QUALITY OF LIFE AND PSYCHOLOGICAL FUNCTIONING IN OBSERVATIONAL AND INTERVENTION STUDIES IN CHILDHOOD MIGRAINE

Jacques Bruijn

The research reported in this thesis was supported by the Nuts-Ohra Foundation (Stichting Nuts-Ohra), Bouw Combinatie Van Der Linden-Strukton and the Nolet Foundation (Nolet Stichting). This thesis was financially sponsored by Shire Pharmaceuticals, Menarini Farma Nederland, Merck Sharp & Dome B.V. and the Erasmus Medical University Centre.

Cover illustration: Melchior Smit (12 years): migraine with metamorphopsia (Alice in Wonderland syndrome)

Printed by: Ridderprint BV
ISBN: 978-90-5335-300-4

QUALITY OF LIFE AND PSYCHOLOGICAL FUNCTIONING IN OBSERVATIONAL AND INTERVENTION STUDIES IN CHILDHOOD MIGRAINE

KWALITEIT VAN LEVEN EN PSYCHOLOGISCH FUNCTIONEREN IN BESCHRIJVENDE EN INTERVENTIE STUDIES IN MIGRAINE BIJ KINDEREN

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
29 september 2010 om 13.30 uur

door

Jacques Klaas Jan Bruijn

geboren te Haarlem

Promotiecommissie

Promotoren

Prof.dr. W.F. Arts

Prof.dr. J. Passchier

Overige leden

Prof.dr. B. Koes

Prof.dr. F. Verhulst

Prof.dr. M. Ferrari

Copromotor

Dr. H. Duivenvoorden

The end of science is not to prove a theory, but to improve mankind.
Manley Hall (1901-1990)

Voor Christine, Simon, Niek en Anna
Voor mijn moeder
Voor mijn vader
Voor alle kinderen met migraine

TABLE OF CONTENTS

Chapter 1

Introduction

INTRODUCTION

To give the reader an idea of what pediatric headache - and especially pediatric migraine - entails, and to illustrate its various aspects and consequences, a case history is presented of a young boy who was referred by his general practitioner to the author of this thesis.

At referral Paul was eight years old and had already been suffering from severe and debilitating headaches (one or two per week) for more than three years. The headache had a throbbing character, was located in his forehead, did not radiate to his neck and shoulders, and was frequently accompanied by nausea, vomiting, and increased sensitivity to light and sound. During a headache attack he was unable to carry out any tasks or duties. A headache attack would last several hours. Paul described the pain as severe. Typically, Paul would go to bed and, preferably, fall asleep. After waking up he would feel much better.

Paul did not suffer from reversible visual or sensory symptoms or motor weakness before, during or after the headache attacks. His mother would occasionally give him paracetamol (500 mg) as a suppository, which provided some relief from the pain but not from the other symptoms.

Because of the headaches he frequently missed school and was unable to engage in sports or outdoor activities with his friends. Consequently, his school grades dropped and he completely stopped playing soccer in his junior team. In addition, his parents were under considerable strain because they frequently had to miss work to take care of Paul, and were extremely worried about him - especially about the cause of his headaches. His father was afraid that Paul was suffering from a severe brain disease.

Eventually, the parents pointed out that because Paul had stopped playing soccer and could not do any other outdoor activities, he spent a lot of time watching TV. Generally, he went to bed at about eight o'clock but did not sleep until as late as nine or ten o'clock because he was playing computer games. They also found that Paul was becoming increasingly withdrawn, had fewer contacts with friends, and occasionally seemed worried and 'down'.

The physical and neurological examinations revealed no abnormalities. Paul was of average height and weight for his age, and had normal blood pressure. Ophthalmologic examination did not reveal any signs of papiloedema or a refraction disorder.

Paul was diagnosed as suffering from migraine without aura. He and his parents were informed about the diagnosis and were relieved that Paul was not suffering from a severe brain disease. He was treated with diclofenac (50 mg) and domperidon (30 mg) suppositories symptomatically. Paul and his parents were instructed not to use both of the drugs more than once a day, and not more than three times a week. They were also advised not to use other analgesics or any

other symptomatic medications. In addition, they were given some basic 'life rules' to help improve Paul's sleeping pattern and were advised to encourage Paul to start some form of physical exercise, preferably outdoor activities.
Six weeks later Paul was seen for a follow-up consultation. In that period he had suffered only one headache attack and had been successfully treated with diclofenac and domperidon suppositories. The parents reported that Paul was sleeping much better after they had removed the computer from his room and let him walk the dog for about 30 minutes before he went to bed. The only migraine attack that Paul had suffered had been preceded by a night with less sleep than usual, because he had attended a friend's party. The parents wondered whether the migraine attack had been triggered by this one night of less sleep, or whether this was just a coincidence.

This case history illustrates many aspects of pediatric headache and raises relevant questions from a clinical, parental and patient viewpoint.
First of all - the diagnosis. Paul is suffering from unilateral headache attacks with a pulsating quality, accompanied by nausea, vomiting, photofobia and phonofobia, together with avoidance of any routine physical activity. In addition, the pain is described as severe. Because Paul has no aura symptoms, and his physical and neurological examinations are normal, the headache is diagnosed as migraine without aura in accordance with the ICHD-II criteria[1].
Second, this case history shows that Paul's migraines have a profound impact on both his life and that of his parents. Paul's school grades deteriorated because of frequent absence due to migraine - and he stopped playing soccer. Moreover, his parents are worried because they often miss work to take care of Paul, and also fear that Paul is suffering from a severe disease - thus increasing the tension in the family.
Due to the headache attacks, Paul has, more or less, adopted a different lifestyle. However, it is questionable whether this lifestyle is considered suitable by the clinician and the parents, or even by Paul himself. In other words, is Paul coping in an adequate and acceptable way? One is more likely to answer 'no', because even with this new lifestyle Paul does not suffer less from the headaches, perhaps he even suffers more. However, to answer this question in an objective way we need to measure the burden of headache before and then after adaptation to his new lifestyle. The question then arises whether we should assess the burden of headache by merely measuring the frequency and intensity of the headache attacks – or are other options available?
It is well known that the burden of migraine in adults and children is high, and that well-being and ability to function are affected in several life domains, such as school or work

performance, mental health and social activities[2,3]. An important outcome for measuring the burden of a disease is 'quality of life' (QoL), which reflects the impact of the disease and treatment on a subjective evaluation by the patient (or, in the case of children, by the parents) of the patient's physical functioning and emotional well-being[4-8].

Studies examining QoL in children with headache and migraine are either population-based[8-10] or hospital-based[8,11-13]. In both types (but particularly in hospital-based studies), children with headache are shown to have significantly lower QoL scores than healthy children. Compared to children with chronic illness (such as rheumatic disorders or cancer) their QoL is similar with respect to impairments in school and emotional functioning[12]. All these hospital-based studies were performed in tertiary pediatric headache centers, providing information from a selected group of children with migraine (referred from general hospitals by pediatricians or neurologists), and they explored only a limited number of life domains of the children themselves. No hospital-based studies have explored QoL in children with migraine in general hospitals or in general pediatric, neurological or pediatric neurological practices, thus raising the question how QoL is affected in children with headache referred to these latter types of hospitals and practices. It is also unknown if and how and to what extent the child's headache influences the life of the parents and family members.

Thirdly, Paul's headaches seem to affect his mental state. He has become more withdrawn, has less social contacts, and sometimes appears worried and 'down'. This might indicate that he is becoming depressed. The raises the question whether this is a consequence of the headache attacks, or whether the headaches are a symptom of an underlying psychological or psychiatric disorder.

Clinical and population studies in children have shown a relationship between headache and psychopathology; in these studies various outcome measurements were used. Behavioral problems and psychological functioning were measured in subgroups of children suffering from different types of headache[14,15] or were compared with those of healthy children[16-21], with children suffering from chronic fatigue[22] or from recurrent pain due to other disorders[23]. One study had a longitudinal design[24], but most studies on psychological functioning in children with headache used a cross-sectional design. To date, no systematic review has explored the occurrence and manifestations of psychological dysfunctioning and/or psychiatric comorbidity in childhood migraine.

Because a substantial proportion of children with headache or migraine seem to demonstrate some form of psychological dysfunctioning or psychiatric comorbidity, the question arises whether (after referral to a specialist) these children should have a consultation with a child psychologist or child psychiatrist. Another question to be

considered is whether the psychological dysfunctioning or psychiatric comorbidity might be positively influenced by an intervention directed at reducing headache attacks. If this is the case, such an intervention should be implemented early on and referral to a child psychologist/psychiatrist should take place at a later stage of treatment. However, in children with migraine, there are no intervention studies directed at decreasing headache attacks that have assessed the effect on psychological (dys)functioning or psychiatric comorbidity as the main outcome. This implies that this aspect of childhood migraine is largely uncharted.

With regard to treatment of childhood migraine a wide range of intervention studies have been performed: both symptomatic (i.e. interventions aimed at decreasing the pain and/or other symptoms of migraine once the attack has started) and prophylactic (i.e. interventions aimed at preventing headache attacks in migraineurs), and both pharmacological and non-pharmacological. At the start of the research leading to this thesis, no systematic review of the literature describing and assessing all treatment modalities in children with migraine had been performed; therefore, no evidence-based recommendations could be made and no guidelines could be designed. From a clinical viewpoint, conducting such a review of intervention studies is highly relevant.
In addition, with regard to treatment, the question arises which treatment modalities are scientifically proven effective in terms of improving headache attacks and have demonstrated a decrease of the burden, especially since some treatment modalities have the potential of adverse effects and therefore can increase the burden of the children involved whilst at the same time decreasing it because of the improvement of the headache[25-27]. From a clinical, parental and patient viewpoint the question of how to measure the combination of the beneficial effects of the intervention in combination with (possible) adverse effects is highly relevant, especially when considering the young age of these patients and their concomitant inability to verbalize abstract concepts such as a net result of 'beneficial and adverse effects'. The use of QoL as outcome, preferably measured on a broad diversity of life domains, might provide an answer to this important question.
The few studies that used QoL as measure of outcome in children with migraine have shown that an intervention which successfully decreases the headache symptoms, has a concomitant beneficial effect on QoL[27,28]. In these studies the pediatric Migraine Disability Scale (pedMIDAS) was used as QoL questionnaire, providing information on a relatively limited number of life domains: i.e. absence or limited performance in school, homework or chores and in social activities (including sports). Until now, these studies have been performed only in tertiary pediatric headache centers.

Treatment of migraine not only encompasses symptomatic or prophylactic treatment, but also the detection and elimination of migraine triggers and improvement of sleep quality. However, prospective studies on the effect of poor sleep quality or decreased sleep duration as a migraine trigger in children are scarce. This means that we still need to explore how, and to what extent, sleep deprivation and poor sleep quality might provoke headache attacks in children with migraine. For Paul, an improvement was seen after starting proper symptomatic treatment combined with following simple life rules to increase sleep quality and resume physical exercise. At his follow-up consultation he had experienced only one headache attack - and this was preceded by a night of less sleep than usual. The parents enquired whether this one night of less sleep could be the main trigger for the attack: the answer to this question is not yet fully elucidated.

All the questions outlined above are of relevance for the clinician, the parents and the children themselves. In the present thesis we have attempted to answer some of them from a clinical-scientific point of view.

THE CURRENT THESIS

Perspectives and goals

The first aim of the work presented in this thesis is to describe and evaluate all currently used treatment modalities for children with migraine. For this, our group of collaborators (mainly from the Dept. of General Practice, Erasmus Medical Center) performed a systemic review of all symptomatic and prophylactic treatment modalities (both pharmacological and non-pharmacological) in children with migraine. This resulted in three publications describing the results of our review, and enabling us to make evidence-based recommendations about symptomatic and prophylactic treatments in children and adolescents with migraine[25,26,29]. Based on the results of this review we concluded that there is a lack of evidence-based treatment modalities in childhood migraine, and that both evidence-based and non-evidence-based treatment modalities may have considerable adverse effects[25,26,29]. For example, anti-epileptics are widely used for migraine prophylaxis in children and adolescents with migraine. Although these drugs may have a beneficial effect on headache frequency and intensity, they may also have a negative effect on mood, cognition or behavior[27]. However, the net result of this combination is difficult to determine. From this perspective, recommendations were made for future studies to use QoL, measured on a broad number of life domains (and possibly other outcomes) to detect this net result of beneficial and adverse effects. This is of particular relevance for children who are too young to adequately describe their improvements on the one hand and their complaints on the other, let alone to subsequently provide reasoned judgment about the overall effect of treatment[25,26]. Therefore, we decided to perform an evidence-based prophylactic intervention study in children with migraine with QoL as the secondary outcome parameter, and with migraine frequency, intensity and duration as the primary outcome parameters.

Subsequently, it was decided to perform an exploratory study in children with primary headache (referred to the outpatient pediatric department of a general hospital) with the purpose of measuring QoL at referral on a broad range of life domains. The Child Health Questionnaire (CHQ) was used as the QoL outcome parameter. This is a generic QoL measurement tool, originally developed by Landgraf and colleagues[30] and translated and validated in Dutch by Raat and colleagues[6,7]. After completion of this study, it was decided to use the CHQ as QoL outcome in the prophylactic intervention study in children with migraine.

Based on a literature search exploring the occurrence and manifestations of psychological (dys)functioning and/or psychiatric comorbidity in children with migraine in clinical studies, it was decided also to use psychological functioning as secondary outcome parameter for the intervention study. This was primarily to be able to observe whether an intervention designed to decrease headache attacks in children with migraine, would also have a concomitant beneficial effect on psychological functioning. The Child Behaviour Check List (CBCL) was chosen as outcome measure for psychological functioning because this was the most widely used outcome measure in the descriptive studies emerging from the literature search. The CBCL was developed by Achenbach and colleagues[31] and translated and validated in Dutch by Verhulst and colleagues[32].

However, a comprehensive systematic review of the occurrence and manifestations of psychological (dys)functioning and/or psychiatric comorbidity in children with migraine in clinical studies was lacking. Therefore, we decided to perform a systemic literature search on this topic which would allow us to make evidence-based recommendations for its diagnosis and treatment.

With regard to the choice of the prophylactic intervention itself, very few evidence-based prophylactic intervention studies have been performed in children with migraine[26]. However, our attention was drawn to riboflavin (vitamin B2), which was used as a prophylactic agent in studies on adults with migraine, including two open-label studies[33,34] and two randomized controlled trials[35,36]. In these latter trials, riboflavin proved to be effective and with minimal adverse effects. Therefore, we considered it of clinical interest to perform a placebo-controlled trial in children with migraine with riboflavin as the active agent. At the start of this intervention study, no other trials were registered to investigate the effect of riboflavin in children with migraine.

Finally, having decided to perform a placebo-controlled, cross-over trial in children with migraine, we considered it of clinical importance to design a prospective study (within the context of this trial) to evaluate sleep deprivation as a potential causative factor for headache attacks in childhood migraine. The effect of resting and sleeping on headache symptoms, after the start of a headache attack, was also explored.

Outline of the thesis

Chapter 2 presents the systematic literature review of all pharmacological prophylactic treatments of migraine in children. This review was conducted as part of a more comprehensive systematic review of all pharmacological and non-pharmacological treatment modalities in childhood migraine. After describing the search strategy, study selection, methodological quality of the studies and method of data extraction, the effectiveness of the different interventions are compared. Finally, the results are discussed and recommendations are made for pharmacological prophylactic treatment modalities in childhood migraine, as well as for future pharmacological prophylactic intervention studies in children with migraine.

Chapter 3 presents the systematic literature review of the prevalence and manifestations of psychiatric comorbidity and psychological functioning in children with migraine. After describing the study protocol, evaluation data on the quality and outcome of the included studies are presented, emphasizing the evidence in relation to psychological functioning in children with migraine. The results are discussed, evidence-based conclusions are drawn, and recommendations are made for clinical practice.

Chapter 4 presents a clinical descriptive study on the generic quality of life (QoL) in children with headache, referred to an outpatient pediatric department of a general hospital. The procedure, selection criteria and rationale for the use of the Child Health Questionnaire (CHQ) as outcome for measuring QoL are described. Demographic information is presented for the children with primary headache, and for the control groups of healthy children and the children with asthma and attention deficit hyperactivity disorder (ADHD). CHQ scores are reported for all investigated groups, which are then compared with each other. Conclusions are drawn and implications for future research are discussed.

Chapter 5 describes the placebo-controlled, randomized, double-blind, crossover trial in children with migraine using riboflavin (vitamin B2) as verum medication. The rationale for selecting riboflavin as prophylactic intervention is presented, and comparable intervention studies in adult migraineurs with riboflavin as the acting agent are described. After presenting baseline information on demographics and clinical characteristics of the children, data are presented on the effect of riboflavin compared with placebo on the primary outcome measures, i.e. headache frequency and intensity, and duration of headache attacks. The results of this study are discussed in the light of comparable

studies in adults and children. Evidence-based conclusions are drawn with regard to the beneficial effects of riboflavin on headache parameters, as well as its adverse effects, in children with migraine.

In *Chapter 6* the effect of riboflavin on generic QoL, measured with the CHQ, and psychological functioning, measured with the Child Behaviour Check List (CBCL), is evaluated in children with migraine. An overview of the literature on QoL as outcome measure in children with headache or migraine is presented. Also presented is a systematic review of psychological functioning and/or psychiatric comorbidity as outcome measure in intervention studies on childhood migraine. After describing the methodology of our study, data are presented on the effect of riboflavin, compared with placebo, on the outcome measures CHQ and CBCL. The results are then discussed and conclusions are drawn. In addition, the advantages and disadvantages of the use of QoL and psychological functioning as outcome measures in intervention studies in children with headache or migraine are discussed.

Chapter 7 investigates the effect of sleep deficit (defined as more than 1 hour sleep less than usual) in the preceding night before a headache attack in children with migraine, as well as the effect of resting and sleeping after the start of the headache attack. This study was designed within the context of the placebo-controlled trial with riboflavin as described in Chapters 5 and 6. The effect of a preceding sleep deficit on headache symptoms are compared with headache attacks without a preceding sleep deficit and, subsequently, with the effect of resting and sleeping on headache symptoms. Results are discussed in the context of the available literature on this subject, conclusions are drawn and recommendations are made for future studies.

Chapter 8 constitutes a general discussion on the main findings of the work presented in this thesis. Finally, recommendations are made for future descriptive and intervention studies in childhood migraine.

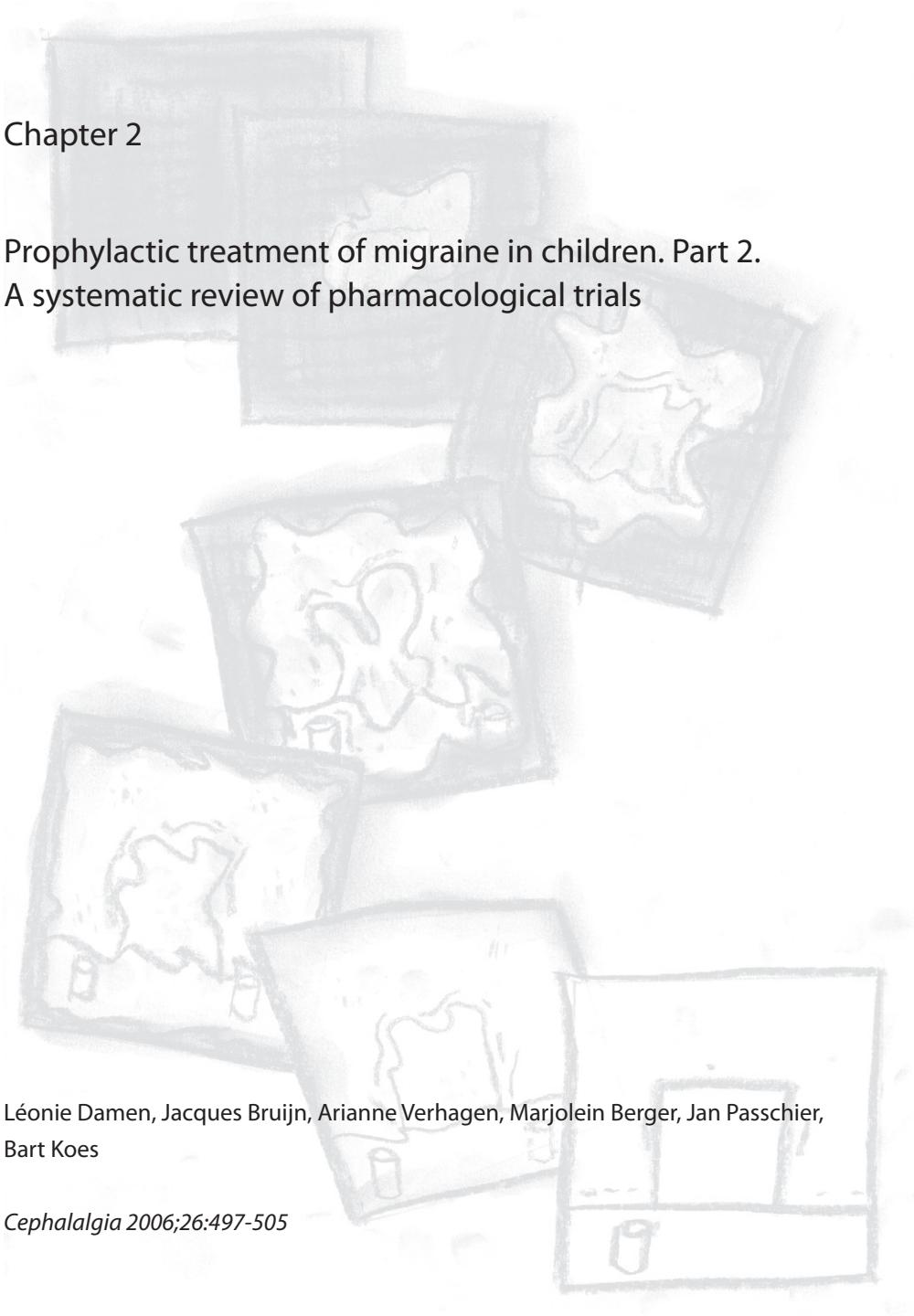
REFERENCES

1. Headache Classification Committee of the International Headache Society. **The International Classification of Headache Disorders 2nd edition (ICHD II).** Cephalalgia 2004:24:suppl. 1:1-160.
2. Leonardi M, Steiner T, Scherer A, Lipton RB. **The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF).** J Headache Pain 2005;6:429-440.
3. D'Amico D, Usai S, Grazzi L, Rigamonti A, Solari A, Leone M, Bussone G. **Quality of life and disability in primary chronic daily headaches.** Neurol Sci 2003;24:S97-S100.
4. Bandell-Hoekstra I, Abu-Saad HH, Passchier J, Knipschild P. **Recurrent headache, coping, and quality of life in children: a review.** Headache 2000;40:357-370.
5. World Health Organization. **Constitution of the World Health Organization basic documents.** Geneva, Switzerland: World Health Organization 1948.
6. Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. **Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples.** J Epidemiol Commun Health 2005;59:75-82.
7. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. **Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index.** J Clin Epidemiol 2002;55:67–76.
8. Kernick D, Campbell J. **Measuring the impact of headache in children: a critical review of the literature.** Cephalalgia 2009;29:3-16.
9. Van Duijn NP, Brouwer HJ, Gooskens RH. **Kinderen met hoofdpijn (Children with headache).** Medisch Contact 2000;26:971-974.
10. Langeveld JH, Koot HM, Loonen MC, Hazebroek-Kampschreur AA, Passchier J. **A quality of life instrument for adolescents with chronic headache.** Cephalalgia 1996;16:183-196.
11. Powers SW, Patton SR, Hommel KA, Hershey AD. **Quality of life in pediatric migraine: characterization of age-related effects using PedsQL.** Cephalalgia 2004;24:120-127.
12. Powers SW, Patton SR, Hommel KA, Hershey AD. **Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses.** Pediatrics 2003;112:e1-5.
13. Nodari E, Battistella PA, Naccarella C, Vidi M. **Quality of life in young Italian patients with primary headache.** Headache 2002;42:268-274.
14. Rossi LN, Cortinovis I, Menegazzo L, Menini S, Carnelli V. **Behaviour during attacks and assessment of intensity in primary headaches of children and adolescents.** Cephalalgia 2006;26:107-112.
15. Passchier J, Orlebeke JF. **Headaches and stress in schoolchildren: an epidemiological study.** Cephalalgia 1985;5:167-176.
16. Guidetti V, Mazzei G, Ottaviano S, Pagliarini M, Paolella A, Seri S. **The utilization of the Rorschach test in a case-controlled study.** Cephalalgia 1986;6:87-93.
17. Mazzone L, Vitiello B, Incorpora G, Mazzone D. **Behavioural and temperamental characteristics of children and adolescents suffering from primary headache.** Cephalalgia 2006;26:194-201.
18. Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, Resch F. **Emotional and behavioural problems in children and adolescents with primary headache.** Cephalalgia 2003;23:206-213.
19. Pakalnis A, Gibbons J, Colvin A. **Comorbidity of psychiatric and behavioral disorders in pediatric migraine.** Headache 2005;45:590-596.
20. Anttila P. Sourander A, Metsahonkala L, Aromaa M, Helenius H, Sillanpaa M. **Psychiatric symptoms in children with primary headache.** J Am Acad Child Adolesc Psychiatr 2004;43:412-419.
21. Vannata K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. **Multiple perspectives on the psychological functioning of children with and without migraine.** Headache 2008;48:994-1004.

22. Smith M, Martin-Herz S, Womack W, Marsigan J. **Comparative study of anxiety, somatization, functional disability and illness attribution in adolescents with chronic fatigue or migraine.** Pediatrics 2003;111:e376-81.
23. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, Cucchiara S, Guidetti V. **Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL).** Cephalalgia 2007;27:211-9.
24. Guidetti V, Galh F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S. **Headache and psychiatric comorbidity: clinical aspects and outcome in an 8-year follow-up study.** Cephalalgia 1998;18:455-62.
25. Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. **Symptomatic treatment of migraine in children: a systematic review of medication trials.** Pediatrics 2005; 116(2):e295-302.
26. Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. **Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials.** Cephalalgia 2006;26(5):497-505.
27. Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche M. **Effectiveness of topiramate in the prevention of childhood headaches.** Headache 2002;42:810-818.
28. Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, Burdine D, Manning P, Kabbouche MA. **Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine.** Headache 2007;47:73-80.
29. Damen L, Bruijn J, Koes BW, Berger MY, Passchier J, Verhagen AP. **Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials.** Cephalalgia 2006;26(4):373-383.
30. Landgraf JM, Maunsell, Speechley KN, Bullinger M, Campbell S, Abetz L, et al. **Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results.** Qual Life Res 1998;7:433-445.
31. Achenbach TM, Edelbrock CS. **Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen.** Monogr Soc Res Child Dev 1981;46:1-82.
32. Verhulst F, van der Ende J, Koot H. **Manual for the CBCL/4-18 (Dutch edition).** ISBN 90-75584-03-2.
33. Schoenen J, Lenaerts M, Bastings E. **High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study.** Cephalalgia 1994;14:328-329.
34. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl K, Arnold G. **High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre.** Eur J Neurol 2004;11:475-477.
35. Schoenen J, Jacquy J, Lenaerts M. **Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial.** Neurology 1998;50:466-470.
36. Sándor P, Áfra J, Ambrosini A, Schoenen J. **Prophylactic treatment of migraine with ß-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.** Headache 2000;40:30-35.

Chapter 2

Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials



Léonie Damen, Jacques Bruijn, Arianne Verhagen, Marjolein Berger, Jan Passchier, Bart Koes

Cephalalgia 2006;26:497-505

ABSTRACT

Objective: To assess the efficacy of pharmacological prophylactic treatments of migraine in children.

Methods: Databases were searched from inception to June 2004 and references were checked. We selected controlled trials on the effects of pharmacological prophylactic treatments in children with migraine. We assessed trial quality using the Delphi list and extracted data. Analyses were carried out according to type of intervention.

Results: A total of 20 trials were included. Headache improvement was significantly higher for flunarizine compared to placebo (RR 4.00 [95% CI 1.60; 9.97]). There is conflicting evidence for the use of propranolol. Nimodipine, clonidine, L-5HTP, trazodone and papaverine showed no effect when compared to placebo. All medications were well-tolerated and adverse events showed no significant differences.

Conclusions: Flunarizine may be effective as prophylactic treatment for migraine in children. Because of the small number of studies and the methodological shortcomings, conclusions regarding effectiveness have to be drawn with caution.

INTRODUCTION

Migraine is the most common cause of chronic recurrent headache in school children. Prevalence of migraine increases with age, ranging from 1.4% to 5% in young children up to 11.6% in adolescents (15-18 years) and the ratio of women to men diverges to become about 2:1 after puberty[1-3]. The International Headache Society has recently revised its diagnostic criteria and classification system[4]. The changes are that migraine may last less than 72 hours, may be bifrontal, and that phonophobia and photophobia may not always be present.

Treatment of paediatric migraine has been the subject of debate for many years. Prophylactic pharmacological treatment could be considered when headache frequency exceeds four episodes per month and/or the attacks are so severe or prolonged that they interfere with school or normal activities. Drugs commonly used for migraine are calcium antagonists, beta-blockers and pizotifen.

To our knowledge, two systematic reviews including prophylactic treatments have been performed on migraine in children[5,6]. One review included 17 behavioural treatment studies and 24 prophylactic drug studies of migraine in children[5]. They concluded that behavioural therapies seemed more effective than prophylactic drug regimens, but they excluded 35% of the behavioural treatment studies and 17% of the drug studies, which they considered to be methodologically inadequate or lacking statistical information. Not all studies analysed had control groups and different study designs were used. The systematic review of Victor and Ryan[6] included 20 studies of which 3 studies were published in a congress book. They identified one single study each of propranolol and flunarizine showing efficacy as prophylactics of paediatric migraine.

The present systematic review distinguishes itself from these reviews by evaluating the literature systematically using up-to-date methodology recommended by the Cochrane Collaboration[7], reporting according to the Quality Of Reporting Of Meta-analyses (QUOROM) statement and by including the most recent literature up to June 2004. In this article, we present a systematic review of controlled trials concerning the efficacy of pharmacological prophylactic treatments of migraine in children. The authors have also reviewed the results of non-pharmacological prophylactic treatments. This is the subject of a separate article (part 1).

METHODS

Search strategy

Medline, Embase, PsycInfo, Web of Science and Cinahl were searched from inception to June 2004 using the terms 'migraine', 'headache', 'cephalgia', 'cephalalgia', 'child*', 'infant', 'teenage', 'adolescent' or 'p(a)ediatric' together with the search strategy for identifying randomised (RCT) and clinical controlled trials (CCT) described by Robinson and Dickerson[8]. The Cochrane Controlled Trials Register, Cochrane Library, issue 2 2004, was searched using the words 'migraine', 'headache', 'cephalgia', 'cephalalgia', 'child*', 'infant', 'teenage', 'adolescent' or 'p(a)ediatric'. Additional strategies for identifying trials included searching the reference lists of review articles and included studies.

Study selection

Only RCTs and CCTs including pharmacological prophylactic interventions used in the treatment or management of migraine conducted among children (age less than 18 years), with criteria designed to distinguish migraine from other types of headache, were selected for our review. The use of a specific set of diagnostic criteria (e.g. IHS 1988)[9,10] was not required, but migraine diagnoses had to be based on at least some of the distinctive features of migraine, e.g. headache attack lasts 2-48 hours, unilateral location, pulsating quality, moderate to severe intensity, aggravation by routine physical activity, nausea and/or vomiting, photophobia and phonophobia. Studies with at least one of the following headache (HA) outcome measures were included: intensity, frequency, duration or improvement. Rescue medication was defined as additional medications different to study medication permitted in non-responders, usually limited to the habitual medications a person uses to treat their migraine headache. No language restriction was applied.

Two authors (LD, JB) independently screened titles and abstracts of studies identified by the literature search for eligibility. Potentially relevant studies were retrieved as full papers and again independently reviewed by two authors (LD, JB). Disagreements regarding the inclusion of trials were resolved through consensus when possible, or by arbitration of a third author (AV).

Methodological quality and data extraction

Two authors (LD and JB or AV) independently assessed the methodological quality of the included trials using the Delphi list[11]. The Delphi list is a generic criteria list developed by international consensus and consists of the following 9 items: 1) randomisation; 2) adequate allocation concealment; 3) groups similar at baseline; 4) specification of eligibility criteria; 5) blinding of outcome assessor; 6) blinding of care provider; 7) blinding of patient; 8) presentation of point estimates and measures of variability; 9) intention-to-treat-analysis. One extra item was added: 10) withdrawal / dropout rate (>20% or selective dropout) unlikely to cause bias because it was found relevant for these studies. All selected methodological criteria were scored as yes (= 1), no (= 0) or don't know (= 0). The quality score was computed by counting the number of positive scores, with equal weights applied on all items. In case of a disagreement between the two authors, consensus was used to resolve disagreement. When consensus could not be reached, a third author made the final decision (JB or AV).

Extraction of data from the original reports was performed by one author (LD) and checked by a second (AV). Disagreements were resolved by consensus. Extracted information included (if available) demographic data, detailed description of the intervention and control (i.e. dose given, study duration), outcome measures and information on adverse effects.

Data-analysis

We calculated standard mean differences (SMD) with 95% confidence interval (CI) for continuous outcomes or relative risks (RR) with 95% CI in case of dichotomous variables. RR above 1 and a SMD above 0 represent a better outcome for the first mentioned intervention group. For all data we include data only on those whose results are known (available case analysis).

In case of crossover trial ideally we would like to restrict our analysis to first period data only, or, in case of a sufficient wash out period and no carry over effect, data of both periods could be combined. In this review we analysed the crossover trials as if they were parallel-group trials, because most data did not permit analysis of paired between patient data. If a carry-over effect was found and data were reported by period, then the analysis was restricted to first-period data only.

A qualitative analysis was performed using a rating system with levels of evidence[12]. The evidence was judged to be strong when multiple (two or more) high quality RCTs produced generally consistent findings. Results were considered consistent if 75% or more of the studies reported similar results on the same outcome measure. It was judged

to be moderate when one high quality RCT and / or multiple (two or more) low quality RCTs and / or CCTs produced generally consistent findings. Evidence was considered to be limited when only one low quality RCT and / or CCT existed and conflicting if the findings of existing trials were inconsistent. No evidence was considered when no RCTs or CCTs were found or when the authors provide no sufficient data for analysis. We regarded trials with methodological quality scores of 6 or more as of high quality[12].

RESULTS

Search results

A total of 3492 publications were identified by our broad and sensitive search strategy (see Flow chart). Finally a total of 16 RCTs and 4 CCTs were included in this review, of which 11 studies used a crossover design (see flow chart).

Description of studies

Full details of the included studies are presented in Table 1.

Participants

The number of included participants in each trial ranged from 19 to 118 (mean 44 ± 21 patients), with a total of 887 patients included in this review. Most studies were small; out of 40 study arms 12 included less than 20 subjects, while eight included over 50 subjects. The mean percentage of participants who dropped out was 14.5% (range 0-43.9%). The mean age of participants was 10.7 ± 1.3 years (range 3-18 years). Overall, the percentage of girls was generally the same as boys (mean 48.8%; range 30.8-68.6%). Two trials used the criteria of the International Headache Society (9), two studies used the Ad Hoc criteria to classify migraine, six studies used the Valhquist definition while the remaining studies used varying definitions (see table 1).

Interventions

The interventions used could be divided into placebo comparisons and drug-drug comparisons. Regarding placebo, comparisons were evaluated for nimodipine[13], flunarizine[14,15], propranolol[16-18], timolol[19], clonidine[20,21], pizotifen[22], L-5-hydroxytryptophan (L-5HTP)[23,24], trazodone[25], magnesium oxide[26], and papaverine[27]. Regarding the different drugs, comparisons were made between flunarizine and propranolol[28], flunarizine and acetylsalicylic acid[29], flunarizine and dihydroergotamine[30], pizotifen 0.5 mg and 1.0 mg[31], and pizotifen and lisuride[32].

Outcome measures

All studies used headache diaries to assess outcomes. Using this diary amongst others HA frequency, intensity and duration were scored on a Likert-scale. In most studies (11 out of 20) a measure of clinical improvement was calculated. In these studies an improvement was regarded as being clinically relevant when the patients' headache declines by 50% or more. This score is presented as 'HA improvement' in Table 1 and is our primary outcome measure. When this outcome measure was not available, we used mainly headache frequency.

Methodological quality

The quality score (with positive items in parenthesis) is presented in the 'Study quality' section of Table 1. The median score for methodological quality was 5 with a range of 1-7. Using a cut-off point of 6 out of 10 criteria, eight studies (40%) were considered to be of high quality. The most prevalent methodological shortcomings were a concealed randomisation method (unclear 79%), the intention-to-treat analysis (unclear 28%, negative 72%) and blinding of the care provider (unclear 63%).

Effectiveness of pharmacological prophylactic treatment

1. Placebo comparisons

Calcium-antagonists

In one crossover study[13] nimodipine was compared to placebo. During the first treatment period no significant differences were found concerning HA frequency and number of adverse events. None of the patients complained of serious side effects except for mild abdominal discomfort during the early days of nimodipine treatment (17%), which disappeared spontaneously without altering dosage. Two studies[14,15] compared flunarizine with placebo, in which one study reported on HA improvement[14]. At three months we found that HA improvement was significantly higher for flunarizine compared to placebo. The number of adverse events was not significant different: drowsiness, gastrointestinal complaints, weight gain and fatigue.

There is limited evidence that flunarizine is more effective than placebo.

Anti-hypertensive medications

Three high quality studies compared propranolol to placebo[16-18]. Two studies reported on HA improvement, showing inconsistent results[17,18] and two on adverse events[16,17]. Adverse events mentioned were increased appetite, abdominal pain, worsening of headache and were not significantly different between groups. One small study compared timolol to

placebo, but no data were available to calculate effect estimates[19]. One high quality[20] and one low quality study[21] compared clonidine to placebo, in which only the low quality study reported on HA intensity and both studies on adverse events. We found no significant differences in HA intensity or the number of adverse events. Adverse events mentioned for clonidine were fatigue and nausea.
There is conflicting evidence for the use of propranolol, and no evidence is found in favour of the use of timonolol and clonidine.

Serotonergic drugs
One high quality crossover study[22] compared pizotifen to placebo, but no data were available to calculate effect estimates. Only one patient mentioned excessive weight gain while on pizotifen. Two studies[23,24] compared L-5HTP to placebo, in which only one reported on HA improvement[24]. We found no significant differences in HA improvement or in HA index. In the study of Longo et al.[23] adverse events were not specified per medication. One high quality crossover study[25] compared trazodone to placebo and reported no significant differences in HA frequency during the first period. None of the patients complained of any serious side effects.
We found no evidence for or against the use of pizotifen, L-5HTP or trazodone.

Other medications
One high quality study compared magnesium oxide with placebo, but no data were available to calculate effect estimates[26]. Adverse events were not significantly different between magnesium oxide and placebo: diarrhoea or soft stools. One small study compared papaverin to placebo and found no significant differences for HA improvement[27].

2. Drug-drug comparisons
All drug-drug comparisons were made in single low quality studies of which three were rather small and reported no significant differences between both drugs on HA improvement, HA frequency or adverse events. Adverse events were all minor and included fatigue, sleepiness, wait gain or abdominal pain.

DISCUSSION

Based on the available literature, we found limited evidence that flunarizine is more effective than placebo. There is conflicting evidence from two studies for the use of propranolol. Nimodipine, clonidine, L-5HTP, trazodone and papaverine showed no HA

improvement or efficacy in HA reduction of frequency attacks compared to placebo. Available studies on drugs like timolol, pizotifen and magnesium oxide compared to placebo reported no sufficient data to calculate effect estimates.

Although systematic reviews offer the least biased method of summarising research literature, our results must be interpreted with consideration of the quality of evidence from which they were obtained. First, we decided not to contact the authors for additional information, because 19 of the 20 trials included in this review were published before 1994 and most authors would be difficult to find. Secondly, our inclusion criteria greatly reduced the number of studies selected. Positive results for the use of prophylactic treatments in children and adolescents have frequently emerged from open-label or uncontrolled studies[33-39]. Third, the methodological shortcomings of many of the currently available studies limit conclusions about the effectiveness of pharmacological prophylactic treatments. These shortcomings include an unconcealed randomisation method, inadequate statistical analysis (intention-to-treat analysis), and most studies suffered from the lack of (reported) credible blinding of the care provider. Finally, most treatments have only been evaluated in 1 or 2 studies with small number of patients, which limits the generalisability of the findings.
Commonly described drugs such as pizotifen and anti-epileptic drugs have not been adequately studied in controlled studies. Calcium antagonists and anti-hypertensive drugs have been well studied, but larger and better trials are still required in children. Therefore we strongly recommend performing large high quality RCTs evaluating most frequently offered pharmacological prophylactic treatments, because at the moment no firm conclusions can be drawn based on the available literature.

One of the reasons most studies show no significant differences is that it is difficult for any prophylactic treatment to show additional benefit taking the favourable natural course of childhood migraine into account. Furthermore, it may also be due to the small sample sizes of most studies or the outcome measure "HA improvement", which was a main outcome measure in most studies. It indicated that only people with over 50% improvement are considered clinically improved, which is a large improvement. The Philadelphia panel advises cut-off scores for clinically relevant differences in muscular skeletal diseases of 15% improvement[40]. Headache improvement and adverse events are two outcome measures frequently used in the included trials. Although most studies described the adverse events as mild and save, the simple description of the kind and number of adverse events often gives insufficient insight into the severity and appreciation of the adverse events for a

child. Therefore, we suggest that other outcome measures like quality of life, satisfaction of child and/or parents, and repeated administration should also be used as an outcome measure in studies involving treatment of migraine in children.

In conclusion, this review shows that there is a clear need of high quality research evaluating pharmacological prophylactic treatment of children with migraine. Favourably high quality studies should be performed and reported according to the Consolidated Standards of Reporting of Trials (CONSORT) statement to improve the quality of trials reports. Headache clinical improvement should be used as the primary outcome measure, but lower cut-of points for recovered and not recovered are recommended. Quality of life and satisfaction of child and/or parents should also be used as an outcome measure in studies involving pharmacological prophylactic treatment of children with migraine.

ACKNOWLEDGEMENTS

The authors thank the Netherlands Organisation for Health Research and Development (ZONMw) for funding this research.

REFERENCES

1. Annequin D, Tourniaire B, Massiou H. **Migraine and headache in children and adolescence.** Pediatr Clinic North Am 2000;37:617-31.
2. Shivpuri D, Rujesh MS, Jain P. **Prevalence and characteristics of migraine among adolescents: a questionnaire survey.** Indian Pediatr 2003;40:665-9.
3. Zencir M, Ergin H, Sahiner T, Kilic I, Alkis E, Ozdel L, Gurses D, Ergin A. **Epidemiology and symptomatology of migraine among school children.** Headache 2004;44:780-5.
4. Headache Classification Committee of the International Headache Society. **The International Classification of headache disorders.** Cephalalgia 2004;24 (Suppl 1):1-152.
5. Hermann C, Kim M, Blanchard EB. **Behavioral and prophylactic pharmacological Intervention studies of pediatric migraine: an exploratory meta-analysis.** Pain 1995;60:239-56.
6. Victor S, Ryan SW. **Drugs for preventing migraine headaches in children (Cochrane review). In: The Cochrane Library, Issue 3, 2003.** Chichester, UK: John Wiley & Sons, Ltd.
7. Alderson P, Green S, Higgings JPT, editors. **Cochrane Reviewers' Handbook 4.2.2 [updated march 2004]. In: The Cochrane library, Issue 1, 2004.** Chichester, UK: John Wiley & Sons, Ltd.
8. Robinson KA and Dickerson K. **Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed.** Int J Epidemiol 2002;31:150-153.
9. Headache Classification Committee of the International Headache Society. **Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.** Cephalalgia 1988;8(Suppl 7):1-96.
10. Ad Hoc Committee on the Classification of Headache of the National Institute of Neurological Diseases and Blindness. **Classification of headache.** JAMA 1962;179:717-8.
11. Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM, Knipschild PG. **The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus.** J Clin Epid 1998;51:1235-41.
12. Van Tulder MW, Furlan A, Bombarbier C, Bouter L, Editorial Board of the Cochrane Collaboration Back Review Group. **Updated method guidelines for systematic reviews in the Cochrane Collaboration Back review Group.** Spine 2003;28:1290-9.
13. Battistella PA, Ruffilli R, Moro R, Fabiani M, Bertoli S, Antolini A, et al. **A placebo-controlled crossover trial of nimodipine in pediatric migraine.** Headache 1990;30:264-8.
14. Sorge F, Marano E. **Flunarizine v. placebo in childhood migraine. A double-blind study.** Cephalalgia 1985;5 suppl 2:45-8.
15. Sorge F, De Simone R, Marano E, Nolano M, Orefice G, Carrieri P. **Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study.** Cephalalgia 1988;8:1-6.
16. Forsythe WI, Gillies D, Sills MA. **Propanolol ('Inderal') in the treatment of childhood migraine.** Dev Med Child Neurol 1984;26:737-41.
17. Ludvigsson J. **Propranolol used in prophylaxis of migraine in children.** Acta Neurol Scand 1974;50:109-15.
18. Olness K, MacDonald JT, Uden DL. **Comparison of self-hypnosis and propranolol in thetreatment of juvenile classic migraine.** Paediatrics 1987;79:593-7.
19. Noronha MJ. **Double blind randomised cross-over trial of timolol in migraine in children.** Cephalalgia 1985;5 (suppl 3):174-5.
20. Sills M, Congdon P, Forsythe I. **Clonidine and childhood migraine: a pilot and double-blind study.** Dev Med Child Neurol 1982;24:837-41.
21. Sillanpaa M. **Clonidine prophylaxis of childhood migraine and other vascular headache. A double blind study of 57 children.** Headache 1977;17:28-31.
22. Gillies D, Sills M, Forsythe I. **Pizotifen (Sanomigran) in childhood migraine. A double-blind controlled trial.** Eur Neurol 1986;25:32-5.

23. Longo G, Rudoi I, Iannuccelli M, Strinati R, Panizon F. **L-5-HTP treatment of primary headache in children. Double-blind cross-over vs. placebo.** Ped Med Chir (Med Surg Ped) 1984;6:241-6.

24. Santucci M, Cortelli P, Rossi PG, Baruzzi A, Sacquegna T. **L-5-hydroxytryptophan versus placebo in childhood migraine prophylaxis: a double-blind crossover study.** Cephalalgia 1986;6:155-7.

25. Battistella PA, Ruffilli R, Cernetti R, Pettenazzo A, Baldin L, Bertoli S, et al. **A placebo-controlled crossover trial using trazodone in pediatric migraine.** Headache 1993;33:36-9.

26. Wang F, Van Den Eeden SK, Ackerson LM, Salk SE, Reince RH, Elin RJ. **Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomised, double-blind, placebo-controlled trial.** Headache 2003;43:601-10.

27. Sillanpaa M, Koponen M. **Papaverine in the prophylaxis of migraine and other vascular headache in children.** Acta Paediatr Scand 1978;67:209-12.

28. Lutschg J, Vassella F. **The treatment of juvenile migraine using flunarizine or propranolol.** Schweiz Med Wochenschr 1990;120:1731-6.

29. Pothmann R. **Calcium-antagonist flunarizine vs. low-dose acetylsalicylic acid in childhood migraine: a double-blind study.** Cephalalgia 1987;7(suppl. 6):385-6.

30. Lastra-Martinez, L, Herranz, J, Arteaga, R. **Flunarizine or dihydroergotamine in the treatment of migraine in childhood. A randomised study of 50 patients.** Anales Españoles de Pediatría. 1990;32:213-8.

31. Behan PO. **Pizotifen in the treatment of severe recurrent headache single and divided dose therapy compared.** Br J Clin Pract 1982;36:13-7.

32. Del Bene E, Poggioni M, Michelacci S. **Lisuride as a migraine prophylactic in children: an open clinical trial.** Int J Clin Pharmacol Res 1983;3:137-41.

33. Caruso JM, Brown WD, Exil G, Gascon GG. **The efficacy of divalproex sodium in the prophylactic treatment of children with migraine.** Headache 2000;40:672-6.

34. Guidetti V, Moscato D, Ottaviano S, Fiorentino D, Fornara R. **Flunarizine and migraine in childhood.** Cephalalgia 1987;7:263-6.

35. Hershey AD, Powers SW, Bentti AL, de Grauw TJ. **Effectiveness of amitriptyline in the prophylactic management of childhood headaches.** Headache 2000;40:539-49.

36. Hersey AD, Powers SW, LeCates S, Bentti AL. **Effectiveness of nasal sumatriptan in 5- to 12-year-old children.** Headache 2001;41:693-7.

37. Hersey AD, Powers SW, Vockell ALB, LeCates S, Kabbouche M. **Effectiveness of topiramate in the prevention of childhood headaches.** Headache 2002;42:810-8.

38. Miller GS. **Efficacy and safety of levetiracetam in pediatric migraine.** Headache 2004;44: 238-43.

39. Serdaroglu G, Erhan E, Tekgul et al. **Sodium valproate prophylaxis in childhood migraine.** Headache 2002;42:819-22.

40. Philadelphia panel. **Philadelpia panel evidence-based clinical practice guidelines on selected rehabilitation interventions for shoulder pain.** Phys Ther 2001;81:1719-30.

Flow chart: Quorum statement flow diagram

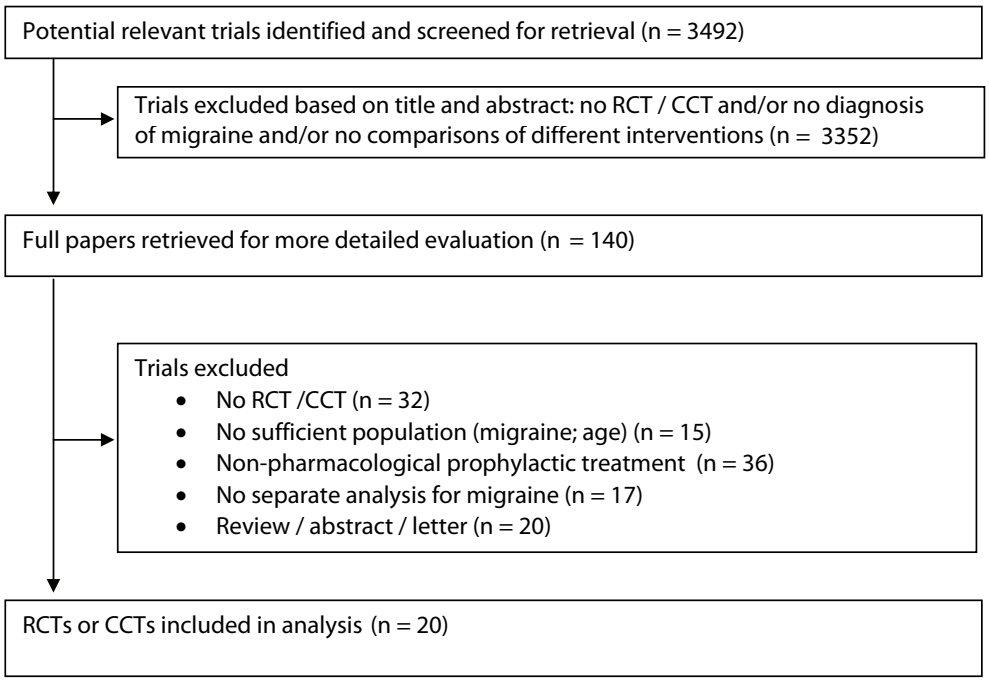


Table 1: Study characteristics of included studies

Reference	Study	Participants	Interventions	Results	
Battistella (13),	RCT-CO QS: 5 (item: 1,3,6,7,8) Migraine (IHS).	N=37, 7 dropouts. Mean age: 12.2 (SD 3.3) yrs	***I: Nimodipine***. For 12 wks. ***C: Placebo***. For 12 wks. Baseline 4 wks, 4 wks wash-out	***HA frequency***: First period I vs. C Second period I vs. C:	 SMD=0.33 [-0.32; 0.98]; SMD=–1.34 [-2.15; -0.54]
Battistella (25),	RCT-CO QS: 6 (item: 1,5,6,7,8,10) Migraine (IHS).	N=40, 5 dropouts. Mean age: 12.6 (SD 3.8) yrs	***I: Trazodone***. For 12 wks. ***C: Placebo***. For 12 wks. Baseline 4 wks, 4 wks wash-out	***HA frequency***: First period I vs. C: Second period I vs. C:	 SMD=0.61 [-0.37; 1.29]; SMD=–1.95 [-2.78; -1.13]
Behan (31),	CCT-PG QS: 2 (item: 4, 8)	N=?, N completed 25. Age range 8-16	***I: Pizotifen 0.5 mg*** twice/ day for 12 wks, N=18. ***C: Pizotifen 1 mg*** single evening dose for 12 wks, N=7.	***HA improvement***: I vs. C:	 RR=0.84 [0.56; 1.28]
Del Bene (32),	CCT-PG QS: 1 (item: 8)	N=?, N completed 45. Mean age: 9.8 yrs	***I: Pizotifen***. For 6 wks, N=22. ***C: Lisuride***. For 6 wks, N=23	***HA improvement***: I vs. C: ***Adverse events***: C:	 RR=1.17 [0.57; 1.57] 13%
Forsythe (16),	RCT-CO QS: 6 (item: 1,3,4,5,6,7)	N=53, 14 dropouts. Age range 9-15	***I: Propranolol***. 40 mg for 6 wks, then optional for 6 wks. ***C: Placebo***. For 12 wks. Baseline 4 wks, 2 wks wash-out	***HA improvement***: ***Adverse events***: I and C	No sufficient data to calculate RR or SMD each 30.7%
Gillies (22),	RCT-CO QS: 7 (item: 1,2,3,5,6,7,10)	N=47, 8 dropouts. Age range 7-14	***I: Pizotifen***. For 12 wks. ***C: Placebo***. For 12 wks.	***HA improvement***: ***Adverse events***:	No sufficient data to calculate RR or SMD I: 10.2%; C: 7.7%
Lastra (30),	RCT-PG QS: 5 (item: 1,3,8,9,10) Migraine (Vahlquist).	N=?, N completed 50. Mean age: 7.8 (SD 2.3) yrs	***I: Flunarizine***. For 26 wks, N=25 ***C: Dihydroergotamine***. For 26 wks, N=25.	***HA frequency***: I vs. C: ***Adverse events***:	 SMD=–0.24 [-0.80; 0.31] I: 20%; C: 12%

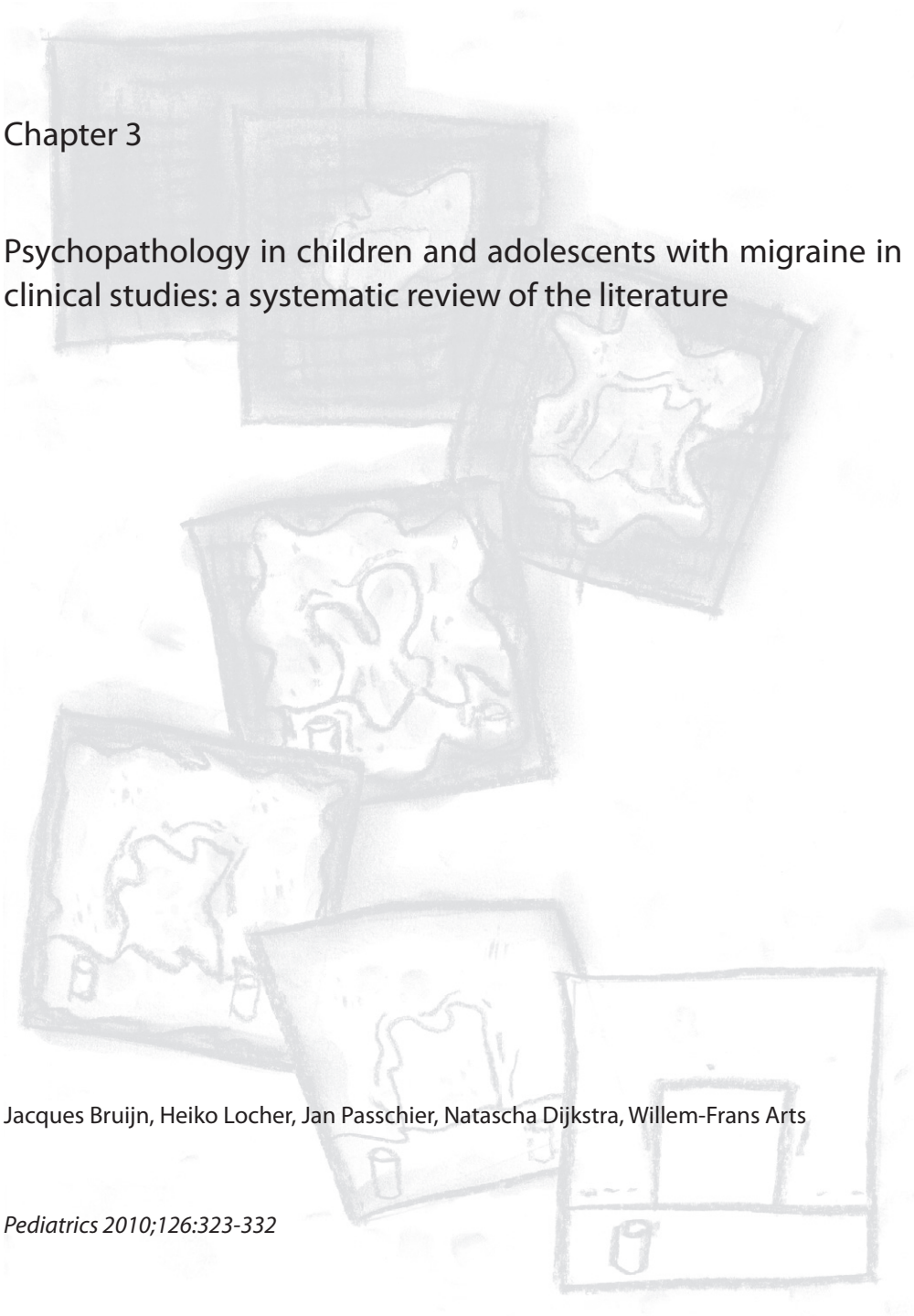
Reference	Study	Participants	Interventions	Results	
Longo (23),	RCT-CO QS: 2 (item 1,7)	N=30, 10 dropouts. Mean age: 10.4 (SD 1.9) yrs	***I: L-5-Hydroxytryptophan***. For 6 wks. ***C: Placebo***. For 6 wks.	***HA improvement***:	No sufficient data to calculate RR or SMD
Ludvigsson (17),	RCT-CO QS: 6 (item: 1,4,5,7,8,10) Migraine (Ad hoc).	N=32, 4 dropouts. Age range 7-16	***I: Propranolol***. For 13 wks. ***C: Placebo***. For 13 wks.	***HA improvement***: First period I vs. C: Second period I vs. C: ***Adverse events***:	 RR=6.35 [1.71; 23.54]; RR=5.63 [1.55; 20.47]; I: 17%
Lutschg (28),	RCT-PG QS: 4 (item: 1,4,8,10)	N=34, 1 dropout in C. Mean age: 10.5 (SD 3.0) yrs	***I: Flunarizine***. For 16 wks, N=17. ***C: Propranolol***. For 16 wks, N=16. Baseline 4 wks.	***HA improvement***: I vs. C: ***Adverse events***:	 RR=1.18 [0.89; 1.56] I 17.6%; C: 33.3%
Noronha (19),	RCT-CO QS: 2 (item: 1,10) Migraine (Vahlquist).	N=19, 2 dropouts. Mean age: 10.2 yrs (range 6-13)	***I: Timolol***. For 8 wks. ***C: Placebo***. For 8 wks. Baseline 4 wks, 4 wks washout.		No sufficient data to calculate RR or SMD
Olness (18),	RCT-CO QS: 6 (item: 1,4,5,7,8,10)	N=33, 12 dropouts. Mean age: 9.6 yrs	***I: Propranolol***. For 12 wks. ***C: Placebo***. For 12 wks. Baseline 4 wks, 1 wk washout.	***HA frequency***: Total I vs. C:	 SMD=0.14 [-0.50; 0.78]
Pothmann (29),	RCT-PG QS: 5 (item: 1,2,3,8,10)	N=31, 1 dropout in I. Mean age: 11.7 yrs (range 7-17)	***I: Flunarizine***. For 8 wks, N=15. ***C: Acetylsalicylic acid***. For 8 wks, N=15 Baseline 4 wks.	***HA improvement***: I vs. C: ***Adverse events***:	 RR=0.97 [0.62; 1.534] I: 57.1%; C: 33.3%
Santucci (24),	RCT-CO QS: 4 (item: 1,5,7,8) Migraine (Ad hoc).	N=27, 6 dropouts. Age range 6-12	***I: L-5-Hydroxytryptophan***. For 12 wks. ***C: Placebo***. For 12 wks. Baseline 4 wks, 2 wks washout.	***HA improvement***: I vs. C: ***HA index***: First period I vs. C: Second period I vs. C:	 R=1.20 [0.43; 3.33] SMD=–0.08 [-0.94; 0.77]; SMD=0.10 [-0.76; 0.96]

Reference	Study	Participants	Interventions	Results	
Sillanpaa (21),	CCT-PG QS: 4 (item: 4,5,7,8) Migraine (Vahlquist).	N=83, 25 dropouts, 9 in I, 16 in C. Mean age: 11.9 yrs	***I: Clonidine***. For 8 wks, N=28. ***C: Placebo***. For 8 wks, N=29. Mean 8 mo follow-up (range 2-14 mo).	***HA intensity***: I vs. C: 8 mo I vs. C: ***Adverse events*:**	 SMD=–0.01[-0.53; 0.51]; SMD=–0.13 [-0.65; 0.39]) I: 39.3%; C: 20.7%
Sillanpaa (27),	CCT-PG QS: 4 (item: 4,5,7,8) Migraine (Vahlquist).	N=42, 5 dropouts. Mean age: 9.5 yrs (range 6-15)	***I: Papaverine***. 5 mg/kg for 4 wks, then 10 mg/kg for 4 wks, N=19. ***C: Placebo***. For 8 wks, N=18. Mean 4.5 mo follow-up (range 1-10 mo).	***HA improvement***: I vs. C:	 RR=1.47[0.86; 2.51]
Sills (20),	RCT-CO QS: 7 (item: 1,2,3,5,6,7,10)	N=51, 8 dropouts. Age range 7-14	***I: Clonidine***. For 3 mo. ***C: Placebo***. For 12 wks.	***HA frequency/duration***: ***Adverse events*:**	No sufficient data to calculate RR or SMD C: 8.7%
Sorge (14),	RCT-PG QS: 4 (item: 1,3,4,8) Migraine (Vahlquist).	N=48, 6 dropouts, 3 in each group. Age range 7-14	***I: Flunarizine***. For 12 wks, N=21. ***C: Placebo***. For 12 wks, N=21.	***HA improvement*:** I vs. C: ***Adverse events*:**	 RR=4.00 [1.60; 9.97] I: 4.8%.
Sorge (15),	RCT-CO QS: 7 (item: 1,3,4,5,6,7,10) Migraine (Vahlquist).	N=70, 7 dropouts, 2 in I, 5 in C. Mean age: 10.8 yrs (range 5-11)	***I: Flunarizine***. For 12 wks. ***C: Placebo***. For 12 wks. Baseline 4 wks, 4 wks washout period.		No sufficient data to calculate RR or SMD
Wang (26),	RCT-PG QS: 7 (item: 1,2,3,4,5,6,7)	N=150, 32 dropouts, 16 in each group. Mean age: 12 (SD 3) yrs	***I: Magnesium oxide***. For 12 wks, N=58. ***C: Placebo***. For 12 wks, N=60.	***HA intensity/ frequency***: ***Adverse events*:**	No sufficient data to calculate RR or SMD I: 19%; C: 6.7%

C: control.; CCT: controlled clinical trial; CO: cross-over; HA: headache; hrs: hours; I: intervention; IHS: International Headache Society 1988; mo: month(s); N: number of subjects; yrs: years; QS: quality score on Delphi list with positive items in brackets; PG: parallel group; RCT: randomised controlled trial; RR: relative risk with 95% confidence interval; SD: standard deviation; SMD: standard mean difference with 95% confidence interval; vs.: versus; wks: weeks.

Chapter 3

Psychopathology in children and adolescents with migraine in clinical studies: a systematic review of the literature



Jacques Bruijn, Heiko Locher, Jan Passchier, Natascha Dijkstra, Willem-Frans Arts

Pediatrics 2010;126:323-332

ABSTRACT

Background: In the last decades, numerous population-based and hospital-based studies have demonstrated a relationship between migraine or headache and psychopathology in children.

Objective: To describe and assess all clinical studies on the prevalence and manifestations of psychological functioning and psychiatric comorbidity in children with migraine, and to provide recommendations for its diagnosis and treatment.

Methods: A literature search was made in Medline, Embase, PsycINFO and the Cochrane database to identify clinical studies that assessed psychological functioning and/or psychiatric comorbidity in children with migraine. Trial quality was assessed according to a standardized and validated set of criteria.

Results: Seven studies met the inclusion criteria. Evidence assessment was performed using the best-evidence synthesis method of Slavin. Based on this method, we found strong evidence that children with migraine in a clinical setting do not exhibit more withdrawn behaviour, do not have more thought problems, do not have more social problems and do not exhibit more delinquent or aggressive behaviour than healthy children. Furthermore, there is strong evidence that children with migraine have more somatic complaints and exhibit more internalizing behaviour which is, given the construct of the outcome measure used, a consequence of the nature of their disease rather than a sign of psychological dysfunctioning. Finally, compared with healthy children, there is limited evidence that children with migraine in a clinical setting are more frequently diagnosed with oppositional defiant disorder and are not more frequently diagnosed with ADHD, conduct disorder, dysthymia and depression.

Conclusions: Based on this review, we conclude that children with migraine at referral to a specialist do not exhibit more psychological dysfunctioning, and (to a lesser extent) do not exhibit more psychiatric comorbidity compared with healthy controls.

INTRODUCTION

Migraine is a common disorder in childhood. Its prevalence is influenced by sex and age and is reported to range from 3 to 15%[1]. Migraine in children is characterized by attacks of intense, throbbing, unilateral or bilateral headache, often accompanied by nausea, vomiting, photophobia and phonophobia[2].

As early as 1937 Harold G. Wolff presented the first extensive paper on psychological functioning in migraineurs, including a chapter addressing possible psychological maladjustments in childhood as well as case reports on psychological dysfunctioning in children and adolescents with migraine[3]. Since then numerous population-based and hospital-based reports have been published demonstrating a relationship between migraine/headache and psychopathology in children. A variety of measurement tools are used in these studies to investigate psychological functioning and psychiatric comorbidity in children with headache or migraine.

In order to produce evidence-based recommendations for diagnostic procedures and treatment related to psychological functioning and psychiatric comorbidity in children with migraine, we reviewed the evidence by performing a literature search for studies conducted in a clinical setting. The aim of this review was to describe and assess all clinical studies on the prevalence, manifestations and treatment of psychological functioning and psychiatric comorbidity in children with migraine in order to provide recommendations for its diagnosis and treatment.

METHODS

Search strategy

We searched Medline, Embase, PsychInfo and the Cochrane database from inception to February 2009 using the terms "migraine", "headache", "cephalgia", "cephalalgia", "child*", "infant", "teenage", "adolescent", "p(a)ediatric", "juvenile", "psychiatric", "psychiatric disorder", "psychiatric comorbidity", "psychiatric comorbid disorder", "depression", "anxiety", "behavioural problem", "behavioral problem", "psychological", "psychological disorder", "psychological comorbidity" and "psychological comorbid disorder".

Additional strategies for identifying trials included searching the reference lists of the included studies for outcome assessment.

Study selection

We selected only descriptive studies concerning psychological functioning or psychiatric comorbidity in clinically-treated children with migraine (≤ 18 years old). Only clinical studies were included. Studies on children in the general population were not included, with the exception of those that performed a separate analysis for clinically-treated children with migraine. The diagnosis of migraine had to be made with criteria designed to distinguish migraine from other types of headache. The use of a specific set of diagnostic criteria (e.g. the ICHD-II[2], the International Headache Society (IHS) criteria[4] and the criteria of the Ad Hoc Committee on the Classification of Headache[5]) was not required, but migraine diagnoses had to be based on the distinctive features of migraine and had to be described in the methods section of the study, e.g. headache attack lasts 2-48 h, unilateral or bilateral location, pulsating quality, moderate to severe intensity, aggravation by routine physical activity, nausea and/or vomiting, photophobia and phonophobia. A separate analysis describing the psychological functioning or eventual psychiatric comorbidity of all included subjects in a standardized, transparent and reliable manner was also necessary for inclusion*. Review articles were included only when a meta-analysis had been performed. A final criterion for study selection was publication in the English language.

Two authors (JB and HL) independently screened the titles and abstracts of the studies identified by the literature search for eligibility. All potentially relevant studies were retrieved as full papers and then again independently reviewed by two authors (JB and HL). Any disagreements were resolved through consensus when possible, or by arbitration of a third author (JP).

* For example, in a study concerning children with clearly described criteria for the diagnosis migraine, a comorbid diagnosis of anxiety disorder or depression solely by consultation of a child psychologist or psychiatrist without specifying the criteria upon which this diagnosis was based, was considered as insufficient for inclusion.

Study quality assessment

The quality of each study was assessed according to a standardized and validated set of criteria based on the protocols of the Cochrane Database of Systematic Reviews as used in randomized controlled trials[6-12] and modified to cover the case-control design of the studies included in this review.

1. Comparison group(s). The presence of at least one comparison group, preferably a sample of healthy children from the same region as the children with headache or migraine.
2. Sample size. Based on power analysis ($\alpha = 0.05$ (two-tailed), power = 0.80, Cohen's $d = 8$, i.e. a large difference between the groups), a sample size of more than 25 participants per comparison group was required.
3. Sample selection. A random selection strategy should be employed.
4. Design. The investigation should be case-controlled and based on quantitative information.
5. Outcome measures. These should be standardized, reliable and valid and cover the child's psychological functioning and/or its eventual psychiatric comorbidity.
6. Statistical analyses. Hypothesis testing using appropriate statistical analyses should be performed on the most important outcome measures.

These six criteria were assessed and scored independently by two investigators (JB and HL). A score of 1 (criterion met) or 0 (criterion not met) was used, leading to a total maximum score of 6 points per study. Inter-reviewer disagreement was primarily solved by discussion. When necessary, arbitration of a third author (JP) was used to resolve disagreement. This led to a uniform score on all included articles. Scores of 0 to 3 points were taken to indicate studies of low quality, and scores of 4 to 6 studies of high quality[6-12].

Outcome assessment

Because only seven studies met the selection criteria and a broad diversity of outcome measures was used, a meta-analysis (whereby statistical data of the studies are pooled and tested between groups), could not be performed. Instead, a best-evidence synthesis method[13] (as used in other systematic reviews[10,11,12,14]) was applied. This consists of four levels of scientific evidence:

1. Strong evidence: more than one relevant high-quality study with generally consistent outcomes.
2. Moderate evidence: one relevant high-quality study and one (or more) relevant low-quality study(ies) with generally consistent outcomes.
3. Limited evidence: one relevant high-quality study or more than one relevant low-quality studies with generally consistent outcomes.
4. Inconclusive evidence: one relevant low-quality study, no relevant studies, or studies with inconsistent outcomes.

Relevant is defined as using appropriate outcome measures for psychological functioning or psychiatric comorbidity. A "generally consistent outcome" is defined as a situation in which 75% of the studies agree on the result that there are no differences between case and control (comparison) groups on outcome measures, or 75% of the studies agree on the result that there are definite differences between case and control (comparison) groups on outcome measures[10-14].

RESULTS

Search results

The results of our search strategy are presented in Fig 1. Seven studies were included that concerned psychological functioning and/or psychiatric comorbidity in children or adolescents with migraine in a clinical setting.

Description of studies

Table I summarizes the seven studies[15-21].

Participants

In the seven studies, the number of children with migraine ranged from 5 to 67 (mean 38) children, with a total of 268 children included in this review. Their ages ranged from 7.5 to 16.5 years; however, this complete age range occurred in only one study with 5 partcipants[17]. In the remaining studies the age range was 8.3 to 15.3 years. Of all children, the mean age was 11.7 years, indicating that most children in the studies were pre-pubertal. Of the seven studies, two[16,21] used the ICHD criteria[2] to classify migraine, three[18-20] used the IHS criteria[4], one study[15] used the Prensky criteria[22] and another study[17] used the Silberstein criteria[23].

Outcome measures

A total of 26 different outcome measures were used. These were: the State-Trait Anxiety Inventory for Children (STAIC)[15], Revised Children's Manifest Anxiety Scale (RCMAS)[15], Children's Self-Report Psychiatric Rating Scale (CSPRS)[15], Coddington's Life Events Scale for Children (LES-C)[15], Coddington's Life Events Scale for Adolescents (LES-A)[15], Matthew Youth Test for Health[17], KidCope[17], Type A achievement[17], Type A agression[17], Parent-rated disability[17], Child-rated disability[17], Rorschach test[18], Thematic Appreciation Test (TAT)[18], Blacky Pictures Test (BPT)[18], Wechsler's Intelligence Scale for Children (WISC)[18], Wechsler's

Adult Intelligence Scale (WAIS)[18], Multidimensional Anxiety Scale for Children (MASC)[19], Conner's Parent Rating Scale (CPRS)[19], Emotionality, Activity, Sociability and Shyness Scale for Childhood (EAS)[19], Child Symptom Inventory 4th edition (CSI-4)[20], Adolescent Symptom Inventory 4th edition (ASI-4)[20], Loneliness and Social Dissatisfaction Questionnaire (LSDQ)[21], Self Perception Profile for Children (SPPC)[21], and Roberts Apperception Task for Children (RATC)[21].

These outcome measures were not used across the studies, but in single studies only.

The Children's Depression Inventory (CDI) was used in two studies[19,21] and the Child Behaviour Check List (CBCL) was used in four studies[16,17,19,21].

The outcome measures were mostly questionnaires to be completed by the parents of the children or by the children themselves. In two studies[17,18] a psychodiagnostic interview with a child psychologist or child psychiatrist was part of the investigation. The comparative data are presented in Table I.

Study quality assessment

The assessment of the six methodological aspects and the quality standard of each study are presented in Table II. All studies used comparison groups; five studies had a sufficient sample size (i.e. more than 25 per comparison group)[15,16,19,20,21]. The median score for methodological quality was 3.1 (range 0-4) whereas 6 was the maximum score possible. Five studies had a quality score of 4[15,16,19,20,21]. One study had a quality score of 0[18] and one study of 2[17]. Using a cut-off point of 3 or more as a high-quality study, five studies were considered as such[15,16,19,20,21]. None of the studies had a quality score of 5 or 6; this was due to criteria 3 and 4 with regard to sample selection and design, respectively. Only if the sample selection was randomized and the design case-controlled and based on quantative information, was a score of 1 given. In none of the included studies was this the case.

Outcome assesment

Outcome assessment of the seven studies proved difficult due to the broad diversity of outcome measures used. Outcome measures in five studies focused on psychological functioning of the children with migraine[15-21], whereas two studies explicitly focused on psychiatric comorbidity[18, 20]. In four studies[16-19] psychological functioning or psychiatric comorbidity in three groups of children with different types headache, or children with other pain-related disorders, were compared with each other; this latter group included two low-quality studies[17, 18] with no healthy control group. The other two studies[16,19] were of high quality and did include healthy controls. Three high-quality studies[15,20,21] included

only children with migraine and healthy controls. For practical purposes, for this review we decided to assess evidence only on the outcome measures that compared children with migraine with healthy children.

For the study of Cooper et al.[15], no significant differences were found between children with migraine and healthy children on anxiety scores as measured on the STAIC and RCMAS, and on the outcome measure CSPRS, LES-C and LES-A.
In the study of Galli et al.[16] a significant difference was found on the CBCL subscales Attention problems and Somatic complaints and on the combined scale Internalizing behaviour, in favour of healthy children. No significant differences were found between children with migraine versus healthy children on the other CBCL scales.
In the study of Gladstein et al.[17] three small groups of children with transformed migraine (n = 5), new persistent daily headache (n = 13), and children with both migraine and tension type headache (n = 15) were compared. No significant differences were found on the outcome measures Matthew Youth Test for Health, KidCope, Type A aggression, Parent-rated disability and Child-rated disability between children with transformed migraine versus children with new persistent daily headache and versus children with both migraine and tension-type headache. Only on the outcome measure Type A achievement was a significant difference found between children with transformed migraine versus children with new persistent daily headache and children with both migraine and tension-type headache, in favour of the latter two groups.
In the study of Lanzi et al.[18] three small groups of children with migraine with aura (n = 13), migraine without aura (n = 8) and children with chronic tension-type headache (n = 9) were compared using various tests and a psychodiagnostic interview resulting in a psychodynamic classification as “neurotic organization”, “borderline organization” and “white relation”. This psychodynamic classification was used as outcome measure. In addition to the low number of participants in each group, no statistical analysis was performed to compare the outcomes.
Mazzone et al.[19] found no significant differences between children with migraine and healthy children on the outcome measures CPRS, EAS Emotionality and EAS Shyness. However, significant differences on anxiety scores and social functioning between children with migraine versus healthy children were found on the outcome measure MASC and on the outcome measure EAS Sociability, respectively, in favour of the healthy children. In addition, a significant difference was found on depression scores in children with migraine versus healthy children as measured on the CDI, in favour of the healthy children. Furthermore, significant differences were found between children with migraine

versus healthy children using the CBCL as outcome measure on the scales of Internalizing and Externalizing behaviour and Total score, in favour of the healthy children. A significant difference was also found between children with migraine and healthy children with regard to pathological internalizing scores (severe enough for referral to a child psychiatrist or child psychologist), in favour of the healthy children. Pathological externalizing and pathological total scores, as measured on the CBCL, showed no significant difference between children with migraine and healthy children. No CBCL subscale analysis was described[19].

Pakalnis et al.[20] found significant differences in the diagnosis of oppositional defiant disorder (ODD) and above average T-scores of CSI symptoms of conduct disorder (CD), ODD and generalized anxiety disorder (GAD) in children with migraine versus healthy children, in favour of healthy children. No significant differences were found in the diagnosis of ADHD, CD, dysthymia and depression between children with migraine versus healthy children although scores were above normative means.

Finally, Vannatta et al.[21] found no significant differences between children with migraine and healthy children on outcome measures of the LSDQ, all subscales of the SPPC, and all subscales of the RATC. In their study, the CBCL was also used to measure psychological functioning. Both the mother as well as the father of all children with migraine and all healthy controls completed the CBCL questionnaires separately. Consequently, separate analyses were performed, referred to as the 'mother's report' and 'father's report'. A significant difference was found between children with migraine versus healthy children in both the mother's and father's report on the subscale of Somatic complaints, in favour of the healthy children. In addition, the mother's report showed a significant difference in favour of healthy children on the scale Internalizing behaviour and the subscale Anxious/depressed, but the father's report did not. On all other CBCL scales, neither the reports of the mothers nor those of the fathers revealed any significant differences between the children with migraine and the healthy children.

Five of the seven included studies were eligible for assessing evidence with regard to psychological functioning in children with migraine[15,16,17,19,21], and two studies were eligible for assessing evidence with regard to psychiatric comorbidity[18,20].

With regard to the first group, four of the five studies were of high quality[15,16,19,21] and one of low quality[17]. This latter study included only 5 children with transformed migraine; moreover, no comparison was made with healthy controls. In addition, the authors used migraine criteria as defined by Silberstein[23], which differ considerably from the IHS criteria[4] and ICHD-II criteria[2] which were used in the three of the four high-quality studies.

Therefore, because the evidence from this study[17] can not realistically be compared with the other studies, we decided to assess the four other studies for evidence and describe the outcome measures separately (Table III).
For the purpose of presenting evidence in a systematic manner, we decided to divide the available outcome measures into eight outcome fields in accordance with the scales as used in the CBCL, i.e. withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour and internalizing and externalizing behaviour, of which the latter two are used only in the CBCL. We decided to allocate the non-CBCL outcome measures over these outcome fields based on their characteristics. Consequently, the outcome measures STAIC, RCMAS, CDI, MASC, EAS Emotionality, RATC Anxiety and RATC Depression were allocated to the outcome field anxious/depressed since all these outcome measures are used to measure signs of anxiety and/or depression in children. Two distinct outcome fields of 'anxiety' and 'depression' were not made because, had we done so, the CBCL outcome measure Anxious/depressed would have to be excluded since this CBCL subscale does not make this distinction. We allocated the outcome measure EAS Shyness to the outcome field withdrawn, the outcome measure EAS Sociability, RATC Rejection and LSDQ to the outcome field social problems, and the outcome measure RATC Aggression to the outcome field aggressive behaviour. We were unable to allocate the outcome measures CSPRS, LES-C, LES-A, CPRS, EAS Activity and SPPC to any specific outcome field. Furthermore, assessing evidence on a number of outcome fields was complicated because the different outcome measures yielded contradictory results. Therefore, we decided to assess evidence on all outcome measures within one outcome field. We specifically decided that 75% of the outcome measures within one outcome field should give equivalent results to provide conclusive evidence.

Based on this methodology and according to the criteria of the best-evidence synthesis method[13], there is strong evidence that children with migraine in a clinical setting do not exhibit more withdrawn behaviour, do not have more thought problems, do not have more social problems and do not exhibit more delinquent or aggressive behaviour than healthy children. Furthermore, based on the same criteria, there is strong evidence that children with migraine have more somatic complaints and show more internalizing behaviour. Finally, there is inconclusive evidence that children with migraine have more signs of anxiety or depression, have more attention problems, and exhibit more externalizing behaviour than healthy children.

Of the studies focusing on psychiatric comorbidity in children with migraine, one of the two selected studies was of high quality[20] and the other of low quality[18]. This latter study included three small groups of children with migraine with aura (n = 13), without aura (n = 8), or with chronic tension-type headache (n = 9). Furthermore, no statistical analysis was performed and there was no comparison with healthy children. Therefore, we decided to assess the first study[20]. Consequently, according to the criteria of the best-synthesis method[13], there is only limited evidence that children with migraine in a clinical setting more frequently have ODD and higher than average T-scores for CSI symptoms of ODD, CD and GAD as compared with healthy children. Furthermore, there is limited evidence that children with migraine in a clinical setting are not more frequently diagnosed with ADHD, CD, dysthymia and depression and do not have higher above average T-scores of CSI symptoms of ADHD, depression and anxiety compared with healthy children.

DISCUSSION and RECOMMENDATIONS

This is the first systematic review to investigate psychological functioning and psychiatric comorbidity in children with migraine in clinical studies. In contrast with previous reviews[26,27], in the present study the methodological quality and strength of evidence of the reviewed studies were assessed in a systematic manner using a standardized set of criteria.

Based on this review, the conclusion seems justified that there is no or only inconclusive evidence that children with migraine in a clinical setting show more problems in psychological functioning and, to a lesser extent, do not exhibit more psychiatric comorbidity in comparison with healthy children. Only with respect to somatic complaints and internalizing behaviour there is strong evidence that children with migraine have more problems than healthy children. With regard to somatic complaints, this conclusion is based on the relevant CBCL subscale score in two studies[16,21]. This subscale contains eight questions of which three concern the symptoms of headache, nausea and vomiting[28,29] which are the hallmarks of migraine in children. Since in both studies[16,21] no correction for migraine-associated symptoms took place in the subscale Somatic complaints, the included children are inclined by the nature of their disease to have a high score on this subscale.

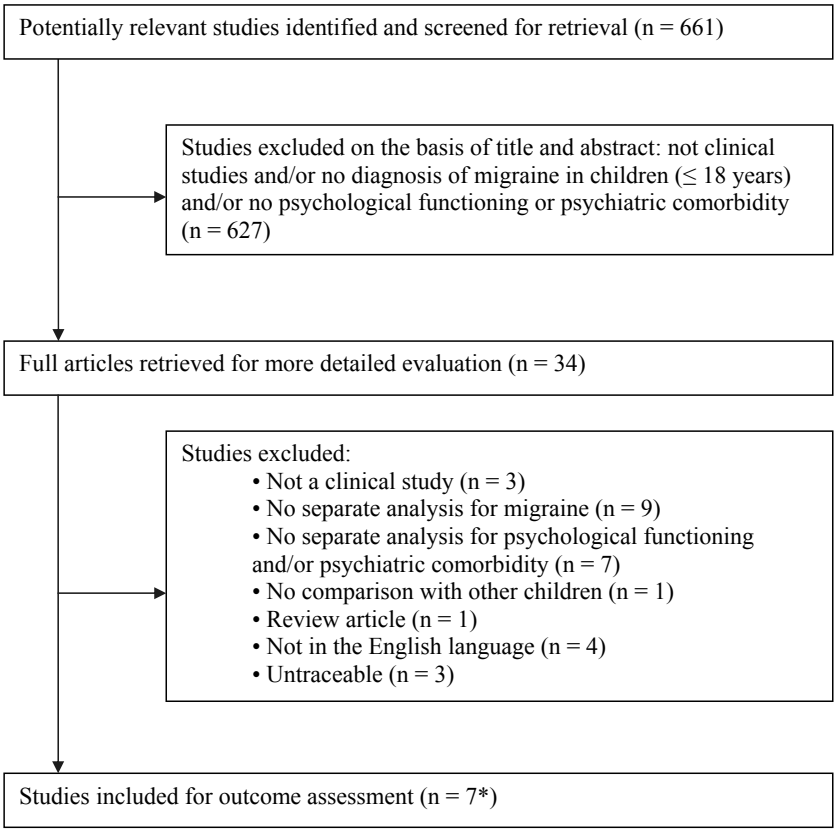


Fig. 1 Flow chart showing the results of the search strategy

* Initially 6 studies were included for outcome assessment. After searching the reference lists of these included studies, one additional study was found eligible for outcome assessment.

Table I: Characteristics of the included studies (n = 7) on psychological functioning and psychiatric comorbidity in clinical studies among children with migraine

Study and Clinic	Migraine Criteria	Participants	Outcome measures	Results
Cooper et al[15] (1987)	Prensky[22]	(a) Children with migraine: 51 % female; mean age 11.0 y (SD: 2.7 y); n = 39; age at migraine onset 8.1 y (SD: 2.7 y) (b) Best friend controls: 51 % female; mean age 11.0 y (SD: 2.7 y); n = 39	State-Trait Anxiety Inventory for Children (STAIC), Revised Children's Manifest Anxiety Scale (RCMAS), Children's Self- Report Psychiatric Rating Scale (CSPRS), Coddington's Life Event Scale for Children (LES-C) or Adolescents (LES-A)	No significant differences between (a) vs. (b) on all outcome measures
Galli et al[16] (2007)	ICHD-II[2]	(a) Children with migraine: 50 % female; mean age 12.4 y (SD: 2.9 y); n = 42; age at headache or migraine onset: not stated (b) Healthy children: 66 % female; mean age 11.7 y (SD: 4.6 y); n = 70	Child Behaviour Checklist (CBCL)	Significant difference of CBCL scale Internalizing and subscale Somatic complaints (both $p< 0.05$) of (a) vs. (b) in favour of (b) Significant difference ($p<0.05$) of CBCL subscale Attention problems of (a) vs. (b) in favour of (b) No significant differences on CBCL scale Externalizing and subscales Withdrawn, Anxiety/depression, Thought Problems, Social problems, Delinquent behaviour and Agressive behaviour between (a) vs. (b)
Gladstein et al[17] (1996)	Silberstein[23]	(a) Children with transformed migraine (TM): % female not stated; mean age 12.0 y (SD: 4.5 y); n = 5; age at headache onset 8.2 y (SD: 5.3 y) (b) Children with new persistent daily headache (NPDH): % female not stated; mean age 11.8 y (SD: 2.5 y); n = 13; age at headache onset 11.1 y (SD: 2.1 y) (c) Children with both migraine and TTH (Comorbid Pattern CP) : % female not stated; mean age 13.9 y (SD: 1.9 y); n = 15; age at headache onset 12.1 y (SD: 2.2 y)	Child Behaviour Checklist (CBCL) Matthews Youth Test for Health KidCope Type A achievement Type A aggression Parent-rated disability Child-rated disability	Significant difference of CBCL scale Externalizing ($p< 0.05$) of (a) vs. (b) and (a) vs. (c) in favour of (b) and (c) respectively Significant difference of Type A achievement ($p<0.05$) of (a) vs. (b) and (a) vs. (c) in favour of (b) and (c) respectively No significant differences on CBCL scales Internalizing between children with (a) vs. (b), (a) vs. (c) and (b) vs. (c) No significant differences on all other used tests between (a) vs. (b), (a) vs. (c) and (b) vs. (c)

Table I: Characteristics of the included studies (n = 7) on psychological functioning and psychiatric comorbidity in clinical studies among children with migraine (continued)

Study and Clinic	Migraine Criteria	Participants	Outcome measures	Results
Lanzi et al[18] (1994)	IHS[4]	(a) Children with migraine without aura (Mw/oA): % female not stated; mean age and SD not stated; n = 13; age at headache or migraine onset not stated (b) Children with migraine with aura (MwA): % female not stated; mean age and SD not stated; n = 8; age at headache or migraine onset not stated (c) Children with chronic tension type headache (CTH): % female not stated; mean age and SD not stated; n = 9; age at headache or TTH onset not stated	Rorschach Test, Thematic Appreciation Test (TAT) or Blacky Pictures Test (BPT), Wechsler Intelligence Scale for Children (WISC) or Wechsler Adult Intelligence Scale (WAIS) and psychodiagnostic interview by a child neuropsychiatrist leading to a diagnosis of "neurotic", borderline or "white relation" organization according to the classic psychodynamic classification[24] and the Paris psychosomatic school[25]	In (a) 46 % (6/13) had a "neurotic organization", 31 % (4/13) a "borderline organization", 23 % (3/13) a "white relation" In (b) 75 % (6/8) had a "neurotic organization", 25 % (2/8) a "borderline organization" In (c) 33 % (3/9) had a "neurotic organization", 44 % (4/9) a "borderline organization", 23 % (2/9) a "white relation" No statistical comparative analysis was performed between group (a) vs. (b), (a) vs. (c) and (b) vs. (c)
Mazzone et al[19] (2005)	IHS[4]	(a) Children with migraine: 51 % female; mean age 11.1 y (SD: 1.9 y); n = 67; age at headache onset 8.7 y (SD: 2.4 y) (b) Healthy children; 44 % female; mean age 10.3 y (SD: 2.4 y); n = 36	Child Behaviour Checklist (CBCL) Children's Depression Inventory (CDI) Multidimensional Anxiety Scale for Children (MASC) Conner's Parent Rating Scale (CPRS) Emotionality, Activity, Sociability and Shyness Scale for Childhood (EAS)	Significant difference of CBCL scales Internalizing ($p<0.01$), Externalizing ($p<0.001$) and Total ($p<0.001$) of (a) vs. (b) in favour of (b) Significant difference of pathological CBCL Internalizing scores of (a) vs (b) in favour of (b) ($p<0.001$) Significant difference of EAS Sociability score of (a) vs. (b) in favour of (b) ($p<0.01$) Significant difference of CDI and MASC scores of (a) vs. (b) in favour of (b) (both $p < 0.05$) No significant differences on CPRS, EAS Emotionality and EAS Shyness of (a) vs. (b)

Table I: Characteristics of the included studies (n = 7) on psychological functioning and psychiatric comorbidity in clinical studies among children with migraine (continued)

Study and Clinic	Migraine Criteria	Participants	Outcome measures	Results
Pakalnis et al[20] (2005)	IHS[4]	(a) Children with migraine: 44 % female; mean age 10.6 y (SD: not stated); n = 47; age at headache or migraine onset: not stated (b) Healthy Children: 56 % female; mean age 10.9 y (SD: not stated); n = 30	Child Symptom Inventory 4th edition (CSI-4) or Adolescent Symptom Inventory 4th edition (ASI-4) Semistructured Interview by psychologist Outcome measueres: CSI-4 diagnosis and T-scores of CSI-symptoms of ADHD/inattentive, ADHD/hyperactive, ADHD combined, Conduct Disorder, Oppositional Defiant Disorder (ODD), Dysthymia, Anxiety, Depression	Significant difference (p = 0.01) of (a) vs. (b) in diagnosis of ODD in favour of (b) Significant difference in above average T-scores of CSI-symptoms of CD (p<0.05), ODD (p<0.05) and Generalized Anxiety Disorder (p<0.05) of (a) vs. (b) in favour of (b) No significant difference in diagnosis of ADHD, CD, Dysthymia, Anxiety and Depression of (a) vs. (b) No significant difference in above average T-scores of CSI symptoms of ADHD, Depression and Dysthymia of (a) vs. (b)
Vannatta et al[21] (2008)	ICHD-II[2]	(a) Children with migraine: 45 % female; mean age 11.8 y (SD: 1.8 y); n = 47; age at headache or migraine onset: not stated (b) Healthy Children: 43 % female; mean age 12.0 y (SD: 1.9 y); n = 46	Child Behaviour Checklist (CBCL) to be filled in by mother and father Children's Depression Inventory (CDI) Loneliness and Social Dissatisfaction Questionnaire (LSDQ) Self Perception Profile for Children (SPPC: (subscales Scholastic competence, Social acceptance, Athletic competence, Physical appearance, Behaviour conduct, Global self-worth) Roberts Apperception Task for Children (RATC: subscales Anxiety, Depression, Rejection, Agression)	Significant difference of CBCL subscale Somatic complaints in both mother and father report (p<0.001) of (a) vs. (b) in favour of (b) Significant difference of CBCL scale Internalizing in mother report (p<0.001) of (a) vs. (b) in favour of (b), however not in father report (p = ns) Significant difference of CBCL subscale Anxious/depressed in mother report (p<0.001) of (a) vs. (b) in favour of (b), however not in father report (p = ns) No significant differences on CBCL scale Externalizing and subscales Withdrawn, Social Problems, Thought problems, Attention Problems, Delinquent Behaviour and Agressive behaviour and all other used tests of (a) vs. (b). No significant differences on CDI, LSDQ, SPPC on all subscales and RATC on all subscales between (a) and (b)

Table II: Quality assessment of the studies on psychological functioning and psychiatric comorbidity in clinical studies among children with migraine (0 = criterion not met, 1 = criterion met)

Author, year of publication	Comparison group(s)		Sample Size	Sample Selection	Design	Outcome measures	Statistical analysis	Sum score	Quality
Cooper et al[15] (1987)	M[a] vs. BFC[b]	1	1	0	0	1	1	4	H[j]
Galli et al[16] (2007)	M[a] vs. HC[c]	1	1	0	0	1	1	4	H
Gladstein et al[17] (1996)	TM[d] vs. NPDH[e] TM[d] vs. CP[f] NPDH[5] vs. CP[6]	0	0	0	0	1	1	2	L[k]
Lanzi et al[18] (1994)	Mw/oA[g] vs. MwA[h] Mw/oA[g] vs. CTH[i] CTH[i] vs. MwA[h]	0	0	0	0	0	0	0	L
Mazzone et al[19] (2005)	M[a] vs. HC[c]	1	1	0	0	1	1	4	H
Pakalnis et al[20] (2005)	M[a] vs. HC[c]	1	1	0	0	1	1	4	H
Vannatta et al[21] (2008)	M[a] vs. HC[c]	1	1	0	0	1	1	4	H

[a]Children with migraine
[b]Best friend controls
[c]Healthy controls
[d]Children with transformed migraine
[e]Children with new persistent daily headache
[f]Children with both migraine and tension-type headache (comorbid pattern)
[g]Children with migraine without aura
[h]Children with migraine with aura
[i]Children with chronic tension-type headache
[j]High-quality study (sum score ≥3)
[k]Low-quality study (sum score <3)

Table III: Evidence table of psychological functioning in children with migraine in high-quality clinical studies

Outcome field	Cooper et al.[15]	Galli et al.[16]	Mazzone et al.[19]	Vannatta et al[21]	Evidence
Withdrawn		CBCL =	EAS Shyness =	CBCL =	Strong
Somatic complaints		CBCL +		CBCL +	Strong
Anxious/depressed	STAIC = RCMAS =	CBCL =	CDI + MASC + EAS Emotionality =	CDI = CBCL =/+* RATC Anxiety = RATC Depression =	Inconclusive
Social problems		CBCL =	EAS Sociability +	CBCL = LSDQ = RATC Rejection =	Strong
Thought problems		CBCL =		CBCL =	Strong
Attention problems		CBCL +		CBCL =	Inconclusive
Delinquent behaviour		CBCL =		CBCL =	Strong
Aggressive behaviour		CBCL =		CBCL = RATC Agression =	Strong
Internalzing		CBCL +	CBCL +	CBCL =/+*	Strong
Externalizing		CBCL =	CBCL +	CBCL =	Inconclusive

= no significant difference between children with migraine vs. healthy children
+ significant difference between children with migraine vs. healthy children in favour of healthy children
* in father's CBCL report =, in mother's CBCL report +

Moreover, the CBCL subscale Somatic complaints is one of the three subscales that together form the Internalizing behaviour score (the other two being the subscale Withdrawn and the subscale Anxious/depressed). Since in both studies[16,21] the subscale Withdrawn showed no significant difference between children with migraine and healthy children, and in one study[16] the subscale Anxious/depressed showed no significant difference between children with migraine and healthy children and in the other study only in the mother's report a significant difference between children with migraine and healthy children in favour of healthy children was revealed[21], the conclusion seems justified that the deviant Internalizing behaviour score in children with migraine (as described by Galli et al.[16] and Mazzone et al.[19]) and in the mother's report (as described by Vannatta et al.[21]) is mainly due to the nature of the disease in children with migraine and not the consequence of psychological dysfunctioning due to the migraine itself.

Although we are able to offer some evidence on several aspects of psychological functioning and psychiatric comorbidity in children with migraine, the investigations reported so

far have limitations and problems that impair the generalizability of the findings. Thus, our classification of the studies into high-quality and low-quality studies, and the other methodological aspects, should be interpreted with the following restrictions in mind.

First of all, very strict criteria were used for the final inclusion of relevant studies. We included only clinical studies and any population studies were excluded. This means that a number of methodologically sound and relevant studies were excluded. For example, the studies of Just et al.[30] and Andrasik et al.[31] were excluded because the patient sample was not, or only partially, clinically based and a separate analysis for the clinical sample was not included. In addition several well-designed clinical studies were excluded because a separate analysis for children or adolescents with migraine, or a separate analysis for psychological functioning or psychiatric comorbidity, was lacking. Furthermore, we excluded studies which were not published in the English language, thereby potentially excluding other relevant studies.

Second, a broad diversity of 26 different outcome measures was used in the seven selected studies, of which only two were used across some studies (CBCL and CDI), thereby complicating comparison of outcome measures between studies. For this reason we decided to allocate different outcome measures to so-called outcome fields with the aim to assess the evidence provided by the high-quality studies of psychological functioning in children with migraine. In doing so, we were not able to allocate the outcome measures CSPRS, LES-C, LES-A, CPRS, EAS Activity and SPPC to a specific outcome field and therefore excluded them from final evidence assessment, potentially causing bias.

Third, another limitation concerns the comparison groups used in the reviewed studies. In the study of Cooper et al.[15] a comparison group of 'best friend' controls was used, potentially causing bias because no concealed randomization was used. In fact, in all of the included studies no concealed randomization was used with regard to the children with migraine or the control group.

Fourth, all included studies have relatively small sample sizes (for children with migraine as well as for healthy children), rarely exceeding 50 persons. Only the study of Galli et al.[16], included 70 children with migraine, and the study of Mazzone et al.[19] included 67 healthy children. Comparing such relatively small groups might also be a potential cause for bias.

Fifth, four different sets of criteria for diagnosing migraine in children were used (Silberstein[23], Prensky[22], IHS[4], ICHD-II[2]), potentially complicating comparison of the patient groups and outcomes. However, the Silberstein and Prensky criteria were used in only two single studies (Cooper et al.[15] and Gladstein et al.[17]), one of which was of low quality[17]. The other five studies either used the IHS criteria (Lanzi et al.[18], Mazzone et al.[19] and Pakalnis et al.[20]) or the ICHD-II criteria (Galli et al.[16] and Vannatta et al.[21]). This makes comparison of

outcome measures in these five studies feasible since the ICHD-II criteria are based on the IHS criteria.

Sixth, the study of Vanatta et al.[21] demonstrated that fathers and mothers of children with migraine complete the questionnaires in different ways, which can cause substantial differences in outcome. This may also be a potential cause for bias in the other selected studies.

Finally, none of the included studies used a random selection strategy and a case-controlled design, meaning that the quality score could not exceed 4, whereas the highest score possible was 6.

CONCLUSIONS

There is strong evidence that children with migraine in a clinical setting do not exhibit more withdrawn behaviour, do not have more thought problems, do not have more social problems and do not exhibit more delinquent or aggressive behaviour than healthy children. Furthermore, there is strong evidence that children with migraine have more somatic complaints and exhibit internalizing behaviour which is, given the construct of the outcome measure used, a consequence of the nature of their disease rather than a sign of psychological dysfunctioning. There is inconclusive evidence that children with migraine have more signs of anxiety and depression, have more attention problems, and exhibit more externalizing behaviour than healthy children. Finally, there is limited evidence that children with migraine in a clinical setting are more frequently diagnosed with oppositional defiant disorder and are not more frequently diagnosed with ADHD, conduct disorder, dysthymia and depression compared with healthy children.

However, in the presence of evident psychological or psychiatric co-morbidities, appropriate mental health referral may have beneficial results regarding treatment and long-term management of the migraines. This should also be an area that warrants closer investigation in the future[20].

More clinical studies are needed to further explore psychological functioning and psychiatric comorbidity in children with migraine using the same outcome measures with relatively large samples and using appropriate statistical testing. For clinical practice, in general, it does not seem necessary to refer a child with migraine to a child psychologist or a child psychiatrist, but only if clinical features or behavior warrant such referral.

ACKNOWLEDGEMENTS

The authors thank the Nolet Foundation and Van Der Linden Strukton for funding this research. Special thanks go to Louis Volkers (librarian at the Erasmus Medical Centre) for his valuable aid in performing the database search. The authors also thank the management of the Vlietland Hospital for their support, especially Gerrit-Jan van Zoelen. Finally, we thank Joke Hunfeld for her comments during the process of writing this article.

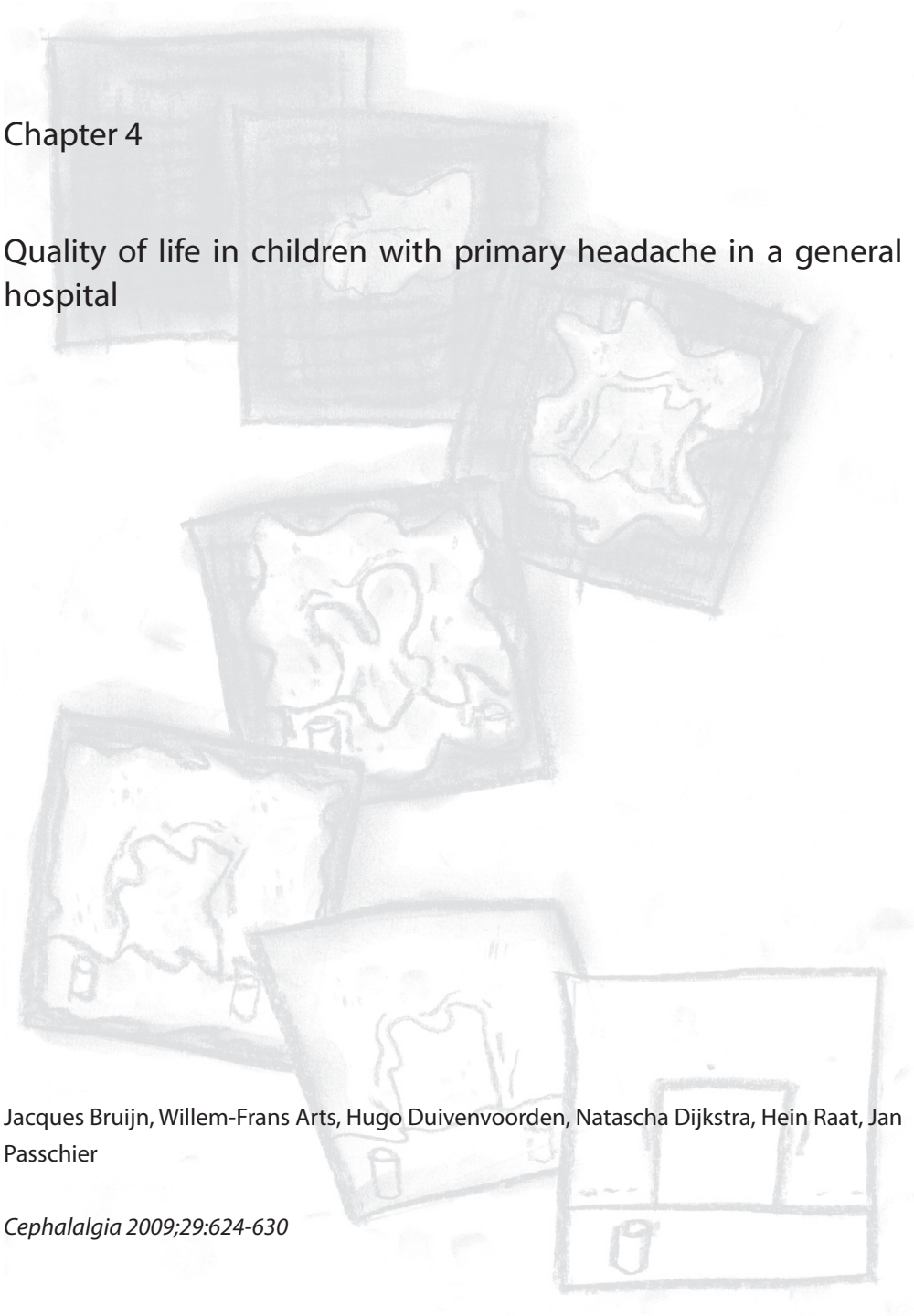
REFERENCES

1. Sillanpaa M. **Changes in the prevalence of migraine and other headaches during the first seven schoolyears.** Headache 1983;23:15-9.
2. Headache Classification Committee of the International Headache Society. **The International Classification of Headache Disorders 2nd edition (ICHD II).** Cephalalgia 2004:24:suppl1:1-160.
3. Wolff HG. **Personality features and reactions of subjects with migraine.** Arch Neurol Psych 1937;37:895-921.
4. Headache Classification Committee of the International Headache Society. **Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.** Cephalalgia 1988;8 (suppl.7):1-96.
5. Ad Hoc Committee on the Classification of Headache of the National Institute of Neurological Diseases and Blindness. **Classification of headache.** JAMA 1962;179:717-8.
6. Sackett DL, Haynes RB, Tugwell P. **Clinical Epidemiology (1991).** Little, Brown and Co., Boston.
7. Von Korff, M: **Studying the natural history of back pain.** Spine 1994;19:2041S-2046S.
8. Cole DC, Hudak PL. **Prognosis of non-specific work-related musculoskeletal disorders of the neck and upper extremity.** Am J Ind Med 1996;29:657-68.
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. **Assessing the quality of randomized clinical trials: is blinding necessary?** Contr Clin Trials 1996;17:1-12.
10. Ezzo J, Berman B, Hadhazy VA, Jahad AR, Lao L, Singh BB. **Is acupuncture effective for the treatment of chronic pain? A systematic review.** Pain 2000;86:217-25.
11. Geurts JW, Van Wijk RM, Stolker RJ, Groen GJ. **Efficacy of radiofrequency procedures for the treatment of spinal pain: a systematic review of randomized clinical trials.** Reg Anesth Pain Med 2001;26:394-400.
12. Hunfeld JAM, Fauser BCJM, de Beaufort LD, Passchier J. **Child development and quality of parenting in lesbian families: no psychosocial indications for a-priori withholding of infertility treatment. A systematic review.** Hum Repro Update 2001;7(1):579-90.
13. Slavin, RE. **Best evidence synthesis: an intelligent alternative to metaanalysis.** J Clin Epidemiol 1995;48:9-18.
14. Van Tulder MW, Ostelo R, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft JW. **Behavioral treatment for chronic low back pain: a systematic review within the framework of the Cochrane Back Review Group.** Spine 2000;25:2688-99.
15. Cooper PJ, Bawden HN, Camfield PR, Camfield CS. **Anxiety and Life Events in Childhood Migraine.** Pediatrics 1987;79;999-1004.
16. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, Cucchiara S, Guidetti V. **Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL).** Cephalalgia 2007;27:211-9.
17. Gladstein J, Holden WE. **Chronic daily headache in children and adolescents: a 2-year prospective study.** Headache 1996;36:349-51.
18. Lanzi G, Balottin U, Pitillo G, Zambrino CA. **Personality characteristics in juvenile tension headache and migraine.** Functional Neurology 1994;(9)2:83-8.
19. Mazzone L, Vitiello B, Incorpora G, Mazzone D. **Behavioural and temperamental characteristics of children and adolescents suffering from primary headache.** Cephalalgia 2006;26:194–201.
20. Pakalnis A, Gibson J, Colvin A. **Comorbidity of psychiatric and behavioral disorders in pediatric migraine.** Headache 2005;45(5):590-6.
21. Vannatta K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. **Multiple perspectives on the psychological functioning of children with and without migraine.** Headache 2008;48(7):994-1004.
22. Presnky A. **Migraine and migrainous variants in pediatric patients.** Pediatr Clin N Am 1976;23:461-71.
23. Silberstein SD, Lipton RB, Solomon S, Mathew NT. **Classification of daily and near-daily headaches: proposed revisions to the IHS criteria.** Headache 1994;34:1-7.

24. Bergeret J: **la personalité normale et patologique.** Paris: Bordas 1974.
25. Kreisler L: **L'enfant du désordre psychosomatique.** Paris: Privat 1981.
26. Powers SW, Gilman DK, Hershey AD. **Headache and psychological functioning in children and adolescents.** Headache 2006;46:1404-15.
27. Karwautz A, Wöber C, Lang T, Bock A, Wagner-Ennsgraber C, Vesely C, Kienbacher C, Wöber-Bingol C. **Psychosocial factors in children and adolescents with migraine and tension-type headache: a controlled study and review of the literature.** Cephalalgia 1999;19:32-43.
28. Achenbach TM. **Manual for the Child Behaviour Checklist/4-18 and 1991 profiles.** Burlington VT 1991: University of Vermont, Department of Psychiatry.
29. Verhulst F, van der Ende J, Koot H. **Manual for the CBCL/4-18 (Dutch edition).** ISBN 90-75584-03-2.
30. Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, Resch F. **Emotional and behavioural problems in children and adolescents with primary headache.** Cephalalgia 2003;23:206-13.
31. Andrasik F, Kabela E, Quinn S, Attanasio V, Blanchard EB, Rosenblum EL. **Psychological functioning of children who have recurrent migraine.** Pain. 1988;34(1):43-52.

Chapter 4

Quality of life in children with primary headache in a general hospital



Jacques Bruijn, Willem-Frans Arts, Hugo Duivenvoorden, Natascha Dijkstra, Hein Raat, Jan Passchier

Cephalalgia 2009;29:624-630

ABSTRACT

Background: Knowledge on the quality of life of children with headache is lacking. Until now only a few studies in this field have provided information on a limited number of life domains.

Objective. To assess the quality of life on a comprehensive number of life domains in children with primary headache presenting at an outpatient paediatric department in a general hospital.

Methods. From October 2003 until October 2005 all children who were referred to the outpatient paediatric department because of primary headache were investigated by protocol. A thorough history was taken and a general physical and neurological examination was performed. The International Headache Society (IHS) criteria were used for classification. Quality of life (QoL) was measured using the Dutch version of the Child Health Questionnaire (CHQ-PF50 Dutch edition) and compared with data from a previously investigated cohort of healthy children from the same region, and with data from a cohort of children from the USA with asthma or with ADHD, investigated with the CHQ-PF50.

Results. A total of 70 primary headache patients were included in the study (25 with tension type headache, 36 with migraine, 7 with chronic tension type headache, 2 with both tension type headache and migraine). Their mean age was 10.6 years (range 4 to 17 years); 37 children were male. On all but 1 subscale (self-esteem) the QoL of the children with primary headache was decreased compared with the cohort of healthy children, especially on the domains of mental health, parental impact time, and family cohesion. Compared with the cohort of children with asthma the QoL was significantly worse for our headache group on 7 subscales and significantly better on 1 subscale (general health perception). Compared with the cohort of children with ADHD the QoL was significantly worse on 6 subscales but significantly better on 3 subscales. There were no significant differences on any QoL subscale between children with tension type headache and children with migraine.

Conclusions. The QoL in children with primary headache presenting at the outpatient paediatric department of a general hospital seems to be considerably diminished. No difference in QoL was found between children with tension type headache and those with migraine.

INTRODUCTION

Headache is a common problem, not only in adults but also in adolescents and even in children. The prevalence of headache and migraine in children is age and gender dependent. Sillanpää reported a prevalence of headache of 50.5% for boys and 49.5% for girls at 7 years of age, and a prevalence of migraine of 2.9% and 2.5%, respectively[1]. At age 14 years, the prevalence of headache is 48.6% and 51.4%, and for migraine the prevalence is 6.4% and 14.8% for boys and girls, respectively[1].

In the Netherlands 15% of children aged 6 to16 years suffers from at least two episodes of headache each month[2]; only 30% of these children is seen by a physician. In most cases the parents give the child a simple analgesic, put the child to bed, or take other measures to give the child some rest. If the child is seen by a physician, it is usually a general practitioner (GP). Children with migraine are more inclined to consult a physician than children with tension type headache (TTH); this is because children with migraine have more alarming symptoms and treatment by the parents with the measures mentioned above is often insufficient. A relatively small percentage of the children with headache seen by the GP is referred to a specialist who can be a paediatrician, neurologist or paediatric neurologist. Children with migraine tend to be overrepresented in the group of children referred[2].

An important outcome measure for effectiveness of treatment is Quality of Life (QoL), which reflects the impact of disease and treatment on a subjective evaluation by the patient (or, in the case of children, by the parents) of the patient's physical functioning and emotional well-being[3-5,9]. QoL studies in children with headache and migraine are either population based[2,9,10] or hospital based[11,12,16]. In both types of study, but particularly in the hospital-based ones, children with headache had significantly lower QoL scores than healthy children. Compared to children with chronic illness (such as rheumatic disorders or cancer) their QoL was similar with respect to impairments in school and emotional functioning. All the hospital-based studies were conducted in tertiary headache centres[11,12,16]; these studies indicate that children with headache have a comparable QoL to children with a chronic illness.

The present study aimed to measure the QoL in children with primary headache presented in an outpatient paediatric department in a general (non-academic) hospital to obtain information on the severity of headache as perceived by the children and their family. It is of clinical interest to compare the QoL in children with migraine with that in children with TTH. In addition, we compared the QoL in children with migraine and TTH with that in the normal population. It was hypothesized that the children with primary headache would

report a lower QoL than healthy children.
In the QoL studies performed in tertiary headache centers, the QoL in children with primary headache was comparable to that in children with chronic illnesses such as cancer or rheumatic disorders[11,12,16]. As attention deficit hyperactivity disorder (ADHD) and asthma are also conditions such as headache, but not as severe as cancer and rheumatic disorders, we found it of additional clinical interest to compare the QoL in children with primary headache with that in children with one of these two chronic afflictions. Therefore, we decided to compare our data with a cohort of children with asthma and ADHD in the USA who were previously investigated with the same QoL questionnaire. It was tested whether there is a significant difference in their QoL compared with that of children with primary headache.

MATERIAL and METHODS

Patients

A consecutive series of 70 children referred (between October 2003 and October 2005) because of primary headache complaints by their GP to the outpatient Department of Paediatrics of the Vlietland Hospital participated prospectively in this study after informed consent was obtained. Headache diagnosis and classification were obtained using the criteria of the International Headache Society (IHS)[13].
With regard to the control group, the study population consisted of 353 schoolchildren in grades 3 to 8 (aged 5-13 years) at three representative elementary schools in Rotterdam, the Netherlands[9]. In both the headache and control group we used the original database for statistical analysis. The ADHD cohort consisted of 83 children who were treated at the behavioural neurology clinic at Sargent College, Boston University, USA[7,18,19,20]. Finally, the QoL data of the asthma cohort were collected from a baseline pharmaceutical study among 158 children with asthma in the USA[7]. In both the ADHD and asthma group we could only use the summarized published data for statistical analysis in this study.

Procedure

In case of the children with primary headache, a thorough history was taken and a complete physical and neurological examination was performed. The Dutch version of the Child Health Questionnaire (CHQ-PF50 Dutch edition)[9] was handed over to the parents or guardians; they were asked to complete it at home and return it at the next visit. For both children and adolescents the parents filled in the questionnaire, which is understandable

given the cognitive developmental level of the included children (11 years or less) that does not permit the abstract formal thinking required for answering quality of life questions. To obtain uniformity in the way the answers were given, we also asked the parents of children older than 12 years to complete the questionnaires. No rewards or other response-increasing policies were applied. To ensure accuracy, the questionnaire was reviewed at the next visit at the outpatient department. At that occasion, if the forms were not returned completely filled out or not filled out at all, the parents or guardians were asked to complete the form during the visit. All questionnaires were filled out completely without any dropouts. All parents were able to read and write Dutch. The data were stored in a database. Only children with primary headache as defined by the International Headache Society (IHS) criteria[13] were included. Children with secondary headache were excluded. There were no other exclusion criteria.

With regard to the control group, the teachers of each class distributed the health questionnaires to the children, to be handed over by them to their parents (or guardians). The children were required to return the forms within two weeks. No rewards or other response-increasing policies were applied. The two criteria for eligibility for analysis were: 1) the parent's ability to read and write Dutch, and 2) at least an 80% response on the CHQ items[9].

The QoL data of the children with ADHD were gathered using two modes of administration (in site completion and mail-out/mail back) at the behavioural neurology clinic where they were treated. A diagnosis of ADHD as defined by DSM-III-R criteria was the primary eligibility criterion[7,18,19,20]. The eligibility criteria in the asthma cohort were: 1) suffering from asthma in accordance with the American Thoracic Society definition of asthma, and 2) using asthma pharmacotherapy daily for at least 3 months prior to screening[7].

Measures

We decided to measure QoL with the CHQ because this questionnaire has already been administered in chronically ill children[7-9]. The CHQ was translated into Dutch in 2001 according to international guidelines[8,9,14,15]. This translated version has previously been validated; the internal consistency [(Cronbach alpha on average 0.72 for the domains (range 0.39-0.96)] appeared to be adequate and the test-retest reliability good[9]. This version was further validated by measuring the QoL in 353 healthy Dutch schoolchildren from the same region in which the present study was performed[9]; this latter validation study provided the data on the QoL in healthy children.

The CHQ-PF50 comprises 50 items over 11 multi-item scales or domains, and two single-item questions[7-9]. The life domains not only give insight in the QoL of the child itself, but

also in the impact of the disease of the child on his or her parents and family (see Table 1 for the separate subscales). Each CHQ domain consists of 3 to 6 items with 4, 5 or 6 possible responses per item. According to the CHQ User's Manual, the domain item scores have to be recoded, recalibrated and finally summed. The final score may range from 0 (worst possible health state) to 100 (best possible health state)[7].

Statistical Analysis

Analyses were performed using the statistical programme SPSS for Windows, for which the syntax was developed with help of the CHQ User's Manual[7]. The QoL data of the children with primary headache were compared with the QoL data of the control group, and with the statistics from the cohort of children with asthma or with ADHD as given in the CHQ manual[7,18,19,20]. To test for differences, two-way ANCOVA and one-way ANOVA were used, respectively.

RESULTS

Demographics

This study evaluated 70 children (37 male, 33 female). Their age ranged from 4 to 17 years, the mean age was 10.6 years (SD ± 3.2 years), and 72.8% of them were aged between 8 and 14 years. Headache diagnosis based on the IHS criteria was TTH only (n = 25), migraine only (n = 36), and chronic tension type headache (n = 7). Two children had both migraine and TTH. The control group included 353 children; their age ranged from 5 to 13 years of age. The mean age was 8.8 years (SD ± 1.9 years); 52% were girls[9].

The ADHD cohort consisted of 83 children. Their age ranged from 6 to 13 years, the mean age was 11 years (SD ± 2.3 years) and 81% was male[7,18,19,20]. The asthma cohort consisted of 158 children with an age range from 4 to 11 years and a mean age of 9 years; 69% was male[7].

CHQ Scores

Children with primary headache compared with healthy children

Table 1 presents the means and standard deviations (SD) for each subscale of the CHQ for children with primary headache compared with healthy children, using ANCOVA analysis with adjustment for gender and age. On all subscales there was a significant difference

(p<0.05) between the children with primary headache and the healthy controls, with the exception of the domain self-esteem (p = 0.34).

Table 1 CHQ-PF50: Children with primary headache compared with healthy children, and with children with asthma or with ADHD

QoL-subscales	Primary headache (n = 70)		Healthy children (n = 353)		Asthma (n = 178)		ADHD (n = 83)	
	mean	sd	mean	sd	mean	sd	mean	sd
Global Health	61.8	20.9	85.8*	20.6	na	na	na	na
Physical Functioning	82.0	10.0	98.9*	9.3	85.5	10.3	96.7#	12.2
Role/Emotional/ Behavioural	83.3	13.3	97.4*	12.7	91.3#	15.1	68.7#	30.0
Role/Physical	70.2	20.0	95.5*	20.6	86.5#	19.4	96.8#	14.7
Bodily Pain	55.6	19.2	85.6*	18.6	75.5#	20.3	85.1#	19.4
Behavior	57.6	13.3	78.4*	13.1	72.4#	15.7	54.5	17.3
Mental Health	36.6	14.9	81.1*	14.4	78.1#	12.3	66.8#	15.6
Self-Esteem	77.3	11.7	78.8	11.4	82.4#	14.6	62.6#	19.5
General Health Perception	65.9	16.2	82.6*	15.5	56.3#	17.7	81.7#	19.0
Parental Impact Emotional	77.0	16.7	86.3*	16.3	71.1	21.7	58.5#	18.8
Parental Impact Time	30.1	15.8	93.9*	15.7	81.6#	19.1	72.9#	21.8
Family Activities	83.6	14.2	91.3*	13.8	na	na	62.1#	24.1
Family Cohesion	38.7	20.9	71.9*	20.6	na	na	na	na

*significant difference (p< 0.05; two-sided) measured by two-way ANCOVA test
#significant difference (p< 0.05; two-sided) measured by one-way ANOVA test
QoL, quality of life; sd, standard deviation; ADHD, attention deficit hyperactivity disorder; na, not available

Children with primary headache compared with children with chronic illness

Table 2 presents the means and standard deviations for each subscale of the CHQ for children with primary headache compared with the cohort of children with asthma or with ADHD, respectively. In the groups of children with asthma and ADHD the scores were not adjusted for demographic variables (e.g. proportion of males and females and age distribution) because we did not have the original databases at our disposal.

Children with migraine compared with children with tension type headache

Table 2 presents the means and standard deviations for each subscale of the CHQ for children with migraine and with TTH. Excluded from this analysis were the children with chronic tension type headache or with two diagnoses. No significant differences were found between TTH and migraine on either subscale using ANCOVA analysis after adjustment for gender and age.

Table 2 CHQ-PF50: Children with migraine compared with TTH

QoL subscales	Migraine (n =36)		TTH (n =25)	
	mean	sd	mean	sd
Global Health*	61.1	27.6	72.3	28.5
Physical Functioning*	81.3	22.2	82.0	22.5
Role/Emotional/Behavioural*	78.8	24.6	85.3	24.0
Role/Physical*	64.8	31.2	71.1	31.0
Bodily Pain*	51.7	21.6	59.2	21.0
Behaviour*	55.6	13.2	58.3	13.0
Mental Health*	34.1	22.8	37.4	22.5
Self-Esteem*	73.6	13.8	79.6	13.5
General Health Perception*	65.9	19.2	64.8	19.0
Parental Impact Emotional*	76.4	18.6	76.7	18.0
Parental Impact Time*	32.8	25.8	28.2	24.5
Family Activities*	81.4	17.4	89.5	17.0
Family Cohesion*	34.6	22.8	37.6	22.5

* no significant difference (p= ns; two-sided) measured by two-way ANCOVA test
QoL, quality of life; sd, standard deviation; TTH, tension type headache

DISCUSSION

The QoL in our group of children with primary headache is significantly decreased on 12 of the 13 life domains of the CHQ compared with a group of healthy children from the same region after adjustment for gender and age. This is in agreement with our hypothesis and the studies of Powers and Nodari in which children with primary headache reported a lower QoL on all subscales compared with a cohort of healthy children[11,12,16]. No data were available regarding the presence of headache among the control group of children. Nevertheless, as the exclusion of these patients would have rendered the differences in QoL between our patient and control group even larger than found, this would not have influenced our conclusions.

QoL research in children is a rapidly expanding area and reports on the impact of various chronic diseases on paediatric and adolescent QoL are beginning to appear[12]. We measured QoL with a validated Dutch version of the CHQ[9]. The CHQ is not disease-specific; it provides information on a broad range of 13 life domains, whereas other clinical studies examined only six or nine domains[7,8,9,11,12,16]. The CHQ also gives insight into the burden placed on the family and parents of the child with primary headache, which is missing in the QoL measurement tools in other clinical studies as the PedsQL[11,12] and the QLH-Y[16].

From this study, the conclusion seems justified that a child with primary headache, severe enough to consult a specialist, places a heavy burden on its parents and brothers and sisters.
The data from this study allow us to conclude that the QoL of children with headache is very poor, with particular impact on the domains of mental health, parental impact time and family cohesion. The question arises whether this is the consequence of the headache of the child itself, or whether the headache is a consequence of the poor QoL. To address this question, longitudinal headache studies in children are needed with headache frequency and intensity as a primary outcome measure, and QoL as a secondary outcome measure, to evaluate how both outcome measures influence each other.

In contrast to most of the above-mentioned clinical studies, we measured QoL in children with TTH as well as with migraine[11,12,16]. Only Nodari et al.[16] have measured QoL with TTH and migraine in a tertiary headache centre using the Quality of Life in Youth Questionnaire (QLH-Y). This latter questionnaire was originally developed by Langeveld et al.[10] and was translated and validated for the Italian population; because there was no analysis tailored to the children with TTH and migraine, it was not possible to detect differences in QoL between them. In the present study we included 26 children with TTH and 36 children with migraine; no significant differences in QoL were found between them on any subscale after adjustment for gender and age. The average difference on the 13 variables in terms of Cohen's d between migraine and TTH patients was 0.15. In order to detect a difference of this size at a nominal level of significance $\alpha = 0.05$ (two-sided) and $\beta = 0.20$, the sample size required is 845 patients in both migraine and TTH patients. Assuming that the 13 variables can be adequately represented in two dimensions, the actual level of significance was $\alpha = 0.025$ (two-sided). Therefore, conclusions about the absence of differences in QoL between children with migraine and TTH have to be drawn with caution because of the low number of children in both groups and, consequently, the low power of this comparison**.** Nevertheless, we speculate that the absence of differences might be due to the system of health care in the Netherlands in which the GP is the key person in referring the child to an outpatient paediatric department. We believe that the most important factor in referral is this physician's perception of the burden placed on the child and its family as induced by the headache. Thus, it is not so much the type of headache that is the reason for referral, but rather the severity of the headache and its impact on the QoL of the child and its family.

We compared the QoL in children with primary headache with that of children in the USA with asthma or with ADHD. Due to absence of data on the subscale of global health and family cohesion, a comparison on these domains was not possible for children with asthma or with ADHD. Also, because there were no data on the subscale of family activities in the children with asthma, a comparison on this domain was also not possible.

In seven subscales (i.e. role/emotional/behavioural, role/physical, bodily pain, behaviour, mental health, self-esteem, and parental impact time) the QoL of the children with primary headache was significantly lower than that of children with asthma; on the subscales physical functioning and parental impact emotional no significant differences were found. On the subscale of general health perception, QoL was significantly higher in children with primary headache. Therefore, we conclude that QoL of children with primary headache is in general lower than in children with asthma.

The QoL of children with ADHD was on six subscales (i.e. physical functioning, role/physical, bodily pain, mental health, general health perception and parental impact time) significantly higher than in children with primary headache. The QoL of the subscales role/emotional/behavioral, self esteem, parental impact emotional and family activities was significantly higher in children with primary headache than in children with ADHD. There was no significant difference on the subscale behaviour between the groups. We conclude that QoL in children with primary headache is in general worse than in children with ADHD but is better with regard to impact on the family. Because of the different origins and cultural background of the children, and possible differences in the meaning of the items due to the different languages, any conclusions about the differences in QoL between children's primary headache on the one hand, and asthma and ADHD on the other, have to be drawn with caution. Also, the different clinical setting and the time elapsed since the study on QoL of children with asthma was performed (in 1994) may be of relevance. Furthermore, adjustment for differences in the demographic character of the samples was not possible because we did not have the original databases at our disposal. We have compared the QoL data of the boys in the headache group with the QoL data of the ADHD and asthma sample as both samples contained a relatively high percentage of boys (81 vs. 69%). We found no marked differences in comparison with the QoL data of the whole headache group. Therefore, we cautiously conclude that adjustment for gender in the ADHD and, to a lesser extent, in the asthma sample, will not substantially influence the original (ANOVA) data.

To gain more insight into the impact of different types of headache, a QoL study using the same questionnaire should be performed in children with ADHD, asthma and headache from the same outpatient department.

Finally, we believe that QoL is an important concept, not only to gain insight in the effect that a disease has on the emotional and physical well-being of a child and the impact on its family, but also to gain insight in the dynamic aspects of the disease or the response to treatment. There is a lack of longitudinal studies with QoL as outcome measure in the field of primary headache in children. More longitudinal studies with QoL as outcome measure are needed to gain more insight in the dynamic aspects of primary headache in children and especially on the relation between headache and QoL. With respect to treatment**,** every treatment or intervention has in general not only expected beneficial effects, but also adverse effects. Most intervention studies in this field (primary headache in children) usually describe the adverse effects as mild and safe. However, the simple description of the kind and number of adverse effects gives insufficient insight into the severity and appreciation by the child[17], combined with the beneficial effects of the intervention. QoL in these studies, measured on a broad range of life domains, combined with primary outcome measures as headache frequency and intensity, can provide this insight. Therefore we recommend that more QoL studies in this field should be performed, not only descriptive but also dynamic assessments, in which QoL is used as an outcome measure in intervention and longitudinal studies.

CONCLUSIONS

Headache is a common problem in childhood. The present study shows that in children with primary headache referred to a paediatric outpatient department of a Dutch general hospital, the QoL is considerably lower than the QoL of healthy controls. Also, we conclude from this study that a child with primary headache places a considerable burden on its parents and family. Within the group of children with primary headache, the QoL of children with TTH is similar to that in children with migraine. There are indications that primary headache in children affects QoL in a broader spectrum of life domains and to a larger degree than does asthma or ADHD.

ACKNOWLEDGEMENTS

The authors thank all the children and their parents who participated in this study. Special thanks go to the pediatricians in the Vlietland Ziekenhuis for their support and referral of the patients: Coby Langendoen M.D., Lia van Wijk M.D., Bert den Exter M.D., Arjan Pijning M.D., Esther Hentzen M.D., Brigitte de Bie M.D. and Evelyne van Boeckel M.D.

REFERENCES

1. Sillanpaa M; **Changes in the prevalence of migraine and other headaches during the first seven schoolyears.** Headache 1983;23:15-9.
2. Van Duijn N.P. et al; **Kinderen met Hoofdpijn (Children with Headache)**; Medisch Contact 2000;26:971-4.
3. Bandell-Hoekstra I, Abu-Saad HH, Passchier J, Knipschild P. **Recurrent headache, coping, and quality of life in children: a review.** Headache 2000;40:357-70.
4. World Health Organization. **Constitution of the World Health Organization Basic Documents.** Geneva, Switzerland: World Health Organization 1948.
5. Raat, H., Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. **Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples.** J Epidemiol Commun Health 2005;59:75-82
6. Testa MA, Simonson DC. **Assessment of quality-of-life outcomes.** N Engl J Med 1996;334:205-11.
7. Landgraf JM, Abetz L, Ware JE. **The CHQ User´s Manual.** Second Printing. Boston, MA. Health Act, 1999.
8. Landgraf JM, Maunsell, Speechley KN, Bullinger M, Campbell S, Abetz L, et al. **Canadian -French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results.** Qual Life Res 1998;7:433-45.
9. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. **Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index.** J Clin Epidemiol 2002;55:67-76.
10. Langeveld JH, Koot HM, Loonen MC, Hazebroek-Kampschreur AA, Passchier J. **A quality of life instrument for adolescents with chronic headache.** Cephalalgia 1996;16:183-96.
11. Powers SW, Patton SR, Hommel KA, Hershey AD. **Quality of life in pediatric migraine: characterization of age-related effects using PedsQL.** Cephalalgia 2004;24:120-7.
12. Powers SW, Patton SR, Hommel KA, Hershey AD. **Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses.** Pediatrics 2003;112:e1-e5.
13. **Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.** Headache Classification Committee of the International Headache Society. Cephalalgia 1988;8 (suppl. 7):1-96.
14. Guillemin F, Bombardier C, Beaton D. **Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines**. J Clin Epidemiol 1993;46:1417-32.
15. Ware JE, Keller SD, Gandek B, Brazier JE, Sullivan M. **Evaluating translations of health status questionnaires.** Methods from the IQOLA project. International Quality of Life Assessment. Int J Technol Assess Health Care 1995;11:525-51.
16. Nodari E, Battistella PA, Naccarella C, Vidi M. **Quality of life in young Italian patients with primary headache.** Headache 2002;42:268-74.
17. Damen L, Bruijn JK, Verhagen AP, Berger MY, Passchier J, Koes BW. **Symptomatic treatment of migraine in children: a review of medication trials.** Pediatrics 2005;116(2):e295-302.
18. Landgraf JM, Ware JE, Schor E, Davies AR, Rossi-Roh K (1993a, June 27). **Comparison of health status profiles for children with medical conditions: preliminary psychometric and clinical results form the Children's Health and Quality of Life Project.** Paper presented at 10th Annual Meeting of the Association for Health Services Research, Washington D.C.
19. Landgraf JM, Ware JE, Schor E, Davies AR, Rossi-Roh K (1993b, June 6) **Health profiles in children with psychiatric and other medical conditions.** Paper presented at 9th World Congress of Psychiatry, Rio de Janeiro, Brazil.
20. Landgraf JM, Ware JE, Rossi-Roh K (1993) **Measuring the Relative Health and Well-Being of Children with Attention Deficit Hyperactivity Disorder.** Results from the Children's Health and Quality of Life Project. (Final report to Ciba Geigy, Inc., Project MCS#447). Boston, MA: The Health Institute, New England Medical Center.

Chapter 5

Medium dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomized, double-blind, crossover trial

Jacques Bruijn, Hugo Duivenvoorden, Jan Passchier, Heiko Locher, Natascha Dijkstra, Willem-Frans Arts

Cephalalgia 2010 (e-Pub ahead of print)

ABSTRACT

Background: Riboflavin seems to have a promising effect on migraine in adults. The present study examines whether riboflavin has a prophylactic effect on migraine in children.
Objective: To investigate whether riboflavin in a dosage of 50 mg per day has a prophylactic effect on migraine attacks in young children.
Methods: This randomized, placebo-controlled, double-blind, crossover trial included 42 children (6 to 13 years) with migraine of which 14 children were also suffering from tension-type headache. Following a 4-week baseline period, all children received placebo for 16 weeks then riboflavin for 16 weeks (or vice versa) with a washout period of 4 weeks in between. The primary outcome measure was reduction in mean frequency of migraine attacks and tension-type headache in the last 4 weeks at the end of the riboflavin and placebo phase, compared with the preceding baseline or washout period. Secondary outcome measures were mean severity and mean duration of migraine and tension-type headaches in the last 4 weeks at the end of the riboflavin and placebo phase, compared with the preceding baseline or washout period.
Results: No significant difference in the reduction of mean frequency of migraine attacks in the last month of treatment was found between placebo and riboflavin ($p = 0.44$). However, a significant difference in reduction of mean frequency of headaches with a tension-type phenotype was found in favour of the riboflavin treatment ($p = 0.04$).
Conclusions: In this group of children with migraine, there is no evidence that 50 mg riboflavin has a prophylactic effect on migraine-attacks. We found some evidence that 50 mg riboflavin may have a prophylactic effect on interval headaches that may correspond to mild migraine attacks or tension type headache attacks in children with migraine.

INTRODUCTION

Migraine is a common disorder in adolescents and children. The prevalence of headache and migraine is age and gender dependent. Sillanpaa reported a prevalence of migraine for boys and girls at 7 years of age of 2.9% and 2.5%, respectively; at age 14 years the prevalence of migraine was 6.4% and 14.8% for boys and girls, respectively[1].
The efficacy of both pharmacological and non-pharmacological interventions in children and adolescents with migraine has been studied extensively[2-5]. Some interventions in the field of symptomatic treatment of migraine in children have been proven effective, such as sumatriptan nasal spray, ibuprofen and acetaminophen[2,5]. In the prophylactic treatment of migraine in children and adolescents, until now only flunarizine is an evidence-based effective drug, and probably also topiramate[4-6]. Adverse effects have been reported in both treatments. In addition, flunarizine is not available in the USA and both flunarizine and topiramate cannot be prescribed to children or adolescents in most European countries[4-6]. Other treatment modalities in this field (which are not evidence based) are antihypertensive medications, antidepressants, serotonergic drugs, 5-HT2-antagonists (such as pizotifen or methysergide) and antiepileptic drugs. However, in all of these agents adverse effects have been described[4,5]. Thus, there is a need for high-quality research to evaluate pharmacological prophylactic treatment that has minimal or no adverse effects in children and in adolescents with migraine.

From this perspective we were interested to examine riboflavin (vitamin B2). Riboflavin is a co-factor for the mitochondrial oxidative phosphorylation (OXPHOS) as it is the precursor for the flavin compounds necessary for the transfer of electrons in the mitochondrial energy cascade. In vivo studies have detected an impairment of OXPHOS in adult migraineurs between attacks[7-9]. Supra-physiological doses of riboflavin might be helpful in reducing this impairment. In patients with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, a subgroup had a reduced frequency of migraine attacks during treatment with riboflavin[10]. Therefore, riboflavin has been used as a prophylactic agent in studies on adults with migraine, including two open-label studies[11,14] and two randomized controlled trials[12,13]. In these latter trials, riboflavin was proven effective with minimal adverse effects. These adverse effects were diarrhoea (1 of 43 adults with migraine treated with riboflavin) and polyuria (1 of 43 adults with migraine treated with riboflavin)[12,13]. A common and harmless side effect of riboflavin is a bright yellow/orange discolouration of the urine.
At the time of the present study, no other trials were registered to investigate the effect

of riboflavin in children with migraine. Therefore, we decided to perform a placebo-controlled, randomized trial in children with migraine using riboflavin as the acting agent.

MATERIAL and METHODS

A 40-week, randomized, double-blind, crossover design was used to examine the effect of riboflavin compared with placebo in young children with migraine. The study was conducted in two hospitals in the Netherlands. The children were prospectively recruited between October 2005 and March 2008, and the trial was completed in December 2008. The children were referred by general practitioners (in the region of Schiedam/Vlaardingen) and by paediatricians, neurologists and paediatric neurologists in the greater Rijnmond region in the Netherlands.
All potentially referring physicians received an information letter about this trial. The children were assessed at the outpatient paediatric department of the Vlietland Hospital (in Schiedam/Vlaardingen) by the principal investigator (JB), and at the department of paediatric neurology of the Erasmus Medical Centre (EMC, Rotterdam) by the principal investigator (JB) and the co-investigators (ND and WFA).
Parental informed consent, and informed consent from children aged 12 years, was obtained. Headache diaries were composed in advance of the trial. The study was approved by the Medical Ethics Committees of the EMC and the Vlietland Hospital.

Patients

The inclusion criteria were:
1) age 6 to 13 years: we deliberately chose this age group because only a limited number of evidence-based interventions on this group are available[2-5]
2) migraine with or without aura according to the ICHD II criteria[15]
3) a frequency of two or more headache attacks per month

The exclusion criteria were:
1) epilepsy or other serious neurological disease
2) diseases of the liver or kidneys, and gastro-intestinal, metabolic or cardiovascular disease
3) use of other prophylactic medication for migraine within 1 month of the trial
4) use of other prophylactic treatment for migraine during the trial
5) inability to comply with the requirements of the trial, and/or inability to speak and read Dutch

Procedure and intervention

The pharmacy department of the EMC manufactured placebo and riboflavin capsules, the latter containing 50 mg riboflavin. To ensure the double-blind design, carotene 100 mg was used as placebo. Both carotene and riboflavin give an orange discolouration of the urine. A PubMed search confirmed the absence of evidence that carotene has any effect on headache frequency or intensity in children.

After a baseline period of 4 weeks, children were randomised in phase 1 to receive either one capsule containing placebo or 50 mg riboflavin daily for 16 weeks. Children were instructed to swallow the capsule at breakfast. Following a wash-out period of 4 weeks, in phase 2 the children received either one capsule containing placebo daily for 16 weeks if they had received riboflavin in phase 1, or one capsule of 50 mg riboflavin daily for 16 weeks if they had received placebo in phase 1. Treatment allocation was concealed from the participants and investigators for the duration of the study. The hospital pharmacists guarded the randomization key. To evaluate blinding, at the last visit parents were asked which treatment they believed that their child had received in which phase, and the reasons for their assumptions.

All children were primarily diagnosed with migraine by paediatric neurologists (JB or WFA). A thorough history was taken, and a complete neurological and physical examination was performed including measurement of blood pressure, body weight, height and skull circumference.

If the child was eligible for inclusion, the child and their parents were informed about all aspects of the trial and asked for their consent. They were informed that they could end their participation at any time during the trial without having to give any reason. No rewards or other response-enhancing policies were applied. A two-week period was allowed for the child/parents to consider possible participation in the study.

The parents of the children were asked to keep a detailed headache diary during all stages of the study. This headache diary documented every headache attack, including: the date, the severity of the headache on a 4-point Likert scale, its location(s), duration and nature (pulsating or non-pulsating), possible aggravation by routine physical activity, associated symptoms such as nausea or vomiting, and the presence or absence of photophobia or phonophobia or fever. The diaries were based on the ICHD-II criteria in order to enable classification of each headache attack as a migraine attack, tension-type headache, headache probably due to an (ear-nose-throat) infection, or a headache attack not fulfilling the ICHD-II criteria of any of these. Parents also completed questionnaires on behavioural problems and life dimensions of the children for a different research focus (not reported here).

All parents and children received information regarding childhood migraine, and all children were treated symptomatically according to state-of-the-art evidence-based guidelines[5,16]. This meant that, in case of a migraine attack, they received acetaminophen and ibuprofen orally or rectally, and sumatriptan nasal spray if they were 12 years old.
Children were given simple instructions on how to improve sleep duration and quality, i.e. to stop the intake of caffeine, and decrease the amount of time spent watching television or computering to a maximum of 2-3 hours a day.
Appointments with parents were made at the end of each stage. At each appointment the headache diary of the preceding stage was given by the parents to the paediatric neurologists (JB or WFA), and in return a new headache diary for the following stage was handed over to the parents. During the trial, halfway in both phase 1 and phase 2, paediatric neurologist JB or co-investigator ND, would hold a telephone conversation with the parents.
At each visit and each telephone appointment, the parents were consistently asked about any possible adverse effects of the medication. This was documented in the personal file of the child. To improve compliance during both phases of the study, parents and child were asked to bring the remaining tablets with them at each visit.
Three months after the conclusion of the trial all parents and children received a letter informing them when their child had received riboflavin or placebo, and the preliminary conclusions of the trial.

Outcome measures

The outcome measures were reduction in the mean frequency, mean severity and mean duration of migraine and tension-type headache in the last four weeks at the end of phase 1 and of phase 2 compared with the baseline and washout period, respectively.
Any adverse effects were documented and compared.

Statistical Analysis

Sample size calculations were based on a clinically relevant difference of 0.60 standard deviation (sd) between the riboflavin and placebo condition in favour of riboflavin with regard to migraine frequency in accordance with the data of the randomized controlled trial by Schoenen et al[12]. In addition, based on a crossover design, an α of 0.05 (two-sided) and a statistical power of 0.80, a minimum number of 20 patients was required to participate in the trial. To allow for dropouts 30 patients were initially enrolled, which was later extended to 42 to also allow for exploratory analysis.
Statistical analysis was performed according to the intention-to-treat principle.

As measures of central tendency, the means (for continuous data) and percentages (for categorical data) were estimated. In case of continuous data, the sd was used as measure of dispersion. To evaluate the effect of riboflavin on the outcome variables the t-test for independent observations was applied[17]. All statistical testing took place at the 0.05 level of significance.

We planned an exploratory analysis with regard to the effect of riboflavin vs. placebo on tension-type headache. We also planned an exploratory analysis in children with a relatively high baseline headache attack frequency vs. children with a relatively low baseline headache attack frequency.

RESULTS

Demographics

A total of 57 children were assessed for eligibility; 15 patients were not enrolled because they did not meet the inclusion criteria, or met one or more exclusion criteria, or because the parents or child refused to participate in the trial (Fig. 1).

Of the 42 children that were randomized, 20 were randomized to receive riboflavin during phase 1 and placebo during phase 2, whereas 22 children received placebo during phase 1 and riboflavin during phase 2. In this latter group, during the placebo phase, one child was lost to follow-up, the parents of two children withdrew their consent for further participation, and one patient proved to be suffering from headache due to medication overuse, discovered after careful study of her baseline headache diary. Both treatment groups had comparable demographic and migraine features (Table 1). Of the 20 children who were randomized to receive riboflavin in the first and placebo in the second phase, 10 (50%) were also suffering from tension-type headache. Of the 22 children who were randomized to receive first placebo and riboflavin in the second phase, 4 (18%) were also suffering from tension-type headache.

Outcome data

The outcome data are summarized in Tables 2a and 2b. No significant difference in the reduction of the mean frequency of migraine attacks in the fourth and last month of treatment was found between placebo and riboflavin ($p = 0.44$). However, we did find a significant difference in the reduction of the mean frequency of attacks of tension-type headache in favour of the riboflavin treatment ($p = 0.04$).

Fig. 1: The CONSORT* flow diagram showing the flow of participants.
*CONSORT indicates Consolidated Standard of Reporting Trials.

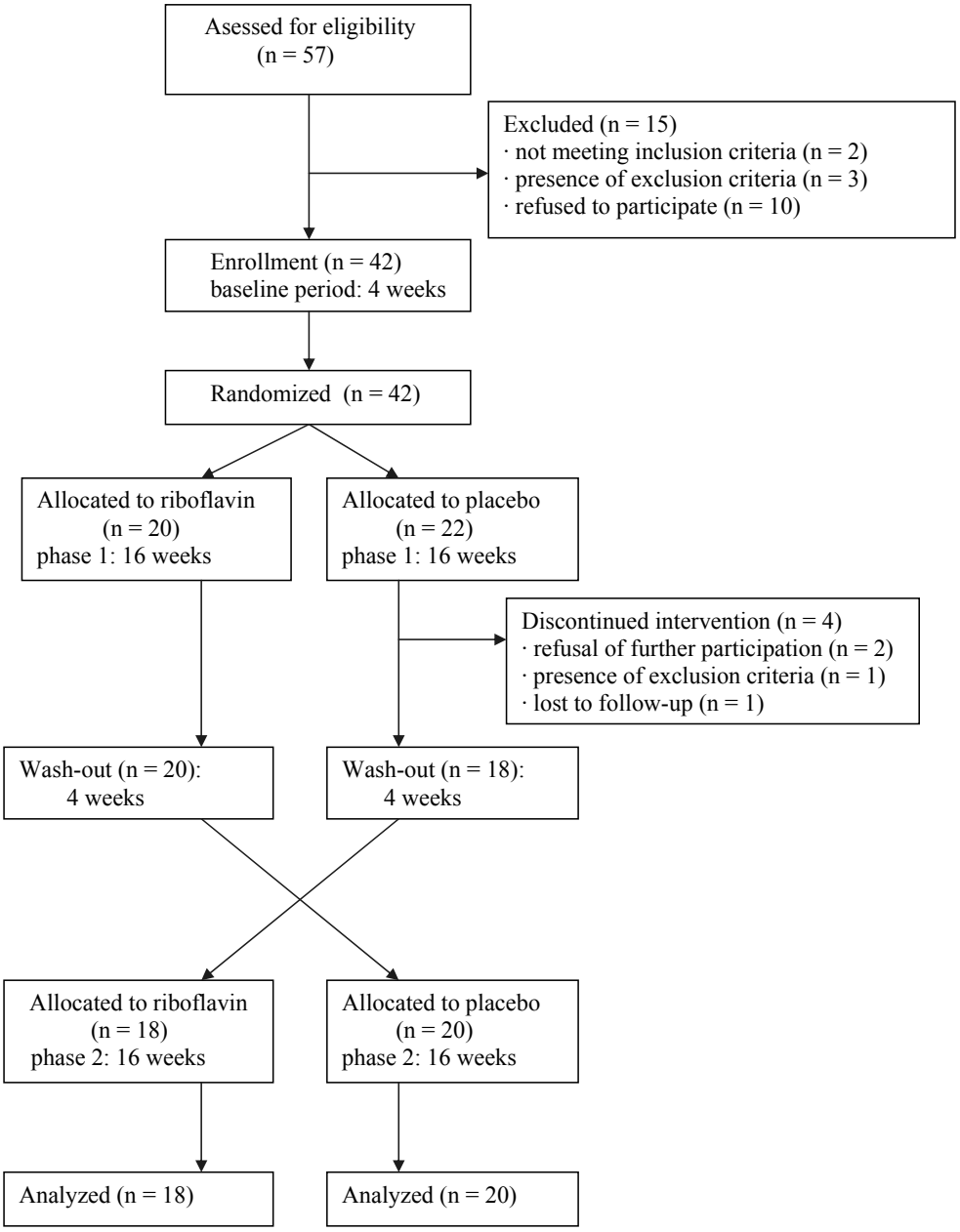


Table 1: Baseline demographic and clinical characteristics

Characteristic	riboflavin-placebo (n = 20)	placebo-riboflavin (n = 22)
Age in years (mean ± sd)	9.91 ± 1.89	9.50 ± 1.63
Male	12 (60%)	12 (54%)
Migraine with aura	9 (45%)	8 (36%)
Other headache types:		
Nil other than migraine	8 (40%)	15 (68%)
Tension-type headache	10 (50%)	4 (18%)
Headache by ENT infection	1 (5%)	0 (0%)
Other	3 (15%)	2 (9%)
Family history of migraine	16 (89%)	19 (95%)
Years since onset of migraine (mean ± sd)	3.06 ± 1.73	2.80 ± 2.14
Number of migraine attacks per month (mean ± sd)	3.60 ± 3.10	3.48 ± 5.41
Duration of migraine attacks in hours (mean ± sd)	2.45 ± 1.19	2.57 ± 1.54
Migraine prophylaxis used in the past	2 (10%)	4 (18%)
Use of paracetamol as symptomatic treatment	13 (65%)	17 (77%)
Use of ibuprofen as symptomatic treatment	4 (20 %)	6 (27%)
Use of sumatriptan as symptomatic treatment	4 (20%)	5 (23%)

sd, standard deviation

No significant difference was found in change or reduction of mean intensity of migraine attacks and tension-type headache attacks in the fourth and last month of treatment between placebo and riboflavin (p = 0.18 and did not apply, respectively). Also, no significant difference was found in change or reduction of mean duration of migraine attacks and tension-type headache attacks in the fourth and last month of treatment

between placebo and riboflavin (p = 0.15 and did not apply, respectively).
Analysis for a period or carry-over effect was performed on all outcome measures but proved to be inconclusive.
An exploratory analysis of attack frequency in children with a relatively high baseline frequency of 5 or more attacks per month, and in children with 4 or less attacks per month at baseline, revealed no significant differences in both of these categories between riboflavin and placebo with regard to migraine prophylaxis (p = 0.36 and p = 0.29, respectively).
During the trial no adverse effects were reported by parents or children; this was recorded in the patient files in both the riboflavin-placebo and the placebo-riboflavin group.

Table 2a. Data on headache frequency, intensity and headache duration in the last four weeks by riboflavin or placebo treatment

Parameter	Period 1 baseline			Period 1 end			Period 2 wash-out			Period 2 end		
	n	mean	sd	n	mean	sd	n	mean	sd	n	mean	sd
RP Migraine frequency (per 4 weeks)	20	3.60	3.10	**20**	**2.05**	**2.69**	*20*	*3.05*	*2.91*	*20*	*1.40*	*1.55*
RP TTH frequency (per 4 weeks)	20	1.35	1.56	**20**	**0.55**	**1.82**	*20*	*0.65*	*0.99*	*20*	*0.60*	*1.05*
PR Migraine frequency (per 4 weeks)	21	3.48	5.41	*18*	*1.61*	*1.42*	18	1.94	1.92	**18**	**2.00**	**2.35**
PR TTH frequency (per 4 weeks)	21	0.24	0.54	*18*	*0.33*	*0.59*	18	0.56	0.98	**18**	**0.17**	**0.38**
RP Migraine intensity (0-3)	19	1.85	0.54	**14**	**2.39**	**0.84**	16	2.28	0.75	*14*	*2.05*	*0.81*
RP TTH intensity (0-3)	10	1.08	0.92	**3**	**1.63**	**0.55**	9	0.67	0.71	*6*	*1.44*	*1.03*
PR Migraine intensity (0-3)	20	1.94	0.80	*13*	*1.85*	*0.88*	12	2.27	0.78	**13**	**2.08**	**0.82**
PR TTH intensity (0-3)	4	1.00	0.82	*5*	*1.00*	*1.00*	5	1.13	1.14	**3**	**1.33**	**1.15**
RP Migraine duration (in hours)	18	2.45	1.19	**13**	**3.08**	**1.23**	15	3.13	1.04	*13*	*2.93*	*1.07*
RP TTH duration (in hours)	9	3.00	1.36	**3**	**2.70**	**1.92**	10	1.50	1.38	*4*	*3.13*	*0.88*
PR Migraine duration (in hours)	20	2.57	1.54	*11*	*2.14*	*1.49*	11	2.76	1.40	**12**	**2.47**	**1.21**
PR TTH duration (in hours)	2	0.25	0.35	*4*	*0.87*	*0.62*	4	2.08	1.89	**3**	**1.50**	**2.32**

n, number of patients; sd, standard deviation; TTH, tension-type headache; RP, order riboflavin-placebo; PR, order placebo-riboflavin; bold numbers = after riboflavin treatment; italic numbers = after placebo treatment.

Table 2b. Analysis of headache frequency, intensity and duration in the last four weeks by riboflavin or placebo treatment

Parameter	Difference a period 1 (start-end)			Difference b period 2 (start-end)			difference a-b			testing	
	n	mean	sd	n	mean	sd	n	mean	sd	t-statistic	p
RP Migraine frequency (per 4 weeks)	**20**	**1.55**	**4.41**	*20*	*1.65*	*2.16*	20	-0.10	4.69	-0.79	0.44
RP TTH frequency (per 4 weeks)	**20**	**0.80**	**1.51**	*20*	*0.05*	*1.05*	20	0.75	1.86	2.12	0.04*
PR Migraine frequency (per 4 weeks)	*17*	*0.94*	*1.92*	**18**	**-0.06**	**1.83**	16	0.86	2.66		
PR TTH frequency (per 4 weeks)	*17*	*-0.06*	*0.97*	**18**	**0.39**	**0.98**	16	-0.43	1.50		
RP Migraine intensity (0-3)	**13**	**-0.62**	**0.78**	*12*	*0.34*	*0.81*	8	0.94	1.08	-1.47	0.18
RP TTH intensity (0-3)	**3**	**-0.70**	**0.69**	*4*	*-0.42*	*0.50*	3	-0.15	0.80	dna	dna
PR Migraine intensity (0-3)	*11*	*0.13*	*0.76*	**8**	**0.15**	**0.64**	5	-0.13	0.86		
PR TTH intensity (0-3)	*dna*	*dna*	*dna*	**dna**	**0.67**	**dna**	dna	dna	dna		
RP Migraine duration	**11**	**-0.71**	**1.26**	*10*	*-0.06*	*1.15*	6	-0.55	1.64	-1.58	0.15
RP TTH duration	**3**	**1.08**	**2.09**	*2*	*-1.71*	*1.47*	2	1.58	1.29	dna	dna
PR Migraine duration	*9*	*0.59*	*1.28*	**8**	**0.06**	**1.09**	5	0.68	0.89		
PR TTH duration	*dna*	*dna*	*dna*	**dna**	**1.33**	**dna**	dna	dna	dna		

n, number of patients; sd, standard deviation; TTH, tension-type headache; dna, did not apply; RP, order riboflavin-placebo; PR, order placebo-riboflavin; *, significant ($p < 0.05$); "-" indicates increase in mean score; "+" indicates decrease in mean score; bold numbers = difference between start and end of riboflavin treatment; italic numbers = difference between start and end of placebo treatment; t-statistic and p-value for difference between difference a-b for order of RP and PR, respectively.

DISCUSSION

With regard to prophylaxis of migraine attacks, there was no significant difference in the mean migraine frequency per 4 weeks (p = 0.44) or mean intensity of migraine attacks (p = 0.18) or mean duration of migraine attacks (p = 0.15) in the last four weeks of treatment between riboflavin and placebo. It could be argued that this result might be due to the fact that we had no upper limit for attack frequency as an exclusion criterion. In children, a high frequency of migraine or headache attacks, especially with an attack frequency of 15 headache attacks per month or more (the main diagnostic criterion for chronic migraine/headache), is often indicative of resistance to pharmacological prophylactic treatment[18]. Therefore, we also performed a separate exploratory analysis of attack frequency in children with a relatively high baseline frequency (5 or more attacks per month), and in children with a relatively low baseline frequency (4 or less attacks per month). In both of these categories no significant differences were found between riboflavin and placebo with regard to migraine prophylaxis.

Our conclusions are in line with those of MacLennan et al. who investigated 48 children with migraine aged 5 to 15 (mean 11.1 ± 2.1) years with a higher dosage of 200 mg riboflavin per day in a placebo-controlled, double-blind, randomized trial with a parallel group design[19]. This latter trial also reported no differences between riboflavin and placebo for primary or secondary outcome variables with regard to migraine prophylaxis. The trial of MacLennan et al. had an upper limit exclusion criterion of 8 migraine attacks per month. They recommended performing future studies with a crossover design, or with larger sample sizes. The fact that both our crossover study and that of MacLennan et al. showed no proof of effectiveness of riboflavin as a prophylactic agent in children with migraine is in contrast to the riboflavin studies conducted among adults with migraine[11-14].

The strength of our study is the double-blind, randomized, placebo-controlled, crossover design, which gives more statistical power than a parallel design. Of the 4 dropouts during the study, all were in the placebo-riboflavin group and dropped out during the placebo phase. It can be argued that this might be due to the lower effect of placebo compared with riboflavin. However, analysis of the other children in the riboflavin-placebo group showed a slightly better (non-significant) response to the placebo phase compared with the riboflavin phase.

A weakness of our study, on the other hand, could be the 50 mg per day dosage of riboflavin. Riboflavin has been used as a therapeutic agent in various mitochondrial diseases in

children and adolescents, such as the NADH-CoQ Reductase Deficient Myopathy and the Mitochondrial Encephalopathy and Stroke studies[10,20]. In these latter studies riboflavin was given in doses approximately 100-fold higher than the normal dietary intake, e.g. between 100 and 300 mg per day. These dosages were well tolerated without adverse effects (except for nausea) and sometimes yielded striking improvement[20].

Before the start of our study, three trials in adults with migraine (all using 400 mg riboflavin per day) had suggested a dosage of 100-200 mg per day for children[12-14]. However, shortly before the start of our trial, Maizels et al. demonstrated no significant difference between a combination of high-dose riboflavin, magnesium and feverfew in comparison with a low dose (25 mg) of riboflavin acting as placebo in adults with migraine, suggesting an equivalent effect of low-dose riboflavin versus high-dose riboflavin[21]. Therefore, we decided to treat our 6 to 13-year-old patients with a dosage of 50 mg riboflavin, which is relatively low compared with the dosage used in mitochondrial diseases and in riboflavin studies in adults with migraine.

On the other hand, if one assumes that children have a much higher metabolic rate than adults, the maximum dosage of riboflavin in children should be even higher than in adults to obtain a similar effect. From this perspective, our attention was drawn to the recent publication of Condò et al.[24] which describes a retrospective open-label study in 41 children or adolescents with migraine who were treated with 200 mg or 400 mg riboflavin on a daily basis for three to six months. In that study, 68.4% of the included children had a reduction of 50% or more in the frequency of all headache attacks. Statistical analysis showed no significant differences between frequency/intensity responders for a 200 or 400 mg/day dose. However, in that study no placebo group was included and treatment was not concealed, which are essential factors for assessing study quality.

Another point for discussion could be the duration of 16 weeks of each treatment period, and the analysis that was limited to the last 4 weeks of both phases of the study. This set-up was based on the original riboflavin trial of Schoenen et al. among adults with migraine. In that study, the maximal effect of riboflavin was seen in the fourth month of treatment[12].

In addition, the relatively small number of participants might be a factor explaining the negative results of our trial. However, our power estimation was according to standard criteria. Future studies using a randomized controlled parallel group design according to IHS guidelines, should employ a larger sample size.

One can also argue that, based on the low percentage of children receiving migraine prophylaxis in both the riboflavin-placebo and the placebo-riboflavin group (10% and 18%, respectively), the effectiveness of riboflavin was less significant due to the limited

severity of the headache symptoms in the included children. However, in our opinion these low percentages of migraine prophylaxis at inclusion do not mean that the severity of symptoms was less significant. First of all, the included children were relatively young (6-13 years) and migraine has a relatively low prevalence in pre-pubertal children compared with adolescents and adults. Therefore, most children in our study had a relatively short history of migraine. Secondly, most children were included after their first consultation with a specialist to whom they were referred by the general practitioner (GP) because of their headache; in the Dutch healthcare system the GP is the key person for referral to a specialist. Referral to, or consultation with a specialist is advised in the national Dutch guidelines for GPs if there is a need for prescribing symptomatic or prophylactic treatment in children with migraine. Finally, an earlier study from our group showed that the quality of life is very poor in children with migraine and tension-type headache at their first visit to one of the two hospitals which were also used for inclusion and follow-up procedures in the present study[25]; this suggests that GPs in the Netherlands tend to refer only children with a high burden of headache or migraine. It is for these reasons that most of the children in the present study did not receive prophylactic treatment, and not because of limited severity of their headache symptoms.

A final drawback is that, in all trials among children with migraine (both for acute treatment and migraine prophylaxis), a high placebo response made it difficult to prove the efficacy of a verum drug[22]. This will also apply to our study, especially since all children were given simple instructions about improving sleep quality and duration, stopping intake of caffeine, and decreasing the amount of time spent watching television or computering (besides receiving state-of-the-art evidence-based symptomatic treatment), which undoubtedly increased the placebo response in all the included children.

In addition, an interesting hypothesis that might explain our negative findings is related to the mitochondrial DNA make-up of our patients.

A recent pharmacogenetic study in adults with migraine showed that patients with non-H mitochondrial DNA haplotype respond better to treatment with riboflavin than patients with H-mitochondrial DNA haplotype[23]. To investigate if this is a significant factor, mitochondrial DNA analysis should be performed and the presence of non-H or H-haplotype mitochondrial DNA should be taken into account in the analysis of our data.

In summary, with regard to effectiveness, based on our present study, the study of Condò et al.[24] and the study of MacLennan et al.[19], we conclude that, at this moment, there is inconclusive evidence for the effectiveness of riboflavin on migraine attacks in children or adolescents with migraine.

With regard to safety, in our present study none of the included children experienced adverse effects. In the study of Condò et al.[24], two patients experienced vomiting and increased appetite, respectively, during riboflavin treatment. This was most likely unrelated to the use of riboflavin. In the study of MacLennan et al.[19], none of the children on riboflavin experienced adverse effects. Therefore, one can now conclude that riboflavin in dosages up to 400 mg daily for a period of several months can be safely used in children with migraine.

Finally, we found some evidence that riboflavin may have a prophylactic effect on tension type headache in children with migraine.
Unfortunately, due to the low numbers of patients involved, calculation of significant differences between placebo and riboflavin as a prophylactic agent in tension-type headache with regard to the secondary outcome variables (mean intensity of headache attacks and mean duration of headache attacks) was not possible.
A prophylactic effect of riboflavin on tension-type headache has not yet been described either in adults or in children[11-14,19,24]. In these latter studies, headache frequency or migraine frequency was used as outcome variable and there was no separate analysis regarding tension-type headache or (other) non-migraine headache attacks.
Based on our study one might argue that a medium dose of riboflavin has a prophylactic effect on tension-type headache in children. From that perspective, one has to bear in mind that the tension-type headaches in our study were an accompanying phenomenon in children with migraine as their main primary headache. Also, at baseline the total number of children with both migraine and tension-type headache in both groups (riboflavin-placebo and placebo-riboflavin) was low, especially in the placebo-riboflavin group (50% and 18%, respectively).
In addition, one can speculate about the nature of accompanying tension-type headaches in children with migraine, especially since the Spectrum Study of Lipton et al. provides evidence that all headache attacks in adults with migraine more or less represent a spectrum of migraine headaches[26]. If one assumes that this is also the case in children, based on the present study one might conclude that riboflavin in a low dose reduces mild, but not severe, headaches in migrainous children. Therefore, caution is required when drawing conclusions about the prophylactic effect of riboflavin on tension-type headache in children. However, this is the first study giving indications that riboflavin can diminish tension-type headache in children with migraine compared with a placebo intervention. To investigate if riboflavin indeed has a primary effect on tension-type headache in children or adults, more placebo-controlled, randomized, double-blind trials need to be

performed in children or adults with primary tension-type headache with and without migraine.

CONCLUSIONS

The present study shows that riboflavin in a dosage of 1 dd 50 mg has no effect on migraine prophylaxis in young children with migraine compared with placebo.
Currently, there is inconclusive evidence that riboflavin has a prophylactic effect on migraine attacks in children. However, in this study we give evidence that riboflavin may have a prophylactic effect on interval headaches that may correspond to mild migraine attacks or tension-type headaches in children with migraine. More studies are needed to investigate whether the same prophylactic effect of riboflavin on migraine as seen in adults can be achieved in children. More studies are also needed to investigate the effect of riboflavin on tension-type headache, both in children and adults with and without migraine.

ACKNOWLEDGEMENTS

The authors thank all the children and their parents who participated in this study.
Special thanks go to the pediatricians in the Vlietland Hospital for their support and referral of patients: Coby Langendoen MD, Lia van Wijk MD, Bert den Exter MD, Arjan Pijning MD, Esther Hentzen MD, and Evelyne van Boeckel MD. Also, special thanks to Sjaan Scholten, physician's assistant at the paediatric outpatient department of the Vlietland Hospital.
The authors thank the management of the Vlietland Hospital for their support, especially Gerrit-Jan van Zoelen.
The authors also thank the referring paediatricians, neurologist and paediatric neurologists, especially P. de Laat, J. Samijn, A. van Rossum, R. van der Lee, D. Kamphuis, B. Koop and C. de Korte. In addition, special thanks to Loes Visser and Hong San Lau, chief pharmacist of the pharmacy department of the Erasmus Medical Centre and the Vlietland Hospital, respectively.

This study was sponsored by the Nuts-Ohra Foundation, the Nolet Foundation and Van Der Linden Strukton.

REFERENCES

1. Sillanpaa M. **Changes in the prevalence of migraine and other headaches during the first seven schoolyears.** Headache 1983;23:15-9.
2. Damen L, Bruijn JK, Verhagen AP, Berger MY, Passchier J, Koes BW. **Symptomatic treatment of migraine in children: a review of medication trials.** Pediatrics 2005;116(2):e295-302.
3. Damen L, Bruijn J, Berger M, Passchier J, Koes W, Verhagen A. **Prophylactic treatment of migraine in children. Part 2: a systematic review of non-pharmacological trials.** Cephalalgia 2006;26(4):373-83.
4. Damen L, Bruijn J, Berger M, Passchier J, Koes W, Verhagen A. **Prophylactic treatment of migraine in children. Part 1: a systematic review of pharmacological trials.** Cephalalgia 2006;26(5):497-505.
5. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. **Practice parameter: pharmacological treatment of migraine headache in children and adolescents.** Neurology 2004;63:2215-24.
6. Lewis D, Winner P, Saper J, Ness S, Polverejan E, Wang S, Kurland C, Nye J, Yuen E, Eerdekens M, Ford L. **Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age.** Pediatrics 2009;123:924-34.
7. Welch KM, Levine SR, D'Andrea G, Schultz LR, Helpern JA. **Preliminary observations on brain energy metabolism in migraine studied by in vivo phosphorus 31 NMR spectroscopy.** Neurology 1989;39:538-41.
8. Barbiroli B, Montagna P, Cortelli P, Funicello R, Iotti S, Monari L, Pierangeli G, Zaniol P, Lugaresi E. **Abnormal brain and muscle energy metabolism shown by 31P magnetic resonance spectroscopy in patients affected by migraine with aura.** Neurology 1992;42:1209-14.
9. Montagna, P, Cortelli, P, Monari, L, Pierangeli G, Parchi P, Lodi R, Iotti, S, Frassineti C, Zaniol P, Lugaresi, E, Barbiroli B. **31P-magnetic resonance spectroscopy in migraine without aura.** Neurology 1994;44:666-9.
10. Panetta J, Smith L, Boneh A. **Effect of high-dose vitamins, coenzyme Q and high-fat diet in paediatric patients with mitochondrial diseases.** Journal of Inherited Metabolic Disease 2004:487-98.
11. Schoenen J, Lenaerts M, Bastings E. **High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study.** Cephalalgia 1994;14:328-9.
12. Schoenen J, Jacquy J, Lenaerts M. **Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial.** Neurology 1998;50:466-70.
13. Sándor P, Áfra J, Ambrosini A, Schoenen J. **Prophylactic treatment of migraine with ß-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.** Headache 2000;40:30-5.
14. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl K, Arnold G. **High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre.** European Journal of Neurology 2004;11:475-7.
15. Headache Classification Committee of the International Headache Society. **The international classification of headache disorders.** Cephalalgia 2004:24:1-160.
16. Evidence Based Guideline **"Migraine in Children"** as part of Dutch National Guideline **"Pain Measurement and Treatment in Children"**; J. Bruijn, R. Gooskens, A. Verhagen, L. Damen, J. Passchier; on-line publication March 2008:53-65. (http://www.nvk.pedianet.nl/pdfs/nvk_richtlijn_pijn_bij_kinderen.pdf).
17. Stephen Senn: **Cross over Trials in Clinical Research 2nd edition**; Statistics in Practice; Wiley; ISBN 0 471 49653 7:41-7.
18. Rothner A, Linder S, Wasiewski W, O'Neill K. **Chronic nonprogressive headaches in children and adolescents.** Seminars in Pediatric Neurology 2001;8:34-9.
19. MacLennan S, Wade F, Forrest K, Ratanayake P, Fagan E, Antony J. **High-dose riboflavin for migraine prophylaxis in children; a double-blind, randomized, placebo-controlled trial.** Journal of Child Neurology 2008;23:1300-4.
20. Arts W, Scholte H, Boogaard J, Kerrebijn K, Luyt-Houwen I. **NADH-CoQ reductase deficient myopathy: successful treatment with riboflavin.** Lancet 1983;2:581-2.

21. Maizels M, Blumenfeld A, Burchette R. **A combination of riboflavin, magnesium and feverfew for migraine prophylaxis: a randomized trial.** Headache 2004;44:885-90.

22. Evers S, Marziniak M, Frese A, Gralow I. **Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies.** Cephalalgia 2009;29:436-44.

23. Di Lorenzo C, Pierelle F, Coppola G, Grieco G, Rengo C, Ciccolella M, Magis D, Bolla M, Casali C, Santorelli F, Schoenen J. **Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs.** Neurology 2009;72:1588-94.

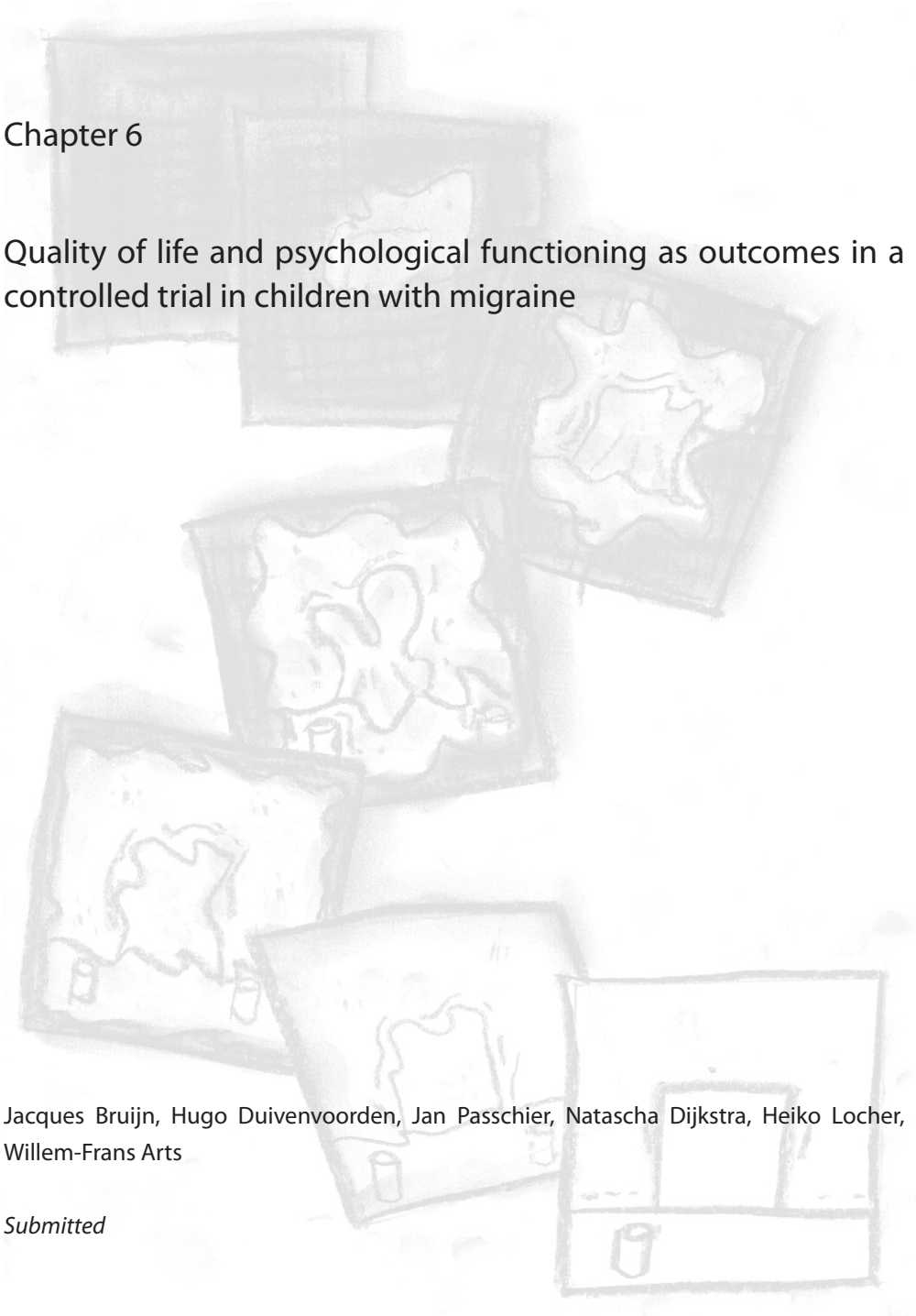
24. Condò M, Posar A, Arbizzani A, Parmeggiani A. **Riboflavin prophylaxis in pediatric and adolescent migraine.** Journal of Headache and Pain 2009;10(5):361-5.

25. Bruijn J, Arts W-F, Duivenvoorden H, Dijkstra N, Raat H, Passchier J. **Quality of life in children with primary headache in a general hospital.** Cephalalgia 2009;29:624-30.

26. Lipton R, Cady R, Stewart W, Wilks K, Hall C. **Diagnostic lessons from the Spectrum Study.** Neurology 2002;58(Suppl 6):S27–S31.

Chapter 6

Quality of life and psychological functioning as outcomes in a controlled trial in children with migraine



Jacques Bruijn, Hugo Duivenvoorden, Jan Passchier, Natascha Dijkstra, Heiko Locher, Willem-Frans Arts

Submitted

ABSTRACT

Background: Several descriptive clinical studies have reported poor quality of life (QoL) and psychological dysfunctioning in children with migraine at referral to a specialist. QoL has been used as outcome in a few intervention studies in children with migraine. Psychological (dys)functioning has not yet been used as outcome in intervention studies in childhood migraine. The present study examines whether a treatment directed at reducing headache attacks in children with migraine has a concomitant improving effect on QoL and psychological functioning.

Objective: To investigate whether riboflavin in a dosage of 50 mg per day has a favourable effect with regard to improving QoL and psychological functioning in children with migraine.

Methods: This randomized, placebo-controlled, double-blind, crossover trial included 42 children (6-13 years) with migraine. Following a 4-week baseline period, all children received placebo for 16 weeks then riboflavin for 16 weeks (or vice versa) with a washout period of 4 weeks in between. The outcome measures were QoL as measured with the Child Health Questionnaire (CHQ-PF50) and psychological functioning as measured with the Child Behaviour Checklist (CBCL) at the end of the riboflavin and placebo phase, compared with the preceding baseline or washout period.

Results: Riboflavin had no superior effect versus placebo in children with migraine with regard to improvement of QoL and psychological functioning on all investigated life domains and psychological subscales. At baseline the QoL was significantly worse on all 13 life domains compared with healthy controls. At baseline all CBCL scores were within the range of healthy controls with the exception of thought problems, somatic complaints and internalizing behaviour; the deviant scores on the latter two probably result from the migraine itself and are not a sign of psychological dysfunction. Throughout the trial there was an improvement on 11 of the 13 QoL domains and on all of the CBCL scales, leading to normalization of scores on the QoL domains mental health, self-esteem, parental impact emotional and parental impact time, and on all of the CBCL scales with the exception of somatic complaints.

Conclusions: In children with migraine QoL at referral to a specialist is poor, not because of psychological dysfunctioning but due to the disease itself. QoL and psychological functioning can be used as outcome in intervention studies on children with migraine. Compared with placebo, riboflavin has no superior effect on improvement of QoL and psychological functioning.

INTRODUCTION

Quality of life (QoL) and psychological functioning are important and related concepts in headache research, both in adults and children. QoL reflects the impact of disease and treatment based on a subjective evaluation by the patient (or, in the case of young children, by the parents) of their physical functioning and emotional wellbeing[1] whereas behavioural and psychiatric problems form an important outcome reflecting a key dimension within QoL, i.e. psychological functioning and wellbeing. In the past, when QoL measures were not available for children, behavioural problems have even been used as a proxy measure for QoL[2].

Several clinical studies have explored QoL in children with headache or migraine. In general, QoL measurement scales are divided into generic and disease-specific ones. Disease-specific QoL scales are designed for one specific group of patients and are used to detect changes induced by therapeutic interventions. Generic QoL questionnaires are applicable to all populations and diseases and are used to compare outcomes between them[3,4]. These questionnaires have up to 50 questions representing a maximum of 13 life domains, including the impact of headache on daily activities, cognitive functioning, social activities and emotional wellbeing, as well as on domains like physical functioning, self-esteem, bodily pain and the impact of headache on the patient's parents and family[5-9]. In general, these studies indicate that, compared with healthy children, children with headache or migraine have significantly lower QoL scores on all investigated life domains[5-9]. Compared to children with chronic illness (such as rheumatic disorders or cancer) their QoL is similar with respect to impairments in school and emotional functioning[6].

We previously investigated a group of children with primary headache (presenting at an outpatient department of a general hospital) using the generic Child Health Questionnaire (CHQ-PF50)[9]. The QoL in the group of children with primary headache was considerably lower than that of healthy controls on all of the 13 investigated life domains, with the exception of the domain self-esteem. Moreover, we found that a child with primary headache places a considerable burden on its parents and family. The QoL of children with tension type headache was similar to that of children with migraine. Furthermore, primary headache in children affected QoL in a broader spectrum of life domains and to a larger degree than does asthma or ADHD[9]. QoL has also been used as outcome in population studies among adolescents with headache; in these studies, an inverse correlation was found between QoL and severity of headache symptoms[10,11].

Studies in children with migraine indicate that an intervention that successfully decreases the burden of headache in these children has a concomitant beneficial effect on QoL[12,13]. In these latter studies the pedMIDAS was used as QoL questionnaire, providing information on a relatively limited number of life domains.

With regard to psychological functioning and psychiatric comorbidity, clinical and population studies have shown a relationship between headache and psychopathology in children. In these studies, various measurement tools were used.
Behavioural problems and psychological functioning were measured in subgroups of children suffering from different types of headache[14,15] or were compared with healthy children[16-21], children suffering from chronic fatigue[22] or recurrent pain due to other disorders[23]. One study had a longitudinal design[24], but most studies on psychological functioning in children with headache used a cross-sectional design. Because a substantial proportion of children with headache demonstrate psychological dysfunctioning, the question arises whether this can be influenced by an intervention directed at reducing headache attacks. To our knowledge, no intervention studies in children with headache or migraine have assessed psychological (dys)functioning or psychiatric comorbidity as outcome variable.

To address this question about the interdependency of migraine on the one hand, and psychological functioning and psychiatric comorbidity on the other, we performed a literature search to assess and describe the evidence from pharmacological randomized controlled trials (RCTs) and pharmacological clinical controlled trials (CCTs) concerning the relationship between headache and psychological (dys)functioning and/or psychiatric comorbidity in children with migraine. Four databases were searched (Medline, PsycINFO, Embase, Cochrane) which identified 2,007 potential trials. All these were screened on title and abstract for possible relevance, selecting only RCTs or CCTs in children/adolescents (aged 0-18 years) with migraine, with criteria designed to distinguish migraine from other types of headache, and with psychological (dys)functioning and/or psychiatric comorbidity as primary or secondary outcome variable. Based on these criteria only one article emerged[25]. This latter article describes a CCT comparing nadolol with topiramate as prophylactic therapy in adults and adolescents with migraine. The mean age of the participants was 37 years (range 16-56 years) and no separate analysis was made for adolescents. However, based on the mean age (and age range) of the patients we assume that few adolescents were included and that such an analysis would offer little value in terms of evidence to answer our research question.

In conclusion, the present literature search provided no evidence-based information on the relationship between headache on the one hand, and psychological (dys)functioning and/or psychiatric comorbidity on the other, in children with migraine in clinical intervention studies.

To establish whether reduction in migraine attacks is associated with changes in QoL, and psychological or psychiatric symptoms and signs during and after treatment, we performed a placebo-controlled, randomized, double-blind, crossover trial to investigate riboflavin as prophylactic agent in children with migraine with headache parameters, generic QoL and psychological functioning as outcome variables.

Our first aim was to investigate whether riboflavin has a superior effect compared with placebo in prophylaxis of migraine attacks in children: the results of this latter study have already been published[26]. The present study examines the effects of riboflavin treatment on generic QoL and psychological functioning in children with migraine.

MATERIAL and METHODS

A 40-week, randomized, double-blind, crossover design was used to compare the effects of riboflavin with placebo in young children with migraine. The detailed methodology has already been reported[26]. Parental informed consent was obtained; for children aged ≥12 years this was supplemented with their own personal consent. The Ethical Review Board of the participating hospitals approved the study.

Patients

Inclusion criteria were:

1) age 6-13 years
2) migraine with or without aura in accordance with the ICHD II criteria[27]
3) frequency of two headache attacks per month or more

Exclusion criteria were:

1) epilepsy or other serious neurological disease
2) diseases of the liver, kidneys, gastro-intestinal, metabolic or cardiovascular disease
3) use of other prophylactic medication for migraine within 1 month of the trial
4) use of other prophylactic treatment for migraine during the trial

Procedure

All children were prospectively recruited between October 2005 and March 2008; they were assessed at the outpatient paediatric department of a general hospital and at the paediatric neurology outpatient department of a university hospital.

At the first visit, the parents or caretakers were asked to complete the Child Health Questionnaire (CHQ-PF50, Dutch edition)[9,28] and the Child Behaviour Checklist (CBCL)[29] in its validated Dutch version[30] at home and return them before the start of the trial. Subsequent CHQ-PF50 and CBCL questionnaires were completed by the parents at the end of the first trial phase, the washout phase, and at the end of the second trial phase.

Intervention

The trial was performed with one dose of 50 mg riboflavin daily as the intervention drug and with one dose of placebo daily in a crossover design as described earlier[26]. All children were also treated symptomatically according to state-of-the-art evidence-based guidelines[31]. This meant that, in case of a migraine attack, they received acetaminophen and ibuprofen orally or rectally, and sumatriptan nasal spray if they were aged 12 years and older.

Children were randomized in a double-blind manner to receive 16 weeks placebo or riboflavin in phase 1. After a washout period of 4 weeks, the child received 16 weeks placebo in phase 2 if it had received riboflavin in phase 1, and 16 weeks riboflavin in phase 2 if it had received placebo in phase 1 (Fig. 1).

Outcome measures

The primary outcome measure was reduction in the mean frequency of migraine attacks and tension-type headache attacks in the last 4 weeks at the end of phase 1 and of phase 2 compared with the baseline and washout period, respectively[26]. Any adverse effects were documented and compared. In all stages of the trial, QoL as measured by the CHQ-PF50 Dutch edition, and psychological functioning as measured by the CBCL Dutch edition, were analyzed as secondary outcome measures.

Statistical Analysis

Sample size calculations were primarily based on calculations with regard to decrease in migraine frequency in the last 4 weeks of the riboflavin phases compared with the last 4 weeks of the placebo phases[26]. For this primary outcome measure, a minimum number of 20 patients was required for sufficient power; to allow for exploratory analyses we extended

this to 42 children. Statistical analysis of the CHQ-PF50 and CBCL data was performed according to the intention-to-treat principle. To evaluate the effect of riboflavin on the continuous outcome variables the t-test for independent observations was applied[32].
To statistically compare possible differences between the patients and healthy controls, data of our study population were compared with raw data of a group of 353 healthy children from the same region in which our study took place, who were previously investigated using the same questionnaire (Child Health Questionnaire CHQ-PF50, Dutch edition)[9,28] by performing an analysis of covariance (ANCOVA) with adjustment for gender and age. For the CBCL data, we performed an analysis of variance (ANOVA) using the published data of a group of 1,241 healthy children (aged 6-11 years) in the Netherlands who were previously investigated using the same questionnaire (CBCL, validated Dutch version)[30]. All statistical testing took place at the 0.05 level of significance (two-tailed).
Analyses were performed using the statistical programme SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

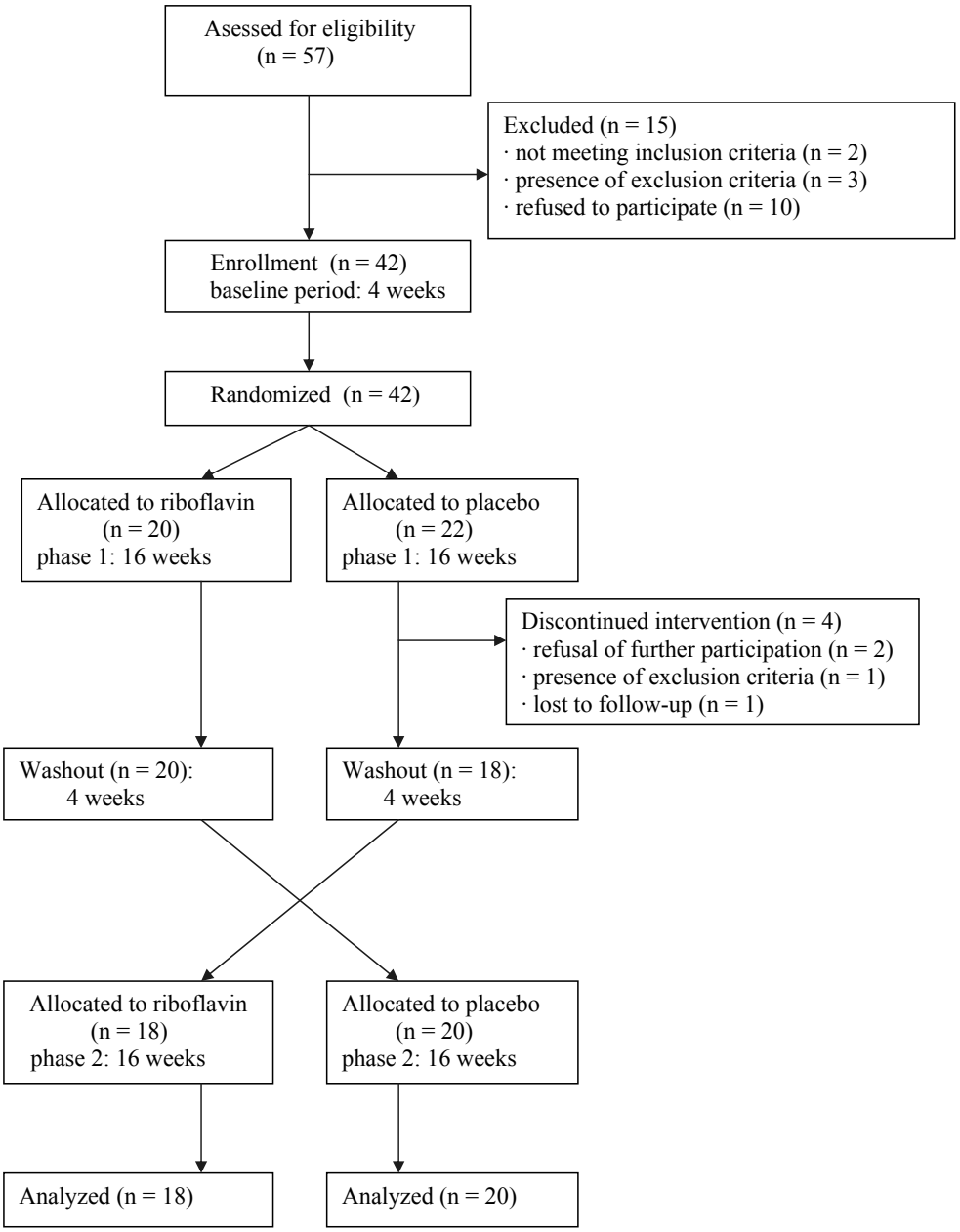
Demographics

A total of 57 children were assessed for eligibility. Of these, 15 patients did not meet the inclusion criteria, or met one or more exclusion criteria, or the parents or child refused to participate in the trial, and were therefore not enrolled (Fig. 1).
Of the 42 children that were randomized, 20 were randomized to receive riboflavin during phase 1 and placebo during phase 2, whereas 22 children received placebo during phase 1 and riboflavin during phase 2. In this latter group, during the placebo phase, one child was lost to follow-up, the parents of two children withdrew their consent for further participation, and one patient proved to be suffering from headache due to medication overuse (revealed after careful study of her baseline headache diary). Both treatment groups had comparable demographic and migraine features (Table 1).

Outcome data

The results concerning headache outcome have already been reported[26]. Briefly, no significant difference was found between the effects of riboflavin versus placebo in the prevention of migraine attacks, or in the severity or duration of the migraine attacks. A steady decrease in migraine frequency throughout the trial was found, both in the riboflavin-placebo group and in the placebo-riboflavin group.

Fig. 1: The CONSORT* flow diagram showing the flow of participants.



*CONSORT indicates Consolidated Standard of Reporting Trials.

Table 1: Baseline demographic and clinical characteristics

Characteristic	Riboflavin-Placebo (n = 20)	Placebo-Riboflavin (n = 22)
Age in years, mean (± sd)	9.91 ± 1.89	9.50 ± 1.63
Male	12 (60%)	12 (54%)
Migraine with aura	9 (45%)	8 (36%)
Other headache types		
Nil other than migraine	8 (40%)	15 (68%)
Tension-type headache	10 (50%)	4 (18%)
Headache by ENT infections	1 (5%)	0 (0%)
Other	3 (15%)	2 (9%)
Family history of migraine	16 (89%)	19 (95%)
Years since onset of migraine (mean ± sd)	3.06 ± 1.73	2.80 ± 2.14
Frequency of migraine attacks per month (mean ± sd)	3.60 ± 3.10	3.48 ± 5.41
Duration of migraine in hours (mean ± sd)	2.45 ± 1.19	2.57 ± 1.54
Migraine prophylaxis used in the past	2 (10%)	4 (18%)
Use of paracetamol as symptomatic treatment	13 (65%)	17 (77%)
Use of ibuprofen as symptomatic treatment	4 (20%)	6 (27%)
Use of sumatriptan as symptomatic treatment	4 (20%)	5 (23%)

sd, standard deviation

During the trial no adverse effects were reported by parents or children[26].

The QoL and CBCL outcome data are summarized in Tables 2a, 2b, 3a and 3b.

No significant differences were found between placebo and riboflavin on all investigated generic QoL domains (Tables 2a and 2b) or on all CBCL scales (Tables 3a and 3b). Since there were no superior effects of riboflavin with regard to placebo (or vice versa) on any

of the QoL or CBCL outcomes, we concluded that the riboflavin condition in fact acted as a placebo with regard to these outcomes. Therefore, we collapsed the data of the riboflavin-placebo group with the placebo-riboflavin group to gain more statistical power for comparison with the data of healthy children, both at baseline and at the end of the trial. The results of these analyses are given in Tables 4 and 5.
During the trial, an improvement of the generic QoL was observed in these combined data on the domains physical functioning, role/emotional/behavioural, role/physical, bodily pain, behaviour, mental health, self-esteem, general health perception, parental impact emotional, parental impact time, and family activities. No improvement was observed on the domains global health and family cohesion during the trial. Furthermore, at the start of the trial, on all QoL domains a significant difference ($p < 0.05$) was found between the included children and healthy controls as measured by ANCOVA, in favour of the healthy controls. At the end of the trial the QoL on four domains (mental health, self-esteem, parental impact emotional and parental impact time) was within the range of healthy controls as measured by ANCOVA.

With regard to psychological functioning, in the combined data of both the riboflavin-placebo and the placebo-riboflavin group there was an improvement on all CBCL scales.
Furthermore, at the start of the trial, on the CBCL subscales somatic complaints and thought problems and on the main scales internalizing behavior and total score, a significant difference ($p < 0.05$) was found between the included children and healthy controls as measured by ANOVA, in favour of the healthy controls. At the end of the trial the CBCL scores on the main scales internalizing behavior and total score were within the range of healthy controls. In addition, at the end of the trial, a significant difference ($p < 0.05$) in the score on the subscale somatic complaints was found in children with migraine versus healthy controls in favour of the healthy controls, despite improvement as measured by ANOVA. With regard to the subscale of aggressive behaviour and the main scale of externalizing behaviour, at the end of the trial the children with migraine had significantly favourable scores ($p < 0.05$) compared to healthy controls as measured by ANOVA.

Table 2a: Quality of life (CHQ-PF50), distinguished by riboflavin and placebo

QoL-subscales	Period 1 baseline			Period 1 end			Period 2 washout			Period 2 end		
	n	mean	sd	n	mean	sd	n	mean	sd	n	mean	sd
RP Global Health	20	56.67	24.42	**17**	**49.02**	**33.58**	20	60.00	27.78	*20*	*56.67*	*21.90*
RP Physical Functioning	20	81.33	27.62	**17**	**83.66**	**23.11**	19	85.09	19.60	*20*	*95.56*	*11.90*
RP Role/Emot/Behavioural	19	91.23	14.14	**16**	**95.14**	**13.44**	20	87.22	21.41	*20*	*92.78*	*14.98*
PR Role/Physical	19	70.18	23.29	**16**	**76.04**	**33.32**	20	80.83	21.81	*20*	*84.17*	*21.95*
RP Bodily Pain	20	51.50	21.83	**17**	**62.35**	**29.27**	20	61.50	23.46	*20*	*61.00*	*15.86*
RP Behaviour	20	61.80	12.34	**17**	**68.94**	**11.45**	20	63.80	16.02	*20*	*64.40*	*7.88*
RP Mental Health	20	75.25	15.93	**17**	**80.59**	**16.94**	19	81.05	15.86	*19*	*79.47*	*16.49*
RP Self-esteem	20	72.92	12.35	**17**	**76.47**	**16.92**	20	77.29	15.79	*19*	*76.75*	*12.21*
RP General Health Perception	20	70.04	19.82	**17**	**72.99**	**19.09**	20	69.92	16.69	*20*	*71.13*	*19.03*
RP Parental Impact Emotional	20	74.58	21.88	**17**	**84.80**	**20.67**	20	80.83	18.75	*20*	*84.58*	*14.63*
RP Parental Impact Time	20	83.89	21.17	**17**	**91.50**	**20.98**	20	92.78	16.23	*20*	*97.22*	*4.94*
RP Family Activities	20	77.50	15.67	**17**	**83.82**	**19.31**	19	82.68	20.14	*20*	*85.63*	*12.13*
RP Family Cohesion	20	38.75	18.98	**17**	**36.76**	**20.00**	19	36.84	19.31	*20*	*35.00*	*17.01*
PR Global Health	21	61.90	28.45	*17*	*64.71*	*18.52*	17	60.78	17.62	**18**	**57.41**	**25.06**
PR Physical Functioning	21	80.16	24.25	*17*	*84.31*	*22.67*	17	84.31	28.95	**18**	**86.42**	**24.20**
PR Role/Emot/Behavioural	21	82.54	29.10	*17*	*94.12*	*14.76*	17	94.77	14.23	**18**	**90.12**	**16.12**
PR Role/Physical	21	69.84	31.89	*17*	*78.43*	*26.20*	17	84.31	26.00	**18**	**88.89**	**18.96**
PR Bodily Pain	21	52.86	22.39	*17*	*65.29*	*23.48*	17	71.18	19.00	**18**	**67.22**	**19.34**
PR Behaviour	21	66.10	9.68	*17*	*68.47*	*11.99*	17	69.41	9.16	**18**	**70.44**	**9.62**
PR Mental Health	21	77.62	13.38	*17*	*81.47*	*12.96*	17	80.00	12.12	**18**	**83.33**	**14.65**
PR Self-esteem	21	75.40	12.00	*17*	*76.72*	*11.51*	17	75.74	13.11	**18**	**75.00**	**16.48**
PR General Health Perception	21	64.01	18.09	*16*	*68.49*	*20.89*	16	64.90	15.27	**18**	**66.06**	**18.03**
PR Parental Impact Emotional	21	67.86	23.61	*16*	*80.21*	*18.23*	16	82.29	15.48	**18**	**88.43**	**14.04**
PR Parental Impact Time	21	83.60	26.20	*16*	*88.19*	*14.89*	16	92.36	11.98	**18**	**92.59**	**9.34**
PR Family Activities	21	80.75	13.08	*16*	*78.13*	*18.54*	16	83.33	16.46	**18**	**86.34**	**16.09**
PR Family Cohesion	21	28.57	18.18	*16*	*35.94*	*18.19*	15	38.33	12.91	**18**	**27.78**	**20.81**

n, number of patients; sd, standard deviation; RP, order riboflavin-placebo; PR, order placebo-riboflavin; bold numbers = after riboflavin treatment; italic numbers = after placebo treatment.

Table 2b: Quality of life (CHQ-PF50), distinguished by riboflavin and placebo: statistical analysis

QoL-subscales	Difference a period 1 (start-end)			Difference b period 2 (start-end)			Difference a-b			testing	
	n	mean	sd	n	mean	sd	n	mean	sd	t-statistic	p
RP Global Health	**17**	**7.84**	**32.34**	*20*	*3.33*	*26.27*	17	0.00	44.10	0.17	0.87
RP Physical Functioning	**17**	**-4.31**	**35.00**	*19*	*-10.23*	*23.22*	17	5.16	42.08	0.38	0.71
RP Role/Emot/Behavioural	**15**	**-1.48**	**20.52**	*20*	*-5.56*	*27.57*	15	5.93	35.35	0.68	0.50
RP Role/Physical	**15**	**-3.33**	**32.85**	*20*	*-3.33*	*27.89*	15	1.11	46.06	0.06	0.95
RP Bodily Pain	**17**	**-10.00**	**32.98**	*20*	*0.50*	*25.02*	17	-10.59	44.23	0.30	0.77
RP Behaviour	**17**	**-6.35**	**9.80**	*20*	*-0.60*	*17.18*	17	-9.18	15.22	-1.29	0.21
RP Mental Health	**17**	**-5.00**	**13.58**	*18*	*3.61*	*17.05*	15	-11.33	27.68	-1.19	0.25
RP Self-esteem	**17**	**-4.17**	**11.97**	*19*	*1.75*	*19.31*	16	-5.47	24.89	-0.28	0.78
RP General Health Perception	**17**	**-3.63**	**17.18**	*20*	*-1.21*	*13.12*	17	-2.55	21.89	-0.72	0.48
RP Parental Impact Emotional	**17**	**-7.84**	**16.53**	*20*	*-3.75*	*15.64*	17	-4.90	26.53	-0.70	0.49
RP Parental Impact Time	**17**	**-9.80**	**19.20**	*20*	*-4.44*	*16.68*	17	-3.27	28.26	-0.40	0.69
RP Family Activities	**17**	**-6.13**	**17.12**	*19*	*-4.17*	*18.53*	16	-1.82	26.87	-0.42	0.68
RP Family Cohesion	**17**	**2.94**	**17.42**	*19*	*1.32*	*21.20*	16	1.56	35.90	1.21	0.24
PR Global Health	*16*	*-4.17*	*26.87*	**17**	**0.00**	**23.57**	14	-2.38	35.72		
PR Physical Functioning	*16*	*-1.04*	*34.44*	**17**	**-1.31**	**21.83**	14	-0.79	44.60		
PR Role/Emot/Behavioural	*16*	*-1.39*	*24.97*	**17**	**5.23**	**17.62**	14	-3.17	36.31		
PR Role/Physical	*16*	*2.08*	*34.36*	**17**	**-3.92**	**28.58**	14	0.00	55.08		
PR Bodily Pain	*16*	*-7.50*	*25.95*	**17**	**4.71**	**19.08**	14	-15.00	37.37		
PR Behaviour	*16*	*-3.25*	*8.16*	**17**	**-0.47**	**6.15**	14	-3.14	10.78		
PR Mental Health	*16*	*-3.13*	*9.81*	**17**	**-2.35**	**15.92**	14	-0.71	19.99		
PR Self-esteem	*16*	*-0.78*	*9.89*	**17**	**1.72**	**17.25**	14	-2.98	24.21		
PR General Health Perception	*15*	*-0.44*	*17.89*	**16**	**0.31**	**14.63**	13	2.44	16.03		
PR Parental Impact Emotional	*15*	*-3.89*	*19.12*	**16**	**-4.69**	**13.93**	13	1.28	21.74		
PR Parental Impact Time	*15*	*2.96*	*12.22*	**16**	**0.69**	**9.49**	13	0.00	16.36		
PR Family Activities	*15*	*3.61*	*12.19*	**16**	**-1.30**	**17.66**	13	2.24	25.55		
PR Family Cohesion	*15*	*-3.33*	*24.76*	**15**	**8.33**	**15.43**	12	-14.58	34.47		

n, number of patients; sd, standard deviation; RP, order riboflavin-placebo; PR, order placebo-riboflavin; "-", increase of mean score; "+", decrease of mean score; bold numbers = difference between start and end riboflavin treatment; italic numbers = difference between start and end placebo treatment; t-statistic and p-value for difference between difference a-b for order RP and PR, respectively.

Table 3a: Psychological functioning (CBCL), distinguished by riboflavin and placebo

Parameter (T-scores)	Period 1 baseline			Period 1 end			Period 2 washout			Period 2 end		
	n	mean	sd	n	mean	sd	n	mean	sd	n	mean	sd
RP Total	19	33.35	26.01	**18**	**22.43**	**22.41**	20	21.0	15.93	*18*	*20.59*	*14.17*
RP Withdrawn	19	2.37	3.50	**18**	**1.83**	**3.40**	20	1.05	2.16	*18*	*1.11*	*1.32*
RP Somatic complaints	18	4.75	3.92	**16**	**4.27**	**4.58**	20	4.61	3.17	*17*	*3.25*	*2.72*
RP Anxious/depressed	19	4.63	5.23	**18**	**2.39**	**4.55**	20	2.46	3.41	*18*	*2.17*	*2.81*
RP Social problems	19	1.90	3.21	**18**	**1.46**	**2.43**	20	1.26	1.65	*18*	*1.00*	*1.37*
RP Thought problems	19	1.27	1.59	**18**	**0.46**	**0.96**	20	0.42	0.81	*18*	*0.44*	*0.78*
RP Attention problems	19	4.66	4.06	**18**	**2.81**	**3.59**	20	2.95	2.89	*18*	*3.17*	*3.16*
RP Delinquent behaviour	19	1.00	1.41	**18**	**0.74**	**1.11**	20	0.60	0.88	*18*	*0.78*	*1.22*
RP Aggressive behaviour	19	6.65	5.64	**18**	**4.61**	**4.33**	20	4.32	3.84	*18*	*4.00*	*4.27*
RP Internalizing	18	11.97	10.01	**16**	**6.77**	**7.09**	20	8.07	7.16	*17*	*6.37*	*5.11*
RP Externalizing	19	7.65	6.63	**18**	**5.34**	**4.88**	20	4.92	4.32	*18*	*4.78*	*5.02*
PR Total	21	29.67	17.52	*18*	*21.03*	*13.22*	17	19.52	16.70	**17**	**17.53**	**17.08**
PR Withdrawn	21	1.47	1.81	*18*	*1.39*	*1.46*	17	1.47	2.21	**17**	**1.23**	**2.14**
PR Somatic complaints	19	6.11	3.00	*16*	*4.10*	*3.30*	17	3.03	3,37	**17**	**3.53**	**2.99**
PR Anxious/depressed	21	3.57	3.26	*18*	*1.72*	*1.60*	17	2.35	3.12	**17**	**2.47**	**3.80**
PR Social problems	21	2.04	1.96	*18*	*1.39*	*1.29*	17	1.35	1.50	**17**	**1.06**	**1.71**
PR Thought problems	21	1.09	0.94	*18*	*0.33*	*0.49*	17	0.65	1.00	**17**	**0.35**	**0.79**
PR Attention problems	21	3.62	3.41	*18*	*3.14*	*3.02*	17	3.03	2.98	**17**	**2.71**	**3.40**
PR Delinquent behaviour	21	0.86	1.15	*18*	*0.61*	*0.98*	17	0.53	1.33	**17**	**0.47**	**1.00**
PR Aggressive behaviour	21	6.05	4.76	*18*	*4.28*	*3.89*	17	3.94	4.67	**17**	**2.71**	**3.75**
PR Internalizing	19	11.17	6.97	*16*	*7.42*	*4.70*	17	6.79	6.59	**17**	**7.12**	**7.07**
PR Externalizing	21	6.90	5.60	*18*	*4.89*	*4.60*	17	4.48	5.78	**17**	**3.18**	**4.36**

n, number of patients; sd, standard deviation; RP, order riboflavin-placebo; PR, order placebo-riboflavin; bold numbers = after riboflavin treatment; italic numbers = after placebo treatment.

Table 3b: Psychological functioning (CBCL), distinguished by riboflavin and placebo: statistical analysis

Parameter	difference a period 1 (start-end)			difference b period 2 (start-end)			difference a-b			testing	
	n	mean	sd	n	mean	sd	n	mean	sd	t-statistic	p
RP Total	**17**	**11.62**	**10.89**	*18*	*-0.80*	*12.63*	15	7.21	9.11	1.16	0.26
RP Withdrawn	**17**	**0.47**	**1.12**	*18*	*-0.44*	*1.10*	15	0.57	0.62	1.16	0.13
RP Somatic complaints	**14**	**1.00**	**2.49**	*17*	*1.44*	*2.14*	13	-0.02	2.03	-1.44	0.16
RP Anxious/depressed	**17**	**2.35**	**3.72**	*18*	*-0.21*	*2.39*	15	1.53	2.29	0.59	0.56
RP Social problems	**17**	**0.66**	**1.37**	*18*	*0.01*	*0.97*	15	0.24	0.73	0.29	0.77
RP Thought problems	**17**	**0.89**	**1.11**	*18*	*-0.04*	*0.73*	15	0.47	0.59	0.93	0.36
RP Attention problems	**17**	**1.69**	**2.36**	*18*	*-0.38*	*2.23*	15	1.19	1.47	1.88	0.07
RP Delinquent behaviour	**17**	**0.29**	**1.05**	*18*	*-0.22*	*1.40*	15	0.20	1.00	-0.04	0.97
RP Aggressive behaviour	**17**	**1.96**	**2.85**	*18*	*0.30*	*3.99*	15	1.03	2.47	0.62	0.54
RP Internalizing	**14**	**4.57**	**4.98**	*17*	*0.80*	*4.11*	13	2.37	3.33	0.22	0.83
RP Externalizing	**17**	**2.26**	**3.55**	*18*	*0.07*	*4.79*	15	1.24	3.31	0.48	0.64
PR Total	*17*	*6.65*	*7.69*	**16**	**0.51**	**10.24**	14	3.48	8.11		
PR Withdrawn	*17*	*0.29*	*1.26*	**16**	**0.25**	**1.44**	14	0.11	0.94		
PR Somatic complaints	*13*	*1.34*	*2.04*	**16**	**-0.34**	**2.92**	10	1.20	1.96		
PR Anxious/depressed	*17*	*1.47*	*2.24*	**16**	**-0.13**	**2.80**	14	1.04	2.27		
PR Social problems	*17*	*0.47*	*1.23*	**16**	**0.00**	**1.55**	14	0.14	1.00		
PR Thought problems	*17*	*0.65*	*0.93*	**16**	**0.31**	**1.08**	14	0.25	0.70		
PR Attention problems	*17*	*0.21*	*2.11*	**16**	**0.04**	**2.09**	14	-0.02	1.99		
PR Delinquent behaviour	*17*	*0.06*	*0.66*	**16**	**-0.18**	**0.64**	14	0.21	0.37		
PR Aggressive behaviour	*17*	*1.59*	*2.47*	**16**	**0.63**	**1.36**	14	0.57	1.38		
PR Internalizing	*13*	*2.50*	*4.39*	**16**	**-0.16**	**5.21**	10	2.00	4.71		
PR Externalizing	*17*	*1.65*	*2.60*	**16**	**0.44**	**1.62**	14	0.78	1.28		

n, number of patients; sd, standard deviation; RP, order riboflavin-placebo; PR, order placebo-riboflavin; "-" means increase of mean score; "+" means decrease of mean score; bold numbers = difference between start and end riboflavin treatment; italic numbers = difference between start and end placebo treatment; t-statistic and p-value for difference between difference a-b for order RP and PR, respectively.

Table 4: Quality of life (CHQ-PF50), not distinguished by riboflavin or placebo, in comparison with healthy controls

QoL-subscales	Period 1 baseline			Period 2 end			Healthy Controls		
	n	mean	sd	n	mean	sd	n	mean	sd
Global Health	41	59.35[1]	26.36	38	57.01[1]	23.13	353	85.72	16.27
Physical Functioning	41	80.73[1]	25.63	38	91.23[1]	19.05	353	99.08	4.25
Role/Emot/Behavioural	40	86.67[1]	23.36	38	91.52[1]	15.37	353	97.87	7.19
Role/Physical	40	70.00[1]	27.79	38	86.40[1]	20.45	353	95.75	15.61
Bodily Pain	41	52.19[1]	21.85	38	63.95[1]	17.64	353	85.67	17.24
Behaviour	41	64.00[1]	11.13	38	67.26[1]	9.15	353	78.54	13.06
Mental Health	41	76.46[2]	14.54	37	81.35	15.53	353	81.40	12.10
Self-esteem	41	74.18[1]	12.08	37	75.90	14.27	353	79.15	10.97
General Health Perception	41	66.95[1]	18.96	38	68.73[1]	18.49	353	82.87	13.44
Parental Impact Emotional	41	71.13[1]	22.75	38	86.40	14.29	353	86.31	15.20
Parental Impact Time	41	83.74[1]	23.58	38	95.02	7.62	353	93.96	13.02
Family Activities	41	79.17[1]	14.31	38	85.96[2]	13.95	353	91.52	11.94
Family Cohesion	41	33.54[1]	19.04	38	31.58[1]	19.00	353	72.22	19.41

n, number of patients; sd, standard deviation
[1]significant difference compared with healthy controls ($p < 0.01$; two-sided) by two-way ANCOVA test
[2]significant difference compared with healthy controls ($p < 0.05$; two-sided) by two-way ANCOVA test

Table 5: Psychological functioning (CBCL), not distinguished by riboflavin or placebo, in comparison with healthy controls

Parameter	Period 1 baseline			Period 2 end			Healthy Controls		
	n	mean	sd	n	mean	sd	n	mean	sd
Total	40	31.41[2]	21.75	35	19.10	15.49	1241	21.40	15.63
Withdrawn	40	1.90	2.74	35	1.17	1.74	1241	1.77	1.94
Somatic complaints	37	5.45[1]	3.50	34	3.39[1]	2.82	1241	0.89	1.44
Anxious/depressed	40	4.08	4.28	35	2.31	3.29	1241	2.53	3.11
Social problems	40	1.98	2.60	35	1.02	1.52	1241	1.39	1.89
Thought problems	40	1.17[1]	1.28	35	0.40	0.77	1241	0.47	1.01
Attention problems	40	4.11	3.72	35	2.95	3.24	1241	3.09	2.90
Delinquent behaviour	40	0.93	1.27	35	0.63	1.11	1241	1.18	1.51
Aggressive behaviour	40	6.33	5.14	35	3.37[1]	4.02	1241	6.40	5.31
Internalizing	37	11.56[1]	8.47	34	6.74	6.09	1241	5.08	5.08
Externalizing	40	7.25	6.04	35	4.00[1]	4.71	1241	7.57	6.32

n, number of patients; sd, standard deviation
[1]significant difference compared with healthy controls ($p < 0.01$; two-sided) by two-way ANOVA test
[2]significant difference compared with healthy controls ($p < 0.05$; two-sided) by two-way ANOVA test

DISCUSSION

This is the first randomized, double-blind, placebo-controlled intervention study in children with headache or migraine in which generic QoL and psychological functioning have been used as outcome variables. Riboflavin was used as intervention medication. As previously reported, no significant difference was found for the effect of riboflavin in the dosage used versus placebo on improvement of mean migraine frequency, mean intensity or mean duration of migraine attacks[26]. In addition, based on the data yielded by the present study, we conclude that riboflavin has no superior effect versus placebo in children with migraine with regard to improvement of QoL and psychological functioning on all investigated life domains and psychological subscales. To gain maximal statistical power, we decided to collapse the data of the riboflavin-placebo group with those of the placebo-riboflavin group to analyze the effect of a structured prophylactic placebo intervention in combination with state-of-the-art symptomatic treatment in children with migraine on generic QoL and psychological functioning over a relatively long period of 9 months. To do this, we decided to compare the data of our cohort with data from healthy controls, at the start and at the end of the trial.

In this combined group, the QoL was significantly lower at baseline on all investigated life domains compared with healthy children. This is in line with other descriptive studies on generic QoL in children with headache or migraine at referral to a specialist[5-9]. On all but two life domains, the QoL improved during the trial. At the end of the trial, on four life domains the QoL was within the range of healthy controls, i.e. mental health, self-esteem, parental impact emotional, and parental impact time. This means that the effect of the headache attacks of a child with migraine on the emotional wellbeing of his/her parents is also susceptible to proper symptomatic treatment and placebo prophylactic treatment of the child. This placebo effect is well known in headache research; it might be induced by the sustained attention paid by physicians and research nurses to the burden placed on the child and/or its family.

Interestingly, during the trial no improvement was seen on the QoL domains global health and family cohesion, in contrast to improvements on the other QoL domains. Regarding the domain global health, the poor QoL might persist because parents of children with migraine are inclined to believe that their child's health is poor, irrespective of any improvement due to treatment. Regarding the domain family cohesion, the poor QoL might persist because the child's headache represents a functional problem within the family (i.e. a symptom of a dysfunction of the family) and is therefore inclined to remain

poor after a treatment predominantly directed at improving the child's headache only. Alternatively, the poor and treatment-resistant QoL on the domains global health and family cohesion might also be due to the fact that both are single-question domains. This means that there is a range of only 5 items for parents to assess their child's health and the quality of the relations within their family, respectively; this is considerably less than the amount of variation available in the other QoL domains. Therefore, additional studies are needed to answer these important questions about the effect of treatment on internal family relations, as well as on parents' perception of the health of their child with migraine. With regard to the association of the primary headache parameters (headache frequency, intensity and duration) and QoL, a post-hoc analysis showed that in general in all phases of the trial most QoL domains are inversely related, not only with headache frequency but also with duration of the headache attacks.

With regard to psychological functioning, at baseline all CBCL scores in the combined group were within the range of healthy controls, with the exception of the subscales somatic complaints and thought problems and the main scale internalizing behaviour. This is in line with the descriptive studies of Galli et al.[23] and Vanatta et al.[21] who also used the CBCL as outcome variable. In the CBCL the subscale somatic complaints contains 8 questions, 3 of which concern the symptoms of headache, nausea and vomiting[29,30] (i.e. the hallmarks of migraine in children). Therefore, due to the nature of their disease, children with migraine are inclined to have a high score on this subscale. Moreover, the subscale somatic complaints is one of the three subscales that form the internalizing behaviour score (the others being the subscales withdrawn and anxious/depressed). Since there were no significant differences in scores on the subscales withdrawn and anxious/depressed in the children with migraine compared with healthy controls, either in the present study or in the study of Galli et al.[23] and in the study of Vanatta et al.[21] in the father's CBCL report, we conclude that the deviant score on the main scale internalizing behaviour in children with migraine, in favour of healthy controls, has to be attributed to the nature of the disease and not to psychological dysfunctioning due to migraine. Therefore, based on the results of the present study and of Galli et al.[23] and Vanatta et al.[21], it seems justified to conclude that children with migraine do not exhibit more psychological dysfunctioning than healthy controls at referral to a specialist. This seems remarkable because several studies have demonstrated that adults with migraine exhibit more psychological dysfunctioning and/or psychiatric comorbidity than healthy controls, suggesting a shared genetic susceptibility to both migraine and psychopathology, especially anxiety disorders and depression[33-36]. However, if a shared genetic susceptibility between migraine and

psychopathology does exist, one would expect this also to be manifest in children with migraine. The results of the present study and of Galli et al.[23] and Vannatta et al.[21] seem to demonstrate the opposite. This suggests that the association between migraine and psychopathology in adults is more likely due to the long-term effect of a chronic disease on the mental state of migraineurs and is therefore not present in children with migraine who have the disease for a relatively short period. However, one may also argue that children are less susceptible for developing psychopathology in comparison with adults due to their relatively protected environment with fewer responsibilities and less stressors and, in addition, that developing symptoms of psychopathology due to a genetic susceptibility might take a considerable amount of time, and that for this reason in children with not-longstanding migraine there is minimal or absent psychopathology.
In addition, in the present study there was an improvement on all CBCL scales throughout the trial; by the end of the trial, scores were within normal range on the subscale thought problems and on the main scales internalizing behaviour and total score. At the end of the trial, despite improvement, only on the subscale somatic problems was the score still significantly deviant from that of healthy controls, in favour of the latter group.
Interestingly, regarding the subscale aggressive behaviour and the main scale externalizing behaviour, at the end of the trial there was also a significant deviant score compared with healthy controls, but this time in favour of children with migraine. The subscale aggressive behaviour is one of the two subscales that form the externalizing behaviour score (the other being delinquent behaviour). Since there was no significant difference between the score on the subscale delinquent behaviour compared with healthy controls at the end of the trial, we conclude that the low score on the main scale externalizing behaviour is mainly due to the low score on the subscale aggressive behaviour. Therefore, based on the present study, we conclude that children with migraine are inclined to have significantly better scores versus healthy controls on the subscale aggressive behaviour and on the main scale externalizing behaviour after a proper symptomatic and placebo prophylactic treatment.
With regard to the association of the primary headache parameters (headache frequency, intensity and duration) and psychological functioning, we performed a post-hoc analysis on the main CBCL-scales of internalizing and externalizing behaviour and total score showing that especially in phase 1 and phase 2 these were in general positively related with headache frequency and headache duration.

At the start of the present study the generic QoL was poor on all life domains compared with healthy controls, which is in line with similar descriptive studies[5-9]. However, with

regard to psychological functioning, no discrepancy with healthy controls was found at the start of the study with exception of the subscale thought problems, somatic complaints and the main scale internalizing behaviour. With regard to the deviant scores on the latter two scales, we conclude that this is mainly due to the nature of the disease itself which inevitably leads to high scores on both scales; this was also demonstrated in similar descriptive clinical studies concerning only psychological functioning in children with migraine[23,21]. We therefore conclude that the QoL of children with migraine at referral to a specialist is poor, not because of psychological dysfunctioning, but rather as a consequence of the disease itself.

Our study certainly has some limitations. It could be argued that improvements on the QoL domains and the CBCL scales might result from entry bias and regression toward the mean; e.g. inclusion of children with migraine at referral to a specialist implies that they are probably at their worst because migraine is typically a paroxysmal disease with periods of relatively frequent attacks, followed by periods with relatively infrequent attacks, so that the included children will be more inclined to improve than to deteriorate after consultation with a specialist. This phenomenon will undoubtedly have occurred in the present study. Moreover, as all children received proper symptomatic treatment and placebo prophylactic treatment in a structured manner, a placebo effect almost certainly occurred. In addition, it could be argued that improvements on the QoL domains and the CBCL scales are due to repeated testing, meaning that parents of the included children are inclined to give higher scores as they expect some results from the treatment. To gain more insight into these topics, we performed a PubMed search to find comparable pharmacological placebo-controlled, randomized intervention studies in children in fields other than headache research which used both psychological functioning and QoL as outcome parameters; however, none were found.
Finally, a major limitation is that we did not use an intervention with a superior effect compared with placebo on the primary headache parameters headache frequency, headache intensity and duration of the headache attacks. If this was the case, and we would have demonstrated that this intervention had a concomitant superior beneficial effect on QoL and psychological functioning, this would give additional evidence that both outcomes are directly related to the burden of headache in children with migraine.

The study also has strong points. This is the first randomized, double-blind, placebo-controlled intervention study in children with headache or migraine in which generic QoL and psychological functioning are used as outcome variables. In addition, this is the

first clinical study in children with migraine in which both generic QoL and psychological functioning are used as outcome variable in the same cohort of patients, providing valuable additional information on the relationship between QoL and psychological functioning.

Finally, we believe that measuring generic QoL and psychological functioning in pharmacological or non-pharmacological intervention studies in children with headache or migraine is an important concept, not only to observe if the intervention itself has a positive effect on QoL and psychological functioning, but also because numerous pharmacological interventions in this field (especially prophylactic interventions) may have an adverse effect on physical, social and psychological wellbeing. For example, anti-epileptic drugs are widely used as migraine prophylaxis in children. As these drugs may have a beneficial effect on headache frequency and intensity, they may also have a negative effect on mood, cognition or behaviour[12]. The net result of this combination may, however, be difficult to determine. The use of generic QoL and psychological functioning as outcome parameter may help to detect this, especially in smaller children who cannot yet adequately voice their improvements and/or their complaints and subsequently provide a reasonable judgement about the overall effect of treatment. Also for this reason, we recommend that future intervention studies in children with headache or migraine use generic QoL and psychological functioning as outcome parameter.

ACKNOWLEDGEMENTS

The authors thank all the children and their parents who participated in this study.
Special thanks go to the pediatricians in the Vlietland Hospital for their support and referral of patients: Coby Langendoen M.D., Lia van Wijk M.D., Bert den Exter M.D., Arjan Pijning M.D., Esther Hentzen M.D. and Evelyne van Boeckel M.D. Special thanks to Sjaan Scholten, physician's assistant at the pediatric outpatient department of the Vlietland Hospital.
The authors thank the management of the Vlietland Hospital for their support, especially Gerrit-Jan van Zoelen, chairman of the board of directors of the Vlietland Hospital.
The authors also thank the referring pediatricians, neurologist and pediatric neurologists, especially P. de Laat, J. Samijn, A.van Rossum, R. van der Lee, D. Kamphuis, B. Koop and C. de Korte.

This study was sponsored by the Nuts-Ohra Foundation, the Nolet Foundation and Van Der Linden Strukton.

REFERENCES

1. **Constitution of the World Health Organization basic documents.** Geneva, Switzerland: World Health Organization 1948.
2. Gladstein J, Holden WE. **Chronic daily headache in children and adolescents: a 2-year prospective study.** Headache 1996;36:349-51.
3. Kernick D, Campbell J. **Measuring the impact of headache in children: a critical review of the literature.** Cephalalgia 2009;29:3-16.
4. Varni J, Burwinkle T, Lane M. **Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application.** Health Qual Life Outcomes 2005;3:34.
5. Powers SW, Patton SR, Hommel KA, Hershey AD. **Quality of life in pediatric migraine: characterization of age-related effects using PedsQL.** Cephalalgia 2004;24:120-7.
6. Powers SW, Patton SR, Hommel KA, Hershey AD. **Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses.** Pediatrics 2003;112:e1-5.
7. Nodari E, Battistella PA, Naccarella C, Vidi M. **Quality of life in young Italian patients with primary headache.** Headache 2002;42:268-74.
8. Connelly M, Rapoff MA. **Assessing Health-Related Quality of Life in Children with Recurrent Headache: Reliability and Validity of the PedsQL™ 4.0 in a Pediatric Headache Sample.** J Pediatr Psychol 2006;31(7):698-702.
9. Bruijn J, Arts W-F, Duivenvoorden H, Dijkstra N, Raat H, Passchier J. **Quality of life in children with primary headache in a general hospital.** Cephalalgia 2009;29:624-30.
10. Langeveld J, Koot H, Passchier J. **Headache Intensity and Quality of Life in Adolescents. How are Changes in Headache Intensity in Adolescents Related to Changes in Experienced Quality of Life?** Headache 1997;37:37-42.
11. Hunfeld JAM, Passchier J, Perquin CW, Hazebroek-Kampschreur AAJM, van Suijlekom-Smit LWA, van der Wouden JC. **Quality of life in adolescents with chronic pain in the head or at other locations.** Cephalalgia 2001;21:201-6.
12. Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche M. **Effectiveness of topiramate in the prevention of childhood headaches.** Headache 2002;42:810-8.
13. Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, Burdine D, Manning P, Kabbouche MA. **Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine.** Headache 2007;47:73-80.
14. Rossi LN, Cortinovis I, Menegazzo L, Menini S, Carnelli V. **Behaviour during attacks and assessment of intensity in primary headaches of children and adolescents.** Cephalalgia 2006;26:107-12.
15. Passchier J, Orlebeke JF. **Headaches and stress in schoolchildren: an epidemiological study.** Cephalalgia 1985;5:167-76.
16. Guidetti V, Mazzei G, Ottaviano S, Pagliarini M, Paolella A, Seri S. **The utilization of the Rorschach test in a case-controlled study.** Cephalalgia 1986;6:87-93.
17. Mazzone L, Vitiello B, Incorpora G, Mazzone D. **Behavioural and temperamental characteristics of children and adolescents suffering from primary headache.** Cephalalgia 2006;26:194-201.
18. Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, Resch F. **Emotional and behavioural problems in children and adolescents with primary headache.** Cephalalgia 2003;23:206-13.
19. Pakalnis A, Gibbons J, Colvin A. **Comorbidity of psychiatric and behavioral disorders in pediatric migraine.** Headache 2005;45:590-6.
20. Anttila P. Sourander A, Metsahonkala L, Aromaa M, Helenius H, Sillanpaa M. **Psychiatric symptoms in children with primary headache.** J Am Acad Child Adolesc Psychiatr 2004;43:412-9.
21. Vannata K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. **Multiple perspectives on the psychological functioning of children with and without migraine.** Headache 2008;48:994-1004.

22. Smith M, Martin-Herz S, Womack W, Marsigan J. **Comparative study of anxiety, somatization, functional disability and illness attribution in adolescents with chronic fatigue or migraine.** Paediatrics 2003;111:e376-81.

23. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, Cucchiara S, Guidetti V. **Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL).** Cephalalgia 2007;27:211-9.

24. Guidetti V, Galh F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S. **Headache and psychiatric comorbidity: clinical aspects and outcome in an 8 year follow-up study.** Cephalalgia 1998;18:455-62.

25. Garcia-Monco JC, Foncea N, Bilbao A, Ruiz de Velasco I, Gomez-Beldarrain M. **Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients.** Cephalalgia 2007;27:920-8.

26. Bruijn J, Duivenvoorden H, Passchier J, Locher H, Dijkstra N, Arts WF. **Medium dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomized, double-blind, crossover trial.** Cephalalgia 2010 (e-Pub ahead of print).

27. Headache Classification Committee of the International Headache Society. **The international classification of headache disorders.** Cephalalgia 2004;24:1-160.

28. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. **Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index.** J Clin Epidemiol 2002;55:67-76.

29. Achenbach TM, Edelbrock CS. **Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen.** Monogr Soc Res Child Dev 1981;46:1-82.

30. Verhulst F, van der Ende J, Koot H. **Handleiding voor de CBCL/4-18 [Manual for the CBCL/4-18 (Dutch edition)].** ISBN 90-75584-03-2.

31. J Bruijn, R. Gooskens, A. Verhagen, L. Damen, J. Passchier. **Evidence Based Guideline "Migraine in Children" as part of Dutch National Guideline "Pain Measurement and Treatment in Children"**; on-line publication March 2008:53-65 (in Dutch). (http://www.nvk.pedianet.nl/pdfs/nvk_richtlijn_pijn_bij_kinderen.pdf).

32. Stephen Senn: **Cross over Trials in Clinical Research 2nd edition; Statistics in Practice**; Wiley; ISBN 0 471 49653 7:41-7.

33. Schoenen J. **Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behaviour and trigeminovascular activation?** Biomed Pharmacother 1996;50:71-8.

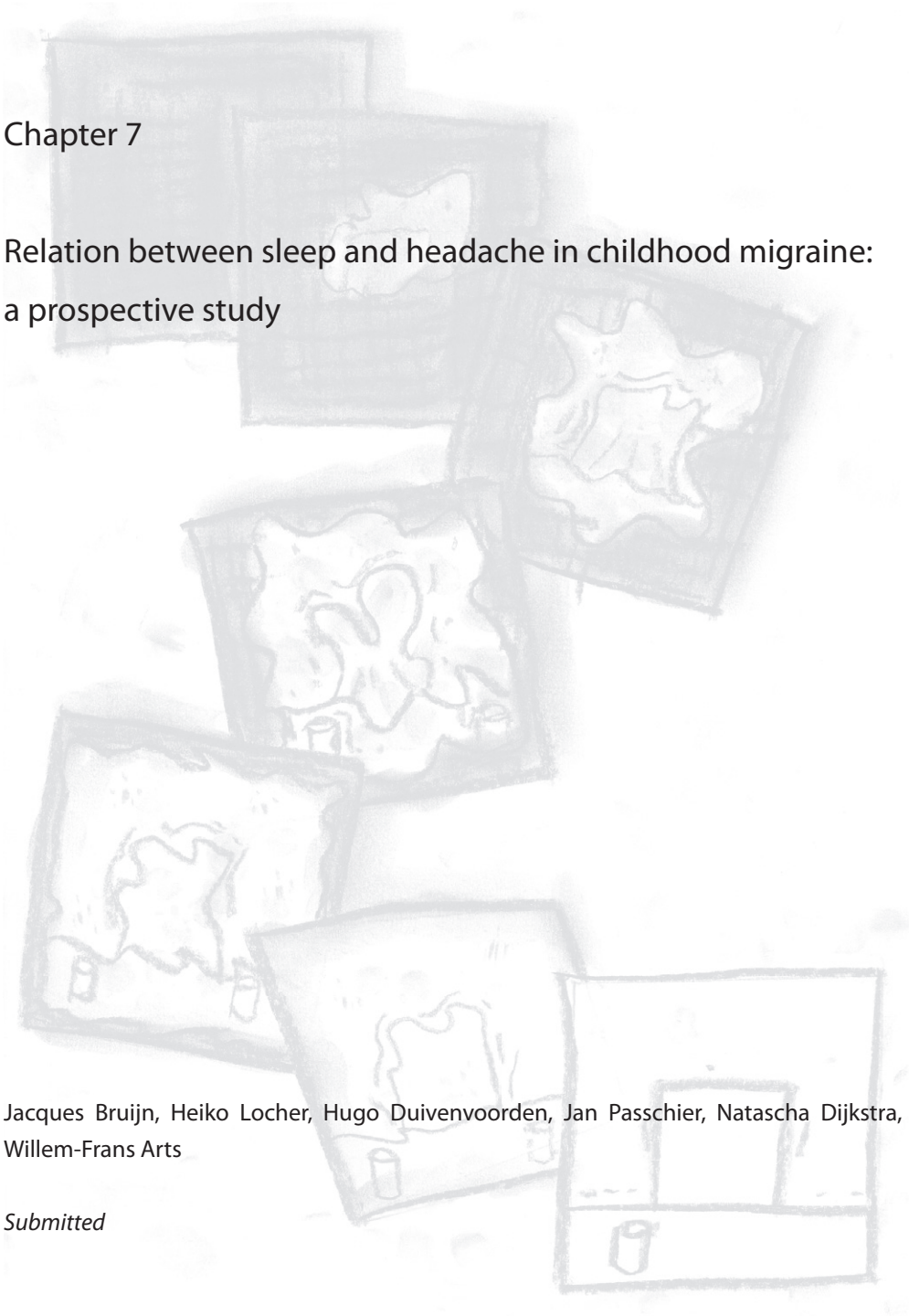
34. Schur EA, Noonan C, Buchwald D, Goldberg J, Afari N.A. **Twin Study of depression and migraine: evidence for a shared genetic vulnerability.** Headache 2009; Apr 27 (e-Pub ahead of print).

35. Radat F, Swendsen J. **Psychiatric comorbidity in migraine: A review.** Cephalalgia. 2005;25:165-78.

36. Hamelsky SW, Lipton RB. **Psychiatric comorbidity of migraine.** Headache 2006;46:1327-33.

Chapter 7

Relation between sleep and headache in childhood migraine: a prospective study



Jacques Bruijn, Heiko Locher, Hugo Duivenvoorden, Jan Passchier, Natascha Dijkstra, Willem-Frans Arts

Submitted

ABSTRACT

Background: Little is known about the effects of sleep on migraine, especially in children.
Objective: To assess the effect of sleep deprivation on headache attacks in children with migraine. The relationship between resting and sleeping and headache symptoms was also explored.
Methods: A prospective study using headache diaries. In 42 children with migraine, sleep pattern and duration were registered in the diaries by the parents.
Results: The study included 42 children (6 to 13 years) with migraine (mean age 9.69 years, 24 male). Only 6.2% of the headache attacks were preceded by the occurrence of one night in which the child slept less than usual. During attacks, resting decreased headache intensity in 76.0% of the attacks occurring after a preceding sleep deficit and in 54.4% of the attacks without preceding sleep deficit ($p = 0.04$). Sleeping decreased headache intensity in 84.0% of the attacks with a sleep deficit and in 63.6% of the attacks without preceding sleep deficit ($p = 0.05$). In case of a favourable effect of resting and sleeping on headache intensity, a significant decrease of headache duration was also found, compared with attacks with no effect of resting and sleeping on headache intensity ($p < 0.001$ and $p = 0.021$, respectively).
Conclusions: In these young children, one night with less sleep was not an important precipitating factor of migraine attacks. Moreover, once a child is suffering from a headache attack, resting and sleeping resulted in a clinically relevant improvement of headache intensity and duration.

INTRODUCTION

In both children and adults a regular and undisturbed sleep is recommended as a treatment goal in many diseases and conditions, but especially in the case of headache disorders. As early as 1853 in his classic *Lehrbuch*, Romberg wrote: *"The attack is generally closed by a profound and refreshing sleep"*[1]. Although sleeping has been the advised treatment for migraine attacks over the centuries, the functions of sleep have not yet been fully unravelled[2]. In fact, more is known about the adverse effects of sleep disturbances. A recent review showed that sleep disorders are associated with headaches and that variations in sleep duration (oversleeping/undersleeping) are commonly identified headache triggers[3]; however, because most of the included studies were of a retrospective or cross-sectional nature and were population based, they were correlative rather than causative.

Also in the paediatric clinical setting data are scarce. A few studies have shown that a variety of sleep disturbances/disorders are present in children and adolescents with migraine[4-8]. Although these studies show an association between sleep and migraine, their design does not allow causal inferences, which is of clinical interest to improve headache treatment. Another topic of clinical interest is whether sleeping actually does resolve migraine attacks.

Therefore, we investigated the effects of sleep in childhood migraine. The current study was designed within the context of a placebo-controlled, randomized, double-blind, crossover trial of riboflavin as a possible preventive drug[9].

The aim of the present study was to assess sleep as a potential causative factor for migraine attacks in a paediatric outpatient department setting. The relation between resting and sleeping and headache symptoms was also explored.

MATERIAL and METHODS

Patients and procedure

A consecutive series of children with migraine (referred to the paediatric neurology departments of either a university children's hospital or at the paediatric outpatient department of a general hospital) were asked to participate in a placebo-controlled, cross-over trial with riboflavin as the acting agent.

The methodology, including the inclusion and exclusion criteria, procedure and design of this trial have been described in detail in our former paper, which also presents the

Consolidated Standard of Reporting Trials (CONSORT) flow diagram and CONSORT statement[9].

During the trial, the parents of the included children were asked to keep a detailed headache diary during all stages of the trial.

Measures

Headache diaries were analyzed in all phases of the trial. We introduced the term 'deficit' to describe the situation in which the diary reported the duration of sleep in the night preceding the headache attack as 1 or more hours less than the patient's usual quantity of sleep. In the present study, the relation between sleep deficit and the occurrence of a migraine attack was the principal outcome measure. In order to exclude statistical bias due to the type of intervention and phase of the trial, sleep deficit was also related to these variables. Finally, we explored a possible relationship between sleep deficit and the type, intensity and duration of the headache attacks. All of these outcome measures were defined as secondary outcome measures in advance of the start of the trial, to be analysed in the present study.

Statistical Analysis

Sample size calculations were based on calculations with regard to a decrease in migraine frequency in the last 4 weeks of the riboflavin phases compared with the last 4 weeks of the placebo phases[9]. Thus, a minimum number of 20 patients were required to participate in the trial. To allow for dropouts, 30 patients were initially enrolled, which was later extended to 42 to allow further exploratory analyses[9].

Statistical evaluation of the headache diary data was performed using Statistical Package for the Social Sciences (SPSS 15.0) software (SPSS Inc., Chicago, IL, USA) in combination with Statistical Analysis Software (SAS 9.2, SAS Institute Inc, Cary, NC, USA).

Chi-square tests were used for categorical date, and for continuous data t-tests for independent observations were used to compare headache diary variables. The level of statistical significance was set at $p \leq 0.05$, two-tailed. The descriptive values are expressed as means, including standard deviations (sd) and percentages.

RESULTS

Demographics

Baseline information on demographics and migraine features of the participants are presented in Table 1. Of the 57 recruited children, 15 were not enrolled because they did not meet the inclusion criteria, or met one or more exclusion criteria, or because they or their parents declined to participate in the trial. Of the 42 remaining children, 20 were randomized to receive riboflavin during phase 1 and placebo during phase 2, and 22 children received placebo during phase 1 and riboflavin during phase 2. In this latter group one child was lost to follow-up, the parents of two children withdrew their consent for further participation, and one patient proved to be suffering from headache due to medication overuse, which was discovered after careful study of her baseline headache diary. Both treatment groups had comparable demographic and migraine features.

During the entire trial a total of 504 headache attacks were reported and used for analysis. In total, 403 headache attacks had relevant data, i.e. 403 attacks reporting headache characteristics concerning the duration of sleep in the preceding night and duration of sleep in general. Of all recorded headache attacks, the mean intensity (on a scale from 0-3) was 1.92 (sd 0.97*)*. On average, the total duration of a single headache attack was 2 h and 48 (sd 81) min.

Outcome data

To investigate the effects of sleep deficit on headache characteristics, we analysed the number of headache attacks that were preceded by a night in which the child slept 1 or more hours less than usual. Of the 403 headache attacks available for analysis, sleep deficit occurred in 25 attacks (6.2%; Table 2). In 21 of these 25 headache attacks (84.0%), sleep deficit ranged from 1-3 h, and in the remaining 4 headache attacks (16.0%) sleep deficit was more than 3 h. Because the present study is part of a placebo-controlled trial, the outcomes might be affected by the type of intervention received (i.e. riboflavin or placebo). Therefore, we compared the headache attacks with or without a preceding sleep deficit in the last 4 weeks of the riboflavin periods and of the placebo periods throughout the trial. However, no difference in the occurrence of a sleep deficit could be found on Chi-square analysis between the two types of intervention ($p = 0.75$; Table 2). The percentage of headache attacks in the placebo and the riboflavin periods is lower than the percentage of headache attacks in the baseline and the washout periods; this is due to the fact that the baseline and washout period had a combined duration of 8 weeks (Table 2).

Subsequently, we explored whether a preceding sleep deficit was related to the type

of headache attack. Of the headache attacks preceded by a sleep deficit, 88.0% were migraine attacks and 12.0% were non-migrainous headache attacks (Table 2). Of the headache attacks not preceded by a sleep deficit, 78.6% were migraine attacks and 21.4% were non-migrainous headache attacks. Because there was no significant difference between the subdivisions in both groups on Chi-square analysis ($p = 0.32$), we conclude that sleep deficit preceding a headache attack does not affect the type of headache attacks in children with migraine.

To measure the effects of a sleep deficit on headache characteristics, we analysed the relation between sleep deficit and pain intensity and total headache duration. The reported values for intensity and duration of the headache attacks showed no significant difference compared to those not preceded by a sleep deficit; the mean values for intensity (on a 0-3 scale) were 1.8 (sd 0.87) and 1.9 (sd 0.97), respectively ($p = 0.59$; Table 2). The mean values for the total duration of the headache attacks were 2 h and 40 min (sd 1 h and 16 min), and 2 h and 49 min (sd 1 h and 20 min), respectively ($p = 0.58$; Table 2).

Finally, we explored the potentially positive effects of resting and sleeping on headache attacks, to assess whether or not these were related to preceding sleep deficits (Tables 3 and 4). Testing for significance took place with two-way ANOVA analysis. The total number of reported headache attacks during which resting or sleeping took place (i.e. 504) exceeds the total number of reported attacks; this is because the parents indicated that both resting and sleeping had occurred in a considerable number of attacks. Resting decreased the headache intensity in 76.0% of the attacks occurring after a preceding sleep deficit compared with 54.4% of the attacks without preceding sleep deficit ($p = 0.04$; Table 3). Sleeping decreased the headache intensity in 84.0% of the attacks with a sleep deficit compared with 63.6% of the attacks without a preceding sleep deficit ($p = 0.05$; Table 3). Without a decreasing effect of resting on headache intensity, the average total duration of the headache attacks was 3 h and 17 min. With a decreasing effect of resting on headache intensity, the duration was reduced by 48 min. Without a decreasing effect of sleeping on the intensity of the headache attack an average total duration of 3 h and 15 min was reported; with a decreasing effect of sleeping on the intensity of the headache attack, the attack was shortened by 39 min. Both effects were highly significant ($p < 0.001$ and $p = 0.021$, respectively; Tables 4a and 4b). The occurrence of a sleep deficit showed no relation with the effects of resting and sleeping on headache duration compared with attacks without a preceding sleep deficit ($p = 0.19$ and $p = 0.63$, respectively; Table 4b).

DISCUSSION

Sleep deprivation

During the trial it was found that 6.2% of the headache attacks were preceded by a night in which the parents reported that their child slept at least 1 hour shorter than usual. This is much less than expected based on earlier reports on sleep disturbances and associations with headache[4-8]. We believe this is the first prospective study to explore the effect of sleep deprivation on headache in children with migraine, making comparison with other studies difficult. One study, in which parents of children with migraine were specifically asked if their child slept too little, yielded an answer of 42%[8]; however, this question was not used to identify sleep deprivation as a trigger factor for migraine attacks, and no definition of 'too little' was given. Consequently, we cannot readily relate this finding to our results.

According to a recent population-based study of 480 Hispanic and Caucasian children (aged 6-11 years), there is a discrepancy between the parental report of sleep time by means of a questionnaire and objectively obtained polysomnographic evidence[10]. In that study, parents reported 578 min as the habitual total sleep time and 547 min as the total sleep time on the night of the recording, whereas using polysomnography a total sleep time of only 480 min was found ($p < 0.001$). The authors warned clinicians that parents substantially overestimate the total sleep time of their children[10]. In a study by Vendrame et al., children (aged 9-15 years) with headache showed polysomnographic values of (on average) 390 min for total sleep time in the migraine group; however, that study lacked a control group of age-matched healthy children[11]. In the present study, parents reported a total sleep time of over 8 hours in 93.8% of the headache attacks. One explanation for the discrepancy between the total sleep times found by Vendrame et al. and our group is that the children with headache in the study of Vendrame were part of a specifically selected subgroup with a positive screening for sleep complaints. Additional explanations could be the difference in the mean age of the patients (11.5 versus 9.7 years, respectively) or over-estimation by the parents in the present trial of the total sleep time of their children. Our way of collection of sleep data has its flaws. Future research should also include data on baseline sleep patterns, nights of normal sleep and nights with oversleeping. However, even allowing for the limitations of not having polysomnographic values, and assuming that parental overestimation is a consistent factor, the present study allows us to draw some conclusions based on the reported values. For example, in our trial, having a sleep deficit precedes only 6.2% of the headache attacks. One possibility for this rare occurrence of sleep deficit, preceding a headache attack in children with migraine, could be that the

trigger factor is not the deficit on the night preceding the attack but rather a sleep debt over multiple nights, particularly because lack of sleep or bad quality of sleep is reported to precipitate headache attacks[4,12]. Future prospective studies should focus on this relationship, preferably using objective measurement tools (such as polysomnography) and using healthy, sex and age-matched children as controls.

No significant relationship was found between the occurrence of sleep deficit and the headache characteristics of pain intensity and headache duration. This allows concluding that a sleep deficit preceding a headache attack does not result in increased pain intensity or prolonged attack duration. An earlier cross-sectional study in children with headache explored the parents' perception of sleep duration as being too little or adequate during the preceding week on the one hand, and headache severity on the other[8]. The authors used the Headache Intake Questionnaire[13] to measure pain severity and headache duration, and the Children's Sleep Habits Questionnaire[14] to measure total sleep duration, all on Likert-type scales. Headache duration was not related to the total sleep duration (in line with our findings), but the pain intensity of migraine attacks was inversely related to the parental report of sleep duration ($p < 0.05$)[8]. Based on this result, one could hypothesize that a prolonged sleep deficit could lead to more intense migraine attacks; however, our study shows no such relationship for one night of diminished sleep.

To elucidate the causative effects of sleep deficit on migraine attacks in children, future studies should use a prospective and intervention design rather than a cross-sectional one. To our knowledge only one case-controlled intervention study on children with migraine has explored the effect of improving sleep hygiene on primary headache parameters, providing evidence that a simple modification of sleep pattern will decrease migraine frequency and duration[15]. Whilst we specifically investigated the causal effects of a single night of sleep deficit, future studies should focus on other possible causal factors and mechanisms. These studies should be aware of the recently reported high placebo rate in trials on childhood migraine and should therefore be appropriately designed[16].

Resting and Sleeping

To the best of our knowledge, the effect of resting and sleeping after the start of a headache attack on headache intensity and duration in children with migraine has not yet been evaluated in intervention studies. Our study confirms the generally accepted positive effects of resting and sleeping on the intensity of headache attacks in children with migraine. Moreover, in case of a positive effect of resting and sleeping on headache intensity, headache duration decreased significantly compared with attacks with no effect of resting and sleeping on headache intensity. The effects of resting and sleeping

on headache intensity were significantly greater after a preceding sleep deficit (resting: $p = 0.04$, sleeping: $p = 0.05$), whereas the preceding sleep deficit had no effect on the reduction of headache duration by resting or sleeping (resting: $p = 0.19$, sleeping: $p = 0.63$, respectively). This might be explained by the fact that children with a preceding sleep deficit were inclined to sleep longer, because of their shortage of sleep, and since the duration of sleeping and resting was not an item in the headache diaries, a possible decreasing effect on the duration of the headache attacks might be masked by an increase of the duration of resting and sleeping themselves. Therefore, precise documentation of these durations could be of added value.

A limitation of the present study is that we did not specifically ask the question for which Romberg already seemed to know the answer, i.e. "Does sleeping end the attack?" We recommend that future studies explore this question. One prospective clinical study on sleep in relation to migraine attacks in children has demonstrated that one-third of the attacks ended in falling asleep[17].

Another point is the use of Likert-type scales to report headache intensity. Different scales are used in different studies; we used a 4-point scale (light, moderate, annoying, strong) whilst others used the scale from the Headache Intake Questionnaire used by Hershey et al.[13] in which a 10-point severity scale was adapted to a 5-point faces scale for younger children. The International Headache Society guideline for controlled trials of drugs in migraine recommends the use of a 4-point Likert scale: 0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache[18]. We recommend use of this Likert scale whenever possible, with the visual analogue scale as the next best alternative[18].

Clinical Advice

Although our results show that a single event of sleep deficit is at most a small factor among those triggering migraine attacks, we recommend focusing on the different aspects of sleep of our migraine patients. Whereas future research needs to define the importance of other aspects of sleep disturbances for the origin of migraine, the positive effects of changing bad sleeping habits on the frequency of migraine or headache attacks have been demonstrated[15,19]. Moreover, having slept less than usual has no relationship with the general advice to children to go to bed during a migraine attacks; in all situations we would strongly recommend going to bed.

CONCLUSIONS

The present study has shown that one night with less sleep is not an important trigger factor for migraine attacks in children. It was also shown that resting and sleeping after the start of the headache attack is likely to decrease the intensity and duration of the attack in children with migraine. This effect on intensity is even more profound when there has been lack of sleep in the night preceding the headache attack.

ACKNOWLEDGEMENTS

The authors thank all the children and their parents who participated in this study. Special thanks go to the paediatricians in the Vlietland Hospital for their support and referral of patients: Coby Langendoen MD, Lia van Wijk MD, Bert den Exter MD, Arjan Pijning MD, Esther Hentzen MD and Evelyne van Boeckel MD. Special thanks to Sjaan Scholten, physician's assistant at the paediatric outpatient department of the Vlietland Hospital.
The authors thank the management of the Vlietland Hospital for their support, especially Gerrit-Jan van Zoelen, chairman of the board of directors of the Vlietland Hospital.
The authors also thank the referring paediatricians, neurologist and paediatric neurologists, especially P. de Laat, J. Samijn, A. van Rossum, R. van der Lee, D. Kamphuis, B. Koop and C. de Korte.

The Nuts-Ohra Foundation, the Nolet Foundation and Van Der Linden-Strukton provided financial support for this study.

REFERENCES

1. Romberg Moritz Heinrich, translated by Sieveking Edward Henry. Chapter XVII, Neuralgia Cerebralis, Hemicrania, la Migrène. **In: A Manual of the Nervous Diseases of Man.** London: the Sydenham Society; 1853.
2. Rains JC, Poceta JS. **Headache and sleep disorders: review and clinical implications for headache management.** Headache 2006;46(9):1344-1363.
3. Vassalli A, Dijk DJ. **Sleep function: current questions and new approaches.** Eur J Neurosci 2009;29(9):1830-1841.
4. Bruni O, Russo PM, Ferri R, Novelli L, Galli F, Guidetti V. **Relationships between headache and sleep in a non-clinical population of children and adolescents.** Sleep Med 2008;9(5):542-548.
5. Gilman DK, Palermo TM, Kabbouche MA, Hershey AD, Powers SW. **Primary headache and sleep disturbances in adolescents.** Headache 2007;47(8):1189-1194.
6. Heng K, Wirrell E. **Sleep disturbance in children with migraine.** J Child Neurol 2006;21(9):761-766.
7. Luc ME, Gupta A, Birnberg JM, Reddick D, Kohrman MH. **Characterization of symptoms of sleep disorders in children with headache.** Pediatr Neurol 2006;34(1):7-12.
8. Miller VA, Palermo TM, Powers SW, Scher MS, Hershey AD. **Migraine headaches and sleep disturbances in children.** Headache 2003;43(4):362-368.
9. Bruijn J Duivenvoorden H, Passchier J, Locher H, Dijkstra N, Arts W-F. **Medium dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomized, double-blind, cross-over trial.** Cephalalgia 2010 (e-Pub ahead of print).
10. Goodwin JL, Silva GE, Kaemingk KL, Sherrill DL, Morgan WJ, Quan SF. **Comparison between reported and recorded total sleep time and sleep latency in 6- to 11-year-old children: the Tucson Children's Assessment of Sleep Apnea Study (TuCASA).** Sleep Breath 2007;11(2):85-92.
11. Vendrame M, Kaleyias J, Valencia I, Legido A, Kothare SV. **Polysomnographic findings in children with headaches.** Pediatr Neurol 2008;39(1):6-11.
12. Spierings EL, Ranke AH, Honkoop PC. **Precipitating and aggravating factors of migraine versus tension-type headache.** Headache 2001;41(6):554-558.
13. Hershey AD, Powers SW, Bentti AL, Degrauw TJ. **Effectiveness of amitriptyline in the prophylactic management of childhood headaches.** Headache 2000;40(7):539-549.
14. Owens JA, Spirito A, McGuinn M. **The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children.** Sleep 2000;23(8):1043-1051.
15. Bruni O, Galli F, Guidetti V. **Sleep hygiene and migraine in children and adolescents.** Cephalalgia 1999;19 Suppl 25:57-59.
16. Evers S, Marziniak M, Frese A, Gralow I. **Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies.** Cephalalgia 2009;29(4):436-444.
17. Aaltonen K, Hamalainen M L, Hoppu K. **Migraine attacks and sleep in children.** Cephalalgia 2000;20(6):580-584.
18. Tfelt-Hansen P, Block G, Dahlof C, Diener H C, Ferrari MD, Goadsby PJ et al. **Guidelines for controlled trials of drugs in migraine: second edition.** Cephalalgia 2000;20(9):765-786.
19. Feikema WJ **[Headache and chronic sleep deprivation: an often missed relationship in children and also in adults].** Ned Tijdschr Geneeskd 1999;143(38):1897-1900.

Table 1: Baseline demographic and headache characteristics of the study population

Parameter	Riboflavin-Placebo (n = 20)	Placebo-Riboflavin (n = 22)
Age, mean (sd)	9.91 (1.89)	9.50 (1.63)
Male	12 (60%)	12 (54%)
Headache		
MA	9 (45%)	8 (36%)
MoA	11 (55%)	12 (64%)
Only migraine	8 (40%)	15 (68%)
TTH	10 (50%)	4 (18%)
ENT infections	1 (5%)	0 (0%)
Other	3 (15%)	2 (9%)
Family history of migraine	16 (89%)	19 (95%)
Years since onset of migraine, mean (sd)	3.06 (1.73)	2.80 (2.14)
Number of migraine attacks per month, mean (sd)	3.60 (3.10)	3.48 (5.41)
Duration of migraine in hours, mean (sd)	2.45 (1.19)	2.57 (1.54)

n, number of patients; MA, migraine with aura; MoA, migraine without aura; TTH, tension-type headache; ENT, ear-nose-throat.

Table 2: Intervention and headache characteristics related to sleep deficit

Parameter	No sleep deficit	Sleep deficit	Statistical analysis
riboflavin	26.5 %	32.0 %	0.75
placebo	16.7 %	12.0 %	
baseline/washout	56.9 %	56.0 %	
f	378	25	
migraine	78.6 %.	88.0 %	0.32
non-migrainous headache	21.4 %	12.0 %	
f	378	25	
intensity (0-3): mean (sd)	1.90 (0.97)	1.80 (0.87)	0.59
f	375	25	
duration (hours): mean (sd)	2.82 (1.33)	2.67 (1.27)	0.58
f	341	24	

f, number of reported headache attacks

Table 3: Effect of resting and sleeping on headache intensity: without and with sleep deficit

Parameter	No sleep deficit	Sleep deficit	Statistical analysis
Resting			
decreasing effect on HI	54.4%	76.0%	0.04
no decreasing effect on HI	45.6%	24.0%	
f	351	25	
Sleeping			
decreasing effect on HI	63.6%	84.0%	0.05
no decreasing effect on HI	36.4%	16.0%	
f	330	25	

f, number of reported headache attacks; HI, headache intensity

Table 4a: Effect of resting and sleeping on headache intensity and headache duration (hours): without and with sleep deficit

Parameter	No sleep deficit			Sleep deficit			Total		
	f	mean	sd	f	mean	sd	f	mean	sd
Resting									
decreasing effect on HI	167	2.01	1.34	18	2.28	2.43	185	2.49	1.33
no decreasing effect on HI	149	3.26	1.17	6	3.84	0.82	155	3.29	1.16
Sleeping									
decreasing effect on HI	182	2.59	1.29	20	2.50	1.27	202	2.58	1.28
no decreasing effect on HI	115	3.25	1.27	4	3.50	1.00	119	3.25	1.26

f, number of reported headache attacks; HI, headache intensity

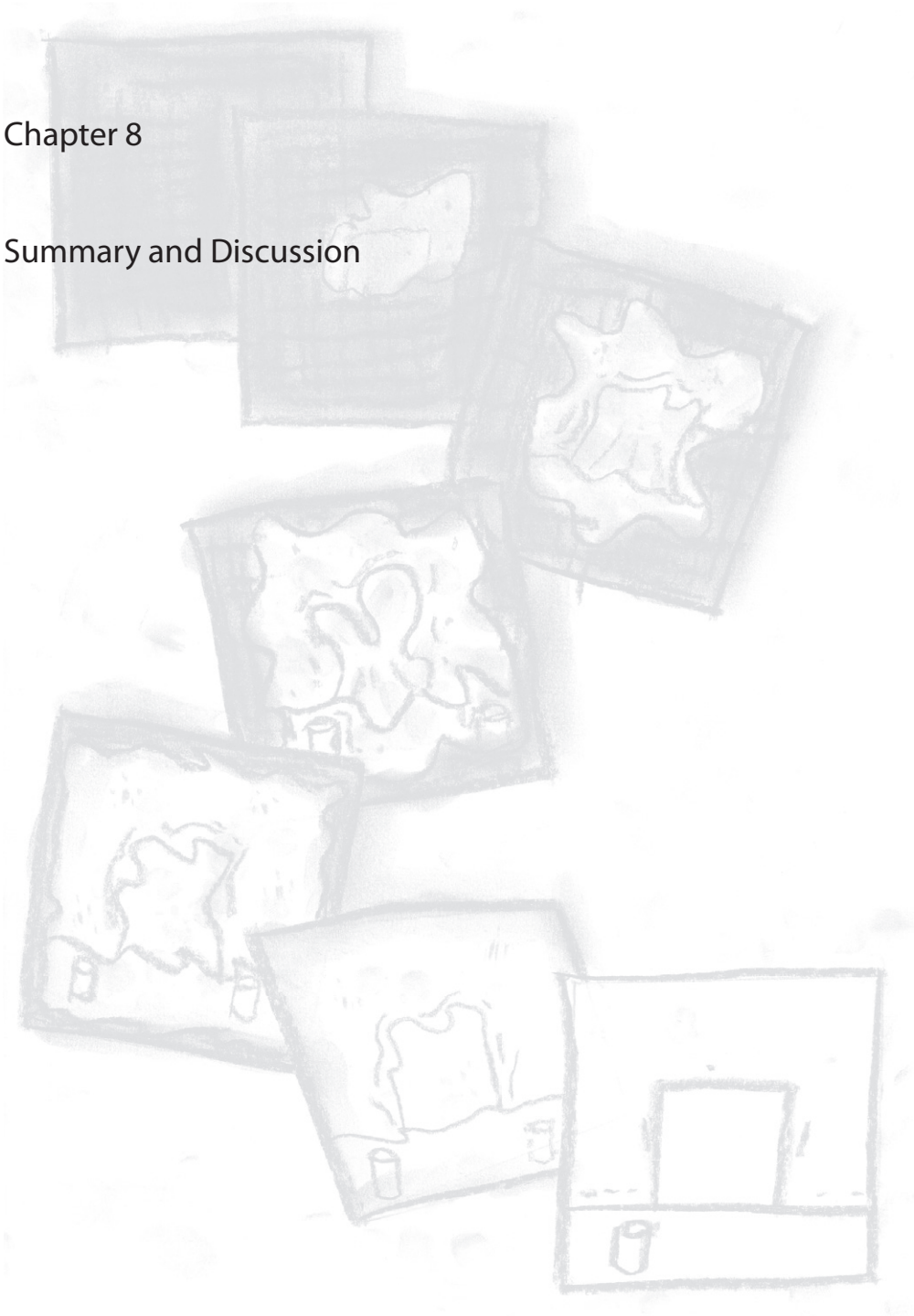
Table 4b: Statistical data on effect of resting and sleeping on headache intensity and headache duration: without and with sleep deficit

Source of variation		dfnum	dfdenom	F-ratio	p-value
Resting	deficit (D)	1	336	0.31	0.58
	rest (R)	1	336	14.47	< 0.001
	D x R	1	336	1.77	0.19
Sleeping	deficit (D)	1	317	0.36	0.81
	sleep (S)	1	317	34.90	0.021
	D x S	1	317	1.51	0.63

dfnum, degrees of freedom in numerator; dfdenom, degrees of freedom in denumerator

Chapter 8

Summary and Discussion



SUMMARY and DISCUSSION

As described in *Chapter 1*, the objectives of this thesis were: (1) To assess all literature concerning prophylactic treatment of migraine in children and adolescents; (2) To describe and evaluate the literature concerning the occurrence and manifestations of psychological (dys)functioning and/or psychiatric comorbidity in children and adolescents with migraine in clinical studies; (3) To evaluate generic health-related Quality of Life (QoL) in children and adolescents with primary headache at an outpatient department in a general hospital; (4) To assess the efficacy of medium-dose riboflavin as a prophylactic drug in childhood migraine; (5) To study generic health-related QoL and psychological functioning as outcomes in a prophylactic intervention study in children with migraine; (6) In a prospective study to investigate sleep deprivation as a potentially causative factor for headache attacks in childhood migraine, and to explore the effect of resting and sleeping after the start of the headache attack on headache symptoms.

With regard to the first aim of the study, *Chapter 2* presents the results of a systematic review of the available evidence for the efficacy of prophylactic pharmacological treatment modalities in children and adolescents with migraine.
The conclusion of this review is that only flunarizine is evidence-based effective as migraine prophylaxis in children and adolescents compared with placebo, and that there is conflicting evidence for the use of propranolol. Nimodipine, clonidine, L-5HTP, trazodone and papaverine showed no effect when compared with placebo. With regard to widely used drugs for migraine prophylaxis in children and adolescents, such as valproic acid and pizotifen, either no studies have been performed or they are methodologically inadequate. Therefore, evidence-based recommendations for these drugs are not possible. Generally, because of the small number of studies and the methodological shortcomings, conclusions regarding effectiveness had to be drawn with caution.
In addition, it appeared that headache improvement and adverse events are the two outcome measures most frequently used in the included trials. Although most studies described the adverse events as 'mild', the simple description of the kind and number of adverse events gave insufficient insight into the appreciation by the child of the severity of the adverse effect in relation to the beneficial effects of the intervention, especially since children are unable to verbalize such abstract concepts. Therefore, it was concluded that, in intervention studies in children with headache or migraine, not only clinical improvement and registration of adverse effects should be used as outcome, but also QoL and satisfaction of the intervention by the child and/or its parents.

Based on the conclusions of this review, it was decided to perform a prophylactic intervention study in children with migraine with headache frequency, intensity and duration as primary outcome and QoL as secondary outcome, measuring QoL on a broad number of life domains to acquire in-depth insight into the net combination of the beneficial and the adverse effects of the intervention.

In addition, it was decided to use psychological functioning as secondary outcome because in several descriptive clinical studies, a substantial proportion of children and adolescents with migraine seemed to demonstrate psychological dysfunctioning and/or psychiatric comorbidity to some extent[1-11], raising the question whether this could be influenced by an intervention directed at reducing the migraine attacks.
Until now, no systematic review has been performed (of clinical studies) regarding the occurrence of psychological dysfunctioning and/or psychiatric comorbidity in children and adolescents with migraine. Consequently, such a review was conducted and is described in *Chapter 3*. We performed an extensive literature search in Pubmed, PsycInfo, Embase and the Cochrane Database and screened the included studies for relevance and quality. Based on the best-evidence synthesis method of Slavin[12], we concluded that there is strong evidence that children and adolescents with migraine in a clinical setting do not exhibit more withdrawn behaviour, do not have more thought problems, do not have more social problems, and do not exhibit more delinquent or aggressive behaviour than healthy children and adolescents. Furthermore, we found strong evidence that children and adolescents with migraine have more somatic complaints and exhibit more internalizing behaviour which, given the construct of the outcome measure used, is a consequence of the nature of their disease rather than a sign of psychological dysfunctioning. Finally, compared with healthy children and adolescents, we found limited evidence that children and adolescents with migraine in a clinical setting are more frequently diagnosed with an oppositional defiant disorder but not more frequently diagnosed with ADHD, conduct disorder, dysthymia or depression. However, because the included studies and the method of assessing the evidence had the potential to cause bias, these conclusions require some caution.

With reference to our third aim, in *Chapter 4* we present an exploratory study in children and adolescents with primary headache, referred to the outpatient paediatric department of a general hospital, with the purpose of measuring QoL at referral on a broad range of life domains. Another goal of this study was to become acquainted with the use of this type of QoL measurement tool in children and adolescents with headache in a clinical

setting, in order to use it as outcome in the prophylactic intervention study in children with migraine.

This study took place between October 2003 and October 2005 at the outpatient paediatric department of the Vlietland Hospital. All children and adolescents referred because of primary headache were investigated according to protocol. QoL was measured using the Dutch version of the Child Health Questionnaire (CHQ-PF50 Dutch edition). On all but one subscale (i.e. self-esteem) the QoL of the children and adolescents with primary headache was decreased compared with a cohort of healthy children and adolescents, especially on the domains of mental health, parental impact time, and family cohesion. Compared with a historic control cohort of children and adolescents with asthma, the QoL was significantly worse for our headache group on seven subscales and significantly better on one subscale (i.e. general health perception). Compared with a historic control cohort of children and adolescents with ADHD, the QoL was significantly worse on six subscales but significantly better on three subscales. There were no significant differences on any QoL subscale between children and adolescents with tension-type headache and children and adolescents with migraine.

On the basis of this study we concluded that the QoL in children and adolescents with primary headache presenting at the outpatient paediatric department of a general hospital seems to be considerably diminished, and that there are no differences in QoL between children and adolescents with tension-type headache and those with migraine. In addition, we concluded that generic QoL, as measured with the CHQ, could be used as outcome in a prophylactic intervention study in children with migraine.

As the QoL in children with migraine is poor at referral to a specialist, one may hypothesize that the poor QoL is due to the headaches the child is suffering from. From this perspective an intervention aiming at decreasing the headache attacks in frequency and/or in intensity is expected to have a concomitant beneficial effect on QoL. However, one might also hypothesize that the headaches the child is suffering from are an expression of a poor QoL whereas the poor QoL may primarily be attributed to other factors, such as psychological dysfunctioning, psychiatric comorbidity, and/or family or school problems. From that perspective an intervention aiming at decreasing the headache attacks in frequency and/or in intensity, would *not* have a concomitant beneficial effect on QoL. Therefore, from a clinical point of view, performing a prophylactic intervention study in children with migraine with QoL as outcome, might also offer additional information to help address this issue. In other words, is the poor QoL in children with migraine due to the migraine itself or due to other factors?

In *Chapter 5,* the results of the prophylactic intervention study in children with migraine are presented with regard to the primary outcomes, i.e. headache frequency and intensity. Riboflavin (vitamin B2) in a dosage of 50 mg per day was chosen as verum medication. Riboflavin had already been used as a prophylactic agent in studies on adults with migraine, including two open-label studies[13,14] and two randomized controlled trials[15,16]. In these latter trials, riboflavin was proven effective with minimal adverse events. These adverse events were diarrhoea and polyuria (each occurring in 1 of 43 adults with migraine treated with riboflavin)[15,16]. As riboflavin seemed to have the qualities of an ideal drug for migraine prophylaxis (low cost, superior effectiveness compared with placebo, and minimal adverse events) and since no intervention studies with riboflavin in children or adolescents with migraine as verum medication had been published at the start of our research, we decided to perform a randomized, placebo-controlled, double-blind, crossover trial in children with migraine with riboflavin as the acting agent. This trial eventually included 42 children (6 to 13 years) with migraine of which 14 children also suffered from tension-type headache. Following a 4-week baseline period, all children received riboflavin or placebo for 16 weeks, and then placebo or riboflavin for 16 weeks with a washout period of 4 weeks in between. The sequence of riboflavin and placebo was determined by randomization and blinded for both the patient and the parents, as well as for the investigators. The primary outcome measure was reduction in mean frequency of migraine attacks and episodic tension-type headache in the last four weeks of the riboflavin and placebo phase, compared with the preceding baseline or washout period. Secondary outcome measures were mean severity and mean duration of migraine and tension-type headaches in the last 4 weeks of the riboflavin and placebo phase, compared with the preceding baseline or washout period.
No significant difference in the reduction of mean frequency of migraine attacks in the last month of treatment was found between placebo and riboflavin ($p = 0.44$, two-tailed). However, a significant difference in reduction of mean frequency of episodic tension-type headache was found in favour of the riboflavin treatment ($p = 0.04$, two-tailed). We concluded that in this group of children with migraine, there is no evidence that riboflavin has a prophylactic effect on migraine attacks. We also concluded that there is some evidence that riboflavin may have a prophylactic effect on episodic tension-type headaches in children with migraine.

With regard to our fifth aim, *Chapter 6* presents a study among children with migraine on the effect of riboflavin on QoL and psychological functioning as secondary outcome measures. Riboflavin did not have any superior effect compared to placebo with

regard to improvement of generic QoL (as measured with the CHQ) and psychological functioning (as measured with the Child Behaviour Checklist = CBCL-Dutch edition), on all investigated life domains and psychological subscales. Therefore, we collapsed the data of the riboflavin-placebo group with the placebo-riboflavin group to gain more statistical power for the comparison with the data of healthy children, both at baseline and at the end of the trial. In this collapsed group, at baseline the QoL was significantly worse on all 13 CHQ life domains compared with healthy controls. On the other hand, all CBCL baseline scores were within the range of healthy controls with exception of the scales thought problems, somatic complaints and internalizing behaviour. The deviant scores on the latter two scales probably resulted from the migraine itself, given the construct of the CBCL, and were therefore not an indication of psychological dysfunctioning.

Throughout the trial, in the collapsed group we saw an improvement on 11 of the 13 QoL domains and on all CBCL scales, leading to normalization of scores on the QoL domains mental health, self-esteem, parental impact emotional and parental impact time, and on all deviant CBCL scales, with the exception of somatic complaints. Additional evidence for the conclusion that the poor QoL in children with migraine at referral is primarily caused by the headache attacks themselves is found in the post-hoc analysis with regard to the association of the primary headache parameters (headache frequency, intensity and duration) and QoL, demonstrating that, in general, in all phases of the trial most QoL domains are inversely related, not only to headache frequency but also to duration of the headache.

The question posed above (i.e. is the poor QoL in children with migraine at referral to a specialist due to the headache attacks themselves or is this poor QoL due to other factors?) could therefore be answered in favour of the first hypothesis. In addition, we concluded that both QoL and psychological functioning can be used as outcome variables in intervention studies in children with migraine. Finally we concluded that, compared with placebo, riboflavin has no superior effect on improvement of QoL and psychological functioning in this group of children.

Interestingly, there were two QoL life domains that did not improve during the trial. These were the domains global health and family cohesion. This might be due to the fact that both are single-question domains. This means that there is a range of only 5 answering alternatives for parents to assess their child's health and the quality of the relations within their family, respectively; this is considerably less than the amount of variation available in the other QoL domains. As to global health, another explanation might be that the poor QoL on this domain persisted because the parents of children with migraine are inclined to believe that their child's health is poor, irrespective of any improvement due to

treatment. Therefore, additional studies are needed to address these important questions about the effect of treatment on internal family relations, as well as on parent's perception of the health of their child with migraine.
In addition, another point of interest regards the CBCL subscale aggressive behaviour and the CBCL scale externalizing behaviour. At the end of the trial there was a significant deviant score on both these scales compared with healthy controls, but in favour of children with migraine. The subscale aggressive behaviour is one of the two subscales that form the externalizing behaviour score, the other being delinquent behaviour. Since there was no significant difference between the score on the subscale delinquent behaviour compared with healthy controls at the end of the trial, we concluded that the low score on the main scale externalizing behaviour has to be attributed to the low score on the subscale aggressive behaviour. This means that, while psychological functioning in children with migraine at referral to a specialist seems (in general) to be within normal limits, improvement is still possible after an intervention which decreases headache frequency, intensity and duration, eventually even resulting in superior scores on some aspects of psychological functioning in comparison with healthy children. This is also demonstrated by the post-hoc analysis with regard to the association of the primary headache parameters (headache frequency, intensity and duration) and the main CBCL scales of internalizing and externalizing behaviour and total score, showing that especially in phase 1 and phase 2 of the trial these parameters were generally positively related with headache frequency and headache duration.

Finally, in reference to our sixth aim, in *Chapter 7* the effect of sleep deprivation as a causative factor on headache attacks in children with migraine, and (once a headache attack has started) the relationship between resting and sleeping on headache symptoms, is explored within the context of the prophylactic intervention study with riboflavin as verum medication (described in the previous two chapters).
In this trial, only 6.2% of the headache attacks were preceded by the occurrence of one night with less sleep than usual. This had no effect on either headache intensity or duration. During the headache attacks, resting decreased headache intensity in 76.0% of the attacks occurring after a preceding sleep deficit and in 54.4% of the attacks without preceding sleep deficit ($p = 0.04$). Sleeping decreased headache intensity in 84.0% of the attacks with a sleep deficit and in 63.6% of the attacks without preceding sleep deficit ($p = 0.05$). In case of a favourable effect of resting and sleeping on headache intensity, a significant decrease of headache duration was also found, compared with attacks with no effect of resting and sleeping on headache intensity ($p < 0.001$ and $p = 0.021$, respectively). We

concluded that in these young children with migraine, one night with less sleep was not an important precipitating factor of migraine attacks. However, once a child was suffering from a headache attack, resting and sleeping resulted in a clinically relevant improvement of headache intensity and duration.

Clinical implications and recommendations for future research

Based on the systematic review described in the second chapter of this thesis, we found that only flunarizine is proven evidence-based effective for childhood migraine. However, this treatment modality has the potential of serious adverse effects and is therefore contraindicated for use in children or adolescents in most European countries and the United States, thereby creating considerable uncertainty for physicians with regard to prescribing migraine prophylaxis in children and adolescents. Nevertheless, a broad variety and ever-increasing number of prophylactic drugs are being prescribed to them, stressing the need for high-quality research to evaluate the pharmacological prophylactic treatment of children and adolescents with migraine. Therefore more high-quality randomized controlled trials evaluating the most frequently used pharmacological prophylactic treatments should be performed. We also recommend that future high-quality studies on existing and novel treatment modalities in children and adolescents with migraine should be conducted and reported according to the Consolidated Standards of Reporting of Trials (CONSORT) statement, as a substantial proportion of the published intervention studies in this field do not match these criteria and therefore do not provide sufficient evidence.

Also, based on this systematic review, we recommend that in future intervention studies in children and adolescents with migraine not only should clinical improvement in headache and registration of adverse events be measured, but also secondary outcomes such as QoL, satisfaction of the intervention by the child and/or its parents, and psychological functioning, to broaden the outcome area to get a more complete picture of the effects of the intervention.

This holds true especially for treatment modalities which have the potential of adverse effects on mood, cognition and behaviour such as anti-epileptic drugs, which are widely used for migraine prophylaxis. Using these outcomes in intervention studies in children with migraine can provide an answer regarding the clinically relevant question with regard to the combined result of the beneficial and adverse effects of these interventions

We also conclude, based on the systematic review of the literature concerning psychological functioning and psychiatric comorbidity in children and adolescents with

migraine that for the involved specialist, in general, it does not seem necessary to refer a child with migraine to a child psychologist or a child psychiatrist. However, since the number of studies included in this review was limited, and both the included studies and the method of assessing the evidence had the potential to cause bias, additional studies are needed to further elucidate the occurrence of psychological dysfunctioning and psychiatric comorbidity in children and adolescents with migraine. In future studies it is preferable that both the mother and father complete the questionnaires independently or, if this is not feasible, the parent who completes the questionnaire should clearly state if he or she is the mother or the father of the child. Subsequently, separate statistical analysis for mother's and father's reports should be performed and described. Relatively large samples of both children and healthy controls should be included, preferably more than 25 in each group. A concealed selection strategy should be employed, preferably in sample selections of children from different hospitals, selected in a randomly ordered fashion. Validated outcome measures should be used which preferably have been used in previous studies in this field in order to consolidate and/or generate further evidence. Finally, appropriate statistical analyses should be performed on the most important outcome measures.

The generic QoL in children and adolescents with primary headache is poor at referral to a paediatric outpatient department in a general hospital on nearly all life domains, and comparable to or worse than the QoL of children with Attention Deficit Hyperactivity Disorder (ADHD) or asthma. However, the statistical comparison method had several shortcomings because we could only compare our data with the published QoL data of groups of children with asthma or ADHD from different countries and studied in a different time period. Also, we found no statistically significant differences in QoL on all life domains between children with tension-type headache or migraine. This has clinical consequences as it implies that the most important factor in referral might be the perception of the referring physician of the burden placed on the child and its family as induced by the headache, and not the type of headache itself. This stresses the need for using generic QoL as outcome in daily practice for a physician, specialized in treatment of these children, in order to objectively evaluate the effect of his or her treatment on the child and its family. Finally, and also relevant from a clinical point of view, this study clearly showed that a child with primary headache, severe enough to consult a specialist, places a heavy burden on its parents and brothers and sisters, implying that the specialist, to whom this child is referred, should inquire about the consequences of the headaches, not only for the child itself, but also for its parents and family and should do so consistently during treatment and follow-up.

In the fifth chapter of this thesis the results of a prophylactic placebo-controlled crossover trial in children with migraine with riboflavin in a daily dosage of 50 mg are presented. Unlike in adults, we could not find evidence of a superior effect of riboflavin compared with placebo. This might be due to the dosage used as a recent study showed[17]. In this retrospective study, 41 children or adolescents with migraine were treated with 200 mg or 400 mg riboflavin on a daily basis for three to six months, eventually demonstrating that 68.4% of the included children had a reduction of 50% or more in the frequency of all headache attacks without any serious adverse effects[17]. However, this study was retrospective, no placebo group was included and treatment was not concealed, all of which are essential for assessing study quality. Future studies should be placebo-controlled, randomized, double-blind trials according to the CONSORT statement. The dosage of riboflavin should be at least 200 mg but preferably 400 mg on a daily basis.
We did find some evidence that riboflavin may have a prophylactic effect on episodic tension-type headaches in children with migraine. To investigate if riboflavin indeed has a primary effect on tension-type headache in children or adults, placebo-controlled, randomized, double-blind trials according to the CONSORT statement in children or adults with primary tension-type headache with and without migraine should be performed. Nevertheless, from a clinical point of view, based upon our study and given the lack of evidence-based effective prophylactic treatment modalities without adverse events in children with migraine, we consider it justified to prescribe riboflavin, in the dosage as described in our study, for a period of at most four months, in children with migraine who also suffer from tension-type headaches.

In the study described in the sixth chapter of this thesis we found that riboflavin in fact acted as a placebo on all investigated QoL domains and CBCL subscales throughout the trial. During the trial the QoL improved on 11 of the 13 life domains and on all CBCL scales, resulting in normalization of scores on 4 of 13 life domains and on all but 1 CBCL scale. This has clinical implications, as this study shows that QoL in children with migraine at referral to a specialist is poor, not due to psychological dysfunctioning, but due to the disease itself. One could argue that referral of a child with migraine to a child psychologist or child psychiatrist should, preferably, be considered after some period of proper treatment. However, this is the first intervention study in children with migraine in which QoL and psychological functioning have been used as outcome, therefore providing only moderate evidence for this assertion. In order to develop this to an evidence-based guideline, more comparative studies are needed. However, we have shown that QoL in children with migraine does not improve on the life domains of global health and family cohesion,

despite improvement of the headache attacks. From this perspective, when consultation of a child psychologist or child psychiatrist is eventually deemed as necessary in the treatment of a child with migraine, the involved psychologist or psychiatrist might explore and (if necessary) try to adjust the QoL on these particular life domains. This implies the need to explore how the parents perceive their child with migraine, and perhaps to try and alter that image. For example, instead of seeing their child as being (more-or-less consistently) sick and helpless, parents might see their child as having a relatively mild condition with a good prognosis when simple life rules are adopted and combined with proper pharmacological treatment. In addition, when required, the quality of the internal relationships within the family of the child with migraine might be altered to promote a more cohesive and beneficial situation.

Finally, we found that a single night of less sleep is not an important migraine trigger in childhood migraine. It was also found that, in case of a headache attack, resting and sleeping resulted in a clinically relevant decrease of intensity and duration of the attack, compared with not resting and sleeping at all. Resting and sleeping had a more profound impact with regard to decrease of headache intensity and duration when the child had slept less than usual the previous night. These findings have clinical relevance because they provide moderate evidence that a shortage of sleep in children with migraine will not automatically provoke a headache attack, and that resting and sleeping are sensible actions when a headache attack has started in children with migraine, especially when the child has slept less than usual in the night preceding the headache attack. However, few studies have focused on sleep and sleeping behaviour in children with migraine. More prospective studies are needed to further unravel the relationship between sleep and headache in children with migraine.

REFERENCES

1. Rossi LN, Cortinovis I, Menegazzo L, Menini S, Carnelli V. **Behaviour during attacks and assessment of intensity in primary headaches of children and adolescents.** Cephalalgia 2006;26:107-12.
2. Passchier J, Orlebeke JF. **Headaches and stress in schoolchildren: an epidemiological study.** Cephalalgia 1985;5:167-76.
3. Guidetti V, Mazzei G, Ottaviano S, Pagliarini M, Paolella A, Seri S. **The utilization of the Rorschach test in a case-controlled study.** Cephalalgia 1986;6:87-93.
4. Mazzone L, Vitiello B, Incorpora G, Mazzone D. **Behavioural and temperamental characteristics of children and adolescents suffering from primary headache.** Cephalalgia 2006;26:194-201.
5. Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, Resch F. **Emotional and behavioural problems in children and adolescents with primary headache.** Cephalalgia 2003;23:206-13.
6. Pakalnis A, Gibbons J, Colvin A. **Comorbidity of psychiatric and behavioral disorders in pediatric migraine.** Headache 2005;45:590-6.
7. Anttila P, Sourander A, Metsahonkala L, Aromaa M, Helenius H, Sillanpaa M. **Psychiatric symptoms in children with primary headache.** J Am Acad Child Adolesc Psychiatr 2004;43:412-9.
8. Vannata K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. **Multiple perspectives on the psychological functioning of children with and without migraine.** Headache 2008;48:994-1004.
9. Smith M, Martin-Herz S, Womack W, Marsigan J. **Comparative study of anxiety, somatization, functional disability and illness attribution in adolescents with chronic fatigue or migraine.** Paediatrics 2003;111:e376-81.
10. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, Cucchiara S, Guidetti V. **Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL).** Cephalalgia 2007;27:211-9.
11. Guidetti V, Galh F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S. **Headache and psychiatric comorbidity: clinical aspects and outcome in an 8 year follow-up study.** Cephalalgia 1998;18:455-62.
12. Slavin, RE. **Best evidence synthesis: an intelligent alternative to meta-analysis.** J Clin Epidemiol 1995;48:9-18.
13. Schoenen J, Lenaerts M, Bastings E. **High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study.** Cephalalgia 1994;14:328-9.
14. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl K, Arnold G. **High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre.** European Journal of Neurology 2004;11:475-7.
15. Schoenen J, Jacquy J, Lenaerts M. **Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial.** Neurology 1998;50:466-70.
16. Sándor P, Áfra J, Ambrosini A, Schoenen J. **Prophylactic treatment of migraine with ß-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.** Headache 2000;40:30-5.
17. Condò M, Posar A, Arbizzani A, Parmeggiani A. **Riboflavin prophylaxis in pediatric and adolescent migraine.** Journal of Headache and Pain 2009;10(5):361-5.

Chapter 9

References

REFERENCES

Aaltonen K, Hamalainen ML, Hoppu K. Migraine attacks and sleep in children. Cephalalgia 2000;20:580-4.

Achenbach TM, Edelbrock CS. Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. Monogr Soc Res Child Dev 1981;46:1-82.

Achenbach TM. Manual for the Child Behaviour Checklist/4-18 and 1991 profiles. Burlington VT 1991: University of Vermont, Department of Psychiatry.

Ad Hoc Committee on the Classification of Headache of the National Institute of Neurological Diseases and Blindness. Classification of headache. JAMA 1962;179:717-718.

Alderson P, Green S, Higgings JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated march 2004]. In: The Cochrane library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Andrasik F, Kabela E, Quinn S, Attanasio V, Blanchard EB, Rosenblum EL. Psychological functioning of children who have recurrent migraine. Pain. 1988;34(1):43-52.

Annequin D, Tourniaire B, Massiou H. Migraine and headache in children and adolescence. Pediatr Clinic North Am 2000;37:617-631.

Anttila P. Sourander A, Metsahonkala L, Aromaa M, Helenius H, Sillanpaa M. Psychiatric symptoms in children with primary headache. J Am Acad Child Adolesc Psychiatr 2004;43:412-419.

Arts W, Scholte H, Boogaard J, Kerrebijn K, Luyt-Houwen I. NADH-CoQ reductase deficient myopathy: successful treatment with riboflavin. Lancet 1983;2:581-582.

Bandell-Hoekstra I, Abu-Saad HH, Passchier J, Knipschild P. Recurrent headache, coping, and quality of life in children: a review. Headache 2000;40:357-370.

Barbiroli B, Montagna P, Cortelli P, Funicello R, Iotti S, Monari L, Pierangeli G, Zaniol P, Lugaresi E. Abnormal brain and muscle energy metabolism shown by 31P magnetic resonance spectroscopy in patients affected by migraine with aura. Neurology 1992;42:1209-14.

Battistella PA, Ruffilli R, Cernetti R, Pettenazzo A, Baldin L, Bertoli S, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache 1993;33:36-39.

Battistella PA, Ruffilli R, Moro R, Fabiani M, Bertoli S, Antolini A, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache 1990;30:264-268.

Behan PO. Pizotifen in the treatment of severe recurrent headache single and divided dose therapy compared. Br J Clin Pract 1982;36:13-17.

Bergeret J: la personalité normale et patologique. Paris: Bordas 1974.

Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl K, Arnold G. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. Eur J Neurol 2004;11:475-477.

Bruijn J, Passchier J, Locher H, Dijkstra N, Arts W-F. Medium dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomized, double-blind, crossover trial. Cephalalgia 2010 (e-Pub ahead of print).

Bruijn J, Arts W-F, Duivenvoorden H, Dijkstra N, Raat H, Passchier J. Quality of life in children with primary headache in a general hospital. Cephalalgia 2009;29:624-630.

Bruijn J, Verhagen A, Damen L, Passchier J. Evidence-Based Guideline "Migraine in Children" as part of Dutch National Guideline "Pain Measurement and Treatment in Children", http://www.nvk.pedianet.nl/pdfs/nvk_richtlijn_pijn_bij_kinderen.pdf.
Nederlandse Vereniging voor Kindergeneeskunde (Dutch Society of Paediatricians) 2008:53-65.

Bruni O, Galli F, Guidetti V. Sleep hygiene and migraine in children and adolescents. Cephalalgia 1999;19 Suppl 25:57-59.

Caruso JM, Brown WD, Exil G, Gascon GG. The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. Headache 2000;40:672-676.

Cole DC, Hudak PL. Prognosis of non-specific work-related musculoskeletal disorders of the neck and upper extremity. Am J Int Med 1996;29:657-668.

Condò M, Posar A, Arbizzani A, Parmeggiani A. Riboflavin prophylaxis in pediatric and adolescent migraine. Journal of Headache and Pain 2009;10(5):361-365.

Connelly M, Rapoff MA. Assessing Health-Related Quality of Life in Children with Recurrent Headache: Reliability and Validity of the PedsQL™ 4.0 in a Pediatric Headache Sample. J Pediatr Psychol 2006;31(7):698-702.

Constitution of the World Health Organization basic documents. Geneva, Switzerland: World Health Organization 1948.

Cooper PJ, Bawden HN, Camfield PR, Camfield CS. Anxiety and Life Events in Childhood Migraine. Pediatrics 1987;79;999-1004.

D'Amico D, Usai S, Grazzi L, Rigamonti A, Solari A, Leone M, Bussone G. Quality of life and disability in primary chronic daily headaches. Neurol Sci 2003;24:S97-S100.

Damen L, Bruijn J, Koes BW, Berger MY, Passchier J, Verhagen AP. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. Cephalalgia 2006;26(4) 373-383.

Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials. Cephalalgia 2006; 26(5):497-505.

Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. Symptomatic treatment of migraine in children: a systematic review of medication trials. Pediatrics 2005; 116(2):e295-302.

Del Bene E, Poggioni M, Michelacci S. Lisuride as a migraine prophylactic in children: an open clinical trial. Int J Clin Pharmacol Res 1983;3:137-41.

Di Lorenzo C, Pierelle F, Coppola G, Grieco G, Rengo C, Ciccolella M, Magis D, Bolla M, Casali C, Santorelli F, Schoenen J. Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. Neurology 2009;72:1588-1594.

Evers S, Marziniak M, Frese A, Gralow I. Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. Cephalalgia 2009;29:436-444.

Ezzo J, Berman B, Hadhazy VA, Jahad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? A systematic review. Pain 2000;86:217-25.

Feikema WJ. [Headache and chronic sleep deprivation: an often missed relationship in children and also in adults]. Ned Tijdschr Geneeskd 1999;143:1897-1900.

Forsythe WI, Gillies D, Sills MA. Propanolol ('Inderal') in the treatment of childhood migraine. Dev Med Child Neurol 1984;26:737-41.

Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, Cucchiara S, Guidetti V. Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL). Cephalalgia 2007;27:211-219.

Garcia-Monco JC, Foncea N, Bilbao A, Ruiz de Velasco I, Gomez-Beldarrain M. Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients. Cephalalgia 2007;27:920-8.

Geurts JW, Van Wijk RM, Stolker RJ, Groen GJ. Efficacy of radiofrequency procedures for the treatment of spinal pain: a systematic review of randomized clinical trials. Reg Anesth Pain Med 2001;26:394-400.

Gillies D, Sills M, Forsythe I. Pizotifen (Sandomigran) in childhood migraine. A double-blind controlled trial. Eur Neurol 1986;25:32-35.

Gilman DK, Palermo TM, Kabbouche MA, Hershey AD, Powers SW. Primary headache and sleep disturbances in adolescents. Headache 2007;47:1189-1194.

Gladstein J, Holden WE. Chronic daily headache in children and adolescents: a 2-year prospective study. Headache 1996;36:349-51.

Goodwin JL, Silva GE, Kaemingk KL, Sherrill DL, Morgan WJ, Quan SF. Comparison between reported and recorded total sleep time and sleep latency in 6- to 11-year-old children: the Tucson Children's Assessment of Sleep Apnea Study (TuCASA). Sleep Breath 2007;11:85-92.

Guidetti V, Galh F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S. Headache and psychiatric comorbidity: clinical aspects and outcome in an 8 year follow-up study. Cephalalgia 1998;18:455-462.

Guidetti V, Mazzei G, Ottaviano S, Pagliarini M, Paolella A, Seri S. The utilization of the Rorschach test in a case-controlled study. Cephalalgia 1986;6:87-93.

Guidetti V, Moscato D, Ottaviano S, Fiorentino D, Fornara R. Flunarizine and migraine in childhood. Cephalalgia 1987;7:263-266.

Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol 1993;46:1417-1432.

Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. Headache 2006;46:1327-1333.

Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988; 8(Suppl 7):1-96.

Headache Classification Committee of the International Headache Society. The International Classification of headache disorders. Cephalalgia 2004; 24 (Suppl 1):1-152.

Hermann C, Kim M, Blanchard EB. Behavioral and prophylactic pharmacological intervention studies of pediatric migraine: an exploratory meta-analysis. Pain 1995;60:239-256.

Hersey AD, Powers SW, LeCates S, Bentti AL. Effectiveness of nasal sumatriptan in 5- to 12-year-old children. Headache 2001;41:693-697.

Hershey AD, Powers SW, Bentti AL, de Grauw TJ. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. Headache 2000;40:539-549.

Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche M. Effectiveness of topiramate in the prevention of childhood headaches. Headache 2002;42:810-818.

Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, Burdine D, Manning P, Kabbouche MA. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache 2007;47:73-80.

Hunfeld JAM, Fauser BCJM, de Beaufort LD, Passchier J. Child development and quality of parenting in lesbian families: no psychosocial indications for a-priori withholding of infertility treatment. A systematic review. Hum Repro Update 2001;7(1):579-590.

Hunfeld JAM, Passchier J, Perquin CW, Hazebroek-Kampschreur AAJM, van Suijlekom-Smit LWA, van der Wouden JC. Quality of life in adolescents with chronic pain in the head or at other locations. Cephalalgia 2001;21:201-206.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of randomized clinical trials: is blinding necessary? Contr Clin Trials 1996;17:1-12.

Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, Resch F. Emotional and behavioural problems in children and adolescents with primary headache. Cephalalgia 2003;23:206-213.

Karwautz A, Wöber C, Lang T, Bock A, Wagner-Ennsgraber C, Vesely C, Kienbacher C, Wöber-Bingol C. Psychosocial factors in children and adolescents with migraine and tension-type headache: a controlled study and review of the literature. Cephalalgia 1999;19:32-43.

Kernick D, Campbell J. Measuring the impact of headache in children: a critical review of the literature. Cephalalgia 2009;29:3-16.

Kreisler L: L'enfant du désordre psychosomatique. Paris: Privat 1981.

Landgraf JM, Abetz L, Ware JE. The CHQ User´s Manual. Second Printing. Boston, MA. Health Act, 1999.

Landgraf JM, Maunsell, Speechley KN, Bullinger M, Campbell S, Abetz L, et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. Qual Life Res 1998;7:433-445.

Landgraf JM, Ware JE, Rossi-Roh K (1993) Measuring the Relative Health and Well-Being of Children with Attention Deficit Hyperactivity Disorder. Results from the Children's Health and Quality of Life Project. (Final report to Ciba Geigy, Inc., Project MCS#447). Boston, MA: The Health Institute, New England Medical Center.

Landgraf JM, Ware JE, Schor E, Davies AR, Rossi-Roh K (1993a, June 27). Comparison of health status profiles for children with medical conditions: preliminary psychometric and clinical results form the Children's Health and Quality of Life Project. Paper presented at 10th Annual Meeting of the Association for Health Services Research, Washington D.C.

Landgraf JM, Ware JE, Schor E, Davies AR, Rossi-Roh K (1993b, June 6) Health profiles in children with psychiatric and other medical conditions. Paper presented at 9th World Congress of Psychiatry, Rio de Janeiro, Brazil.

Langeveld J, Koot H, Passchier J. Headache Intensity and Quality of Life in Adolescents. How are Changes in Headache Intensity in Adolescents Related to Changes in Experienced Quality of Life? Headache 1997;37:37-42.

Langeveld JH, Koot HM, Loonen MC, Hazebroek-Kampschreur AA, Passchier J. A quality of life instrument for adolescents with chronic headache. Cephalalgia 1996;16:183-196.

Lanzi G, Balottin U, Pitillo G, Zambrino CA. Personality characteristics in juvenile tension headache and migraine. Functional Neurology 1994;(9)2:83-88.

Lastra-Martinez, L, Herranz, J, Arteaga, R. Flunarizine or dihydroergotamine in the treatment of migraine in childhood. A randomised study of 50 patients. Anales Españoles de Pediatría. 1990; 32:213-8.

Leonardi M, Steiner T, Scherer A, Lipton RB. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). J Headache Pain 2005;6:429-440.

Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents. Neurology 2004;63:2215-24.

Lewis D, Winner P, Saper J, Ness S, Polverejan E, Wang S, Kurland C, Nye J, Yuen E, Eerdekens M, Ford L. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 2009;123:924-34.

Lipton R, Cady R, Stewart W, Wilks K, Hall C. Diagnostic lessons from the Spectrum Study. Neurology 2002;58(Suppl 6):S27-S31.

Longo G, Rudoi I, Iannuccelli M, Strinati R, Panizon F. L-5-HTP treatment of primary headache in children. Double-blind cross-over vs. placebo. Ped Med Chir (Med Surg Ped) 1984;6:241-6.

Luc ME, Gupta A, Birnberg JM, Reddick D, Kohrman MH. Characterization of symptoms of sleep disorders in children with headache. Pediatr Neurol 2006;34:7-12.

Ludvigsson J. Propranolol used in prophylaxis of migraine in children. Acta Neurol Scand 1974;50:109-15.

Lutschg J, Vassella F. The treatment of juvenile migraine using flunarizine or propranolol. Schweiz Med Wochenschr 1990;120:1731-6.

MacLennan S, Wade F, Forrest K, Ratanayake P, Fagan E, Antony J. High-dose riboflavin for migraine prophylaxis in children; a double-blind, randomized, placebo-controlled trial. Journal of Child Neurology 2008;23:1300-4.

Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium and feverfew for migraine prophylaxis: a randomized trial. Headache 2004;44:885-90.

Mazzone L, Vitiello B, Incorpora G, Mazzone D. Behavioural and temperamental characteristics of children and adolescents suffering from primary headache. Cephalalgia 2006; 26:194-201.

Miller GS. Efficacy and safety of levetiracetam in pediatric migraine. Headache 2004;44: 238-43.

Miller VA, Palermo TM, Powers SW, Scher MS, Hershey AD. Migraine headaches and sleep disturbances in children. Headache 2003;43:362-8.

Montagna, P, Cortelli, P, Monari, L, Pierangeli G, Parchi P, Lodi R, Iotti, S, Frassineti C, Zaniol P, Lugaresi, E, Barbiroli B. 31P-magnetic resonance spectroscopy in migraine without aura. Neurology 1994;44:666-9.

Nodari E, Battistella PA, Naccarella C, Vidi M. Quality of life in young Italian patients with primary headache. Headache 2002;42:268-74.

Noronha MJ. Doeble blind randomised cross-over trial of timolol in migraine in children. Cephalalgia 1985;5 (suppl 3):174-5.

Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. Paediatrics 1987;79:593-7.

Pakalnis A, Gibbons J, Colvin A. Comorbidity of psychiatric and behavioral disorders in pediatric migraine. Headache 2005;45:590-596.

Panetta J, Smith L, Boneh A. Effect of high-dose vitamins, coenzyme Q and high-fat diet in paediatric patients with mitochondrial diseases. Journal of Inherited Metabolic Disease 2004:487-98.

Passchier J, Orlebeke JF. Headaches and stress in schoolchildren: an epidemiological study. Cephalalgia 1985;5:167-176.

Philadelphia panel. Philadelpia panel evidence-based clinical practice guidelines on selected rehabilitation interventions for shoulder pain. Phys Ther 2001;81:1719-30.

Pothmann R. Calcium-antagonist flunarizine vs. low-dose acetylsalicylic acid in childhood migraine: a double-blind study. Cephalalgia 1987;7(suppl. 6):385-6.

Powers SW, Gilman DK, Hershey AD. Headache and psychological functioning in children and adolescents. Headache 2006;46:1404-15.

Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses. Pediatrics 2003;112:e1-5.

Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in pediatric migraine: characterization of age-related effects using PedsQL. Cephalalgia 2004;24:120–127.

Prensky A. Migraine and migrainous variants in pediatric patients. Pediatr Clin N Am 1976;23:461-71.

Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. J Clin Epidemiol 2002;55:67-76.

Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. J Epidemiol Commun Health 2005;59:75-82.

Radat F, Swendsen J. Psychiatric comorbidity in migraine: A review. Cephalalgia. 2005;25:165-78.

Rains JC, Poceta JS. Headache and sleep disorders: review and clinical implications for headache management. Headache. 2006;46:1344-63.

Robinson KA and Dickerson K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol 2002;31:150-153.

Romberg MH, translated by Sieveking EH. Chapter XVII, Neuralgia Cerebralis, Hemicrania, la Migrène. In: A Manual of the Nervous Diseases of Man. London: the Sydenham Society, 1853.

Rossi LN, Cortinovis I, Menegazzo L, Menini S, Carnelli V. Behaviour during attacks and assessment of intensity in primary headaches of children and adolescents.Cephalalgia 2006;26:107-12.

Rothner A, Linder S, Wasiewski W, O'Neill K. Chronic nonprogressive headaches in children and adolescents. Seminars in Pediatric Neurology 2001;8:34-9.

Sackett DL, Haynes RB, Tugwell P. Clinical Epidemiology (1991). Little, Brown and Co., Boston.

Sándor P, Áfra J, Ambrosini A, Schoenen J. Prophylactic treatment of migraine with ß-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache 2000;40:30-35.

Santucci M, Cortelli P, Rossi PG, Baruzzi A, Sacquegna T. L-5-hydroxytryptophan versus placebo in childhood migraine prophylaxis: a double-blind crossover study. Cephalalgia 1986;6:155-7.

Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. Neurology 1998;50:466-470.

Schoenen J, Lenaerts M, Bastings E. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. Cephalalgia 1994;14:328-329.

Schoenen J. Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behaviour and trigeminovascular activation? Biomed Pharmacother 1996;50:71-8.

Schur EA, Noonan C, Buchwald D, Goldberg J, Afari N.A. Twin Study of depression and migraine: evidence for a shared genetic vulnerability. Headache 2009; Apr 27 (e-Pub ahead of print).

Serdaroglu G, Erhan E, Tekgul et al. Sodium valproate prophylaxis in childhood migraine. Headache 2002;42:819-22.

Shivpuri D, Rujesh MS, Jain P. Prevalence and characteristics of migraine among adolescents: a questionnaire survey. Indian Pediatr 2003;40:665-9.

Silberstein SD, Lipton RB, Solomon S, Mathew NT. Classification of daily and near-daily headaches: proposed revisions to the IHS criteria.Headache 1994;34:1-7.

Sillanpaa M, Koponen M. Papaverine in the prophylaxis of migraine and other vascular headache in children. Acta Paediatr Scand 1978;67:209-12.

Sillanpaa M. Changes in the prevalence of migraine and other headaches during the first seven schoolyears. Headache 1983;23:15-9.

Sillanpaa M. Clonidine prophylaxis of childhood migraine and other vascular headache. A double blind study of 57 children. Headache 1977;17:28-31.

Sills M, Congdon P, Forsythe I. Clonidine and childhood migraine: a pilot and double-blind study. Dev Med Child Neurol 1982;24:837-41.

Slavin, RE. Best evidence synthesis: an intelligent alternative to metaanalysis. J Clin Epidemiol 1995;48:9-18.

Smith M, Martin-Herz S, Womack W, Marsigan J. Comparative study of anxiety, somatization, functional disability and illness attribution in adolescents with chronic fatigue or migraine. Paediatrics 2003;111:e376-81.

Sorge F, De Simone R, Marano E, Nolano M, Orefice G, Carrieri P. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. Cephalalgia 1988;8:1-6.

Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double-blind study. Cephalalgia 1985; 5 suppl 2:145-8.

Spierings EL, Ranke AH, Honkoop PC. Precipitating and aggravating factors of migraine versus tension-type headache. Headache 2001;41:554-8.

Stephen Senn: Cross over Trials in Clinical Research 2nd edition; Statistics in Practice; Wiley; ISBN 0 471 49653 7:41-7.

Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996;334:205-11.

Tfelt-Hansen P, Block G, Dahlof C, Diener HC, Ferrari MD, Goadsby PJ, et al. Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia 2000;20:765-86.

The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.

Van Duijn NP, Brouwer HJ, Gooskens RH. Kinderen met hoofdpijn (Children with headache). Medisch Contact 2000;26:971-974.

Van Tulder MW, Furlan A, Bombarbier C, Bouter L, Editorial Board of the Cochrane Collabaration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back review Group. Spine 2003;28:1290-9.

Van Tulder MW, Ostelo R, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft JW. Behavioral treatment for chronic low back pain: a systematic review within the framework of the Cochrane Back Review Group. Spine 2000;25:2688-99.

Vannata K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. Multiple perspectives on the psychological functioning of children with and without migraine. Headache 2008;48:994-1004.

Varni J, Burwinkle T, Lane M. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 2005;3:34.

Vassalli A, Dijk DJ. Sleep function: current questions and new approaches. Eur J Neurosci 2009;29:1830-41.

Vendrame M, Kaleyias J, Valencia I, Legido A, Kothare SV. Polysomnographic findings in children with headaches. Pediatr Neurol 2008;39:6-11.

Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epid 1998; 51:1235-41.

Verhulst F, van der Ende J, Koot H. Handleiding voor de CBCL/4-18 [Manual for the CBCL/4-18 (Dutch edition)]. ISBN 90-75584-03-2.

Victor S, Ryan SW. Drugs for preventing migraine headaches in children (Cochrane review). In: The Cochrane Library, Issue 3, 2003. Chichester, UK: John Wiley & Sons, Ltd.

Von Korff, M: Studying the natural history of back pain. Spine 1994;19:2041S-2046S.

Wang F, Van Den Eeden SK, Ackerson LM, Salk SE, Reince RH, Elin RJ. Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomised, double-blind, placebo-controlled trial. Headache 2003;43:601-10.

Ware JE, Keller SD, Gandek B, Brazier JE, Sullivan M. Evaluating translations of health status questionnaires. Methods from the IQOLA project. International Quality of Life Assessment. Int J Technol Assess Health Care 1995;11:525-51.

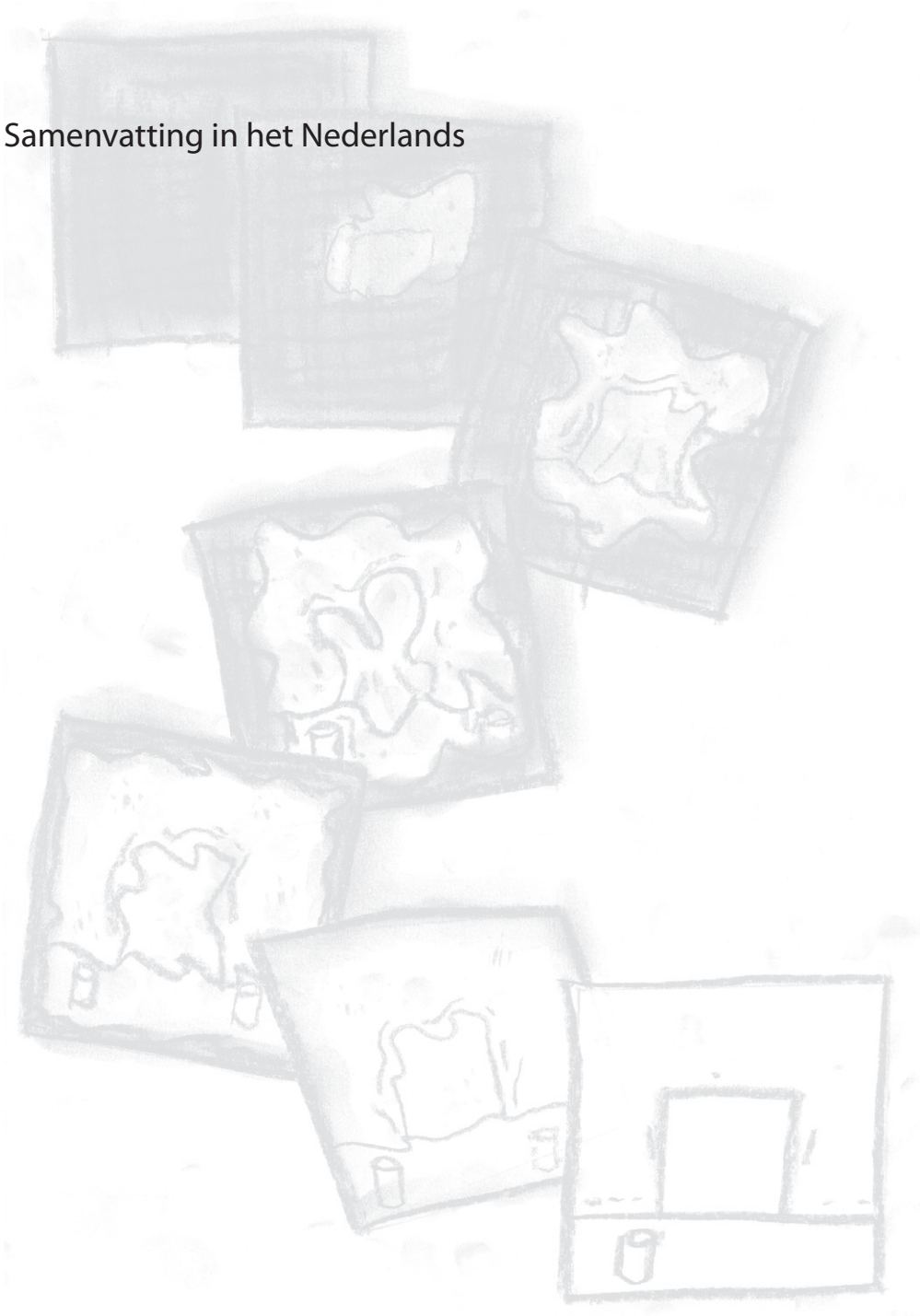
Welch KM, Levine SR, D'Andrea G, Schultz LR, Helpern JA. Preliminary observations on brain energy metabolism in migraine studied by in vivo phosphorus 31 NMR spectroscopy. Neurology 1989;39:538-41.

Wolff HG. Personality features and reactions of subjects with migraine. Arch Neurol Psych 1937;37:895-921.

World Health Organization. Constitution of the World Health Organization basic documents. Geneva, Switzerland: World Health Organization 1948.

Zencir M, Ergin H, Sahiner T, Kilic I, Alkis E, Ozdel L, Gurses D, Ergin A. Epidemiology and symptomatology of migraine among school children. Headache 2004;44:780-5.

Samenvatting in het Nederlands



SAMENVATTING in het NEDERLANDS

In dit proefschrift worden de resultaten gepresenteerd die betrekking hebben op het onderzoek dat uitgevoerd is naar migraine bij kinderen.

De doelstellingen van dit proefschrift worden in hoofdstuk 1 toegelicht. Deze zijn:

1. het beoordelen van alle wetenschappelijke literatuur met betrekking tot de effectiviteit van profylactische medicatie bij kinderen en adolescenten met migraine, dat wil zeggen medicatie die gegeven wordt om migraineaanvallen te voorkómen bij deze doelgroep (hoofdstuk 2),
2. het beschrijven en beoordelen van alle wetenschappelijke literatuur met betrekking tot het vóórkomen en de uitingen van psychisch (dys)functioneren en/of psychiatrische comorbiditeit bij kinderen en adolescenten met migraine (hoofdstuk 3),
3. het onderzoeken en evalueren van de kwaliteit van leven (KvL) bij kinderen en adolescenten met primaire hoofdpijn die verwezen worden naar een polikliniek kindergeneeskunde in een algemeen ziekenhuis (hoofdstuk 4),
4. het beoordelen van de werking van riboflavine als profylactische medicatie bij kinderen met migraine (hoofdstuk 5),
5. het onderzoeken en evalueren van KvL en psychologisch functioneren als uitkomstmaten in een trial waarbij tevens gekeken wordt naar het effect van een profylactische behandeling op hoofdpijnklachten bij kinderen met migraine (hoofdstuk 6),
6. in een prospectieve studie bestuderen in hoeverre slaaptekort een potentieel oorzakelijke factor kan zijn voor hoofdpijn en migraine aanvallen in de kinderjaren en onderzoeken wat het effect is van rusten en slapen na het begin van de hoofdpijn aanval op de hoofdpijn symptomen (hoofdstuk 7).

In *hoofdstuk 2* worden de resultaten beschreven van de systematische literatuurstudie ten aanzien van de effectiviteit van profylactische medicatie bij kinderen en adolescenten met migraine. De conclusie van deze studie is dat alleen flunarizine effectief is als migraineprofylacticum bij deze doelgroep in vergelijking met placebo. Daarnaast werd tegenstrijdig bewijs gevonden voor een superieur effect van propranolol ten opzichte van placebo als profylactische medicatie.
Medicatie zoals nimodipine, clonidine, L-5HTP, trazodon en papaverine toonden geen superieur effect in vergelijking met placebo. Ten aanzien van het gebruik van medicatie

zoals valproïnezuur en pizotifeen – middelen die op grote schaal gebruikt worden voor de profylaxe van migraine bij kinderen en adolescenten - bleek dat er ofwel geen studies zijn uitgevoerd naar de effectiviteit hiervan ofwel dat deze studies methodologisch ontoereikend waren. Om die reden zijn met wetenschappelijk bewijs onderbouwde, zogenaamde evidence-based (EB), aanbevelingen voor deze middelen niet mogelijk.
Concluderend kan gezegd worden dat vanwege het geringe aantal studies en de methodologische tekortkomingen, conclusies over effectiviteit van profylactische medicatie bij kinderen met migraine met de nodige voorzichtigheid moeten worden getrokken.
Uit deze literatuurstudie bleek verder dat hoofdpijnverbetering en bijwerkingen als meest voorkomende uitkomstmaten worden gebruikt. Hoewel in veel studies de bijwerkingen als mild worden beschreven, geeft het eenvoudig weergeven van het soort, het aantal en de ernst van de bijwerkingen onvoldoende inzicht in de waardering door het kind van de bijwerking(en) in combinatie met het gunstige effect van het geneesmiddel. Dit is met name het geval bij jonge, prepuberale kinderen, omdat juist deze kinderen niet of onvoldoende in staat zijn om dergelijke abstracte begrippen goed te verwoorden. Daarom werd geconcludeerd dat, in studies bij kinderen met hoofdpijn of migraine, niet alleen klinische verbetering en de registratie van bijwerkingen van de geneesmiddelen moet worden gebruikt als uitkomstmaat, maar ook andere uitkomstmaten zoals KvL en tevredenheid met de behandeling door het kind en/of de ouders. Op basis van de conclusies van deze studie werd besloten om een profylactische interventie- studie uit te voeren bij kinderen met migraine waarbij de frequentie, de intensiteit en duur van hoofdpijn als primaire uitkomstmaten werden genomen en KvL als secundaire uitkomstmaat waarbij het effect op KvL zou worden onderzocht op een groot aantal levensdomeinen om zodoende tot een optimale evaluatie te komen van de positieve en de negatieve effecten van de interventie.

Daarnaast werd ook besloten om 'psychologisch functioneren' te gebruiken als secundaire uitkomstmaat, dit omdat uit verschillende klinische studies duidelijk werd dat een aanzienlijk deel van de kinderen en adolescenten met migraine psychologische en/of psychiatrische problemen vertonen[1-11] wat de vraag opriep of een interventie, gericht op vermindering van de migraineaanvallen, kan leiden tot een verbetering van deze psychische comorbiditeit. Verder viel op dat er geen systematisch literatuuronderzoek was uitgevoerd ten aanzien van het optreden van psychologisch dysfunctioneren en/of psychiatrische problematiek bij kinderen en adolescenten met migraine in klinische studies. Besloten werd daarom een dergelijke literatuurstudie op te zetten en uit te voeren. De resultaten

hiervan worden beschreven in *hoofdstuk 3.* Een systematisch literatuuronderzoek werd uitgevoerd in Pubmed, PsycINFO, Embase en de Cochrane Database. De geincludeerde studies werden onderzocht op relevantie en kwaliteit. Op basis van de "best-evidence synthesis" methode van Slavin[12] werd vastgesteld dat er sterke aanwijzingen zijn dat kinderen en adolescenten met migraine in een klinische setting in vergelijking met gezonde kinderen en adolescenten niet meer teruggetrokken gedrag vertonen, niet meer cognitieve problemen vertonen, niet meer sociale problemen hebben en niet vaker delinquent of agressief gedrag vertonen. In een aantal studies werden sterke aanwijzingen gevonden dat kinderen en adolescenten met migraine meer somatische klachten en meer internaliserend probleemgedrag vertonen wat, gezien de opzet van deze studies en de gebruikte vragenlijsten, veel meer een gevolg is van de aard van hun ziekte dan een teken van psychologisch dysfunctioneren. Tenslotte liet dit systematische literatuuronderzoek zien dat kinderen en adolescenten met migraine in een klinische setting in vergelijking met gezonde kinderen en adolescenten vaker gediagnosticeerd worden met een oppositionele gedragsstoornis (Oppositional Defiant Disorder = ODD), maar niet vaker gediagnosticeerd worden met een aandachtstekort/hyperactiviteitstoornis (Attention Deficit Hyperactivity Disorder = ADHD), antisociale gedragsstoornis (Conduct Disorder = CD), dysthymie of depressie. Echter, omdat de onderzochte studies en de gebruikte methode van beoordeling potentieel bias met zich mee kunnen brengen dienen deze conclusies met enige terughoudendheid te worden geïnterpreteerd.

In *hoofdstuk 4* worden de resultaten beschreven van de studie waarin de KvL bij kinderen en adolescenten met primaire hoofdpijn, verwezen naar een polikliniek kindergeneeskunde in een algemeen ziekenhuis, werd onderzocht. Het primaire doel van deze studie was het vaststellen van de KvL op een groot aantal levensdomeinen. Ook werd in deze studie onderzocht in hoeverre KvL als uitkomstmaat gebruikt kon worden in de nog op te zetten profylactische interventie studie bij kinderen met migraine. Deze studie vond plaats tussen oktober 2003 en oktober 2005 op de polikliniek kindergeneeskunde van het Vlietland Ziekenhuis. Alle kinderen en adolescenten die werden verwezen door hun huisarts met primaire hoofdpijn werden volgens protocol onderzocht. De KvL werd gemeten met behulp van de Nederlandse versie van de Child Health Questionnaire (CHQ-PF50 Nederlandse editie). Uiteindelijk werden 70 kinderen in deze studie opgenomen. Er bleek bij hen overwegend sprake te zijn van migraine of spierspanningshoofdpijn, of een combinatie van deze beide vormen van primaire hoofdpijn.
Uit de studie bleek dat de KvL van kinderen en adolescenten met primaire hoofdpijn op alle levensgebieden was verminderd in vergelijking met de KvL van gezonde kinderen

en adolescenten, met name op het levensdomein mental health (geestelijke gezondheid zoals de ouders die inschatten), parental impact time (de tijd die ouders extra aan het kind moeten besteden als gevolg van de hoofdpijn) en family cohesion (de kwaliteit van de onderlinge relaties in het gezin). Alleen het domein self esteem (gevoel van eigenwaarde van de kinderen in de perceptie van de ouders) was niet verminderd in vergelijking met gezonde kinderen. In vergelijking met een historisch controle cohort van kinderen en adolescenten met astma, was de KvL van de groep kinderen met hoofdpijn significant slechter op zeven levensdomeinen en significant beter op één domein (general health perception = gezondheid van het kind zoals gezien door ouders). In vergelijking met een historische controle groep van kinderen en adolescenten met ADHD, was de kwaliteit van leven significant slechter op zes levensdomeinen, en significant beter op drie domeinen. Er waren geen significante verschillen in KvL op elk levensdomein tussen kinderen en adolescenten met spierspanningshoofdpijn en kinderen en adolescenten met migraine.
Geconcludeerd werd op basis van deze studie dat de KvL van kinderen en adolescenten met primaire hoofdpijn op een polikliniek kindergeneeskunde van een algemeen ziekenhuis aanzienlijk verminderd is in vergelijking met gezonde kinderen en dat er geen verschil is in KvL tussen kinderen en adolescenten met spierspanningshoofdpijn en kinderen met migraine. Daarnaast werd geconcludeerd dat KvL, zoals gemeten met de CHQ, gebruikt kan worden als uitkomstmaat in een profylactische interventie studie bij kinderen met migraine. De vraag is waarom de KvL slecht is bij kinderen met primaire hoofdpijn die naar een specialist verwezen worden. Een verklaring kan zijn dat de slechte kwaliteit van leven het gevolg is van de hoofdpijn van het kind. Vanuit dit perspectief zal een behandeling gericht op vermindering van de hoofdpijn aanvallen in frequentie en/of in intensiteit ook een gunstig effect hebben op de KvL. Echter, een andere mogelijkheid is dat de hoofdpijn waaraan het kind lijdt juist een uitdrukking is van een slechte KvL waarbij deze slechte KvL het gevolg is van andere factoren, zoals psychologisch dysfunctioneren en/of psychiatrische problematiek en/of problemen in de familie en/of problemen op school. Vanuit dat perspectief zal een behandeling, gericht op vermindering van de hoofdpijn aanvallen in frequentie en/of in intensiteit, juist geen gunstig effect op de KvL hebben. Vanuit een klinisch oogpunt kan het uitvoeren van een profylactische interventie studie bij kinderen met migraine, met KvL als uitkomstmaat, aanvullende informatie opleveren die inzicht geeft op dit punt. Met andere woorden, is de slechte KvL bij kinderen met migraine het gevolg van migraine zelf of is dit het gevolg van andere factoren?

In *hoofdstuk 5* worden de resultaten beschreven van het profylactisch geven van riboflavine bij kinderen met migraine waarbij gekeken werd naar primaire uitkomstmaten, dat wil

zeggen naar het effect op hoofdpijn-frequentie en -intensiteit. Riboflavine (vitamine B2) in een dosering van 50 mg per dag was gekozen als verum-medicatie. Riboflavine is al eerder gebruikt als profylacticum in studies bij volwassenen met migraine in twee "open-label" studies[13,14] (dat wil zeggen zonder placebocontrole groep) en twee gerandomiseerde gecontroleerde trials (met een placebocontrole groep)[15,16]. In deze twee laatste studies bleek riboflavine effectief te zijn met minimale bijwerkingen. Deze bijwerkingen waren diarree en vaker plassen, elk optredend bij 1 van 43 volwassenen met migraine behandeld met riboflavine. Aangezien riboflavine een ideaal medicament leek te zijn voor de profylaxe van migraine (lage kosten, superieure effectiviteit in vergelijking met placebo en minimale bijwerkingen), en omdat er geen interventie studies met riboflavine bij kinderen of adolescenten met migraine bekend waren toen dit onderzoek begon, werd besloten om een gerandomiseerde, placebogecontroleerde, dubbelblinde, cross-over studie bij kinderen met migraine uit te voeren met riboflavine als verum medicatie. In deze trial werden uiteindelijk 42 kinderen (6 tot 13 jaar) met migraine opgenomen, waarvan 14 kinderen tevens last hadden van spierspanningshoofdpijn. Na een 4-weekse observatieperiode (baseline periode) kregen alle kinderen dagelijks 50 mg riboflavine of placebo gedurende 16 weken (eerste fase). Daarna kregen de kinderen in de tweede fase een placebo indien zij in de eerste fase riboflavine hadden gekregen of dagelijks 50 mg riboflavine indien zij in de eerste fase placebo hadden gekregen. Tussen de eerste en tweede fase zat een "uitwasperiode" (wash-out periode) van 4 weken. De volgorde van eerst riboflavine en daarna placebo of eerst placebo en daarna riboflavine werd bepaald door randomisatie. Zowel de patiënten als hun ouders, evenals de onderzoekers, waren niet op de hoogte van de randomisatiecode gedurende de trial. De primaire uitkomstmaat was de reductie in gemiddelde frequentie van migraine- en spierspanningshoofdpijn-aanvallen in de laatste vier weken van de riboflavine- en placebo-fase, in vergelijking met de voorgaande baseline of wash-out periode. Secundaire uitkomstmaten waren ernst en de duur van de migraine- en spierspanningshoofdpijn-aanvallen in de laatste 4 weken van de riboflavine en placebo fase, in vergelijking met de voorgaande baseline of wash-out periode. Er werd geen significant verschil gevonden in de vermindering van de gemiddelde frequentie van migraine-aanvallen in de laatste maand van de behandeling tussen placebo en riboflavine ($p = 0,44$, tweezijdig). Wel werd er een significant verschil gevonden in vermindering van de gemiddelde frequentie van spierspanningshoofdpijn-aanvallen in het voordeel van de riboflavine behandeling ($p = 0,04$, tweezijdig). Geconcludeerd werd dat er geen bewijs is dat riboflavine in de gebruikte dosering een profylactisch effect op migraine-aanvallen heeft bij deze groep kinderen met migraine. Verder werd geconcludeerd dat er enig bewijs is dat riboflavine in de gebruikte dosering een

profylactisch effect heeft op spierspannings-hoofdpijn-aanvallen bij kinderen met migraine.

Hoofdstuk 6 geeft de resultaten weer van de studie bij kinderen met migraine ten aanzien van het effect van riboflavine op KvL en psychologisch functioneren als secundaire uitkomstmaten. Riboflavine bleek geen superieur effect te hebben ten opzichte van placebo voor wat betreft verbetering van de KvL (zoals gemeten met de CHQ) en voor het psychologisch functioneren (zoals gemeten met de Child Behaviour Checklist = CBCL-Dutch edition) op alle onderzochte levensdomeinen van de KvL en alle (sub)schalen van de CBCL. Om meer statistische power te verkrijgen voor de vergelijking met gezonde kinderen, zowel bij aanvang als aan het einde van de trial, werd besloten om de gegevens van de riboflavine-placebo-groep met de placebo-riboflavine groep samen te voegen. In deze samengevoegde groep bleek in de baseline periode dat de KvL significant slechter was op alle 13 onderzochte levensdomeinen in vergelijking met gezonde kinderen. Verder waren in de baseline periode de scores op alle CBCL (sub)schalen binnen het bereik van gezonde controles met uitzondering van de subschalen thought problems (een maat voor het cognitief functioneren), somatic complaints (lichamelijke klachten) en de hoofdschaal internalizing behaviour (internaliserend gedrag, dat wil zeggen de neiging van het kind om problemen en spanningen om te zetten in lichamelijke klachten en "terugtrekgedrag"). De afwijkende scores op de twee laatste schalen zijn waarschijnlijk veel meer het gevolg van de migraine zelf, gezien de bijbehorende vragen en de samenstelling van de CBCL, en veel minder een gevolg van psychologisch dysfunctioneren. Gedurende de trial werd in de samengevoegde groepen een verbetering op 11 van de 13 KvL levensdomeinen gezien evenals op alle CBCL (sub)schalen, met als gevolg een normalisering van de KvL scores op de domeinen mental health (geestelijke gezondheid zoals de ouders die inschatten), self esteem (gevoel van eigenwaarde), parental impact time (de tijd die ouders extra aan het kind moeten besteden als gevolg van de hoofdpijn), parental impact emotional (het effect dat de hoofdpijn van het kind heeft op de emoties van de ouders), en een normalisering van alle afwijkende CBCL schalen, met uitzondering van de subschaal Somatic complaints (lichamelijke klachten). Aanvullende ondersteuning voor de conclusie dat de slechte KvL bij kinderen met migraine, verwezen naar een specialist, waarschijnlijk primair wordt veroorzaakt door de hoofdpijn zelf werd ook gevonden in de post-hoc analyse met betrekking tot de samenhang van de primaire hoofdpijnparameters (hoofdpijn frequentie, intensiteit en duur) en KvL, waaruit bleek dat in alle fasen van de trial de scores op de meeste KvL-domeinen omgekeerd evenredig waren met de frequentie en duur van de hoofdpijnaanvallen.

De vraag zoals hierboven gesteld (is de slechte KvL bij kinderen met migraine bij verwijzing naar een specialist te wijten aan de hoofdpijn zelf of is de slechte KvL een gevolg van andere factoren ?) - kon derhalve beantwoord worden in het voordeel van de eerste hypothese. Bovendien kon geconcludeerd worden dat zowel KvL als psychologisch functioneren gebruikt kunnen worden als uitkomstvariabelen in interventie studies bij kinderen met migraine. Ten slotte werd geconcludeerd dat riboflavine ten opzichte van placebo geen superieur effect heeft op verbetering van KvL en verbetering van psychologisch functioneren in deze groep kinderen.

Er waren twee KvL domeinen die niet verbeterden tijdens de trial. Dit waren de domeinen global health (algemene gezondheid van het kind) en family cohesion (kwaliteit van de onderlinge relaties in het gezin). Dit zou te maken kunnen hebben met het feit dat beide domeinen "enkele vraag domeinen" zijn in de gebruikte CHQ vragenlijst. Dit betekent dat er voor de ouders een reeks van slechts vijf alternatieven was om respectievelijk hun inschatting van de gezondheid van hun kind en de kwaliteit van de relaties binnen hun gezin weer te geven. Dit is aanzienlijk minder dan de variabiliteit van de andere KvL domeinen.
Een andere verklaring kan zijn dat de slechte KvL op het domein global health blijft bestaan gedurende de trial omdat ouders van kinderen met migraine geneigd zijn er van uit te gaan dat de gezondheid van hun kind slecht is, ongeacht verbetering door behandeling. Daarom zijn aanvullende studies nodig om de vragen ten aanzien het effect van behandeling op onderlinge familierelaties, en op de perceptie van de ouders van de gezondheid van hun kind met migraine, te beantwoorden,

Een ander belangrijk punt in dit verband is de CBCL subschaal agressive behaviour (agressief gedrag) en de CBCL hoofdschaal externaliserend gedrag (dat wil zeggen, de neiging van het kind om problemen en spanningen om te zetten in agressief en delinquent gedrag). Aan het einde van de trial werd een significant afwijkende score op beide schalen in vergelijking met gezonde controles gevonden ten gunste van de kinderen met migraine. De subschaal agressive behaviour is een van de twee subschalen die de basis vormen van de hoofdschaal externaliserend gedrag. De andere subschaal is delinquent gedrag. Aangezien er geen significant verschil was tussen de score op de subschaal delinquent gedrag in vergelijking met gezonde controles aan het eind van de trial, werd geconcludeerd dat de lage score op de CBCL hoofdschaal externaliserend gedrag moet worden toegeschreven aan de lage score op de subschaal agressief gedrag. Dit betekent dat, hoewel het psychologisch functioneren bij kinderen met migraine bij

verwijzing naar een specialist (in het algemeen) binnen de normale grenzen lijkt, er nog verbetering mogelijk is na een interventie waardoor hoofdpijn frequentie, intensiteit en duur afnemen, waarbij uiteindelijk zelfs significant betere scores mogelijk zijn op sommige aspecten van psychologisch functioneren in vergelijking met gezonde kinderen.
Dit wordt ook aangetoond door de post-hoc analyse met betrekking tot de samenhang van de primaire hoofdpijnparameters (hoofdpijnfrequentie, intensiteit en duur) en de scores op de belangrijkste CBCL hoofdschalen internaliserend gedrag, externaliserend gedrag en de totale score, waaruit blijkt dat met name in fase 1 en fase 2 van de trial deze parameters over het algemeen positief evenredig zijn met frequentie en duur van de hoofdpijnaanvallen

Ten slotte wordt in *hoofdstuk 7* de prospectieve studie besproken waarin onderzocht werd in hoeverre slaaptekort een oorzakelijke factor is voor hoofdpijnaanvallen bij kinderen met migraine, en wat het effect is van rusten en slapen na het begin van de hoofdpijn aanval op de hoofdpijn symptomen. Een en ander werd onderzocht binnen de context van de riboflavinetrial zoals beschreven in de vorige twee hoofdstukken. Uit deze studie bleek dat slechts 6,2% van de hoofdpijnaanvallen voorafgegaan werd door een nacht met minder slaap dan normaal. Een voorafgaand slaaptekort had geen effect op de intensiteit of de duur van de hoofdpijn. Tijdens de hoofdpijnaanval gaf rusten een vermindering van de hoofdpijn intensiteit in 76,0% van de aanvallen die ontstonden na een voorafgaand slaaptekort en in 54,4% van de aanvallen zonder voorafgaand slaap tekort ($p = 0,04$). Door te gaan slapen verminderde de hoofdpijn intensiteit in 84,0% van de aanvallen met een voorafgaand slaaptekort en in 63,6% van de aanvallen zonder voorafgaand slaap tekort ($p = 0,05$). In het geval van een gunstig effect van rusten en slapen op hoofdpijn intensiteit, werd ook een significante daling van hoofdpijnduur gevonden, in vergelijking met aanvallen waarin geen effect van het rusten en slapen op hoofdpijnintensiteit was gezien ($p < 0,001$ en $p = 0,021$, respectievelijk). Concluderend kunnen we stellen dat in deze groep jonge kinderen met migraine een nacht minder slapen geen belangrijke uitlokkende factor is voor een migraine aanval. Echter, wanneer een kind een hoofdpijnaanval heeft, dan zal rusten en slapen hoogstwaarschijnlijk resulteren in een klinisch relevante verbetering van de intensiteit en duur van de hoofdpijn.

Klinische implicaties en aanbevelingen voor toekomstig onderzoek

Op grond van de systematische literatuurstudie, zoals beschreven in het tweede hoofdstuk van dit proefschrift, kan worden geconcludeerd dat alleen flunarizine effectief is voor de behandeling van migraine bij kinderen. Echter, in de meeste Europese landen en in de Verenigde Staten is flunarizine gecontraïndiceerd bij kinderen of adolescenten vanwege de ernstige bijwerkingen. Hierdoor is er onzekerheid bij artsen met betrekking tot het voorschrijven migraineprofylactica bij kinderen en adolescenten. Desondanks wordt aan deze groep patiënten toch een grote variëteit en een toenemend aantal profylactische geneesmiddelen voorgeschreven. Dit betekent dat er een noodzaak is voor het verrichten van gerandomiseerde, placebogecontroleerde interventiestudies van hoge kwaliteit bij kinderen en adolescenten met migraine om het effect van deze migraineprofylactica te evalueren.

Wij raden daarom aan dat toekomstige studies ten aanzien van bestaande en nieuwe migraineprofylactica bij kinderen en adolescenten moeten worden uitgevoerd en gerapporteerd volgens de vigerende hoge kwaliteitsnormen voor trials (= CONSORT statement). Bovendien zijn we op basis van deze literatuur studie van mening dat in de toekomst bij interventie studies bij kinderen en adolescenten met migraine niet alleen klinische verbetering van de hoofdpijn en de registratie van bijwerkingen wordt gemeten, maar ook secundaire uitkomstmaten zoals KvL en psychologisch functioneren, zodat een volledig beeld van de effecten van de interventie verkregen kan worden. Dit geldt met name voor het vaststellen van mogelijke nadelige effecten van de interventie op stemming, cognitie en gedrag zoals veroorzaakt kan worden door onder andere de anti-epileptica die op grote schaal worden gebruikt voor de profylaxe van migraine. Door het gebruiken van deze uitkomstmaten kan in toekomstige interventiestudies bij kinderen met migraine een antwoord worden gegeven op de klinisch relevante vraag wat het gecombineerde resultaat is van de gunstige en nadelige effecten van de interventie.

Daarnaast concluderen we, op basis van de systematische literatuurstudie ten aanzien van het psychologisch functioneren en psychiatrische comorbiditeit bij kinderen en adolescenten met migraine, dat het voor de behandelend specialist in het algemeen niet nodig is om een kind met migraine door te verwijzen naar een kinderpsycholoog of een kinderpsychiater. Echter, omdat het aantal opgenomen studies in dit onderzoek beperkt was en omdat de methode voor bepaling van het wetenschappelijk bewijs de potentie had om bias te veroorzaken, is het aan te raden om aanvullende studies uit te voeren om meer inzicht te krijgen in het voorkomen van psychologisch dysfunctioneren en psychiatrische comorbiditeit bij kinderen en adolescenten met migraine. In

toekomstige studies is het verder wenselijk dat zowel de moeder als de vader de vragenlijsten onafhankelijk van elkaar invult. Indien dit niet mogelijk is het wenselijk dat de ouder die de vragenlijst invult aangeeft of hij of zij de moeder of de vader van het kind is. Vervolgens dienen afzonderlijke statistische analyses voor de vragenlijsten van moeder en vader te worden uitgevoerd en beschreven. Relatief grote groepen kinderen en gezonde controles dienen te worden opgenomen in toekomstige studies in dit veld, bij voorkeur meer dan 25 in elke groep. Een "verborgen selectiestrategie" moet worden toegepast, bij voorkeur in de vorm van steekproeven van kinderen met migraine uit verschillende ziekenhuizen, geselecteerd in een willekeurige volgorde. Gevalideerde uitkomstmaten dienen te worden gebruikt die bij voorkeur zijn toegepast in eerdere studies op dit gebied om zo meer wetenschappelijk bewijs te genereren. Tenslotte dienen adequate statistische analyses worden uitgevoerd op de belangrijkste uitkomstmaten.

De KvL bij kinderen en adolescenten met primaire hoofdpijn is slecht bij verwijzing naar een polikliniek kindergeneeskunde in een algemeen ziekenhuis op bijna alle levensdomeinen en vergelijkbaar of slechter met de KvL van kinderen met ADHD of astma. Echter, de statistische vergelijkingsmethode voor wat betreft deze laatste twee groepen had een aantal tekortkomingen. Immers, de gegevens van onze studie konden alleen worden vergeleken met de gepubliceerde KvL gegevens van groepen van kinderen met astma of ADHD die bovendien afkomstig waren uit een ander land en onderzocht waren in een andere periode. Verder waren er geen statistisch significante verschillen in KvL tussen kinderen met spierspanningshoofdpijn of migraine op alle levensdomeinen. Dit heeft klinische consequenties omdat dit betekent dat de belangrijkste factor voor de verwijzing van kinderen met hoofdpijn naar een specialist de perceptie is van de verwijzend (huis)arts ten aanzien van de impact van de hoofdpijn voor het kind en zijn familie, en niet zozeer het type hoofdpijn. Dit onderstreept ook het belang voor het gebruik van generieke KvL criteria als uitkomstmaat in de dagelijkse praktijk van een arts, gespecialiseerd in de behandeling van deze kinderen, om objectief te evalueren wat het effect is van zijn of haar behandeling op het kind en zijn familie. Ten slotte maakt deze studie duidelijk dat een kind met primaire hoofdpijn, ernstig genoeg om een specialist te raadplegen, een zware last legt op ouders en broertjes of zusjes. Dit betekent dat de specialist, naar wie dit kind wordt verwezen, niet alleen moet informeren naar de gevolgen van de hoofdpijn voor het kind zelf, maar ook voor de ouders en de rest van het gezin en dit ook consequent moet blijven doen tijdens de behandeling en follow-up.

In het vijfde hoofdstuk van dit proefschrift worden de resultaten van een profylactische placebo-gecontroleerde cross-over trial bij kinderen met migraine met riboflavine in een dagelijkse dosering van 50 mg beschreven. In tegenstelling tot bij volwassenen, konden we geen bewijs vinden voor een superieur effect van riboflavine ten opzichte van placebo. Dit kan te maken hebben met de gebruikte dosering zoals een recente studie laat zien[17]. In deze retrospectieve studie werden 41 kinderen en adolescenten met migraine dagelijks met 200 mg of 400 mg riboflavine behandeld gedurende drie tot zes maanden. Uit deze studie bleek dat 68,4% van de geincludeerde kinderen een vermindering had in de frequentie van hoofdpijn aanvallen van 50% of meer, zonder ernstige bijwerkingen[17]. Echter, deze studie was retrospectief van opzet, er was geen placebo-groep en de behandeling was niet geblindeerd, parameters die stuk voor stuk essentieel zijn voor een hoge kwaliteit van onderzoek. Toekomstige studies naar het effect van riboflavine bij kinderen met migraine dienen derhalve placebogecontroleerde, gerandomiseerde, dubbelblinde trials te zijn conform het CONSORT statement. De dosering van riboflavine dient tenminste 200 mg of 400 mg dagelijks te zijn. In onze trial werden aanwijzingen gevonden dat riboflavine een profylactisch effect kan hebben op de episodische spierspanningshoofdpijn bij kinderen met migraine. Dit is nog niet eerder beschreven, ook niet bij volwassenen. Echter, om definitief vast te stellen of riboflavine inderdaad een primair effect heeft op episodische spierspanningshoofdpijn bij kinderen of volwassenen dienen placebogecontroleerde, gerandomiseerde dubbelblinde studies te worden uitgevoerd bij kinderen en volwassenen met spierspanningshoofdpijn met of zonder migraine conform het CONSORT statement. Desalniettemin, vanuit een klinisch perspectief, gebaseerd op onze studie en gegeven het gebrek aan wetenschappelijk bewezen effectieve migraine profylactica zonder bijwerkingen, lijkt het ons gerechtvaardigd om riboflavine schrijven in de dosering zoals beschreven is in onze trial voor kinderen met migraine die tevens last hebben van spierspanningshoofdpijn, voor een periode van ten hoogste vier maanden.

In de studie zoals beschreven in het zesde hoofdstuk van dit proefschrift werd aangetoond dat riboflavine in feite optrad als een placebo op alle onderzochte aspecten van de KvL en de CBCL (sub)schalen gedurende de hele trial. Tijdens de trial verbeterde de KvL in 11 van de 13 KvL domeinen en op alle CBCL (sub)schalen. Dit resulteerde in normalisatie van de scores op 4 van de 13 KvL domeinen en alle CBCL (sub)schalen op één na. Dit heeft klinische consequenties omdat deze trial laat zien dat de KvL bij kinderen met migraine bij verwijzing naar een specialist slecht is, waarbij dit niet komt door psychologisch dysfunctioneren, maar door de ziekte zelf. Men zou daarom kunnen

stellen dat het doorverwijzen van een kind met migraine naar een kinderpsycholoog of kinderpsychiater bij voorkeur moet worden overwogen bij uitblijven van verbetering na een bepaalde periode van medicamenteuze behandeling. Echter, deze trial is de eerste studie bij kinderen met migraine waarin KvL en psychologisch functioneren zijn gebruikt als uitkomstmaat voor behandeling, wat derhalve beperkt bewijs geeft voor deze stelling. Om tot definitief wetenschappelijk bewijs te komen en deze stelling te ontwikkelen tot een richtlijn zijn meer vergelijkbare studies nodig.
Aangetoond is verder dat de KvL bij kinderen met migraine niet verbetert op het domein global health (algemene gezondheid van het kind) en family cohesion (kwaliteit van de onderlinge relaties in het gezin) ondanks verbetering van de hoofdpijn aanvallen. Vanuit dit perspectief, wanneer een kind met migraine wordt verwezen naar een kinderpsycholoog of kinderpsychiater, kan de betrokken psycholoog of psychiater deze KvL domeinen verkennen en (zo nodig) proberen aan te passen. Dit betekent dat hij of zij onderzoekt hoe de ouders hun kind met migraine in figuurlijke zin zien, en zo nodig probeert dat beeld te veranderen, bijvoorbeeld door in plaats van het zien van hun kind als min of meer ziek en hulpeloos, de ouders te leren hun kind te zien als een kind dat een betrekkelijk milde aandoening heeft met een goede prognose indien eenvoudige leefregels worden toegepast gecombineerd met een adequate medicamenteuze behandeling. Daarnaast kan, indien nodig, de kwaliteit van de verhoudingen binnen de familie van het kind met migraine worden aangepast om een meer samenhangende en gezonde gezinssituatie te bevorderen.

Tenslotte werd vastgesteld dat een nacht minder slaap niet een belangrijke uitlokkende factor is voor het krijgen van hoofdpijn bij kinderen met migraine. Wel werd vastgesteld dat, indien er sprake is van een hoofdpijnaanval, rust en slapen resulteren in een klinisch relevante vermindering van de intensiteit en de duur van de hoofdpijnaanval, vergeleken met het in het geheel niet gaan rusten of slapen. Rusten en slapen had meer effect op de vermindering van de intensiteit en de duur van de hoofdpijn wanneer het kind de voorgaande nacht minder dan gewoonlijk had geslapen. Deze bevindingen zijn klinisch relevant omdat ze beperkt bewijs leveren dat een tekort aan slaap bij kinderen met migraine niet automatisch een hoofdpijn aanval hoeft uit te lokken en dat rusten en slapen verstandige maatregelen zijn wanneer een hoofdpijn aanval begonnen is bij kinderen met migraine, vooral wanneer het kind minder heeft geslapen dan normaal in de nacht voorafgaande aan de hoofdpijn aanval. Er zijn echter weinig studies uitgevoerd waarbij onderzocht is wat het effect is van slaap bij kinderen met migraine. Meer prospectieve studies zijn nodig om verder de relatie tussen slaap en hoofdpijn bij kinderen met migraine op te helderen.

REFERENCES

1. Rossi LN, Cortinovis I, Menegazzo L, Menini S, Carnelli V. **Behaviour during attacks and assessment of intensity in primary headaches of children and adolescents.** Cephalalgia 2006;26:107-12.
2. Passchier J, Orlebeke JF. **Headaches and stress in schoolchildren: an epidemiological study.** Cephalalgia 1985;5:167-76.
3. Guidetti V, Mazzei G, Ottaviano S, Pagliarini M, Paolella A, Seri S. **The utilization of the Rorschach test in a case-controlled study.** Cephalalgia 1986;6:87-93.
4. Mazzone L, Vitiello B, Incorpora G, Mazzone D. **Behavioural and temperamental characteristics of children and adolescents suffering from primary headache.** Cephalalgia 2006;26:194-201.
5. Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, Resch F. **Emotional and behavioural problems in children and adolescents with primary headache.** Cephalalgia 2003;23:206-13.
6. Pakalnis A, Gibbons J, Colvin A. **Comorbidity of psychiatric and behavioral disorders in pediatric migraine.** Headache 2005;45:590-6.
7. Anttila P, Sourander A, Metsahonkala L, Aromaa M, Helenius H, Sillanpaa M. **Psychiatric symptoms in children with primary headache.** J Am Acad Child Adolesc Psychiatr 2004;43:412-9.
8. Vannata K, Getzoff EA, Powers SW, Noll RB, Gerhardt CA, Hershey AD. **Multiple perspectives on the psychological functioning of children with and without migraine.** Headache 2008;48:994-1004.
9. Smith M, Martin-Herz S, Womack W, Marsigan J. **Comparative study of anxiety, somatization, functional disability and illness attribution in adolescents with chronic fatigue or migraine.** Paediatrics 2003;111:e376-81.
10. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, Cucchiara S, Guidetti V. **Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL).** Cephalalgia 2007;27:211-9.
11. Guidetti V, Galh F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S. **Headache and psychiatric comorbidity: clinical aspects and outcome in an 8 year follow-up study.** Cephalalgia 1998;18:455-62.
12. Slavin, RE. **Best evidence synthesis: an intelligent alternative to meta-analysis.** J Clin Epidemiol 1995;48:9-18.
13. Schoenen J, Lenaerts M, Bastings E. **High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study.** Cephalalgia 1994;14:328-9.
14. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl K, Arnold G. **High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre.** European Journal of Neurology 2004;11:475-7.
15. Schoenen J, Jacquy J, Lenaerts M. **Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial.** Neurology 1998;50:466-70.
16. Sándor P, Áfra J, Ambrosini A, Schoenen J. **Prophylactic treatment of migraine with ß-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.** Headache 2000;40:30-5.
17. Condò M, Posar A, Arbizzani A, Parmeggiani A. **Riboflavin prophylaxis in pediatric and adolescent migraine.** Journal of Headache and Pain 2009;10(5):361-5.

DANKWOORD

Op de eerste plaats wil ik de kinderen en ouders bedanken die hebben deelgenomen aan de studies zoals nu verschenen in dit proefschrift. Ik hoop dat dankzij hun deelname aan dit onderzoek er meer inzicht is ontstaan in wat het betekent om op jonge leeftijd migraine te hebben, zowel voor het kind als zijn of haar familie.

Verder ben ik een aantal personen veel dank verschuldigd.

Geachte professor Arts, beste Willem-Frans, dank voor het mogelijk maken dat ik onderzoek kon gaan doen en voor het vertrouwen wat jij steeds in mij hebt gehouden. Onze eerste ontmoeting vond plaats in 2000, kort nadat ik in het Vlietland Ziekenhuis was gaan werken. Jij maakte het toen mogelijk dat ik een part-time aanstelling kon krijgen op de afdeling kinderneurologie om zo de werkwijze van de afdeling kinderneurologie van het EMC en de kinderneurologen persoonlijk goed te leren kennen. Nadat ik enige tijd bij jou op deze manier werkzaam was, zijn wij gezamenlijk gaan kijken naar een onderwerp voor onderzoek en kwamen we uit op hoofdpijn bij kinderen. Jij hebt mij hiervoor geïntroduceerd bij professor Passchier. Samen met hem en later de andere betrokkenen bij dit onderzoek hebben wij hard gewerkt om deze promotie mogelijk te maken. Steeds heb jij mij gesteund en ben je achter mij blijven staan, ook als het tegenzat. Voor het uiteindelijk doen slagen van dit project is jouw grote ervaring als kinderneuroloog naast je expertise als wetenschapper van doorslaggevend belang geweest in alle fasen van het onderzoek. Ik ben er buitengewoon gelukkig mee dat ik met dit project mijn onderzoekskwaliteiten heb kunnen laten zien en verder heb kunnen ontwikkelen. Zonder jouw hulp was dit niet mogelijk geweest.

Geachte professor Passchier, beste Jan, ook jou wil ik bijzonder bedanken voor de hulp en ondersteuning die jij me hebt geboden tijdens het gehele promotietraject. Je input in de ontwikkelingsfase van de studies, je begeleiding tijdens deze studies, je visie op de data-analyses en jouw deskundige aanvullingen en correcties voor de verschillende hoofdstukken zijn maar een klein deel van de zaken die jij hebt ingebracht. Ook heb ik het bijzonder gewaardeerd dat jij er nooit een probleem van maakte als ik jou belde of mailde om een aspect van een artikel te bespreken waar ik mee worstelde of als er andere zaken waren met betrekking tot het onderzoek waar ik graag overleg over wilde hebben. Vrijwel altijd lukte het je om mij snel terug te bellen of snel terug te mailen (zelfs als je in het buitenland verbleef!) waardoor het onderzoek zijn vaart behield.

Geachte doktor Van Duivenvoorden, beste Hugo, ook jou ben ik veel dank verschuldigd voor je hulp en ondersteuning. Deze was veel breder dan alleen de ondersteuning ten aanzien van de statistiek. Niet alleen heb je mij geholpen met aspecten van het onderzoek zoals het maken van keuzes uit de data en de verschillende statistische analyse methoden, ook heb je waardevolle adviezen gegeven voor het schrijven van de artikelen waar ik veel aan heb gehad. Gaandeweg het promotietraject ben ik jou dan ook veel meer gaan beschouwen als copromotor dan als statisticus. Ook heb ik genoten van onze gesprekken en discussies tussen de bedrijven door over de actualiteit, geneeskunde en gezondheidszorg, Frankrijk en vele andere zaken. Het is zonder meer passend dat jij uiteindelijk ook officieel mijn copromotor bent geworden!

Geachte mevrouw Dijkstra, beste Natascha, aan jouw inspanningen als researchverpleegkundige heb ik bijzonder veel te danken. Jij en ik zijn in 2005 tegelijkertijd begonnen aan de studies waar uiteindelijk het grootste gedeelte van het proefschrift op is gebaseerd. Niet alleen zorgde je ervoor dat de data op een correcte manier werden ingevoerd in de vele databases, ook was je inbreng onmisbaar in de vele overlegmomenten met Hugo toen wij de databases en de statistische software aan het opzetten waren en vervolgens de data gingen analyseren. Verder heb jij nog met vele andere hand- en spandiensten je het vuur uit de sloffen gelopen voor het onderzoek. Ik ben heel blij voor je dat je, mede dankzij je inspanningen als researchverpleegkundige voor dit project, nu al weer enige tijd een baan als gespecialiseerd kinderneurologieverpleegkundige hebt op de polikliniek kinderneurologie van het Havenziekenhuis, een plek waar je alleen al door je expertise op het gebied van kinderhoofdpijn meer dan op je plaats bent.

Geachte collega Locher, beste Heiko, jij kwam in een relatief laat maar wel cruciaal stadium bij het project waarbij ook jouw inbreng van grote waarde is geweest. Je hebt een belangrijke bijdrage geleverd in de data-analyse van de riboflavinetrial maar met name was je inbreng essentieel bij het uitvoeren van het systematische literatuuronderzoek naar het voorkomen van psychische comorbiditeit bij kinderen met migraine en de studie over de effecten van slaap op hoofdpijnklachten bij kinderen met migraine. Het is dan ook zonder meer terecht dat jij mede-auteur bent geworden van de publicaties voortkomende uit de riboflavinetrial en tweede auteur van deze laatste twee publicaties. Ik ben blij dat jij, mede door jouw inspanningen voor dit onderzoek, er in bent geslaagd een promotie- en opleidingsplaats voor KNO-arts te verwerven, iets wat jij heel graag wilde. Jij bent nu gestart met je eigen promotieonderzoek op de afdeling KNO in het LUMC. Doe je voordeel met de opgedane kennis door je medewerking aan dit project en aarzel niet om te bellen voor advies of als je nog een keer een (race)fietstochtje naar het Woudt wil maken !

Verder wil ik ook bedanken Brigitte de Bie, Evelyne van Boeckel, Bert den Exter, Esther Hentzen-Alders, Sandra Kenter, Coby Langendoen, Arjan Pijning en Lia van Wijk, mijn collega-kinderartsen in het Vlietland Ziekenhuis. Ik wil hen met name bedanken voor het doorverwijzen van hun hoofdpijnpatiëntjes en het vertrouwen wat zij steeds in mij hebben gehad om dit onderzoek succesvol af te ronden tot een promotie.

Speciaal dank ben ik verschuldigd aan Sjaan Scholten, polikliniekassistente op de polikliniek Kindergeneeskunde van het Vlietland Ziekenhuis. Beste Sjaan, jij was vanaf het begin betrokken bij het onderzoek. Dankzij jouw "hoofdpijnschriftje" (dat overigens nu nog steeds dienst doet) was het mogelijk om een goede systematiek in het onderzoek aan te houden. Ook veel dank voor het punctuele uitreiken, verzamelen en categoriseren van de vele formulieren die de ouders van de patiënten steeds moesten invullen voor de studies zoals in dit proefschrift beschreven. Daarnaast heb jij ook nog veel andere hand- en spandiensten geleverd voor het onderzoek. Ik heb dat zeer gewaardeerd.

In het bijzonder wil ik noemen Gerrit-Jan van Zoelen, voorzitter van de Raad van Bestuur van het Vlietland Ziekenhuis. Beste Gerrit-Jan, wij spraken elkaar voor het eerst toen jij zes weken was aangesteld en ik bij je kwam omdat het onderzoek dreigde vast te lopen. Jij heb het toen mogelijk gemaakt dat de voorwaarden werden gecreëerd om de verdere voortgang van het onderzoek te waarborgen. Hiervoor mijn grote dank.

Verder ben ik blij met de inspanningen die Adrie Noteboom van de Afdeling EAD van het Vlietland Ziekenhuis heeft verricht. Adrie, jij was de grootboekrekeninghouder voor de riboflavinetrial en jij hebt dit keurig gedaan. Ook veel dank voor het regelen van de benodigde stukken voor de accountantsverklaring (en wat was ik blij dat deze uiteindelijk werd afgegeven!). Ook wil ik bedanken Adrie Pelgrim van het CKCL laboratorium. Adrie, dank voor je inspanningen.
Ook wil ik bedanken alle verpleegkundigen, secretaresses en andere medewerkers van de kinderafdeling van het Vlietland Ziekenhuis voor hun steeds aanwezige interesse in dit onderzoek.

Wat ik bijzonder op prijs stelde was de belangstelling voor dit onderzoek van Corien Catsman, Renee de Coo, Liesbeth Smit, Marie-Claire de Wit, Liesl Rehbock, Hannerieke van den Hout en Rinze Neuteboom, collega-kinderneurologen in het EMC en het Havenziekenhuis. Ook dank voor het doorverwijzen van de hoofdpijnpatiëntjes en de adviezen die ik van hen mocht ontvangen.

Arianne Verhagen van de afdeling Huisartsgeneeskunde van het EMC wil ik bedanken voor haar vriendelijke uitnodiging om lid te worden van de "Werkgroep Kinderhoofdpijn". Arianne, door mijn lidmaatschap hiervan en het intensief meewerken aan de gerealiseerde publicaties heb ik veel geleerd op het gebied van systematisch "evidence based" literatuuronderzoek. Deze ervaring kwam mij goed van pas bij het schrijven van mijn "eigen" systematische literatuurstudie ten aanzien van psychische comorbiditeit bij kinderen met migraine, wat uiteindelijk heeft geleid tot een publicatie in Pediatrics.

Ook een woord van dank voor de medewerkers van de afdeling Medische Psychologie en Psychotherapie van het EMC, waar ik ook enige tijd een eigen werkkamer had. In het bijzonder wil ik Margreet Langendoen en Miranda Spek, afdelingssecretaresses, bedanken voor de nodige hand- en spandiensten die zij geleverd hebben voor het onderzoek.

Ook wil ik bedanken de kinderartsen, neurologen en kinderneurologen die patiëntjes naar mij hebben doorverwezen voor de riboflavinetrial. In het bijzonder collega P. de Laat, J. Samijn, A. van Rossum, R. van der Lee, D. Kamphuis, B. Koop and C. de Korte. Ook wil ik bedanken Loes Visser and Hong San Lau, ziekenhuisapothekers in respectievelijk het Erasmus MC en het Vlietland Ziekenhuis, voor het regelen, opslaan en verstrekken van de riboflavine- en placebocapsules voor de riboflavinetrial. Veel dank hiervoor, dit was een van de aspecten van het onderzoek dat werkelijk uitstekend verliep.

Niet in de laatste plaats ben ik Laraine Visser dankbaar, die door haar "native speaker activiteiten" gewaarborgd heeft dat de correcte Engelse spelling en grammatica steeds is gebruikt. Bedankt hiervoor, geen enkele referee of editor heeft hierover opmerkingen gemaakt!

Tenslotte wil ik graag nog diegenen in mijn persoonlijke leven bedanken die mij zoveel steun hebben gegeven in de afgelopen jaren.

Ik wil mijn vrienden door de jaren heen, Franc Petrus, Jonathan en Sontje Go, Erwin en Carola Melger, Patrick en Uraida van Wonderen, Paul en Martine Staneke, Inge en Arthur de Jong, Benjamin Go, Fay ten Berge en Rosseel van den Broek, Lennie en Ton van Osch, Joop en Mihaela Plaisier, Maarten en Betty Derickx en Mikel Kors bedanken voor hun steun in de afgelopen jaren maar vooral ook voor hun begrip omdat ik me weer eens moest afmelden voor een van hun verjaardagen of een festiviteit anderszins vanwege het onderzoek. Jonathan en Franc, fantastisch dat jullie paranimf zijn op de promotie!

Mijn broer Niek Bruijn, zijn vrouw Ignia en mijn zus Lydie-Anne Bruijn wil ik ook bedanken voor hun steeds aanwezige interesse en belangstelling voor mijn onderzoek.

Lieve mama, wij weten allebei dat het bereiken van deze promotie voor mij heel veel betekent. Het zou ook veel betekend hebben voor mijn vader en jouw man, Simon Bruijn, die helaas veel te vroeg is overleden. Ten tijde van zijn overlijden was ik net begonnen aan mijn opleiding tot kinderarts en moest het sindsdien zonder hem doen. Dat is voor ons niet altijd even makkelijk geweest, met name in de zware en verdrietige periode na zijn overlijden. Ons leven heeft zich verder ontwikkeld sindsdien. Het bereiken van deze mijlpaal was niet mogelijk geweest zonder je aandacht en toewijding naar mij en later ook naar Christine en de kinderen. Mama, heel veel dank en een hartelijke omhelzing voor jou.

Allerliefste Christine, dit lange dankwoord wil ik bij jou laten eindigen omdat ik bovenal dankzij jou deze klus heb kunnen klaren. Ik wil je bedanken voor je steun naar mij toe terwijl ik met mijn promotie bezig was en vooral voor je regelmatige benadrukken dat er meer in het leven is dan werken en promoveren. Jij hield me gelukkig met beide benen op de grond als ik weer eens over een probleem of een formulering in een artikel zat na te denken. In de loop van dit promotietraject hebben wij drie kinderen gekregen, Simon, Niek en Anna, van wie ik zielsveel houd en waar ik je nog veel dankbaarder voor ben. Ik hoop dat wij samen met onze kinderen nog veel mooie en goede momenten zullen beleven. Ik kijk uit naar de jaren die nog voor ons liggen en hoop dat ik jou daarin dezelfde zorg en steun kan verschaffen die jij mij en de kinderen al zo lang en zo liefdevol geeft.

Jacques Bruijn
Zomer 2010

PUBLICATIES

Bruijn J, Rotteveel J, Brouwer OF, Barth PG. Oral-facial-digital syndromes and cerebral malformations. Developmental Medicine & Child Neurology 1995; Supplement 71:37(3):17.

Bruijn J, Mullaart R, Rotteveel J, Thijssen J. Detectie van cerebrale bloedstromen m.b.v. color coded Doppler ultrasound: een vergelijking tussen power Doppler imaging en velocity Doppler imaging. Nederlands Tijdschrift voor Kindergeneeskunde 1995; Supplement 1:59.

Medeauteur Nederlandstalig cursusboek "Pediatric Advanced Life Support" (eindredactie J. Draaisma), Stichting Spoedeisende Hulp bij Kinderen (SSHK), december 2001, hoofdstuk 7, "Opvang van de Pasgeborene:35-49.

"Advanced Pediatric Life Support", (eindredactie N. M. Turner en A.J. van Vught), Elseviers Gezondheidszorg, Maarssen 2004, SSHK, ISBN 978 90 352 2855 9, hoofdstuk "Vergiftigingen":153-158.

"Advanced Pediatric Life Support", (eindredactie N. M. Turner en A.J. van Vught), Elseviers Gezondheidszorg, Maarssen 2004, SSHK, ISBN 978 90 352 2855 9, hoofdstuk "Praktische Vaardigheden-Circulatie":219-227.

Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. Symptomatic treatment of migraine in children: a systematic review of medication trials. Pediatrics 2005;116:295-302.

Bruijn J, Arts WF: Hoofdpijn bij kinderen. Werkboek Kinderartsenweek 2005 "De Adolescent" (redactie B.J. Sibbles, W.P. Atema) 2005; Commissie PAOK, Erasmus MC-Sophia Kinderziekenhuis, ISBN 90 76220 17 4:87-92.

Bruijn J: Hoofdpijn bij kinderen. Kinderfysiotherapie, tijdschrift van de Nederlandse Vereniging voor Fysiotherapie bij Kinderen (NVFK) 2005;17;46:28-31.

Verhagen AP, Damen L, Bruijn J, Berger MY, Paschier J, Koes BW. Effectiviteit van interventies bij kinderen met migraine. Huisarts en Wetenschap 2006;49(3):123-9.

Damen L, Bruijn J, Berger MY, Passchier J, Koes BW, Verhagen AP. Prophylactic treatment of migraine in children. Part 1: a systematic review of non-pharmacological trials. Cephalalgia 2006; 26(4):373-83.

Damen L, Bruijn J, Berger MY, Passchier J, Koes BW, Verhagen AP. Prophylactic treatment of migraine in children. Part 2: a systematic review of pharmacological trials. Cephalalgia 2006;26(5):497-505.

Bruijn J, Gooskens R, Verhagen AP, Damen L, Paschier J. Richtlijn "Diagnostiek en behandeling kindermigraine"; onderdeel richtlijn "Pijnbestrijding bij kinderen", Nederlandse Vereniging van Kinderartsen (NVK) werkgroep "Pijnbestrijding bij kinderen" (voorzitter dr. R. van Lingen) 2008:53-65.
Online publicatie: http://www.nvk.pedianet.nl/pdfs/nvk_richtlijn_pijn_bij_kinderen.pdf

Bruijn J, Passchier J. Richtlijn "Gevolgen van pijn voor kwaliteit van leven"; onderdeel richtlijn "Pijnbestrijding bij Kinderen", Nederlandse Vereniging van Kinderartsen (NVK) werkgroep "Pijnbestrijding bij Kinderen" (voorzitter dr. R. van Lingen) 2008:75-77.
Online publicatie: http://www.nvk.pedianet.nl/pdfs/nvk_richtlijn_pijn_bij_kinderen.pdf

Bruijn J, Arts WF, Duivenvoorden H, Passchier J. Quality of life in children with headache in a general hospital in the Netherlands. Cephalagia 2008;28(4):439.

Verhagen AP, Damen L, Bruijn J, Berger MY, Passchier J, Koes BW. Onderzoek effectiviteit van interventies bij kinderen met migraine. In: "Schatjes zijn het" (eindredactie Henk van Weert), Bohn Stafleu van Loghum, Houten 2008, ISBN 978 90 313 5342 2:137-153.

Bruijn J, Arts WF, Duivenvoorden H, Dijkstra N, Raat H, Paschier J. Quality of life in children with primary headache in a general hospital. Cephalalgia 2009;29(6):624-630.

Bruijn J, Duivenvoorden H, Passchier J, Locher H, Dijkstra N, Earts WF. Medium dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomized, double-blind, crossover trial. Cephalalgia 2010 (e-Pub ahead of print).

Bruijn J, Duivenvoorden H, Passchier J, Locher H, Dijkstra N, Arts WF. Quality of life and psychological functioning as outcomes in a controlled trial in children with migraine. (submitted).

Bruijn J, Locher H, Duivenvoorden H, Passchier J, Dijkstra N, Arts WF. Relation between sleep and headache in childhood migraine: a prospective study. (submitted).

Bruijn J, Locher H, Duivenvoorden H, Passchier J, Dijkstra N, Arts WF. Psychopathology in children and adolescents with migraine in clinical studies: a systematic review of the literature. Pediatrics 2010;126:323-332.

CURRICULUM VITAE

Jacques Bruijn werd geboren op 4 augustus 1965 te Haarlem. Na het basisonderwijs ging hij naar het Triniteitslyceum te Overveen. Hij beëindigde aldaar zijn gymnasium-ß opleiding in mei 1983 en begon aansluitend met de opleiding Geneeskunde aan de Vrije Universiteit van Amsterdam. In september 1990 slaagde hij cum laude voor zijn artsexamen. Hierna ging hij werken als AGNIO op de afdeling Kinderneurologie van het Universitair Medisch Centrum Utrecht (hoofd prof. dr. O. Van Nieuwenhuizen) waarna hij van juli 1991 tot februari 1992 werkzaam was als AGIO op de afdeling Oogheelkunde van het Academisch Ziekenhuis van de Vrije Universiteit te Amsterdam (hoofd prof. dr. K. Tan). Omdat de kindergeneeskunde en kinderneurologie bleven trekken solliciteerde hij naar een opleidingsplaats voor kinderarts in het opleidingscluster Nijmegen. In februari 1992 begon hij hiermee op de afdeling Kindergeneeskunde van het Canisius Wilhelmina Ziekenhuis te Nijmegen (hoofd dr. P. Van Wieringen). In mei 1993 ging hij werken op de afdeling Kindergeneeskunde (hoofd prof. dr. R.C.A. Sengers) van het Universitair Medisch Centrum Nijmegen (UMCN). In het kader van het ontwikkelen van kinderneurologie als subspecialisatie werkte hij in totaal 9 maanden op de afdeling kinderneurologie van het UMCN (hoofd prof. dr. F. Gabreëls) en deed hij onderzoek op het echografielaboratorium van deze afdeling. Tevens werkte Jacques van februari 1996 tot februari 1997 als arts-assistent op de afdeling Neurologie van het UMCN (hoofd prof. dr. G. Padberg). Hij beëindigde zijn opleiding in februari 1998. Hierna ging hij werken als chef de clinique op de afdeling Kindergeneeskunde van het Sint Maartens Gasthuis te Venlo. In december 1999 maakte hij de overstap naar de afdeling Kindergeneeskunde van het Vlietland Ziekenhuis in Schiedam waar hij nog steeds werkzaam is.

Vanaf februari 2001 tot februari 2003 had Jacques een part-time aanstelling op de afdeling Kinderneurologie van het EMC-Sophia Kinderziekenhuis (hoofd prof. dr. W.F. Arts). In augustus 2002 werd hij geregistreerd als kinderneuroloog NVKN (Nederlandse Vereniging voor Kinderneurologie). Naast de algemene kinderneurologie en gedragsneurologie heeft Jacques kinderhoofdpijn als aandachtsgebied. In het kader van dit laatste aandachtsgebied verrichte hij de studies waaruit dit proefschrift uiteindelijk is voortgekomen.

Verder heeft Jacques als aandachtsgebied acute kindergeneeskunde. Hij werd in oktober 1999 geregistreerd als Pediatric Advanced Life Support (PALS)-instructeur en in maart 2005 als European Pediatric Life Support (EPLS)-instructeur bij de Stichting Spoedeisende Hulp Kindergeneeskunde (SHK). Van december 2000 tot oktober 2005 was hij course-

director voor de PALS. In oktober 2004 werd hij geregistreerd als Newborn Life Support (NLS)-instructeur.

Jacques is lid van het Pediatric Subcomittee van de International Headache Society. Hij was lid van de commissie Protocollen en Consensus (voorzitter dr. C. Lincke) van de Nederlandse Vereniging van Kinderartsen (NVK) en van de NVK-werkgroep "Pijnherkening en Behandeling bij kinderen" (voorzitter dr. R. Van Lingen). Als lid van deze laatste werkgroep stelde hij onder meer de richtlijn "Diagnostiek en Behandeling van Kindermigraine" op. Hij is verder lid van de werkgroep Kinderhoofdpijn (voorzitter Dr. G. Hageman) en de werkgroep Gedragsneurologie (voorzitter drs. F. Visscher) van de NVKN.

Jacques is in 1996 getrouwd met Christine. Samen hebben zij twee zonen, Simon en Niek, en een dochter, Anna.