



Butterbur root extract and music therapy in the prevention of childhood migraine: An explorative study

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Abstract

Background: Migraine is very common in school-aged children, but despite a number of pharmacological and non-pharmacological options for prophylaxis, randomized controlled evidence in children is small. Evidence-based prophylactic drugs may have considerable side effects.

Objective: This study was to assess efficacy of a butterbur root extract (Petadolex[®]) and music therapy in primary school children with migraine.

Design: Prospective, randomized, partly double-blind, placebo-controlled, parallel-group trial.

Methods: Following a 8-week baseline patients were randomized and received either butterbur root extract ($n = 19$), music therapy ($n = 20$) or placebo ($n = 19$) over 12 weeks. All participants received additionally headache education (“treatment as usual”) from the baseline onwards. Reduction of headache frequency after treatment (8-week post-treatment) as well as 6 months later (8-week follow-up) was the efficacy variable.

Results: Data analysis of subjects completing the respective study phase showed that during post-treatment, only music therapy was superior to placebo ($p = 0.005$), whereas in the follow-up period both music therapy and butterbur root extract were superior to placebo ($p = 0.018$ and $p = 0.044$, respectively). All groups showed a substantial reduction of attack frequency already during baseline.

Conclusion: Butterbur root extract and music therapy might be superior to placebo and may represent promising treatment approaches in the prophylaxis of paediatric migraine.

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Keywords: Migraine prophylaxis; Children; Butterbur root extract; Music therapy; Efficacy

Abbreviations: RCT, randomized controlled trial; MO, migraine without aura; MA, migraine with aura; DIPS, diagnostic interview for mental disorders in children and adolescents; CBCL, Child Behaviour Check List; DIKJ, Depression Inventory for Children and Adolescents; SSK, stress questionnaire for children.

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1. Introduction

Migraine becomes increasingly important in children: it is a frequent pain disorder that often considerably reduces quality of life (Powers et al., 2003). It may affect a child's school career by reducing school attendance (Abu-Arafeh and Russell, 1994) and has a high risk of chronification into adulthood (Bille, 1997). The

incidence peak has shifted to younger age (for boys now approximately 11 years; Laurell et al., 2004) and prevalence increased over the last decades, e.g. in first-grade schoolchildren from 1.9% (1974) to 5.7% (1992) (Sillanpaa and Anttila, 1996).

Despite a substantial number of studies, especially randomized controlled evidence for the prophylactic treatment of paediatric migraine is poor: because of the small number of studies and the methodological shortcomings (especially the absence of placebo-control groups), conclusions about the effectiveness should be drawn with caution (Damen et al., 2006a,b). Nevertheless, different pharmacological and psychological options are recommended by experts. For pharmacological treatment, the prophylactic drugs propranolol (conflicting evidence is reported, Damen et al., 2006b) and flunarizine (Victor and Ryan, 2004) have been shown to be effective but may have side effects such as fatigue, orthostatic hypotension or weight gain (Silberstein and Goadsby, 2002). A recent study reported promising results for topiramate (Winner et al., 2005) that causes side effects like weight loss or somnolence.

Non-pharmacological interventions are also promising in paediatric migraine (Hermann et al., 1995; Damen et al., 2006a). Relaxation, self-hypnosis, and cognitive behavioural therapy are effective; biofeedback (Eccleston et al., 2002; Holden et al., 1999), acupuncture and instructions for a better sleep hygiene (Damen et al., 2006a) are auspicious too. However, there are only few studies that directly compared pharmacological (propranolol, metoprolol) and non-pharmacological migraine prophylaxis in children (Olness et al., 1987; Sartory et al., 1998). Both studies underline efficacy of psychological interventions.

Petadolex[®] is a patented special butterbur root extract used for prevention of migraine and asthma for decades. Recent double-blind placebo-controlled trials in adults gave evidence for efficacy in migraine prophylaxis (Diener et al., 2004; Lipton et al., 2004). Headache relief might be mediated by the anti-inflammatory and vasodilatory main components petasine and isopetasine (Scheidegger et al., 1998). Even the most frequent adverse events (nausea and stomach pain) are rare (<0.01%) (Danesch and Rittinghausen, 2003). Until now, there are no systematic placebo-controlled trials investigating butterbur in paediatric migraine despite promising results in an open-label study (Pothmann and Danesch, 2005).

Music therapy has not been evaluated in paediatric migraine until now but might be a promising non-pharmacological approach, as it seems to be effective in children with psychopathology (Gold et al., 2004) and in adults with headache (Risch et al., 2001) or chronic pain (Hillecke, 2002). For this study, an interdisciplinary developed and evaluated concept for music therapy of adults with chronic pain (Hillecke and Bolay, 2000) has been adapted for children with migraine.

The aim of this study is to investigate the efficacy of butterbur root extract and music therapy in children with migraine in a prospective, randomized, partly double-blind, placebo-controlled parallel-group trial.

2. Methods

2.1. Subjects

Patients were enrolled from August 2001 to September 2002 and were recruited from the catchments area of Heidelberg University Hospital using local newspaper and study advertisement. Follow-up assessment six months after the end of treatment phase was performed from July 2002 to November 2003. Inclusion criteria were: age between 8 and 12 years, initial onset of migraine at least one year before and number of attacks: participants had to report on average two or more migraine attacks each of the three months prior to the screening (determined retrospectively) and for the two months of baseline (determined prospectively).

Exclusion criteria were: intake of prophylactic medication of migraine in the three months before screening, additional non-migraine types of headaches on more than 6 days/month, intake of analgesics on 10 or more days/months, alcohol/drug abuse, neuroleptic or antidepressive medication within the three months before screening and/or allergy to ingredients of Petadolex[®].

Groups were demographically similar; characteristics are given in Table 1. Migraine attack frequency during baseline was highest in the butterbur group, but the difference did not reach statistical significance. Group means are strongly influenced by outliers and therefore not necessarily a good measure of the average frequency of attacks during baseline. The estimated group means using robust regression analysis are much more similar: 5.49 for the butterbur group, 4.18 for the placebo group, and 4.83 for the music therapy group.

2.2. Study design

This was a 28-week randomized, placebo-controlled, partly double-blind (butterbur root extract versus placebo), three-arm parallel-group study comprising two “medication” treatments (butterbur root extract and placebo) and one psychotherapeutic treatment (music therapy) with a follow-up assessment six months after the end of treatment (Fig. 1). The study consisted of four phases: 8-week baseline phase; 12-week treatment phase; 8-week post-treatment phase and 8-week follow-up phase. The design was based on the International Headache Society (IHS) committee guidelines for controlled trials in migraine (2nd edition) (Tfelt-Hansen et al., 2000). Headache diagnosis was made by a physician according to IHS criteria valid at the time

Table 1
Sample characteristics

	Butterbur	Placebo	Music therapy	<i>p</i>
Number of subjects treated	19	19	20	
Number of <i>M/F</i>	10/9	13/6	17/3	0.098
Age mean \pm SD [y]	10.6 \pm 1.2	10.6 \pm 1.5	9.9 \pm 1.4	0.259
Headache diagnosis (<i>n</i> MO: <i>n</i> MO + MA)	11:8	16:3	15:5	0.362
Attack frequency/28d (baseline), mean \pm SD	9.8 \pm 7.6	5.5 \pm 4.4	5.0 \pm 2.5	0.409
Headache intensity (baseline), mean \pm sd [VAS 0–6]	4.9 \pm 1.7	5.0 \pm 1.4	4.6 \pm 1.5	0.701
DIPS, number of subjects with current diagnosis	3	4	5	0.776
DIPS, number of subjects with former diagnosis	6	3	6	0.157
CBCL total problem score, mean \pm sd	33.3 \pm 24.7	36.5 \pm 22.3	37.6 \pm 21.0	0.830
DIKJ <i>t</i> -score, mean \pm SD	49.8 \pm 9.5	47.9 \pm 6.0	43.7 \pm 4.6	0.121
SSK, perceived stress score, mean \pm SD	20.9 \pm 4.6	20.9 \pm 5.0	18.6 \pm 6.0	0.293
SSK, stress symptoms score, mean \pm SD	14.5 \pm 3.4	13.9 \pm 2.9	11.6 \pm 2.5	0.008

For the treatment groups, sex, age, headache characteristics and mean scores of the psychological assessment during baseline are given (MO = migraine without aura, MA = migraine with aura). Sample characteristics refer to the patients who completed the treatment period (Fig. 2). Statistical comparisons between groups were performed using a one-way analysis of variance for continuous variables and a Fisher's exact *F*-test for categorical variables. For attack frequency during baseline and DIKJ *t*-score, the preconditions of equal variances were strongly violated due to outliers, so comparison was made using robust regression analysis.

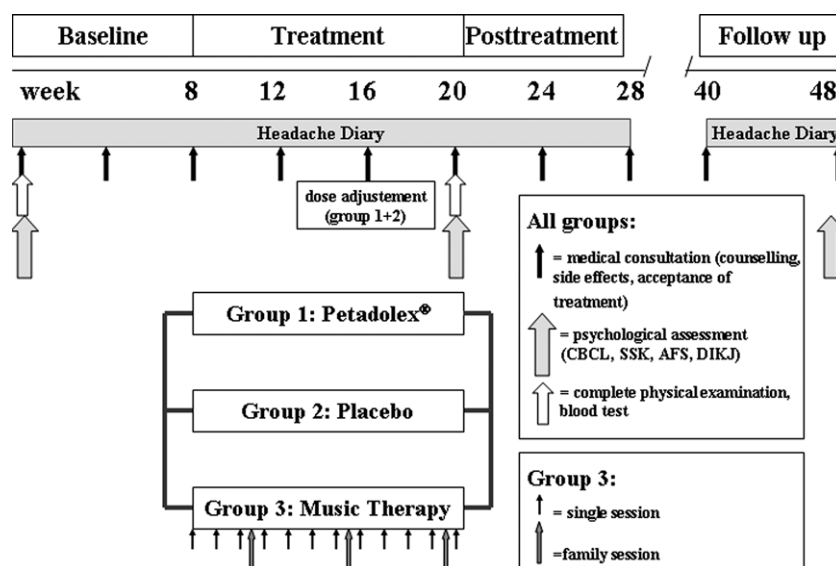


Fig. 1. Study design: all patients and their parents were seen for medical consultations monthly from the beginning of baseline to the end of posttreatment and before and after follow-up period.

of data acquisition (IHS, 1988) by a self-designed, structured interview with the child and a parent (Just et al., 2003). The study was conducted according to the Declaration of Helsinki (current version, 1996) on biomedical research involving human subjects (Tokyo amendment) and the IASP's guidelines for pain research in humans (Charlton, 1995), and the protocol was approved by the University of Heidelberg Ethical Committee. All children and their parents were instructed about the study and written informed consent was obtained.

2.2.1. Randomization

Patients were allocated to one of the three treatment groups after baseline by computerized randomi-

zation. The randomization code and the labelled study medication were provided by Weber & Weber, Biologische Arzneimittel, Inning. Randomization was accomplished by the first author (not involved in patient contacts) who assigned the subject numbers in ascending numerical sequence (block randomization à 9) to the subjects who qualified for randomization. Treatment assignments for the "medication" arms (Petadolex® or placebo) were provided to the clinical sites in sealed envelopes that could have been opened if needed in an emergency. The integrity of all envelopes has been verified at the end of the follow-up period for each subject.

2.3. Assessment

2.3.1. Headache

A child-adapted prospective daily headache diary (Pothmann, 1993) was modified according to the needs of the trial and used continuously during all study phases, except a break between post-treatment and follow-up (week 28 until week 40). All migraine attacks and interval headaches had to be recorded (severity, onset time, duration, accompanying symptoms and intake of symptomatic medication). Severity was evaluated using a 6-point scale. Activities, general feeling and special events had to be noted. Children were rewarded daily for filling in the diary with coloured stickers and received an additional prize (little toys) for the completed diary at the monthly visits. It was ensured that the 8-week baseline and follow-up phases were not performed during long vacation, because childhood headache often shows spontaneous improvement during holidays (Rossi et al., 2001).

2.3.2. Compliance and adverse events

All patients and their parents were seen for 10 medical consultations (about 30 min each) monthly from the beginning of the baseline period to the end of the post-treatment period and at the beginning and the end of the follow-up period (Fig. 1). Adverse events and acceptance of treatment were recorded; headache diaries were checked and collected. Patients and their parents were informed and basically advised on management of their headache in a semi-standardised way:

- education about headache diagnosis and possible pathophysiological models;
- non-pharmacological treatment options for the acute migraine attack (withdrawal, dimming, cooling, etc.);
- symptomatic pharmacological treatment options according to the recommendation of the German Migraine and Headache Society (DMKG),
- management of individual trigger factors of the attacks,
- stress management, relaxation techniques, withdrawal, timetable of leisure time, etc.

All participants received medical consultations and headache education that can be regarded to represent “treatment as usual”. Additional benefit of butterbur and music therapy could be analysed.

Compliance of drug intake was monitored by pill count in the medication groups: at the monthly medical consultations, patients received containers with new study medication and had to restore the old containers, enclosed capsules were recounted. Additionally, compliance was monitored using the number of dropouts between randomization and the end of treatment period in all groups.

The tolerability and safety of study medication was monitored through *adverse events reporting* at the monthly medical consultations. Monitoring of liver enzymes was done according to the prescribing information of Weber & Weber, Biologische Arzneimittel, Inn-Ing (Germany). To maintain blinding of subjects, families and investigators, laboratory evaluations were performed identically in both medication groups (Petadolex® and placebo). Adverse events were recorded in all groups during all study periods (baseline, treatment, post-treatment and follow-up) using spontaneous reports supplemented by response to open questions.¹ Patients rated intensity of adverse events on a scale from 0 (no adverse event) to 10 (highest intensity).

2.3.3. Psychological assessment

Psychiatric comorbidity was investigated using a semi-structured diagnostic interview for mental disorders in children and adolescents, Kinder-DIPS ((Unne-wehr et al., 1995), test–retest reliability for diagnoses kappa coefficient 0.71, validity (referenced to expert’s rating) 64%) and dimensional tools to investigate sub-threshold symptoms: depression was measured using the self-report questionnaire “Depression Inventory for Children and Adolescents” ((Stiensmeier-Pelster et al., 1989), German version (DIKJ) based on the Children’s Depression Inventory by (Kovacs, 1985), 8-week test–retest reliability .76, sufficient validity). Two subscales of the stress questionnaire for children (SSK (Lohaus et al., 1996)) were used to monitor self-rating of perceived stress: score for actual experience of stress (test–retest reliability 0.73), score for physical symptoms of stress (test–retest reliability 0.52), sufficient validity. The parental rating for behavioural and emotional problems was investigated using the Child Behaviour Check List (CBCL, (Achenbach, 1991), German parental version, 1991, one-week test–retest reliability 0.93), sufficient content validity.

2.4. Treatment

2.4.1. Medication

Dosing: In the treatment phase, dosing of Petadolex® was based on the instructions provided by the manufacturer. At start of the treatment phase children aged 8–9 years received one capsule twice daily (50 mg/d), children aged 10–12 years received two capsules twice daily (100 mg/d) continuously for 8 weeks. The identical dose rising scheme was used in an open study in children

¹ Gastrointestinal symptoms (nausea, vomiting, abdominal pain, eructation, heartburn, diarrhoea, acholic faeces, etc.), cardiovascular symptoms (dizziness, collapse, faint, tachycardia, orthostatic symptoms, etc.), respiratory symptoms (dyspnoea, asthmatic symptoms, cough, rhinitis, etc.), dermal symptoms (redness, skin rash, itching, urticaria, etc.) and miscellaneous symptoms (sedation, etc.).

(Pothmann and Danesch, 2005). Effectiveness was evaluated at medical consultation after 8 weeks of treatment by the physician, the child and the parents. If the child and its parents reported a satisfying reduction of headache attacks and report was congruent with the headache diary, Petadolex[®] dosing was kept constant over the last 4 weeks of treatment. If headache relief was absent or marginal, dose was raised to 75 mg/d for children aged 8–9 years and to 150 mg/d for children aged 10–12 years. The dosing of placebo capsules was performed analogously with a “dose increment” after 8 weeks in case of insufficient headache relief, thus, the dosing instruction did not unblind the patients or their physicians as to the treatment allocation. All subjects, their families, the investigators and all personnel directly involved in monitoring the study or reviewing the data were blinded to the treatment until completion of the follow-up period.

2.4.2. Music therapy

Music therapy treatment consists mainly of music-aided relaxation training, body awareness techniques and conflict training in musical role play and comprised 12 weekly single sessions for the child and monthly family sessions for the child and its parents (see Table 2) according to a specific concept. For that the “Heidelberg model”, an evaluated concept for music therapy of adults with chronic pain (Hillecke and Bolay, 2000) was adapted for children as previously published (Nickel, 2004). The concept includes active coping techniques and is more than a prophylactic approach. The manual is based on the phase model for psychotherapy

outcome, which has been empirically well founded by Lueger (1995): in the first phase of therapy the patients improve mainly in the dimension “subjective well-being” (remoralization), then on “symptoms” (remediation) and towards the end of therapy on “general functioning” (rehabilitation). These dimensions (remoralization, remediation and rehabilitation) are focussed successively and realised with specific music therapeutic techniques. Table 2 shows therapeutic goals, assumed specific factors and music therapy techniques in the described phases. Each therapy session is framed by rituals (“hello”- and “good-bye”-songs or musical rituals are created with the child and then repeated in every session). Imagery and relaxation exercises established in the first session are also repeated every session. Stress and conflict management training as well as relaxation (for use in acute situations) are part of this manual. Results are described and discussed in detail elsewhere (e.g. Nickel, 2004).

Symptomatic treatment according to the recommendations of the German Migraine and Headache Society (DMKG) for childhood migraine (www.dmkg.org) (Evers et al., 2002) was permitted for all subjects.

2.5. Statistics

Outcome parameters: the 4-week migraine attack frequency was taken as the primary efficacy variable. The 24-h headache-free rule was modified because in children migraine attacks are usually shorter than in adults. None of the included children had migraine attacks that lasted longer than one day, so attacks were recorded as

Table 2

Music therapy: therapeutic goals, assumed specific factors and music therapy techniques (adopted from Nickel et al., 2003)

Goals after the phase model by Lueger (1995)	Therapeutic goals	Specific factors of music therapy	Music therapy techniques
Phase I: improvement of subjective well-being (4 sessions)	Building of a relationship	Relationship building by the unifying experience of musical interaction	Duo plays
	Activation of “remembered well-being”	Musically supported activation of cognitive and emotional resources	Musically guided imagery with induction of relaxation
	Training of body awareness	Music as a tool for increasing physical perception and expression	Body percussion Guided movement with music Vibro-tactile stimulation
Phase II: improvement of symptoms (5 sessions)	Work on symptoms	Externalization of pain in music	Symptom improvisation
	Work on inhibited expressiveness	Increase of musical flexibility Imaginative activation and reproduction through music	Variation of musical parameters Ritual improvisation Daydream improvisation Musical family symbolization
Phase III: improvement of general functioning (3 sessions)	Learning and implementation of flexible/alternative forms of behaviour and experience	Training of adequate forms of interaction through non-verbal techniques	Reality improvisation Musical role play
	Generalization	Stabilization of therapeutic accomplishments and preparation of end of therapy	Musical self-portrait and treatment evaluation

two attacks when they were separated by at least 18 h. None of the included children reported to have two or more kinds of headache attacks that were qualitatively different when asked: “Do you have different types of headache?”² so all headache attacks in the diaries were counted as migraine attacks. The primary efficacy variable was the reduction of headache frequency (percentage of reduction) from baseline to post-treatment (period of 8 weeks immediately after the end of the treatment phase) and follow-up (period of 8 weeks 6 months after the end of the treatment phase). One *secondary efficacy variable* was the responder rate which was defined as the percentage of subjects in a treatment group with 50% or greater reduction in attack frequency for both phases post-treatment and follow-up, respectively compared with the baseline period (according to Tfelt-Hansen et al., 2000). Another secondary efficacy variable was the clinical level of improvement for intensity. Intensity of headache was defined to be clinically improved when improvement was at least 50% during post-treatment and follow-up, respectively compared with the baseline period.

Furthermore, the effects of differential dropout after treatment were investigated by reporting outcomes not only for completers of the respective phases (post-treatment and follow-up) but, more conservative, also for all patients completing treatment using the method of last-observation-carried-forward.

Planning of sample size: before the start of the study, power analysis was performed: we estimated the sample size that would be necessary to detect group differences of the main efficacy variable “reduction of headache frequency baseline”. Differences in reduction of headache frequency between butterbur root extract and placebo conditions were assumed to be 30–40% according to previous results in adults (Diener et al., 2004). According to an assumed difference of 30% versus placebo, a sample size of 20 subjects randomized to each treatment condition was estimated to achieve at least 83% power for rejection of the null hypothesis on $p < 0.05$ level that reduction of headache attacks was not different in the butterbur root or music therapy versus placebo group.

Comparisons: groups were compared with regard to demographic variables using a one-way analysis of variance for continuous variables and a Fisher’s exact test for categorical variables (see Table 1). If the preconditions of the analysis of variance were strongly violated (outliers), comparisons were made using robust regression analysis, as been indicated in text and tables. Robust regression (Huber, 1964; Berk, 1990) is a form of regression analysis designed to circumvent some limitations of traditional parametric methods, e.g. when the

data contain outliers. This method weights outliers to prevent their undue high influence on the regression coefficients. Robust regression analysis was performed because of outliers for the comparison of attack frequency (percent reduction from baseline) between groups to post-treatment and follow-up period. The dependent variable was relative reduction of headache rate and the explanatory variables were dummy variable codings of group membership for butterbur and music therapy. The means and differences not directly estimated were calculated using linear combinations of the estimates.

Group differences in the number of responders and the number of patients with clinical levels of improvement of intensity were tested with Fisher’s exact test.

The numbers of the adverse events were compared using a repeated measurement ANOVA with the factors treatment groups and study period (baseline, treatment, post-treatment and follow-up); p -values were adjusted with the Huynh–Feldt correction.

Dependence of headache reduction at post-treatment and follow-up on baseline variables (attack frequency, CBCL total score, DIKJ depression score, SSK score for actual experience of stress and SSK score for physical symptoms of stress) was tested in an explorative way using robust regression analysis with headache reduction as dependent variable, treatment group as dummy variable coded factor, baseline variable as explanatory variable (in the case of diagnosis also dummy variable coded) and interactions treatment with baseline variable, separately for post-treatment and follow-up and for each baseline variable.

Significance level was set to 5%. All hypotheses on regression coefficients were tested using Wald tests.

3. Results

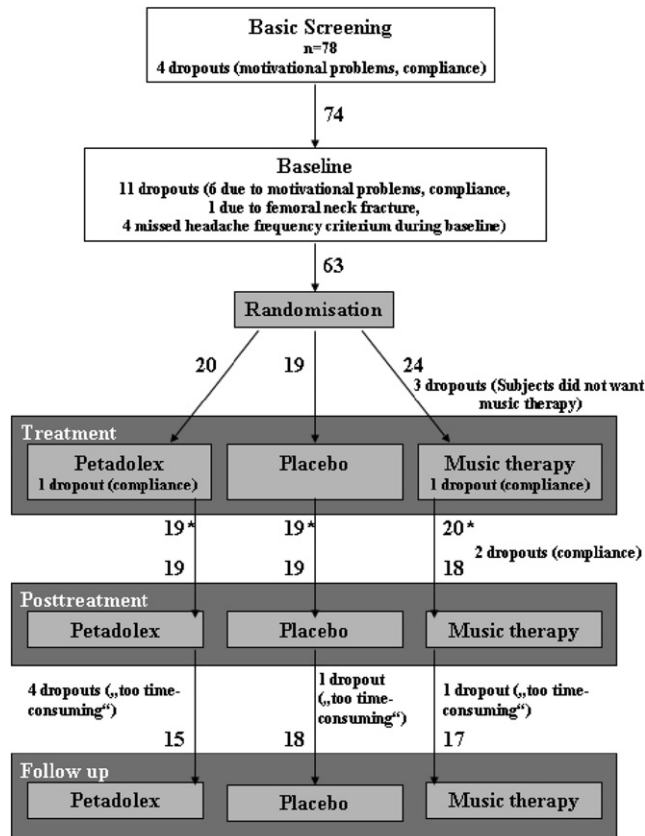
3.1. Participant flow and follow-up (see Fig. 2)

The overall dropout rate between randomization and follow-up 6 months later (week 48) was 20.6% (13 out of 63), i.e. 25% (5/20) in the butterbur group, 5% (1/19) in the placebo group and 29% (7/24) in the music therapy group (Fig. 2, group differences $p = 0.133$). The dropout rate that might be correlated to treatment itself (between randomization and the end of the treatment phase) was much lower, i.e. 5% (1/20) in the butterbur group,³ 0% (0/19) in the placebo group and 16.7% (4/24) in the music therapy group (group differences $p = 0.112$).⁴

³ After 8 weeks of treatment, the child was not willing to keep on taking the pills.

⁴ Three children dropped out before start of treatment (difficulties with schedule or journey), one child refused participation in music therapy after two sessions.

² After that statement, we did not ask more specifically either the children or the parents. So some subjects might have additional TTH which was not detected.



* subject sample characteristics (table 1) refer to these numbers

Fig. 2. Participant flow and follow-up: numbers of dropouts during the study phases are given before and after randomization to the three treatment groups.

The dropouts after treatment had received treatment but did not produce post-treatment data. No subject dropped out due to adverse events of treatment. The number of patients included in statistical analysis is given in the respective tables or figures.

3.2. Dose rising and efficacy

Medication dose was raised in case of insufficient response after the first 8 weeks of treatment in 8 of 19 patients in both the butterbur and the placebo group. Reduction of headache frequency from baseline was higher to both post-treatment and follow-up period in patients with stable dose over the treatment period compared to those with dose rising after the first 8 weeks of treatment; this effect seemed to be more pronounced in the butterbur group. Robust regression analysis which was performed because of outliers showed a significant impact of the factor “dose rising” ($p = 0.008$ and $p = 0.026$ for post-treatment and follow-up, respectively), but not for “treatment” alone or the interaction “treatment” with “dose rising”.

3.3. Adverse events

Mean scores of the patient’s rating for all adverse events were different neither between study periods (no increase during the treatment period versus baseline or follow-up, effect of factor “phase”, $F(3, 154) = 0.65$, $p = 0.564$) nor between treatment groups in their time course over the different phases (interaction “phase” with “group”, $F(6, 154) = 0.98$, $p = 0.433$). Scores of all symptom groups (gastrointestinal, cardiovascular, respiratory, dermal/allergic and miscellaneous symptoms) showed a similar pattern. During the double-blind treatment period 15/19 patients in the butterbur group reported 42 adverse events compared to 44 adverse events in 15/19 patients of the placebo group and 28 adverse events in 12/20 patients of the music therapy group. Differences between groups were not significant ($p = 0.282$ for number of adverse events and $p = 0.320$ for number of patients with adverse events). Frequency of adverse events is very similar in the butterbur and in the placebo group, and tends to be lower (albeit this does not reach significance) in the music therapy group. In the butterbur group, the most frequent complaints were gastrointestinal symptoms ($n = 15$, nausea, mild diarrhoea, abdominal pain, regurgitation and bitter taste sensation) and dermal/allergic symptoms ($n = 12$, itching, rash and allergic rhinitis). Other complaints in the butterbur group were pain symptoms ($n = 7$, arthralgia, limb pain, etc.), dizziness ($n = 4$), fatigue ($n = 2$), and asthmatic symptoms ($n = 2$). Symptoms were generally mild and self-limiting.

Routine laboratory evaluations showed transient and self-limiting mild elevation of liver enzymes in two patients of the butterbur group and three placebo patients.

3.4. Efficacy

3.4.1. Reduction of attack frequency

The primary efficacy variable was the relative reduction from baseline in the 4-week migraine headache rate to the post-treatment (over 8 weeks after the end of treatment period) and the follow-up period (over 8 weeks 6 months after the end of treatment). Analyses of patients completing the respective study phases were supplemented by analyses of all patients completing treatment to better describe the effects of differential dropouts after treatment. Results for both analyses are given in Table 3. In all groups, baseline headache frequency was significantly reduced during post-treatment and follow-up period. In the post-treatment period, only music therapy was superior to placebo ($p = 0.005$ for completers and $p = 0.042$ for all treated patients). In the follow-up period 6 months later both music therapy and butterbur root extract were superior to placebo ($p = 0.018$ and $p = 0.044$, respectively) and did not differ

Table 3

Migraine attack frequency reduction from baseline in (A) completers of the respective study phases (“completers”) and (B) all patients completing treatment (“all treated patients”)

	Bu	Pl	Mu	Comp	<i>p</i> (C)	95%CI (%)
<i>(A) Completers: post-treatment</i>						
RfB (%)	36.1 ± 57.3	28.8 ± 39.5	65.7 ± 31.0	Bu vs. Pl	0.159	[−7.0; 41.7]
				Mu vs. Pl	0.005	[11.8; 61.9]
				Mu vs. Bu	0.124	[−5.5; 44.6]
P	0.000	0.001	0.000			
N	19	19	17 ^a			
<i>(A) Completers: follow-up</i>						
RfB (%)	58.7 ± 34.6	31.4 ± 41.8	63.2 ± 33.9	Bu vs. Pl	0.044	[0.8; 57.7]
				Mu vs. Pl	0.018	[6.0; 61.0]
				Mu vs. Bu	0.766	[−24.5; 33.1]
P	0.000	0.002	0.000			
N	15	18	17			
<i>(B) All treated patients: post-treatment</i>						
RfB (%)	36.1 ± 57.3	28.8 ± 39.5	55.0 ± 37.2	Bu vs. Pl	0.196	[−9.2; 43.8]
				Mu vs. Pl	0.042	[1.0; 53.3]
				Mu vs. Bu	0.456	[−16.4; 36.0]
P	0.000	0.002	0.000			
N	19	19	20			
<i>(B) All treated patients: follow-up</i>						
RfB (%)	47.9 ± 38.8	31.9 ± 40.6	55.8 ± 36.9	Bu vs. Pl	0.227	[−10.8; 44.5]
				Mu vs. Pl	0.076	[−2.6; 52.0]
				Mu vs. Bu	0.568	[−19.5; 35.1]
P	0.000	0.002	0.000			
N	19	19	20			

Reduction of migraine attack frequency from baseline (RfB) for post-treatment and follow-up period in (A) completers of the respective study phases and (B) all treated patients of the butterbur (Bu), Placebo (Pl) and Music therapy (Mu) group: Reduction from baseline (RfB) is given in percent (mean ± standard deviation), significance levels for reduction versus baseline and number of subjects are also presented. Comparisons (Comp) between groups were made using robust regression analysis; significance level for comparisons (*p*(C)) and 95% confidence intervals on differences are given (95%CI). Significant values are given in bold. In the post-treatment period, only music therapy was superior to placebo for both completers and all treated patients, whereas in the follow-up period both music therapy and butterbur were superior to placebo only for the analysis of completers. When all treated patients are analyzed, there are no significant group differences during follow-up. Both treatment groups did not differ significantly in reduction of attack frequency.

^a One subject was excluded from analysis because incomplete headache diary data during post-treatment period.

from each other (*p* = 0.766) only when the completers of the respective study periods were analyzed. In the analysis including all treated patients treatment groups did not differ significantly during follow-up.

3.4.2. Time course of headache reduction

Note that in all groups substantial reduction of attack frequency occurs during baseline, i.e. before the start of study treatment (Fig. 3). Effects during baseline can represent unspecific effects of expectation or might be mediated by the monthly medical consultations (which started at the beginning of the baseline period) or the headache diary. Headache reduction followed different time courses in the three groups: the main reduction occurred during baseline and treatment period (week 1–20) for the music therapy group, during baseline period (i.e. before treatment, week 1–8) in the placebo group, and during baseline and even after the end of treatment in the butterbur group. Note that unspecific reduction during baseline accounts for a substantial part (more than 50%) of the total effect (Fig. 3),

additional specific treatment effects are small for placebo (about 25%) and greater for butterbur (about 40%) and music therapy (about 65%).

3.4.3. Clinical levels of improvement

During post-treatment, responder rate (at least 50% reduction of attack frequency) in the music therapy group was significantly higher than in the placebo or butterbur group (Table 4). During follow-up, responder rates in the three treatment groups did not differ significantly from each other. Clinical improvement of headache intensity (at least 50% reduction compared with the baseline) occurred only in a minority of subjects, treatment groups did not differ significantly (Table 4).

3.5. Compliance

The mean intake (±SD) of prescribed capsules was 92.4 ± 11.8% in the butterbur group and 84.1 ± 24.8% in the placebo group. Minimum intake was 65.2%

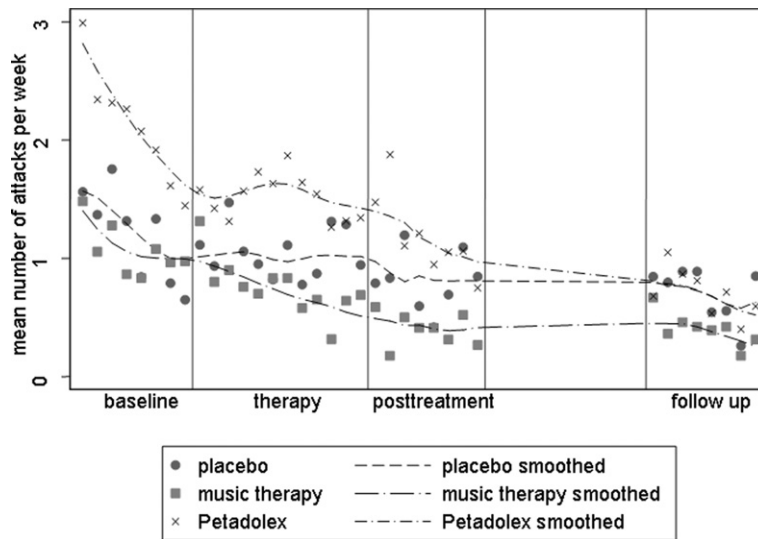


Fig. 3. Migraine frequency in the treatment groups during baseline, treatment, post-treatment and follow-up. Data are depicted as mean frequency per week as measured (symbols) and smoothed (lines). Smoothing was performed using locally weighted regression analysis (lowess).

Table 4

Responder rate and clinical improvement of intensity

		Bu	Pl	Mu	<i>p</i> (C)
Responder rate	Post-treatment % (<i>n</i> / <i>N</i>)	26.3 (5/19)	26.3 (5/19)	70.6 (12/17 ^a)	0.010
	Follow-up % (<i>n</i> / <i>N</i>)	53.3 (8/15)	33.3 (6/18)	58.8 (10/17)	0.312
Clinical improvement of intensity	Post-treatment % (<i>n</i> / <i>N</i>)	21.1 (4/19)	15.8 (3/19)	5.9 (1/17 ^a)	0.505
	Follow-up % (<i>n</i> / <i>N</i>)	33.3 (5/15)	22.2 (4/18)	29.4 (5/17)	0.793

Responder rate (defined as 50% or more reduction of headache frequency compared with the baseline) and clinical improvement of intensity (defined as 50% or more reduction of headache intensity compared with the baseline) are given in percent for post-treatment and follow-up for the butterbur (Bu), placebo (Pl) and music therapy (Mu) group. Absolute numbers (in parentheses) and significance levels for comparisons are given. During post-treatment, responder rate in the music therapy group is significantly higher than in the placebo or butterbur group. During follow-up, differences between groups did not reach significance. Clinical improvement of intensity is not significantly different between groups during both post-treatment and follow-up.

^a One subject was excluded from analysis because incomplete headache diary data during post-treatment period.

(*n* = 1) in the butterbur group and 0% in the placebo group (*n* = 1).

After randomization and before the end of the treatment period, 4 out of 24 children (16.7%) assigned to music therapy and 1 out of 20 children (5%) assigned to the butterbur group did not comply with their randomized intervention and withdrew from the trial. Taken together with the compliance measure derived from the pill count, 4/24 patients (16.7%) in the music therapy group were “non-compliers” compared to 4/20 (20%) in the butterbur group and 4/19 (21.1%) in the placebo group. Group differences were not significant.

3.6. Psychological assessment

Psychological assessment gave evidence for sufficient matching of groups (Table 1). Only the stress symptoms score derived from the SSK (but not the SSK perceived

stress score) differed between groups before treatment with the lowest score in the music therapy group. A number of 16 current psychiatric diagnoses according to DSM IV-R or ICD-10 classification (Kinder-DIPS) were found in 12 of the 58 patients (20.7%) who completed the treatment period. The most frequent diagnoses were phobic, depressive or obsessive compulsive disorders. Additionally, 19 former psychiatric diagnoses were found in 15 of these 58 patients (25.9%); the most frequent diagnoses were depressive episodes (in 7 patients), enuresis, separation anxiety disorder and obsessive compulsive disorder.

3.7. Dependence of headache reduction on baseline variables

In an exploratory analysis we included baseline variables and their interaction with group membership in

the regression relating the treatment to the reduction of attack frequency (see above). Neither for the baseline to post-treatment reduction nor for the baseline to follow-up reduction, a significant effect of one of the baseline variables (attack frequency, CBCL total score, DIKJ depression score, SSK score for actual experience of stress, SSK score for physical symptoms of stress and presence of a psychiatric diagnosis according to ICD-10 or DSM-IV) could be found. Here, exemplarily for the baseline attack frequency the non-significant results in detail: main effect on the reduction post-treatment $F(1,49) = 0.42$, $p = 0.521$ and follow-up $F(1,44) = 3.85$, $p = 0.056$; interaction of the baseline attack frequency with the treatment group for post-treatment phase $F(2,49) = 1.70$, $p = 0.194$ and follow-up $F(2,44) = 1.82$, $p = 0.174$.

4. Discussion

Paediatric migraine is very common, but little evidence exists for pharmacological and non-pharmacological prophylaxis. This prospective, randomized, partly double-blind, and placebo-controlled trial found evidence that butterbur and music therapy might be superior to drug placebo.

This study is one of very few studies that compare pharmacological and non-pharmacological interventions. Music therapy is not only a prophylactic approach but also includes active coping techniques. One other study that compared pharmacological (propranolol) and non-pharmacological (self-hypnosis) prophylaxis in children (Olness et al., 1987) gave evidence for efficacy of self-hypnosis but was rated to lack sufficient methodological information (Hermann et al., 1995). In contrast to others (reviewed in Hermann et al., 1995; Victor and Ryan, 2004; Damen et al., 2006a,b), this study has some methodological strength: It was based on the IHS criteria and guidelines for controlled trials in migraine, randomized, placebo-controlled, and drug treatment was performed strictly double-blind. Placebo-control groups are lacking in most recent studies addressing non-pharmacological treatment; that limits previous conclusions about effectiveness of those interventions (Damen et al., 2006a). This study included a prospective baseline, 12 weeks of treatment and a follow-up 6 months later. Similar sample characteristics of the treatment groups prove sufficient matching. Our sample was no “clinical” sample as all subjects were recruited via study advertisements to avoid a bias towards psychiatric comorbidity, but psychological characteristics and gender ratio fit in with epidemiological data (Lipton et al., 1994).

Music therapy as a form of creative psychotherapy is the therapeutic use of musical activities for patients suffering from somatic and mental diseases. It seems to be

effective in adults with headache (Risch et al., 2001) or chronic pain (Hillecke, 2002) and has been promising in children (Gold et al., 2004). Because musical interaction is used as a means of nonverbal communication, it is particularly effective in children who are directly accessible through nonverbal contact and less familiar with verbal approaches. Our results give evidence that a specific music therapy concept tailored to the demands of children (Nickel, 2004) might be able to reduce headache frequency substantially. Music therapy encourages active coping and rather prevents passive coping strategies. Relaxation is one important element, and its impact can't be separated from the additional effect of music, body awareness techniques and conflict training. It is not easy to determine effective components of treatment packages: studies that compare non-pharmacological treatments often fail to find differences between conditions: Richter et al. (1986) compared efficacy of relaxation and cognitive coping with a non-specific placebo control and found that both active treatments were superior to placebo. A comparison of biofeedback, relaxation and pain behaviour management versus wait-list-control revealed similar results: Relaxation with/without biofeedback, combined with pain behaviour management, was effective (Fentress et al., 1986). Labbe (1995) tried a component analysis of thermal biofeedback and compared it with/without autogenic training to wait-list control: thermal biofeedback did not have an additional advantage. McGrath et al. (1988) described even “efficacy” of psychological placebo – compared with relaxation and “own best efforts”: all three treatments were equally effective. Similar to these studies, we found that both treatment conditions (butterbur and music therapy) but also placebo caused profound and sustained reduction of headache with a potentially higher effect of the treatment conditions (Fig. 3).

Headache frequency showed a further decrease during the months after treatment, this “carry-over” effect has been reported for prophylactic medication (Silberstein, 1997; Sorge et al., 1988). Increased self-awareness associated with keeping of the headache diary (Klassen and Dooley, 2000; Pothmann, 1999) may contribute to that. The headache diary accounts for a part of the *non-specific treatment effect* that is an essential mediator of response in paediatric migraineurs (Hermann et al., 1995). Other non-specific effects are probably mediated by enrolment into a medical setting, positive expectancy, and the medical consultations.

The design of this study allows to approximately separating unspecific effects of expectancy, setting and “treatment as usual” (headache diary, headache education, etc.) from a drug placebo effect in its narrow sense. Note that the unspecific setting effects started (paralleling the start of medical consultations) immediately after enrolment (Fig. 3) and preceded the treatment phase in

all groups. This “setting” effect including also “treatment as usual” components accounts for about a half of the total headache reduction. Additional specific treatment effects are found for butterbur (about 40%) and music therapy (about 65%) versus drug placebo. Attack reduction in the butterbur group was somewhat lower (due to the blinded design) than in a recent open-label study in children (Pothmann and Danesch, 2005).

The drug placebo effect in its narrow sense is minor (leading to about 25% reduction) and much smaller than the unspecific “setting” effect before treatment. This is in accordance with the (relatively high) reported mean placebo response in paediatric migraine prophylaxis (van der Kuy and Lohman, 2002).

Dose rising (in case of insufficient response) was associated with a smaller response. Insufficient response to Petadolex® over 8 weeks might therefore be indicative of a general non-response; a potential response to Petadolex® seems to be noticeable during the first weeks of treatment – although the full effect develops over months even after the end of treatment (Fig. 3). Further studies investigating the impact of different doses of Petadolex® on the extent and the time-course of headache reduction are warranted to extract recommendations for dosing and duration of treatment.

Psychiatric comorbidity of the study sample is similar to that in the normal population (Costello et al., 1996). Response to treatment does not depend on the headache characteristics, psychiatric comorbidity or psychopathology scores during baseline.

However, limitations of the current study are as follows: (i) subject sample is small, (notwithstanding power analyses were performed before the start of the study), so generalizability is limited and replication of results should be tried with larger samples. (ii) Evidence that butterbur and music therapy are superior to placebo comes from a more liberal methodological approach, i.e. analyses restricted to subjects completing the respective study phase. To balance that, these analyses were supplemented by more conservative analyses of all patients completing treatment (Table 3) as well as investigation of responder rates and clinical improvement of intensity (Table 4). These conservative approaches confirm that significant and sustained improvement of headache occurred in all treatment groups but failed to show superiority of butterbur and music therapy to placebo 6 months after treatment. The analysis of all treated patients was based on last-observation-carried-forward for the patients that dropped out after treatment. This might lead to an underestimation of treatment effects because completers showed an ongoing headache reduction even after treatment, and dropouts probably did not experience full relief when they stopped filling in the diaries. This bias affected both treatment groups more than the placebo group because the latter had the lowest dropout after treatment ($n = 4$

butterbur root, $n = 3$ music therapy, $n = 1$ placebo). Thus especially the effectiveness of butterbur and music therapy might be underestimated. On the other hand, the conservative approaches underline the explorative character of the study. Conclusions of superiority to placebo have to be drawn with caution; and other studies investigating butterbur and music therapy in paediatric migraine should challenge these explorative results. This recommendation is supported also by the analysis of responder rates (another conservative measure) that also failed to find group differences during follow-up. Responder rates are highest in the music therapy group directly after treatment ($>70\%$); perhaps relaxation and coping techniques are then most accessible for the children. During follow-up responder rates in the treatment groups are higher than for placebo but still moderate ($<60\%$). This might be due to the fact that many patients experience a headache reduction frequency that is substantial but below 50%. Furthermore, the dichotomised responder analysis has less power than the comparison of headache reduction. (iii) Music therapy was not performed blindly; and it was controlled by a drug placebo condition but not by a “psychotherapeutic placebo”. Thus conclusions regarding music therapy have to be drawn with caution.

Regardless of limitations, two preventive “interventions” that have not been investigated before systematically in paediatric migraine may represent promising alternatives because of their favourable side effect-value ratio. The herbal drug Petadolex® is applied in children since decades; adverse events are usually mild and rare (Danesch and Rittinghausen, 2003); and the potential to interact with other drugs is low (Grossmann and Schmidramsl, 2000). Petadolex® was well tolerated which is in accordance with the results of an open-label study (Pothmann and Danesch, 2005).

In conclusion, controlled studies are essential in childhood migraine because the non-specific effect is even greater than in adults and an important mediator of the therapeutic effect. In this study, the non-specific effect accounted for about half of the total response. In contrast, effect of the drug placebo itself was small. Evidence for efficacy of butterbur root and music therapy in prevention of paediatric migraine came from the fact that both treatments caused a greater additional headache reduction than drug placebo when completers were analyzed. These promising treatment approaches should be further evaluated in larger samples (perhaps using a multi-centre design and a psychological “placebo” condition).

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References

- Abu-Arafeh I, Russell G. Prevalence of headache and migraine in schoolchildren. *BMJ* 1994;309:765–9.
- Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. University of Vermont: Department of Psychiatry; 1991.
- Berk RA. A primer on robust regression. In: Fox G, Long JS, editors. Modern methods of data analysis. Newbury Park: Sage; 1990. p. 292–324.
- Bille B. A 40-year follow-up of school children with migraine. *Cephalalgia* 1997;17:488–91 [discussion 487].
- Charlton E. Ethical guidelines for pain research in humans. Committee on Ethical Issues of the International Association for the Study of Pain. *Pain* 1995;63:277–8.
- Costello EJ, Angold A, Burns BJ, Stangl DK, Tweed DL, Erkanli A, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. *Arch Gen Psychiat* 1996;53:1129–36.
- Damen L, Bruijn J, Coes BW, Berger MY, Passchier J, Verhagen AP. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. *Cephalalgia* 2006a;26:373–83.
- 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* 2006b;26:497–505.
- Danesch U, Rittinghausen R. Safety of a patented special butterbur root extract for migraine prevention. *Headache* 2003;43:76–8.
- Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol* 2004;51:89–97.
- Eccleston C, Morley S, Williams A, Yorke L, Mastroiannopoulou K. Systematic review of randomised controlled trials of psychological therapy for chronic pain in children and adolescents, with a subset meta-analysis of pain relief. *Pain* 2002;99:157–65.
- Evers S, Pothmann R, Uberall M, Naumann E, Gerber WD. Treatment of idiopathic headache in childhood - recommendations of the German Migraine and Headache Society (DMKG) [Therapie idiopathischer Kopfschmerzen im Kindesalter Empfehlungen der Deutschen Migräne- und Kopfschmerzgesellschaft DMKG]. *Schmerz* 2002;16:48–56.
- Fentress DW, Masek BJ, Mehegan JE, Benson H. Biofeedback and relaxation-response training in the treatment of pediatric migraine. *Dev Med Child Neurol* 1986;28:139–46.
- Gold C, Voracek M, Wigram T. Effects of music therapy for children and adolescents with psychopathology: a meta-analysis. *J Child Psychol Psychiat* 2004;45:1054–63.
- Grossmann M, Schmidramsl H. An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. *Int J Clin Pharmacol Therapeut* 2000;38:430–5.
- Hermann C, Kim M, Blanchard EB. Behavioral and prophylactic pharmacological intervention studies of pediatric migraine: an exploratory meta-analysis. *Pain* 1995;60:239–55.
- Hillecke T. Effectivity and theoretical aspects of music therapy in patients with chronic non-malignous pain [Effektivität und theoretische Aspekte von Musiktherapie bei Patienten mit chronischen, nicht-malignen Schmerzen]. Medical Faculty, Heidelberg: Ruprecht-Karls-Universität; 2002.
- Hillecke T, Bolay HV. Music therapy in chronic pain – theoretical basis – the Heidelberg model [Musiktherapie bei chronischen Schmerzen - theoretische Grundlagen - das Heidelberger Modell]. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2000;35:394–400.
- Holden EW, Deichmann MM, Levy JD. Empirically supported treatments in pediatric psychology: recurrent pediatric headache. *J Pediatr Psychol* 1999;24:91–109.
- Huber PJ. Robust estimation of a location parameter. *Ann Math Stat* 1964;35:73–101.
- IHS. 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.
- Just U, Oelkers R, Bender S, Parzer P, Ebinger F, Weisbrod M, et al. Emotional and behavioural problems in children and adolescents with primary headache. *Cephalalgia* 2003;23:206–13.
- Klassen BD, Dooley JM. Chronic paroxysmal hemicrania-like headaches in a child: response to a headache diary. *Headache* 2000;40:853–5.
- Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull* 1985;21:995–8.
- Labbe EE. Treatment of childhood migraine with autogenic training and skin temperature biofeedback: a component analysis. *Headache* 1995;35:10–3.
- Laurell K, Larsson B, Eeg-Olofsson O. Prevalence of headache in Swedish schoolchildren, with a focus on tension-type headache. *Cephalalgia* 2004;24:380–8.
- Lipton RB, Silberstein SD, Stewart WF. An update on the epidemiology of migraine. *Headache* 1994;34:319–28.
- Lipton RB, Gobel H, Einhaupl KM, Wilks K, Mauskop A. *Petasites hybridus* root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004;63:2240–4.
- Lohaus A, Fleer B, Freitag P, Klein - Heßling J. Fragebogen zur Erhebung von Streßerleben und Streßbewältigung im Kindesalter (SSK). Göttingen: Hogrefe; 1996.
- Lueger RJ. Ein Phasenmodell der Veränderung in der Psychotherapie. *Psychotherapeutics* 1995;40:267–78.
- McGrath PJ, Humphreys P, Goodman JT, Keene D, Firestone P, Jacob P, et al. Relaxation prophylaxis for childhood migraine: a randomized placebo-controlled trial. *Dev Med Child Neurol* 1988;30:626–31.
- Nickel AK. Effectivity of music therapy in children with migraine [Effektivität von Musiktherapie bei Kindern mit Migräne]. Medical Faculty, Heidelberg: Ruprecht-Karls-Universität; 2004.
- Nickel AK, Hillecke TK, Resch F, Bolay HV. Music therapy in the treatment of children with migraine. *Mus Ther Today* 2003;4. Available from: <http://musictherapyworld.net>.
- Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. *Pediatrics* 1987;79:593–7.
- Pothmann R. Migräne im Kindesalter. Erläuterungen zum Migränetagebuch für Kinder für die Handhabung in der Praxis. München: Arcis Verlag; 1993.
- Pothmann R. Kopfschmerz im Kindesalter. Stuttgart: Hippokrate; 1999.
- Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache* 2005;45:196–203.
- 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.
- Richter IL, McGrath PJ, Humphreys PJ, Goodman JT, Firestone P, Keene D. Cognitive and relaxation treatment of paediatric migraine. *Pain* 1986;25:195–203.
- Risch M, Scherg H, Verres R. Music therapy for chronic headaches. Evaluation of music therapeutic groups for patients suffering from

- chronic headaches [Musiktherapie bei chronischen Kopfschmerzen. Evaluation musiktherapeutischer Gruppen für Kopfschmerzpatienten]. *Schmerz* ;15:116–25.
- Rossi LN, Cortinovis I, Menegazzo L, Brunelli G, Bossi A, Macchi M. Classification criteria and distinction between migraine and tension- type headache in children. *Dev Med Child Neurol* 2001;43:45–51.
- Sartory G, Muller B, Metsch J, Pothmann R. A comparison of psychological and pharmacological treatment of pediatric migraine. *Behav Res Ther* 1998;36:1155–70.
- Scheidegger C, Dahinden C, Wiesmann U. Effects of extracts and of individual components from *Petasites* on prostaglandin synthesis in cultured skin fibroblasts and on leucotriene synthesis in isolated human peripheral leucocytes. *Pharm Acta Helv* 1998;72:376–8.
- Silberstein SD. Preventive treatment of migraine: an overview. *Cephalalgia* 1997;17:67–72.
- Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia* 2002;22:491–512.
- Sillanpaa M, Anttila P. Increasing prevalence of headache in 7-year-old schoolchildren. *Headache* 1996;36:466–70.
- 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.
- Stiensmeier-Pelster J, Schürmann M, Duda K. *Depressions-Inventar für Kinder und Jugendliche*. Testzentrale Göttingen, Hogrefe 1989.
- 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.
- Unnewehr S, Schneider S, Margraf J. *Kinder-DIPS: diagnostisches Interview bei psychischen Störungen von Kindern und Jugendlichen*. Berlin: Springer; 1995.
- van der Kuy PH, Lohman JJ. A quantification of the placebo response in migraine prophylaxis. *Cephalalgia* 2002;22:265–70.
- Victor S, Ryan SW. Drugs for preventing migraine headaches in children. *The Cochrane Library* 2004;1–43.
- Winner P, Pearlman EM, Linder SL, Jordan DM, Fisher AC, Hulihan J. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. *Headache* 2005;45:1304–12.