Chronic frequent headache in the general population

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Chapter 1

Introduction to
chronic frequent headache in the general population

Chronic frequent headache (CFH) is a collective term for primary headaches occurring on more than 14 days per month for at least three months. Almost all patients start with episodic migraine or tension-type headache, which gradually becomes more frequent until their headaches are almost daily. As attack frequency increases, headache characteristics change. Migraine headaches often lose typical migraine features and become less severe, and tension-type headaches gain migraine features like nausea, making it difficult for the physician to diagnose the original headache type. The term chronic daily headache (CDH) is commonly used to describe these headaches. However, since patients do not necessarily have headaches every day, we prefer the term CFH.

The prevalence of CFH in the general population is around 4% worldwide.[1-4] CFH occurs in all ages. In elderly the prevalence of CFH was found to be 4%, while the actual prevalence in children has not been determined, but is estimated to be around 1%.[5] In the Netherlands, 13% of schoolchildren between the age of 10 and 17 years reported having headaches a few times per week.[6] The relatively high prevalence of CFH together with a low quality of life indicates that CFH is a serious health problem.

Quality of life of CFH patients in the general population is greatly impaired when compared to healthy controls.[7] Comorbidity can have a negative influence on quality of life as well. In migraineurs, quality of life reduces with increasing attack frequency and when combined with other chronic conditions.[8] In headache clinics, the majority of patients with CFH have a comorbid psychiatric disorder.[9-11] And there is evidence that anxiety and depression are associated with CFH in the general population as well. The extent to which comorbidity influences quality of life in CFH has not been studied.

There are limited data on the incidence and natural course of CFH. In a general population sample in the USA with a headache frequency of 2-104 days/year, the one-year cumulative incidence of CFH was 3%.[12] Subjects with a relatively high baseline frequency had an elevated risk for incident CFH. In a specialized headache centre in Germany 14% of patients with episodic migraine developed chronic headache during one year of follow-up.[13] A relatively high headache frequency of 10 – 15 days/month and use of acute headache medication on > 10 days/month were risk factors for chronification.

Overuse of acute headache medication is considered an important risk factor for CFH. In a community-based study conducted among Chinese elderly (> 64 years) CFH was associated with analgesic overuse and overuse was a predictor of persistent CFH at follow-up four years later.[14] Clinical experience suggests a causal relationship with overuse of acute headache medication because withdrawal of medication often results in a dramatic improvement of headache frequency.[15] Other factors that have been associated with CFH in the general population include female sex, low educational level, previously married status, arthritis, habitual snoring, and a history of migraine.[12,14,16] Because the control groups in these studies included subjects who rarely had headaches (only two headaches a year), these factors could be associated with having headaches regularly, rather than with chronic headache in particular.

Psychological factors may also play an important role in the chronification of headache. Multidimensional models of pain distinguish between sensory and affective components of pain perception, and many different brain regions are activated with pain perception.[17] Cognitive processes, like attention and distraction, can modulate pain perception as has been demonstrated by using functional magnetic resonance imaging.[18] The Gate Control Theory of Pain proposes that specific brain activity may open or close spinal-gating mechanisms, thereby increasing or decreasing pain.[19] Psychological factors may impact on pain experience via their influence on these mechanisms. Cognitive factors like catastrophizing and locus of control are associated with increased pain ratings and predict disability,[20] and personality factors have been associated with chronic headaches and substance abuse.[10,21] Since both cognitive and personality measurements can be influenced by presence of depression and anxiety, psychiatric comorbidity should be accounted for when studying relationships between psychological factors and CFH.

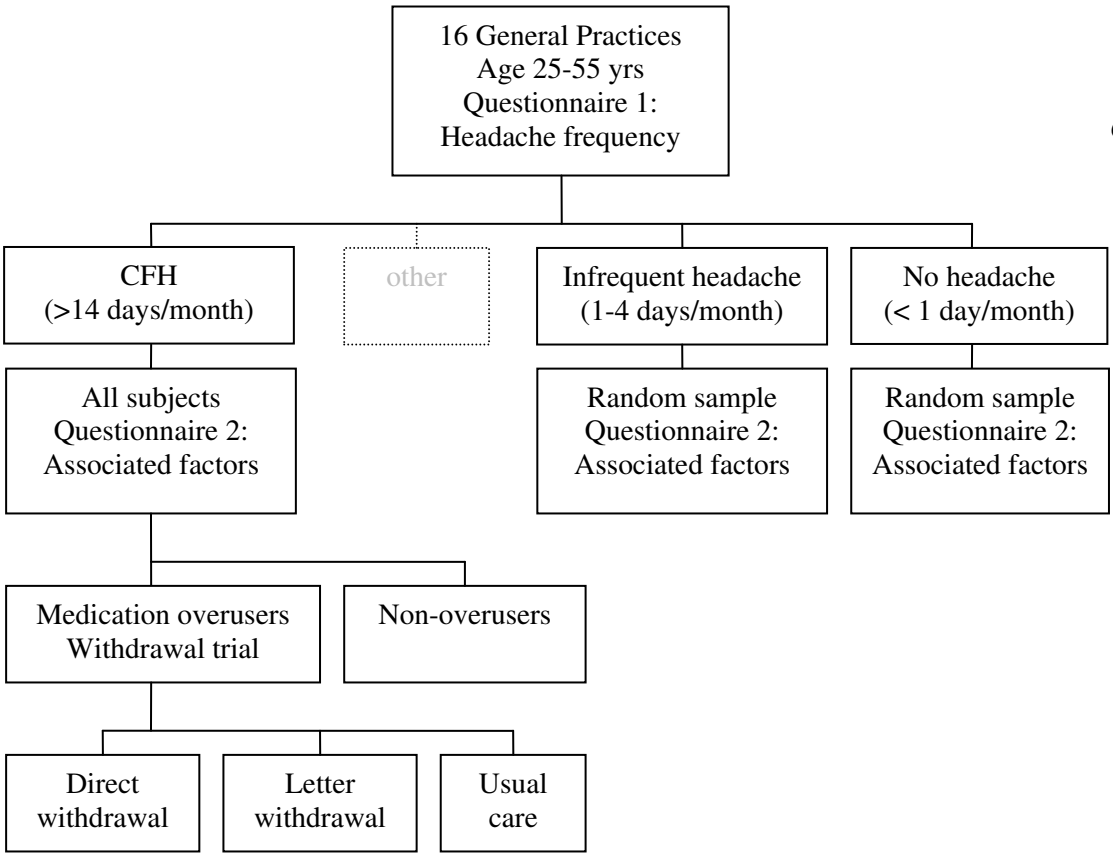
In general, if headache frequency increases to more than four days a month, preventive drug therapy should be considered. About two-thirds of migraine patients will have a 50% reduction in frequency.[24] Many patients however do not consult a doctor for headaches and treat themselves with over-the-counter products.[25] A temporary increase in headache frequency is often accompanied by an increase in acute medication use, which can lead to medication-overuse-headache (MOH) in susceptible patients. Pain relief by drug intake is a strong reinforcing factor, together with withdrawal headache when intake is reduced.

Withdrawal of all acute headache medication is the only appropriate treatment. There are however no placebo-controlled trials demonstrating efficacy of drug withdrawal, and spontaneous decrease of headache frequency has also been observed in general population surveys.[3,12] Most information on the effect of withdrawal comes from headache clinics, while the majority of MOH patients are to be found in the general population. It makes more sense to advise probable MOH patients to discontinue overuse in General Practice, before they are referred to headache specialists. Studies on the efficacy of withdrawal in General Practice are needed.

In conclusion, CFH is a serious health problem which affects a significant number of people. It is still largely unknown why some patients with episodic headache evolve into chronic frequent headache. Early detection of risk factors may improve prevention and management of CFH.

Aims of this thesis

We studied the prevalence and associated factors of CFH in the adult population in the Netherlands. The study is questionnaire-based, a quick overview is presented below. To identify putative risk factors for chronification of headache we compared subjects with CFH to subjects with infrequent headaches. Clinical and psychological features are described and the extent to which these factors contribute to the impact of headache on quality of life. In addition, we used data from the Drug Information Project (GIP database) of the Health Care Insurance Board (CVZ) to study triptan use and overuse in the Dutch general population. Given that medication overuse is a major problem in CFH in the general population and little is known about the optimal treatment, we evaluated the effect of withdrawal in medication overusing patients in General Practice. And lastly, we retrospectively studied clinical features of CFH in children and adolescents presenting to the neurology clinic of Leiden University Medical Centre.



Overview questionnaire study.

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Chapter 2

Chronic frequent headache in the general population - prevalence and associated factors –

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Abstract

We studied the prevalence and short-term natural course of chronic frequent headache (CFH) in the general population and identified risk factors. In the Netherlands everyone is registered at a single General Practice (GP). We sent questionnaires to all persons (n = 21,440) aged 25-55 years, registered at 16 GPs. We compared characteristics of 177 participants with CFH (> 14 headache days/month for > 3 months) to 141 participants with infrequent headache (1-4 days/month) and 526 without headache (<1 day/month). The prevalence of CFH was 3.7% (95% CI 3.4-4.0%). In five months, 12% showed a clinically relevant decrease to < 7days/month. In both headache groups 70% were women vs. 41% in the group without headache. Compared to the group with infrequent headache, the CFH group had more subjects with low educational level (35% vs. 11%; OR=4.3, 95% CI 2.3-7.8), medication overuse (62% vs. 3%; OR=38.4, 95% CI 13.8-106.9), sleeping problems (44% vs. 8%; OR=8.1, 95% CI 3.6-18.1), a history of head/neck trauma (36% vs. 14%; OR=4.0, 95% CI 2.2-7.1), high scores on the General Health Questionnaire (62% vs. 34%; OR=2.7, 95% CI 1.3-3.6), and more smokers (45% vs. 19%; (OR=3.1, 95% CI 1.9-5.3). We conclude that headache frequency fluctuates. Chronic frequent headache is common and associated with overuse of analgesics, psychopathology, smoking, sleeping problems, a history of head/neck trauma, and low educational level. Female sex is a risk factor for headache, not for chronification of headache.

Introduction

Chronic frequent headache (CFH), also known as chronic daily headache, is a collective term for primary headaches occurring on more than 14 days per month for at least three months. The prevalence of CFH in the general population is around 4% worldwide.[1-4] Many patients start with an infrequent episodic headache type (migraine or tension-type) that gradually becomes more frequent over time until their headaches are almost daily. The cause of this chronification process is unknown.

Clinical experience suggests a causal relationship with overuse of acute headache medication because withdrawal of medication often results in a dramatic improvement of headache frequency.[5] Several cross-sectional studies have reported an association between overuse and chronic headache. Two population-based studies in Spain and Taiwan reported that 25% and 34% of subjects with CFH overused acute headache medication.[1,4] These percentages were however not compared to control groups. In a community-based study conducted among Chinese elderly (> 64 years) CFH was associated with analgesic overuse (OR=79, 95% CI 19-321) and overuse was a predictor of persistent CFH at follow-up four years later.[6] Other factors that have been associated with CFH in the general population include female sex, low educational level, previously married status, arthritis, habitual snoring, and a history of migraine.[6-8] Because the control groups in these studies included subjects who rarely had headaches (only two headaches a year), these factors could be associated with having headaches regularly, rather than with chronic headache in particular.

There are limited data on the incidence and natural course of CFH. It is estimated that in a specialized headache centre 14% of patients with episodic migraine develop chronic headache during one year of follow-up.[9] In a general population sample in the USA with a headache frequency of 2-104 days/year, the one-year cumulative incidence of CFH was 3%.[8]
We studied the prevalence and short-term natural course of CFH in the Dutch general population. To identify risk factors for chronification of headache we compared subjects with CFH to subjects with infrequent headaches. Details on clinical features, comorbidity, personality profile, and impact on quality of life will be reported separately.

Methods

We studied the prevalence of CFH in the Dutch general population by sending a postal questionnaire (Q1) between January 2002 and September 2003 to all persons, aged 25-55, registered at 16 General Practitioners (GP), located in the regions of Leiden and The Hague. In the Netherlands almost everyone is registered at a single GP, which makes GPs' registers suitable for population-based studies. Leiden and The Hague are cities of 117,000 and 457,000 inhabitants respectively, located in the province of South-Holland, a mixed area with both urbanisation and agriculture. To minimise selective response, the primary objective (assessment of headache) was not explained, but a more general objective, namely evaluation of common health problems and self-treatment, was stated in a standard letter, signed by the GP. The questionnaire contained a number of headache-unrelated questions for masking reasons. We assessed headache frequency and medication use by the following questions: "On how many days per month on average did you suffer from headache in the past three months?" and "On how many days per month on average did you take medication to treat your headache?" We sent two reminders. Answers were given on a five-point frequency scale: on > 14 days/month (chronic frequent), on 8-14 days/month (very frequent), on 5-7 days/month (frequent), on 1-4 days/month (infrequent), and on < 1 day/month (none). Respondents were allocated into five groups according to headache frequency: Chronic Frequent Headache (CFH), Very Frequent Headache (VFH), Frequent Headache (FH), Infrequent Headache (IH) and No Headache (NH).

To identify factors associated with chronification of headache, we compared subjects with CFH (headache on > 14 days/month) to subjects with infrequent headaches (1-4 days/month). We also compared the CFH group to the No Headache group (< 1 day/month) to discern chronification factors from factors associated with headache in general. After about five months (range three to seven), all individuals who reported CFH and two random samples of the Infrequent Headache group and No Headache group (each twice as large as the case group), received a second, more detailed questionnaire (Q2) containing questions on demographics, lifestyle factors, and headache characteristics. We re-assessed headache frequency with the following question: "On how many days per month on average did you suffer from headache in the past six months?" For further analyses we selected subjects who had the same headache frequency in both Q1 and Q2 (i.e. the stable frequency group). The following additional risk factors were recorded: age of onset of headache, a family history

(first degree relatives) positive for headache, a history of head or neck trauma prior to the onset of headache, sleeping problems, tranquillizer use, use of acute headache medication and caffeine intake. Overuse was defined as: use of analgesics on ≥ 3 days/week, use of triptans on ≥ 2 days/week, use of ergots on ≥ 1 day/week, use of narcotics on ≥ 10 days/month, and use of > 5 caffeine units a day. A caffeine unit is one cup of tea, coffee, or caffeine containing soda. We also asked subjects whether they had consulted their GP for headache in the past six months.

The General Health Questionnaire (GHQ-28) was used to screen for psychopathology.[10] It includes four subscales: somatic physical illness and distress, anxiety/insomnia, social dysfunction, and severe depression, each consisting of 7 items. Answers are given on a 4-point Likert scale, ranging from 0 "better than normally" to 3 "much worse than normally", with scores ranging from 0 to 21 for each subscale. Scores can be recoded into (0,0,1,1) with a total scoring range of 0 to 28 (the GHQ scoring method). We used a cut-off score of 4/5 to define a GHQ case.[10] The GHQ-28 has a sensitivity of 0.84 and a specificity of 0.82 in detecting psychopathology.[10]

Q2 also contained other questions on clinical features of headache, comorbidity, quality of life, coping strategies, and personality profile. These results will be published separately. Subjects in the CFH group received one reminder. Non-respondent CFH subjects received a short questionnaire to assess possible selection bias and included main items such as demographic variables, headache frequency, and medication and caffeine use. The Very Frequent Headache (8-14 days/month) group were to be followed over time to study the incidence of and risk factors for CFH. The Frequent Headache group did not receive Q2 and was not further analysed.

Statistical analysis was performed with SPSS, version 11.0. Prevalences and differences between groups are presented with 95% confidence intervals (95% CI). We evaluated factors associated with chronification by comparing the CFH group to the Infrequent Headache group. Odds ratios are given for putative risk factors. We used the Mantel-Heanszel procedure to adjust for potential confounders.

The Medical Ethics Committee of Leiden University Medical Center approved the study.

Results

Sixteen GP practices participated in the study; seven located in the cities of Leiden and The Hague, five in urban areas and four in villages in rural areas. All GPs estimated the percentage of immigrants in their practice to be less than 10%, except for one practice, where 50% of patients were non-western immigrants, mainly from Turkey, Morocco, the Dutch Antilles and Suriname. In total 21,440 subjects received Q1, 16,232 (76%) completed Q1 and 1160 (5%) refused to participate or had moved (Figure 1). The response per practice varied between 69% and 84%, except for the practice with the high number of immigrants, where only 53% of subjects completed Q1.

Prevalence

Of all 16,232 participants, 679 reported to have CFH (4.2%, 95% CI 3.9-4.5). In the practice with the high number of immigrants the prevalence of CFH was 12.3% (95% CI 10.1–14.5). Without this practice, the prevalence of CFH was 3.7% (95% CI 3.4-4.0). Prevalences of the other headache frequency groups are shown in Figure 1. Of 679 CFH subjects, 430 (63%) used headache medication on more than 14 days/month, compared to 32 (4%) in the Very Frequent Headache group, 33 (2%) in the Frequent Headache group, 15 (0%) in the Infrequent Headache group, and 1 (0%) in the No Headache group.

Follow-up

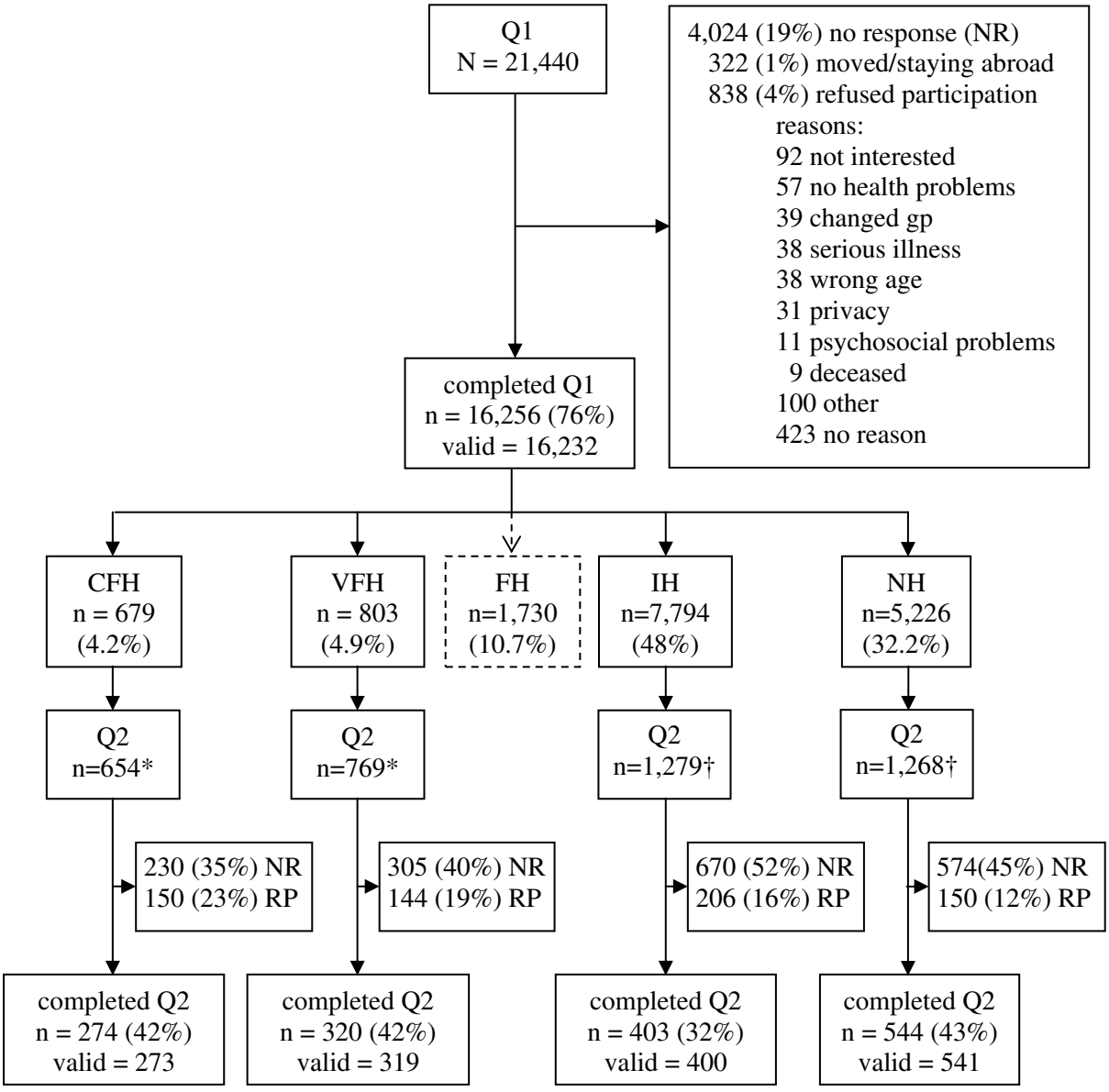
Q2 was sent to 3970 subjects. Time between Q1 and Q2 was five months on average (range three to seven months). A total of 1541 subjects (39%) completed Q2, 650 (16%) subjects refused to participate, and 1779 subjects (45%) did not respond. We excluded five subjects from analysis because they proved to be older than their registered age. Three subjects didn't complete Q2 properly and were excluded. Figure 1 shows the response per headache frequency group. Participants who had reported Infrequent Headache in the first survey (Q1) completed Q2 less often than the others.

Non-respondents analysis

In the CFH group 230 (35%) did not respond to Q2. Mean age of the non-respondents was 40 (SD 8), and 140 (61%) were female. Ninety-two (40%) non-respondents had a non-Dutch name indicating a foreign nationality. Sixty-eight (30%) non-respondents completed the short

non-response questionnaire, of which 24 (35%) had a low educational level and 37 (54%) did not have CFH anymore.

Figure 1. Flowchart of response.



* Some subjects didn't receive Q2 because they returned Q1 after the Q2 mailing date, † random sample (twice as large as the CFH group), Q1 = general health survey, Q2 = second detailed questionnaire, CFH = chronic frequent headache (>14 days/month), VFH = very frequent headache (8-14 days/month), FH = frequent headache (5-7 days/month), IH = infrequent headache (1-4 days/month), NH = no headache (<1 day/month), NR = no response, RP = refused to participate.

Frequency changes

Re-assessment of headache frequency in Q2 showed that of 273 subjects with CFH in Q1, 177 (65%) had a stable headache frequency of > 14 days/month, 62 (23%) had changed to Very Frequent Headache (8-14 days/month) and 34 (12%) now reported a headache frequency of less than 8 days/month (Table 1).

Table 1 Changes in headache frequency between Q1 and Q2

Headache frequency group Q1		Headache frequency group Q2 n (% of Q1 frequency group)				
Group	N	CFH (>14 d/m)	VFH (8-14 d/m)	FH (5-7 d/m)	IH (1-4 d/m)	NH (<1 d/m)
CFH (>14 d/m)	273	**177 (65%)**	62 (23%)	20 (7%)	12 (4%)	2 (1%)
VFH (8-14 d/m)	319	65 (20%)	**115 (36%)**	80 (25%)	41 (13%)	18 (6%)
IH (1-4 d/m)	400	3 (1%)	14 (4%)	45 (11%)	**141 (35%)**	197 (49%)
NH (<1 d/m)	540	1 (0%)	1 (0%)	1 (0%)	11 (2%)	**526 (97%)**
Q1 missing data	1					1 (100%)
Total Q2	1533	246	192	146	205	744

Q1 = general health survey, Q2 = second detailed questionnaire, CFH = chronic frequent headache (>14 days/month), VFH = very frequent headache (8-14 days/month), FH = frequent headache (5-7 days/month), IH = infrequent headache (1-4 days/month), NH = no headache (< 1 day/month). Numbers in bold are stable headache frequency groups (Q1 = Q2), in total 959 of 1533 subjects (63%). Time between Q1 and Q2 ranged from 3 – 7 months.

Overuse at baseline (Q1) was not a predictor for persistent CFH at Q2 (OR: 1.5, 95% CI 0.9 to 2.5). Vice versa, 65 (20%) subjects who had Very Frequent Headache (8-14 days/month) in Q1, changed to CFH over five months. Overuse at baseline (Q1) in this group was not a predictor for CFH in Q2 either (OR: 2.4 , 95% CI 0.9 to 6.5). In Q2, 109 (62%) of the stable CFH group still reported overuse of acute headache medication, compared to 26 (27%) of

those who had changed to lower headache frequencies, a difference of 35% (95% CI 23 to 46%). So, in the group who changed to lower frequencies, the percentage of overusing subjects decreased from 51% at baseline to 27% in Q2, while in the stable CFH group there was no change. To assess whether the subjects who changed to lower frequencies had received specific headache treatment we looked at GP consultation and prophylactic use. Remission was not attributable to treatment; only 20 (22%) subjects had consulted their GP for headache in the past six months compared to 56 (33%) in the stable CFH group (difference -11%, 95% CI –23 to 0%), and there was only a 3% difference in the use of prophylactic medication between both groups (95% CI –10 to 3%).

Demographics

Further analyses were limited to the groups in which the reported headache frequency did not change over the two surveys (i.e. the stable frequency groups). Table 2 shows the differences in demographic variables between subjects with CFH, Infrequent Headache and No Headache. In both headache groups the majority were women in contrast to the No Headache group where the majority were men.

Table 2 Demographic variables in stable CFH group vs. stable IH and NH groups

	NH N = 526	IH N = 141	CFH N = 177	difference CFH-IH (95%CI)	difference CFH-NH (95%CI)
Mean age, y (SD)	45 (9)	42 (8)	43 (8)	0.5 (-1.5 to 2.4)	-1.9 (-3.4 to -0.4)
Female, n (%)	215 (41)	97 (70)	125 (72)	2% (-8 to 12)	31% (22 to 39)
Educational level					
Low, n (%)	87 (17)	16 (11)	62 (35)	24% (15 to 33)	19% (12 to 26)
Medium, n (%)	180 (34)	47 (34)	70 (40)	6% (-4 to 17)	6% (-3 to 14)
High, n (%)	257 (49)	77 (55)	43 (25)	-30% (-41 to -20)	-24% (-33 to -17)

NH = no headache (< 1 day/month), IH = infrequent headache (1-4 days/month), CFH = chronic frequent headache (>14 days/month).

Risk factors

Mean age at onset of headache was 19 (SD 11) for the CFH group and 18 (SD 9) for the Infrequent Headache group. In both headache groups 62% of subjects had a family history positive for headache. Table 3 summarizes the prevalence and odds ratios for putative risk factors for chronification of headache.

Overuse of acute headache medication was strongly associated with CFH. Of the 109 subjects in the CFH group overusing acute headache medication, 90 (83%) subjects overused one class of medication, 16 (15%) and three (3%) subjects overused two and three different classes respectively. The percentage of smokers was similar in medication over-users (43%) and non-over-users (46%), mean difference 3% (95% CI -19 to 12%). Caffeine overuse was not associated with CFH. The average intake of caffeine in each group was seven units a day, including coffee, tea, ice-tea, and cola.

CFH subjects reported sleeping problems more frequently than subjects with Infrequent Headache. Sleeping problems were not related to caffeine use. In the CFH group 74 of 170 (44%) reported sleeping problems on > 3 nights/week; 66 (39%) had problems falling asleep and 26 (15%) awoke at night with headache. In contrast, 11 of 139 (8%) subjects with Infrequent Headache had sleeping problems on > 3 nights/week; all had problems falling asleep, none awoke at night with headache. Tranquillizer use was higher in the CFH group than in both control groups but was no longer associated with CFH after adjusting for frequent sleeping problems.

In the CFH group, 62% of subjects screen positive for psychopathology. This percentage was the same for the new CFH group (those who changed to CFH). With a sensitivity and specificity of 0.84 and 0.82 respectively, the true prevalence of psychiatric comorbidity in CFH is estimated to be 66%. Results of the GHQ-28 are presented in Table 4.

Table 3 Prevalence and odds ratios of putative risk factors for chronification of headache

	NH (n=526)	IH (n=141)	CFH (n=177)	difference CFH-IH (95%CI)	OR CFH-IH (95%CI)
Low educational level	87 (17)	16 (11)	62 (35)	24% (15, 33)	4.3 (2.3, 7.8)
Head/neck trauma prior to onset of headache	-	20 (14)	64 (36)	23% (14, 33)	4.0 (2.2, 7.1)*
Smoking	142 (27)	27 (19)	79 (45)	25% (15, 36)	3.1 (1.9, 5.3)*
Alcohol, glass/week	9	5	5	-0.5 (-2.4, 1.4)	-
Caffeine overuse	341 (65)	90 (64)	115 (65)	1% (-10, 12)	1.0 (0.6, 1.6)*
Acute headache medication overuse	19 (4)	4 (3)	109 (62)	59% (50, 67)	38.4 (13.8, 106.9)†
Paracetamol	4 (1)	1 (1)	79 (45)	44% (36, 52)	
NSAID's	14 (3)	3 (2)	41 (23)	21% (14, 28)	
Triptans	0	0	3 (2)	2% (-1, 4)	
Ergots	0	0	1 (1)	1% (-1, 2)	
Narcotics	1 (0)	0	7 (4)	4% (1, 7)	
Prophylactic medication	23 (4)	7 (5)	23 (13)	8% (2, 15)	2.3 (0.9, 5.9)*
Headache indication‖	1 (0)	0	15 (9)	8% (4, 13)	
Other indications	22 (4)	7 (5)	8 (5)	0% (-5, 4)	
Sleeping problems	-	11 (8)	74 (44)	36% (26, 45)	8.1 (3.6, 18.1)‡
Tranquillizer use	16 (3)	12 (9)	36 (20)	12% (4, 20)	1.7 (0.8, 3.7)§
Hypnotics	8 (2)	9 (6)	19 (11)	4% (–2, 11)	
Anxiolytics	9 (2)	4 (3)	20 (11)	8% (3, 14)	
GHQ-28 case	80 (16)	45 (34)	102 (62)	29% (18, 40)	2.7 (1.3, 3.6)§

Values are number of subjects (%) unless stated otherwise. * Adjusted for educational level, † adjusted for educational level and smoking, ‡ adjusted for educational level, smoking and medication overuse, § adjusted for sleeping problems. ‖ Subjects used medication which could have been prescribed for either headache or a

comorbid disorder (e.g. propanolol for migraine or hypertension). NH = no headache (< 1 day/month), IH = infrequent headache (1-4 days/month), CFH = chronic frequent headache (>14 days/month), NSAID = non-steroidal anti-inflammatory drugs, GHQ = General Health Questionnaire.

Table 4 General Health Questionnaire-28 scores

	NH (n=503)	IH (n =134)	CFH (n=164)	Mean difference CFH vs IH (95%CI)	Mean difference CFH vs NH (95%CI)
Total GHQ score	2.2 (4.0)	3.9 (4.8)	8.5 (7.4)	4.5 (3.1, 6.0)	6.3 (5.4, 7.2)
GHQ score > 4, n (%)	80 (16)	45 (34)	102 (62)	29% (18, 40)	46% (40, 53)
GHQ subscales:					
Somatic symptoms	3.2 (2.5)	5.8 (2.7)	9.7 (4.2)	3.9 (3.1, 4.7)	6.5 (6.0, 7.0)
Anxiety/insomnia	3.7 (3.7)	5.0 (4.2)	8.0 (5.1)	3.0 (1.9, 4.1)	4.3 (3.6, 5.0)
Social dysfunction	7.2 (1.9)	7.6 (2.4)	9.0 (3.4)	1.4 (0.7, 2.1)	1.8 (1.4, 2.2)
Severe depression	0.8 (2.4)	1.2 (2.2)	3.8 (4.9)	2.7 (1.8, 3.6)	3.0 (2.4, 3.5)

Values are means (SD) unless stated otherwise. NH = no headache (<1 day/month), IH = infrequent headache (1-4 days/month), CFH = chronic frequent headache (>14 days/month), GHQ = General Health Questionnaire.

Discussion

We found a prevalence of CFH in the Dutch general population of 3.7%. This is in accordance with previous population-based studies.[1-4] Although the prevalence worldwide is around 4%, we found a much higher prevalence in the practice with a high number of non-western immigrants. Even if we consider all non-respondents in this particular practice to have a low headache frequency, the prevalence would still be higher. In the Netherlands, prevalence of poor reported health is highest among Turks and Moroccans.[11] An adverse social and economic position may contribute to the poor health status of these ethnic minorities.

Our prevalence number is a reliable estimate due to the high response to the first questionnaire. The response to the second detailed and extensive questionnaire was low, but yielded high enough numbers to compare risk factors. Demographic characteristics were similar in the respondent and non-respondent CFH subjects, except for the higher percentage of non-Dutch names in the latter. As this is an indication for a foreign ethnic origin, the language of the questionnaire might have been too difficult. The question is whether non-response introduced bias in the associations. If non-respondents are healthier than respondents, prevalence estimates of risk factors based on respondents could be overestimated. However, non-response does not necessarily cause bias in associations. In a large population-based study on risk factors for chronic disease conducted in the Netherlands (MORGEN-project) the response rate was 45%. Associations between lifestyle factors and health did not vary according to response status.[12]

In many subjects headache frequency changed over time without specific headache treatment. Twelve percent had a clinically relevant decrease from >14 days to <8 days/month. This could be an underestimation, because the time between questionnaires ranged from three to seven months, meaning that some participants were asked about overlapping time periods. This spontaneous change in headache frequency can be seen as regression towards the mean[13] and underscores the need for control groups when assessing efficacy of treatments for CFH. A decrease in headache frequency was associated with a decrease in headache medication overuse. However, medication use at baseline could not predict outcome in Q2. Our data correspond with two population-based follow-up studies in the US and Taiwan, where after

one and two years respectively, only 44% and 35% still had CFH.[4,8] Whether subjects had received treatment or whether this was a spontaneous remission was not described.

We found that the majority of CFH subjects overused analgesics. The cross-sectional design of this study makes it impossible to determine the direction of causality. Improvement after withdrawal would make a causal relationship between overuse and chronification of headache likely. Since analgesics are mostly Over-The-Counter (OTC) products, the GP may not be informed about the overuse. In fact, the majority did not consult their GP for headache in the past six months. Many CFH subjects however frequently suffer from sleeping problems as well, and a substantial percentage use tranquillizers. Sleeping problems could be a possible cue for GPs to ask about headaches and analgesic use. Only 9% of CFH subjects used prophylactic medication to reduce headache frequency. To prevent overuse physicians should inform the headache patient about restricting use of acute headache medication and the possibility of prophylactic therapy.

Smoking is associated with CFH. We assumed that medication over-users would show an overall tendency towards substance use; however, tobacco use did not differ between over-users and non-over-users. Nicotine induces dopamine release in the ventral striatum causing positive mood changes, which may relieve negative consequences of pain. Since we don't have information on the age of onset of smoking, we don't know whether smoking could be more than a secondary phenomenon.

As found in other studies, CFH subjects had a lower educational level than subjects without CFH.[2,14] A low educational level is an indication of low socio-economic status, which is associated with poor health status in general. We don't think that headache interfered with scholarly achievements, because the mean age at onset of headache was 19.

About one third of CFH subjects reported a history of head or neck trauma prior to the onset of headache. This may be partly due to recall bias. On the other hand, tissue injury might have triggered central sensitisation, a pathologic change in central pain processing observed in models of chronic pain.[15]

In headache clinics, the majority of patients with CFH have co-morbid psychiatric disorders.[16-18] The most commonly reported disorders are major depression and generalized anxiety disorder, panic disorder, and phobias. In our population-based study, 62% of subjects with CFH screened positive for psychopathology, twice as many as in the Infrequent Headache group. Breslau et al. found a bi-directional relationship between migraine and major depression, suggesting shared etiologic factors.[19] Alternatively, pain may exacerbate a pre-existing vulnerability to psychopathology, which in turn intensifies the pain and so on.[20] This would imply that either condition cannot be treated independently of the other.

The strength of our study is the large number of participants and the identification of associated factors by comparing the CFH group to control groups with infrequent headache and no headache. In both headache groups the majority were women, in contrast to the No Headache group. Female sex seems to be a risk factor for headache, not for the chronification of headache. A limitation of our study is that prevalence of risk factors is based on self-report, which is not as accurate as studies based on interviews by specialists and headache diaries. We conclude that headache frequency fluctuates spontaneously and chronification is common. In the Netherlands the prevalence of CFH in the general population, aged 25-55 years, is 3.7%. We identified several risk factors to be associated with CFH including overuse of analgesics, psychiatric comorbidity, smoking, sleeping problems, a history of head/neck trauma, and low educational level.

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Chapter 3

Chronic frequent headache in the general population - comorbidity and quality of life -

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Abstract

We studied the nature and extent of comorbidity of chronic frequent headache (CFH) in the general population and the influence of CFH and comorbidity on quality of life. Subjects with CFH (headache on >14 days/month) were identified in a general health survey. We sent a second questionnaire including questions on comorbidity and quality of life to subjects with CFH and subjects with infrequent headache (IH) (1-4 days/month). We recoded comorbidity by using the Cumulative Illness Rating Scale (CIRS) and measured quality of life with the RAND-36, a Dutch version of Short Form-36. CFH subjects (n=176) had higher comorbidity scores than the IH subjects (n=141). Mean CIRS scores were 2.94 for CFH and 1.55 for IH (mean difference 1.40, 95%CI 0.91-1.89). Mean number of categories selected was 1.92 in CFH and 1.10 in IH (mean difference 0.82, 95%CI 0.54-1.11). Fifty percent of CFH subjects had a comorbidity severity level of at least two, indicating disorders requiring daily medication, compared to 28% of IH subjects (mean difference 22%, 95%CI 12 to 33). CFH subjects had more musculoskeletal, gastro intestinal, psychiatric and endocrine/breast pathology than the IH subjects. Quality of life in CFH subjects was lower than IH subjects in all domains of the RAND-36. Both headache frequency and CIRS score had a negative influence on all domains. We conclude that patients with CFH have more comorbid disorders than patients with infrequent headaches. Many CFH patients have a comorbid chronic condition requiring daily medication. Both high headache frequency and comorbidity contribute to the low quality of life in these patients.

Introduction

Epidemiologic studies on comorbidity of headache disorders have focused primarily on psychiatric disorders. Migraine has been repeatedly found to be associated with major depression and anxiety disorders.[1-4] Breslau et al. found a bi-directional relationship between migraine and major depression; a history of major depression is a risk factor for migraine and migraine increases the risk for major depression.[3] They suggested that shared underlying factors explain the co-occurrence of the two disorders, rather than major depression being a psychological response to recurrent severe headaches.

Chronic frequent headache (CFH), also known as chronic daily headache, is defined as headache on more than 14 days per month for at least three months. Around 4% of the general population suffer from CFH.[5,6] In headache clinics, the majority of patients with CFH have a comorbid psychiatric disorder.[7-9] The most commonly reported disorders are major depression and generalized anxiety disorder, followed by panic disorder and phobias. High headache frequency and chronic substance use are associated with higher scores on anxiety and depression scales.[10,11] In a general population sample, aged > 64 years, a high score on a depression scale was associated with CFH and subjects with CFH were at increased risk of major depression at follow-up.[12]

Few studies have explored comorbidity of headache with somatic disorders. Associations of migraine with epilepsy, stroke, asthma, and chronic musculoskeletal pain have been reported [13-15]. CFH has been associated with allergies, asthma, hypothyroidism, hypertension, sleep disorders, and fibromyalgia.[16,17] These studies were conducted in headache clinics, which might have led to an overestimation of associations, because referred patients may represent a selected, difficult to treat, population. To avoid this bias, population-based studies are preferred.

The overall comorbidity of CFH in the general population has not been studied systematically. Co-occurrence of diseases can complicate diagnosis, due to symptomatic overlap of both conditions, and can have important implications for treatment. Moreover, comorbidity can have a negative influence on quality of life. Quality of life is reduced in subjects with CFH and is greatly influenced by anxiety and depressive disorders.[18-20] We

studied the nature and extent of comorbidity in CFH patients in the general population and examined the influence of CFH and comorbidity on quality of life.

Methods

We conducted a general health survey amongst all persons, aged 25-55, registered at 16 general practices in the province of South-Holland in The Netherlands in 2003. This sample represents the general population because in the Netherlands all individuals are registered at a general practice. The study design and methodology have been described in detail previously.[21] In short, 76% completed the general health survey. We identified subjects with CFH, defined as headache on > 14 days per month during the past three months, and sent them a second, more detailed, questionnaire containing questions on comorbidity and quality of life. Forty percent completed the questionnaire. Non-responders showed no relevant demographic differences with the responders. A random sample of subjects with infrequent headache (IH), defined as headache on 1-4 days per month, served as control group. The majority (62%) of subjects with CFH overused acute headache medication. This study was conducted before the publication of the revised IHS criteria for medication overuse headache. We defined overuse as: the use of analgesics on ≥ 3 days/week, the use of triptans on ≥ 2 days/week, the use of ergots on ≥ 1 day/week, or the use of narcotics on ≥ 10 days/month. Overuse consisted mainly of analgesics, only 3 (2%) overused triptans, 1 ergotamine, and 7 (4%) narcotics.

Comorbidity was assessed by the following open questions: 1) "Do you have a disorder for which you have to consult your physician regularly?", 2) "Do you have other disorders for which regular consultation is not necessary at the moment?", 3) "Have you been admitted to hospital in the past? If yes, please specify.", 4) "Which medication (including painkillers) do you use?". We recoded answers by using the Cumulative Illness Rating Scale (CIRS).[22] The CIRS is a reliable and validated comorbidity questionnaire and shows close resemblance to common clinical practice: it is structured according to 14 body systems and uses a clear severity ranking that is clinically sound.[23-27] The worst problem in a specific organ system is rated on a scale from 0 to 4 (0=none, 1=current mild problem or significant problem in the past, 2=moderate disability/requires daily medication, 3=severe/constant disability, uncontrollable chronic problem, 4=extremely severe/immediate treatment required/end organ

failure/severe impairment in function). Five summary scores can be calculated (total CIRS score, total number of categories endorsed, severity index (total score/total number of categories), and number of level 3 and 4 severity.[22] Total CIRS score was our main outcome measure. Headache, our index disease, was not rated as a comorbid disorder. Whenever the manual of the CIRS was not clear about how to rate a certain symptom or disease, we rated the symptom by consensus and used a data file to record our decisions. We modified the psychiatric illness rating as follows: current usage of daily antidepressants or anxiolytics without sleeping problems was rated as severity 2, and psychiatric illness with daily use of two medications as severity 3. Frequent sleeping problems were listed under neurological comorbidity, with occasional use of hypnotics as severity 1 and daily use of hypnotics as 2. Use of benzodiazepines without a specified indication was rated according to their registered indication (e.g. diazepam as anxiolytic).

Quality of life was measured by the RAND-36, a Dutch version of the RAND-36-Item Short Form Health Survey, a commonly used generic quality of life questionnaire.[28] The RAND-36 has been shown to have excellent reliability and validity when employed with diverse patient populations in the Netherlands.[29] It consists of eight domains of well-being and functioning, including Physical Functioning (PF), Social Functioning (SF), Physical Role Functioning (PRF), Emotional Role Functioning (ERF), Mental Health (MH), Vitality (V), Bodily Pain (BP), and General Health (GH), and an additional item, Health Transition (HT). The scales range from zero to 100, with higher scores indicating better quality of life.

Data analysis was performed using SPSS 11.0. Differences are presented with 95% confidence intervals (95%CI). Differences in comorbidity categories and quality of life domains between CFH subjects and IH subjects were tested for significance. Due to multiple comparisons we applied a Bonferroni adjustment yielding an alpha level of 0.003 for the CIRS categories and 0.006 for the RAND-36 domains.[30] The relationship between RAND-36 scores and CIRS scores was investigated using Spearman's rank order correlation. Values between 0.10 and 0.29 were considered to indicate a weak correlation, between 0.30 and 0.49 a medium strong correlation, and between 0.50 and 1.0 a strong correlation. Hierarchical multiple regression analysis was used to examine the relationship between each RAND-36 domain and headache frequency (case status) while controlling for educational level and CIRS score.

Results

Table 1 shows the demographic characteristics of both headache groups. The CFH group had more subjects with a lower educational level.

Table 1 Demographic characteristics of CFH and IH groups

	CFH N = 177	IH N = 141	difference % (95% CI)
Mean age, y (SD)	43 (8.4)	42 (8.0)	0.5 (-1.5 to 2.4)
Female, n (%)	125 (72)	97 (70)	2% (-8 to 12)
Low educational level, n (%)	62 (35)	16 (11)	24% (15 to 33)

CFH = chronic frequent headache (>14 days/month), IH = infrequent headache (1-4 days/month).

The presence of comorbidity is summarised in Table 2. One CFH subject didn't complete the comorbidity section of the questionnaire and was excluded from analysis. In both headache groups, the majority currently had or had had in the past at least one comorbid problem. Sixty percent of 149 CFH subjects with any comorbidity had a severity level of at least two, indicating disorders requiring daily medication (e.g. hypertension).

In both groups the most prevalent comorbid disorders were in the gastro intestinal and musculosketal/skin categories. In the CFH group 21 of 24 subjects (88%) with upper gastro intestinal problems reported heartburn, 19 used antacids or acid suppressants of which six in combination with NSAIDs. In the IH group four of seven subjects (57%) used acid suppressants. Lower gastro intestinal problems were mainly appendectomies in the past; 16 (9%) CFH, 5 (4%) IH, or other operations; 7 (4%) CFH, 7 (5%) IH. In the musculoskeletal/skin category, joint operations in the past; 19 (11%) CFH, 14 (10%) IH, and arthritis; 10 (6%) CFH, 5 (4%) IH, were the most commonly reported disorders, followed by back pain; 9 (5%) CFH, 6 (4%) IH, and neck pain/whiplash; 7 (4%) CFH, 0 IH. Six CFH subjects (3%) reported fibromyalgia, none in the IH group. Dermatologic disorders were reported only once in the CFH group and four times in the IH group.

Table 2 Presence of comorbidity in the CFH group vs. IH group

	CFH, N = 176	IH, N = 141	difference % (95% CI)
Presence of any comorbidity	149 (85)	91 (65)	20% (11 to 29)*
Comorbidity with severity level ≥ 2	88 (50)	39 (28)	22% (12 to 33)*
Comorbidity with severity level ≥ 3	29 (17)	13 (9)	7% (0 to 15)
Comorbidity categories endorsed*			
Heart	6 (3)	3 (2)	1% (-2 to 5)
Vascular	24 (14)	17 (12)	2% (-6 to 9)
Haematopoietic	4 (2)	2 (1)	1% (-2 to 4)
Respiratory	19 (11)	7 (5)	6% (0 to 12)
Eyes, Ears, Nose, and Throat	33 (19)	19 (14)	5% (-3 to 14)
Gastro Intestinal	54 (31)	23 (16)	14% (5 to 24)*
Upper Gastro Intestinal	24 (14)	7 (5)	9% (2 to 15)*
Lower Gastro Intestinal	37 (21)	16 (11)	10% (1 to 18)*
Liver	7 (4)	2 (1)	3% (-1 to 6)
Renal	4 (2)	4 (3)	-1% (-4 to3)
Genitourinary	24 (14)	16 (11)	2% (-5 to 10)
Musculoskeletal/Skin	60 (34)	32 (23)	11% (1 to 21)*
Neurological	41 (23)	18 (13)	11% (2 to 19)*
Endocrine/Breast	21 (12)	3 (2)	10% (4 to 16)*†
Psychiatric	33 (19)	8 (6)	13% (6 to 20)*†

Values are n (%). *95% CI excludes the neutral value of no difference (0%), † Bonferroni: $p < 0.003$. CFH = Chronic Frequent Headache, IH = Infrequent Headache.

CFH subjects had more endocrine/breast, psychiatric and neurological pathology than the IH subjects. The endocrine/breast group consisted of a sum of several disorders; thyroid pathology, diabetes, and breast cancer. In the psychiatry group the following comorbid problems contributed most to the ratings: depressive mood or current use of antidepressants; 11 (6%) CFH, 2 (1%) IH, anxiety disorder or current use of anxiolytics; 13 (7%) CFH, 3 (2%) IH, current use of both antidepressants and anxiolytics; 5 (3%) CFH, 1 (0%) IH. The differences in neurological ratings were mainly due to sleeping problems or current use of hypnotics; 22 (13%) CFH, 9 (6%) IH. Other reported disorders were epilepsy; 6 (3%) CFH, hernia; 5 (3%) CFH, 3 (2%) IH, and miscellaneous disorders; 8 (5%) CFH, 6 (4%) IH. In both psychiatric and endocrine/breast categories the difference between CFH subjects and IH subjects was significant at the adjusted alpha level of 0.003, however not in the gastro intestinal, musculoskeletal and neurological categories.

CFH subjects had higher total CIRS scores than the IH subjects (Table 3). Median number of categories endorsed was two in the CFH group vs. one in the IH group. CFH was associated with a CIRS comorbidity level of at least 2 with a crude odds ratio of 2.6 (95%CI 1.6 to 4.2), and adjusted for educational level 2.2 (95%CI 1.3 to 3.5). In the CFH group overusers had higher total CIRS scores than non-overusers (Table 4), but severity was not significantly higher.

Table 3 CIRS scores

	CFH N = 176	IH N = 141	difference (95% CI)
Total CIRS score	2.94 (2.52)	1.54 (1.75)	1.40 (0.91 to 1.89)
Number of categories endorsed	1.92 (1.42)	1.10 (1.10)	0.82 (0.54 to 1.11)
Severity Index	1.47 (0.48)	1.36 (0.51)	0.11 (-0.02 to 0.23)
Comorbidity severity level 3, n (%)	27 (15)	13 (9)	6% (-1 to 14)
Comorbidity severity level 4, n (%)	2 (1)	0 (0)	1% (-1 to 3)

Values are means (SD), unless stated otherwise. CIRS = Cumulative Illness Rating Scale, CFH = chronic frequent headache, IH = infrequent headache.

Table 4 CIRS scores in overusers compared to non-overusers

	Overuse N = 109	No overuse N = 67	difference (95% CI)
Total CIRS score	3.34 (2.62)	2.28 (2.21)	1.06 (0.30 to 1.81)
Number of categories endorsed	2.11 (1.43)	1.60 (1.35)	0.51 (0.08 to 0.94)
Severity Index	1.51 (0.50)	1.38 (0.44)	0.13 (-0.03 to 0.29)
Comorbidity severity level ≥ 2, n (%)	61 (56)	27 (40)	16% (0 to 31)
Comorbidity severity level 3, n (%)	21 (24)	6 (9)	15% (-1 to 14)
Comorbidity severity level 4, n (%)	2 (2)	0 (0)	2% (-1 to 5)

Values are means (SD), unless stated otherwise. CIRS = Cumulative Illness Rating Scale.

Quality of life of CFH subjects was lower in all domains of the RAND-36 compared to the IH subjects (Figure 1).

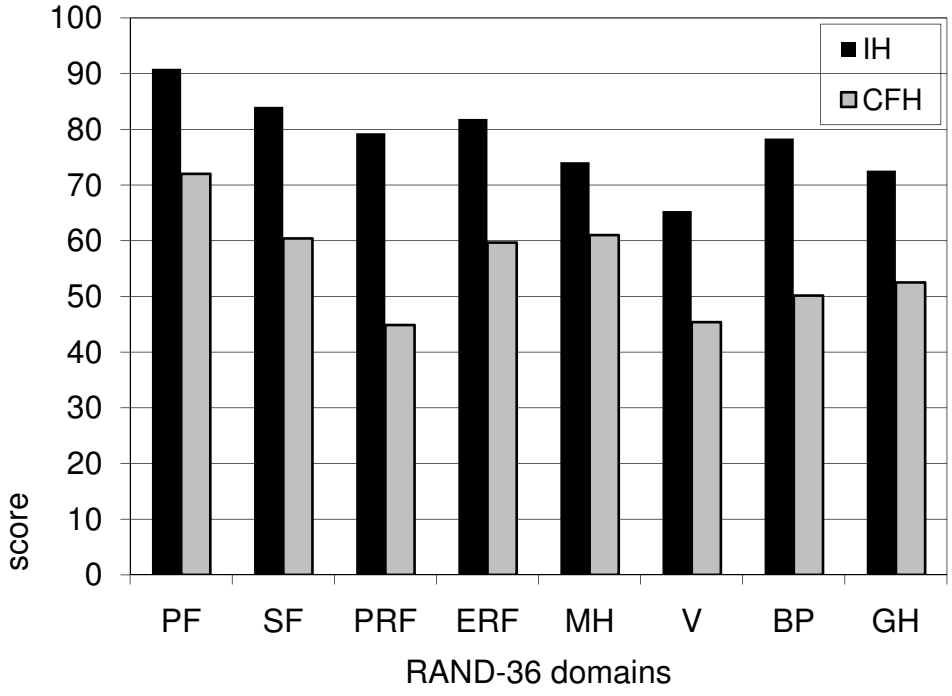

Figure 1 Mean RAND-36 scores[28] in the Chronic Frequent Headache (CFH) (n=173) and Infrequent Headache (IH)(n=141) group. CFH differs significantly from IH in all domains ($p<0.001$). PF = physical functioning, SF = social functioning, PRF = physical role functioning, ERF = emotional role functioning, MH = mental health, V = vitality, BP = bodily pain, GH = general health.

Scores for Health Transition were 45.2 in the CFH group and 54.6 in the IH group, mean difference –9.4 (95%CI –14.3 to –4.5). Small differences in quality of life between subjects who overused acute headache medication and those who didn't were not statistically significant (Figure 2).

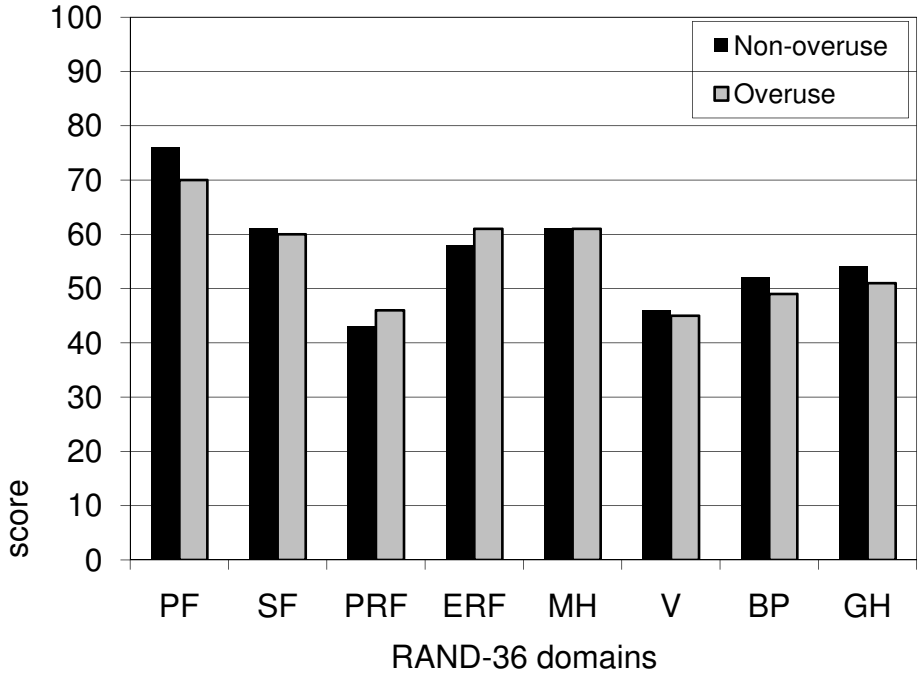

Figure 2 Mean RAND-36[28] scores in the Chronic Frequent Headache(CFH) group with (n=107) and without (n=66) overuse of acute headache medication. Differences are not statistically significant. PF = physical functioning, SF = social functioning, PRF = physical role functioning, ERF = emotional role functioning, MH = mental health, V = vitality, BP = bodily pain, GH = general health.

All domains of the RAND-36 were negatively correlated with CIRS score (Table 5). Hierarchical multiple regression showed that after controlling for educational level and CIRS score, CFH case status remained an independent predictor of all RAND-36 domains. Case status explained 5% (Emotional Role Functioning) to 25% (Bodily Pain) of the variance.

Table 5 Relation between quality of life and comorbidity.

Quality of life: RAND-36 domains	Comorbidity: Correlations with CIRS score
Physical functioning	-.47*
Social functioning	-.29*
Physical role functioning	-.28*
Emotional role functioning	-.20*
Mental health	-.24*
Vitality	-.31*
Bodily pain	-.34*
General health	-.50*

Values are Spearman's rho. * P < 0.001. CIRS = Cumulative Illness Rating Scale [22], RAND-36 = quality of life questionnaire[28].

Discussion

As far as we know, the overall comorbidity of CFH has not been studied systematically in a population-based sample before. Subjects with CFH reported more somatic and psychiatric comorbidity than subjects with infrequent headaches. Overusers reported more comorbidity than non-overusers. Fifty percent of the CFH subjects had a comorbid problem causing at least moderate disability or requiring daily medication (severity level 2 or more).

The CIRS is meant to give a global estimate of medical burden taking into account both the presence and the severity of disorders. Its accuracy depends on the ability of subjects to report diseases. Self-reports have shown to be reasonably accurate for estimations of prevalent health conditions.[24,31] The number of comorbid problems in our study is lower than reported in other studies using the CIRS.[24,25] This is probably due to the lower mean age of our participants and the population-based setting. We think our results are a reliable estimate of the overall prevalence of comorbidity in headache patients in the general population. Twenty-eight percent of subjects in the Infrequent Headache group had a comorbid disorder of at least severity level 2. This is in accordance with another study conducted in The Netherlands,[32]

where the prevalence of two or more co-occurring chronic or recurrent diseases within one person in general practice was 29.7%.

Musculoskeletal problems were frequently reported. Although not significant after Bonferroni correction, chronic pain conditions tended to be present more frequently in CFH subjects than in IH subjects. Headache has been associated with musculoskeletal pain in the general population before; migraine was associated with chronic back pain, and low back pain in adolescents with headache.[15,33] In a headache clinic, Peres et al. diagnosed fibromyalgia in 36% of chronic migraine patients.[16] Although we didn't find such a high prevalence, six CFH subjects reported fibromyalgia vs. none in the IH group. Central sensitization, a pathologic change in central pain processing, could play a role in the co-occurrence of these chronic pain conditions.[34]

Many CFH subjects reported gastro intestinal problems. Heartburn, a symptom of gastroesophageal reflux disease, was the most frequently reported upper gastro intestinal disorder. It is a common health problem and has considerable impact on quality of life.[35] Heartburn in the CFH group could not be contributed entirely to NSAID gastropathy since only 25% of CFH subjects with heartburn used NSAIDs. The higher gastro intestinal comorbidity in CFH subjects compared to IH subjects might reflect a higher anxiety and perceived stress level in CFH subjects.[36]

The prevalence of psychiatric disorders in CFH in the general population has never been studied. In elderly in Taiwan, CFH was associated with high scores on a depression scale.[12] Studies in headache clinics showed that CFH was associated with depression and anxiety disorders.[7-9] It was not surprising therefore to find more psychiatric pathology in the CFH group than in the IH group. However, the percentage of subjects with psychiatric comorbidity in the CFH group was lower than expected. Previously we found that the majority of our CFH subjects screen positive for psychopathology on the General Health Questionnaire.[21] The prevalence of self-reported psychiatric comorbidity might be underestimated due to hesitation to report psychiatric problems or simply because they have not been diagnosed yet. True prevalence of psychiatric disorders can only be assessed by an interview based on criteria of the Diagnostic and Statistical Manual of Mental Disorders.

Endocrine/breast disorders were present more frequently in the CFH group than in the IH group. The endocrine/breast category consisted of various disorders, the numbers were too small for meaningful sub-analyses.

The RAND-36 scores in the IH group are similar to normal values. Quality of life is clearly impaired in the CFH group. Physical Role Functioning and Vitality scored the lowest. The difference between CFH and IH is most marked for Physical Role Functioning and Bodily Pain. The Physical Role Functioning domain measures whether one cannot fulfill their role/work because of a physical problem. Considering the high prevalence of CFH, the low score in this particular domain implies that CFH does not only affect a subject's personal life but has a major impact on society as well. Our results are comparable to other studies. In Spain, two studies found similar decreases of quality of life measured with the SF-36 in subjects with CFH in the general population. Both Colas et al. and Guitera et al. found Physical Role Functioning, Bodily Pain and Vitality to be the most affected domains.[19,20] Guitera et al. also found that subjects with analgesic overuse scored lower than the non-overusers in all domains, especially Physical Functioning and Bodily Pain. In our study the small differences between overusers and non-overusers were not statistically significant, indicating that overuse causes only minor to no extra impairment. Both headache frequency and comorbidity had a negative influence on quality of life. Logically, headache frequency showed a strong influence on Bodily Pain and CIRS score on General Health.

A limitation of this study is that comorbidity rating is based on open general questions on comorbid disorders. If questions on specific symptoms, like joint or back pain, would have been included, we assume that certain body systems (e.g. musculoskeletal) might have scored higher. Our data also lacked information on various objective parameters like body mass index, and levels of serum cholesterol and hemoglobin, data that would surely have increased endocrine, vascular, and hematopoeitic comorbidity scores. However, we did not aim to find specific disease prevalence rates or associations, but rather wanted to have an impression of the extent of comorbidity known to and thus most likely providing burden to the headache patient. Causal relationships cannot be proved by this cross-sectional study.

In conclusion, CFH patients in the general population have more somatic and psychiatric comorbidity than patients with infrequent headaches. Many CFH patients have a comorbid

chronic condition requiring daily medication. Both high headache frequency and comorbidity contribute to the low quality of life in these patients. The relatively high prevalence of CFH, the high comorbidity rate, and the low quality of life, indicate that CFH is a major health problem.

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Chapter 4

The role of catastrophizing and locus of control in chronic frequent headache

Submitted

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Abstract

We studied the role of cognitive and personality factors in the chronification of episodic headache and headache impact. Subjects from the general population with chronic frequent headache (CFH: headache on ≥ 15 days/month) and subjects with infrequent headache (IH: 1-4 days/month) received a questionnaire including the Pain Coping and Cognition List, the Temperament and Character Inventory, the Headache Impact Test, and the General Health Questionnaire. The CFH group (n=171) scored higher on catastrophizing (2.8 vs. 1.9), degree of pain coping (3.4 vs. 3.0) and external pain control (3.0 vs. 2.3) than the IH group (n=140), and lower on internal pain control (3.2 vs. 3.7). CFH subjects scored lower on the personality dimension self-directedness than the IH subjects, difference -1.6 (95% CI (-2.3 to -1.0), and higher on harm-avoidance, difference 1.1 (95% CI 0.2 to 1.9). After adjusting for educational level and presence of psychopathology, personality dimensions were no longer associated with CFH. Headache impact scores were 61 in the CFH group compared to 51 in the IH group (difference 10, 95% CI 8 to 11). Only catastrophizing and internal pain control made a unique contribution to headache impact after controlling for demographics, headache status and psychopathology. In conclusion, CFH is associated with catastrophizing, low internal pain control and high external pain control. Personality factors do not pose an additional risk factor for chronification. Headache impact is primarily determined by headache frequency and catastrophizing.

Introduction

Chronic frequent headache (CFH) is a collective term for primary headaches occurring on 15 days per month or more, for at least three months. The prevalence in the general population is 4% worldwide.[1-5] The cause of CFH is unknown.

Psychological factors play an important role in pain perception. Cognitive processes can modulate pain perception as has been demonstrated by fMRI.[6-8] Catastrophizing is a negative pain-related cognition and refers to individuals who exaggerate the seriousness of a pain sensation, constantly focus their attention on pain and worry about the consequences. Catastrophizing has been shown to be associated with increased pain ratings and disability, also when the presence of depression is taken into account.[9] Another important psychological construct is locus of control, which refers to the belief that the factors that influence the onset and course of pain are either within the individual's control (internal, e.g. self-imposed work pressure) or outside the individual's control (external, e.g. inherited vulnerability). Internal locus of control has been associated with positive adjustment to frequent headaches because of greater confidence to self-manage pain and use of positive psychological coping strategies.[10] Coping is defined as efforts to manage events that are perceived as stressful.[11] Personality factors have also been associated with heightened pain responses, and chronic headaches.[12,13]

The objective of our study was the identification of putative cognitive and personality risk factors for chronic frequent headache in the general population. A secondary objective was to examine which factors contributed most to the impact of frequent headaches.

Methods

Participants. We conducted a general health survey (Q1) from 2002 – 2003 amongst all persons, aged 25-55, registered at 16 general practices in The Netherlands. This sample represents the general population because in the Netherlands virtually all individuals are registered at a single general practice. The study design and methodology have been described in detail previously.[5] Subjects were asked on how many days per month they had had headaches in the past three months. We categorized headache frequency because patients often have difficulty estimating retrospectively the exact number of headache days per month.

All CFH subjects (defined as headache on ≥ 15 days/month during the past three months) and a random sample of subjects with infrequent headache (1-4 days/month) received a second, more detailed, questionnaire (Q2). In addition to questions on headache characteristics and treatment, Q2 contained validated questionnaires described below. In total 21,440 subjects received Q1, and 16,232 (76%) completed Q1. Q2 was sent to 654 CFH subjects and completed by 273 (42%) subjects. In the infrequent headache group 1,279 subjects received Q2, which was completed by 400 (32%). The non-respondent analysis showed no relevant differences in age, sex and educational level. Re-assessment of headache frequency in Q2 showed that headache frequency had changed in many subjects. We limited further analyses to the groups in which the reported headache frequency did not change over the two surveys; 177 CFH subjects and 141 infrequent headache subjects.

The majority (62%) of the CFH group overused acute headache medication. We conducted our study before the revised criteria for medication overuse were published in 2005.[14] Therefore, we retrospectively reclassified our subjects according to the new criteria. Overuse is present when patients use simple analgesics on ≥ 15 days/month or other acute headache medication like combination analgesics or triptans on ≥ 10 days/month.

Headache Impact Test. We assessed the impact of headache on daily life by the Headache Impact Test (HIT-6).[15] This is a validated questionnaire consisting of six items that cover various content areas of health-related quality of life: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Answers are given on a five-point scale ranging from "never" to "always", each answer counts for 6, 8, 10, 11, or 13 points respectively. All items are summed to a total HIT-6 score that ranges from 36 to 78. Higher scores indicate a greater disability, with scores of 49 or lower reflecting "little or no impact" and above 60 "severe impact".

Pain Coping and Cognition List. We assessed coping and cognitions by the Pain Coping and Cognition List (PCCL), a validated Dutch self-report questionnaire.[16] The PCCL consists of 42 items, subdivided into four subscales: degree of pain catastrophizing (negative thoughts about the consequences of pain and dramatization), degree of pain coping (adopting different strategies, like seeking distraction, to deal with pain), internal pain control (positive expectancies about personal control over pain), and external pain control (positive

expectancies about control over pain by doctors or God). Answers are given on a six-point Likert scale ranging from "totally disagree" to "totally agree". For each subscale the scores are summed and divided by the number of items to calculate mean scores. To make the differences in scores more insightful, we dichotomized scores into low and high at a cut-off score of 3.5 and calculated odds ratios.

Temperament and Character Inventory. We assessed personality by the short version of the Temperament and Character Inventory (TCI).[17] The TCI assesses the seven dimensions of personality described by Cloninger,[18] in which personality can be assessed along four temperament dimensions (novelty seeking, harm avoidance, reward dependence, and persistence), which are thought to be heritable and stable throughout life and influence learning processes, and three character dimensions (self-directedness, cooperativeness, and self-transcendence) which are assumed to be socio-culturally determined. The short version of the TCI is a true-false questionnaire, consisting of 105 items, 15 items per dimension, and has been validated in the Dutch general population.[19] Each dimension has a scoring range of 0 – 15. To dichotomize the personality dimensions self-directedness and harm avoidance, we used normative data from the manual and set the cut-off score at 10 (low self-directedness < 10, high harm avoidance > 10).

General Health Questionnaire. We used the General Health Questionnaire (GHQ-28) to measure the level of psychopathology.[20] It includes four subscales: somatic physical illness and distress, anxiety/insomnia, social dysfunction, and severe depression, each consisting of 7 items. Answers are given on a 4-point Likert scale, ranging from 0 "better than normally" to 3 "much worse than normally", with scores ranging from 0 to 21 for each subscale. Scores can be recoded to a total scoring range of 0 to 28 (the GHQ scoring method). A GHQ score above 4 indicates presence of psychopathology.

Statistical analysis. Statistical analysis was performed with SPSS, version 12.01. Differences between headache groups are presented with 95% confidence intervals (95% CI). Scores were dichotomized to calculate odds ratios. We used logistic regression analysis with headache group as the dependent variable to adjust for potential confounders. Relationships between CFH, headache impact and other variables were explored by calculating Pearson coefficients. Variables with significant correlations were entered as independent variables into a multiple

regression analysis with HIT score as dependent variable to explore how much cognitive and personality factors contribute to headache impact after controlling for demographic variables and presence of psychopathology. We entered the following independent variables: demographic variables and psychopathology score in block 1, PCCL scores in block 2, and personality scores in block 3.

The Medical Ethics Committee of Leiden University Medical Center approved the study and subjects gave their written informed consent.

Results

Participants. We compared 177 CFH subjects to 141 infrequent headache subjects. Demographic characteristics of both headache groups are presented in table 1. The CFH group had more subjects with a low educational level than the infrequent headache group. The majority of CFH subjects overused acute headache medication. Mean HIT score for the CFH group was 61 compared to 51 for the infrequent headache group (mean difference 10, 95% CI 8 to 11).

Table 1 Demographic characteristics

	CFH N = 177	IH N = 141	difference (95% CI)
Mean age, y (SD)	43 (8)	42 (8)	0.5 (-1.5 to 2.4)
Female, n (%)	125 (72)	97 (70)	3% (-7 to 13)
Educational level			
Low, n (%)	62 (35)	16 (11)	24% (15 to 33)
Medium, n (%)	70 (40)	47 (34)	6% (-4 to 17)
High, n (%)	43 (25)	77 (55)	-30% (-41 to -20)
Overuse, n (%) *	109 (62)	3 (2)	

CFH = chronic frequent headache (≥15 days/month), infrequent headache = 1-4 days/month). * Overuse of acute headache medication, mainly analgesics.

Pain Coping and Cognition List. The PCCL was completed by 171 CFH subjects and 140 subjects with infrequent headache. Table 2 shows the mean scores of the four subscales of the PCCL. The CFH group scored higher on catastrophizing, pain coping and external control, and lower on internal control than the infrequent headache group. In the CFH group there were no significant differences in PCCL scores between medication overusers and non-overusers (Table 3).

Table 2 Differences in PCCL scores between headache groups

	CFH N = 171	Infrequent headache N =140	difference (95% CI)
Catastrophizing	2.8 (1.1)	1.9 (0.6)	0.9 (0.7 to 1.1)
Pain coping	3.4 (1.0)	3.0 (1.0)	0.4 (0.2 to 0.6)
Internal control	3.2 (0.9)	3.7 (1.0)	-0.5 (-0.7 to -0.3)
External control	3.0 (1.1)	2.3 (0.9)	0.7 (0.4 to 0.9)

Values are means (SD). PCCL = Pain Coping and Cognition List, CFH = chronic frequent headache (≥15 days/month), infrequent headache = 1-4 days/month.

Table 3 Differences in PCCL scores between overusers and non-overusers

	Overuse N =107	Non-overuse N = 64	difference (95% CI)
Catastrophizing	2.8 (1.0)	2.7 (1.1)	0.1 (-0.2 to 0.4)
Pain coping	3.3 (1.0)	3.5 (1.0)	-0.3 (-0.6 to 0.0)
Internal control	3.1 (0.9)	3.4 (0.9)	-0.3 (-0.6 to 0.0)
External control	3.0 (1.1)	2.8 (1.1)	0.2 (-0.2 to 0.5)

Values are means (SD). PCCL = Pain Coping and Cognition List.

Temperament and Character Inventory. The TCI was completed by 166 CFH subjects and 139 subjects with infrequent headache. Table 4 shows the mean scores of the TCI for both groups. The CFH group scored lower on the self-directedness dimension and higher on the harm avoidance dimension than the infrequent headache group.

Table 4 Mean scores Temperament and Character Inventory (short version)

	CFH N=166	Infrequent headache N=139	difference (95% CI)
Novelty seeking	6.2 (3.1)	6.3 (3.0)	-0.1 (-0.8 to 0.6)
Harm avoidance	8.5 (4.3)	7.4 (4.0)	1.1 (0.2 to 1.9)*
Reward dependence	8.7 (2.8)	9.0 (3.0)	-0.2 (-1.0 to 0.5)
Persistence	9.3 (3.1)	8.8 (3.1)	0.6 (-0.1 to 1.3)
Self-directedness	10.4 (3.8)	12.1 (3.1)	-1.6 (-2.3 to -1.0)*
Cooperativeness	12.9 (2.2)	13.3 (2.2)	-0.4 (-0.9 to 0.1)
Self-Transcendence	4.0 (3.7)	3.6 (3.1)	0.4 (-0.4 to 1.2)

Values are means (SD). * 95% CI excludes the neutral value of no difference (0). CFH = chronic frequent headache (≥15 days/month), infrequent headache = 1-4 days/month.

Compared to normal values, 61 (37%) CFH subjects scored low on self-directedness vs. 26 (19%) in the infrequent headache group, a difference of 18% (99% CI 5 to 31). Sixty-four CFH subjects (39%) had high scores on harm avoidance compared to 36 (26%) subjects with infrequent headache, mean difference 13% (95% CI 2 to 23). There were no relevant differences in TCI scores between overusers and non-overusers in the CFH group (Table 5).

Table 5 Differences in Temperament and Character Inventory (short version) scores between overusers and non-overusers in the CFH group

	Overuse N=105	Non-overuse N=61	difference (95% CI)
Novelty seeking	6.0 (3.1)	6.6 (3.0)	-0.6 (-1.6 to 0.4)
Harm avoidance	8.5 (4.3)	8.5 (4.3)	0.0 (-1.4 to 1.4)
Reward dependence	8.7 (2.7)	8.8 (3.0)	-0.1 (-1.0 to 0.8)
Persistence	9.1 (3.2)	9.7 (3.1)	-0.6 (-1.6 to 0.4)
Self-directedness	10.5 (3.6)	10.3 (4.1)	0.2 (-1.0 to 1.4)
Cooperativeness	13.1 (2.1)	12.7 (2.3)	0.4 (-0.3 to 1.1)
Self-Transcendence	4.0 (3.6)	4.0 (3.8)	-0.1 (-1.2 to 1.1)

Values are means (SD). CFH = chronic frequent headache (≥15 days/month).

GHQ-28. We have reported the results of the GHQ-28 scoring previously (chapter 3).[5] Total GHQ score was 8.5 (SD 7.4) in the CFH group compared to 3.9 (SD 4.8) in the infrequent headache group, mean difference 4.5 (95% CI 3.1 to 6.0). In the CFH group 102 (62%) subjects scored above 4, indicating presence of psychopathology, compared to 45 (34%) in the infrequent headache group, mean difference 29% (95% CI 18 to 40). The CFH group scored higher than the infrequent headache group on all subscales. Total GHQ score was similar in both overusers and non-overusers (mean difference 0.43, 95% CI -2.8 to 2.0).

Relationships. Table 6 summarizes the prevalence and odds ratios for cognitive and personality risk factors for CFH. Cognitive factors were still associated with CFH after adjusting for low educational level and presence of psychopathology. Low self-directedness was no longer associated with CFH after adjusting for catastrophizing; adjusted OR 1.5 (95% CI 0.8 to 2.7).

Table 6 Correlations between headache group, headache impact and psychological factors

	CFH	HIT	GHQ	CAT	COP	INT	EXT	HA	SD
CFH	1.00								
HIT	0.57*	1.00							
GHQ	0.33*	0.44*	1.00						
CAT	0.46*	0.56*	0.58*	1.00					
COP	0.19*	-0.02	0.08	-0.05	1.00				
INT	-0.26*	-0.33*	-0.10	-0.32*	0.53*	1.00			
EXT	0.31*	0.36	0.27*	0.50*	0.11	-0.12	1.00		
HA	-0.13	0.21*	0.34*	0.46*	-0.12	-0.07	0.16*	1.00	
SD	-0.23*	-0.32*	-0.55*	-0.59*	-0.01	0.06	-0.27*	-0.62*	1.00

Values are Pearson coefficients. * $p < 0.01$. CFH = chronic frequent headache, HIT = Headache Impact Test score, GHQ = General Health Questionnaire total score, CAT = Catastrophizing, COP = Pain Coping, INT = Internal Pain Control, EXT = External Pain Control, HA = Harm Avoidance, SD = Self-Directedness.

Table 7 shows correlations between headache impact and cognitive and personality factors. HIT score correlated with CFH, total GHQ score, scores for catastrophizing and internal locus of control on the PCCL, and scores for harm avoidance and self-directedness on the TCI. Correlations did not exceed 0.8, indicating no problems with multicollinearity. Multiple regression with HIT score as dependent variable showed that scores for catastrophizing and

internal pain control on the PCCL made a unique contribution to headache impact after controlling for educational level, headache status and level of psychopathology (Table 8).

Table 7 Prevalence and odds ratios of cognitive and personality risk factors for CFH

	CFH N = 177	IH N = 141	crude OR (95% CI)	adjusted OR (95% CI)
Age > 40 years	101 (61)	78 (59)	1.1 (0.7-1.7)	
Female sex	125 (72)	97 (70)	1.1 (0.7-1.8)	
Low educational level	62 (35)	16 (11)	4.3 (2.3-7.8)	
GHQ-28 case	102 (62)	45 (34)	3.3 (2.0-5.2)	3.2 (1.9-5.2)*
PCCL	N = 171	N = 140		
High catastrophizing	46 (27)	3 (2)	17.2 (5.2-56.7)	9.8 (2.8-33.8)†
High degree of coping	84 (51)	40 (30)	1.7 (1.3-2.5)	1.8 (1.3-2.6)†
Low internal control	93 (58)	44 (34)	2.7 (1.6-4.3)	2.2 (1.3-3.8)†
High external control	52 (30)	15 (11)	3.6 (1.9-6.8)	2.4 (1.3-4.9)†
TCI	N = 166	N = 139		
High harm avoidance	64 (39)	36 (26)	1.8 (1.1-2.9)	1.3 (0.8-2.3)†
Low self-directedness	61 (37)	26 (19)	2.5 (1.5-4.3)	1.9 (1.0-3.4)†

Values are number of subjects (%). CFH = Chronic frequent headache (≥15 days/month), IH = infrequent headache (1-4 days/month). GHQ-28 case = General Heath Questionnaire total score > 4, indicating presence of psychopathology, PCCL = Pain Coping and Cognition List, TCI = Temperament and Character Inventory.
* Adjusted for educational level, † adjusted for educational level and presence of psychopathology.

Table 8 Multiple regression of headache impact on psychological risk factors while controlling for demographic variables and level of psychopathology

	Beta*	P	R^2	R^2 change
Step 1:				
CFH status	0.36	0.000	0.41	0.41
Female sex	0.11	0.02		
Age	-0.12	0.007		
Educational level	0.06	0.190		
GHQ score	0.10	0.076		
Step 2:				
CAT	0.31	0.000	0.50	0.10
INT	-0.16	0.001		
Step 3:				
HA	-0.04	0.451	0.50	0.00
SD	-0.03	0.642		

* Standardized regression coefficients step 3.

CFH = chronic frequent headache, GHQ = General Health Questionnaire, CAT = Catastrophizing, COP = Pain Coping, INT = Internal Pain Control, HA = Harm avoidance, SD = Self-Directedness.

Discussion

In our population-based study we found that CFH is associated with catastrophizing, pain coping, low internal pain control, and high external pain control, also after controlling for demographic variables and level of psychopathology. Personality factors do not pose an additional risk for CFH. There were no differences in psychological factors between overusers and non-overusers. Headache impact was primarily determined by headache status (CFH) and catastrophizing.

Although our cross-sectional design does not permit conclusions on the direction of a causal relation we speculate that catastrophizing contributed to the chronification of headache and impact of headache on daily life. Catastrophizing has been shown to be associated with increased pain ratings and disability. Pain-free individuals who catastrophize report more intense pain and increased emotional distress during subsequent painful stimulation,[9] and catastrophizing predicted pain intensity and prolonged sick leave in workers with low back pain.[21] Sullivan proposed that by engaging cognitive activity that amplifies pain signals, central neural mechanisms in catastrophizers might become more sensitized, yielding a chronic hyperalgesic state.[9] On the other hand, cognitive-behavioral therapy in chronic pain patients aimed at reducing catastrophizing does not reduce pain intensity ratings per se but has shown to reduce disability.[22] It has been suggested that catastrophizers exaggerate pain expression to maximize empathic responses from others in their social environment.[9] Other authors emphasize an appraisal model of pain catastrophizing in that individuals seek assurance because they focus on their pain, experience their pain as threatening and feel helpless in dealing with their pain and that these primary appraisal processes determine which coping style will be adopted.[23]

Degree of coping was related to CFH. The degree of coping primarily seems to reflect the need to find different ways to deal with pain and is therefore probably secondary to chronic pain.[22] Contrary to what we expected, a high degree of pain coping was not associated with better adjustment and less impact of headache on daily life. We did not find any relation between coping and headache impact. An explanation may be the lack of distinction between active and passive coping strategies in the Pain Coping subscale of the PCCL. Passive coping has been found to be a risk factor for pain disability. A single measure combining these types of coping strategies may obscure an existing relationship.[24]

Both CFH and catastrophizing were inversely related to self-directedness. Self-directedness reflects self-determination and "will-power" to control, regulate and adapt behavior to fit the situation in accord with individually chosen goals and values.[18] Individuals with low scores have low self-esteem, lack initiative in overcoming challenges and blame others for their problems. Their behavior is often driven by encouragement from others or peer pressure instead of inner values. It is conceivable that pain is more threatening to people who rely heavily on others and that they will tend to catastrophize more. Indeed, personality characteristics did not add to chronification of headache or headache impact when catastrophizing was taken into account. Possibly, catastrophizing mediates the weak relation between low self-directedness and chronification of headache.

Intake of analgesics is generally considered to represent external pain control. Surprisingly, in our study overuse of analgesics was not associated with high external pain control scores. This could be explained by the type of questions of the external pain control scale of the PCCL which consisted of eight items; three were about the influence of praying and four were about the influence of doctors on pain control ("Only doctors can help me with my pain"). Pain control by medication use in particular was not actually measured. The CFH group as a whole did have a lower internal pain control than the infrequent headache group, but there was no difference between overusers and non-overusers. Perhaps the unlimited availability of OTC analgesics gives the patient a sense of self-control, which might change when the patient is encouraged to withdraw from medication and has to rely on other coping strategies. Indeed, many patients find withdrawal difficult because they feel they have less control over their life without analgesics, despite the fact that analgesics were not very effective before. It is possible that internal pain control scores are even lower during withdrawal and enhancing perceived control over pain may be an important adjuvant for patients withdrawing from medication.

In headache clinics, withdrawal of medication results in improvement of headache frequency in 70% of patients. However, relapse rate is high; after one year 40% of patients overuse medication again.[25] Overuse should be prevented by proper instruction and prophylactic medication. Prophylactic medication reduces frequency of headaches in about two thirds of patients. Unfortunately, the required doses often cause intolerable side effects.[26] There is some evidence that non-pharmacological treatment could be a valuable alternative or adjunct

treatment option. Stress management therapy proved to be equally effective as tricyclic antidepressant medication in patients with chronic tension-type headache (CTTH).[27] Reviews evaluating behavioral therapies in migraine support efficacy of these therapies.[28] Most studies however, are limited by small sample size and the lack of an active control group.[29]
Moreover, the many different types of cognitive behavioral therapies make it difficult for the clinician to compare and interpret the value of these therapies. Clearly, randomized controlled trials with a standardized cognitive behavioral therapy and an active placebo control group are needed.

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Chapter 5

Oral contraceptive use and headache frequency
- a cross-sectional study –

Submitted

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Abstract

Oral contraceptive (OC) use is associated with an increase of headache prevalence. It is not known whether use of OCs can increase headache frequency. We studied the association of oestrogen containing oral contraceptive (OC) use with chronic frequent headache in the general population. A general health survey was held in sixteen general practices in the Netherlands amongst all registered patients, aged 25-55 years, by sending a questionnaire. Respondents were allocated into groups according to headache frequency: Chronic Frequent Headache (CFH: > 14 days/month), Very Frequent Headache (8-14 days/month), Infrequent Headache (1-4 days/month) and No Headache (< 1 day/month), and received a second questionnaire. Several factors possibly associated with chronic frequent headache were studied, including oral contraceptive use. In the headache groups 136 (29%) of 465 women used OCs, compared to 71 (21%) of 340 in the No Headache group, adjusted OR 1.4 (95% CI 1.0 to 2.1). In the CFH group 8% (95% CI -18 to 0) fewer women used OCs than the Infrequent Headache group. Odds ratio for the association between OC use and CFH was 0.7 (95% CI 0.4 to 1.1), and after adjusting for age and educational level 0.6 (95% CI 0.4 to 1.1). OC use in the VFH group was similar to the Infrequent Headache group, 32% vs. 33% respectively, a difference of 1% (95% CI -1 to 1). We conclude that there is no association between oestrogen containing OC use and CFH.

Introduction

Headache is more prevalent in women and menstruation is often reported to be a precipitating factor, suggesting that female hormones play a role in the aetiology of headache.[1] Many headache patients wonder whether they should start or discontinue OC use to improve headache. A recent review of studies on the effect of OC use on headache shows inconsistent results, some women improve, and others worsen.[2] In a large population-based study in Norway an increased prevalence of headache among users of oestrogen containing OCs was found.[3] The association was found for both migraine (OR 1.4, 95% CI 1.2 to 1.7) and for non-migraine headache (OR 1.2, 95% CI 1.0 to 1.4). There was no dose-response relationship between oestrogen content and headache prevalence, nor was there an association with OCs containing progestagen only.

One in 25 people suffers from chronic frequent headache (CFH), defined as headaches on more than 14 days per month, for at least 3 months.[4-6] Usually their headaches start as an episodic migraine or tension-type headache, which gradually increases in frequency until headaches occur almost daily. The cause of this chronification process is not known, but several risk factors have been associated with CFH.[6-9] It is not known whether use of OCs can increase headache frequency.

In our population-based study on the prevalence and associated factors of CFH,[6] participants recorded all medication use, including oral contraceptives. Here we report whether oestrogen containing OC use was associated with CFH in the Netherlands.

Methods

The study design and methodology have been described in detail previously.[6] Briefly, we conducted a general health survey (Q1) in the general population (aged 25-55) in the Netherlands, which contained a question on headache frequency in the past three months. In total 21,440 subjects received Q1, and 16,232 (76%) completed Q1. Respondents were allocated into groups according to headache frequency: Chronic Frequent Headache (CFH: headache on > 14 days/month), Very Frequent Headache (VFH: headache on 8-14 days/month), Frequent Headache (FH: 5-7 days/month), Infrequent Headache (IH: 1-4 days/month) and No Headache (NH: headache on < 1 day/month). All CFH and VFH subjects

and a random sample of the subjects with Infrequent Headache and No Headache received a second, more detailed, questionnaire (Q2) containing questions on headache characteristics and medication use. To identify factors associated with chronification of headache, we compared subjects with CFH to subjects with Infrequent Headache (1-4 days/month). To discern chronification factors from factors associated with headache in general we also compared the headache groups to the No Headache group (< 1 day/month). The Very Frequent Headache group was added because these subjects have a high headache frequency and may be in the process of developing daily headache.[10] The Frequent Headache group was not further analyzed.

Q2 was sent to 654 CFH subjects and completed by 273 (42%) subjects. The non-respondent analysis showed that non-responders were slightly younger and were more often male than the respondents. In the VFH, IH and NH groups the response percentages were similar; 42%, 32% and 43% respectively. Re-assessment of headache frequency in Q2 (time between questionnaires was five months) showed that headache frequency had changed in many subjects. We first analyzed all subjects who completed Q2, and then repeated analysis in a subset of subjects in whom the reported headache frequency had not changed between the two surveys (i.e. the stable frequency group).

First we compared all headache groups to no headache. Secondly, we compared CFH to infrequent headache to analyze the association between OC use and chronification of headache. And finally, we compared the VFH to the infrequent group because this group is at greatest risk of becoming CFH. Differences between groups are presented with 95% confidence intervals (95% CI). Odds ratios are calculated. We used logistic regression to adjust for confounders (age and educational level).

The Medical Ethics Committee of Leiden University Medical Centre approved this study.

Results

There were 465 women in the headache groups and 340 in the No Headache group. Differences in age and educational level per group are presented in table 1. More CFH subjects had a low level of education compared to the Infrequent Headache group (difference 17%, 95%CI 8 to 26).

Table 1 Age and educational level

	CFH N = 176	VFH N = 146	IH N = 143	NH N = 340
Mean age, y (SD)	42 (8)	42 (9)	41 (8)	44 (9)
Educational level	n = 174	n = 145	n = 143	n = 340
Low, n (%)	53 (31)	31 (21)	19 (13)	48 (14)
Medium, n (%)	73 (42)	69 (47)	53 (37)	125 (37)
High, n (%)	48 (28)	45 (31)	71 (50)	167 (49)

CFH = chronic frequent headache (>14 d/m), VFH = very frequent headache (8-14 d/m), IH = infrequent headache (1-4 d/m), NH = no headache (< 1 d/m).

Overall, 136 (29%) women in the headache groups use oestrogen containing OCs, compared to 71 (21%) in the No Headache group, a difference of 8% (95% CI 2 to 14). Crude odds ratio for the association between OC use and headache was 1.6 (95% CI 1.1 to 2.2), and after adjustment for age and educational level 1.4 (95% CI 1.0 to 2.1).

OC use per headache group is presented in table 2. Results in the subgroups with a stable headache frequency were similar to the results of the whole group, so there was no need to study the stable frequency group separately.

In the CFH group 24% used oestrogen containing OCs, which is 8% (95% CI -18 to 0) less than the Infrequent Headache group, and 4% (95% CI -4 to 11) more than the No Headache group. Crude odds ratio for the association between OC use and CFH was 0.7 (95% CI 0.4 to 1.1), and after adjusting for age and educational level 0.6 (95% CI 0.4 to 1.1). Oestrogen containing OC use in the VFH group was similar to the Infrequent Headache group, 32% vs. 33% respectively, a difference of 1% (95% CI -1 to 1).

Table 2 Oestrogen containing oral contraceptive use per group

All subjects	CFH N = 176	VFH N = 146	IH N = 143	NH N = 340
OC use, n (%)	43 (24)	46 (32)	47 (33)	71 (21)
Stable frequency	n = 125	n = 89	n = 97	n = 215
OC use, n (%)	30 (24)	28 (32)	29 (31)	46 (21)

CFH = chronic frequent headache (>14 d/m), VFH = very frequent headache (8-14 d/m), IH = infrequent headache (1-4 d/m), NH = no headache (< 1 d/m).

Discussion

We found no association between oestrogen containing OC use and CFH in the general population in the Netherlands. The percentage of women using OCs was even lower in the CFH group than in the Infrequent Headache group. We could argue that OC use protects against chronification of headache, however it is more likely that women with CFH had discontinued OC use because of their frequent headaches. As in the Norway study[3] we found that headache is associated with OC use, but we did not find an association with increasing headache frequency and OC use. Even in the Very Frequent Headache group, which is a group at high risk of developing CFH,[10] OC use was comparable to the Infrequent Headache group.

This is a cross-sectional study based on self-reported use of medication. We think our results are a reliable estimate of OC use in women aged 25-55 years, because the percentage is in accordance with earlier reports from the Netherlands.[11] Although the response to Q2 was low, it is unlikely that this may have caused a bias in the associations, because we have no reason to believe that OC use is dependent on response status. A limitation of our study is that we have no information on duration of OC use, or about previous use of OCs, and the effect on headache. In a cross-sectional study, questions on headache patterns and OC use in the past are unreliable due to recall bias. A cohort study would be needed to address important questions like the incidence of CFH in women starting to use OCs and the effect of stopping OCs on headache frequency.

To our knowledge, there are no studies examining the effect of OCs in patients with CFH. The increased prevalence of headache in OC users may reflect withdrawal headache as a side effect during the pill-free week. Sulak et al. demonstrated that compared to the traditional 21/7 OC/placebo regimen, an extended 168-day placebo-free OC regimen actually led to a reduction in daily headaches.[12] There is as yet no evidence that discontinuing or switching OCs will improve headache frequency in patients with CFH.

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Chapter 6

Medication overuse in patients with chronic frequent headache in the general population

Submitted

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Abstract

We studied patterns and type of medication overuse in patients with chronic frequent headache (CFH: headache on >14 days/month for three months) from the Dutch general population. Patients were identified in a general health survey and were asked questions about headache characteristics and medication use. We compared CFH subjects with medication overuse (as defined by the International Classification of Headache Disorders – II) to those without overuse. Of 177 CFH subjects, 104 (59%) overused medication and 73 (41%) did not. Overuse consisted of analgesics (96%), triptans (2%), opioïds (4%), and various combinations (1%). The majority of subjects with overuse showed signs of drug tolerance; 71% had increased dosage gradually (vs. 41% in the group without overuse, difference 29%, 95% CI 14 to 43), and 64% took medication despite lack of efficacy (vs 27% without overuse, difference 37%, 95% CI 23 to 51). Fourty subjects with overuse (39%) regularly took analgesics to prevent headache, compared to only 14 (19%) in the group without overuse (difference 19%, 95% CI 6 to 33). Only 23 CFH subjects (13%) used prophylactic medication. Distribution of headache types was similar in both groups; we classified 94 (53%) subjects as having chronic tension-type headache, 42 (24%) as chronic migraine, 12 (7%) as miscellaneous, and 29 (16%) could not be classified. We conclude that medication overuse in the general population mainly concerns analgesic overuse. Many subjects show drug tolerance, inappropriate use of analgesics and lack prophylactic medication.

Introduction

Chronic frequent headache is an increasing problem worldwide.[1] Clinical observation suggests that overuse of acute headache medication and caffeine increases headache frequency in susceptible patients. A causal relationship between overuse and chronification of headache is assumed because discontinuation of overused medications and caffeine frequently results in improvement of headache.[2] Moreover, many headache patients with medication overuse fulfil criteria for substance dependence as described in the Diagnostic and Statistical Manual of Mental Disorders, Edition IV (DSM-IV).[3] The International Classification of Headache Disorders – II (ICHD-II) now includes criteria for medication overuse headache (MOH): chronic headache induced by overuse of acute headache medication like analgesics or triptans.[4] The diagnosis of MOH becomes definite only when headache improves after withdrawal. Until then, patients are classified as having *probable* MOH. Most information about MOH comes from headache clinics where the majority of patients are severe migraine patients.[5] Little is known about the clinical characteristics of medication overuse in the general population. Our objective was to study the patterns and type of medication overuse in chronic frequent headache in the general population.

Methods

We conducted a general health survey (Q1) amongst all persons, aged 25-55, registered at 16 general practices in the province of South-Holland in The Netherlands in 2003. This sample represents the general population because in the Netherlands all individuals are registered at a single general practice. The study design and methodology have been described in detail previously.[6] Briefly, we identified subjects with CFH, which was defined as headache on > 14 days per month during the past three months. All CFH subjects received a second, more detailed, questionnaire (Q2) containing questions on headache characteristics and treatment. In total 21,440 subjects received Q1, and 16,232 (76%) completed Q1. Prevalence of CFH was 4% (n = 679). Q2 was sent to 654 CFH subjects and completed by 273 (42%) subjects. The non-respondent analysis showed no relevant differences in age, sex and educational level; non-responders were slightly younger and were more often males than the respondents. Re-assessment of headache frequency in Q2 showed that headache frequency had changed in many subjects. We limited further analyses to the 177 CFH subjects in whom the reported headache frequency had not changed between the two surveys.

Because the study was conducted in 2003, we reclassified our subjects according to the new ICHD-II criteria for MOH in 2005.[4] Overuse is present when patients use simple analgesics on ≥ 15 days/month or other acute headache medication like triptans on ≥ 10 days/month. Because withdrawal had not been attempted at the time subjects completed the questionnaire, we could only diagnose probable MOH. Clinical features of CFH subjects with overuse were compared to CFH subjects without overuse. We asked subjects which headache pattern fitted their situation best: a) headaches come in attacks, in between there is no headache at all, b) a continuous headache which is present almost daily, and does not vary much in intensity, or c) a continuous headache which is present almost daily, with superimposed attacks of moderate to severe headache (Figure 1). We classified CFH into three subgroups: chronic tension-type headache (CTTH), chronic migraine (CM), and new daily persistent headache (NDPH), according to the ICHD-II. Associated symptoms were considered present when subjects answered to be nauseated or suffer from photo- and/or phonophobia most of the time when having headaches. For the diagnosis CTTH, mild nausea or mild photo- and/or phonophobia were allowed. Vomiting excluded CTTH. NDPH was diagnosed when headaches had started suddenly or had evolved into a daily headache in only a few days, with CTTH characteristics. If subjects reported that daily headaches started after an accident with head or neck trauma or whiplash injury, we classified them accordingly.

Descriptive statistics were performed with SPSS, version 12.0.1. Differences between groups are presented with 95% confidence intervals (95% CI). The Medical Ethics Committee of Leiden University Medical Centre approved this study.

Results

Demographic characteristics of 177 subjects with CFH are presented in table 1. There were slightly more subjects with a high educational level in the group without overuse. Of the 177 CFH subjects, 145 (82%) subjects used analgesics, 12 (7%) subjects used triptans, only one used ergotamine, and nine (5%) used opioïds. Overuse was present in 104 CFH subjects (59%), 73 (41%) had no overuse.

Table 1 Characteristics of CFH subjects with overuse vs. CFH subjects without overuse

	Total N = 177	Overuse N = 104	No overuse N = 73	mean difference (95%CI)
Mean age, y (SD)	43 (8)	44 (8)	42 (9)	2 (-0.3 to 4.8)
Female, n (%)	127 (72)	78 (75)	49 (67)	8% (-6 to 22)
Educational level				
Low, n (%)	62 (35)	37 (36)	25 (34)	2% (-13 to 17)
Medium, n (%)	70 (40)	47 (46)	23 (32)	15% (0 to 29)
High, n (%)	43 (25)	18 (18)	25 (34)	-17% (-30 to -4)
Age at onset headache, y (SD)	19 (11)	18 (10)	20 (13)	-2 (-5 to 2)
Age at onset CFH, y (SD)	25 (12)	24 (11)	26 (13)	-2 (-5 to 2)

Table 2 shows use and percentage of overuse per drug. Overuse consisted mainly (96%) of analgesics; 83 subjects overused simple analgesics, and 17 overused combination analgesics. Only two subjects (2%) overused triptans, and these two also overused analgesics. Four (4%) overused opioïds, two in combination with analgesic overuse. Two subjects (1%) overused various combinations of acute medication. There was no ergotamine overuse.

Table 2 Use and overuse per drug in 177 CFH subjects

	Analgesics	Triptans	Ergotamine	Opioïds
Number of users in total CFH group	145	12	1	9
Number of overusers	100	2	0	4
Percentage overuse in total CFH group	56%	1%	0%	2%
Percentage overuse in users	69%	17%	0%	44%

Differences in intake behaviour between CFH subjects with overuse and those without overuse are presented in Table 3. The majority of overusing subjects had gradually increased dosage of acute medication and took medication despite lack of efficacy. Many admitted to take analgesics regularly to prevent headache. Few used prophylactic medication.

Table 3 Medication use characteristics of CFH subjects with overuse vs. without overuse

	Total N = 177	Overuse N = 104	No overuse N = 73	mean difference (95%CI)
Gradual increase dosage	105 (59)	74 (71)	31 (42)	29% (14 to 43)
Intake despite lack of efficacy	87 (49)	67 (64)	20 (27)	37% (23 to 51)
Intake to prevent headache	54 (31)	40 (39)	14 (19)	19% (6 to 33)
Prophylactic medication*	23 (13)	17 (16)	6 (8)	8% (-2 to 18)
Headache indication	15 (8)	11 (11)	4 (6)	5% (-4 to 13)
Comorbid indication	8 (5)	6 (6)	2 (3)	3% (-4 to 10)

*Prophylactic medication can be either used for prevention of chronic headache, or for a comorbid disorder (e.g. propanolol for migraine or hypertension).

Headache patterns were similar in both the overuse group and the group without overuse; in 22 of the 177 subjects (12%) headaches came in attacks, with no headache in between (figure 1, pattern A), in 62 subjects (35%) headache was continuous without attacks (figure 1, pattern B), and 91 subjects (51%) experienced their headaches as continuous with superimposed attacks of moderate to severe headache (figure 1, pattern C). Two subjects did not answer the question on headache patterns.

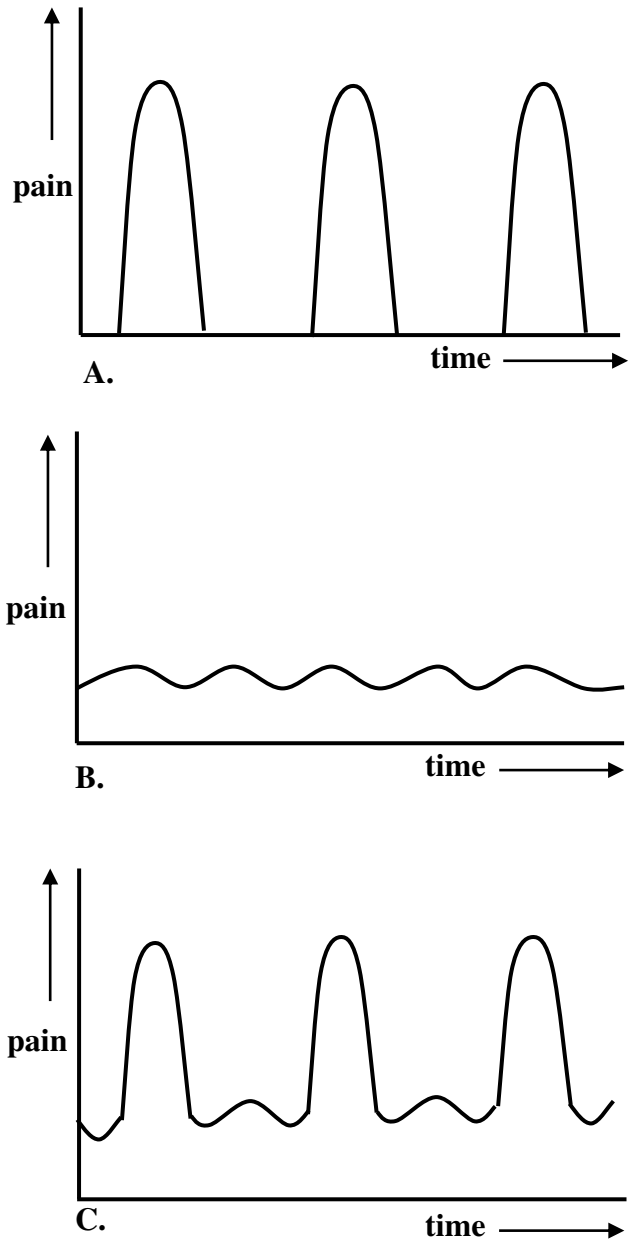

Figure 1 *Headache patterns*

Headache type according to ICHD-II is presented in table 4. There were no relevant differences in diagnosis between the overuse group and the group without overuse. Most subjects could be classified as chronic tension-type headache, of which 21 (22%) also had migraine attacks without aura, and six (6%) migraine with aura. A considerable number could not be classified, mostly (in 72%) due to a combination of tension-type headache characteristics with vomiting or photo- and phonophobia, and to a lesser extent (in 21%) due to migraine headache characteristics without associated symptoms. The diagnostic category "miscellaneous" consisted of chronic posttraumatic headache (n=3) and chronic headache due to whiplash injury (n=2).

Table 4 Headache diagnosis according to ICHD-II

	Total N = 177	Overuse N = 104	No overuse N = 73	mean difference (95%CI)
CTTH*	94 (53)	56 (54)	38 (52)	2% (-13 to 17)
CM*	42 (24)	25 (24)	17 (23)	1% (-12 to 14)
NDPH*	7 (4)	1 (1)	6 (8)	-7% (-13 to -2)
Miscellaneous	5 (3)	1 (1)	4 (5)	-4% (-10 to 1)
Not classifiable	29 (16)	21 (20)	8 (11)	9% (-2 to 20)

Values are number (%). CTTH = chronic tension-type headache, CM = chronic migraine, NDPH = new daily persistent headache. * In case of overuse, the headache diagnosis should be preceded by *probable,* until causation by medication can be refuted after withdrawal.

Discussion

In our population-based study the majority (56%) of CFH subjects overused analgesics, only a few (2%) overused triptans or opioïds. When expressed as percentage of medication users, the pattern was the same: 69% of analgesic users were overusers, 17% of triptan users and 44% of opioïd users. Overuse of analgesics is likely to be more prevalent in the general population than triptans, because analgesics are over-the-counter products. Twelve CFH subjects (7%) currently used triptans. Only two of them overused triptans and in combination with analgesic overuse. The low percentage of triptan overuse, despite high headache frequency, suggests that the risk of overuse in triptan users is low.

The majority could be classified as chronic tension-type headache. This is in contrast to studies in headache clinics where the majority of patients with MOH are migraine patients and many overuse triptans.[1] The different distribution of headache type and overuse illustrates that referred patients in headache clinics comprise a totally different, selected, population. One cannot extrapolate conclusions from studies conducted in headache clinics to the general population without accounting for differences in clinical characteristics. Although the distribution of headache types was similar in both the overuse group and the group without overuse, almost twice as many subjects with overuse could not be classified. It is possible that overuse obscures typical features and that the underlying headache type becomes apparent only after withdrawal.

Some general aspects of our study should be taken into account when interpreting our results. First, our sample consisted of non-consulting patients who are possibly different from consulting patients in general practice. Our results therefore apply to the general population, not to general practice. Secondly, our study is questionnaire based. Although headache diagnosis is always more reliable when obtained by interview, our questionnaire was based on diagnostic criteria of the International Headache Society, and the distribution of chronic headache types is in agreement with other population-based studies.[7,8] Lastly, because of the cross-sectional design, we did not study the direction of a possible causal relation between overuse and chronic headache. However, many overusers showed characteristics of dependence, which makes a diagnosis of MOH more likely. The majority had noticed a gradual increase in dosage over time and took medication despite lack of efficacy suggesting development of drug tolerance. This is in accordance with the clinic-based study by Fuh et al.,

where over 70% of patients with probable MOH fulfilled DSM-IV criteria of tolerance.[3] Another mechanism for the development of overuse could be inappropriate use of analgesics; many took analgesics to prevent headache. The use of prophylactic medication in a population with chronic headaches is remarkably low, leaving room for improvement of treatment.

We conclude that medication overuse headache in the general population in the Netherlands mainly concerns analgesic overuse. To prevent overuse in the general population, public information should be primarily aimed at appropriate use of analgesics and the possibility of prophylactic treatment when headache frequency increases.

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Chapter 7

Triptan use and overuse in the Netherlands – a national pharmaco-database analysis -

Submitted

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Abstract

We studied the prevalence and associated costs of triptan overuse in the Netherlands. Therefore, we used the Drug Information Project (GIP) database of the Health Care Insurance Board (CVZ), which registers prescribed drugs dispensed at pharmacies for patients insured by sickness funds (sample size n = 6.7 million, in the year 2005). We defined triptan overuse as intake of: 1) at least 120 defined daily doses (DDDs) per year (International Headache Society (IHS) criteria) and 2) at least 216 DDDs per year (stringent criteria). Among 85,172 triptan users (1.3% of all insured persons), 8,844 persons overused according to the IHS criteria (10.4%, 95% CI 10.2 to 10.6), and 2,787 persons according to stringent criteria (3.3%, 95% CI 3.2 to 3.4). The contribution of injections to overuse was negligible, indicating that triptan use in cluster headache patients did not bias results. Overusers were older than non-overusers. The risk of overuse differed per triptan. Compared to sumatriptan, the odds ratio (OR) for the risk of IHS-overuse was 0.11 (95% CI 0.08-017) for frovatriptan, 0.27 (95% CI 0.25-0.28) for rizatriptan, 0.48 (95% CI 0.40-0.57) for almotriptan, 0.68 (95% CI 0.62-0.74) for naratriptan, 0.83 (95% CI 0.72-0.95) for eletriptan and 0.86 (95% CI 0.80-0.93) for zolmitriptan. When corrected for duration of availability and number of users, the relative risk differences versus sumatriptan virtually disappeared, except for rizatriptan which remained to the triptan associated with the lowest risk of overuse. Similar results were obtained when using the stringent criteria. Total annual costs of triptans were 29.7 million Euros in 2005, with overusers accounting for 46% (IHS criteria) and 32% (stringent criteria) of total costs. Of the patients overusing triptans according to IHS criteria 30% used medication which can be prescribed as prophylaxis for migraine and according to the stringent criteria 32%. In conclusion, ten percent of triptan users are overusers, which accounts for half of total annual triptan costs. Rizatriptan is associated with the lowest risk of overuse.

Introduction

Triptans, selective serotonin $5HT_1$ agonists, are specific acute migraine drugs of which the efficacy is well established.[1-3] Because of their higher costs, triptans are prescribed only after analgesics and anti-emetics have been tried and failed (step care).[4,5] For migraine patients with severe disabling attacks, however, it is appropriate to prescribe triptans earlier in the course of treatment (stratified care).[6]

Some patients tend to overuse triptans and analgesics, leading to an increase in headache frequency until headaches become almost daily. This condition is called medication overuse headache (MOH).[7] MOH is an increasing problem worldwide; the prevalence of MOH in the general population is estimated to be 1-2%.[8] Clinical experience suggests a causal relationship between overuse of acute headache medication and chronic headache because withdrawal in MOH often results in dramatic improvement of headache frequency.[9] Based on clinical observations in headache clinics, triptans can induce headache when used two days a week or more.[10] In 2005, the International Headache Society (IHS) published revised criteria for triptan-overuse headache (TOH), which require a triptan intake on more than 10 days a month for more than 3 consecutive months. [7] With the increased availability of triptans and the now advocated, but unproven, patient instruction to treat attacks early, prevalence of triptan overuse is likely to increase.[11] This is an unfavourable situation because chronic frequent headache has a major impact on quality of life of the patient[12,13], and the cost of overuse for society is considerable.[14] It is also unnecessary since overuse of triptans can be prevented by restricting use and starting prophylactic medication in patients with high attack frequency.

To gain more insight into the magnitude and nature of the problem we studied the characteristics of triptan users in the Netherlands. Furthermore, we estimated the prevalence of overuse and the financial burden of overuse on health care resources.

Methods

Study Setting

Data were obtained from the Drug Information Project (GIP database) of the Health Care Insurance Board (CVZ). The CVZ is a public authority in the domain of drugs. As an independent non-profit governing body, it monitors conditions of the health insurance scheme

in the Netherlands. In 2005, more than 10 million persons (65% of the inhabitants in the Netherlands) were mandatorily insured on the grounds of the Sickness Fund Act. People were eligible for sickness fund insurance if they had a yearly income of less than € 33.000. The GIP registered prescribed drugs dispensed at pharmacies for all patients insured by sickness funds. All prescription drugs are coded according to the Anatomical, Therapeutic and Chemical (ATC) classification. [15] Data are available for 6.7 million people in 2005, covering 46% of the total Dutch population and 67% of the sickness fund insured patients. For migraine patients in the Netherlands, there were no financial restrictions in administering headache therapy (attack treatment or prophylaxis) in the study year 2005 if physicians prescribed the medication. In the Netherlands there was no over-the-counter sale of triptans in 2005. Each registered patient has an anonymous unique identification number, which allows observation of medication use over time per patient.

Definitions

We defined a triptan user as a patient for whom minimally one prescribed triptan was dispensed in 2005. We used two definitions for triptan overuse. One according to the IHS, i.e. intake on ≥10 days/month on a regular basis for > 3 consecutive months,[7] and a second more stringent definition based on studies in headache clinics, i.e. use of 18 single doses or more per month for > 3 consecutive months.[16] We converted these criteria into defined daily dose (DDD) per year, which is, according to the World Health Organization (WHO), the standardised dosage per day of a drug when prescribed for the registered indication (Table 1).[15] Accordingly, 'IHS triptan overuse' was defined as intake of at least 10 DDDs per month, or 120 DDDs per year and the 'stringent triptan overuse' as at least 18 DDDs per month, or 216 DDDs per year. In contrast to the IHS, which takes a 3-month period, our study carries a 12-month period for determining overuse.

Patients with cluster headache, but not so much those with migraine, may sometimes use very high quantities of subcutaneous injections of sumatriptan which could bias the results towards overuse of sumatriptan. To avoid such bias, we extracted the administration route and estimated the number of injection users.

Use of prophylactic medication was defined as minimally one dispensed prescription in 2005 of any medication registered for migraine prophylaxis. Since in the database the indication for the prophylactic prescription is not recorded, it is not known whether the medication was actually prescribed for migraine or for another comorbid disorder (e.g. propranolol, which can be prescribed for migraine, hypertension or other diseases).

Table 1 Defined daily dose per triptan according to the World Health Organisation.[15]

Triptan	Year of introduction in the Netherlands	Formulation	Defined daily dose (DDD)
Sumatriptan	1991 (1996*)	50-mg tablet	1 tablet
		100-mg tablet	½ tablet
		25-mg suppository	1 supp
		20-mg nasal spray	1 spray
		6-mg subcutaneous injection	1 injection
Naratriptan	1997	2.5 mg tablet	1 tablet
Zolmitriptan	1997	2.5 mg tablet	1 tablet
Rizatriptan	1998	5-mg tablet	2 tablets
		10-mg tablet	1 tablet
Eletriptan	2000	20-mg tablet	2 tablets
		40-mg tablet	1 tablet
Almotriptan	2000	12.5 mg tablet	1 tablet
Frovatriptan	2001	2.5 mg tablet	1 tablet

* First year of full availability of tablets without any surcharge.

Statistical analysis

Data was categorized and are presented as numbers with percentages. Differences between groups are presented with 95% confidence intervals (Δ, 95% CI). To assess the association with overuse of the various triptans relatively to sumatriptan, we calculated the odds ratios (OR) with sumatriptan as the reference. Because sumatriptan is the longest available and most widely prescribed triptan in the Netherlands, we chose sumatriptan as reference. We used the Mantel-Haenszel procedure to adjust for age.

Results

In 2005, 85,172 patients (1.3% of the total sample) received a triptan. Of these 31,841 (37.4%) received only one prescription in 2005 and 5,536 (6.5%) received a prescription for more than one type of triptan. Almost all triptans (95%) were prescribed by general practitioners (GP), and only 4% by specialists, mainly neurologists. Table 2 shows the characteristics of triptan users compared to the total population. The majority of triptan users were female and over thirty years old. Nineteen percent of triptan users used medication that can be prescribed as prophylactic medication for migraine.

Amongst the 85,172 triptan users, 8,844 persons overused according to the IHS criteria (10.4%; 95%CI: 10.2-10.6), and 2,787 persons according to the stringent criteria (3.3%; 95%CI: 3.2-3.4). Characteristics of overusers versus non-overusers are presented in table 3 (page 105). Percentages of overuse are similar in females and males. Overusers are older than non-overusers; in both overuse groups 60% of patients are in the fifth and sixth decade of life. Prophylactic medication is more frequently dispensed in overusers (according to IHS criteria 30.4 % and according to stringent criteria 32.1 %) than in non-overusers (17.9%).

As there are four different routes of administration for sumatriptan we studied the relative prevalences. In the total sample, 6.7% used more than one route of administration, in the non-overusers this was 5.5%. Of the 45,639 patients who used sumatriptan, exclusive use of tablets was the formulation most commonly prescribed: 64% of the total sample, 62% of the non-overusers, 76% of the IHS overusers, and 74% of stringent overusers. Exclusive use of injections was found in 9.8% of all sumatriptan users, for 10.3% of sumatriptan non-overusers, for 6.6% of the IHS sumatriptan overusers and for 4.6% of stringent sumatriptan overusers.

Table 2 Characteristics of triptan users compared to the total population.

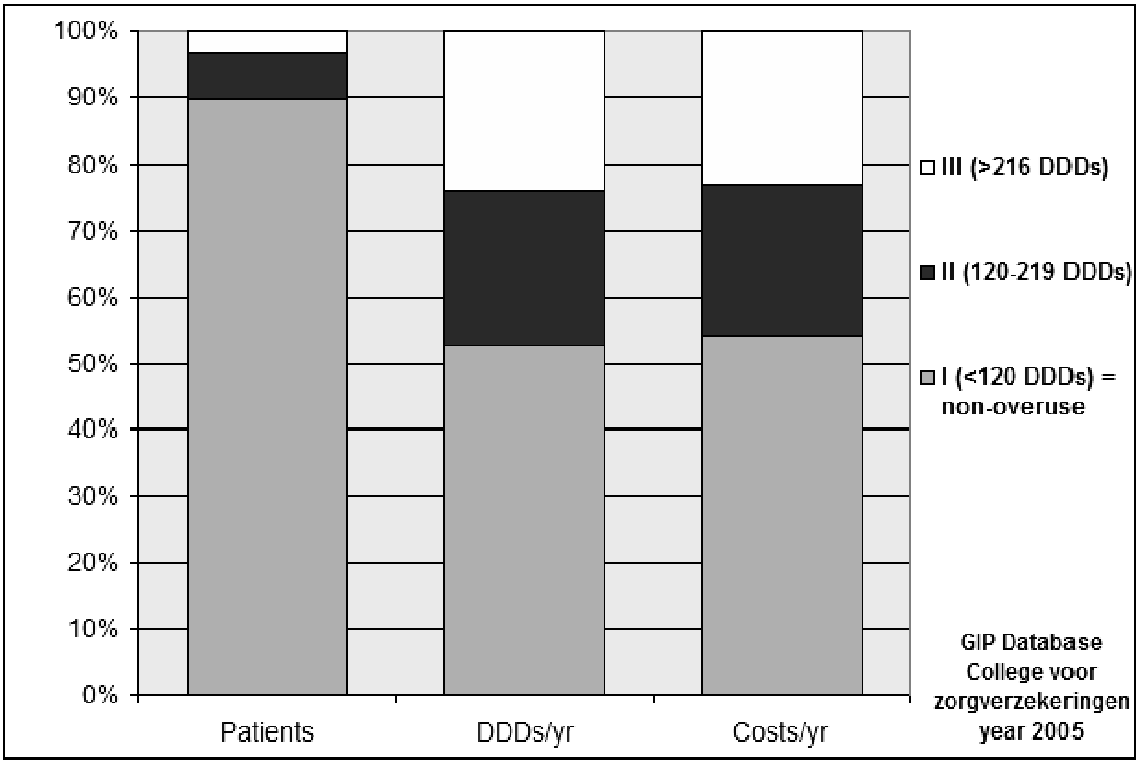
	Total population N = 6,704,627 n (%)		Triptan users N = 85,172 n (%)	
Females	3,665,773	(55)	71,047	(83)
Age < 20	685,352	(19)	1,916	(3)
20 – 29	459,630	(13)	9,616	(14)
30 – 39	586,641	(16)	16,620	(23)
40 – 49	588,504	(16)	21,628	(30)
50 – 59	503,518	(14)	14,615	(21)
60 – 69	365,634	(10)	4,926	(7)
≥ 70	476,494	(13)	1,726	(2)
Males	3,038,854	(45)	14,125	(17)
Age < 20	719,131	(24)	871	(6)
20 – 29	447,465	(15)	1,782	(13)
30 – 39	486,320	(16)	3,499	(25)
40 – 49	433,975	(14)	3,644	(26)
50 – 59	371,537	(12)	2,725	(19)
60 – 69	297,714	(10)	1,194	(9)
> 70	282,712	(9)	410	(3)
Prophylactic medication*	437.354	(6.5)	16.327	(19.2)
Propranolol	54,254	(0.8)	6,267	(7.4)
Metoprolol	339,244	(5.1)	6,985	(8.2)
Pizotiphen	4,028	(0.1)	1,400	(1.6)
Flunarizine	2,803	(0.0)	218	(0.3)
Valproic acid	30,228	(0.5)	1,713	(2.0)
Clonidine	13,363	(0.2)	747	(0.9)
Topiramate	3,325	(0.0)	1,084	(1.3)

Source: GIP database, College voor Zorgverzekeringen. *Medication which can be prescribed as prophylactic therapy for migraine. Amitriptyline is not registered and not prescribed as migraine prophylaxis in the Netherlands. Methysergide can only be prescribed for a short period to prevent adverse events and was therefore excluded.

Table 4 (page 106) shows differences in use of triptan type between non-overusers and overusers. Sumatriptan is the most prescribed triptan. The majority of triptan users and overusers used only one triptan. Some triptans have different dosages (Table 1). In patients overusing sumatriptan, the 100 mg tablets are more often prescribed than the 50 mg tablets (ratio 50:100mg: 1:2.7 in IHS overusers and 1:5.3 in stringent overusers). For all sumatriptan users the 50 mg to 100 mg ratio is 1:1.

Overuse was observed for all triptans, but the risk of overuse differed per triptan. Compared to sumatriptan, the odds ratio (OR) for the risk of IHS overuse was 0.11 (95% CI 0.08-0.17) for frovatriptan, 0.27 (95% CI 0.25-0.28) for rizatriptan, 0.48 (95% CI 0.40-0.57) for almotriptan, 0.68 (95% CI 0.62-0.74) for naratriptan, 0.83 (95% CI 0.72-0.95) for eletriptan and 0.86 (95% CI 0.80-0.93) for zolmitriptan. When corrected for duration of availability the relative risk differences versus sumatriptan virtually disappeared, except for rizatriptan which remained to the triptan associated with the lowest risk of overuse. Compared to sumatriptan the risk in the IHS group was three times smaller (OR 0.34, 95% 0.32 – 0.37). Similar results were obtained when using the stringent criteria (Table 5, page 107), the risk of overuse was nearly eight times smaller for rizatriptan compared to that for sumatriptan (corrected OR 0.17, 95% CI 0.15-0.20).

The costs of triptan use and overuse are shown in Figure 1. Total costs of triptan use in our study (85,172 triptan users, 6.7 million total population) were 29.7 million Euros in 2005, i.e. 349 Euro per triptan users and 4.43 Euros per inhabitant. Patients overusing triptans according to the IHS criteria account for 46% of total costs and according to the stringent criteria for 23% of total costs, i.e. 1,543 Euros per IHS overuser and 2,468 Euros per stringent overuser.



DDD: daily defined dose. I= non-overuse, II + III = overuse according to IHS criteria, III = overuse according to Stringent criteria.

Figure 1 *Relative costs of triptan use and overuse.*

Discussion

We analysed the prescription and dispense data for triptans in the year 2005 by using an unique database of the National Health Care Insurance Board, which covers medication use of 6.7 million people, nearly half of the total population in the Netherlands. Triptans were used by 1.3% of all persons, of which 10% were overusing triptans accounting for almost half of the total costs. Remarkably, the risk of overuse differed per triptan,with rizatriptan and possibly frovatriptan being associated with the lowest risk.

The results from our analysis appear robust and representative. We use an extensive and unbiased, nation-wide, population-based database with an accurate count of actual dispense of triptans at pharmacies. Although we couldn't measure the actual use of triptans by the patient, it seems very unlikely that large proportions of patients would not use medication that was dispensed. Furthermore, our results are in agreement with a population-based study in Denmark where 5% of sumatriptan users used > 30 DDDs per month and was responsible for

38% of the total sumatriptan consumption.[17] A French study estimated that 25-30% of the triptan users are overusing these drugs.[18]

We calculated the average triptan consumption over a 12 month period rather than only over three month periods because use and overuse of acute antimigraine medication are known to fluctuate substantially. Of the 9,120 IHS overusers in the first quarter, only 5,891 (65%) were overusers in the second quarter, 5,732 (63%) in the third, and 5,860 (64%) in the last quarter. By using dispense of 120 DDDs or more over a 12-month period as cut-off criterion, we found 8,844 IHS overusers. This appears a better estimate of true long-term consistent triptan overuse.

The most striking finding of our study was that risk of overuse appears to differ among triptans. In particular, use of frovatriptan and rizatriptan was associated with remarkably lower proportions of overusers compared to the reference agent sumatriptan and the other triptans. Several confounding factors could potentially explain this finding and need to be discussed first before assuming that rizatriptan and frovatriptan are indeed associated with a lower risk of overuse.

A possible confounding factor could be that we used DDDs for the threshold for overuse rather than total amount of mg. In 2001, the DDD for sumatriptan was changed from 100 mg to 50 mg (http://www.whocc.no/atcddd/).[15] Thus, if patients continued using the 100 mg rather than the 50 mg dose, the threshold for overuse could have been artificially lowered. This could, however, not be confirmed by the number of dispensed DDDs per patient in 2005. For sumatriptan 52 DDDs in average per patient were prescribed with an average prescription size of 14.8 DDDs. The average DDDs per patient and prescription size of sumatriptan is comparable to the other triptans. Respectively, the numbers for naratriptan are 47 and 13.8, for zolmitriptan 50 and 13.9, for rizatriptan 27 and 9.7, for almotriptan 34 and 10.7, for eletriptan 45 and 12.4, and for frovatriptan 20 and 9.6.

Secondly, high use of subcutaneous sumatriptan by cluster headache patients could have biased the results towards overuse of sumatriptan. However, use of the subcutaneous formulation of sumatriptan made up for only 8.8% of the total sumatriptan overuse in the IHS

group and for only 5.7% in the stringent group. This is less than in the non-overuse group (10.5%), making a major impact of overuse of subcutaneous sumatriptan unlikely.

A third potential confounding factor is the difference in duration of availability of the various triptans (Table 1). This might have led to preferential use of the earlier available agents by the most disabled patients who potentially could have a higher risk of overuse. Sumatriptan was the first available triptan (1991), but because of complicated reimbursement issues in the Netherlands, the oral formulation became fully reimbursed only in 1996. Sales for sumatriptan really started only then. Overuse before that time was rare in the Netherlands. The other triptans were always fully reimbursed from the date of introduction. When corrected for duration of availability (for sumatriptan from year of full reimbursement), the risk differences for naratriptan, zolmitriptan, eletriptan, and almotriptan compared to sumatriptan almost disappeared, but remained for frovatriptan and rizatriptan. Although we cannot fully exclude that the later introduction of rizatriptan and frovatriptan has contributed to their lower association with overuse, it seems unlikely to have been a major contributor, especially not in the case of rizatriptan.

Taken together, rizatriptan and frovatriptan were associated with substantially lower proportions of overusers in 2005. We consider this a true benefit for rizatriptan, but find it too early to arrive at the same conclusion for frovatriptan. Frovatriptan is the most recently introduced triptan, 10 years later than sumatriptan, and was marketed as a triptan with a slower and lower onset of efficacy. This would not seem a profile well suited for many highly disabled migraine patients. Indeed, the absolute numbers for users (N=957) and overusers (N=17) of frovatriptan in 2005 were extremely small compared to those for sumatriptan (N= 41,352 and N= 5,554), rizatriptan (N=25,796 and N=1,026) and the other triptans. The small numbers make meaningful assessment of true risk of overuse difficult.

We can only speculate why rizatriptan, and possibly frovatriptan, are associated with a lower risk of overuse. Risk of overuse may be influenced by the initial efficacy of the agent (how fast does it completely stop the migraine symptoms) and the subsequent duration of action (absence of recurrence of the symptoms precluding redosing). In a large meta-analysis of 53 controlled trials with all available triptans, use of rizatriptan was associated with the highest rates for initial efficacy (pain free at two hours post dose) and sustained effect (24 hrs

sustained pain free)[1]. The differences with the other triptans were, however, in absolute terms hardly large enough to explain the remarkable reduction in risk of overuse for rizatriptan in the present study.

Overusers account for almost half of the total costs of triptans. These costs can be greatly reduced if physicians would monitor their prescriptions better and would consider prophylactic treatment earlier in case of increasing headache frequency to prevent overuse. Once overuse is established, withdrawal of overused medication is the most appropriate therapy.[19]

A limitation of our study is firstly the lack of information on the indication for the prescribed drug, as we already noted for cluster headache. The prophylactic medication for instance, can be prescribed for other disorders than migraine (e.g. propranolol for hypertension, among other diagnoses). The reported use of migraine prophylaxis may therefore be slightly overestimated. Secondly, we do not have information on the number of headache days of the triptan users. It is likely though that patients who overuse triptans have chronic frequent headache (CFH), which is defined as headache on at least 15 days per month and leads to a considerable decrease in quality of life.[13] CFH is more prevalent in people with a low educational level.[20,21] Given the nature of our sickfund-based database our patients had a relatively lower socio-economic status, which could imply that the prevalence of triptan overuse is slightly overestimated. However, the database covers 6.7 million people and represents 65% of the Dutch population in 2005 and data from these patients are generally no different from those in the general population.[22]

To our knowledge, this is the first large study reporting the prevalence of overuse of all currently available triptans in the general population. Although the overall prevalence of triptan overuse is low, overuse accounts for a large percentage of total costs of migraine therapy. The risk of overuse differs per triptan. Rizatriptan had the lowest risk of overuse.

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Table 3 Characteristics of triptan overusers compared to non-overusers

	Total		Non-overusers		Overusers							
	N = 85,172		< 120 DDDs/yr N = 76,328		IHS criteria: ≥120 DDD/yr N = 8,844		Difference IHS-overusers vs non-overusers (95% CI)		Stringent criteria* ≥216 DDD/yr N = 2,787		Difference stringent-overusers vs non-overusers (95% CI)	
Female, n (%)	71,047	(83)	63,622	(83)	7,425	(84)	1%	(-0.2 to 1.4)	2,294	(82)	-1%	(-2.5 to 0.4)
Mean age, y (SD)	43	(13)	42	(13)	47	(11)	5 yrs	(4.7 to 5.3)	48	(11)	6 yrs	(5.2 to 6.2)
Age, n (%)												
< 20	2,787	(3)	2,765	(4)	22	(0)	-3%	(-3.5 to -3.2)	6	(0)	-3%	(-3.6 to -3.1)
20 - 29	11,398	(13)	10,913	(14)	485	(6)	-9%	(-9.3 to -8.3)	113	(4)	-10%	(-11.0 to -9.4)
30 - 39	20,119	(24)	18,439	(24)	1,680	(19)	-5%	(-6.0 to -4.3)	515	(19)	-6%	(-7.1 to 4.2)
40 - 49	25,272	(30)	22,275	(29)	2,997	(34)	5%	(3.7 to 5.7)	964	(35)	5%	(3.6 to 7.2)
50 - 59	17,340	(20)	14,861	(20)	2,479	(28)	9%	(7.6 to 9.5)	789	(28)	9%	(7.2 to 10.6)
60 - 69	6,120	(7)	5,210	(7)	910	(10)	4%	(2.8 to 4.1)	298	(11)	4%	(2.8 to 5.1)
≥70	2,136	(2)	1,865	(2)	271	(3)	1%	(0.3 to 1.0)	102	(4)	1%	(0.6 to 2.0)
Prophylaxis, n (%)†												
Propranolol	6,267	(7.4)	5,287	(6.9)	980	(11.1)	4%	(3.5 to 4.8)	326	(11.7)	5%	(3.6 to 6.0)
Metoprolol	6,985	(8.2)	5,868	(7.7)	1,117	(12.6)	5%	(4.2 to 5.7)	352	(12.6)	5%	(3.7 to 6.2)
Pizotifeen	1,400	(1.6)	1,133	(1.5)	267	(3.0)	2%	(1.2 to 1.9)	106	(3.8)	2%	(1.7 to 3.1)
Flunarizine	218	(0.3)	165	(0.2)	53	(0.6)	0%	(0.2 to 0.6)	17	(0.6)	0%	(0.2 to 0.8)
Valproic acid	1,713	(2.0)	1,352	(1.8)	361	(4.1)	2%	(1.9 to 2.8)	123	(4.4)	3%	(1.9 to 3.5)
Clonidine	747	(0.9)	628	(0.8)	119	(1.3)	1%	(0.3 to 0.8)	38	(1.4)	1%	(0.2 to 1.0)
Topiramate	1,084	(1.3)	757	(1.0)	327	(3.7)	3%	(2.3 to 3.1)	130	(4.7)	4%	(2.9 to 4.5)
Any of the above	16,327	(19.2)	13,635	(17.9)	2,692	(30.4)	13%	(11.6 to 13.6)	895	(32.1)	14%	(12.5 to 16.0)

Source: GIP Database/College voor Zorgverzekeringen. * Stringent-overusers are a subgroup of IHS-overusers. † Medication which can be prescribed as prophylactic medication for migraine, but may have been prescribed for other co-morbid disorders.

Table 4 Triptan use in non-overusers versus overusers

	Total	Non-overusers		Overusers		
		< 120 DDDs/yr	IHS criteria: ≥120 DDDs/yr	Difference IHS-overusers – non-overusers	Stringent criteria* ≥216 DDDs/yr	Difference stringent-overusers – non-overusers
	N = 85,172	N = 76,328	N = 8,844	(95% CI)	N = 2,787	(95% CI)
Single triptan use	79,636 (94)	71,837 (94)	7,799 (88)	-6% (-6.6 to -5.3)	2,416 (87)	-7% (-8.8 to -6.2)
Sumatriptan	41,352 (52)	35,798 (50)	5,554 (71)	21% (20 to 22)	1,952 (81)	31% (29 to 33)
Naratriptan	3,798 (5)	3,437 (5)	361 (5)	0% (-0.6 to 0.4)	86 (4)	-1% (-1.9 to -0.4)
Zolmitriptan	4,983 (6)	4,397 (6)	586 (8)	1% (0.8 to 2.0)	134 (6)	-1% (-1.4 to 0.4)
Rizatriptan	25,796 (32)	24,770 (35)	1,026 (13)	-21% (-22 to -21)	182 (8)	-27% (-28 to -26)
Eletriptan	1,455 (2)	1,289 (2)	166 (2)	0% (0.0 to 0.7)	37 (2)	0% (-0.7 to 0.3)
Almotriptan	1,295 (2)	1,206 (2)	89 (1)	-1% (-0.8 to -0.3)	23 (1)	-1% (-1.1 to -0.2)
Frovatriptan	957 (1)	940 (1)	17 (0.2)	-1% (-1.2 to -0.9)	2 (0.1)	-1% (-1.3 to -1.0)
Multiple triptans	5,536 (6)	4,491 (6)	1,045 (12)	6% (5.3 to 6.6)	371 (13)	7% (6.2 to 8.8)

Values are numbers (%). * Stringent-overusers are a subgroup of IHS-overusers. Source: GIP Database/College voor Zorgverzekeringen

Table 5 The association with overuse for all triptans relative to sumatriptan tablets.

	Total	Non-overuse		Overuse							
		< 120 DDD/yr		IHS criteria: >120 DDD/yr		Odds (95%CI)		Stringent criteria* >216 DDD/yr		Odds (95%CI)	
	N = 85,172	n	(%)	n	(%)			n	(%)		
Sumatriptan	41,352	35,798	(87)	5,554	(13)	1.00	(ref)	1,952	(5)	1.00	(ref)
Naratriptan	3,798	3,437	(91)	361	(10)	0.68	(0.62-0.74)	86	(2)	0.46	(0.38-0.55)
Zolmitriptan	4,983	4,397	(88)	586	(12)	0.86	(0.80-0.93)	134	(3)	0.56	(0.48-0.65)
Rizatriptan	25,796	24,770	(96)	1,026	(4)	0.27	(0.25-0.28)	182	(1)	0.13	(0.12-0.15)
Eletriptan	1,295	1,206	(93)	89	(7)	0.48	(0.40-0.57)	23	(2)	0.35	(0.25-0.50)
Almotriptan	1,455	1,289	(89)	166	(11)	0.83	(0.72-0.95)	37	(3)	0.53	(0.40-0.69)
Frovatriptan	957	940	(98)	17	(2)	0.11	(0.08-0.17)	2	(0)	0.04	(0.01-0.13)

Values are numbers (%).*Stringent-overusers are a subgroup of IHS-overusers. Source: GIP Database/College voor Zorgverzekeringen.

Chapter 8

Withdrawal therapy in medication overuse headache in General Practice

Submitted

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Abstract

We evaluated the effect of a proactive approach by General Practitioners (GP) of patients with medication overuse headache (MOH) to advise withdrawal. Patients received either 1) an invitation from their GP to visit the practice where withdrawal was advised, or 2) a letter with a discontinuation advice. We compared both interventions to a usual care control group and to outpatients of a university headache centre. Primary outcome measures were success of withdrawal after 3 months and reduction of headache frequency to ≤ 8 days per month after 6 months. Randomisation was done on practice level. In the direct contact group 27 of 79 (34%) patients responded to the invitation, and 21 (27%) consented in withdrawal. Only four of 21 (19%) participants actually discontinued their medication. In the letter group, five of 47 (11%) patients who received the letter actively reported discontinuation. After 6 months, improvement of headache was reported by two of 21 (10%) participants in the direct contact group, 13 of 47 (28%) in the letter withdrawal group, and six of 68 (9%) in the usual care group. Of the 25 referred patients, 22 (88%) reported successful withdrawal after 3 months and seven (28%) improvement after 6 months. We conclude that a direct contact approach by the GP of patients with MOH to advise withdrawal is not effective. A letter with a discontinuation advice seems to be more effective. The perceived need for treatment and compliance is low in non-consulting patients with MOH in the general population.

Introduction

Clinical observation suggests that overuse of analgesics and triptans increases headache frequency in susceptible patients, leading to chronic frequent headache (CFH). Chronic frequent headache is a collective term for primary headaches occurring on more than 14 days per month for at least 3 months, often referred to as Chronic Daily Headache. The prevalence is around 4% worldwide.[1] Overuse of acute headache medication is considered the most important risk factor of CFH. The revised International Classification of Headache Disorders (ICHD-II) now includes clinical criteria for Medication Overuse Headache (MOH).[2] A causal relationship between overuse and chronification of headache is assumed because discontinuation of overused medication results in improvement of headache in the majority of patients.[3] There are however no placebo-controlled trials demonstrating efficacy of drug withdrawal, and spontaneous decrease of headache frequency has also been observed in general population surveys.[4,5] Most information on the effect of withdrawal comes from headache clinics with selected and motivated patients, while the majority of MOH patients are to be found in the general population.

The aim of this study was to evaluate the effect of a proactive approach by GPs of patients with MOH to advice withdrawal. Because patients mostly overuse over-the-counter analgesics and do not consult their GP regularly for headaches, GPs are usually unaware of medication overuse in their patients. Hence, eligible patients had to be identified by a general health survey. We compared two types of active approach by the GP: 1) an invitation to the practice where the intervention (abrupt outpatient withdrawal without replacement therapy) was explained, and 2) a letter from the GP advising patients to abruptly discontinue overuse, without further consultation or replacement therapy. Abrupt outpatient withdrawal has been shown to be effective in analgesic abusing migraineurs seen at specialized headache clinics.[6,7] The discontinuation letter approach has been applied successfully in long-term benzodiazepine users in family practice.[8] Both interventions were compared to a usual care control group and to abrupt withdrawal in outpatients consulting a university headache centre.

Methods

General practice

We identified subjects with CFH from a general health survey conducted in 16 general practices in The Netherlands in 2003. CFH was defined as headache on > 14 days per month during three months. We sent a short questionnaire (Q1) to all registered persons aged 25 – 55 years to screen for headache frequency. This sample represents the general population because in The Netherlands almost all persons are registered at a single general practice. Subjects with CFH received a second detailed questionnaire (Q2) on headache characteristics and medication use. The study design and methodology have been described in detail elsewhere.[5] Of the 246 subjects with CFH, 200 (81%) overused acute headache medication and/or caffeine products. This study was conducted before the publication of the revised IHS criteria for MOH in 2005.[2] We defined overuse as: use of analgesics on ≥ 3 days/week, triptans on ≥ 2 days/week, ergots on ≥ 1 day/week, narcotics on ≥ 10 days/month, and/or use of > 5 cups of caffeine containing beverages a day. Compared to the new IHS criteria, more patients are classified as overusers with our criteria, mainly because of the caffeine overuse subgroup. Caffeine overuse is still an experimental category in the revised ICHD-II.

CFH subjects with medication and/or caffeine overuse were allocated into three trial arms: 1) direct contact, 2) discontinuation letter, and 3) usual care. We randomized on general practice level by drawing practice numbers from a box. Subjects in the direct contact group were invited to participate in a study on treatment of chronic headaches. Interested subjects could make an appointment with their GP. Because abrupt withdrawal of medication needs careful explanation and motivation, the exact treatment plan was not revealed until the first visit: three months of abrupt withdrawal, followed by re-evaluation of headache type. If necessary, prophylactic therapy would be started according to the treatment guidelines of the Dutch General Practitioners' Association.[9] The letter group received a letter from their GP stating that chronic headaches could be caused by overuse of analgesics and caffeine. Subjects were advised to abruptly discontinue analgesic and caffeine use for three months. It was explained that withdrawal usually leads to withdrawal symptoms with an increase of headache, but is then followed by an improvement of headache. They received an invitation for an appointment with their GP after three months to evaluate their headaches. The usual care group was not contacted. In the letter withdrawal group and the usual care group all subjects

received a third questionnaire (Q3) after six months to measure outcome. In the direct contact group only subjects who attended visit 1 and had started withdrawal received Q3.

Outpatient neurology clinic

To provide evidence that abrupt withdrawal can be effective in an outpatient setting, we compared the results of withdrawal in the GP setting to those at the headache centre of the outpatient neurology clinic of Leiden University Medical Centre (LUMC). Consecutive patients with CFH and medication and/or caffeine overuse who were referred to our clinic were invited to participate in the study. The need for abrupt withdrawal was carefully explained and patients were motivated in the same way as in the direct contact group in general practice. Patients returned for visit 2 after three months, in which headache was evaluated and prophylaxis started if necessary. During the three month withdrawal period they received no supportive medication or help. Participating patients completed Q2 at baseline and Q3 after 6 months to measure outcome.

Outcome measures

Primary outcome measures were success of withdrawal and improvement of headache. Withdrawal was considered successful if subjects reported use of acute headache medication and caffeine on less than 3 days in total during the withdrawal period of 3 months. Improvement of headache was defined as a headache frequency of ≤ 8 days per month after 6 months. Secondary outcome measure was reduction of headache related disability.

We assessed the impact of headache on daily life and disability by the Headache Impact Test (HIT-6).[10] This is a validated questionnaire consisting of six items that cover various content areas of health-related quality of life: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Answers are given on a five-point scale ranging from "never" to "always", each answer counts for 6, 8, 10, 11, or 13 points respectively. All items are summed to a total HIT-6 score that ranges from 36 to 78. Higher scores indicate a greater impact, with scores of 49 or lower reflecting "little or no impact" and above 60 "severe impact".

Statistical analysis

Statistical analysis was performed with SPSS, version 12.01. Differences between groups are presented with 95% confidence intervals (95% CI). One-way ANOVA was used to compare continuous variables between groups, and chi-square test for categorical variables. Paired samples t-test was used to compare continuous variables between baseline and after treatment. We analysed according to the intention-to-treat principle. We used last-observation-carried forward method to fill in missing values.

The Medical Ethics Committee of the Leiden University Medical Center approved the study.

Results

General practice

Six practices were randomised into the direct contact arm (number of CFH patients = 79), five into letter withdrawal (n = 47), and five into usual care (n = 68). Demographic characteristics of subjects in the three treatment arms are presented in Table 1. There were no relevant differences in demographic variables between treatment arms. Only 53 (28%) of all CFH subjects had consulted their GP for headaches in the past six months. Medication overuse consisted mainly of over-the-counter analgesics. Only five patients overused triptans.

Table 1 Demographic characteristics by treatment arm

	General Practice			LUMC
	Direct contact	Letter	Usual care	
	N = 79	N = 47	N = 68	N = 25
Age, y (SD)	44 (9)	41 (9)	43 (7)	45 (12)
Female	58 (77)	30 (64)	49 (72)	17 (68)
Low education	32 (41)	14 (30)	16 (24)	3 (12)
Medication overuse	58 (73)	36 (77)	45 (66)	25 (100)
Analgesics	58 (73)	35 (74)	43 (63)	16 (64)
Triptans	1 (5)	2 (4)	2 (3)	13 (52)
Caffeine overuse	50 (63)	32 (68)	54 (79)	7 (28)

Values are n (%) unless stated otherwise. LUMC: outpatient neurology clinic at Leiden University Medical Centre.

Flow of patients in the trial is shown in Figure 1. In both the direct contact and the letter withdrawal group only one third responded to an invitation for treatment of chronic headaches. In the direct contact group 21 subjects started withdrawal. Mean number of headache days per month was 21 (SD 8). The number of drop-outs in the direct contact group was high: only five patients returned for visit 2 after three months, four reported successful withdrawal. In the letter withdrawal group five of fourteen patients who showed up for visit 1 reported successful withdrawal at t = 3 months. Six patients attempted, but did not succeed in withdrawal. Three did not even try because they did not believe it would help them.

At t = 6 months, Q3 was completed by 11/21 patients (52%) in the direct contact group, 27/47 patients (57%) in the letter withdrawal group and by 44/68 (65%) in the usual care group. Assuming that non-respondents had no improvement of headache, improvement to ≤ 8 headache days per month was reported by two of 21 (10%) patients in the direct contact group, and by six of 68 (9%) patients in the usual care group (difference 1%, 95% CI -11 to 20), and thirteen of 47 (28%) in the letter withdrawal group, a difference of 19% (95% CI 5 to 34) with usual care.

HIT scores at baseline and at t = 6 months are presented in Table 2. Using last observation carried forward, HIT scores decreased 0.6 (SD 3.8) in the direct contact group and increased 0.9 (SD 4.0) in the usual care group, mean difference in change 1.5 (95% CI -2.8 to -0.2). In the letter withdrawal HIT scores decreased 0.9 (SD 3.2), difference in change with usual care -1.8 (95% CI -3.2 to -0.4).

Table 2 HIT scores in General Practice

	Treatment arm			Difference	
	Direct withdrawal	Letter withdrawal	Usual care	Direct-Usual (95% CI)	Letter-Usual (95% CI)
Baseline	n = 78	n = 47	n = 67		
	62 (6)	62 (6)	59 (7)	2.8 (0.6 to 5.0)	2.7 (0.2 to 5.1)
At 6 months	n = 11	n = 27	n = 44		
	61 (10)	61 (7)	60 (5)	0.6 (-3.7 to 5.0)	0.4 (-2.5 to 3.4)

Values are mean (SD) unless stated otherwise.

Outpatient neurology clinic

Of 36 eligible patients, 25 participated in the study and completed Q2. Characteristics are presented in table 1. Mean number of monthly headache days was 24 (SD 6). Main differences with the GP patients were the higher educational level in LUMC patients and the overused medication. Nine patients (36%) overused triptans only, 12 (48%) analgesics only, and four (16%) both. Seven subjects (28%) also overused caffeine. Flow of patients is shown in Figure 1. Of the 25 participants, 22 returned for visit 2; 21 succeeded and one did not succeed in withdrawal. Of the three patients who did not return, two did not succeed in withdrawal and one did. Thus, of the 25 patients who started withdrawal, 22 (88%) indeed succeeded in withdrawal. Eighteen patients completed Q3 at t = 6 months, of whom seven (39%) reported improvement to ≤ 8 headache days per month, which is 28% of all participants.

HIT score at baseline (n = 25) was 66 (SD 5). At t = 6 months, the 18 respondents had a mean HIT score of 64 (SD 4), a mean decrease of 3.3 (95% CI 1.3 to 5.3). Using last observation carried forward, mean decrease of HIT score at t = 6 months was 2.4 (95% CI 0.9 to 3.9) in the total group. HIT scores decreased 5.3 points in patients who improved (n=7) and 2.1 points in those who didn't (n=11), mean difference in change -3.2 (95% CI -7.1 to 0.7).

Discussion

This study shows that an active approach by GP's to identify patients with CFH and analgesic overuse and invite them to the practice for a discontinuation advice has no beneficial effects. Two important conclusions can be drawn from this study. First, the perceived need for treatment is low if patients do not consult their GP for headache; even though the impact of headache is high, only one third responded to an invitation for treatment for chronic headaches. Secondly, when patients are informed about medication overuse headache and are advised to discontinue their medication, most of them will not comply. This is in contrast to patients who are referred to the neurology clinic where most patients comply with abrupt outpatient withdrawal. The difference in compliance is probably due to difference in motivation.

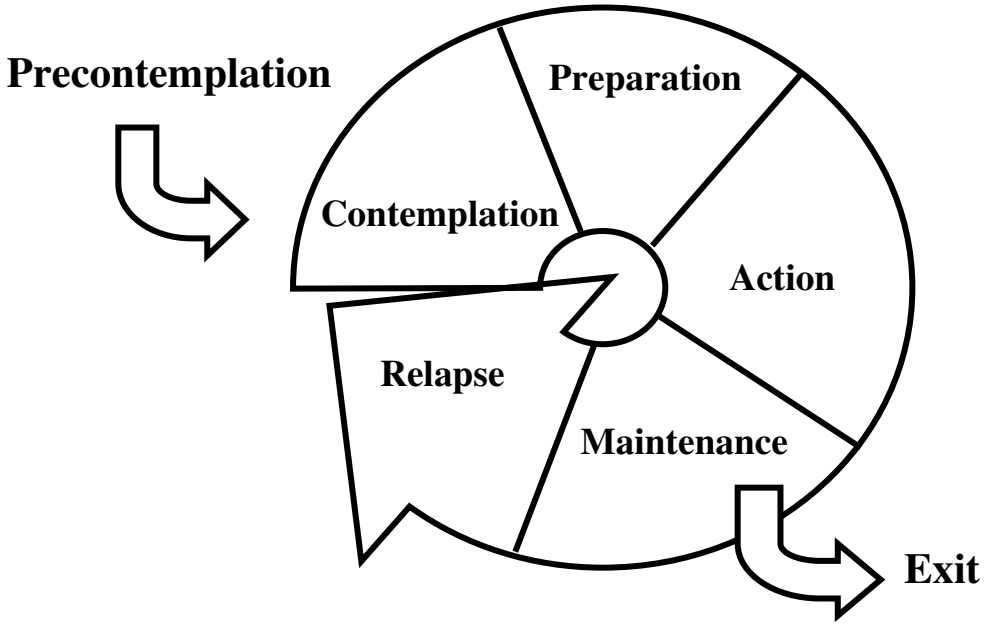

Figure 2 Circel of motivation. Modified from Prochaska and DiClemente (Prochaska, 1992).

Medication overuse headache has characteristics of substance dependence disorders.[11] Drop-outs and relapse are common problems in studies on modification of addictive behaviours. Prochaska and DiClemente have done extensive research on self-initiated and professionally facilitated change of addictive behaviours and constructed a Stages of Change model.[12] The circle of motivation is shown in Figure 2. Individuals modifying addictive behaviour move through a series of stages from precontemplation to maintenance. Precontemplation is the stage at which there is no intention to change behaviour. These people are unaware of their problems and show resistance to recognizing a problem. They only consult therapists under pressure from others. In the contemplation stage, they are aware of their problem, weighing the pros and cons of the problem and are thinking about overcoming it. Preparation is a stage that combines intention and behaviour. They have made some reductions, such as smoking five cigarettes less, but have not yet reached full abstinence. They are intending to take real action in the next month. Action is the stage in which individuals truly modify their behaviour. This stage requires considerable commitment of time and energy. After action comes maintenance. This is the stage in which people work to prevent relapse and consolidate the gains attained during action. Two important implications can be derived from this model. First, relapse is part of modifying addictive behaviours. Individuals typically recycle through the stages several times before achieving long-term maintenance. Secondly, interventions should be tailored according to the stage of readiness to change of the patient. When action-

oriented treatment programs are offered to patients who are not in the action stage, only small numbers will be interested in joining and large numbers will drop out of the program after registering. Several self-help programs have been launched for smoking cessation with great publicity, and have typically recruited only 1-5% of eligible smokers.[13] The vast majority of addicted people are not in the action stage.

If we assume that MOH is a behavioural disorder, we could speculate that non-consulting patients, who are actively approached by their GP to discuss withdrawal, will not comply because they are in the precontemplation stage. General public information about medication overuse headache could move medication overusers into the contemplation stage. Consulting patients in primary care can move from contemplation into preparation stage. Most patients, however, like to be referred to a specialist to make sure that their headaches are not secondary before they are convinced that medication overuse is the key problem and that they are the only ones who can change this. The neurologist will therefore see more patients who are in the preparation stage and are willing to take action. Key feature of treatment will be motivating patients into the action stage and keeping patients in the maintenance stage by installing prophylaxis. Once patients have relapsed, the GP can try to convince patients to try withdrawal again, referring to the patient's previous success.

The discontinuation letter seems to have been more effective than the direct approach. Perhaps the direct approach is perceived as too much interference from the GP. Most MOH patients have had frequent headaches for years and are used to buy analgesics themselves. Our letter with information about MOH and the advice to discontinue analgesics led to improvement of headache in a considerable percentage of patients. The effect was comparable to a discontinuation letter to long-term benzodiazepine users in family practice in the Netherlands.[8] Apparently, the information offered in the letter increases awareness of the paradoxical effect of analgesics and the effect of withdrawal, which may enhance responsibility and move patients into the action stage. Outcome could theoretically be improved by a stage-tailored letter aimed at inducing forward stage transition.[14] A mailing of letters from general practices may be a cost effective minimal intervention but will be limited by the fact that MOH is a hidden epidemic: the GP does not know who has MOH since most patients overuse analgesics, which are OTC products and most patients do not consult their GP for chronic headaches.

Even more patients could improve if they were treated with prophylactic medication. The percentage of referred patients who improved to ≤ 8 days per month after six months was disappointing when compared to success rates in other studies.[6,15] However, if we view the referred patients as a highly selected, difficult to treat population, improvement to ≤ 8 days/month in 28% of patients could be considered a clinically relevant outcome. The referred patients had a higher HIT score than the GP patients, indicating a higher impact of headaches and more disability. Unfortunately, we did not have a usual care control group of referred patients to compare improvement. Since most patients succeeded in discontinuing their medication, we need to focus on improving headache treatment after withdrawal.

Although HIT scores decreased in both GP withdrawal groups as opposed to an increase in the usual care group, there were no differences in headache disability between three GP treatment arms after six months. In referred patients withdrawal with subsequent improvement of headache led to a slight reduction of disability. We expected the HIT scores to change more than five points, since previously we found that the difference between HIT scores in CFH patients and patients with infrequent headaches was ten points (Chapter 4, Wiendels et al., *submitted*). After six months, mean HIT score was still above 60, indicating severe impact. The fact that the remaining headaches after withdrawal are as disabling as before withdrawal could reflect suboptimal treatment in these patients. On the other hand, the responsiveness of the HIT could be suboptimal. Recently, it was found that among patients with CFH a decrease of 2.3 points over time reflects a meaningful improvement.[16] And HIT scores declined three points on average among headache patients reporting improvement in performing daily activities.[10] Although it has shown to be responsive to self-reported change in headache impact, more studies are needed to better understand the responsiveness of the HIT in clinical trials.

The reason for randomisation on practice level was to accommodate the GP. It would have been very difficult for a GP to motivate some patients into withdrawal and conduct "usual care" in others. A disadvantage of randomisation on practice level is that a doctor's effect on success of withdrawal is difficult to rule out. But the low number of patients with improved headache made it impossible anyhow to analyse determinants of success.

We conclude that an active approach of analgesic overusing patients by the GP to offer them a treatment program including withdrawal is not effective, while a letter with information on medication overuse headache and an advice to discontinue may be more effective and simpler. Whether differences in compliance between non-consulting patients, consulting patients and referred patients are due to differences in motivational stage of change has to be studied. Outpatient withdrawal in referred patients is successful. However, treatment after withdrawal is of equal importance to improve headache and prevent relapse.

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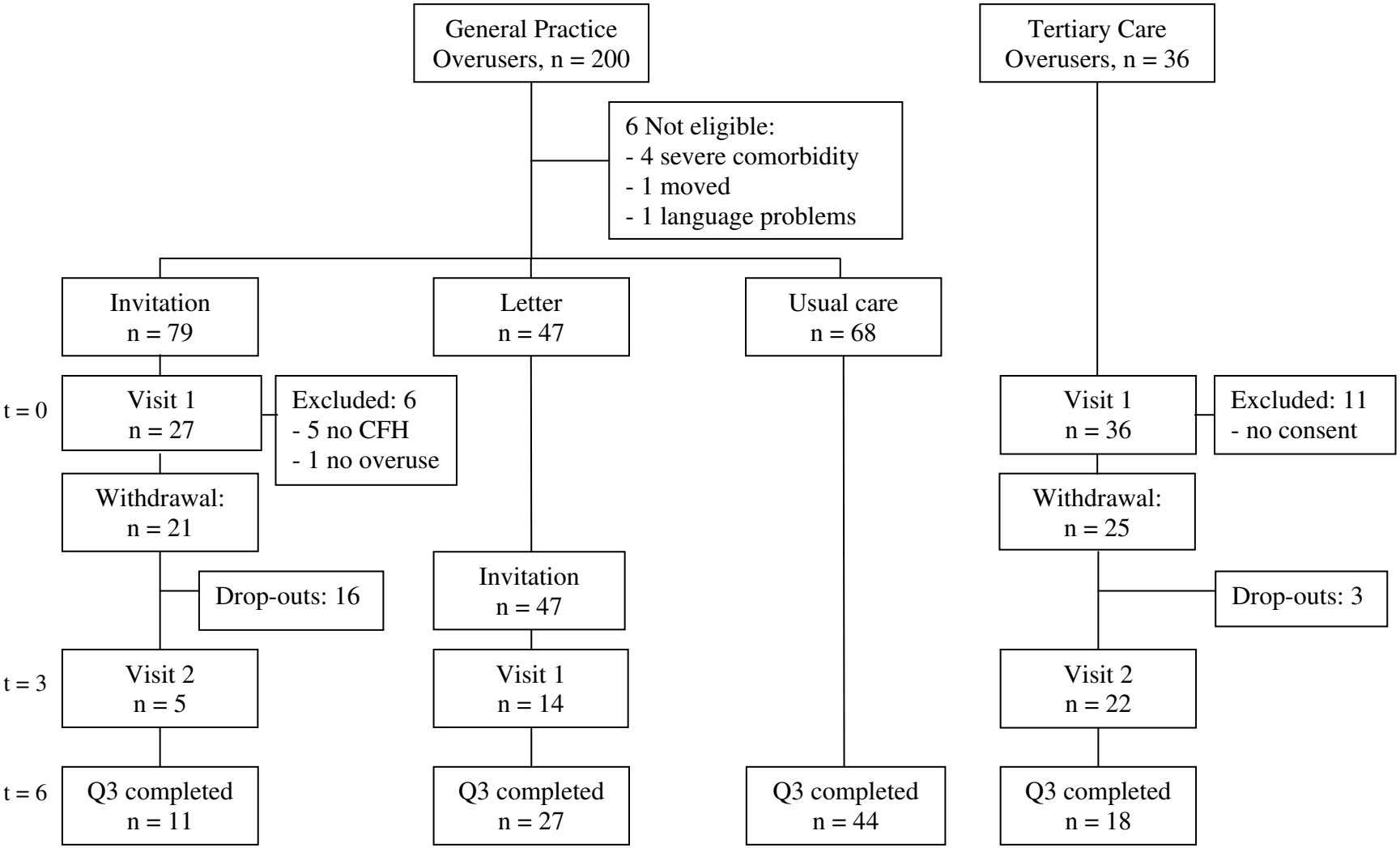
Figure 1 Flow of patients.



Chapter 9

Chronic frequent headache in children and adolescents

Headache 2005;45:678-683

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Abstract

Few data are available on chronic frequent headache and analgesic overuse in children and adolescents and there are no specific criteria for headache in children. The objective was to describe the clinical features of children with chronic frequent headache and examine the usefulness of the International Classification of Headache Disorders-II. We retrospectively reviewed all charts of 79 children and adolescents (< 16 years) with headache on ≥ 15 days per month presenting to the outpatient clinic of the Department of Neurology of the Leiden University Medical Center between 1994 and 2001. We classified their headaches according to the International Classification of Headache Disorders-II. Fifty-seven (72%) children had chronic frequent headache for more than six months, with a duration of more than four hours a day in 60% of them. Quality, severity and location of pain varied. Sixty patients (76%) used analgesics, ten patients more than one type. Thirteen patients (16%) used analgesics daily. In one third of patients, headache led to frequent school absenteeism and sleeping problems. Twenty-eight (35%) patients could be classified, 17 (22%) as chronic tension-type headache, five (6%) as chronic migraine and six (8%) as probable medication overuse headache. Fifteen patients (19%) didn't fit into any category, and 36 (46%) couldn't be classified due to insufficient data. We conclude that chronic frequent headache in children is a serious disorder which leads to frequent school absenteeism and sleeping problems. A relatively large number of patients overuse medication. It remains difficult to classify their headaches with the new criteria for headache disorders.

Introduction

Headache is a common disorder in children and adolescents. In the Netherlands, 23% of schoolchildren between the age of 10 and 17 years report weekly headaches, 13% suffer from headaches a few times per week.[1] Chronic frequent headache (CFH) is a collective term for primary headaches occurring on ≥ 15 days per month, lasting more than four hours a day. In adults, the prevalence of CFH is around 4%.[2,3] The actual prevalence of CFH in children has not been determined, but is estimated to be around 0.9%.[4]

The 2nd, revised, edition of the International Classification of Headache Disorders (ICHD-II) includes four types of CFH: chronic migraine (CM), chronic tension-type headache (CTTH), new daily persistent headache and hemicrania continua.[5,6] This classification was primarily developed for headache disorders in adults. There are no specific criteria for children, which makes it difficult to classify their headaches.[7,8]

Overuse of acute headache medication is the most frequent cause of CFH in adults. Headache frequency may increase in headache-prone patients with intake of ergotamine or triptans on ≥ 10 days/month, or analgesics, opioïds or combination medication on ≥ 15 days/month. Few data are available on analgesic overuse headache in children and adolescents. In tertiary headache centres about 30% of children with CFH use analgesics daily.[7,9] Vasconcellos et al[10] retrospectively reviewed charts of children with headaches seen in a paediatric headache clinic. Most patients with CFH and analgesic overuse successfully discontinued their analgesics, which reduced the mean headache frequency from 27.5 to 5.4 days per month (a reduction of 80%).

This is a retrospective study of children presenting to the outpatient clinic of the Department of Neurology for evaluation of frequent headaches. We describe the clinical features of children with CFH and discuss the usefulness of the ICHD-II in this group of children.[5]

Methods

We retrospectively reviewed all charts of children and adolescents (< 16 years) presenting with headache to the outpatient clinic of the Department of Neurology of the Leiden University Medical Center between January 1994 and January 2001. Patients were coded in

the hospital database as migraine, tension-type headache or headache of unknown origin. We identified patients with CFH, which was defined as headache on ≥ 15 days per month, without an underlying serious medical condition.

The following clinical features were recorded: demographic variables and headache characteristics, including frequency, duration, quality, severity, location and aggravating factors. Headache was considered severe if the child could no longer participate in daily activities because of headache, moderate if the child could still participate but in a lower tempo and mild if headache didn't interfere with daily activities. Associated symptoms, including nausea, photo- and phonophobia, were considered present only when patients reported presence "most of the times" or "always". Frequency of medication and caffeine use, co-morbidity, family history, sleeping problems, school absenteeism and psychological problems possibly contributing to headache were also noted. When a variable could not be found in the charts, it was recorded as unknown. Patients were classified according to the ICHD-II.[5]

Results

Two hundred and seven patients were coded in the hospital database as migraine, tension-type headache or headache of unknown origin. We identified 79 (38%) children and adolescents with CFH. There were 32 boys and 47 girls, a ratio of 1:1.5. Mean age at presentation was ten years with a range of two to 15 years. The mean frequency of headache days per month was 28 (SD 5.7). Fifty-seven (72%) children had CFH for more than six months at presentation (Table 1).

Table 1 Duration of chronic frequent headache at presentation

	N = 79 n (%)
1-3 months	9 (11)
4-6 months	12 (15)
>6 months	57 (72)
Unknown	1 (1)

Headache duration per day was more than four hours in 47 (60%) patients (Fig. 1).

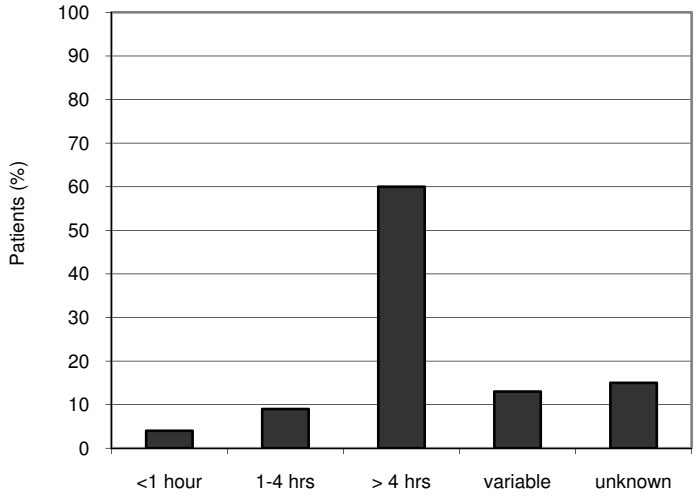

Figure 1 Duration of headache per day

Quality, severity and location of pain varied (Fig. 2). In 23 (29%) patients headache was severe. A frontotemporal location was noted 44 times, which is 51% of all locations noted (Table 2). Some numbers in the table and figure add up to more than 79 and 100% respectively, because several patients described more than one pain quality, location of pain and aggravating factor. Twenty-one (27%) patients had ≥ 2 migraine headache characteristics and 19 (24%) had ≥ 2 tension-type headache characteristics.

Table 2 Location of pain

	N = 79* n (%)
Frontal	36 (46)
Temporal	8 (10)
Occipital	7 (9)
Top of head	7 (9)
Other	23 (29)
Unknown	6 (8)

* Several patients described more than one location of pain.

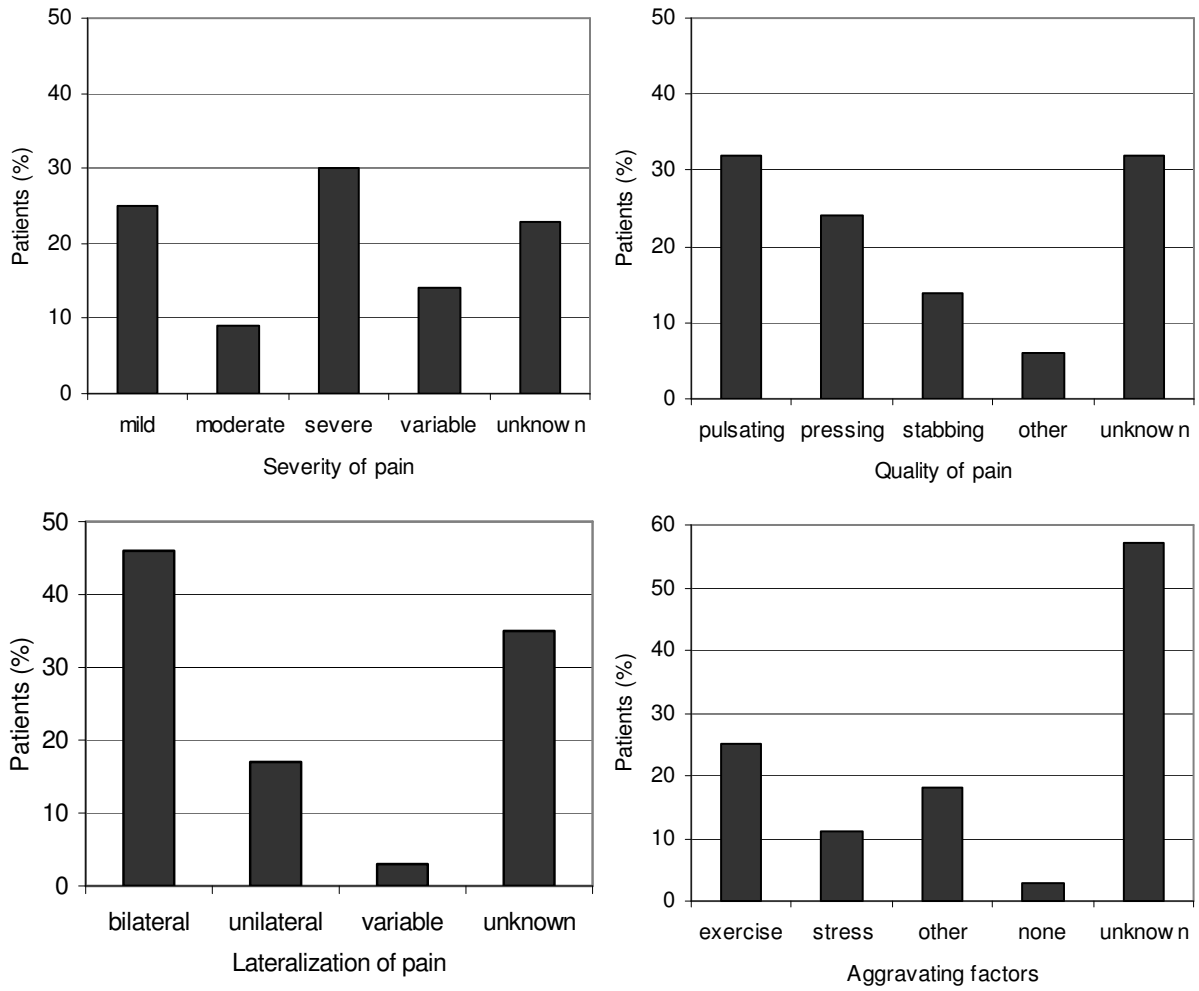

Figure 2 Headache characteristics.

Presence of associated symptoms is shown in Figure 3. In 20 patients (25%) nausea was sometimes present, in seven patients (9%) usually or always.

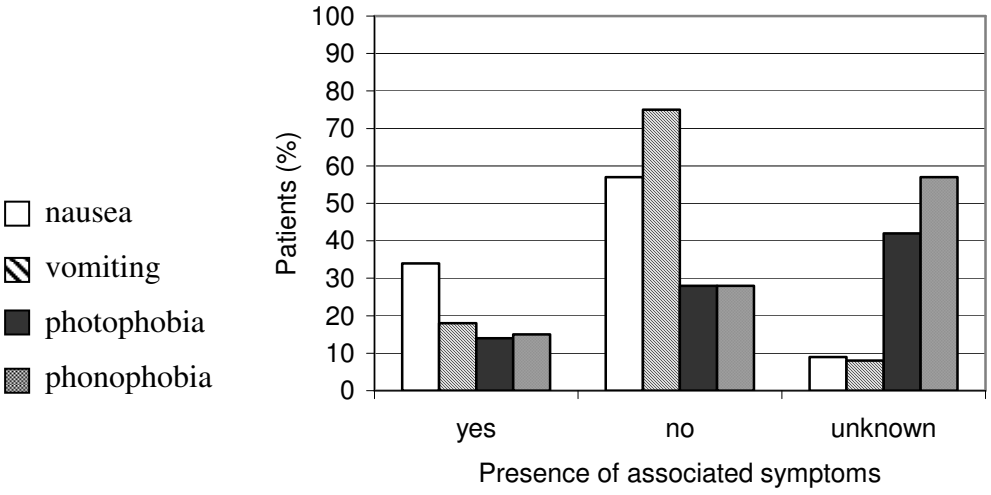

Figure 3 Presence of associated symptoms.

The use of headache medication is listed in Table 3. Sixty patients (76%) used analgesics, of which ten patients used more than one type. Thirteen patients used analgesics daily, which is 24% of the 55 patients with a known frequency. Caffeine use was recorded in nine charts. One patient drank four cups of tea per day, the others drank less or nothing at all. Nine patients were currently using or had used prophylactics in the past; four tried beta-blockers with no success, two of them also tried pizotifen without success, five patients had only tried pizotifen, with two achieving a self-reported moderate effect.

Table 3 Headache medication use

	N = 79 n (%)
Analgesics	60 (76)*
Paracetamol	52 (66)
Acetylsalicylic acid	6 (8)
NSAID	6 (8)
Combination preparation	6 (8)
Prophylactics	9 (11)
Beta-blocker	4 (5)
Pizotifen	7 (9)
Other	6 (8)

* Ten patients used more than one type of analgesic. NSAID = non-steroidal anti-inflammatory drugs.

In seven patients the diagnosis analgesic-induced headache was recorded. They were advised to withdraw all headache medication for three months. In three patients headache frequency reduced dramatically, but in one patient daily headache returned after a few months. One patient started propanolol prophylaxis simultaneously and was complete headache free. Headache returned after tapering of propanolol, but was less frequent. One patient still had daily headaches after withdrawal. Two patients were lost to follow-up.

Sixteen patients (20%) had a history of head injury. Six patients (8%) had a co-morbid neurological disorder; epilepsy (2), psychomotor retardation (2), Down's syndrome (1), and

hemiparesis due to perinatal asphyxia (1). Twenty-four patients (30%) had other non-neurological disorders (Table 4).

Table 4 Other non-neurological disorders

	N = 79 n (%)
Asthma	12 (15)
Urogenital disorder	3 (4)
Diabetes type I	2 (3)
Eczema	1 (1)
Haemophilia B	1 (1)
Aortic Stenosis	1 (1)
Constipation	1 (1)
Ear-nose-throat problems	1 (1)
History of psittacosis	1 (1)
History of haemolytic uremic syndrome and hypertension	1 (1)
None	55 (70)

Three children with asthma were treated with salbutamol, which can cause headache as an adverse-event. Additional problems were noted in 16 (20%) patients; insecurity (3), attention-deficit-hyperactivity-disorder (2), behavioural problems (2), inability to make friends (2), anxiety (1), compulsive disorder (1), somatisation (1), irritability (1), stressful life-event (1), linguistic deficiency (1), and achievement pressure (1). Twenty-two patients (28%) experienced stressful family events, such as divorce and chronically ill family members. Frequent school absenteeism because of headache occurred in 28 (35%) patients, seven (9%) didn't go to school at all. Twenty-five (32%) patients reported sleeping problems. Family history for headache was positive in 40 patients (51%), of which 23 (29%) had first-degree family members with migraine.

The classification of patients according to the ICHD-II is presented in Table 5. We were able to classify 28 (35%) patients, the majority had chronic tension-type headache. The following 15 (19%) patients could not be classified because their features didn't match any category.

Five patients used analgesics daily, but three had not used them for three months, and two had too many migraine features. Three patients had chronic tension-type headache characteristics, but one patient had nausea and photophobia as well and two were sometimes vomiting. Six patients had headache characteristics of chronic migraine, but three of them had no associated symptoms at all and three were only "sometimes" nauseated without other associated symptoms. One patient had chronic migraine with a duration of less than three months. Thirty-six patients (46%) could not be classified due to insufficient data. Two of these patients used analgesics on a daily basis.

Table 5 Diagnosis according to ICHD-II

	N = 79 n (%)
Chronic migraine	5 (6)
Chronic tension-type headache	17 (22)
Probable medication-overuse headache	6 (8)
Not classifiable	15 (19)
Insufficient data	36 (46)

ICHD-II = International Classification of Headache Disorders 2nd edition.

Discussion

We retrospectively studied the clinical features of 79 children and adolescents with CFH presenting to a secondary paediatric neurology outpatient clinic over a period of seven years. Sixty percent of the patients had (near-) daily headaches for more than six months, which lasted for more than four hours a day. CFH occurs at any age, our youngest patient was only two years old. In at least one third of the patients, headache led to frequent school absenteeism and sleeping problems.

At least 13 (16%) of our patients used analgesics daily. The frequency of analgesic use wasn't always recorded because at the time not all physicians were familiar with medication-overuse-headache. We expect that the actual percentage of analgesic overuse in our population is higher. Of the seven patients who were advised to discontinue their headache medication, headache frequency reduced dramatically in four. Although these numbers are too small to draw any conclusions on the effect of withdrawal, a high success percentage in children has

been reported. Hering-Hanit et al[11] described a group of 26 adolescents with CFH and almost-daily analgesic intake. Withdrawal of analgesics led to complete cessation of all headaches in 20 patients, and to intermittent episodic headache in five patients.

This is the first attempt to classify children and adolescents with (near-) daily primary headaches according to the ICHD-II. Of the 43 patients of whom we could find sufficient data, six patients (14%) could be classified as probable medication overuse headache (PMOH). Seven patients, who couldn't be classified because their features didn't match any category (5) or because there was insufficient data on headache characteristics (2), used analgesics on a daily basis, which would logically make them candidates for probable medication-overuse headache (PMOH). The diagnosis PMOH however, requires a duration of overuse of three months and tension-type headache characteristics. These two criteria are in our opinion not practical. We advise withdrawal of all headache medication when a child presents with daily headaches and daily analgesic intake, regardless the duration of overuse and headache characteristics. If frequency of analgesic use would be the only criterion for PMOH, then 29% (13 out of 45 patients) would be classified as such.

Of the 28 classifiable patients, the majority had CTTH (61%), and only five (18%) had CM. This is in agreement with a prospective study done by Abu-Arafeh in a tertiary headache clinic.[12] The majority of children with almost daily headache could be classified as CTTH, and one third had a combination of CTTH and migraine according to the 1988 criteria of the International Headache Society.[6] He made use of headache diaries to diagnose children more accurately. Maybe we would find more associated symptoms in our population when patients and parents kept a headache diary and were specifically asked about these symptoms. Both Hershey and Koenig[9] found that most children and adolescents with CFH have migraine headache characteristics and associated symptoms. [7] We do not have an explanation for these differences.

A major limitation of our study is the retrospective study design. We had to rely on data recorded by different physicians with varying expertise in headache. Missing data could not be retrieved, which resulted in the fact that 46% of patients could not be classified.
We found a relatively high percentage of asthma in our population. In 1994, the prevalence of diagnosed asthma in schoolchildren was 6.2% in the Netherlands.[13] The prevalence of asthma

in children aged six to thirteen in our population is 14%. Only three children used salbutamol, which can cause headache as an adverse-event. Frequent use of paracetamol has been positively associated with asthma, but this doesn't seem to play a role in our population since only three children with asthma used paracetamol.[14] Asthma has been associated with headache, migraine in particular, but a pathophysiologic explanation has not been found so far.[15]

In conclusion, CFH is a serious disorder which can occur at any age and leads to significant school absenteeism and sleeping problems. A significant percentage of patients overuse headache medication. Withdrawal of all headache medication is the appropriate therapy, regardless the duration of overuse or type of headache characteristics. We could classify 65% of the patients with sufficient data of which the majority had CTTH according to the ICHD-II. A prospective study in the general population is needed to study the prevalence of children and adolescents with CFH and accurately describe the headache characteristics and medication use and test the efficiency of the ICHD-II.

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Chapter 10

Summary and discussion

Summary

This thesis describes the results of a large questionnaire-based study on the epidemiology of chronic frequent headache (CFH) in the Dutch adult population. It also includes information on triptan (over)use from the Drug Information Project (GIP database) and the results of a withdrawal trial in General Practice. Lastly, clinical features of children with CFH seen at a tertiary referral centre are presented.

The general introduction, **chapter 1**, begins with a definition of chronic frequent headache (also known as chronic daily headache). The current epidemiologic knowledge on CFH is presented and the lack of evidence-based therapeutic options emphasized. The aims of the study and a quick overview of study methods are provided.

In **chapter 2** the methods of the questionnaire study are described in detail. Following chapters refer to this section. The prevalence of CFH in the Dutch population, aged 25-55 years, was 3.7%. The prevalence amongst non-western immigrants was much higher. In many subjects headache frequency changed over time without specific headache treatment. Twelve percent had a clinically relevant decrease from >14 days to <7 days/month in five months. To identify putative risk factors, we compared 177 CFH subjects to 141 subjects with infrequent headache (1-4 days/month), and to 526 subjects with no headache (<1 day/month). In both headache groups 70% were women, in contrast to 41% in the No Headache group. Sixty-two percent of CFH subjects overused analgesics and only 9% used prophylactic medication to reduce headache frequency. There was no difference in caffeine use between groups. The majority screened positive for presence of psychopathology. Other factors associated with CFH were low educational level, smoking, and a history of head or neck trauma prior to onset of headache.

Headache frequency fluctuates. CFH is common and associated with analgesic overuse, psychiatric comorbidity, sleeping problems, smoking, a history of head/neck trauma and low educational level. Female sex is a risk factor for headache, not for chronic headache in particular.

Chapter 3 describes the comorbidity and quality of life of CFH subjects. We rated comorbidity according to the Cumulative Illness Rating Scale (CIRS) and measured quality of

life with the RAND-36. CFH subjects had higher overall comorbidity scores than the IH subjects. Analgesic overusers reported more comorbidity than non-overusers. Fifty percent of the CFH subjects had a comorbid problem requiring daily medication. Quality of life in CFH subjects was lower than IH subjects in all domains of the RAND-36. And all domains were negatively correlated to CIRS score. Both headache frequency and CIRS score had a negative influence on quality of life.

CFH patients have more somatic and psychiatric comorbidity than patients with infrequent headaches. Both high headache frequency and comorbidity contribute to the low quality of life in these patients.

In **chapter 4** the role of cognitive and personality factors in the chronification of headache is explored. We used the Pain Coping and Cognition List to measure cognitive factors, The Temperament and Character Inventory to measure personality factors, the General Health Questionnaire to screen for psychiatric comorbidity, and the Headache Impact Test to measure quality of life. The CFH group scored higher on catastrophizing, higher on degree of pain coping, lower on internal pain control and higher on external pain control than the group with infrequent headaches. After adjusting for presence of psychopathology, personality factors were no longer associated with CFH. As expected, CFH subjects had high headache impact scores. Only catastrophizing and low internal locus of control made a unique contribution to headache impact after controlling for confounders.

CFH is associated with catastrophizing, use of coping strategies, low internal pain control, and high external pain control. Personality factors do not pose an additional risk factor for chronification. Especially catastrophizing seems to be important for the impact of headache on daily life.

Since headache is a frequently reported side effect of oral contraceptives (OC), headache patients often discuss whether they should start or discontinue OC use to improve headache. **Chapter 5** reports that the percentage of combined oral contraceptive use was similar in CFH subjects and subjects with infrequent headache. We found no association between oestrogen containing OC use and CFH.

There is no association between use of oestrogen containing OC use and the occurrence of CFH, and therefore no evidence that discontinuing or switching OCs will improve headache frequency.

Medication overuse is generally considered an important risk factor for CFH. Patients with overuse are classified as having probable medication overuse headache (pMOH) until headache improves after withdrawal and the diagnosis MOH becomes definite. **Chapter 6** deals with differences between CFH subjects with pMOH (n = 104) and those who do not overuse medication (n = 73). There was no difference in headache type between overusers and non-overusers. Overall, half could be classified as having chronic tension-type headache and 24% as chronic migraine. Overuse consisted mainly of analgesics, only 2% overused triptans. The majority had increased dosage gradually and took medication despite lack of efficacy. Fourty percent took analgesics to prevent headache, while only 13% used prophylactic medication.

Probable MOH in the general population mainly concerns analgesic overuse. Many use analgesics inappropriately and lack prophylactic medication.

In **chapter 7** we present information on triptan use and overuse from the Drug Information Project of the Health Care Insurance Board. Data were available for 6.7 million people in 2005, and covers almost half of the total Dutch population. Triptan overuse is defined by the International Classification of Headache Disorders (ICHD-II) as intake on ≥10 days/month on a regular basis for > 3 months. However, Limmroth et al. estimated the mean critical dosage to be 18 single doses per month. Amongst triptan users, the estimated 1-year prevalence of overuse was 10% according to the ICHD-II criteria and 3% if we adhere to the more stringent criteria of Limmroth et al. Compared to sumatriptan, rizatriptan had the lowest risk of overuse (OR 0.27; 95% CI 0.25-0.28) Triptan overusers use 50% of total DDDs dispensed at pharmacies and account for 50% of total triptan costs.

In the Netherlands, 10% of triptan users are overusers and account for half of the total costs of triptan therapy.

Chapter 8 describes the results of a withdrawal trial in General Practice. The aim of this study was to evaluate the effect of an active approach by GPs of patients with medication overuse headache to advise withdrawal. We compared two types of active approach by the GP: 1) an invitation to the practice where the intervention (abrupt outpatient withdrawal) was explained, and 2) a letter from the GP advising patients to abruptly discontinue analgesic and triptan use. Both interventions were compared to a usual care control group and to abrupt withdrawal in outpatients of a tertiary referral headache centre. The study showed that the perceived need for treatment and compliance is low in non-consulting headache patients resulting in high dropout rates during withdrawal. After 6 months, improvement of headache was reported by 10% of patients in the direct withdrawal group and by 28% in the letter withdrawal group, compared to 9% in the usual care group and 28% of the referred patients. It was not possible to make meaningful analyses of determinants of success.

An active approach by GP's to identify patients with CFH and analgesic overuse and invite them to the practice to explain the need for withdrawal is not effective. A letter with discontinuation advice may be more effective.

In **chapter 9** the clinical features of children and adolescents with CFH are described. We retrospectively reviewed charts of 79 children, seen at a tertiary neurology clinic. The majority of children had headaches lasting more than four hours a day. Most children used analgesics, of which 24% daily. In one third, headache led to frequent school absenteeism and sleeping problems. Most children who could be classified fulfilled criteria for chronic tension-type headache.

CFH and analgesic overuse also occurs in children and leads to frequent school absenteeism and sleeping problems.

General discussion

Some general aspects of our studies should be taken into account when interpreting the results. I will discuss the issues that potentially affect the generalisability and interpretation of the results presented in this thesis.

Population

The findings of the questionnaire study apply to the general population. Studying prevalence of CFH and associated factors in the general population is not only important to gain more insight in the etiology of chronic headaches, but may also increase awareness of patients, physicians and policy makers in terms of impact of CFH and the need for prevention. Our study population consisted of non-consulting patients who are possibly different from consulting patients in general practice. Although only one third of our CFH subjects had consulted their GP for headaches in the six months prior to the questionnaire, 54% had consulted their GP for other, headache unrelated, issues. In fact, 50% of CFH subjects have a comorbid disorder requiring daily medication. So CFH subjects are patients regularly seen at general practices, but they are seen for other comorbid disorders. This is interesting from the point of view of reaching the right population for prevention interventions and recruiting options for future studies.

The results on triptan use and overuse from the GIP database are based on patients who were insured by sickness funds in 2005, for which people were eligible if they had a yearly income of less than € 32.000. This means that the data apply to the somewhat lower educated and social class in the Netherlands, as opposed to the highly educated population who are likely to be privately insured. However, since the GIP data includes almost all sickness funds, the studied population can hardly be seen as a sample, but actually is half of the Dutch population.

Bias

A potential limitation of our questionnaire study may be that presence of risk factors is based on self-report, which is not as accurate as studies based on interviews by specialists and headache diaries. Face-to-face interviews have disadvantages as well. Besides the fact that interviews are more expensive than mailed questionnaires, interviewers can have different questioning styles and attributes which may affect the responses given. We measured

presence of psychological risk factors and quality of life by validated questionnaires. Questions about headache characteristics, medical history and medication use were not validated. However, because all groups received the same questionnaire and response was comparable, any possible misclassification will be non-differential.

The response to the second detailed questionnaire was only 40%, but yielded high enough numbers to compare risk factors. The question is whether non-response introduced bias in the associations. The non-responders analyses of the CFH group showed that 50% did not meet criteria for CFH anymore. If non-respondents are healthier than respondents, prevalence estimates of risk factors based on respondents could be overestimated. However, non-response does not necessarily cause bias in associations. In a large population-based study on risk factors for chronic disease conducted in the Netherlands (MORGEN-project) the response rate was 45%.{Van Loon, 2003 892 /id} Associations between lifestyle factors and health did not vary according to response status. I believe that the low response to the second questionnaire in our study does not bias the results because the response percentage was equal in all groups and it is unlikely that prevalence of the studied risk factors is dependent on both participation and headache frequency.

Causality

In this thesis we tried to identify several risk factors for the development of chronic frequent headache. The cross-sectional design of the study limits conclusions about the direction of a causal relationship and therefore we can only refer to these factors as associations. A longitudinal study registering the incidence of CFH in a cohort exposed and unexposed patients with infrequent headaches could demonstrate a temporal relationship between the associated factor and CFH. Another approach to study causality is to take away the associated factor and observe whether this results in a decrease in headache frequency. An example of this approach in clinical practice is withdrawal of overused analgesics and triptans in patients with CFH.

Clinical implications and future research

Our studies have identified several factors which are clearly associated with CFH and which can be modified to improve headache frequency. Below I will discuss the clinical implications and ideas for future research.

Medication overuse

There is debate about the causal relationship between overuse of acute headache medication and CFH. Overuse is common in patients with CFH and considered the most important risk factor. However, it is also likely that patients with frequent headache take medication in response to pain. A returning argument against the idea of overuse as a risk factor is that there are no randomized placebo-controlled trials proving the efficacy of withdrawal, probably because the choice of a placebo control group is difficult. Remarkably, our withdrawal trial in General Practice failed to interest enough patients indicating that the perceived need for treatment in the general population is low. Informing patients about the paradoxical effect of analgesics and the possibility of dependence may increase awareness. Indeed, a letter with discontinuation advice was effective in reducing headache days. A randomized controlled trial in motivated patients with probable medication overuse headache is needed. It would be particularly interesting to analyze the determinants of success. Not all patients with medication overuse succeed in withdrawal and not all patients benefit from withdrawal.

Psychological factors

Factors other than analgesic overuse are important in the development of CFH. In our study 40% of CFH subjects did not overuse medication. We identified several psychological factors which were associated with CFH and high headache impact. Especially catastrophizing is of interest because it has shown to be an important cognitive factor in other chronic pain conditions as well and it can be successfully modified in cognitive therapy.[1] In general, physicians should propose prophylactic medication to patients with increasing headache frequency to prevent overuse. Prophylactic medication is however not effective in at least one third of patients and medication options are limited in case of chronic tension-type headache, which is the most common headache type in the general population. Cognitive behavioral therapy can be a valuable alternative or adjunct treatment option and should be tried in randomized controlled trials in CFH patients.

It is increasingly recognized that headache patients often suffer from psychiatric comorbidity. Migraine has been associated with depression and anxiety disorders, suggesting shared etiologic factors. Alternatively, pain can exacerbate a pre-existing vulnerability to psychopathology, which in turn intensifies the pain. In our study we found that the majority of CFH subjects screen positive for psychopathology. Whether psychiatric comorbidity is a cause or a consequence of CFH could not be determined. The co-occurrence of headache and psychiatric disorders warrants more attention. It may complicate diagnosis and has implications for treatment. Screening headache patients for presence of psychiatric disorders and vice versa may be important to enable simultaneous treatment of both conditions in a multidisciplinary fashion.

Other risk factors

A pathologic change in central pain processing is thought to underlie chronification of headache. Patients with chronic tension-type headache have shown to have a generalized increased pain sensitivity.[2] It is hypothesized that continuous nociceptive input from pericranial tissues induces sensitization of central neurons leading to generalized hyperalgesia. Genetic factors probably play a role in the susceptibility for chronic pain conditions. Possible mechanisms include influencing pain sensitivity. The variability in pain perception between people is substantial. Certain combinations of alleles encoding for the gene catecholamine-O-methyltransferase (COMT) determine levels of COMT enzymatic activity which inversely correlates with pain sensitivity and the risk of developing chronic pain conditions.[3] There is also a large interindividual variability in the response to analgesics. Genetic polymorphisms of the μ-opioid receptor gene, the melanocortin-1 receptor gene, and cytochrome P450 gene influence opioid potency and metabolism which makes dose adaptation necessary.[4] Finally, genes involved in addictive behavior could also play a role in medication overuse and subsequent chronification of headache. It is clear that we should look carefully at different genotypes in CFH in future studies as genetic risk factors may become important predictors for CFH. In the long run, we will learn more about pathophysiologic mechanisms in the development of CFH which will hopefully open up new therapeutic options.

To conclude

In this thesis I demonstrated that CFH is a major health problem, which concerns one in 25 adults, and deserves more attention. Overuse of acute headache medication seems to be an important (iatrogenic) risk factor for the development of CFH in a vulnerable subgroup of patients. Physicians and patients should be aware of the possible paradoxical effect of acute headache medication when headache frequency increases. Although better prophylactic medication is needed, CFH patients do not optimally use the currently available medication. Pharmacists could cooperate with GP's in monitoring triptan and analgesic use. Analgesic overuse however will be difficult to detect because these are OTC products. One way of increasing public awareness is to include an advice in the product information leaflet of analgesics to consult a physician when analgesics are used on more than 15 days per month for headache. GPs should monitor triptan prescriptions and consider prophylaxis earlier to prevent patients from overusing triptans and analgesics. When overuse is evident, withdrawal is the appropriate treatment. Patients are likely to comply better after consulting a neurologist who can confirm diagnosis and treatment. A multidisciplinary approach could be of additional value in case psychological and psychiatric risk factors are present.

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Chapter 11

Nederlandse samenvatting

Samenvatting

Dit proefschrift beschrijft de resultaten van een groot vragenlijstonderzoek over de epidemiologie van chronisch frequente hoofdpijn in de Nederlandse volwassen bevolking. Het bevat ook informatie over het (overmatig) gebruik van triptanen uit het Geneesmiddelen Informatie Project (GIPdatabank) en de resultaten van een onttrekkingstudie in de huisartspraktijk. Tenslotte worden de klinische verschijnselen van kinderen met CFH die gezien werden in een tertiair verwijscentrum beschreven.

De introductie, **hoofdstuk 1**, begint met een definitie van chronisch frequente hoofdpijn (ook wel bekend als chronische dagelijkse hoofdpijn). De huidige kennis over CFH wordt weergegeven en het gebrek aan wetenschappelijke bewezen behandelingen benadrukt. Daarna volgen de onderzoeksdoelen en een klein overzicht van het onderzoek.

In **hoofdstuk 2** wordt de methode van de vragenlijststudie in detail beschreven. De hoofdstukken die volgen verwijzen naar dit hoofdstuk. De prevalentie van CFH in de Nederlandse algemene bevolking, in de leeftijd van 25-55 jaar, was 3,7%. De prevalentie onder allochtonen was heel hoger. Bij veel mensen fluctueerde de hoofdpijnfrequentie over de tijd, zonder specifieke behandeling. Twaalf procent vertoonde een klinisch relevante daling, van > 14 dagen naar < 7 dagen per maand, binnen 5 maanden. Om mogelijke risicofactoren voor het ontwikkelen van CFH te identificeren, vergeleken we 177 mensen met CFH met 141 mensen met infrequente hoofdpijn (1-4 dagen/maand), en met 526 mensen zonder hoofdpijn (<1 dag/maand). In beide hoofdpijngroepen was 70% vrouw, in tegenstelling tot 41% in de groep zonder hoofdpijn. Tweeënzestig procent van de mensen met CFH gebruikten overmatig veel analgetica en maar 9% gebruikten profylactica om de hoofdpijnfrequentie te reduceren. Er was geen verschil in cafeïnegebruik tussen de groepen. De meerderheid screende positief voor de aanwezigheid van psychopathologie. Andere geassocieerde factoren waren laag opleidingsniveau, slaapproblemen, roken, en hoofd- of nekletsel voorafgaand aan het begin van hoofdpijn.

Hoofdpijnfrequentie fluctueert. CFH komt veel voor en is geassocieerd met overmatig gebruik van analgetica, psychiatrische comorbiditeit, een laag opleidingsniveau, slaapproblemen, roken, en hoofd- of nekletsel in de voorgeschiedenis. Het vrouwelijk geslacht is een risicofactor voor hoofdpijn, maar niet voor het chronisch worden van hoofdpijn.

Hoofdstuk 3 beschrijft de comorbiditeit en kwaliteit van leven van mensen met CFH. Comorbiditeit werd gescoord volgens de Cumulative Illness Rating Scale (CIRS) en kwaliteit van leven met de RAND-36. Mensen met CFH hadden een hogere comorbiditeit score dan de infrequente hoofdpijngroep. De mensen met overmatig analgeticagebruik rapporteerden meer comorbiditeit dan degenen die niet overmatig gebruikten. Vijftig procent van de mensen met CFH hadden een aandoening waarvoor zij dagelijks medicatie nodig hadden. De kwaliteit van leven van mensen met CFH was in alle domeinen van de RAND-36 lager dan mensen met infrequente hoofdpijn. Alle domeinen hadden een negatieve correlatie met CIRSscore. Zowel hoofdpijnfrequentie als CIRSscore heeft een negatieve invloed op kwaliteit van leven.

CFH patiënten hebben meer somatische en psychiatrische comorbiditeit dan patiënten met infrequente hoofdpijn. Zowel hoofdpijnfrequentie als comorbiditeit dragen bij aan de lage kwaliteit van leven van deze patiënten.

In **hoofdstuk 4** bestuderen we de rol van cognitieve en persoonlijkheidsfactoren in het chronisch worden van hoofdpijn. We gebruiken de Pijn Coping en Cognitie Lijst voor het meten van cognitieve factoren, de Temperament en Karakter Vragenlijst voor het meten van persoonlijkheidsfactoren, de General Health Questionnaire voor het screenen op psychiatrische comorbiditeit, en de Headache Impact Test voor het meten van kwaliteit van leven. De CFHgroep scoorde hoger op catastroferen, hoger op mate van pijncoping, lager op interne pijnbeheersing en hoger op externe pijnbeheersing, dan de infrequente hoofpijngroep. Na correctie voor aanwezigheid van psychopathologie waren persoonlijkheidsfactoren niet langer geassocieerd met CFH. Zoals verwacht, hadden de mensen met CFH hogere impact scores. Catastroferen en lage interne pijnbeheersing droegen significant bij aan de impact van hoofdpijn op kwaliteit van leven.

CFH is geassocieerd met catastroferen, pijncoping, lage interne pijnbeheersing en hoge externe pijnbeheersing. Persoonlijkheidsfactoren vormen geen additioneel risico voor het ontwikkelen van CFH. Vooral catastroferen lijkt een belangrijke factor voor de impact van hoofdpijn op het dagelijks leven.

Hoofdpijn is een veel gerapporteerde bijwerking van orale anticonceptiva (OAC). Hoofdpijnpatiënten vragen daarom regelmatig of het nuttig is om te starten of stoppen met OAC om hun hoofdpijn te verbeteren. In **hoofdstuk 5** staat dat het percentage OAC gebruik hetzelfde was in de CFHgroep als in de infrequente hoofdpijngroep. Wij vonden geen associatie tussen oestrogeenhoudende OAC en CFH.

Er is geen associatie tussen oestrogeenhoudende OACgebruik en het voorkomen van CFH, en daarom geen bewijs dat het stoppen of switchen van OAC's hoofdpijnfrequentie gunstig zal beïnvloeden.

Overmatig pijnstillergebruik wordt over het algemeen gezien als een belangrijke risicofactor voor het ontwikkelen van CFH. Patiënten met overmatig gebruik worden geclassificeerd als mogelijk medicatie afhankelijke hoofdpijn (mMAH) tot de hoofdpijn verbeterd is na onttrekking en de diagnose MAH definitief gesteld kan worden. **Hoofdstuk 6** beschrijft de verschillen tussen CFHpatiënten met mMAH (n=104) en CFHpatiënten zonder overmatig gebruik (n=73). Er was geen verschil in hoofdpijntype tussen overmatige gebruikers en normale gebruikers. Globaal kon de helft geclassificeerd worden als chronische spanningshoofdpijn en 24% als chronische migraine. Het medicatiegebruik bestond voornamelijk uit analgetica, maar 2% hadden een overmatig triptangebruik. De meerderheid gebruikte langzamerhand een steeds hogere dosis en namen pijnstillers in ondanks dat het nauwelijks werkte. Veertig procent nam pijnstillers in uit voorzorg, terwijl maar 13% profylactica gebruikten.

Het overmatig medicatiegebruik bij mensen met mogelijk medicatie afhankelijke hoofdpijn bestaat in de algemene bevolking voornamelijk uit analgetica. Veel mensen gebruiken pijnstillers op een verkeerde manier en zouden meer profylactica moeten gebruiken.

In **hoofdstuk 7** presenteren we informatie over (overmatig) triptan gebruik uit het Geneesmiddelen Informatie Project van het College van Zorgverzekeraars. Data waren beschikbaar van 6,7 miljoen mensen in 2005 wat bijna de helft van de Nederlandse populatie betreft. Overmatig triptan gebruik is door de International Classification of Headache Disorders (ICHD-II) gedefinieerd als regelmatig gebruik op ≥10 dagen per maand gedurende > 3 maanden. Echter, Limmroth schatte de gemiddelde kritische dosis voor het optreden van

triptanafhankelijkheid op 18 doses per maand. Onder triptangebruikers is de geschatte prevalentie voor overmatig gebruik volgens de ICHD-II 10%, en volgens de strengere criteria van Limmroth 3%. Vergeleken met sumatriptan, trad er minder overmatig gebruik op bij rizatriptan (OR 0,27; 95% CI 0,25-0,28). Het overmatig gebruik beslaat 50% van de totale uitgifte van triptanen en neemt 50% van de totale kosten voor zijn rekening.

In Nederland gebruikt 10% van de triptangebruikers overmatig veel triptanen, wat 50% van de totale kosten van triptanbehandeling beslaat.

Hoofdstuk 8 beschrijft de resultaten van een onttrekkingstudie in de huisartspraktijk. Het doel van deze studie was het evalueren van het effect van een actieve benadering van de huisarts van patiënten met overmatig medicatiegebruik om onttrekking te adviseren. We vergeleken twee benaderingen door de huisarts: 1) een uitnodiging om naar de praktijk te komen om de behandeling (acuut staken van pijnstillers en triptanen) te bespreken, en 2) een brief waarin de huisarts adviseert acuut te stoppen met pijnstillers en triptanen. Beide interventies werden vergeleken met een controle groep met natuurlijk beloop en met de onttrekkingsresultaten van poliklinische patiënten in een tertiair verwijscentrum. De studie toonde aan dat de behoefte aan behandeling en therapietrouw zeer laag is bij niet-consulterende patiënten, wat leidde tot hoge uitvalspercentages tijdens onttrekking. Na zes maanden rapporteerde 10% van de patiënten in de directe benaderingsgroep verbetering van hoofdpijn, 28% van de patiënten in de briefgroep, vergeleken met 9% in de natuurlijk beloop groep en 28% in de tertiaire verwijsgroep. Het was niet mogelijk om determinanten van succes te analyseren.

Een actieve benadering van huisartsen om patiënten met CFH en overmatig analgeticagebruik te identificeren en te adviseren om te stoppen werkt niet. Een brief met een stopadvies lijkt effectief te zijn.

In **hoofdstuk 9** worden de klinische karakteristieken van kinderen en adolescenten met CFH beschreven. We hebben retrospectief alle dossiers bestudeerd van 79 kinderen die gezien waren op de polikliniek kinderneurologie in een tertiair verwijscentrum. Bij de meerderheid van de kinderen duurde de hoofdpijn meer dan 4 uur per dag. De meeste kinderen gebruikten analgetica, en 24% dagelijks. Een derde van de kinderen verzuimde regelmatig van school

door hoofdpijn en sliep slecht. De hoofdpijn kon meestal worden geclassificeerd als chronische spanningshoofdpijn.

CFH en overmatig analgeticagebruik treedt ook op in de kinderleeftijd en leidt vaak tot schoolverzuim en slaapproblemen.

Tot besluit

In dit proefschrift laat ik zien dat CFH een belangrijk gezondheidsprobleem is dat één op de 25 mensen treft en daarom meer aandacht verdient. Overmatig gebruik van acute hoofdpijnmedicatie lijkt een belangrijke (iatrogene) risicofactor voor het ontwikkelen van CFH binnen een kwetsbare subgroep van patiënten. Artsen en patiënten moeten zich bewust zijn van het mogelijke paradoxale effect van pijnstillers en triptanen, vooral wanneer hoofdpijnfrequentie stijgt. Hoewel betere profylactica nodig zijn, worden de huidige beschikbare medicijnen niet optimaal benut. Apothekers zouden met huisartsen samen kunnen werken in het bewaken van triptan en analgeticagebruik. Overmatig analgeticagebruik zal echter moeilijk te detecteren zijn omdat analgetica vrij verkrijgbaar zijn. Een manier om het publiek bewust te maken van het gevaar van overmatig gebruik is om in de bijsluiter van analgetica een advies op te nemen om een arts te consulteren bij gebruik voor hoofdpijn op meer dan 14 dagen per maand. Wanneer overmatig gebruik evident is, is onttrekking de juiste therapie. Waarschijnlijk zullen patiënten meer therapietrouw zijn als zij een neuroloog geconsulteerd hebben die de diagnose en behandeling bevestigt. Een multidisciplinaire benadering kan waardevol zijn indien er sprake is van bijkomende psychologische en/of psychiatrische risicofactoren.

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Curriculum Vitae

Natalie Janette Wiendels was born in Durban, South-Africa, on February 6, 1973. She attended secondary school at KSG "De Breul" in Zeist, the Netherlands, and graduated in 1991. She started medical school at Utrecht University and conducted a research project concerning intractable epilepsy at the British Columbia's Children's Hospital in Vancouver, Canada. She obtained her medical degree in 1998 and worked as a resident for one year at the department of neurology at Spaarne Ziekenhuis Haarlem. Until December 2006 she worked as a research-physician at the departments of Neurology and Public Health and Primary Care of Leiden University Medical Center (LUMC) under supervision of prof.dr. Michel D. Ferrari, neurologist, and dr. Arie Knuistingh Neven, general practitioner, which resulted in this thesis. The main focus of her work was on the epidemiology of chronic frequent headache in the general population. The results have been presented on several international headache congresses. She received a review lecture award at the 16th Migraine Trust International Symposium held in London in 2006. In addition, she set up and conducted two preference trials for the acute treatment of migraine. In January 2007 she started a residency in neurology at Rijnland Ziekenhuis in Leiderdorp, and is currently working at LUMC in Leiden.

Natalie Janette Wiendels werd op 6 februari 1973 geboren in Durban, Zuid-Afrika. Ze volgde het VWO, gymnasiumstroom, aan de KSG "De Breul" in Zeist en slaagde in 1991. Daarna studeerde ze geneeskunde aan de Universiteit Utrecht en deed een wetenschappelijke stage in het British Columbia's Children's Hospital in Vancouver, Canada. Ze behaalde haar artsexamen in 1998 en werkte voor een jaar als arts-assistent op de afdeling neurologie in het Spaarne Ziekenhuis te Haarlem. Van november 1999 t/m december 2006 werkte ze als arts-onderzoeker op de afdelingen Neurologie en Public health en Eerstelijnsgeneeskunde van het Leids Universitair Medisch Centrum (LUMC) onder supervisie van prof.dr. Michel D. Ferrari, neuroloog, en dr. Arie Knuistingh Neven, huisarts, wat resulteerde in dit proefschrift. Het hoofdonderwerp van haar promotie onderzoek betrof de epidemiologie van chronisch frequente hoofdpijn in de Nederlandse algemene bevolking. De resultaten heeft zij gepresenteerd op diverse internationale hoofdpijncongressen. In 2006 ontving ze een review lecture award op het 16e Migraine Trust International Symposium te Londen. Daarnaast heeft zij twee patiëntenvoorkeurstudies voor de acute behandeling van migraine opgezet en uitgevoerd. In januari 2007 begon zij als arts-assistent neurologie in het Rijnland Ziekenhuis te Leiderdorp en sinds juli 2007 in het LUMC te Leiden.