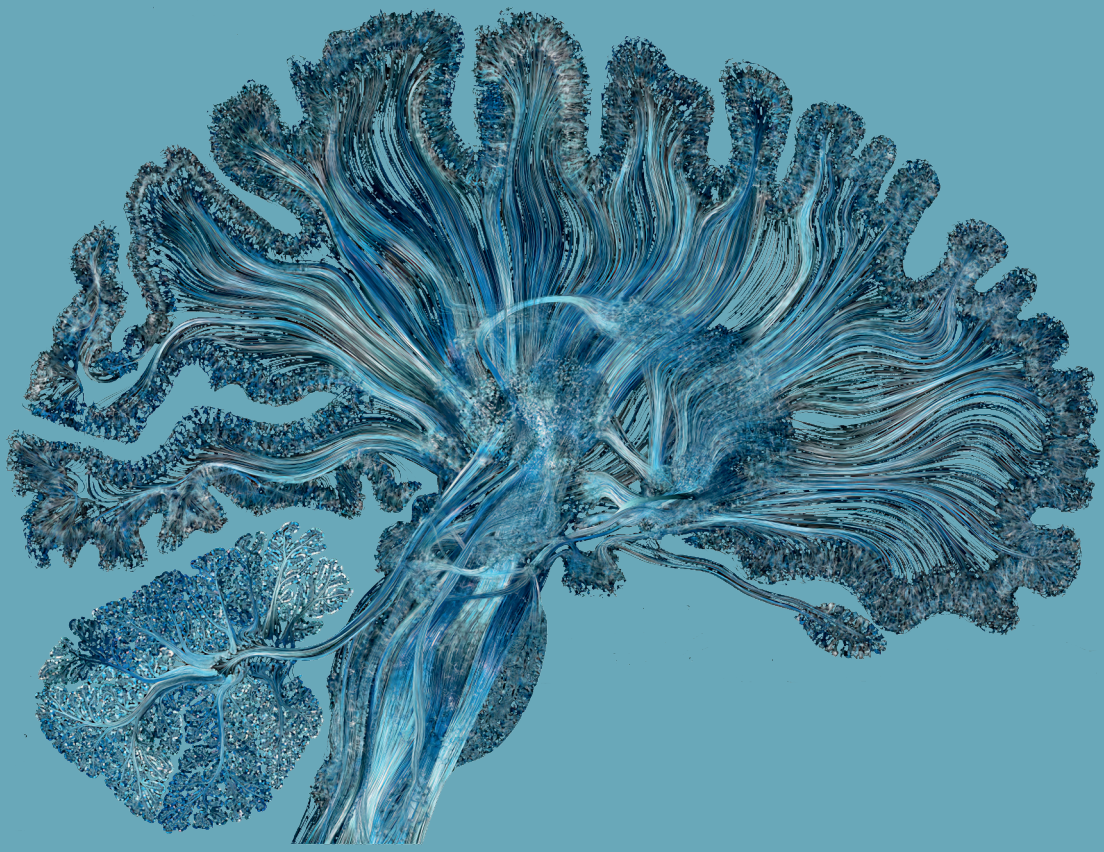

Chapter 6

Cutaneous allodynia as predictor for treatment response in chronic migraine

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Submitted

Abstract

Objective Central sensitisation is an important mechanism in migraine chronification. It is presumed to occur in second and third order neurons sequentially, resulting in an analogous spatial distribution of cutaneous allodynia with cephalic and extracephalic symptoms. We investigated whether allodynia, and its subtypes based on spatial distribution and type of stimulus, predict response to treatment in chronic migraine patients.

Methods This study was conducted as part of the CHARM study (NTR3440), a randomized, double-blind, placebo-controlled trial in chronic migraine patients with medication overuse to assess whether therapy with Botulinum toxin A enhances efficacy of withdrawal. We included 173 patients, aged 18-65 years. The presence of cutaneous allodynia at baseline was established with the Allodynia Symptom Checklist, and subdivided in i) spatial distribution and ii) type of stimulus. Primary endpoint was reversion from chronic to episodic migraine.

Results Of all patients, 129 (74.6%) reported cutaneous allodynia. Absence of allodynia was predictive for good outcome compared to presence of allodynia, as the odds ratio of reversion from chronic to episodic migraine was 2.45 (95%CI: 1.03-5.84, p=0.042). The predictive value was more pronounced when subdivided for spatial distribution, with odds ratios of 4.16 (95%CI: 1.21-14.30, p=0.003) and 7.32 (95%CI: 1.98- 27.11, p=0.024) for participants without allodynia versus cephalic and extracephalic allodynia respectively. Mechanical allodynia, but not thermal allodynia, was associated with outcome. Similar predictive associations were found for other migraine specific outcome measures.

Interpretation Cutaneous allodynia, an important marker for central sensitization, has predictive value for treatment response in chronic migraine.

Introduction

Migraine is a common, multifactorial brain disorder, characterized by recurrent headache attacks with nausea, vomiting and hypersensitivity to movement, light and sound, and sometimes with aura symptoms. Most patients have the episodic form, with a median attack frequency of 1-2 per month [1]. However, every year 3% of these patients convert from less-frequent episodic migraine to high-frequent chronic migraine (≥ 15 headache days per month, of which ≥ 8 migraine days), a process called migraine chronification [2,3]. Frequent use of acute headache medication is a major risk factor for migraine chronification, and as such, the majority of chronic migraine patients have medication overuse. Discontinuation of the overused medication is an important therapy, which is effective in the majority, but not of all patients [3–5].
Migraine chronification is hypothesised to be a decreased threshold problem, in which patients have increased susceptibility for migraine attacks. This increased susceptibility may be a consequence of central sensitisation, a state of ongoing excitability and hyper-responsiveness of central regions of the brain [3,6–8]. During the headache phase of a migraine attack, the trigeminal afferents surrounding meningeal blood vessel become activated [6,9]. Recurrent activation of these trigeminal afferents induces sensitisation of the trigeminal nucleus caudalis. Due to convergence of sensory input from both the dura and the periorbital skin, sensitisation of the trigeminal nucleus caudalis results into referred ipsilateral cephalic cutaneous allodynia, i.e. the perception of pain due to a normally non-painful stimulus. Subsequently, thalamic neurons become sensitised, leading to referred extended cephalic and extracephalic cutaneous allodynia, as all sensory input from the skin converges in the thalamus [6–8].

Thus, cutaneous allodynia, and especially the spatial distribution of cutaneous allodynia, may be used as a clinical marker of the presumably sequential central sensitisation processes. Cutaneous allodynia can be perceived upon thermal or mechanical stimuli. Hence, it is experienced during daily activities, such as combing hear, exposure to cold, wearing tight clothes, and resting the head on a pillow [10–13]. Cutaneous allodynia is associated with a higher prevalence of depression in migraine patients [14] and is an (independent) predictor for migraine chronification [10]. Preclinical and clinical studies suggests that central sensitization of the trigeminal nociceptive system is a reversible phenomenon

in medication overuse [4,15,16]. However, cutaneous allodynia as predictor for treatment response in chronic migraine patients has not been studied. Moreover, spatial distribution of cutaneous allodynia has never been studied in the light of migraine chronification and its reversibility or as predictor of response. Therefore, the aim of this study was to investigate the association between cutaneous allodynia and its subtypes (based on spatial distribution and type of stimulus) to response to treatment in patients with chronic migraine with medication overuse.

Material and methods

Study design and population

This study was conducted as part of the Chronification and reversibility of migraine (CHARM) study at the outpatient headache clinic of Leiden University Medical Centre, the Netherlands, which is described in detail elsewhere [17]. Briefly, consecutive patients aged 18-65 years, diagnosed with chronic migraine and medication overuse according to the formerly International Classification of Headache Disorders (ICHD) 3-beta criteria, but also fulfilling ICHD 3 criteria [2], who provided written informed consent, were enrolled. Exclusion criteria were: (i) other primary headache or neurological disorders; (ii) other chronic pain disorders with medium to high pain intensity or requiring pain medication; (iii) major psychiatric disorders, other than depression; (iv) major cognitive, behavioural or oncologic disorders; (v) contraindications for treatment, or inability to adhere to the study protocol (vi) (planned) pregnancy or breastfeeding (vii) use of ergots, opioids or barbiturates; (viii) abuse of drugs in the past 12 months.

All participants started with a 4-week baseline-assessment period, followed by a 12-week withdrawal period, consisting of instruction to withdraw abruptly from all acute anti-headache medications and caffeine ('advice-only'). Prophylactic treatment was tapered off and rescue medication was not allowed. Immediately prior to withdrawal, botulinum toxin A or placebo injections were administered in a 1:1 randomised, double-blind manner [17] .

The study was performed in accordance with the declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the local and national ethics committees.

Measurements and outcomes

*A*ll participants prospectively kept a 4-week diary, with daily registration of headache characteristics, accompanying symptoms and use of acute headache medication, during the baseline assessment period and the post treatment period (weeks 9-12) In addition, questionnaires were filled out at baseline regarding allodynia, depression and anxiety. Allodynia was questioned by the previously used and published Dutch Allodynia Symptom Checklist (ASC) [10], which is analogous to the validated English ASC [11,18]. The ASC comprises 12 symptoms of cutaneous allodynia, namely pain or unpleasant sensation on the skin during: i) combing the hair; ii) wearing a pony tail; iii) shaving the face; iv) wearing eyeglasses; v) wearing contact lenses; vi) wearing earrings; vii) wearing a necklace; viii) wearing tight cloths; ix) taking a shower; x) resting the head on a pillow; xi) exposure to heat and xii) exposure to cold. Allodynia was scored as present when at least two of these symptoms occurred [10,11]. To distinguish subtypes of allodynia, the 12 items were recoded based on i) spatial distribution and ii) type of stimulus. Based on the spatial distribution of referred hypersensitivity, allodynia was scored as cephalic allodynia (presence of allodynia whilst combing the hair, wearing a pony tail, shaving the face, wearing eyeglasses, wearing contact lenses, wearing earrings, taking a shower, resting the head on a pillow, exposure to heat, or exposure to cold) or extracephalic allodynia (presence of allodynia whilst wearing a necklace or wearing tight cloths). In case of both cephalic and extracephalic allodynia, the complaints were categorised as extracephalic allodynia, as extracephalic (thalamic, third order sensitisation) can be considered as more severe or advanced than cephalic (trigeminal nucleus caudalis, second order sensitisation). Based on previously performed factor analysis [10], the items were recoded based on type of stimulus as thermal (presence of allodynia whilst exposure to heat, exposure to cold or resting the head on a pillow), mechanical (presence of allodynia whilst combing the hair, wearing a pony tail, shaving the face, wearing eyeglasses, wearing contact lenses, wearing earrings, wearing a necklace, wearing tight cloths or taking a shower) or both thermal and mechanical. For the recoding into subtypes, 'no allodynia' was defined as absence of any allodynia symptoms. Hence, presence of cephalic, extracephalic, mechanical or thermal was scored as positive if one or more symptoms were reported, and was thus less strict compared with the overall allodynia definition, as the items per subgroup are more limited. Anxiety and depression were scored as present using a cut-off

score of at least eight on the subscales of the Hospital Anxiety and Depression scale (HADS-A and HADS-D) [19].

Primary outcome was reversion from chronic to episodic migraine (i.e. headache no longer fulfils criteria of chronic migraine) from baseline to the last 4 weeks of the treatment period (weeks 9-12). Secondary outcomes were i) ≥ 50% response in migraine days, i.e. reduction in monthly migraine days (MMD) of 50% or more; ii) reduction in number of monthly migraine days (MMD); iii) reduction in number of monthly headache days (MHD). A migraine day was defined as a day fulfilling criteria for migraine with or without aura, or treated with migraine specific acute medication [2]. A headache days was defined as a day with migraine or non-migraine headache of any duration.

Data analysis and statistics

Descriptives are reported as means ± standard deviations or numbers with proportions, and differences between groups were tested with independent sample t-tests and χ^2 tests.

Multivariate regression models were used to test the association between presence of (subtypes of) cutaneous allodynia and reversion from chronic to episodic migraine (primary endpoint), a 50% or greater reduction in migraine days, reduction in number of MMD and reduction in number of MHD (secondary endpoints). Gender, age, depression and anxiety were included in the model. Medication intake and migraine or headache days at baseline were added to the model in separate supplementary analyses, since these factors are likely related to cutaneous allodynia and the outcomes, but the magnitude and direction of these influences are not yet established. Treatment with botulinum toxin A or placebo was not included in the models, as this factor was extensively tested previously, and botulinum toxin A did not significantly improve any of the outcome measures [17].

Primary analysis included all patients providing baseline data (n=173). Missing data on migraine days or headache days during follow-up, defined as less than 14 completed days on a headache diary, were handled using multiple imputation. In case of 14-27 completed days, the existing data were extrapolated to a 28 days period. In all analyses, two-sided p values <0.05 were considered statistically significant. Analyses were performed in SPSS Statistics 23.0 (SPSS Inc., ICM, USA).

Results

The study flow is shown in figure 1. Of 179 participants in the CHARM study, 173 provided baseline allodynia data and were included in this current study. Of these participants, 74.6% experienced cutaneous allodynia. Participants with cutaneous allodynia were mainly female and reported more often current anxiety symptomology, but did not differ on age, number of monthly migraine or headache days, age of onset, use of acute or prophylactic treatment, or current depressive symptomatology (Table 1). Of all participants, 27 (16%) did not experience any allodynia symptom at all, 79 (46%) experienced at least one cephalic allodynia symptom, and 67 (38%) experienced at least one extracephalic allodynia symptom. Almost all participants who experienced extracephalic symptoms, also experienced cephalic symptoms (65 (97%)). Divided into type of stimulus, 16 participants (9%) experienced only thermal allodynia symptoms, 16 (9%) only mechanical allodynia symptoms, and 114 (66%) both thermal and mechanical allodynia symptoms.

Figure 1. Flowchart

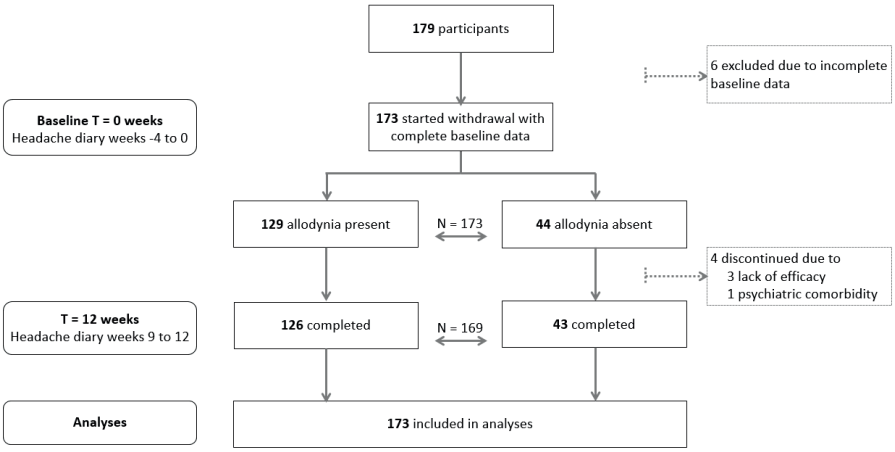


Table 1. Baseline characteristics

Variable	Allodynia (n=129)	No allodynia (n=44)	P
Female	110 (85.3%)	22 (50.0%)	**<0.001**
Age (years)	44.3 ± 10.5	47.3 ± 11.2	0.120
Age at onset	17.4 ± 9.5	17.7 ± 9.2	0.858
Monthly Migraine days (MMD)	14.9 ± 5.3	15.9 ± 6.1	0.311
Monthly Headache days (MHD)	21.5 ± 4.7	21.1 ± 5.0	0.661
Days with use of acute anti-headache medication[a]	16.1 ± 5.4	17.1 ± 6.0	0.306
Days with use of triptans	11.1 ± 5.7	12.0 ± 7.5	0.391
Prophylactic treatment [b]			
Current use	50 (38.8%)	13 (29.5%)	0.273
History of use	115 (89.1%)	43 (97.7%)	0.081
Depression, % present (HADS-D ≥ 8)	51 (39.5%)	15 (34.1%)	0.521
Anxiety, % present (HADS-A ≥ 8)	50 (38.8%)	5 (11.4%)	**0.001**

Values are means ± SD or n (%)

[a] Any anti-headache medication: Simple analgesics (paracetamol, NSAID's) triptans and/or combination drugs.

[b] Commonly used prophylaxis for migraine, such as beta-blockers, valproic acid or topiramate.

The absence of cutaneous allodynia was predictive for good outcome after 12 weeks. For the primary endpoint, the odds for reversion from chronic migraine to episodic migraine was 2.5 times higher for participants without allodynia compared to participants with allodynia (OR 2.45; 95%CI 1.03 to 5.84; p=0.042, Table 2 and Fig 2), as 75.0% of participants without allodynia versus 57.4% of participants with allodynia reverted to episodic migraine. The predictive value was more pronounced when allodynia was specified according to spatial distribution, with a 4 and 7 times higher odds for reversion to episodic migraine for participants without allodynia compared to participants with cephalic allodynia and extracephalic allodynia respectively (no allodynia versus cephalic allodynia OR 4.16; 95%CI 1.21 to 14.30; p = 0.003, no allodynia versus extracephalic allodynia OR 7.32; 85%CI 1.98 to 27.11, p = 0.024). When subdivided by type of stimulus, both the combination of mechanical plus thermal allodynia and mechanical allodynia alone were predictive for reversion to episodic migraine, whereas thermal allodynia alone was not predictive (Table 2 and Fig 2).

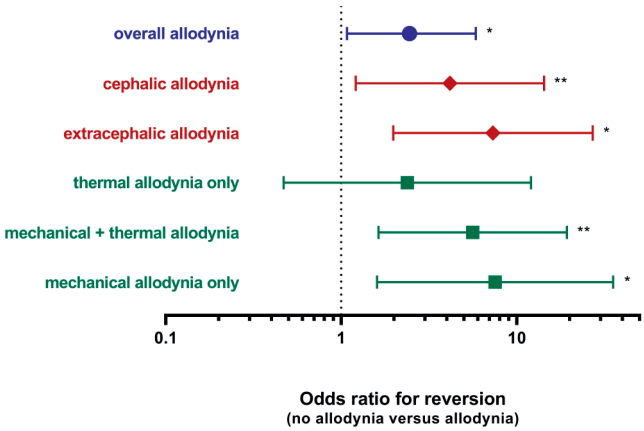
Table 2. Allodynia as a predictor for the odds to revert from chronic migraine to episodic migraine.

	Overall allodynia			*Spatial distribution*			*Type of stimulus*		
	Multivariate OR (95% CI)		*p*	Multivariate OR (95% CI)		*p*	Multivariate OR (95% CI)		*p*
No allodynia *versus* allodynia	**2.45**	**(1.03 ; 5.84)**	**0.042**	.	.	.	.	.	.
No allodynia									
versus cephalic allodynia	.	.	.	**4.16**	**(1.21; 14.30)**	**0.003**	.	.	.
versus extracephalic allodynia	.	.	.	**7.32**	**(1.98 ; 27.11)**	**0.024**	.	.	.
No allodynia									
versus thermal allodynia only	.	.	.	.	.	.	2.38	(0.47 ; 12.05)	0.297
versus mechanical + thermal allodynia	.	.	.	.	.	.	**5.61**	**(1.63 ; 19.30)**	**0.006**
versus mechanical allodynia only	.	.	.	.	.	.	**7.52**	**(1.60 ; 35.39)**	**0.011**

* Adjusted for: gender, age, depression and anxiety.

Figure 2. Odds ratio for reversion from chronic to episodic migraine of no allodynia compared to different subtypes of allodynia.

* p < 0.05; ** p < 0.01



Cutaneous allodynia and the subtypes based on spatial distribution and type of stimulus were also predictive for the migraine specific secondary outcome measures. Participants without allodynia had a more than 2 times higher odds on ≥50% response (defined as ≥50% reduction in monthly migraine days) (OR 2.28; 95%CI 1.01 to 5.16; p = 0.048, Supplementary Table 1). The absence of allodynia was also predictive for the absolute reduction in monthly migraine days (MMD), with a reduction of 9.4 versus 5.9 MMD in participants without allodynia versus participants with allodynia (difference 3.49, 95% CI 0.95 to 6.02, p = 0.007). Similar to the primary outcome, the predictive value was more pronounced when subdivided by spatial distribution, and mainly related to mechanical allodynia, not thermal allodynia (mean differences in Table 3).
However, neither cutaneous allodynia in general, nor the subtypes of cutaneous allodynia were predictive for reduction in monthly headache days (MHD) (Table 3). All the associations on primary and secondary outcomes did not alter after adjusting for medication days and migraine (MMD) or headache days (MHD) at baseline in supplementary analyses (data not shown).

Table 3. Allodynia as a predictor for reduction in monthly migraine days (MMD) and monthly headache days (MHD).

	Overall allodynia			*Spatial distribution*			*Type of stimulus*		
	Difference (95% CI)		*p*	Difference (95% CI)		*p*	Difference (95% CI)		*p*
Reduction in MMD									
Allodynia (no allodynia vs allodynia)	**3.49**	**(0.95 ; 6.02)**	**0.007**	.	.	.	.	.	.
No allodynia									
versus cephalic allodynia	.	.	.	**3.35**	**(0.24 ; 6.45)**	**0.035**	.	.	.
versus extracephalic allodynia	.	.	.	**4.96**	**(1.60 ; 8.32)**	**0.004**	.	.	.
	.	.	.				.	.	.
No allodynia									
versus thermal allodynia only	.	.	.	.	.	.	2.02	(-2.19 ; 6.23)	0.348
versus mechanical + thermal allodynia	.	.	.	.	.	.	**4.17**	**(1.06 ; 7.27)**	**0.009**
versus mechanical allodynia only	.	.	.	.	.	.	**5.22**	**(0.88 ; 9.55)**	**0.018**
Reduction in MHD									
Allodynia (no allodynia vs allodynia)	1.30	(-1.00 ; 3.59)	0.267						
No allodynia									
versus cephalic allodynia				2.09	(-0.74 ; 4.91)	0.148			
versus extracephalic allodynia				2.62	(-0.43 ; 5.66)	0.093			
No allodynia									
versus thermal allodynia only							2.57	(-1.24 ; 6.38)	0.187
versus mechanical + thermal allodynia							2.15	(-0.67 ; 4.97)	0.135
versus mechanical allodynia only							2.61	(-1.32 ; 6.54)	0.192

* Adjusted for: gender, age, depression and anxiety.

Discussion

This study shows that the absence of cutaneous allodynia is predictive for a good outcome after withdrawal therapy in patients with chronic migraine with medication overuse. The predictive value was even more pronounced when comparing with extracephalic allodynia, which is indicative of trigeminothalamic involvement [6–8]. Our findings further suggest a migraine specific relationship because allodynia was only a strong predictor for migraine-related outcome measures.

These findings are relevant to clinical practice and current treatment concepts and expectations. Chronic migraine is a highly disabling migraine variant, in which the majority of patients overuse acute anti-headache medication [3,4,20]. Withdrawal of acute medication results into reversion to episodic migraine in the majority, but not of all, patients. Previous studies at predictors for response to withdrawal treatment in mixed populations of patients with migraine or tension type headache with medication overuse, mainly showed the underlying primary headache type as predictive factor [21,22]. Daily headache or daily use of medication was a predictor in univariate analysis [21,23], but did not predict outcome when adjusted for covariates [21]. Psychological factors have been indicated as predictor for response [24], but require extensive assessment. This is the first study to show cutaneous allodynia as a predictor of response in chronic migraine, using a simple validated diagnostic tool for clinical practice. The effect size is moderate when comparing absence of allodynia versus allodynia in general (cohen's d = 0.42), but increases to a moderate-large effect when considering spatial distribution, comparing no allodynia versus extracephalic allodynia (cohen's d = 0.65). Especially with the emergence of promising, but high-cost treatment with antibodies to CGRP or its receptor [25,26], identification of predictors for response to treatment is warranted. Various trials in chronic migraine demonstrated, partly in sub-analyses, that chronic migraine patients with medication overuse will be able to respond [27,28]. However, no predictors for response to monoclonal antibodies against CGRP or its receptor have yet been established [29]. It is of great interest to investigate whether allodynia provides a specific predictor to chronic migraine and withdrawal therapy, or relates to other treatments in chronic migraine (with and without medication overuse) as well. Sustained exposure to acute anti-headache medication in animal models causes allodynia and an increased sensitivity to cortical spreading depression. The associated increased

CGRP release may mediate central sensitisation, thus leading to allodynia [6,16,29–31] Therefore, we expect that allodynia may also be a predictor of response to CRGP(-receptor) monoclonal antibody treatment in chronic migraine.

The association between cutaneous allodynia, and its spatial distribution, and response to treatment may have additional value for current pathophysiological concepts on migraine chronification. The predictive value for failure on treatment was most pronounced for extracephalic allodynia, which is considered indicative for thalamic involvement [6–8]. Therefore, we hypothesize that especially thalamic involvement will be a predictor for unresponsiveness to treatment in chronic migraine patients. Until now, cutaneous allodynia has mainly been studied as a predictor of response to acute treatment with triptans or non-migraine specific acute pain medication, yielding contradictory results. Some studies suggest that patients are unresponsive to triptans once cutaneous allodynia has manifested [32,33], others suggest a preserved triptan response despite of cutaneous allodynia [34,35] although the distinction between ipsi- and contra-lateral cephalic and/or extracephalic allodynia is not always made. Nonetheless, this has led to the hypothesis that response to triptans may be indicative for different underlying sensitization mechanisms [7,8,34,36]. As triptans act both peripherally and post-synaptic on second order neurons, but not on third order neurons, we can hypothesize that triptan-response would cease upon thalamic involvement.

In our study, mechanical allodynia was associated with change in monthly migraine days, as opposed to thermal allodynia. This finding would suggest that mainly mechanoreceptors, such as the low threshold Aβ fibres and C-type mechanorecepters [13,36,37] may be involved in migraine chronification. Although thermal allodynia is present in migraineurs as well during attacks, and in lesser extent in between attacks [7,38], heat pain thresholds were not related to headache frequency [38], supporting our findings. This also fits with our conclusion that the predictive association was only present for migraine-related outcomes and not for headache days in general. In line with other studies, this suggests that central sensitization is more pronounced in migraine and not in other types of headaches [12]. Concordantly, a recent study investigating the ability to trigger cutaneous allodynia after nitroglycerine provocation, did not find an association between headache frequency and the occurrence of allodynia after nitroglycerine [34], whereas migraine frequency and occurrence of (spontaneous) cutaneous allodynia during migraine are shown to be related [10].

Strengths of this study are the large well-defined, representative chronic migraine population, with a high follow-up rate after withdrawal therapy and detailed information on headache characteristics, allodynia and psychiatric comorbidity. Due to detailed and prospective headache diaries, a distinction in migraine days and headache days could be made. The division in subtypes of cutaneous allodynia have never been studied related to chronic migraine in a longitudinal design. However, the subdivision on spatial distribution also has limitations. The Allodynia Symptom Checklist does not discern ipsilateral cephalic allodynia (second order neurons) and contralateral cephalic allodynia (third order neurons), as this cannot be reliably assessed in a questionnaire. Due to the division into different subgroups and the limited number of symptoms in the questionnaire, we used the criterion of at least one symptoms present for each subcategory, and not two or more as for the overall allodynia scores. Secondly, the study was part of a clinical trial on the effect of botulinum toxin A versus placebo, and we cannot fully rule out potential influence of the trial on the results. However, botulinum toxin A did not have additional benefit over placebo on all outcomes measures [17], and adjusting for botulinum toxin A treatment did not alter the associations between (subtypes of) cutaneous allodynia and migraine-related outcome. Theoretically, the injection of any fluid (independently medication or saline) might cause a general immune reaction and influence results as immune cells are involved in hypersensitivity. Animal studies suggest a different immune-mediated pathway for male and female [39], which might explain the difference in prevalence of cutaneous allodynia in male and female chronic migraine patients. Nevertheless, the association between cutaneous allodynia and response was adjusted for gender, and remained unchanged when analysis was rerun in female patients only making immune mediated influences of injection very unlikely.

This study shows that cutaneous allodynia, an important marker for central sensitization, is a predictor for response to withdrawal therapy in patient with chronic migraine and medication overuse. Allodynia might be an important predictor for treatment response in chronic migraine in general. Furthermore, considering subtypes of cutaneous allodynia, especially extracephalic allodynia and mechanical allodynia, enhances the predictive value for migraine-related outcomes and might help to increase insight in the mechanisms of chronification in migraine.

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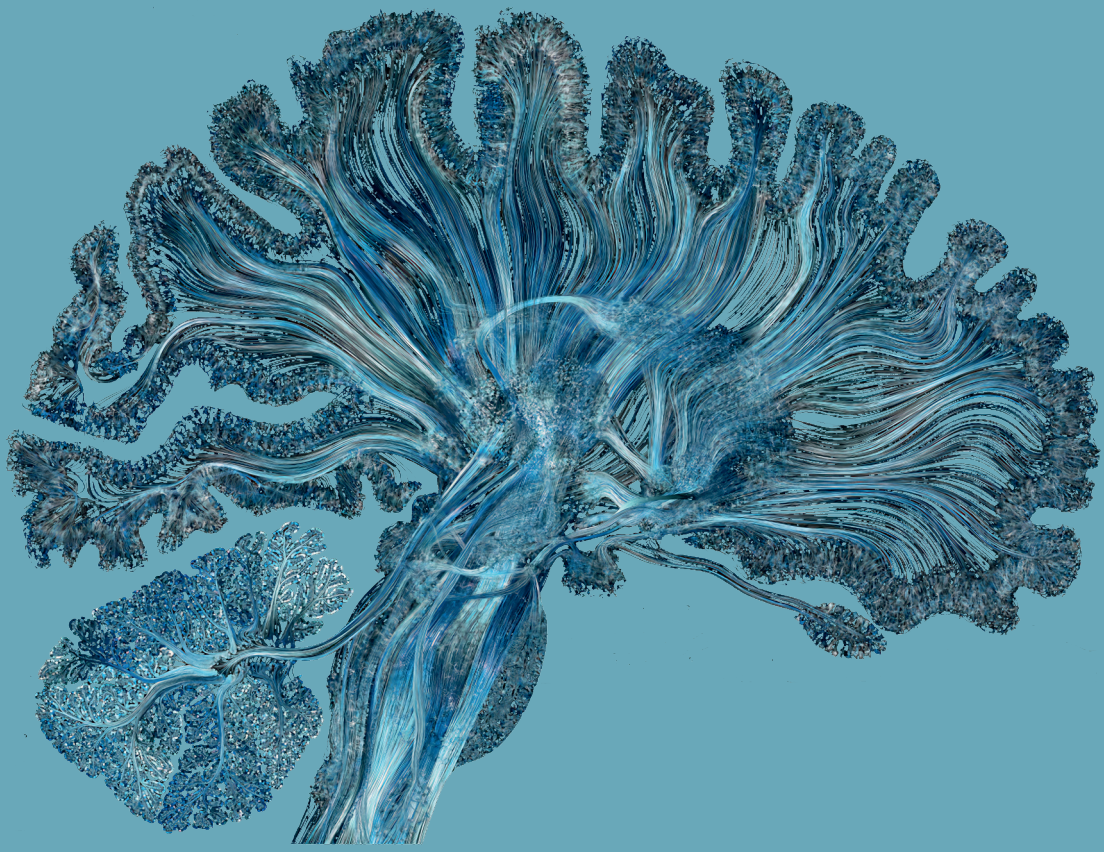
Supplementary Table 1. Allodynia as a predictor for the odds on ≥50% response in migraine days, i.e. a reduction in monthly migraine days (MMD) of 50% or more.

	Overall allodynia			*Spatial distribution*			*Type of stimulus*		
	Multivariate OR (95% CI)		*p*	Multivariate OR (95% CI)		*p*	Multivariate OR (95% CI)		*p*
No allodynia *versus* allodynia	**2.28**	**(1.01 ; 5.16)**	**0.048**	.	.	.	.	.	.
No allodynia									
versus cephalic allodynia	.	.	.	**3.88**	**(1.33; 11.35)**	**0.013**	.	.	.
versus extracephalic allodynia	.	.	.	**6.17**	**(1.85 ; 19.45)**	**0.002**	.	.	.
No allodynia									
versus thermal allodynia only	.	.	.	.	.	.	**4.57**	**(1.12 ; 18.69)**	**0.035**
versus mechanical + thermal allodynia	.	.	.	.	.	.	**4.34**	**(1.49 ; 12.64)**	**0.007**
versus mechanical allodynia only	.	.	.	.	.	.	**6.47**	**(1.52 ; 27.55)**	**0.012**

* Adjusted for: gender, age, depression and anxiety.



Chapter 7

Summary and general discussion

J.A. Pijpers

Summary and General discussion

Thesis derived perspectives on clinical aspects and management of chronic migraine

This thesis explores various clinical aspects of chronic migraine. Due to the complexity of the underlying processes involved in migraine chronification, this form of migraine is challenging to prevent and treat. This thesis pays attention to modifiable risk factors for chronic migraine, and treatment of chronic migraine by means of withdrawal therapy, Botulinum toxin A and behavioural intervention.

Chapter 1 first describes epidemiology and criteria of (chronic) migraine, and current knowledge on its pathophysiology. Three main component in the pathophysiology are stressed: i) the activation of the trigeminal vascular system (either initiated by cortical events or central generators), causing intracranial hypersensitivity and experience of headache; ii) enhanced pain facilitation of the ascending pain pathway by central sensitisation: hypersensitivity of the trigeminal nuclei in the brainstem and the thalamus, clinically causing cephalic and extracephalic allodynia; and iii) lack of pain inhibition by alterations in the descending pain modulating pathways (See chapter 1, figure 1 and 2). Major risk factors for chronic migraine are medication overuse, psychiatric comorbidity such as depression, and the presence of allodynia. Chronic migraine is a highly disabling and difficult to treat disorder. Since the majority of patients also overuse acute headache medication, the first step in treatment is medication withdrawal. In the Netherlands, withdrawal therapy comprises abrupt cessation of all acute headache medication and caffeine for 12 weeks in an outpatient setting. Since the registration trials in chronic migraine, treatment with botulinum toxin A (before withdrawal of overuse medication) has been a matter of debate.

Chapter 2 elaborates on the psychiatric risk factors for chronic migraine. Symptom dimensions of affective disorders of migraine patients were compared to patients with current and past psychopathology and healthy controls. Migraine patients differ from healthy controls on all three dimensions of affective disorders, with a lack of positive affect (depression specific), a higher negative affect (non-specific) and higher somatic arousal (anxiety specific). The difference is most striking for somatic arousal, for which the scoring is comparable to

patients with a current psychopathology of anxiety and/or depression. Within migraine patients, all three dimensions were independently associated with higher attack frequency and cutaneous allodynia. These findings imply that not only depression, but also anxiety might be an important risk factor for migraine chronification, and concurrent treatment is warranted. Furthermore, this tripartite model of affective disorders is relevant to biological research on chronification pathophysiology.

Chapter 3 describes in a retrospective, controlled follow-up study that support by a specialised headache nurse increases success rates for withdrawal therapy in patients with chronic headache (both migraine and tension type headache) with medication overuse. Withdrawal therapy itself results into a reduction of headache days, especially if the underlying primary headache disorder is migraine alone, as opposed to tension-type headache or a combination of both types. In regard to participants who succeeded to withdraw, the reduction in headache days was independent of the support by a headache nurse. Hence support by a headache nurse is effective to enhance treatment adherence and success of withdrawal, but does not affect the underlying headache type or other 'intrinsic' factors and thus the number of headache days. Therefore, in prospective behavioural studies, outcome measurements based on success of withdrawal therapy, coping and grip on pain strategies seem appropriate instead of headache-specific measures.

Chapter 4 enters into the discussion on treatment with Botulinum toxin A (BTA) in chronic migraine, and the initiation of preventatives before withdrawal of acute headache medication. Botulinum toxin A is widely used as treatment of chronic migraine. Efficacy in studies, however, was only modest and likely influenced by unblinding due to Botox-induced removal of forehead wrinkles. Moreover, 65% of study participants were overusing acute headache medication and might have benefitted from withdrawal. In a double blind, placebo-controlled randomised clinical trial in chronic migraine patients with medication overuse, we assessed whether add-on therapy with BTA enhances efficacy of acute withdrawal. At the start of a 12-week withdrawal period, participants were randomised to receive BTA (155 units; 31 injection sites) or placebo (saline). To prevent unblinding, placebo-treated participants received a low dose of BTA in the forehead region (17.5 units; 7 injection sites) next to saline (24 injection sites).

Withdrawal was well tolerated and blinding was successful. After withdrawal, mean number of headache days had decreased by 5 days (25% reduction) and of migraine days by 6–7 days (45% reduction). In total 60% of patients had reverted back to episodic migraine. BTA did not afford any additional benefit over acute withdrawal alone, neither on short term (12 weeks) nor long term measurements (up to 48 weeks). These results confirm that acute withdrawal is associated with meaningful improvement and should be tried first before initiating more expensive treatment with BTA.

Chronic conditions are of augmenting prevalence in the population, posing several challenges on both individual care as health care management. Interventions such as behavioural therapy, lifestyle intervention and mindfulness are gaining importance to cope with chronic diseases and reduce its burden. Similarly, in headache disorders psychological treatment seems beneficial, although the available research is of poor quality. A major concern is the risk of bias by unblinding, as it is difficult to perform blinded trials due to the nature of the intervention. **Chapter 5** is the first study investigating a behavioural intervention in a double blind, placebo-controlled randomized clinical trial. Intensive support versus minimal support by a specialised headache nurse seems to increase the success rate of withdrawal therapy, and reduces medication intake after withdrawal therapy. By concealing the study within the BTA-trial (chapter 4), the patients were unaware of the two treatments arms, by which blinding of participants was assured. Intensive support by a headache nurse in medication overuse management of chronic migraine patients is effective. A concealed design may also be useful to investigate non-pharmacological therapies in other central nervous system disorders.

Chronic migraine is a highly disabling and difficult to treat disorder, especially in case of concomitant medication overuse. Acute withdrawal is beneficial in most, but not all patients. However, strong predictors for response are lacking. Especially with the emergence of promising but high cost therapies for chronic migraine, the identification of predictors for response is warranted. **Chapter 6** shows that absence of cutaneous allodynia is a predictor for good response to withdrawal therapy in patients with chronic migraine and medication overuse. Moreover, the predictive value was even more pronounced when compared with extracephalic allodynia, which is indicative of trigeminothalamic involvement.

Furthermore, especially mechanical allodynia, as opposed to thermal allodynia, was related to outcome. The predictive value of cutaneous allodynia was limited to migraine-specific outcome, not to reduction in headache days in general. The study indicates the relevance of cutaneous allodynia as marker for central sensitization in chronic migraine and its predictive value for response to withdrawal therapy. As central sensitization, mediated by CGRP, is a key mechanism in migraine chronification, cutaneous allodynia may very well be an important predictor for treatment response in chronic migraine in general. Furthermore, the subtypes of cutaneous allodynia have never been studied in this context, and could enhance the predictive value for migraine-related outcomes and increase insight in the mechanisms of chronification in migraine.

Chronic migraine definition

As the clinical studies within this thesis embrace a time period from 2006 (**chapter 3**) to 2016 (**chapter 4 – 6**), different views and classifications on chronic migraine definitions have passed. Chronic migraine was first considered as a distinct entity in 2004, defined by the international Classification of Headache Disorders (ICHD) 2nd edition.[1] In the following years, the definition of ≥15 migraine days per month appeared too restrictive and was loosened to ≥15 headache days per month, of which ≥8 migraine days (ICHD-2R, 2006).[2] Diagnosis of a primary headache disorder, both (chronic) migraine or tension-type headache, could not be established in the light of concurrent medication overuse. In the most recent classifications, ICHD 3 beta, 2013[3] and subsequently ICHD-3, 2018[4], the latter was changed, such that the diagnoses of chronic migraine and medication overuse could co-occur. Complicating the classification by this co-occurrence is the circular reasoning in which a headache day is called a migraine day in case of triptan use. This is inevitable as intake of a triptan will prevent the evolution of migraine characteristics, but will also blur the diagnosis of CM in case of medication overuse.

Classifications can both have a clinical purpose, in which classification rules represent common phenotypes or indicated treatment, or a research purpose, ensuring homogenous subgroups.[5,6] In the context of research, for which the ICHD was designed,[5] a chronic migraine population in a clinical trial can now comprise patients with a primary headache disorder of migraine alone or a combination with tension-type headache in various frequencies, possible concomitant with a secondary headache due to medication overuse. In this case, the diagnosis chronic migraine might be inaccurate and only driven by a high and inappropriate triptan usage. Furthermore, chronic patients with medication overuse require a different treatment strategy as opposed to chronic migraine patients without medication overuse. This heterogeneity hampers appropriate population selections for clinical trials, and also hinders pathophysiological research. Whether or not a consequence of these limitations, the implementation of the ICHD criteria is falling short, as only 50% of clinical trials on chronic migraine use the correct criteria.[7] Clinically, the discernment between episodic migraine and chronic migraine appears artificial. A recent study states that high-frequent episodic migraine (≥8 migraine days) is as disabling as chronic migraine, and should be included in revised criteria of

chronic migraine.[6] This conclusion is based on comorbidity and sick-leaf related data, and disability, headache impact or phenotypic characteristics such as allodynia or photo- and phonophobia are not taken into account. Nonetheless, a similar disability of both groups appears reasonable. Figure 3 in chapter 4 shows the reversion of chronic migraine to episodic migraine upon treatment and highlights the potential overlap between the different subgroups.
Hence, for future revision of the ICHD criteria, I propose a discernment between chronic migraine *with* and *without* medication use. Furthermore, criteria for chronic migraine should be based on number of migraine days, without taking any non-migraine headache days into account.

Pathophysiology

Migraine headache is caused by activation of the trigeminal system, either by cortical events or central generators, causing intracranial hypersensitivity and thereby experience of headache.[8–12] As described more elaborate in the introduction of this thesis, migraine chronification can be considered as a state of increasing susceptibility for migraine attacks.[11] This increased susceptibility is assumed to be the consequence of both enhanced pain facilitation of the ascending pain pathway, known as central sensitisation,[10,13,14] and lack of pain inhibition by alterations in the descending pain modulating pathways.[15,16]

New insights on central sensitization

This thesis touches on these assumed mechanisms in migraine chronification by studying cutaneous allodynia, a clinical marker of central sensitisation. Sensitisation of second order neurons in the brainstem (trigeminal nucleus caudalis) results into referred hypersensitivity of the skin (cutaneous allodynia) of the ipsilateral cephalic region. Sensitisation of third order neurons in the thalamus causes extracephalic allodynia (see Introduction, Figure 1 and 2). **Chapter 6** stresses the importance of central sensitization in migraine chronification and reversibility as the absence of cutaneous allodynia is a predictor of good response to acute withdrawal. Moreover, this predictive value of cutaneous allodynia was more pronounced when subdivided based on spatial distribution: no allodynia versus cephalic allodynia (second order sensitization) versus extracephalic allodynia (third order sensitization), suggesting that in

the context of migraine chronification cutaneous allodynia should not only be studied as one entity, but the extension of sensitization should be taken into account.

This division might shed light on a recently stated hypothesis of different underlying mechanisms of central sensitization. The hypothesis was evoked by the observation in clinical studies that some patient become unresponsive to triptans once cutaneous allodynia manifested[17,18], and some patients remain responsive to triptans despite of cutaneous allodynia.[19–21] Acknowledging different stages of central sensitization (second and third order), and considering that triptans act both peripherally and post-synaptic on second order neurons,[19] but not third order neurons, could explain this discrepancy: Patients with second order sensitization (cephalic allodynia) alone remain responsive to triptans, whereas patients with extension to third order sensitization (extracephalic allodynia) are unresponsive.

Alternatively, two hypotheses on the origin of central sensitization can be stated: i) central sensitization is initiated by peripheral activation of the trigeminal afferents, and sequentially causes second and third order sensitization (triptan responsive allodynia);[10,13,22] ii) central sensitization is initiated by central changes, for instance the hypothalamus as part of the descending pain pathway, directly causing both second and third order sensitization (triptan unresponsive allodynia). The second hypothesis is supported by imaging studies, suggesting an important role of the hypothalamus in migraine chronification and brainstem as generator of migraine attacks.[16,23] Although not directly studied, the dose-response relationship between cephalic versus extracephalic allodynia and response in **chapter 6**, suggests a sequential gradual extension of central sensitization. Nonetheless, the difference is small, and does not exclude a central origin. These mechanisms (sequential events of sensitization extension initiated by peripheral sensitization or central sensitization directly caused by central changes) might even coincide and facilitate each other. In this thesis, I propose a role for both mechanisms. In episodic migraine, central sensitization may mainly originate from a peripheral stimulus, and is reversible after removal of this stimulus (i.e. the end of migraine attack). In the process of migraine chronification, the recurrent attacks and medication intake may lead to central changes by both functional and structural neuroplasticity[24], increasing the importance of a persistent state of central sensitization caused by central changes.

Chronic migraine and other chronic pain conditions

Patients with chronic migraine also experience more non-cephalalgic pain than episodic migraine patients,[25] presumably due to more prevalent and more severe central sensitization.[26] After all, central sensitization is not unique for migraine, but is an important manifestation in many chronic pain conditions, such as low back pain, fibromyalgia, non-headache neuropathic pain, post-surgery pain.[27] In such pain disorders, allodynia is also a predictor for pain chronification, although the definition of chronic is usually defined in periods of time (presence of pain for ≥ 3 months) instead of frequency (presence of headache on ≥ 15 days).[27] For most chronic pain conditions, central sensitization can be reversed upon removal of the peripheral pain generator, or blockage of specific central receptors.[27] In headache disorders, the peripheral pain generator will end by itself due to the paroxysmal character of the disorder, and might result in a more dynamic character of central sensitization.

Despite similarities in shared mechanisms for chronicity, there is also an important difference: medication overuse is the most important risk factor for migraine chronification, but pain medication is generally not associated with aggravation of other pain conditions, and withdrawal of pain medication is not advocated. However, awareness of opioid-induced hyperalgesia is rising, and in some patients, opioid reduction or cessation improves pain scores. Whether opioid-induced hyperalgesia is the consequence of opioid therapy, or caused by pre-existing risk factors, such as dysfunction of endogenous opioid systems, potentially located in the brainstem, is not clear yet.[28]

The mechanism of hyperalgesia due to pre-existing risk factors would again be a link between chronic migraine and other chronic pain conditions. Clinical data on headache disorders also suggest an essential role for pre-existing risk factors. Patients with a primary headache disorder overusing pain medication for another pain condition are at risk for chronification of headache but this increased risk seems absent for patients without a tendency for headaches.[29–31] Alternatively, non-headache patients who do develop headaches de novo upon use of acute pain medication, consider this as a side-effect and will stop the medication. However, the latter seems less likely, and there is no evidence to support this hypothesis. Hence the limited available data suggest that there has to be an intrinsic increased sensitivity (i.e. pre-existing primary headache disorder; pre-existing dysfunctional endogenous opioid system) in order for medication overuse to cause or aggravate pain. In animal models, the overuse

of migraine-specific acute medication is associated with persistent alterations in dural afferents in animal studies.[32] The evident peripheral effect of medication overuse on the trigeminovascular system might explain that medication overuse is a more prominent risk factor for migraine chronification as opposed to pain chronification in general.

Chronic migraine and affective disorders

This thesis also stresses the association between affective disorders, migraine chronification and central sensitization processes. Depression is a known major risk factor for migraine chronification,[33,34] which was confirmed in **chapter 2** by showing that both depression-specific and general symptom dimensions of affective disorders are associated with both high attack frequency and cutaneous allodynia. Moreover, this association was strongest for somatic arousal, anxiety specific symptoms.

Recently, kappa opioid receptors (KOR) and their ligand dynorphin in the amygdala have been related to central sensitisation in animal models of medication overuse. Allodynia and lack of pain inhibition after triptan or morphine sensitisation, were reverted by blockage of KOR in the amygdala.[30,35,36] The dynorphin-KOR pathway in the amygdala is also described in the pathophysiology of anxiety: KOR agonists induce anxiety, whereas KOR antagonists diminish anxiety. Similar relations have been identified with depressive behaviour and substance dependency.[37] Therefore the dynophin-KOR pathway could (partly) explain the close relationship between frequent medication use, anxiety, depression and allodynia as risk factors for migraine chronification.

Future research perspectives

The pathways associated with migraine chronification, including trigeminovascular activation, central sensitization by enhanced pain facilitation of the ascending pain pathway and lack of pain inhibition by the descending pain pathway, are described as separate processes, but in reality these mechanism are closely related and co-dependent. Therefore, to understand pathophysiology, a combination of multiple read-outs in episodic and chronic migraine patients would be necessary. Although time consuming, long term follow-up studies in (low frequent) episodic migraine patients with elaborate baseline measurements, would be highly advantageous to specify characteristics of

risk for migraine chronification, and ultimately answer the question why some episodic migraine patients will develop to chronic migraine and others won't.
Due to the similarities of chronic migraine and other chronic pain conditions, some techniques used in the chronic pain field are interesting to apply in this setting. A technique used to quantify the trigeminal nerve in a non-invasive manner, is corneal confocal microscopy. The corneal nerve plexus is a densely innervated and highly dynamic plexus of small nerve fibers, mainly C-fibers, formed by the ophthalmic branch of the trigeminal nerve.[38] Abnormalities in corneal nerve parameters haven been demonstrated in patients with peripheral (non-trigeminal) neuropathies, correlated to the severity of pain and used as a marker of dieseas.[38,39] Corneal nerve fiber changes have also been suggested in a small study of chronic migraine patients.[40] As the plexus is highly dynamic, the quantification by corneal confocal microscopy can be used for longitudinal measurements,[41,42] even demonstrating posttreatment changes after 4 weeks.[42]
Another technique of interest is conditioned pain modulation, which assesses inhibition of pain by the descending pain pathway. Conditioned pain modulation tests comprise an isolated pain stimulus, and later on a second similar pain stimulus preceded by a conditioning stimulus, usually cold or hot water immersion. The read-out is the change in pain rating between the two pain stimuli. [43] Applying a conditioned stimulus has been shown to reduce migraine pain in episode migraine patients,[44] suggesting a functional descending pain pathway.
A combination of these read-outs with Quantitative Sensory Testing to assess different types of allodynia (i.e. dynamic mechanical, static mechanical and thermal allodynia) and temporal summation (i.e. increment of pain at the end of a set of stimuli)[27,45] would enhance interpretation of the involved mechanisms. As shown in **chapter 6**, an assessment of both a cephalic and extracephalic location is important.

Management of chronic migraine

Prevention of migraine chronification

Despite of the advancing insights in processes of central sensitization and lack of pain inhibition, direct intervention in these pathways in chronic migraine is not yet possible. With the role of CGRP in central sensitization, antibodies

against CGRP or its receptor could be a possibility. As these antibodies are widely studied, the near future will probably show whether migraine chronification and associated mechanisms can be prevented. In addition, the capability of KOR antagonists to reduce central sensitization[35] and restore pain inhibitory controlI[36] in animals might be promising. The first clinical studies for substance abuse and affective disorders were terminated because of adverse events, but trials at new generation KOR antagonists with potentially less adverse events are ongoing.[37,46]

Direct intervention on pain facilitation or inhibition pathways in other pain conditions has yielded contradictory results: not all studies show a beneficial effect of similar pharmacological interventions on these pathways. However, in case of a reduction in central sensitization there is a parallel effect on pain intensity, suggesting potential for future treatment.[27] Replication of these effects in migraine patients are important, as direct translation might be impaired. For instance amitriptyline, used as a preventative in headache, increased central sensitization.[27]

Prevention of risk factors for chronic migraine

Awaiting these developments, the best strategy in the prevention of migraine chronification is addressing its risk factors, of which medication overuse is the main factor. **Chapter 3, 4, and 5** show the relevance of cessation of overuse and **chapter 3 and 5** demonstrate effect of education, support and behavioural intervention by a headache nurse on successful medication withdrawal and a reduced medication intake in the months after withdrawal therapy. In line, prolongation of support by a headache nurse would likely enhance a long-lasting reduction in medication use or even prevent medication overuse. So far, only a small study has been performed with intervention by a headache nurse in a heterogeneous migraine population in a tertiary headache clinic which could not show a reduction of medication intake or a lower percentage of medication overuse.[47]

This discrepancy might be related to an important question in preventive care: which part of the population should be subjected to the preventive strategy? The population in **chapter 5** is a 'high risk' migraine population, suffering from chronic migraine and initially medication overuse, with prevalence of other risk factors (cutaneous allodynia 75%, depression 37%, and anxiety 31%). These risk factors are not described in the previous study on a intervention

by a headache nurse,[47] but a proportion of only 35% with chronic migraine suggest a population at lower risk. Therefore, when considering secondary or tertiary preventive strategies by a headache nurse, a selection of patients could be made on presence of known risk factors, to select those in need.

Some secondary and even primary prevention strategies can be considered for a broader population in order to prevent medication overuse. A multicenter trial suggests a role for electronic monitoring. Patients using an electronic headache diary with an alert system and communication option had a lower rate of medication overuse compared to patients using paper a headache diary.[48]
As primary prevention, a national awareness campaign including online videos, publications at news websites, distribution of information brochures, and education of general practitioners was implemented in Denmark for a period of 4 months.[49] Two independent surveys on awareness on existence of medication overuse headache before and after the campaign suggested some effect (30.8% versus 38.2% of respondents were aware of medication overuse headache), but it did not result in better knowledge on a safe pain killer dosage, and the survey did not include data on the prevalence of medication overuse headache. Hence, the (cost-)effectiveness of such a campaign is uncertain.

Together with medication overuse, depression is indicated in a large systematic review as one of the most important (modifiable) risk factors for migraine progression, both in magnitude as in level of evidence.[34] **Chapter 2** suggests anxiety as a risk factor as well, which is a largely unexplored area. Some preliminary data support this finding, but this data was not included in the systematic review, as it is only available via conference abstracts, and was not peer reviewed.[34] A population study with a long follow-up period (11 years) did identify comorbid depression and/or anxiety as a risk factor for medication overuse headache, but did neither differentiate between migraine and non-migraine headache as underlying diagnosis, nor separate depression and anxiety as a risk factor.[50] A recent population study replicated the stronger association between migraine and anxiety as compared migraine and depression, but a potential association with migraine attack frequency was not examined.[51]
Screening for and concurrent therapy of psychiatric comorbidity is advised, based on the known increased risk for chronification, and the burden of psychiatric comorbidity. Nevertheless, the risk reduction of migraine chronification upon

reducing anxiety and depression has never been studied. As for depression, the comorbidity is thought to occur due to shared etiology and even shared heritability.[52–55] Hence, treatment of concurrent depression might not eliminate the added risk for chronification. Still, some risk reduction is to be expected. A large cohort study showed a kind of dose-response relationship, in which the risk of chronification increases when the severity of depression symptoms increases,[34] implying a risk reduction for migraine chronification when the severity of depression is reduced.

Treatment of chronic migraine

This thesis emphasizes the importance of withdrawal of overused medication. **Chapter 2 and 4** show in a retrospective and prospective manner the efficacy of medication withdrawal. In the prospective trial, the mean number of migraine days per month had decreased by 6-7 days after withdrawal, and 60% of patients had reverted back to episodic migraine. Furthermore, over 30% of patients did not need preventatives after withdrawal. Withdrawal therapy was well-tolerated by patients as almost 50% rated their treatment as very good (≥8/10) and almost 70% would recommended this therapy to friends and family. These numbers show that withdrawal therapy is accepted, especially considering that chronic migraine is difficult to treat, and the nature of the intervention is difficult to endure. The hesitance to initiate withdrawal therapy in clinical practice might be dictated by physicians, as 'we' tend to have a preference to give, instead of withhold medication. **Chapter 2 and 5** also demonstrate the relevance of a multidisciplinary approach, as a headache nurse reduces medication intake, and decreases the potentially higher drop-out rate in an outpatient versus inpatient setting, seen in a previous study.[56]

Taken together with previous studies, these chapters provide class III level of evidence of acute withdrawal in case of medication overuse. Although class I/II level of evidence (at least one randomized placebo controlled trial) is preferable in evidence-based medicine, obtaining this level of evidence seems inheritably impossible due to the nature of the intervention. Double-blind comparison is hardly attainable, as placebo matching for all types and combinations of overused medication seems an impossible assignment. Besides this practical issue, controlling for the psychological effect of withdrawal is truly impossible. Therefore, it is important to test new therapeutic interventions against withdrawal, and investigate the additional benefit.

Chapter 4 shows that Botulinum toxin A (BTA) does not afford any benefit over withdrawal therapy alone. BTA did not improve any of the primary or secondary outcomes after the double-blind placebo-controlled phase (12 weeks), open label phase (24 weeks) or long term follow-up (48 weeks). Hence, in case of medication overuse, withdrawal therapy should be advised first to chronic migraine patients. After this study, the question remains whether BTA is indicated for chronic migraine patients without medication overuse. The lack of any additional benefit of BTA at all in our clinical trial described in chapter 4 cautiously suggests against the use of BTA in chronic migraine in general, but was not formerly studied. A common response to our trial by physicians in favour of implementation of BTA in chronic migraine treatment, is that we didn't find any effect because the placebo-dose of 17.5 units is already biologically effective, resulting in significant improvement. This explanation seems unlikely, as 17.5 units is significantly lower than the lowest doses reported for headache[57,58] or other applications, such as psychiatric disorders, peripheral neuropathy or even regular cosmetic purposes.[59–61] Furthermore, animal studies on putative mechanisms of effect show that low doses are clearly less effective[62] or not effective at all.[63,64] Hence, there is no evidence that a low dose of 17.5 units would cause a clinically relevant effect. More importantly, if such a low dose is indeed effective, why should we treat patients with a nine fold higher dose?
A meta-analysis published before our trial proves that BTA is not effective in episodic migraine and in (chronic) tension-type headache.[57] BTA did have a modest effect in chronic migraine,[11,57] which was mainly based on the PREEMPT trials. [65,66] The main remarks on these trials are i) a modest effect with a therapeutic gain of only 9% compared to placebo, ii) potential bias by unblinding, iii) potential selection bias due to a selection of less severe chronic migraine patients without depression and without daily headache. Since the registration trials, many observational cohort studies have been published. The longest open label observational study with repeated BTA cycles during 108 weeks implies a long-term effect, but the interpretation of these results is hampered due to bias because of a high rate of loss to follow-up (50%).[67] The one-cycle open label administration of BTA in patients who still suffer from chronic migraine after withdrawal, described in **chapter 4**, is shorter compared to other observational studies, but led to a limited reduction in headache days only. Comparing BTA to other preventatives used in chronic migraine, the limited available data suggests that BTA is not superior to topiramate or valproate.[57]

In conclusion, the efficacy of BTA is at best modest, but taking into account the low risks of adverse events, and the severity of chronic migraine without many other therapeutic options, BTA can be considered for patients with chronic migraine, without medication overuse, who failed on previous preventatives (either due to adverse events of lack of efficacy). As indicated by the discussion on whether or not 17.5 units could be as effective as 155 units of BTA, studies on dose-response curves are warranted. Since BTA is not effective in episodic migraine,[57] therapy should be ceased when patients are reverted from chronic to episodic migraine.

A new subclass of preventative are the antibodies against CGRP or its receptor (further referred to as CGRP-antibodies).[68] Several trials have been performed in chronic migraine, but direct comparison with our trial described in **chapter 4** and previous BTA-trials is hampered due to differences in design and selection of patients. However, with these limitations in mind, the anti-CGRP treatment groups in these trials seem to yield similar reduction in migraine or headache days per month as the placebo group (withdrawal therapy only) described in **chapter 4**. The withdrawal therapy only group in **chapter 4** had a mean reduction of 4.4 headache days and 7.0 migraine days per month. The mean reduction of the CGRP-antibody treatment groups were 4.6 monthly headache days for Fremanezumab (baseline headache days 12.8)[69], 6.6 monthly migraine days for Erenumab (baseline migraine days 17.9)[70] and 4.8 monthly migraine days for Galcanezumab (baseline migraine days 19.2)[71]. The mean additional therapeutic gain versus placebo was 11-17%.[69–71]
Whilst the mean therapeutic gain is still moderate, the potential benefit of the CGRP-antibodies has been suggested to be in a large treatment effect in a subgroup of patients, called responders (at least 50% reduction in headache or migraine days) or even super responders (75-100% reduction in headache or migraine days).[72] The odds for response in the chronic migraine trials is approximately 2 - 2.5 times higher for the treatment group versus placebo.[69–71]
Considering the high costs of CGRP-antibodies, defining predictors for response is very important. As for withdrawal therapy (**chapter 6**), cephalic and extracephalic cutaneous allodynia might be a relevant predictor.
Furthermore, a comparison or added value of this preventive medication to standard care (withdrawal of medication) has not been studied. Hence it is still unknown whether medication overuse should be treated first by withdrawal

before administration of CGRP-antibodies, or whether CGRP antibodies enhance efficacy of withdrawal. Therefore, further research is warranted, which is also emphasized by the European headache federation guideline on the use of CGRP-antibodies.[73] A design as used in **chapter 4** for BTA would be feasible to answer some of these questions.

Methodology in this thesis – placebo effect

Apart from the contentual contribution to our knowledge on migraine chronification and its treatment, this thesis is unique in its methodology. Most chapters comprise longitudinal study designs, enhancing the establishment of causal associations. More specifically, the randomized controlled trials both contained new techniques to ensure blinding of participants, using a low dose versus high dose principle. In **Chapter 4** blinding was ensured by using a low dose of BTA in the forehead region in the placebo group. In this manner, one of the major limitations of the previous BTA trials was tackled.[74,75] Placebo-controlled trials and adequate blinding of participants are particularly complicated in behavioural interventions, due to the nature of the treatment. In **chapter 5**, this was accomplished by the concealment of the behavioural intervention in another trial, so patients were unaware of the existence of two treatment arms. Also in this chapter, a low dose versus high dose principle was applied with minimal versus intensive support by a headache nurse.

These techniques aim to reduce bias by placebo effect due to unblinding, which is particularly important in the research field of pain conditions due to the high placebo response. Placebo response is a complex phenomenon, often referring to various types of effects like regression to the mean, reporting-bias, and psychologically induced responses to treatment.[76] Studies investigating the mechanisms of placebo response suggest anti-nociceptive effects by enhancement of endogenous opioid-related analgesia and activation of the descending pain modulation pathway, initiated in limbic regions of the brain and transmitted to the brainstem nuclei by the periaqueductal grey.[76,78] The placebo response would be largely independent from ascending nociceptive processing.[79] The anti-nociceptive effects might to some extend explain the high placebo responses in pain studies, and the designs described in this thesis can be used to improve discernment between the intervention induced response from the placebo response.

Conclusion

Chronic migraine is a disabling, high frequent variant of migraine, in which patients experience headache on at least 15 days per month, of which at least 8 migraine days. The definition of chronic migraine is ambiguous, due to the heterogeneity within this subgroup. A revised classification discerning chronic migraine *with* and *without* medication overuse, mainly based on number of migraine days would be beneficial. Medication overuse is an important independent risk factor for migraine chronification, as well as anxiety and depression. These factors are implied to promote central sensitisation, a process of enhanced pain facilitation, which is a key mechanism in chronification pathophysiology. A clinical marker of central sensitisation is cutaneous allodynia, the perception of pain to a non-painful stimulus to the skin. Cutaneous allodynia is not only a clinical risk factor for migraine chronification, but seems also predictive for treatment response. Withdrawal therapy is the first choice of treatment in case of chronic migraine with medication overuse. It is a cost-effective therapy, associated with meaningful improvement. Intensive support by a headache nurse during withdrawal therapy is important to increase success rates. Botulinum toxin A has no additional benefit over withdrawal therapy alone, and should not be included in withdrawal therapy. Also for other new developed preventatives (antibodies against CGRP or it's receptor) a comparison with withdrawal therapy alone or the combination of both may be of great importance for the highly disabled patients who suffer from chronic migraine with overuse of acute medication.

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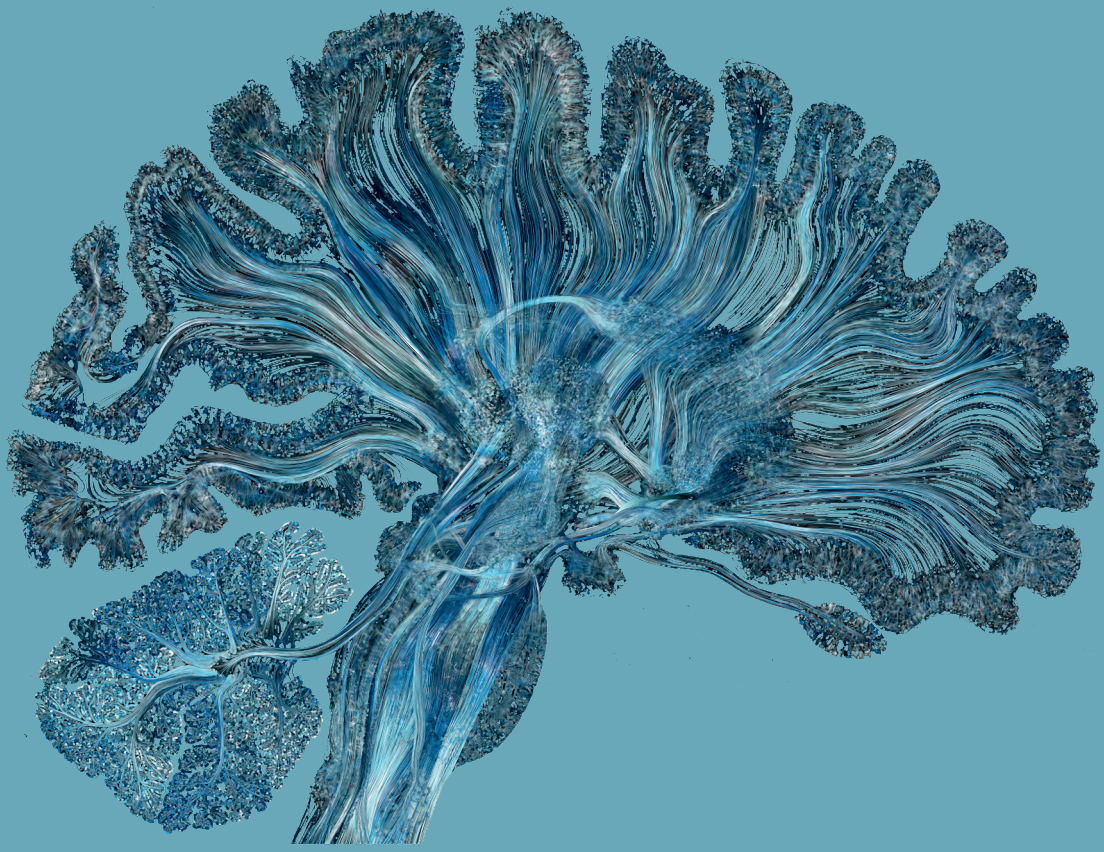

Addendum

Nederlandse samenvatting

Dit proefschrift focust op het klinische beloop, de behandeling en de pathofysiologie van migraine chronificatie. De kennis over risicofactoren en hun rol in de ontstaansmechanismen zijn belangrijk in de preventie van migraine chronificatie, maar ook voor de therapie wanneer migraine is getransformeerd naar chronische migraine. Alle factoren en processen die betrokken zijn bij migraine chronificatie, zijn sterk aan elkaar gelinkt en interacteren met elkaar, waardoor het belangrijk is deze gezamenlijk te analyseren en met name te interpreteren.

Hoofdstuk 1 geeft een introductie op deze betrokken factoren en processen. Migraine is een complexe, multifactoriële aandoening, die gekenmerkt wordt door herhaalde aanvallen van matig tot ernstige hoofdpijn en vaak gepaard gaat met misselijkheid, braken en overgevoeligheid voor beweging, licht en geluid. De meeste patiënten hebben episodische migraine (< 15 hoofdpijndagen per maand), met een mediane aanvalsfrequentie van één per maand. Daarentegen transformeert elk jaar 3% van deze patiënten naar chronische migraine, een hoog frequente en zeer invaliderende migraine variant (≥ 15 hoofdpijn dagen per maand, waarvan tenminste 8 migrainedagen). Dit proces wordt migraine chronificatie genoemd.
De voornaamste risicofactoren voor migraine chronificatie zijn frequent gebruik van anti-hoofdpijn medicatie, depressie en allodynie (i.e. de perceptie van pijn na een normaliter niet pijnlijke stimulus op de huid). Allodynie is in het bijzonder interessant omdat dit beschouwd kan worden als een klinische marker van centrale sensitisatie: de persisterende overgevoeligheid van centrale delen van het brein. Dit is een van de 3 componenten die belangrijk lijken in de pathofysiologie van migraine chronificatie, en verder worden toegelicht in de hoofdstuk 1.
Kort samengevat zijn de volgende mechanismen van belang: i) activatie van het trigeminovasculaire systeem, leidend tot intracraniële overgevoeligheid en derhalve de hoofdpijn; ii) toegenomen pijn facilitatie van het ascenderende pijn netwerk door centrale sensitisatie: overgevoeligheid van de trigeminale nucleus in de hersenstam en de thalamus, welke klinisch leidt tot cephalische en extracephalische allodynie; iii) afgenomen pijn inhibitie door veranderingen van het descenderende modulerende pijn netwerk.

Met frequent medicatie gebruik als belangrijkste risicofactor voor migraine chronificatie, heeft de meerderheid van de patiënten met chronische migraine medicatie overgebruik. Derhalve is ontwenning van deze overgebruikte medicatie de eerste stap in de behandeling. In de Nederlandse richtlijnen wordt hiervoor als eerste keuze een poliklinische, volledige, abrupte ontwenning van de overgebruikte medicatie geadviseerd. Sinds de studies naar botuline toxine A in chronische migraine, staat de behandeling met botuline toxine A (voordat van de overgebruikte medicatie is ontwend) ter discussie.

Hoofdstuk 2 gaat dieper in op de psychiatrische risicofactoren voor migraine chronificatie. Deze studie maakt voor het eerst onderscheid in symptoom dimensies van affectieve stoornissen, waarbij niet alleen depressie, maar ook angst wordt onderzocht. Deze symptoom dimensies van migraine patiënten werden vergeleken met patiënten met een huidige affectieve stoornis, een affectieve stoornis in het verleden, en gezonde vrijwilligers. Migraine patiënten verschillen van gezonde controles op alle drie domeinen: gebrek aan positief affect (depressie specifiek), hoger negatief affect (niet-specifiek) en hogere somatische opwinding (angst specifiek). Het verschil is het meest opvallend voor de somatische opwinding, waarbij de scores vergelijkbaar zijn met patiënten met een huidige affectieve stoornis. Zowel angst en depressie lijken gerelateerd aan migraine chronificatie, gezien binnen de groep met migraine patiënten alle domeinen onafhankelijk geassocieerd zijn met aanvalsfrequentie en allodynie (cross-sectionele data).

Hoofdstuk 3 beschrijft een retrospectieve, gecontroleerde follow-up studie waarin ontwenningstherapie onder begeleiding van een gespecialiseerde hoofdpijn verpleegkundige vergeleken wordt met ontwenningstherapie zonder verdere begeleiding. Begeleiding door de hoofdpijnverpleegkundige verhoogt het succespercentage voor ontwenning van medicatie bij patiënten met chronische hoofdpijn (met onderliggend migraine en/of spanningshoofdpijn). De relatieve reductie in hoofdpijndagen was niet verschillend tussen de beide groepen.

Hoofdstuk 4 gaat in op de discussie over behandeling met botuline toxine A (BTA) in chronische migraine, en het starten van profylactica voor ontwenning van de overgebruikte medicatie. In een dubbelblinde, placebo-gecontroleerde,

gerandomiseerde klinische trial onderzochten we of het toevoegen van BTA de effectiviteit van ontwenningstherapie vergroot. Aan het begin van de 12 weken durende ontwenningsperiode werden patiënten met chronische migraine en medicatie overgebruik gerandomiseerd voor BTA (155 units; 31 injecties) of placebo (saline). Om deblindering te voorkomen door het cosmetische effect van BTA, bevatten enkel de injecties in de voorhoofd regio van de placebo behandeling een lage dosering BTA (17.5 units; 7 injecties). BTA had geen voordeel ten opzichte van alleen ontwenningstherapie, noch op een van de korte termijn uitkomsten (12 weken), noch op de lange termijn uitkomsten (24, 36, 48 weken). Derhalve concludeerden we dat ontwenning van de medicatie nog steeds voorkeursbehandeling is voor patiënten met chronische migraine en medicatie overgebruik.

Hoofdstuk 5 onderzoekt het effect van een gedragsinterventie door een hoofdpijnverpleegkundige tijdens ontwenningstherapie. Door het unieke design, is dit de eerste studie waarbij dit op een volledig geblindeerde en gecontroleerde manier gebeurt. In deze gerandomiseerde klinische trial werd intensieve begeleiding door de hoofdpijnverpleegkundige, met educatie, motiverende gesprekstechnieken en waarde-gebaseerde planning, vergeleken met minimale begeleiding met een enkel kort consult. Omdat deze studie werd gemaskeerd binnen de BTA studie (hoofdstuk 4) waren patiënten zich niet bewust van de twee behandelingen, en was blindering gegarandeerd. Intensieve begeleiding door de hoofdpijnverpleegkundige lijkt ook in deze studie het succespercentage van ontwenning te verhogen, en vermindert het medicatie gebruik na de ontwenning.

Hoofdstuk 6 toont aan dat de afwezigheid van allodynia een goede reactie op ontwenningstherapie voorspelt. Bovendien was deze predictie sterker wanneer allodynie was onderverdeeld op basis van locatie (geen allodynie versus cephalische allodynie versus extracephalische allodynie). Dit is de eerste studie die op deze manier onderscheid maakt tussen de subtypen van allodynie. Daarnaast bestond de predictieve associatie met name voor mechanische allodynie, maar was afwezig bij enkel thermale allodynie. Het valt op dat allodynie enkel een voorspeller voor migraine-gerelateerde uitkomstmaten is, maar niet voor vermindering van hoofdpijndagen in het algemeen.

Hoofdstuk 7 plaatst de bevindingen uit dit proefschrift in een breder perspectief. Hierbij wordt de relevantie besproken voor de pathofysiologie en klinisch beloop van chronische migraine, waarbij ook een link wordt gelegd naar andere chronische pijn aandoeningen en neurologische ziekten. Daarnaast wordt de volgende stap voor klinische onderzoek naar chronische migraine besproken. Dit proefschrift levert aanvullend bewijs voor de relevantie van ontwenningstherapie in geval van medicatie overgebruik. Begeleiding door een gespecialiseerde hoofdpijnverpleegkundige is hierbij een belangrijke component. Daarnaast is dit de eerste goed geblindeerde studie naar BTA, waarbij geen verschil werd gevonden tussen de 2 groepen. Een effect van de zeer lage dosering BTA is onwaarschijnlijk, maar niet geheel uitgesloten. Dit zou echter betekenen dat de doseringen van BTA drastisch vermindert kunnen worden.

Een belangrijke ontwikkeling sinds de start van de studies beschreven in dit proefschrift, is behandeling van (chronische) migraine middels antilichamen tegen CGRP of de CGRP receptor. CGRP speelt een belangrijke rol in de activatie van het trigeminovasculaire systeem en het ontstaan van centrale sensitisatie door medicatie overgebruik. Een vergelijkbare studie zoals beschreven in hoofdstuk 4, waarbij ontwenningstherapie en antilichamen tegen CGRP of haar receptor wordt onderzocht, is daarom belangrijk. Gezien de waarschijnlijk hoge kosten van deze antilichamen, is het vaststellen van predictoren voor een goede reactie op therapie belangrijk. Eenzelfde verdeling van allodynie op basis van lokalisatie, zoals beschreven in hoofdstuk 6, is een potentieel interessante voorspeller.

List of abbreviations

ASC	allodynia symptom checklist
BTA	botulinum toxin A
CGRP	calcitonin gene-related peptide
CHARM study	chronification and reversibility of migraine study
CI	confidence interval
CM	chronic migraine
EM	episodic migraine
HADS	hospital anxiety and depression scale
ICHD	international classification of headache disorders
KOR	kappa opioïd receptor
LC	locus coeruleus
LUMC	Leiden university medical center
LUMINA	Leiden university medical center migraine neuro-analysis programme
MASQ	mood and anxiety symptoms questionnaire
MDD	major depressive disorder
MHD	monthly headache days
MMD	monthly migraine days
MO	medication overuse
MOH	medication overuse headache
MRI	magnetic resonance imaging
NESDA	Netherlands study of depression and anxiety)
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PAG	peri aqueductal grey
RCT	randomized controlled trial
SD	standard deviation
TG	trigeminal ganglion
TNC	trigeminal nucleus caudatus

Curriculum Vitae

Judith Pijpers was born on September 27th 1989 in Alphen aan den Rijn, the Netherlands. She attended the Groene Hart Lyceum in Alphen aan den Rijn for pre-university education, and graduated cum laude in 2007. She had always felt the ambition to study Medicine, but her feeling for research was encouraged during a pre-university summer research internship on Multiple Sclerosis in the Weizmann institute in Israel in 2007.

She started her medical studies in the same year at the Leiden University Medical Centre (LUMC). During her studies, she received a grant from the LUMC to initiate PhD research during the bachelor, participating in the field of medication overuse headache and related psychiatric comorbidity. After graduating, she extended her PhD research, studying the clinical course and pathophysiology of chronic migraine under supervision of prof. Gisela Terwindt and prof. Michel Ferrari. Her research focuses on risk factors for migraine chronification, such as medication overuse, and involves different modalities to study chronification pathophysiology. Another important focus is the treatment of chronic migraine, for which she combined her PhD research with a clinical position in the LUMC headache clinic.

Whilst finalizing her thesis, she worked as a medical doctor in the Reinier de Graaf Gasthuis, Delft (January 2018 – September 2018) and HagaZiekenhuis, The Hague (October 2018 – September 2019) on the neurology department. She continued to work as a medical doctor in the LUMC, and started her training to become a clinical neurologist in 2020.

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Dankwoord

In de eerste plaats wil ik graag alle deelnemers aan mijn onderzoeken bedanken. Niet alleen de benodigde tijd, maar ook het ondergaan van (zoutoplossing) injecties, MRI scans in de avonduren en pijnprikkels was geen belemmering voor deelname. Jullie hebben geholpen om enkele puzzelstukken in de behandeling van chronische migraine te leggen.

Uiteraard ook mijn dank naar mijn promotoren Gisela Terwindt en Michel Ferrari. Gisela, als student heb je me altijd al geënthousiasmeerd en gemotiveerd voor het migraine onderzoek. Ik waardeer je inspanningen voor het tot stand komen van dit proefschrift, je supervisie tijdens het promotie traject, en niet in de laatste plaats de momenten dat we even met een kop koffie alle ontwikkelingen in de groep en het veld doornamen. Michel, dank voor de kansen die je hebt geboden, in internationale commissies of door presentaties op conferenties. Daarnaast voor je gevoel voor het overbrengen van een boodschap, scherpzinnige argumentatie en professionele verontwaardiging.

Natuurlijk wil ik ook de vele collega's waarmee ik in de decade die dit proefschrift omspant heb samengewerkt bedanken voor jullie gezelligheid, een gezonde portie humor en sarcasme op z'n tijd en de vele koffies en borrels. In het bijzonder mijn mede CHARMeurs, K5-roomies, congres-slapies, alle PhD's en betrokken verpleegkundigen. Zonder het gezamenlijke schuitje had onze onderzoeksperiode er anders uitgezien: het was goed om enkele jaren als een groot dispuut lief en leed, rebuttals en publicaties, bruiloften en kraamvisites met jullie te delen!

Maar geen enkel onderzoek wordt uiteindelijk een proefschrift zonder de hulp van het stafsecretariaat: hartelijk bedankt voor jullie ondersteuning gedurende de promotiejaren, gezelligheid, courgettes en vele tips and tricks.

Daarnaast mijn dank aan de neurologen in het Reinier de Graaf Gasthuis, Haga ziekenhuis en LUMC. Jullie hebben me met enthousiasme klaargestoomd voor de opleiding, laten zien hoe mooi ons vak is, maar ook hoe je dat vak op een mooie manier kunt uitoefenen. Dank voor de tijd danwel ondersteuning om dit proefschrift af te maken. Daarbij een speciale plek voor alle assistent-collega's,

verpleegkundigen, secretaresses, beveiliging en vele anderen, het ziekenhuis was met jullie, zeker tijdens alle weekenden en nachten, een gezellig tweede thuis!

Verder wil ik de vele vrienden bedanken die altijd met interesse bleven vragen hoe het met het proefschrift ging en ook nog het geduld en de empathie hadden voor het antwoord. Jullie vriendschap is ontzettend waardevol en heeft me door menig promotie-dip heen geholpen.

Tot slot aan mijn familie en inmiddels ook schoonfamilie: jullie weten hoeveel jullie voor mij betekenen en hoezeer ik jullie waardeer. Papa en mama, bedankt voor jullie onvoorwaardelijke steun en liefde. Waarschijnlijk zijn jullie de trouwste lezers van de rest van dit proefschrift. Robert, van tafeltennistafel vroeger op de camping tot doctorschap altijd mijn grote broer en vriend, dank je wel. Arco, mijn thuis, geluk is samen met jou door het leven gaan. Bedankt voor het stimuleren en structuren van mijn gedachten, en daarvoor bij dezen een officieuze acknowledgement voor menig inleiding en discussie in dit proefschrift.