DOI:10.14753/SE.2016.1860

Examining the Quality of Life in Primary Headaches

PhD Thesis

Nora Manhalter, MD

Semmelweis University
János Szentágothai Doctoral School of Neurosciences

Supervisor: Csaba Ertsey, MD, PhD

Official reviewers: Délia Szok, MD, PhD
György Purebl, MD, PhD

Head of the Final Examination Committee: Professor Ferenc Túry, MD, DSc

Members of the Final Examination Committee: Ildikó Vastagh, MD, PhD
Attila Valikovics, MD, PhD

Budapest
2015

DOI:10.14753/SE.2016.1860

Table of contents

DOI:10.14753/SE.2016.1860

DOI:10.14753/SE.2016.1860

DOI:10.14753/SE.2016.1860

1. List of abbreviations

24-hour MQoLQ	24-hour Migraine Quality of Life Questionnaire
BP	bodily pain
CDH	chronic daily headache
CH	cluster headache
CHQQ	Comprehensive Headache-related QOL Questionnaire
CM	chronic migraine
CTTH	chronic tension type headache
EF	emotional function
EM	episodic migraine
GH	general health
HDI	Headache Disability Inventory
HIT-6	Headache Impact Test
HRQoL	health-related quality of life
IHS	International Headache Society
M	migraine
MH	mental health
MIDAS	Migraine Disability Assessment Score
MOH	medication overuse headache
MOS	Medical Outcomes Study
MSQ2.1	Migraine-specific Quality of Life Questionnaire
MSQOL	Migraine-Specific Quality of Life measure
PF	physical functioning
PROs	patient reported outcomes
QOL	quality of life
QVM	Qualite´de Vie et Migraine
RE	role emotional functioning
RP	role physical functioning
RP	role-preventive
RR	role-restrictive
SF	social functioning
SF-20	20-Item Short Form Health Survey

DOI:10.14753/SE.2016.1860

SF-36	36-Item Short Form Health Survey
TTH	tension type headache
VAS	visual analogue scale
VT	vitality

DOI:10.14753/SE.2016.1860

2. Background and literature

2.1 Introduction

In medical practice several outcome measures are used to describe the patients' condition. Some of these are objective, i.e. they can be observed by the investigator (eg. tremor, gait), and/or they can be reproducibly measured by appropriate methods (eg. blood pressure, lab results). Other health relevant indicators are subjective and described using the patient's own assessment (eg. pain, mood, sleep quantity or sleep quality). In recent decades the measurement of these patient reported outcomes has become very frequent.

Patient reported outcomes (PROs) include all information, which is communicated directly by the patient and describes his/her health and emotional status, or medical conditions, and the consequences thereof. As follows, the information gathered by PROs is not influenced by the interpretation of health care providers. These pieces of information thus create a unique picture of the patient's perspective about his/her illness and the impact of medical treatment. Table 1 summarizes the most important aspects and examples of objective and subjective indicators.

Table 1. Indicators in medical practice VAS: visual analogue scale

OBJECTIVE	**SUBJECTIVE**
observable by the investigator	communicated by the patient
measurement methods: physical, chemical, histological, etc.	measurement methods: questionnaire, interview, VAS, etc.
measurable	measurable (with limitations)
reproducible	reproducible (with limitations)
Examples ▪ Blood pressure ▪ Body temperature ▪ Laboratory results ▪ DNA tests ▪ Histology resuls	Examples ▪ Burden of illness ▪ Pain ▪ Sleep quantity ▪ Mood ▪ Quality of life

2.1.1. Health related quality of life

Quality of life is „a broad-ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationship and their relationship to salient features of their environment" (1).

Health-related quality of life (HRQoL) is a more circumscript entity. Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO definition of Health) (1). Health-related quality of life represents the overall effect of illness and its therapy, as reported and evaluated by the patient (2). In this respect, HRQoL is to be distinguished from functional status, which provides an objective assessment of a patient's physical and emotional capabilities by medical personnel (3). HRQoL questionnaires are among the most commonly used PRO measurement tools.

Beside the 'hard' indicators – i.e. mortality, morbidity – which are traditionally applied for measuring the efficiency of health care activities, PROs describing the patients' subjective experiences – including life quality measurements – are gaining more and more attention. Practical experiences confirm – mainly in case of chronic diseases– that better values, shown by objective indicators used in medical work, are not necessarily accompanied by patients' sense of feeling better (4, 5). On the other hand, in case of several medical conditions, the quality of life is an independent predictor of disease progression and/or outcome. In end-stage renal disease perceived mental health was found to be an independent predictor of mortality and morbidity (7). Quality of life is a predictor of survival in pancreatic cancer and HIV-infected adults, too (8, 9). Information about quality of life is therefore very important for decision making in very different, and also severe diseases (8).

2.1.2. Objective and subjective indicators in headache disorders

In the field of headache research, 'objective' indicators (ie. indicators which are not dependent on any input from the patients) are not available. As headache is a subjective experience, the most commonly used indicators, such as number of days with headache,

headache severity, or analgesic consumption, are all reported by the patients. To try to overcome this issue, a number of standardized endpoints have been developed, such as the Visual Analogue Scale (VAS) and – more importantly – the International Headache Society's 4-point headache severity scale. A number of headache diaries, both paper-and-pencil and electronic ones, have also been conceived and are used both in clinical trials and everyday medical practice. Lately, these indicators have increasingly been supplemented by other subjective indicators, such as quality of life, disability, or headache impact.

2.1.3. Health related quality of life in headache disorders

HRQoL assessment tools can either assess the patients' quality of life as a whole or assess the effect of a given condition. Accordingly, a distinction between overall HRQoL and disease-specific HRQoL is necessary. Overall HRQoL is a concept that includes physical and mental functioning and well-being, social and role disability, and general health perceptions of the individual (10). On the other hand, disease-specific HRQoL describes the particular impact of a selected condition on HRQoL.

2.2 HRQoL questionnaire types

Although HRQoL can most precisely be assessed by a detailed patient interview, this approach is not practical because of a number of reasons, including issues regarding the reproducibility and comparatibility of data, feasibility and examiner burden. To overcome these difficulties while aiming at assessing the patients' quality of life in detail, a number of HRQoL questionnaires (also commonly called HRQoL instruments) were developed. There are two basic types of HRQoL questionnaires: generic or disease-specific questionnaires.

Generic HRQoL questionnaires measure overall HRQoL. They include questions that represent those aspects of health that are important for the majority of people. Thus, these instruments permit the comparison of the impact of one illness with that of others

and also with values of those who are well. They can measure the effect of various healthcare interventions and therefore can be useful, among others, in analysing cost-efficiency or planning resource allocation in health economics studies. Generic instruments may, however, be unresponsive to changes in specific conditions (10). There are numerous generic quality of life (QOL) instruments in use, the most widely used being the Short Form Health Survey (11).

Disease-specific HRQoL questionnaires focus on problems associated with single disease states, allow comparisons of illnesses which share the leading symptoms, and can be helpful in selecting the most appropriate therapy for the patient and monitoring its efficiency. Moreover, they may better reflect the particular impact of a selected condition (10). On the other hand, these questionnaires are not suitable to compare the impacts of different conditions with different symptomatologies.

Measuring health related quality of life has become a widely accepted and popular method for assessing health status, it is a relevant and quantifiable outcome of care, therapy quality and effectiveness (12, 13). The standardized evaluation of HRQoL makes it possible to quantify the burden of illness. Although measuring health related quality of life can be useful in individual persons, it is particularly useful in assessing the impact of disease in groups of patients and it is often used as end point tool in clinical studies. Further, it is also helpful in pharmacoeconomic evaluations and appropriate allocation of health care resources. The subjective evaluation of the impact of a disease on the individual's quality of life has become possible with the development of HRQoL instruments and the demonstration of their statistical and psychometrical properties. HRQoL scales are used to complement available measurements by incorporating the patient's point of view. The primary advantages of using such scales in addition to clinical rating scales is the reflection of the patients own assessments of their health, which often differs considerably from clinicians or even carers views (4).

DOI:10.14753/SE.2016.1860

2.3 HRQoL questionnaire construction

QOL instruments usually study more domains of QOL. A domain refers to a specific area of behaviour or experience, such as work performance, social functioning, sleep, leisure activities, etc. The domains usually cover the three main dimensions of health-related QOL: physical, mental and social (10), which have their roots in the World Health Organization's definition of health (1).

The first important step in the development of a QOL instrument is the identification of relevant items. This is usually based on interviews with the members of the target population (i.e. patients suffering from a given condition). The items have to be meaningful both for the patients and for their treating clinicians. The next step is testing the draft version on a group of patients. An important aspect is that the questions have to be easily understood, so a detailed input from this patient group is required about the items and instructions of the questionnaire. After making the adjustments that were suggested, the corrected version of the instrument should be tested on a larger group in order to have data to apply quality criteria to item selection. Redundant or insignificant items must be removed after testing the corrected version, and the resulting final version is then to undergo the validation process.

2.4 Validation of a HRQoL questionnaire

Like in the case of other scales, the properties of HRQoL scales should be established in the population studied before the scale can be used for further investigations (4). The validation of a questionnaire requires testing its psychometric properties, most importantly its reliability and validity. Besides the adequate psychometric properties, the length and ease of use of a questionnaire are important aspects of its usability (14) and questionnaire length can have a threshold effect on response rate (15).

DOI:10.14753/SE.2016.1860

2.5 Reliability

Reliability is the degree to which a test consistently measures what it aims to measure. The methods of assessing reliability include the test–retest method, the use of two alternative questionnaires, and measuring the internal consistency.

Test–retest method (test–retest analysis) means the repeated application of the same questionnaire. Test–retest analysis usually requires a 4-week period between the two test sessions in order to avoid recall bias. During this period every circumstance that could possibly influence the patients' responses, including the therapy, should be unchanged. The correlation coefficient obtained during the analysis is called stability coefficient, which is considered adequate if it exceeds 0.8 (16). Although determining the stability coefficient seems to be straightforward, a number of problems arise in connection with this method. Basically, the two applications of the questionnaire are not fully independent, as the patients may remember their answers given at the first time. On the other hand, if the time interval between the two tests is too long, the measured parameter can no longer be considered as unchanged (17) .

The use of two alternative questionnaires measures the equivalence of two questionnaires, this requires prior statistical evaluation one of the questionnaires. The alternative questionnaires have to be developed independently. To assess the equivalence of the questionnaires a further analysis is required, which may be a limitation for using this method (18).

Measuring the internal consistency requires calculating either the split-half reliability, or Cronbach's alpha. The so-called "split-half" method analyses the correlation of the scores of half-questionnaires, after an accidental division of the instrument's items in two parts. A limitation of this method is, that a questionnaire can be divided in two parts in several ways, resulting in different internal consistency values for the same instrument. Another method is calculating the inter-item correlation, determined by the Cronbach's alpha coefficient. In this case, the correlation between each item and the whole instrument is calculated: Cronbach's alpha coefficient shows the average of the

correlation values (17). Internal consistency is generally considered adequate if Cronbach's alpha exceeds 0.7, and considered excellent with values in excess of 0.9. If an instrument is to be used in the clinical setting, rather than for the comparison of groups only, an alpha exceeding 0.9 is the minimum requirement (19).

2.6 Validity

Validity refers to the degree to which an instrument can accurately assess the specific concept that the research is attempting to measure (10). A high-quality QOL instrument is required to demonstrate different forms of validity, such as criterion validity, construct validity and content validity (20).

Criterion validity

Criterion validity is usually defined as the extent to which scores of an instrument are related to a criterion measure, i.e. a measure of the target construct that is widely accepted as a valid representative of that construct (21). The criterion measure can be a previously validated instrument measuring a similar construct, or a clinical variable that is conceptually related to the construct that the new instrument purports to measure. In headache research, the clinical characteristics of the individual's headaches (such as the frequency, severity or duration of the attacks) are frequently used as criterion measures, and criterion validity is assessed by measuring the correlation of the patient's headache characteristics with the questionnaire's items, dimensions and total score.

Construct validity

Construct validity refers to an agreement between a theoretical concept ('construct') and the instrument designed for measuring it. The necessity of examining the construct validity of the instruments stems from the fact that an instrument can only examine the observable aspects of the construct. Convergent and discriminative validity are two subcategories of construct validity.

Convergent validity

Convergent validity shows the correlation with another, already validated instrument. Correlation of the individual items, the dimensions and the total score can be analysed.

Discriminative (known groups) validity

Discriminative validity is measured by comparing the results of the instrument in two diagnostic groups.

Content validity

Content validity expresses the degree to which the underlying construct (QOL) is comprehensively sampled by the instrument's items. Unlike other forms of validity, content validity cannot be formally tested, but is assured by (and can be judged by) the methods followed at the instrument's development process (10).

Responsivity

Responsivity means that the instrument is able to follow and measure changes in the HRQoL (caused for example by a medical treatment).

2.7 Validating an instrument in different languages

A validated instrument can only be used in the original language in which the validation studies were done. Before using in another language, the instrument has to be validated in the new language. The first step in the translation process is that two independent "bilingual" translators translate the instrument into the target language. After that, the two translators' versions are compared and a consensus version is created. This version is translated back into the original language by a further bilingual translator who did not have access to the original version, then the original and back-translated versions are compared for differences in content. In case of translation errors necessary changes are made to the final version on the target language. This final version is than pilot-tested in a small group of patients, to assess the intelligibility of the instrument. If the result is

good, the whole validation process (same as in the original instrument) has to be repeated in the new instrument (22).

2.8 Burden of headache and measuring HRQoL in headache

2.8.1 Introduction

Headache is one of the most frequent complaints in medical practice, and it causes a significant burden both for the individual and for the society. The classification of the International Headache Society defines two groups of headache disorders: primary and secondary (symptomatic) headaches (23). Primary headaches are caused by the dysfunction of the structurally intact nervous system; they are characterized by stereotyped headache attacks which recover usually spontaneously after a time which is specific to the particular headache type. The diagnosis is based on a careful headache history (localization, intensity, characteristics, temporal relationships, accompanying symptoms, provoking and mitigating factors) and negative neurological examination. The most common primary headache is tension type headache (TTH), which global prevalence exceeds 40%, while the prevalence of migraine is approximately 12% (24). Cluster headache is one of the most intense human pain syndromes; its name denotes the characteristic grouping of headache attacks over a period that usually lasts some weeks and months (cluster episode) , which is then followed by a longer headache-free period. Its global prevalence is less than 1%, but its prevalence is over 5% in headache centers (25). About 2% of the population has medication overuse headache. This disorder develops from primary headaches, most often from migraine and it is hard to treat; its relative frequency is much higher in secondary and tertiary care (over 30% in headache centers) (26, 27).

Primary headaches constitute a public health problem, affecting 46% of the adult population globally, causing a significant amount of disability (24) and poor health related quality of life (28). According to data from 2010, the third costly neurological disease in the European Union is primary headache. Migraine and medicine overuse

headaches are the most costly headaches (28). The importance of the most common type of primary headaches, tension-type headache, is due to its high prevalence, while cluster headache deserves attention due to the very intensive pain (30).

A representative epidemiological survey which includes several headache types has not been made in Hungary up to now, but according to moderate estimates at least 3.5 million Hungarian people have regular headaches. Approximately 1 million Hungarians suffer from migraine, and the migraine-related economic loss due to lost work hours is about 15 billion Forints per year (based on a 80000 Forint minimum wage). The number of patients with episodic tension-type headache in Hungary is about 3 to 4 million, the number of patients with chronic tension type headache is about 2-300000, the number of patients who suffer from medication overuse headache is also approximately 2-300000 and there live about 10,000 patients in the country who have cluster headache. For comparison, there are 30 accredited headache centers in Hungary, which treat approximately 20-30000 patients per year (30, 31).

2.8.2 HRQoL instruments used in headache

In the last 20 years, a number of studies were conducted about the effect of headache disorders on HRQoL. Depending on the purpose of these studies, different instruments were employed. Initial studies focused on the effect of migraine and other primary headaches on overall HRQoL, using generic instruments. Later, headache-specific instruments were developed and used both alone or in combination with generic HRQoL instruments and/or measures of disability. There is a significant amount of scientific evidence about the negative effect of episodic and chronic migraine, cluster headache (32-34), TTH (35) and chronic daily headache (36) on generic and headache-specific QOL. The effects of acute and prophylactic (37, 38, 40-44) migraine treatment on QOL have also been documented.

2.8.2.1 Generic Instruments

20-Item Short Form Health Survey (SF-20)

This instrument was one of the two constructed to survey health status in a large representative study surveying health-related quality of life in the United States, i.e. the Medical Outcomes Study. As the name denotes, the questionnaire consists of 20 items. SF-20 measures physical, role and social functioning, mental health, pain and health perceptions; many of its questions are included in SF-36 but the latter also studies emotional role functioning and vitality and collects more information about physical functioning, physical role functioning and pain (39). In an early HRQoL study by Solomon et al, the SF-20 was used to measure quality of life in different headache types (migraine, cluster headache, tension-type headache and 'mixed headache'). Pain scores were significantly worse in cluster headache patients than in migraineurs. Social functioning was worse in cluster and tension-type headache patients than in migraine patients. Mental health scores were worse in tension-type headache than in migraineurs. Physical functioning was worse in tension-type headache than in cluster headache (45) .

36-Item Short Form Health Survey (SF-36)

The SF-36 was also constructed to survey health status in the Medical Outcomes Study. It was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone (46). The SF-36 is one of the most frequently used generic QOL instrument, it was validated in 50 countries. The SF-36 is a multipurpose, short-form generic health survey that yields an eight-scale profile of functional health and well-being by asking only 36 questions. The eight health concepts measured by SF-36 were selected from 40 included in the Medical Outcomes Study (MOS) that used a 149-item Functioning and Well-Being Profile (47). The 36 items of SF-36 are aggregated in eight scores, each representing 2–10 items. Table 2 lists the names and definitions of these scores. Four items [physical functioning (PF), role physical functioning (RP), bodily pain (BP) and general health (GH)] represent physical health and four [vitality (VT), social functioning (SF), role emotional functioning (RE), mental health (MH)] are

related to mental health; accordingly, physical and mental composite scores can also be calculated (48). Extensive statistical testing proved that all items in each score met strict predefined criteria of convergent validity (i.e. each item was substantially related to the total score of that scale) and of discriminant validity (i.e. each item correlated significantly higher with its scale than with other scales) (49). Widely accepted as it is, the SF-36 is far from examining all notable aspects of QOL. Among other aspects, the SF-36 does not collect data about sleep and its quality, cognitive features, leisure activities, sexual life, self-confidence, worries, and the quality of interpersonal communication. As it is a generic measure, SF-36 does not gather data about symptoms or problems that are specific to one condition. Nevertheless, SF-36 was found to be a reliable and useful means of studying the functioning and well-being of patients, as testified by the high number of publications. In fact, a PubMed search done on 3^{d} January 2015 retrieved 10241 publications mentioning "SF-36 quality life". The original version of the SF-36 (also validated in Hungarian) does not calculate any dimensions or a total score. It measures only the scores of the eight domains, thus producing quality of life profiles which are often represented in graphical form. The later version, the SF-36v2 allows the calculation of physical and mental dimensions. Data collected with the first version can be converted to the second version only after a study on a large sample in the general population. This was not made for the Hungarian version, therefore the second version is not validated in Hungarian language (50).

Studies with SF-36 have established that the impact of migraine on patients' health status and quality of life may be similar or grater than that of chronic illnesses, such as osteoarthritis (37), diabetes (37), low back pain (38), depression (38, 39) or congestive heart failure (38).

Table 2. Structure of the SF-36 questionnaire. SF-36 measures eight health concepts.

SF-36		
Full name	**Abbreviation**	**Definition**
Physical functioning	PF	Extent to which health influenced physical activity (eg. sports) in the past 4 weeks
Role physical	RP	Extent to which health influenced daily (workplace) activities in the past 4 weeks
Bodily pain	BP	Extent of bodily pain experienced in the past 4 weeks
General health	GH	Overall ratings of current health in general
Vitality	VT	Energy level and fatigue
Social functioning	SF	Extent to which health influenced normal social activities in the past 4 weeks
Role emotional	RE	Extent to which emotional problems influenced daily (workplace) activities in the past 4 weeks
Mental health	MH	General mood or affect in the past 4 weeks

2.8.2.2 Headache specific instruments

Since the 1990s several headache-specific QOL instruments have been developed.
These include the Migraine-specific Quality of Life Questionnaire (MSQ2.1) (51), the Migraine-Specific Quality of Life measure (MSQOL) (52), the 24-hour Migraine Quality of Life Questionnaire (24-hour MQoLQ) (53), the French Qualite´de Vie et Migraine (QVM) (54) questionnaire, and two questionnaires measuring related concepts: the Headache Impact Test (HIT-6) (55) measuring headache impact, and the Migraine Disability Assessment Score (MIDAS) (56) that measures migraine-related disability.

The headache-specific QOL instruments were mainly developed to follow the status of migraineurs. Although they were used several times in other types of headache, most of them had not been validated in these headache types. Based on PubMed and Scopus searches, only MSQ2.1 and HIT-6 have been psychometrically validated for chronic migraine and MSQOL for TTH, but none have been validated in other headache types. The above mentioned instruments are briefly described below (Table 3).

Table 3. Headache specific HRQoL instruments List of abbreviations: M: migraine, EM: episodic migraine, CM: chronic migraine, TTH: tension type headache, CTTH: chronic tension type headache, CH: cluster headache, MOH: medical overuse headache, CDH: chronic daily headache

Instrument	Validation	Used in other headache types without validation	Endpoint	
			Acut treatment	Prophylactic treatment
MSQOL	M, TTH	-	-	botulin toxin
MQoLQ **(24h MQoLQ)**	EM	CM, „chronic headache"	telcagepant rizatriptan (and so on)	botulin toxin
HIT-6	EM, CM	TTH, CTTH, CH, MOH, CDH, fibromyalgic headache	sumatriptan	topiramate, botulin toxin (and so on)
MSQ2.1	M, EM, CM	CH, Trigeminal neuralgia	sumatriptan, naproxen (and so on)	beta blockers botulin toxin (and so on)
QVM	M	TTH, CDH, other episodic headaches, CM	sumatriptan naratriptan	

Migraine-specific Quality of Life Questionnaire (MSQ2.1)

The MSQ2.1 is the current 14-item version of the former 16-item Migraine Specific Questionnaire. It measures three dimensions of headache impact: role-restrictive, role-preventive and emotional function. Seven questions ask about the extent of limitation in daily activities caused by migraine (work, leisure activities, concentration, energy, etc). This is the MSQ's so-called role-restrictive area. Four questions are about how often are these activities limited- this is the role-preventive domain. Three questions probe the emotional impact of migraine (feelings of frustration and helplessness).

MSQ2.1 was found to be reliable and valid in assessing QOL in migraine and has been formally validated for patients undergoing prophylactic migraine treatment (40, 51). It

has also been used in cluster headache (33). More recently, MSQ2.1 was validated for clinical use in episodic and chronic migraine (57) and was found to demonstrate significant differences between these, with chronic migraine patients having lower values in all dimensions.

Migraine-Specific Quality of Life measure (MSQOL)

The MSQOL is a 25-item instrument that was found to be a valid and reliable measure for cross-sectional comparisons that encompass a migraine patient's subjective well-being (52). Further testing of the instrument revealed three dimensions (avoidance, relationships and feelings) and provided evidence for the calculation of total score (58). Interestingly, another group described a different structure of the MSQOL with four dimensions (physical, psychical, social and life rhythms) in a study of patients with migraine or tension-type headache (TTH) (58). The MSQOL has been successfully used as an outcome measure in prophylactic drug trials for migraine (41).

24-hour Migraine Quality of Life Questionnaire (24-hour MQoLQ)

The MQoLQ was developed to measure the acute changes in QOL in migraineurs during a migraine attack. The questionnaire has 15 items grouped in five domains: work functioning, social functioning, energy, feelings/concerns, and migraine symptoms. In the validation study the domains showed good internal consistency and construct and discriminant validity, and responsiveness to acute migraine attacks. It detected significant changes of QOL during the acute migraine attack. Moderate to strong negative correlations were found between QOL and headache severity, limitations of activity, number of migraine symptoms, and headache duration (53). The MQoLQ was validated and primarily used among migraineurs, but also as an endpoint in drug trials (43), and it was found to be useful in the long-term follow-up of chronic headache patients (60). The MQoLQ showed significant improvement of QOL during an acute migraine attack in a randomized, triple-blind, placebo-controlled clinical trial with rizatriptan for acut migraine treatment (43).

QVM (Qualite´de Vie et Migraine)

QVM is a French migraine-specific QOL instrument, with four domains: psychological, somatic, social repercussion and disturbance generated by the treatment (54). In the validation study, the reliability assessed by test–retest reproducibility was good (r_0.70–0.80). In a later study on a nationwide sample, frequency, severity and treatment resistance of headaches, as well as headache-related disability, were significantly correlated with QVM's total score and subscales; correlation coefficients were not reported (61). QVM was used in many French studies, including acute drug trials in migraine (44) and also in patients with chronic daily headache (61) and TTH (62). The use of sumatriptan nasal spray 20 mg for the treatment of migraine attacks during a 12 week period was associated with a significant improvement in migraine patients' quality of life measured by the QVM (44).

Headache Impact Test (HIT-6)

In 2003 the 6-item Headache Impact Test (HIT-6) was introduced. HIT-6 is an instrument designed to measure headache impact, a concept that is strongly related to QOL (55). The HIT-6 covers six content categories represented in widely used surveys of headache impact, including social and role functioning, vitality, cognitive functioning and psychological distress. It was developed using an existing item pool of 54 items and from 35 items suggested by clinicians, using advanced methods of item response theory. In a large study, HIT-6 was found to be efficient, reliable and valid for the screening and monitoring of patients with headache (63). Subsequently, it has been extensively used in clinical practice, and applied in studies measuring headache impact and also in drug trials in migraineurs. The HIT-6 has been validated in episodic and chronic migraine (63). It has also been used in chronic daily headache (64) and TTH (65).

Migraine Disability Assessment Score (MIDAS)

MIDAS is a five item headache-specific tool designed to assess headache-related disability on three activity domains (paid work, household work, social/family activities). It was developed to improve doctor-patient communication about the functional consequences of migraine (56). MIDAS is able to detect difference in disability between migraine without aura and chronic migraine. Different values were

DOI:10.14753/SE.2016.1860

measured also, when migraine and tension type headache were compared. Gesztelyi et al found that the MIDAS scores were higher for patients with tension type headache in association with migraine, than those who did not have migraine (66).

3. Aims

The Headache Group of the Department of Neurology, Semmelweis University has systematically collected data for more than 10 years about the clinical features of headaches. A significant part of our research investigated the impact of primary headaches on HRQoL. In my PhD thesis, I present the results of these studies.

The aim of or studies was to assess the impact of common headache types on HRQoL. First, we investigated the health-related and condition-specific quality of life in episodic cluster headache. Second, we aimed to develop a new comprehensive headache-specific questionnaire, which assesses several aspects of QOL and which is useable in common headache types.

We then examined the psychometrical properties of our new questionnaire, called Comprehensive Headache-related QOL Questionnaire, in several headache types. We tested the new questionnaire in migraineurs, tension type headache patients and medical overuse headache patients. To assess the responsiveness of the Comprehensive Headache-related QOL Questionnaire for following QOL of headache patients during headache treatment we tested the questionnaire on a sample with medication overuse headache.

During these studies, our hypotheses were the following:

1. Cluster headache patients during the active phase have lower general and headache-specific QOL than migraineurs.
2. After the termination of the cluster episode the patients' general and headache-specific QOL improves significantly.
3. The new comprehensive headache-specific QOL instrument will show adequate reliability and validity in migraine and tension type headache.
4. The comprehensive headache-specific QOL instrument will also show adequate psychometric properties in medication overuse headache.
5. The prophylactic treatment of medication overuse headache will result in better clinical endpoints, which will be paralleled by better QOL as measured by the new QOL instrument.

DOI:10.14753/SE.2016.1860

4. Methods

4.1 Common elements of the studies

4.1.2 Patients

Outpatients, consecutively visiting the headache center of the Department of Neurology, Semmelweis University, who fulfilled the International Headache Society (IHS) criteria (23) for migraine with and without aura (episodic type; ICHD-II codes 1.1 and 1.2) or tension type headache (either episodic or chronic; ICHD-II codes 2.1–2.3) or episodic cluster headache (ICHD-II code 3.1.1) or medication overuse headache (ICHD-II code 8.2.) took part in the studies. During the psychometric testing of the draft version of the Comprehensive Headache-related QOL Questionnaire data of 25 outpatients visiting the headache center of the National Institute of Neuroscience with the diagnosis of episodic migraine were also included.

In all studies, we excluded patients suffering from the rare adult migraine subtypes (hemiplegic migraine, basilar-type migraine, retinal migraine and complications of migraine (ICHD-II codes 1.2.4–1.2.6, 1.3–1.5). According to the IHS criteria, patients meeting one of the sets of criteria for probable tension type headache (ICHD-II. code 2.4) may also meet the criteria for one of the subforms of probable migraine (ICHD-II. code 1.6), therefore we also excluded patients with the diagnosis of probable migraine and probable tension type headache in order to minimize the chance of misdiagnosing the patients. Patients with significant somatic or mental diseases were excluded (e.g. concomitant chronic pain syndromes, untreated hypertension, and untreated or severe kidney or liver disease). Other concomitant treated disorders were not excluding criteria, but their possible effect on QOL was not taken into account in the statistical analysis. Mild to moderate depression was not an exclusion criterion. The more detailed description of the patients taking part in the studies can be found in the respective chapters. The studies were approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University.

4.1.2 Data recording

Generic QOL was measured with the validated Hungarian version of the SF-36 questionnaire (67) in all studies. Headache-specific quality of life was measured with MSQ2.1 in the first study, which investigated the health-related and condition-specific quality of life in episodic cluster headache. In the other studies, after our working group developed the new Comprehensive Headache-related QOL Questionnaire, headache-specific quality of life was measured by this new instrument.

The patients completed the questionnaires in the Headache Unit, after their outpatient visit; the questionnaires were administered by the headache specialist seeing outpatients on the given day. The questionnaires were filled in on the spot and given back to the staff. Missing data were not complemented.

The patient's headache characteristics and other clinical data were recorded during their outpatient visit. Headache severity was assessed by the patient (visual analogue scale (VAS); 0–100mm) and also by the specialist during the clinical interview (IHS rating scale, 0=pain free, 1=mild, 2=moderate, 3=severe). Headache diagnoses were made by the same headache specialists during the outpatient visit, using the IHS criteria. Depression was not formally tested during the visit. The HRQoL data were not used in the diagnostic and therapeutic evaluation of the patients during their medical visits.

4.1.3 Methods

Statistics were calculated using Statistica software, versions 8.0 to 11.0. The level of significance was set to $p<0.05$. As the data distribution of most HRQoL domains was not Gaussian, we used nonparametric tests in all studies. Wilcoxon signed rank tests were used to check differences within the groups. Spearman's non-parametric tests were used to check for correlation between the QOL instruments and between HRQoL scores and patient characteristics. Differences between groups were assessed with either Kruskal–Wallis ANOVA with Dunn's multiple comparisons tests or Mann–Whitney tests.

DOI:10.14753/SE.2016.1860

4.2 Examination of health-related and condition-specific quality of life in episodic cluster headache

4.2.1 Background and objective

Cluster headache (CH) is characterized by recurrent unilateral attacks of severe headache, accompanied by local signs and symptoms of cranial autonomic dysfunction (23). CH attacks may occur several times throughout the day over periods of several weeks. The stabbing, often excruciating pain can disrupt the daytime activity both at the workplace and in the family setting. Leisure and social activities may also be affected. The night-time occurrence of attacks can lead to sleep deprivation, which further degrades performance (68). Personal accounts of patients underline these considerations (69). While HRQoL in migraine and chronic headaches was widely studied, the effects of CH received much less attention. In our first study about HRQoL in headache we therefore set out to assess overall and disease-specific HRQoL in episodic CH patients, using a generic and a headache-specific instrument.

4.2.2 Methods

Patients

Thirty-five patients with episodic cluster headache were involved in the study. The general inclusion and exclusion criteria were the same as described in chapter 4.1.2. Moreover, CH patients also having other significant headaches (migraine, chronic or frequent episodic tension-type headache, chronic daily headache) were not included in this study. The results were compared with those of a group of migraineurs (n=53) and a control group from the general population (n=62) who did not have migraine, cluster or daily headaches. Both comparator groups were matched for sex and age. A detailed description of the groups is to be found in Results (chapter 5.1).

Methods

All patients completed the Hungarian versions of the generic HRQoL instrument SF-36 and MSQ version 2.1.The patients filled in the questionnaires during their first visit due to the new CH period. At least 3 months after the termination of the CH period telephone interviews were used to clarify the health status of the patients and then follow-up questionnaires were sent to them by mail. In order to make data comparable we changed the word “migraine” to “headache attack” in MSQ2.1 in all three study groups. As in non-medical Hungarian usage ’migraine’ is used interchangeably with’ (severe) headache attack’, we felt that this change would not compromise the study. Moreover, head pain is probably the most important source of migraineurs’ limitations, as suggested by a study from Santanello et al, where rapid, complete, and sustained pain relief were shown to be the main determinants of HRQoL (70). The high frequency of ’migrainous’ headache accompaniments (nausea, vomiting, photo- or phonophobia) found in our CH sample (see Table 7), similar to those observed by Bahra et al. (71), further decreased the possibility that the different accompanying symptoms of CH and migraine would cause large scale-differences in HRQoL. Although we were not aware of MSQ2.1 being used in conditions other than migraine, we thought that its application in the CH sample was justified and MSQ2.1 scores of CH patients and migraineurs could be compared.

4.3 Development and validation of the Comprehensive Headache-specific Quality of life Questionnaire

4.3.1 Introduction

There are some observations that raise the possibility that the previously used QOL instruments do not fully capture headache patients’ perceptions. As already mentioned, despite the obvious differences in the clinical picture and the patients’ complaints, there were only a few differences between the generic QOL profiles of migraine, cluster headache and TTH (45). In our first study, the SF-36 profiles of migraine and cluster headache were also surprisingly very similar. Although CH patients had lower scores than migraineurs on most scales, the difference was significant only on SF-36 scores

measuring bodily pain and social functioning. The headache-specific MSQ2.1 also failed to show any difference between the QOL profiles of cluster headache patients and migraineurs in this study (33).

Patients may also feel that the instruments do not capture some important areas of their QOL, as was the case of our patients (suffering from cluster headache or migraine) during the above-mentioned trial (33). Moreover, a clinically effective therapy is not necessarily reflected by an improvement of the QOL scores of migraineurs (85).

Besides these observations there is a methodological caveat when using headache-specific QOL instruments. As discussed in chapter 2, the headache specific instruments were mainly developed for, and validated in migraineurs.

Taken together, these limitations suggested that an instrument probing several important facets of life and validated in different headache types might provide patients and healthcare providers with more precise information about QOL in headache. In order to test this hypothesis, we have decided to develop a comprehensive headache-specific questionnaire in Hungarian language, assessing several aspects of QOL.

4.3.2 Development process of the new headache-specific questionnaire

We followed the recommendations outlined in (10) and (20) during the development phase of CHQQ. The development of the questionnaire consisted of the following steps (Table 4):

1. relevant item identification
2. development of a draft version
3. psychometric testing of a draft version and development of the final version

Table 4. Development process of the new headache-specific questionnaire

Step		**Source / Population**
Relevant item identification	Creating a question pool	Literature Headache experts (5)
	Open interviews	Headache patients (25)
Psychometric testing of the 25-item draft version		Migraineurs (117)
Validation of the 23-item final version		Migraineurs (168) TTH (34) MOH (68)

4.3.2.1 Relevant item identification

First one of our team conducted open interviews with 25 persons suffering from the most important primary headache types (10 migraine, 10 TTH and 5 cluster headache patients). The questions for these interviews were based on the experience of five clinicians and literature reviews of QOL in headaches and other pain conditions. A question was considered a potential item if at least two clinicians and two patients from each diagnostic group felt the respective issue was important. Twelve of the 37 original questions were found redundant or insignificant and therefore removed, resulting in a 25-item draft version. Consequentially, the items included in the final version were the ones that were meaningful both for the patients and the clinicians involved (86).

4.3.2.2 Development of a draft version

In a second step, 11 migraineurs from a larger group studied for the effect of migraine (87) were asked to complete the draft version and were then interviewed about it. These

interviews were used to determine whether each individual understood the items, felt them meaningful and whether they felt the answer categories were sufficient. Minor changes of content and format were applied accordingly.

4.3.2.3 Psychometric testing of a draft version, and the development of the final version

The 25-item questionnaire was tested in a group of 117 migraineurs and quality criteria for item selection applied (29). There was no ceiling effect in the sample. One item asking about the influence of headache on parental responsibilities ('How much do your headaches interfere with your role as a parent?') had by far the biggest proportion of missing answers (31% of the sample; mostly patients with grown-up children or no children) and therefore was not included in the final version. An item about prophylactic medication use ('How often have you used prophylactic treatment for your headaches?') had a very low (0.214) item-total correlation. Analysis of the clinical data revealed that beside those who regularly took a prophylactic medicine, a significant part of the study population considered the early administration of acute medications as 'prophylactic' treatment. This item was also problematic because taking a migraine prophylactic is the joint decision of the patient and the physician and therefore it is less likely to reflect the patient's QOL. Therefore this item was also omitted from the final version of the questionnaire.

The reliability and validity assessments confirmed that the resulting 23-item questionnaire was adequate for further testing. Reliability was assessed by internal consistency, measured by Cronbach's α of all items. The questionnaire demonstrated good reliability, with Cronbach's alpha being 0.893. Convergent validity was examined by calculating the correlation of the items with subscales of the SF-36 measure. Convergent validity was adequate; most "physical" items of the new questionnaire showed significant correlations with the bodily pain and role physical SF-36 subscales and most "psychical" and "social" items were correlated with mental health and social functioning SF-36 subscales. The correlation of the patients' migraine characteristics

with the questionnaire's items was used to assess criterion validity. Criterion validity was adequate, with headache severity being correlated with most of the items (29).

Exploratory factor analysis with varimax rotation found that a single factor accounted for 47% of the total variance, while a second factor was responsible for 3.7%, and further factors accounted for even smaller amounts of variance: this was interpreted as the basis of calculating a total score (88). In the preliminary study we grouped the items according to the classical dimension structure used in QOL research (physical, mental and social), relying on the content of the items. This is considered a valid approach. Clinically useful scales are sometimes organized into subscales according to rational (rather than mathematical) principles and the two do not necessarily coincide. An example is the Headache Disability Inventory (89), where the authors rationally organized items into emotional and functional subscales; in a later study by Holroyd et al. the factor analysis of HDI items revealed that all items loaded on a single factor (90). Different studies may find a different underlying structure within the same instrument, as exemplified by the MSQOL, which was found to have three dimensions (avoidance, relationships and feelings) in an American study (58), and four dimensions (affective, social, energetic and life rhythms) in a Hungarian one (59).

4.3.2.4 Description of the Comprehensive Headache-related QOL Questionnaire

The 23-item QOL questionnaire, hereafter referred to as the Comprehensive Headache-related QOL Questionnaire (CHQQ), examines the impact of headache on QOL in detail. The questions cover the 4 weeks before the data recording. All questions have five possible answers (5-point Likert scale), ranging from the absolute absence of restriction to maximal restriction. After scoring, the values are transformed to a 0–100 point scale, the absence of restriction being equal to 100 points and the full restriction to 0 points. Total score and the three dimensions (physical, mental and social) are calculated; they are the mean values of the relevant transformed item scores, i.e. the item scores are not weighted. It is also possible to use the questionnaire as a profile, in this case the scores of each item should be represented in graphical form. This can be useful among others to assess the effectiveness of a special therapy (29, 113).

DOI:10.14753/SE.2016.1860

4.4 Validation of the Comprehensive Headache-specific Quality of life Questionnaire

4.4.1 Validation in migraineurs and tension type headache patients

4.4.1.1 Objective

The aim of the study was to assess the psychometric properties of the headache-specific questionnaire on a large group of headache patients suffering from migraine and TTH. The main hypotheses were the following:

1. The questionnaire's internal consistency will be adequate (Cronbach's alpha >0.7) in the total sample and both headache types.
2. The individuals' QOL, as indicated by the items, domains and total score, will be negatively correlated with clinical characteristics of their headache.
3. The new questionnaire's items, domains and total score will be positively correlated with the relevant domains of the SF-36 measure.
4. Patients with TTH will have a better QOL (higher scores on the instrument) than patients suffering from migraine.

4.4.1.2 Methods

Patients

A total of 202 patients suffering from migraine (n=168) or tension-type headache (TTH) (n=34) were involved in the study. Consecutive outpatients visiting the headache center of the Department of Neurology, Semmelweis University, in 2008–2010, who fulfilled the International Headache Society (IHS) criteria (23) for migraine with and without aura (episodic type; ICHD-II codes 1.1 and 1.2) or TTH (either episodic or chronic; ICHD-II codes 2.1–2.3) took part in the study. We excluded patients suffering from the rare adult migraine subtypes and those whose analgesic consumption reached the criteria of analgesic abuse (91). Patients with the diagnosis of probable migraine and probable TTH were also excluded to minimize the chance of misdiagnosing the patients.

All patients had headache as the main complaint at the time of the study. For general inclusion and exclusion criteria see chapter 4.1.2.

Data recording

The patients all completed the validated Hungarian version of the SF-36 and the CHQQ in the Headache Unit, after their outpatient visit; the questionnaires were administered by the headache specialist seeing outpatients on the given day. The questionnaires were filled in on the spot and given back to the staff. Missing data were not complemented. The patient's headache characteristics and other clinical data were recorded on the same day, during their clinical interview. Headache severity was assessed by the patient (visual analogue scale (VAS); 0–100mm) and also by the specialist during the clinical interview (IHS rating scale, 0=pain free, 1=mild, 2=moderate, 3=severe). Headache diagnoses were made by the same headache specialists during the outpatient visit, using the IHS criteria. Depression was not formally tested during the visit. As this was a validation study, the data were not used in the evaluation of the patient's functional status, disease severity or therapeutic needs.

Methods

To assess the reliability of our questionnaire, we calculated the Cronbach's alpha for the whole instrument and its dimensions. We used several methods to assess the validity of the instrument. First we examined the correlation of the patients' headache characteristics with the questionnaire's items, dimensions and total score (criterion validity). We then examined the correlation of the individual items, the three dimensions and the total score with the domains of the SF-36 measure, a means of assessing convergent validity. In these analyses the degree of correlation was measured by calculating Spearman's rank correlation coefficients. We also assessed discriminative (known groups) validity, by comparing the results of the instrument in the two diagnostic groups, M and TTH, using Mann–Whitney tests. In order to assess the structure of the instrument we performed an analysis of item-dimension correlations using Spearman's rank correlation coefficients. Statistics were calculated using Statistica software, version 8.0. The level of significance was set to $p<0.05$.

DOI:10.14753/SE.2016.1860

4.4.2 Validation in medication overuse headache

4.4.2.1 Introduction

Medication overuse headache (MOH) affects 1 to 2% of the population (26), and may be found in as many as 30% of patients seen at tertiary headache centers (27). It hallmarks are frequent headache, and the presence of medication overuse, the latter being instrumental in the development or worsening of the headache (103). Medication overuse headache is associated with a poor health-related quality of life. As reviewed by Lanter-Minet et al., the generic QOL instrument SF-36 consistently showed lower scores for patients with chronic daily headache (CDH) and medication overuse compared to patients with CDH but without medication overuse or patients with episodic headache in both patients recruited from headache specialty centers and also in samples from the general population (103). On the other hand, it is worth mentioning that the previously used generic and headache-specific QOL instruments have not been formally validated in MOH, and therefore these data may not reflect the burden of MOH. This chapter reports our as yet unpublished data about the validation of CHQQ in medication overuse headache.

4.4.2.2 Objective

To assess the psychometric properties of CHQQ in patients diagnosed with MOH.

4.4.2.3 Methods

Patients

We involved 68 MOH patients (53 women and 15 men; mean age 42.1 ± 14.2 years), followed up at the Department of Neurology, Semmelweis University. The majority of the patients had a clinical headache diagnosis of chronic migraine (51 patients, ie. 75%); 15 had chronic tension type headache and two had chronic daily headache not otherwise

specified. Forty-four patients (65%) were overusing simple NSAIDs, 11 combined NSAIDs, while 10 had triptan-, and 3 ergot-overuse at the time of the study. The detailed inclusion and exclusion criteria were the same as described in chapter 4.1.2.

Data recording

As in the previous studies, the patients completed the CHQQ instrument and the validated Hungarian version of the SF-36 generic QOL instrument during their outpatient visits. The questionnaires were administered by the headache specialist seeing outpatients on the given day. The questionnaires were filled in on the spot and given back to the staff. Missing data were not complemented.

The patients' headache characteristics and other clinical data were recorded during their clinical interview at the same outpatient visit. Headache severity was assessed by the patient (visual analogue scale (VAS); 0–100mm) and also by the specialist during the clinical interview (IHS rating scale, 0=pain free, 1=mild, 2=moderate, 3=severe). Headache diagnoses were made by the same headache specialist during the outpatient visit, using the IHS criteria. Depression was not formally tested during the visit. The QOL data were not used in the evaluation of the patient's functional status, disease severity or therapeutic needs.

Statistical methods

The validation process was similar to the validation of the CHQQ in migraine and tension type headache (see chapter 4.4.1.2). Briefly, we assessed the reliability of the questionnaire by calculating the Cronbach's alpha for the whole instrument and its dimensions. The validity of the instrument was examined by assessing its criterion validity (the correlation of the patients' headache characteristics with the questionnaire's items, dimensions and total score), convergent validity (the correlation of the items, dimensions and total score with the domains of the SF-36 questionnaire), and discriminative validity (comparing the results of the instrument in the two diagnostic groups, MOH and chronic tension type headache). Correlations between the SF-36 and the clinical data were also calculated for comparisons between the two instruments' criterion validity. Statistics were calculated using Statistica software, version 11.0. The level of significance was set to $p<0.05$. As the data distribution of

most HRQoL domains was not Gaussian, we used nonparametric tests in all studies. When assessing criterion and convergent validity, the degree of correlation was measured by calculating Spearman's rank correlation coefficients. We also assessed discriminative (known groups) validity, by comparing the results of the instrument in the two diagnostic groups, MOH and chronic tension type headache, using Mann–Whitney tests. Statistics were calculated using Statistica software, version 11.0. The level of significance was set to $p<0.05$.

4.4.3 Examination of responsivity in medication overuse headache

4.4.3.1 Introduction

Medication overuse headache is notoriously difficult to treat. There is a growing consensus that the basic requirement of its treatment is detoxification (withdrawal therapy) supplemented by adequate preventive measures (106). Depending on the pharmacological type of overused medication and also on the organization of the healthcare facility, both in-, and outpatient treatment programs have been advocated. The current evidence suggests that both settings may be adequate. There is moderate evidence that topiramate is an effective prophylactic option for MOH, while corticosteroids and amitryptiline are possibly effective (106). Recently, a subgroup analysis of medication overusers among chronic migraine patients participating in the PREEMPT study demonstrated that onabotulinum toxin was also effective (104), a finding that had also been substantiated in an independent Italian study (107). It was demonstrated that the SF-36 and the headache-related disability tool, MIDAS (Migraine Disability Assessment Score) were sensitive to the effect of treatment (108). Two studies found that low SF-36 scores may be predictors of treatment outcome. In an Austrian study of an inpatient withdrawal program, poor mental SF-36 composite scores at baseline correlated with frequent headaches at follow-up (109). A Norvegian study following 80 MOH patients for one year found that lower scores on the Bodily Pain and General Health Perception domains of the SF-36 were associated with poor outcome (110). It was suggested that the SF-36 may be used as a predictor of outcome of

withdrawal therapy in MOH. Headache-specific QOL instruments were employed less frequently in MOH, mostly in longitudinal studies about the effect of treatment (104, 111, 112). In a placebo-controlled randomized study about topiramate as a preventive agent of chronic migraine, 78% of the patients met the criteria of MOH. In this study, various PROs including the MSQ2.1, HIT-6 and MIDAS were used. From an intent-to-treat population of 59, only 38 patients finished the study. Topiramate significantly reduced the mean number of monthly migraine days. MIDAS showed improvement in the verum group, but there were no significant differences between the two groups' HIT-6 and MSQ2.1 scores (111). In a small randomized, double-blind, active-controlled, crossover trial, nabilone proved superior to ibuprofen in reducing the severity and frequency of headache, the quantity of analgesic intake and in increasing the quality of life as measured by the generic SF-36 QOL questionnaire and also decreasing headache impact measured by the HIT-6. The changes in SF-36 and HIT-6 scores were small but statistically significant (112). Finally, in a subgroup analysis of the PREEMPT trial database, the effect of onabotulinumtoxin A on chronic migraine patients with acute headache medication overuse was studied. The endpoints included changes in HIT-6 and MSQ2.1. Both instruments showed significant improvement in the active group as compared to the placebo group (104).

4.4.3.2 Objective

The aim of this pilot study was to assess the feasibility of using CHQQ as an outcome indicator in a group of patients suffering from medication overuse headache. Our main hypotheses were the following:

1. The questionnaire will show low QOL values before treatment of MOH. These values will be lower than those of episodic migraine patients studied in the same headache center.
2. The patients' headache characteristics will improve after the treatment.
3. The patients' quality of life (individual items as well as domains and total score) will also improve after the treatment.

4. The improvement of quality of life will show mild to moderate correlations with the improvement of headache characteristics.

4.4.3.3 Methods

Patients

Consecutive patients with headaches fulfilling the diagnostic criteria of MOH (91) were involved. Mild to moderate depression was not an exclusion criterion, but due to the small number of patients was not taken into consideration as a grouping variable. The detailed inclusion and exclusion criteria were the same as in chapter 4.1.2. On the whole, our sample consisted of 15 MOH patients. The quality of life of the MOH patients at baseline was compared to our previously obtained QOL values of 177 patients suffering from episodic migraine (EM). The demographic and selected clinical data of the MOH patients and the control group of episodic migraineurs are summarized in Table 5.

Table 5. Demographic and clinical data of the study participants. Data are presented as mean ± SD if not otherwise indicated. VAS: Visual analogue scale. MOH: medication overuse headache

	MOH patients	**Episodic migraineurs**
Mean age (years)	39,7 ± 12,5	34,9± 11,2
Gender	Female: 13 Male: 2	Female: 156 Male: 21
Primary headache type	Migraine without aura: 13 Tension type headache: 2	Migraine without aura: 139 Migrane with aura: 38
Mean number of headache days per month	24,3 ± 5,7	4,4 ± 2,2
Mean pain intensity (VAS)	67 ± 13,6	70,7 ± 18,0
Number of patients overusing different types of analgesics	Simple NSAID: 6 Combined NSAID: 2 Triptan: 7	not applicable
Mean analgesic dose per month	Simple NSAID: 59,6 ± 44,6 Combined NSAID: 28,5 ± 9,2 Triptan: 19,3 ± 5,0	not recorded

DOI:10.14753/SE.2016.1860

Treatment / Intervention

The patients were enrolled to a complex treatment program consisting of acute medication withdrawal, preventive pharmacological treatment, structured advice and lifestyle intervention. All patients were offered the possibility of an in-patient first phase: seven of them opted for it, the others were excusively treated as outpatients. For those who preferred it, the inpatient period lasted 7 to 10 days. The demographic and clinical data of the inpatient and outpatient groups were not significantly different (Table 6).

Table 6. The clinical characteristics and baseline QOL values of the in-, and outpatient groups. There were no significant differences in this sample (Mann-Whitney tests or Fisher's exact tests). VAS: Visual analogue scale.

	Inpatients	**Outpatients**	**p value**
Mean age (years)	43,6 ± 12,4	36,4± 12,3	0,3244
Gender (F/M)	Female: 5 Male: 2	Female: 8 Male: 0	0,2000
Primary headache type	Migraine without aura: 6 Tension type headache: 1	Migraine without aura: 7 Tension type headache: 1	1,000
Mean number of headache days per month	26,4 ± 5,4	22,4 ± 5,6	0,2147
Mean number of attacks per month	25,9 ± 5,1	21,8 ± 6,3	0,2408
Mean pain intensity (VAS)	69,1 ± 13,2	63,6 ± 14,1	0,3541
Number of patients overusing different types of analgesics	Simple NSAID: 3 Combined NSAID: 1 Triptan: 3	Simple NSAID: 3 Combined NSAID: 1 Triptan: 4	1,000
Mean analgesic dose per month	50 ± 40,2	20,2 ± 5,7	0,0822

Prophylactic medications were chosen according to the primary headache type, the patients' previous experience with headache prophylactics, and individual contraindications or allergies. The most commonly used prophylactics were valproic

acid and tricyclic antidepressants (amitriptyline or clomipramin); onabotulinum toxin was administered to three. Controlled quantities of naproxen and/or paracetamol were used as acute medications.

Structured advice was given about the patients' headache, the role of medication overuse in the chronification of headaches in general, the importance of the withdrawal, the possibilities of acute and prophylactic medication use during the study period, and the possible difficulties of the withdrawal phase. Lifestyle intervention was aimed at helping the patients establish a more balanced daily and weekly rhythm (of work, meals, sleep and leisure activities) and identifying and reinforcing individual strategies of coping.

Data recording

Clinical data were collected using a detailed headache diary which is routinely used in our Headache Service. Patients were asked to record all their headaches, regardless of the severity or length of the attacks. Information was requested about the duration, quality and severity of the head pain, about the accompanying symptoms, and also about the type and dose of acute pain medications. As the patients had already been followed at our outpatient service before the actual study, the patients' diaries also contained the relevant clinical data from the month before the actual treatment. The average headache severity was assessed by the patient (VAS; Visual Analogue Scale 0-100 mm continuous version) on a sheet accompanying the CHQQ, and also by the headache specialist during the clinical interview (International Headache Society Rating scale, 0=pain free, 1=mild, 2=moderate, 3=severe). The CHQQ was completed at the beginning of the treatment period and at the end of the second month of treatment.

Methods

The statistical analyses were performed using Graphpad Prism 4.0. As some of the data were not following a normal distribution, we used nonparametric tests throughout the study (Mann-Whitney tests for comparing the MOH and EM group, Wilcoxon tests for the comparison of baseline and post-treatment clinical and QOL values, and Spearman's tests to look for correlations between the change in clinical characteristics and QOL).

DOI:10.14753/SE.2016.1860

When analyzing the correlations between the improvement of clinical variables and QOL, the improvement was expressed as the percentage of the baseline value, ie. improvement = (baseline value – post-treatment value) x100.

DOI:10.14753/SE.2016.1860

5. Results

5.1. Examination of health-related and condition-specific quality of life in episodic cluster headache

Patient characteristics

A total of 35 CH patients were studied. Twenty-four (69%) did not have any relevant medical condition other than CH. Eleven patients (31%) also had other health problems, including five cases with medically treated hypertension, three with mild depression, one with low back pain and one with essential tremor. One patient had Type 2 diabetes mellitus, while one of the hypertensive patients had a mild degree of leukoaraiosis confirmed by magnetic resonance imaging. The majority of CH patients did not receive prophylactic treatment at the time of the study. In five, prophylactic verapamil treatment had already been started, but they were still experiencing daily attacks. Only 11 (31/%) of the 35 used subcutaneous sumatriptan as abortive agent; other options were oxygen, indomethacin or soluble non-steroidal anti-inflammatory drugs. The infrequent use of sumatriptan was due to financial issues (the local health system covered only 50% of its price at the time of the study). The demographic data of the patient groups is presented in Table 7. The two comparator groups were matched to the CH group for sex and age. There was no significant difference in disease duration and percentage of sumatriptan users in the CH and migraine groups. The percentage of depressed patients was significantly greater and that of hypertensive patients somewhat smaller in migraineurs; the concomitant disease profile in the headache-free control group was similar to the CH group.

Table 7. Demographic data of CH patients. Data are expressed as mean ± SD if not otherwise indicated

Age	44.73 ± 14.71 years, range 21-76
Gender ratio (male : female)	25 : 10
Disease duration	12.72 ± 9.26 years, range 1-32
Duration of present episode	5.48 ± 3.46 weeks, range 2-17
Number of attacks per day	1.74 ± 0.81, range 0.5-4
Night-time attacks (yes : no)	28 : 7
Nausea and/or vomiting (yes : no)	18 : 17
Photophobia and/or phonophobia (yes : no)	21 : 14
Smokers vs non-smokers	31 : 4
Acute treatment (sumatriptan : oxygene : other)	11 : 7 : 17
Prophylactic treatment (yes : no)	5 : 30

Generic HRQoL

During the cluster period, CH patients had lower scores in all SF-36 domains than non-migrainous controls. The difference was statistically significant in six domains (role physical, bodily pain, general health, vitality, social functioning and mental health). CH patients also scored significantly lower than migraineurs in the bodily pain and social functioning domains. Table 8 and Figure 1 show SF-36 scores of the respective groups; Table 9 summarizes the *P* values. After the termination of the cluster period, CH patients' scores were higher in 7 of the 8 SF-36 domains (the exception being the physical functioning domain): this improvement was significant in the role physical, bodily pain and social functioning domains ($P < 0.002$). Vitality and mental health scores also tended to improve ($P = 0.063$ and $P = 0.074$, respectively). There was no statistical difference between CH patients outside the bout and headache-free controls (Figure 1). There was no correlation between SF-36 scores and the characteristics (age, disease duration, length of the present CH period and number of attacks) of CH patients, with the exception of a correlation between VT scores and age ($r = 0.402$, $P = 0.0275$) and MH with disease duration ($r = 0.621$, $P = 0.0103$). There was no significant

difference between the scores of sumatriptan users and non-users. Migraineurs scored lower than controls in all SF-36 domains; the differences were statistically significant for physical functioning, role physical, bodily pain, general health and social functioning scores.

Table 8. Generic HRQoL: SF-36 scores of CH patients, migraineurs and controls. PF: physical functioning, RP: role physical functioning, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional functioning, MH: mental health

SF-36 domains	Cluster headache				Migraine		Controls	
	during the period		after the period					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PF	78.23	23.29	76.62	22.25	71.5	30.04	94.0	6.32
RP	30.15	37.83	59.56	43.09	52.68	35.58	86.67	26.50
BP	17.17	16.85	69.85	22.91	43.54	25.92	88.53	12.57
GH	53.75	21.60	51.85	20.36	54.82	18.42	72.27	18.06
VT	44.37	25.93	53.97	22.01	51.96	19.69	62.33	20.86
SF	47.14	25.02	69.12	22.45	60.70	25.62	83.33	16.14
RE	39.57	43.52	51.93	46.54	60.65	31.47	57.72	38.73
MH	54.25	20.44	63.06	19.07	64.12	20.06	73.33	17.35

Table 9. Generic HRQoL: p values (Kruskal-Wallis ANOVA and Dunn's Multiple Comparisons Tests); ns: non significant ($p>0.05$). See Table 8 for abbreviations

SF-36 domains	Kruskal-Wallis ANOVA	CH period vs migraine	CH period vs controls	migraine vs controls
PF	0.0329	ns	ns	<0.05
RP	<0.0001	ns	<0.001	<0.05
BP	<0.0001	<0.001	<0.001	<0.01
GH	0.0171	ns	<0.05	<0.05
VT	0.0454	ns	<0.05	ns
SF	<0.0001	<0.05	<0.001	<0.05
RE	ns	ns	ns	ns
MH	0.0095	ns	<0.01	ns

DOI:10.14753/SE.2016.1860

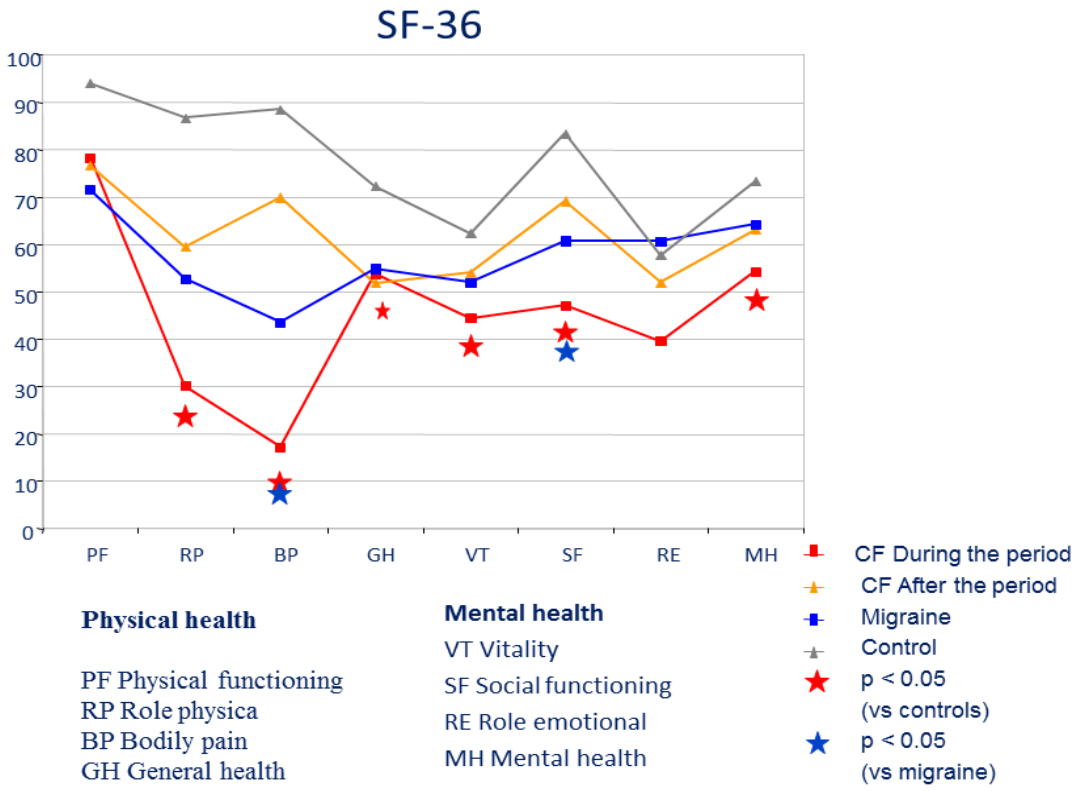


Figure 1. Generic HRQoL: graphical representation of the SF-36 scores in the respective groups

Headache-specific HRQoL

Patients during the CH period scored the lowest on all three MSQ 2.1 subscores. There was a significant difference between CH patients and controls as well as between migraineurs and controls ($P < 0.001$ on all subscores for both patient groups vs. controls). The difference between CH patients' scores and those of migraineurs was not significant. After the bout, CH patients' subscores improved dramatically and were similar to the headache-free control values (Figure 2). There was no correlation between MSQ2.1 scores and the characteristics (age, disease duration, length of the CH period, number of attacks, type of abortive drug) of CH patients. MSQ2.1 scores and *P*-values are presented in Table 10 and depicted in Figure 2.

DOI:10.14753/SE.2016.1860

Table 10. Headache-specific HRQoL in CH patients, migraineurs and controls: MSQ2.1 scores RR: Role-restrictive, RP: role-preventive, EF: emotional function.

MSQ 2.1 domains	Cluster headache				Migraine		Controls	
	during the period		after the period					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RR	39.64	20.39	92.16	10.74	46.92	15.31	97.26	5.18
RP	52.19	26.33	95.97	10.12	67.37	17.27	99.2	2.77
EF	50.96	25.44	94.84	13.52	75.43	14.58	99.19	2.21

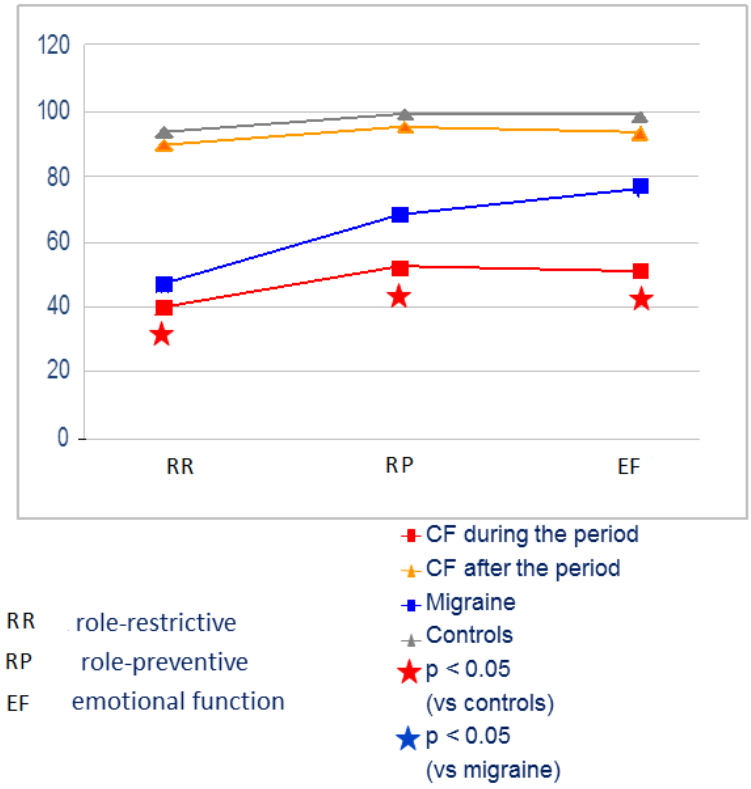


Figure 2. Headache-specific HRQoL: graphical representation of MSQ2.1 scores in the respective groups

Correlation between the SF-36 and MSQ2.1 questionnaires

As expected, the bodily pain subscore of SF-36 correlated with all MSQ2.1 subscores: more severe pain was associated with more pronounced limitations in role and emotional functioning. Limitations in the role physical domain also correlated with loss of functioning in all MSQ2.1 subscores. Of the four SF-36 subscores reflecting physical health, role physical and bodily pain scores correlated with both the role [role function-restrictive (RR), role function-preventive (RP)] and emotional (EF) components of MSQ2.1, while SF-36's physical functioning score correlated with emotional functioning on MSQ2.1. The fourth, i.e. the general health score, showed no correlation. Of the four SF-36 subscores related to mental health (vitality, social functioning, role emotional and mental health) three (VT, SF and MH) positively correlated with emotional functioning, and two (VT and RE) with the role-function preventing aspect of CH. Surprisingly, there was no correlation between physical functioning and the role functioning items of MSQ2.1 or between the emotional functioning subscores of the two instruments (RE and EF). The correlation between the SF-36 and MSQ2.1 subscores is presented in Table 8.

Table 11. Correlation between SF-36 and MSQ2.1 subscores (Spearman Rank Order Correlations). See Table 8 and 10 for abbreviations.

	RR	**RP**	**EF**
PF	ns	ns	r=0,4635 p=0.0099
RP	r=0.4293 p=0.0159	r=0.4553 p=0.0101	r=0.4327 p=0.0169
BP	r=0.4933 p=0.0041	r=0.3983 p=0.024	r=0.4062 p=0.0234
GH	ns	ns	ns
VT	ns	r=0.3691 p=0.0488	r=0.5042 p=0.0062
SF	ns	ns	r=0.3657 p=0.043
RE	ns	r=0.4477 p=0.0149	ns
MH	ns	ns	r=0.4740 p=0.0108

5.2 Validation of the Comprehensive Headache-specific Quality of life Questionnaire

5.2.1 Validation in migraineurs and tension type headache patients

Observations about completing the questionnaire

The questionnaires were administered to a total of 217 patients. On average, it took less than 20 minutes to complete both of the questionnaires. Filling in the questionnaire did not present any difficulty, as reported by the patients. The majority of the patients answered all questions. Of CHQQ's 23 questions, 13 had no missing answers. Fifteen participants did not answer the question about the influence of their headaches on their sexual life. For the remaining nine questions, the rate of missing answers was very low (1 to 3 per question). All questions were completely answered by 202 patients (93% of the 217 patients). As Statistica excludes subjects with missing data from reliability and validity analyses, these were calculated taking the 202 patients into account.

Patient characteristics

Among the 202 patients we studied 169 were females and 33 were males. The mean age was 35.1 years, (SD 11.53; range 18–68). All patients were Caucasian. One hundred and forty-one patients were in paid employment (70%), 20 were students (10%), 10 were on maternity leave (5%), 9 were retired (4.5%) and 3 unemployed (1.5%); 19 preferred not to answer the question about employment status. One hundred and sixty-eight patients (83.2%) were migraineurs and 34 patients (16.8%) had TTH (11 episodic and 23 chronic). Patients with chronic TTH had a significantly higher attack frequency (mean 33.5, SD 13.5 vs. mean 6.5, SD 4.0, $p<0.001$) and more headache days (mean 27.7, SD 5.07 vs. mean 7.61, SD 4.33, $p<0.001$) but smaller minimum (mean 1.97, SD 1.56 vs. mean 4.91, SD 6.19 hours, p¼0.027) and maximum (mean 9.4, SD 6.67 vs. mean 33.71, SD 24.0 hours, $p<0.001$) lengths of treated attack than patients with episodic TTH. The other headache characteristics were not significantly different in the chronic and episodic TTH groups. The male:female ratio was non-significantly higher in the chronic group (10 males and 13 females vs. 2 males and 9 females, $p=0.252$, Fisher's exact test). Fifty-three patients (26.2%) also had a history of depression. Of

these, 42 were migraineurs and 11 TTH patients (4 episodic and 7 chronic). Depression occurred in 25% of the migraine group and 32% of the TTH group (p¼0.396, Fisher's exact test). Data about the patient group are presented in Table 12.

Table 12. Patient characteristics. Data are presented as mean±SD. All: All patients; M: Migraine group; TTH: Tension-type headache group; IHS: International Headache Society; VAS: Visual analogue scale.

Variable	All	M	TTH	p M vs TTH
Age (year)	35.1±11.5	34.77±10.8	36.20±14.5	0.899
Disease length	12.23±10.4	13.31±10.1	6.80±10.4	<0.001
Minimum length of treated attack (hour)	10.8±12.9	11.51±13.5	7.48±9.6	0.004
Maximum length of treated attack (hour)	41.15±31.7	45.72±32.6	19.91±14.2	<0.001
Mean attack length (hour)	24.8±20.9	27.61±21.5	11±9.5	<0.001
Headache severity (IHS rating scale)	2.32±0.6	2,45±0.5	1.68±0.5	<0.001
Headache severity (VAS)	67.52±21.1	72.13±18.0	46.94±20.9	<0.001
Attack frequency last month	7.49±10.8	4.10±3.6	24.13±17.4	<0.001
Number of days with headache last month	8.59±8.2	6.14±4.6	20.54±11.3	<0.001

Reliability

The questionnaire demonstrated excellent reliability, with Cronbach's alpha being 0.913 for the whole sample, 0.892 in the subgroup of migraineurs and 0.928 in the subgroup of TTH patients. The physical, mental and social dimensions also showed good reliability in the whole population and also in the diagnostic subgroups (Table 13).

Table 13. The reliability of the questionnaire and its main dimensions: Cronbach's alpha values. TTH: tension type headache

	Migraine group	TTH group	Whole sample
Whole questionnaire	0.892	0.928	0.913
Physical dimension	0.819	0.807	0.832
Mental dimension	0.801	0.874	0.814
Social dimension	0.814	0.846	0.829

Validity

Criterion validity

In the whole sample, headache severity was negatively correlated with almost all items (22 items correlated significantly with the VAS and 21 with the IHS headache severity scale). Mean attack length and attack frequency showed significant negative correlations with 19 and 13 items, respectively. Age and length of disease were the clinical variables that showed significant correlations with the smallest amount of items (Table 14). The results were similar in the subgroup of migraineurs. In the TTH subgroup, headache severity (measured in both ways) and age were negatively correlated with six items each. Other clinical data showed significant correlations with a smaller number of items. In the whole sample, the physical dimension of the instrument was significantly correlated with all clinical characteristics. The mental dimension was significantly correlated with six of the nine clinical characteristics (the exceptions being attack frequency, headache days per month and maximum length of attacks). The social dimension was correlated with eight of the nine clinical characteristics; age did not show a significant correlation with this dimension. In the migraine subgroup most correlations were also significant. Neither dimension was correlated with the number of headache days per month, the mental dimension was not correlated with attack frequency and the maximum length of attacks, and the social dimension was not correlated with age. In the TTH group the questionnaire's physical and social dimensions were negatively correlated with headache severity, whereas the mental dimension showed no significant correlation with the clinical characteristics. In the

DOI:10.14753/SE.2016.1860

whole sample the total score of the instrument correlated significantly with seven of the nine headache characteristics; there was no significant correlation with age and the number of headache days per month. In the subgroup of migraineurs the total score also showed significant correlations with most (7/9) clinical data, the exceptions being attack frequency and days with headache in the last month. There were no significant correlations between the clinical data and the total score in the subgroup of patients with TTH.

DOI:10.14753/SE.2016.1860

Table 14. Criterion validity: the correlations between the items, dimensions and total scores of the instrument with the clinical characteristics (Spearman Rank Order Correlations). For the sake of brevity only the whole group's results are presented about the correlation of the individual items and headache characteristics. Marked correlations (bold and italic) are significant. ($p<0.05$).All: All patients, M: Migraine subgroup, T: Tension-type headache subgroup.

		Age	Disease length (year)	Headache days last month	Attack frequency last month	Headache severity (IHS)	Headache severity (VAS)	Mean attacklength (hour)	Minimum length of treated attack(hour)	Maximum length of treated attack(hour)
Work performance	All	0.018	-0.111	-0.089	*-0.231*	*-0.545*	*-0.472*	*-0.331*	*-0.312*	*0.263*
Household chores	All	-0.019	-0.114	*-0.251*	*-0.337*	*-0.535*	*-0.490*	*-0.305*	*-0.296*	*-0.226*
Social life	All	-0.020	**-0.157**	**-0.204**	**-0.315**	**-0.453**	*-0.449*	**-0.341**	**-0.266**	**-0.250**
Leisure activities	All	0.011	-0.117	*-0.181*	*-0.297*	*-0.511*	*-0.425*	*-0.348*	*-0.235*	*-0.219*
Vacations/ awaydays	All	*-0.146*	*-0.227*	*-0.230*	*-0.300*	*-0.396*	*-0.275*	*-0.211*	*-0.178*	-0.132
Physical health	All	-0.018	*-0.179*	*-0,232*	*-0,307*	*-0,455*	*-0,409*	*-0,274*	*-0,261*	*-0,197*
Appearance	All	-0.039	*-0.167*	*-0,264*	*-0,354*	*-0,380*	*-0,479*	*-0,291*	*-0,205*	*-0,212*
Relationship with other family members	All	-0.085	-0.119	*-0,205*	*-0,284*	*-0,406*	*-0,386*	*-0,352*	*-0,297*	*-0,208*
Sexual life	All	-0.061	-0.001	**-0,204**	*-0,188*	*-0,336*	*-0,307*	*-0,287*	*-0,243*	*-0,176*
Sleep	All	-0.116	-0.099	-0,012	-0,085	*-0,293*	*-0,256*	*-0,238*	-0,114	-0,132
Energy	All	-0.035	-0.118	*-0,158*	*-0,224*	*-0,268*	*-0,221*	*-0,296*	*-0,235*	*-0,164*
Mood	All	*0.141*	-0.006	-0.109	*-0.182*	*-0.283*	*-0.281*	*-0.179*	*-0.192*	*-0.152*
Memory	All	*0.198*	*-0.212*	-0.010	-0.047	*-0.191*	*-0.182*	*-0.157*	*-0.184*	-0.124
Concentration	All	-0.051	*-0.189*	*-0.166*	*-0.226*	*-0.349*	*-0.310*	*-0.201*	*-0.189*	*-0.170*
Thinking	All	-0.078	*-0.150*	-0.071	*-0.150*	*-0.405*	*-0.313*	*-0.206*	*-0.209*	*-0.160*
General health perceptions	All	*0.190*	-0.128	*-0.139*	*-0.211*	*-0.334*	*-0.263*	*-0.210*	*-0.228*	-0.126
Irritability	All	*0.140*	0.007	0.126	0.064	-0.088	*-0.209*	-0.089	*-0.153*	-0.094
Frustration	All	0.111	0.011	*0.172*	0.074	-0.073	*-0.179*	*-0.167*	-0.135	-0.100
Abortive medication use	All	0.057	-0.101	0.005	-0.054	*-0.204*	*-0.322*	*-0.204*	-0.096	-0.139
Financial situation	All	*-0.233*	*-0.303*	0.103	0.050	*-0.219*	*-0.277*	-0.125	-0.071	-0.033
Embarrassment due to headaches	All	*-0.214*	*-0.165*	-0,000	-0,085	*-0,182*	-0,130	-0,120	-0,105	-0,057
Worries about headache	All	-0.003	-0.085	0,085	0,025	*-0,205*	*-0,210*	-0,116	-0,015	-0,007
Life enjoyment	All	*-0.140*	-0.121	0,067	-0,020	*-0,208*	*-0,180*	*-0,251*	*-0,176*	*-0,168*
Physical score	All	*-0.149*	*-0.243*	*-0,148*	*-0,293*	*-0,534*	*-0,481*	*-0,390*	*-0,286*	*-0,255*
	M	*-0.189*	*-0.155*	-0,012	*-0,180*	*-0,471*	*-0,367*	*-0,337*	*-0,253*	*-0,194*
	T	-0.044	-0.095	0.182	0.109	*-0.442*	*-0.428*	-0.122	-0.111	-0.034
Mental score	All	*-0.157*	*-0.236*	0.054	-0.054	*-0.325*	*-0.334*	*-0.227*	*-0.216*	-0.132
	M	*-0.236*	*-0.176*	0.135	0.018	*-0.286*	*-0.294*	*-0.186*	*-0.183*	-0.088
	T	-0.252	-0.301	0.272	0.328	-0.188	-0.181	0.091	-0.045	-0.051
Social score	All	-0.096	*-0.220*	*-0.154*	*-0.289*	*-0.472*	*-0.471*	*-0.393*	*-0.311*	*-0.260*
	M	-0.141	*-0.157*	-0.024	*-0.186*	*-0.398*	*-0.394*	*-0.334*	-0.274	*-0.216*
	T	-0.021	0.008	0.188	0.206	-0.274	*-0.352*	-0.118	-0.171	0.131
Total score	All	-0.138	*-0.246*	-0.040	*-0.191*	*-0.490*	*-0.449*	*-0.364*	*-0.306*	*-0.223*
	M	*-0.213*	*-0.173*	0.052	-0.108	*-0.439*	*-0.394*	*-0.303*	*-0.256*	*-0.168*
	T	-0.026	-0.379	0.435	0.370	-0.336	-0.223	-0.129	-0.103	0.026

DOI:10.14753/SE.2016.1860

Convergent validity

In the whole group, and also in the diagnostic subgroups (migraine and TTH), the majority of items relevant to physical functioning showed significant correlations with the physical domains of SF-36, especially with the bodily pain and role physical domains. The mental and social items of the instrument correlated with the four mental health domains of S0F-36, particularly with social functioning and mental health. The questions asking about general health perceptions and irritability correlated significantly with all eight domains of the SF-36, and six more items showed significant correlations with seven SF-36 domains (Table 15). The physical dimension of the new instrument showed significant correlations with all 'physical' domains of the SF-36 in the total sample and also in the M and TTH groups, except for the correlation with SF-36's bodily pain domain in the TTH group. The mental dimension had significant correlations with all SF-36 domains, with the exception of the correlation with the role emotional domain in TTH patients. The social dimension had significant correlations with the majority of SF-36 domains, except for the role emotional SF-36 domain, which was significantly correlated with it only in the TTH group, and the physical functioning SF-36 domain, which was not significantly correlated with the social dimension in TTH sufferers. The total score of the instrument correlated significantly with all SF-36 domains in the whole sample and in the migraine group; the total scores in the TTH group did not correlate with the social functioning domain of SF-36, but showed significant correlations with all other SF-36 domains.

Table 15. Convergent validity: the correlation of the questionnaire's individual items, dimensions and total score with the SF-36 instrument (Spearman Rank Order Correlations). For the sake of brevity only the whole group's results are presented about the correlation of the individual items and SF-36 domains. Marked correlations (bold and italic) are statistically significant ($p<0.05$). All: All patients, M: Migraine group, T: Tension-type headache group, SF-36 domains: PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health.

		PF	RP	BP	GH	VT	SF	RE	MH
Work performance	All	0.085	***0.371***	***0.601***	0.117	0.005	***0.239***	-0.000	0.032
Household chores	All	0.086	***0.305***	***0.455***	0.090	0.012	***0.186***	-0.019	0.024
Social life	All	0.026	***0.320***	***0.439***	0.020	-0.005	***0.195***	-0.037	-0.016
Leisure activities	All	0.074	***0.297***	***0.394***	0.061	0.016	***0.147***	0.005	0.014
Vacations/ awaydays	All	***0.183***	***0.392***	***0.431***	0.138	0.028	***0.221***	0.069	0.048
Physical health	All	***0.204***	***0.416***	***0.495***	0.101	0.065	***0.221***	0.030	-0.007
Appearance	All	0.023	***0.292***	***0.406***	0.036	0.053	***0.264***	0.063	0.030
Intrafamiliar relations	All	***0.150***	***0.337***	***0.384***	***0.188***	***0.206***	***0.345***	0.097	***0.201***
Sexual life	All	0.108	***0.328***	***0.367***	0.046	0.021	***0.160***	0.048	0.006
Sleep	All	*0.262*	***0.231***	***0.345***	0.135	*0.163*	***0.223***	0.129	0.152
Energy	All	0.134	***0.222***	***0.306***	0.109	0.104	0.116	0.125	0.131
Mood	All	0.116	0.080	***0.222***	0.105	***0.171***	0.130	0.069	***0.246***
Memory	All	***0.277***	0.045	**0.155**	***0.267***	***0.254***	***0.289***	***0.251***	***0.298***
Concentration	All	***0.289***	0.128	***0.171***	***0.300***	***0.187***	***0.310***	***0.254***	***0.238***
Thinking	All	0.095	***0.213***	***0.299***	***0.192***	***0.219***	***0.332***	***0.149***	***0.288***
General health perceptions	All	***0.279***	***0.358***	***0.262***	***0.400***	***0.214***	***0.268***	***0.254***	***0.256***
Irritability	All	***0.170***	***0.209***	***0.283***	***0.183***	***0.230***	***0.344***	***0.205***	***0.246***
Frustration	All	*0.128*	*0.128*	***0.205***	***0.223***	***0.220***	***0.301***	***0.202***	***0.308***
Abortive medication use	All	**0.153**	***0.168***	***0.233***	0.036	-0.026	***0.235***	0.038	-0.008
Financial situation	All	***0.185***	***0.203***	***0.289***	0.034	0.026	***0.197***	-0.007	-0.010
Embarrassment due to headaches	All	0.073	***0.254***	0.141	0.074	0.023	0.127	0.136	0.067
Worries about headaches	All	***0.148***	***0.181***	***0.326***	***0.221***	0.102	***0.299***	0.129	***0.197***
Life enjoyment	All	***0.212***	***0.195***	***0.195***	***0.334***	***0.354***	***0.336***	0.109	***0.350***
Physical score	**All**	***0.252***	***0.419***	***0.503***	***0.186***	0.117	***0.318***	0.109	0.142
	M	***0.270***	***0.343***	***0.487***	***0.204***	0.142	***0.346***	0.131	***0.185***
	T	***0.428***	***0.454***	0.338	***0.437***	***0.460***	0.245	***0.374***	***0.440***
Mental score	All	***0.263***	***0.318***	***0.384***	***0.378***	***0.254***	***0.436***	***0.256***	***0.351***
	M	***0.252***	***0.249***	***0.335***	***0.378***	***0.267***	***0.411***	***0.254***	***0.373***
	T	***0.492***	***0.593***	***0.545***	***0.676***	***0.567***	***0.536***	0.378	***0.589***
Social score	All	***0.221***	***0.414***	***0.500***	***0.219***	***0.234***	***0.392***	0.101	***0.204***
	M	***0.233***	***0.291***	***0.431***	***0.200***	***0.268***	***0.405***	0.098	***0.245***
	T	0.321	***0.649***	***0.580***	***0.637***	***0.575***	***0.416***	***0.420***	***0.523***
Total score	All	***0.270***	***0.413***	***0.525***	***0.291***	***0.203***	***0.443***	***0.188***	***0.264***
	M	***0.274***	***0.338***	***0.478***	***0.295***	***0.235***	***0.429***	***0.179***	***0.304***
	T	***0.498***	***0.645***	***0.553***	***0.778***	***0.591***	0.458	***0.486***	***0,512***

DOI:10.14753/SE.2016.1860

Discriminative validity

When comparing the results of the two diagnostic groups (M and TTH), we found that patients suffering from TTH had higher scores (better QOL) at each item. The difference was significant for 16 of the 23 items (8/8 items of the physical dimension, 4/5 items of the social dimension and 3/10 items of mental dimension) (Table 16). The differences between M and TTH on CHQQ's three dimensions and total score were also highly significant ($p<0.004$); again, TTH sufferers had higher scores (better QOL). Within the TTH group, there was no significant difference in the CHQQ scores (items, dimensions and total score) of episodic and chronic patients, apart from work performance (p¼0.014) and physical health (p¼0.016), which were more severely affected in chronic TTH.

DOI:10.14753/SE.2016.1860

Table 16. Discriminative validity. Item, dimension and total scores (mean±SD) of the migraine group versus the tension-type headache group. Marked differences (bold and italic) are significant ($p<0.05$, Mann-Whitney tests). Higher scores reflect a better QOL. M: migraine group, TTH: tension type headache group.

	Mean±SD M	**Mean±SD TTH**	**p level**
Work performance	32.74±25.5	51.47±24.26	***<0.001***
Household chores	31.85±25.74	54.41±26.83	***<0.001***
Social life	29.17±27.4	52.21±30.5	***<0.001***
Leisure activities	27.98±25	53.68±27.24	***<0.001***
Vacations/awaydays	43.30±35.56	69.12±32.89	***<0.001***
Physical health	30.06±26.82	58.09±29.25	***<0.001***
Appearance	40.62±24.81	61.03±25.24	***<0.001***
Relationship with other family members	42.11±24.83	58.82±27.67	***<0.001***
Sexual life	35.57±33.20	61.03±32.61	***<0.001***
Sleep	38.8±29.23	50.74±29.16	***0.030***
Energy	31.99±19.3	42.65±20.11	***0.002***
Mood	28.57±19.86	36.03±22.41	0.080
Memory	65.48±30.39	73.53±25.68	0.177
Concentration	37.65±26.1	55.15±24.39	***<0.001***
Thinking	43.75±25.53	62.5±26.58	***<0.001***
General health perceptions	54.46±26.86	70.59±27.5	***0.001***
Irritability	44.20±32.19	52.21±35.59	0.252
Frustration	39.43±28.11	44.85±26.44	0.298
Abortive medication use	22.62±27.6	44.85±40.34	***0.005***
Financial situation	68.01±28.51	77.21±29.56	***0.039***
Embarrassment due to headaches	82.44±27.39	89.71±23.09	0.073
Worries about headaches	39.14±25.98	47.79±30.5	0.170
Life enjoyment	44.94±30.81	54.41±25.35	0.052
Physical dimension	**35.84±19.29**	**56.53±18.76**	***<0.001***
Mental dimension	**45.77±17.75**	**55.88±17.39**	***0.004***
Social dimension	**42.11±22.01**	**62.21±21.27**	***<0.001***
Total score	**41.52±17.24**	**57.48±16.87**	***<0.001***

DOI:10.14753/SE.2016.1860

Dimension structure of the questionnaire

In order to examine whether the individual items were mathematically related to the hypothesized dimensions of the instrument, we performed an analysis of item–dimension correlations on the sample. Spearman's rank order correlations were significant for all items and all dimensions. With the exception of the Energy item (which showed the highest correlation with the Physical dimension), all the items showed the highest correlation with their intended dimensions (Table 17).

DOI:10.14753/SE.2016.1860

Table 17. Item–dimension correlations (Spearman Rank Order Correlations) on the sample. All correlations are significant (p <0,05).

	Physical	**Mental**	**Social**	**Total**	**Highest correlation is with relevant dimension**
Physical dimension					
Work performance	0,757728	0,458167	0,700616	0,726158	+
Household chores	0,710302	0,350793	0,664333	0,639927	+
Physical health	0,751094	0,449268	0,694886	0,715548	+
Appearance	0,724138	0,408714	0,575937	0,645952	+
Sexual life	0,737800	0,399855	0,635344	0,660815	+
Sleep	0,577862	0,371600	0,424831	0,515695	+
General health perceptions	0,582935	0,501696	0,416129	0,571881	+
Abortive medication use	0,465216	0,313194	0,345622	0,427700	+
Social dimension					
Social life	0,709962	0,320357	0,810299	0,670466	+
Leisure activities	0,690247	0,323934	0,786617	0,655385	+
Vacations/awaydays	0,663661	0,351846	0,801158	0,662569	+
Relationship with other family members	0,599443	0,561760	0,679819	0,681815	+
Financial situation	0,471571	0,419525	0,609110	0,543625	+
Mental dimension					
Energy	0,549684	0,476992	0,408685	0,537868	-
Mood	0,455913	0,548833	0,328400	0,505074	+
Memory	0,331657	0,620747	0,298023	0,483458	+
Concentration	0,493701	0,607196	0,444419	0,589018	+
Thinking	0,543115	0,710080	0,460009	0,666515	+
Irritability	0,297053	0,653614	0,285495	0,481545	+
Frustration	0,291822	0,690378	0,251766	0,483403	+
Embarrassment due to headaches	0,237955	0,427475	0,235983	0,348968	+
Worries about headaches	0,366430	0,684187	0,375621	0,555774	+
Life enjoyment	0,359789	0,624671	0,307846	0,505788	+

Observations of the SF-36 measure

In order to compare the performance of the new questionnaire and the SF-36, we calculated the correlations between the SF-36 domains and the clinical characteristics. In general, significant correlations were rare and of low to moderate strength. In the whole sample attack frequency was negatively correlated with role physical, vitality, role emotional and mental health domains, and headache severity was negatively correlated with the role physical and bodily pain domains. In the migraine group attack frequency was not correlated with any SF-36 domain, and headache severity was negatively correlated with the role physical and bodily pain domains. In the TTH group attack frequency was negatively correlated with the role physical and bodily pain domains, and headache severity with the bodily pain domain (these data are not shown in the tables). We also assessed the discriminative validity of the SF-36 measure in the two groups. Patients suffering from TTH had significantly higher scores (reflecting better QOL) in two of the eight dimensions (role physical and bodily pain), whereas migraineurs had numerically higher scores in six domains, the difference being significant only in two, vitality and mental health (Table 18).

Table 18. Discriminative validity of the SF-36 questionnaire. SF-36 scores of the migraine and TTH groups (mean±SD). Marked differences (bold and italic) are significant ($p<0.05$, Mann-Whitney tests). M: migraine group, TTH: tension-type headache group. SF-36 domains: PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health.

SF-36 domain	M	TTH	p
PF	78.94±27.78	76.89±29.07	0.383
RP	32.12±45.43	61.49±43.54	***<0.001***
BP	29.83±20.24	40.95±20.51	***0.002***
GH	59.34±22.23	54.31±18.51	0.091
VT	54.97±20.93	47.16±20.09	***0.030***
SF	63.33±23.55	62.50±21.13	0.895
RE	65.19±46.28	50.40±44.14	0.052
MH	64.87±20.64	54.81±19.16	***0.004***

DOI:10.14753/SE.2016.1860

5.2.2. Validation in medication overuse headache

The reliability of the questionnaire was adequate (Cronbach alpha = 0,869 for the whole questionnaire, and 0.679 to 0.759 for its dimensions) in this group of MOH patients (Table 19).

Table 19. The reliability of the questionnaire and its main dimensions in medication overuse headache patients: Cronbach's alpha values.

Physical dimension	0.700
Mental dimension	0.759
Social dimension	0.679
Total score	**0.869**

When examining the criterion validity of the instrument, we found negative correlations between the clinical data and CHQQ scores of the patients, as we had expected. Significant, mild to moderate correlations were observed between headache severity (measured both with a visual analogue scale and the IHS scale) and the questionnaire's social dimension and total score. The questionnaire's dimensions and total score were not significantly correlated with the other clinical data. In order to compare the two QOL questionnaires' performance, we also examined the criterion validity of the SF-36 in this sample. We found significant, but weak negative correlations between headache severity (measured both by VAS and IHS scales) and SF-36's bodily pain dimension. The patients' age, headache and attack frequency showed mild, but significant negative correlations with SF-36's physical functioning domain. Surprisingly, we found significant positive correlations between disease duration and 4 of the 8 SF-36 domains (bodily pain, vitality, social functioning, and mental health) (Table 20).

Table 20. Criterion validity of the CHQQ and SF-36 questionnaires in medication overuse headache patients (Spearman Rank Order Correlations). Marked differences (bold and italic) are significant ($p<0.05$). CHQQ: Comprehensive Headache-related QOL Questionnaire VAS: Visual analogue scale. SF-36 domains: PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health.

	Age	**Length of disease**	**Number of headache days**	**Number of attacks**	**Length of attacks**	**Minimum length of attacks**	**Maximum length of attacks**	**Pain severity (IHS scale)**	**Pain severity (VAS)**
CHQQ Physical	-0,199	0,077	0,123	0,124	-0,171	-0,227	-0,208	-0,239	-0,244
CHQQ Mental	-0,067	0,236	0,009	0,027	-0,140	-0,235	-0,134	-0,180	-0,193
CHQQ Social	-0,238	-0,031	0,130	0,166	-0,090	-0,158	-0,234	***-0,257***	***-0,330***
CHQQ Total	-0,205	0,088	0,101	0,118	-0,172	-0,252	-0,220	***-0,287***	***-0,290***
PF	***-0,408***	0,081	***-0,360***	***-0,354***	-0,211	***-0,327***	-0,060	-0,095	0,163
RP	-0,222	0,194	-0,104	-0,082	-0,080	-0,250	-0,205	-0,158	-0,059
BP	0,079	***0,343***	0,151	0,176	0,009	***-0,401***	-0,205	***-0,382***	***-0,358***
GH	***-0,301***	0,118	-0,057	-0,025	-0,238	-0,219	-0,164	-0,111	0,060
VT	0,084	***0,322***	-0,041	-0,048	-0,038	-0,254	-0,117	0,044	0,034
SF	-0,139	***0,381***	-0,040	-0,085	0,044	-0,113	0,058	-0,121	-0,071
RE	***-0,297***	0,207	-0,245	***-0,288***	-0,146	-0,165	0,038	0,049	0,251
MH	-0,097	***0,317***	-0,145	-0,171	-0,100	-0,278	0,048	0,001	0,055

During the examination of convergent validity the dimensions of the questionnaire showed positive and almost always significant correlations with the SF-36 domains. The physical dimension was significantly correlated to all SF-36 domains except for vitality. The mental dimension was significantly correlated to all SF-36 domains except for the role physical domain. The social dimension was significantly correlated to 5 of the 8 SF-36 domains (physical functioning, role physical, bodily pain, general health

and social functioning). Most of the significant correlations of the CHQQ's dimensions and SF-36 domains were mild to moderate. The total score of the questionnaire showed significant, mostly mild to moderate correlations with all SF-36 domains; it was strongly correlated to the bodily pain domain of the SF-36 (Table 21).

Table 21. Convergent validity of the CHQQ in medication overuse headache patients: the correlation of the questionnaire's dimensions and total score with the SF-36 instrument (Spearman Rank Order Correlations). Marked differences (bold and italic) are significant ($p<0.05$). CHQQ: Comprehensive Headache-related QOL Questionnaire SF-36 domains: PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health.

CHQQ	PF	RP	BP	GH	VT	SF	RE	MH
Physical	***0,4707***	***0,325***	***0,538***	***0,411***	0,1625	**0,543**	**0,328**	**0,411**
Mental	***0,356***	0,246	***0,581***	***0,418***	***0,560***	***0,474***	***0,342***	***0,609***
Social	***0,377***	***0,454***	***0,556***	***0,311***	0,131	***0,498***	0,166	0,256
Total	***0,461***	***0,396***	***0,637***	***0,450***	***0,361***	***0,576***	***0,328***	***0,522***

During the examination of discriminative validity we compared the QOL of MOH patients and chronic tension type headache patients. All dimensions scores and the total score were lower in MOH patients than in CTTH patients; the difference was significant except for the mental dimension (p=0,055). SF-36 scores of MOH patients were also lower, the difference was not significant in three of the four SF-36 mental domains (SF, RE, MH) (Table 22).

DOI:10.14753/SE.2016.1860

Table 22. Discriminative validity of the questionnaire and its main dimensions in medication overuse headache patients and chronic tension type headache. Marked correlations (bold and italic) are significant ($p<0.05$, Mann-Whitney tests). MOH: medication overuse headache, CTTH: chronic tension type headache

	MOH	**CTTH**	**p value**
Physical dimension	36,9	52,6	***0,0002***
Mental dimension	42,9	51,0	0,0545
Social dimension	41,8	56,6	***0,0053***
Total score	40,6	52,8	***0,0009***

5.2.3 Examination of responsivity in medication overuse headache

Baseline CHQQ values and comparison to episodic migraine patients

The headache-specific quality of life of MOH patients, as measured by the CHQQ instrument, was low as regards the physical, mental and social dimensions as well as the total score. With the exception of the physical dimension the values were numerically lower than those of episodic migraine (EM) patients; the difference was statistically significant only for the mental dimension of the CHQQ (Table 23). There was no difference between the baseline CHQQ values of the in-, and outpatient groups (Table 24).

Table 23. The quality of life of medication overuse headache (MOH) patients compared to patients suffering from episodic migraine (EM). Data are presented as mean ± SD. With the exception of the physical domain, MOH patients had lower values; the difference was significant only for the mental domain (Mann-Whitney tests). CHQQ: Comprehensive Headache-related QOL Questionnaire MOH: medication overuse headache, EM: episodic migraine.

	CHQQ scores			
	Physical	**Mental**	**Social**	**Total**
MOH	41,6 ± 8,7	39,3 ± 8,9	41,5 ± 9,5	40,6 ± 5,5
EM	39,2 ± 17,3	47,6 ± 15,4	45,6 ± 19,9	44,2 ± 14,4
p value	0,3252	0,0315	0,3930	0,2593

Table 24. The baseline quality of life of MOH patients in the in-, and outpatient groups. Data are presented as mean ± SD. There were no significant differences between the groups (Mann-Whitney tests). CHQQ: Comprehensive Headache-related QOL Questionnaire

	CHQQ scores			
	Physical	**Mental**	**Social**	**Total**
Inpatients	38,8 ± 10,2	39,3 ± 8,3	40 ± 11,9	39,3 ± 4,4
Outpatients	44,1 ± 7,1	39,4 ± 10,1	42,9 ± 7,5	41,8 ± 6,4
p value	0,4150	0,9072	0,5586	0,3837

Improvement of the clinical characteristics and quality of life

The clinical characteristics of the patients' headaches and their quality of life before and after the treatment period are summarized in Table 25. After the treatment period the clinical characteristics of patients' headaches improved significantly. In particular, the mean number of headache days and of attacks decreased by almost 50%. A meaningful effect (defined as a 50% or greater decrease of headache frequency or attack frequency) was seen in five patients. The quality of life also improved. All the individual items of the CHQQ questionnaire showed higher values (better quality of life) after treatment, which was significant in 17 of the 23 items (Figure 3). The dimensions and total score of CHQQ also showed a significant increase after the treatment period; an increase of at

DOI:10.14753/SE.2016.1860

least 50% of the CHQQ total score was observed in seven patients. In four of these seven patients a meaningful decrease of headache and attack frequency was also observed. The dimensions and total score of the CHQQ showed remarkably uniform changes in all patients (Figure 4).

Table 25. The headache characteristics and quality of life before and after the treatment period. Data are presented as mean ± SD. Significant improvement was seen in all clinical variables as well as the CHQQ dimensions and total score. The p values reflect the results of Wilcoxon tests. VAS: visual analogue scale, IHS: International Headache Society, CHQQ: Comprehensive Headache-related QOL Questionnaire

		Baseline	**Post-treatment**	**p value**
Headache characteristics	Number of headache days per month	24,3 ± 5,7	13,5 ± 8,7	0,0025
	Number of attacks per month	23,7 ± 5,9	12,7 ± 9,2	0,0025
	Headache severity (VAS)	66,2 ± 13,5	41,2 ± 20,9	0,0025
	Headache severity (IHS)	2,1 ± 0,28	1,78 ± 0,38	0,0112
	Duration of attacks (hours)	9,9 ± 4,6	7,3 ± 4,4	0,0023
	Analgesic dose per month	36,2 ± 32,6	12,2 ± 8,9	0,0002
Quality of life	CHQQ Physical dimension	41,6 ± 8,7	63,7 ± 20,5	0,0021
	CHQQ Mental dimension	39,3 ± 8,9	57,8 ± 18,6	0,0041
	CHQQ Social dimension	41,5 ± 9,5	67,7 ± 18,1	0,0011
	CHQQ Total score	40,6 ± 5,5	62 ± 18,2	0.0011

DOI:10.14753/SE.2016.1860

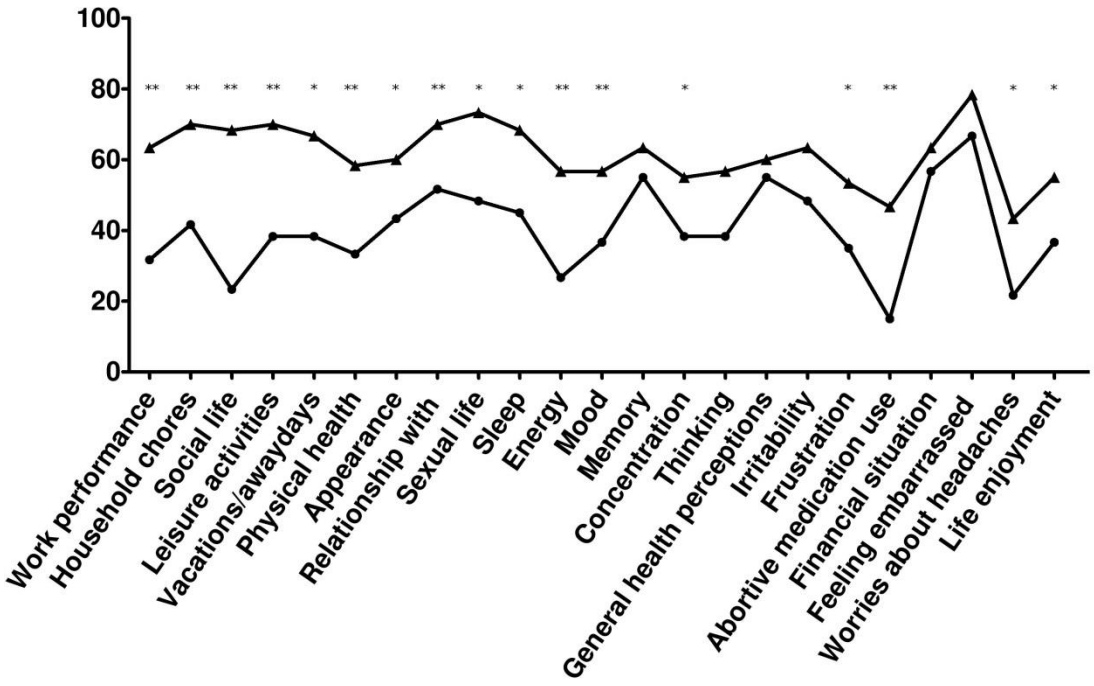


Figure 3. Baseline and post-treatment means of individual CHQQ items. The asterisks mark the items where the improvement was statistically significant (*= $p<0.05$; **=$p<0.01$). CHQQ: Comprehensive Headache-related QOL Questionnaire

DOI:10.14753/SE.2016.1860

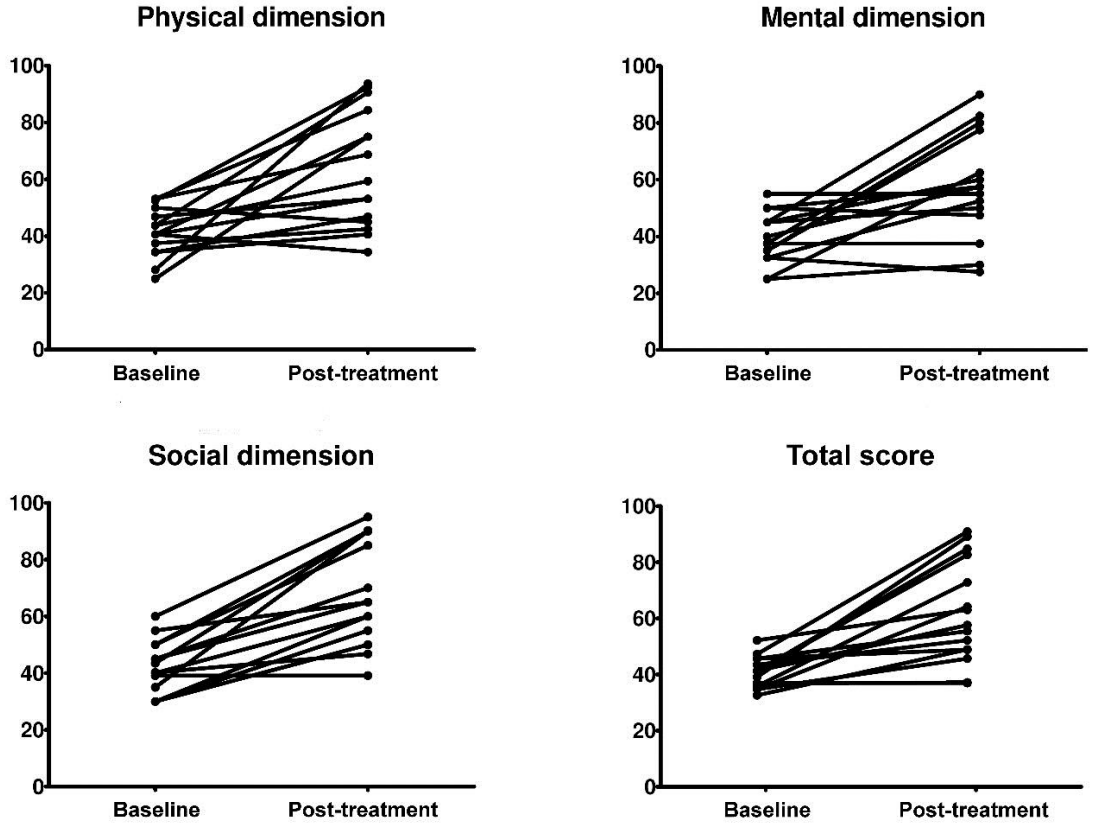


Figure 4. Individual baseline and post-treatment CHQQ results: dimensions and total score. Higher values represent better QOL. CHQQ: Comprehensive Headache-related QOL Questionnaire

Correlations between the changes of clinical and QOL data

As the data in Table 25 show, the significant improvement of the clinical outcome variables was parallelled by a significant improvement of headache-specific QOL. Most of the correlations between the change in clinical characteristics and that of CHQQ's dimensions and total score were mild to moderate (Spearman's r 0,2-0,4 and 0,4-0,6 respectively) (Table 26). With the exception of the correlations between the improvement of headache severity (VAS) and the improvement of the total CHQQ score, the correlations were not significant.

DOI:10.14753/SE.2016.1860

Table 26. Correlation between the improvement of the patients' headache characteristics and quality of life (dimensions and total score). Most correlations were mild to moderate (Spearman Rank Order Correlations). Marked differences (bold and italic) are significant ($p<0.05$). Significant correlation was only found between the improvement of headache severity (VAS) and the increase in CHQQ's total score ($p=0,037$). VAS: visual analogue scale, IHS: International Headache Society, CHQQ: Comprehensive Headache-related QOL Questionnaire

	CHQQ			
	Physical	**Mental**	**Social**	**Total**
Number of headache days per month	0,176	0,108	0,075	0,152
Number of attacks per month	0,179	0,101	0,072	0,149
Duration of attacks (hours)	0,178	0,190	0,097	0,135
Headache severity (VAS)	0,307	0,459	0,217	***0,541***
Headache severity (IHS)	0,002	0,122	0,216	0,134
Analgesic dose per month	0,419	0,132	0,327	0,327

DOI:10.14753/SE.2016.1860

6. Discussion

6.1 Examination of health-related and condition-specific quality of life in episodic cluster headache

In our study, generic and headache-specific HRQoL were found to be seriously impaired during the cluster period. This impairment was at least as severe as in migraineurs for most HRQoL domains; bodily pain and social functioning were significantly worse in CH. Using generic HRQoL measures for the comparison of different groups have the inherent disadvantage of not clarifying whether the results are caused by the index condition (at present, headache) or by concomitant illness. We tried to correct the possible bias by selecting control populations with a similar concomitant disease profile. Other possibilities would be either the careful elimination of all patients with any concomitant illness, or the study of large numbers of patients selected from the general population. Due to the small prevalence of CH none of these seemed feasible.

Before this study, there was only a limited amount of data concerning overall quality of life in CH. One study used the MOS 20-Item Short Form Health Survey (SF-20) to assess the QOL and well-being of 208 consecutive patients in a headache clinic (38). Thirteen CH sufferers were included; other diagnoses were migraine, tension-type headache and ‘mixed headache’. CH patients had significantly worse pain scores and greater limitation in social functioning than migraine patients. Physical functions and general health perception of CH patients, however, were not different from those of other headache patients. The latter finding was in contrast with our observations of impaired general health during the cluster period. Due to the difference between the two generic HRQoL instruments the interpretation of the differences between the two studies was somewhat difficult. As the number of CH patients in the SF-20 study was small (only 10 to 12 CH patients were included when calculating the above-mentioned health scale scores) and part of them were examined outside the bout (34), the generalizability of their results seemed doubtful.

D'Amico et al. administered the SF-36 to 56 Italian CH patients (34 episodic and 22 chronic) during the active periods and compared the results with Italian normative data (34). Cluster headache was associated with a significant decrease ($P < 0.0001$) in six of the eight scales (role physical, bodily pain, general health, social functioning, role emotional and mental health). It is of interest that in our study five of these scales (role physical, bodily pain, general health, social functioning and mental health) were also significantly worse. There was no significant difference between the HRQoL of episodic and chronic CH patients. Surprisingly (but in accordance with our results), the comparison of sumatriptan users and those using a different abortive drug did not show any significant difference. Episodic patients were studied only in the active phase and mention was not made of any concomitant disease the patients may have had. Notwithstanding these limitations, there was a striking similarity between the SF-36 profiles of Italian and Hungarian CH patients during the episode: five of the eight scales decreased in both populations, while physical functioning was not statistically different from controls. Italian CH patients had worse emotional role functioning than controls whereas Hungarian patients scored lower on the vitality subscore. On the whole, these data indicate that the HRQoL impairment in CH may be quite uniform in different cultural and linguistic contexts.

The generic instrument SF-36 makes it possible to compare HRQoL in different medical conditions. Based on literature searches, our CH patients seemed to have a very unfavourable profile. All SF-36 subscores of the present CH population were significantly lower than those of patients with previous myocardial infarction (73). CH patients had significantly worse scores in all SF-36 dimensions except physical functioning than patients who had survived peritonitis (74). CH patients had more severe bodily pain, lower vitality, worse social functioning and mental health than patients with surgically treated hip arthrosis (75, 76), peripheral artery disease (76), or coronary artery disease (76). The comparison of SF-36 scores obtained in different languages and cultures is to be made with caution (77, 78). Nevertheless, as the similar profiles of Italian (34) and Hungarian CH sufferers indicated that the consequences of CH may be similar in other countries, too, the comparisons made above between the effects of CH and other medical conditions on HRQoL are not entirely unjustified.

MSQ2.1 has been widely used to study migraine-specific quality of life (79, 80). Results of a multinational investigation of HRQoL in migraineurs suggest that while migraine does interfere with quality of life, MSQ2.1 scores are also dependent on the socio-cultural setting (78). In our study, migraineurs' role-function restrictive scores were comparable to values obtained in Australia and Canada, while role-function preventive and emotional functioning scores resembled Italian and Swedish values (78). MSQ2.1 was found to be more sensitive in detecting HRQoL changes of migraineurs than SF-36 (81). The same was observed when comparing scores of the present CH population during and after the bout. Due to its sensitivity, relative brevity and simplicity, MSQ2.1 may be useful as a measure of therapeutic efficacy in CH drug trials.

Most of the items of SF-36 and all items of MSQ 2.1 concern the limitations in the 4 weeks preceding the completion of the instrument. The similar time window allows for a comparison between the two instruments and also lets us appreciate the impact of the condition in a more precise way. In the present CH population the two instruments showed good correlation. It was surprising that limitations caused by CH were not significantly more severe than those of migraineurs, as would have been expected from personal accounts of patients (not included in this study) who suffer from both headache types.

Being a generic HRQoL measure, SF-36 may not be sensitive enough to certain effects of CH on the patients' functionality and well-being. The relative insensitivity of MSQ to the consequences of CH may be explained by the item selection process during the development of MSQ, which aimed at achieving a highly migraine-specific measure (79). We felt that these two instruments may not capture some essential aspects of CH. A simple example for the different effects of CH and migraine on QOL, not measured by SF-36 or MSQ, could be the way these headaches influence the quality of sleep. Differences in item selection and concept definition may also explain why subscales measuring seemingly related concepts (e.g. SF-36's role emotional subscale and the emotional functioning subscale of MSQ2.1) do not correlate. That the partial lack of

correlation between the two instruments was not caused solely by the difference between CH and migraine was underlined by the finding of only low to modest correlation ($r < 0.4$) between MSQ2.1 and SF-36's physical and mental composite scores in a large sample of migraineurs (79).

This study, as well as the previous studies about quality of life in CH, may be criticised for the method of patient selection. Although CH is a severe condition that prompts medical consultation in most cases (82), patients with more severe limitations may be more motivated to seek medical advice in a specialized headache center. It is therefore possible that the self-perceived health limitations of our CH sample were more severe than those of an 'average' CH sufferer. A population-based approach may yield more precise results. In spite of these limitations, our study further demonstrated that CH can severely affect the sufferer's functioning and well-being during the active period. The limitations seem to be at least as severe as those caused by migraine and are probably more severe than in a number of important conditions.

As far as the effect of CH is concerned, two later studies are worth mentioning, although these did not measure HRQoL. A multicentric prospective German study assessed the effect of CH, examining patients with chronic CH (n=27), episodic CH in the active phase (n=26), episodic CH outside the active period (n=22), migraine patients (n=24) and healthy controls (n=31). Measurement tools included the German version of the Headache Disability Inventory (HDI), a 25-item questionnaire that calculates a total score as well as Emotion and Function domains, and a screening tool for psychiatric complaints. Quality of life was not formally assessed. Patients with active CH (chronic CH or episodic CH in the active phase) had significantly higher disability than migraineurs. Interestingly, CH patients outside of the bout had disability levels comparable to migraineurs, and significantly worse than controls. A higher number of attacks in the active CH groups was significantly correlated with higher disability (Emotion domain and total score). Although quality of life and disability are different (partially overlapping) concepts, the German study underlines that CH (in the active phase) severely affects the patients' everyday life (83).

A Danish study investigated the socioeconomic burden of cluster headache in patients from a tertiary headache center. In total, 85 patients were included in the study, of these 59 patients had episodic cluster headache (79%) and 16 patients chronic headache (21%). A specific questionnaire about quality of life was not included in the study. Lifestyle changes (mostly sleeping habits and avoidance of alcohol) were observed in 96% of the patients. Daily living was restricted in 66 patients (79%), and 11 patients (13%) had inhibition also outside the cluster period. 82% of the employed patients reported decreased work ability during cluster periods, one-third of the patients felt that cluster headache had limited their career. Work absence was higher in CH patients than among the general population. The use of medical services (specialists, off-hour services) and non-medical treatments was also significantly higher in these patients than among the general population (84).

6.2 Validation of the Comprehensive Headache-specific Quality of life Questionnaire

6.2.1 Validation in migraineurs and tension type headache patients

We evaluated the psychometric properties of the Comprehensive Headache-related QOL Questionnaire in patients suffering from migraine or TTH headache. The questionnaire was easy to administer. The internal consistency of the questionnaire was excellent in the whole sample and also in the diagnostic subgroups. Tests of criterion and convergent validity were also adequate. The questionnaire was able to detect significant differences between the impact of two different headache types (migraine and TTH). The dimension structure of the instrument was confirmed. Thus, CHQQ seems to be a reliable and valid means of measuring the impact of headache on the individual's QOL. The study population consisted of patients with episodic migraine and TTH. Patients with episodic and chronic TTH had very similar clinical characteristics (apart from attack frequency and number of days with headache) and similar QOL profiles (no significant differences were found in 21/23 items, 3/3 dimensions and the total score), and therefore were treated as a single group. The reason

for this similarity may be the fact that patients were recruited at a tertiary center and patients with infrequent TTH or those whose headache did not cause a certain amount of impairment were not referred to this center for evaluation.

The study population would have been larger if patients with probable migraine and probable TTH had also been included. We decided not to include these patients to avoid diagnostic errors, as the IHS classification foresaw a diagnostic overlap between these two headache types. We also aimed to define clearly distinguishable diagnostic groups because we felt that the assessment of discriminative validity could have been compromised by including the respective 'probable' cases.

The length and ease of use of a questionnaire are important aspects of its usability (14) and questionnaire length can have a threshold effect on response rate (15). In our study the questionnaire did not present any difficulty for the patients and 93% filled in all questions. The question about the effect of headache on sex life was the most frequently unanswered one (7% of the patients), much lower than the 17% missing answers for a similar question in a French QOL study (61). The other questions were answered by more than 98% of the participants; equally high answer rates had been observed in previous studies of QOL in headache (52, 61). The high response rate indicated that the length of this questionnaire would probably not be a significant limiting aspect of its clinical use. This notion was confirmed in our later studies. While shorter QOL instruments can clearly have an important role in everyday practice (92), longer instruments such as the CHQQ may present a more detailed QOL profile, which could be especially useful in the areas of clinical and pharmacoeconomic research and/or healthcare planning.

The reliability of an instrument can be assessed by different methods. Test–retest analysis, ie. the repeated application of an instrument to the same study population is the most commonly used alternative to measuring internal consistency. Test–retest analysis usually requires a 4-week gap between the two sessions, and therefore was not applied in this study. (This method would have been ethically incorrect, because the

majority of our patients clearly needed a change in their acute medications, and a significant portion also needed prophylactic therapy).

If an instrument is developed for use in a clinical setting (ie. for following up individual patients), rather than for the comparison of groups in experimental circumstances, a high level of internal consistency (ie. an alpha exceeding 0.9) is the minimum requirement (19). In this respect CHQQ seemed to be adequate for use as a follow-up tool in individual patients, but we underline that formal clinical testing should precede its use for this purpose. On the other hand, CHQQ's reliability was comparable to that of MSQ2.1 and quite noticeably better than the reliability of the MSQ, the dimensions of which had internal consistency values between 0.70 and 0.85 (51).

A QOL instrument is required to demonstrate content validity, criterion and construct validity (20). Content validity expresses the degree to which the underlying construct (QOL) is comprehensively sampled by the instrument's items (93). As already mentioned, the items included in the final version were the ones that were meaningful both for the patients and the clinicians involved, which is an aspect of content validity. The small number of missing responses may also reflect that the patients felt the questions covered important aspects of their condition. It is therefore reasonable to suggest that the instrument's content validity was adequate.

The instrument's validity was formally assessed by measuring its criterion, convergent and discriminative validity. By assessing criterion validity in this study, most QOL instruments had low to moderate correlations with the clinical data. During the validation of the MSQ2.1 measure, self-reported frequency and severity of headaches, duration of the attacks, and the time since the last severe headache were used to test for criterion validity (51). These showed significant but moderate correlations with the MSQ2.1 dimensions and total score. The validation study of the MQoLQ- 24 (53), an instrument designed for assessing the acute changes in QOL during a migraine attack, found that most correlations between the instrument's domains and clinical data were moderate: the strongest correlations were between the work domain of the instrument and limitation of activity (r=0.30 to r=0.51); the weakest correlations were seen with the

concerns/feeling domain, but even there, the strongest correlation was with activity limitation (r=0.19 to r=0.41). In the validation study of the French QVM instrument, the frequency, severity, and treatment resistance of headaches, as well as headache-related disability, were significantly correlated with QVM's total score and subscales; correlation coefficients were not reported (54). During the validation study of the MSQOL correlations with clinical variables were not calculated; instead, groups were created according to the severity of clinical symptoms and ANOVAs of MSQOL scores calculated: increased disease severity was associated with worse QOL (52). In this study more severe external measures of headache were related to a worse QOL. The strength of the correlations we observed (weak to moderate) was comparable to those found in the above-mentioned studies. The strength of correlations, and the fact that the items, dimensions and total score of the instrument did not correlate significantly with all clinical data, are not surprising: the symptoms of a disease do not invariably correlate with QOL scores (94). This is partly explained by the fact that the items in a QOL instrument can be divided into two main types: causal indicators and effect indicators. Studies of the relationship between symptoms and QOL indicate that while some symptoms, such as obstipation, vomiting or hemiparesis, are almost always evident before, and have a direct influence on the deterioration of QOL (causal indicators), other symptoms including pain, anxiety or depression probably have a bidirectional relationship with QOL (effect indicators) (95). It is also important to note that different symptoms or aspects of their conditions can have differing importance for primary headache patients. This is exemplified by studies of the determinants of patient satisfaction with migraine treatment, with fast and complete headache relief being described by most migraineurs as their main preference, and freedom from associated symptoms being important for a smaller number of patients (96). The difference in the frequency of accompanying symptoms within the study populations (97) may also influence the correlations between clinical data and QOL scores. Finally, it must be borne in mind that, theoretically, symptom scores and QOL instruments measure two fundamentally different constructs, and the correlations we found support this notion.

While the CHQQ scores of migraineurs showed significant correlations with most clinical data, the scores of TTH patients were not significantly correlated with the

clinical characteristics, apart from moderate correlations of headache severity and the physical and social dimensions. This may be explained in part by the fact that this group consisted of a fewer number of patients, and was itself heterogeneous as regards the headache frequency of the individuals. On the other hand, areas conceptually related to QOL, such as the ability to study, had been found to be more severely affected by migraine than by TTH, even after correction for pain intensity (98). Moreover, in this study significant correlations between the TTH group's clinical characteristics and SF-36 domains were also very rare: previous studies about QOL in TTH had similar results. In a sample of 25 chronic TTH patients, only four (bodily pain, vitality, social functioning and mental health) of the eight SF-36 domains were significantly correlated with headache frequency, and only one (social functioning) with headache intensity (99). In a German study, the SF-36 physical composite score (PCS) of TTH sufferers was significantly correlated with days with disability and days with analgesic use, but not with headache days/hours, days with severe headache and headache score. In the same study the PCS of migraineurs was significantly correlated with all clinical variables. Interestingly, the mental health composite score was not correlated with the clinical characteristics in either of the diagnostic groups (100). These studies and our results seem to indicate that the perceived effect of TTH on QOL is largely independent of the clinical characteristics of headache.

Convergent validity was assessed by calculating the correlations between CHQQ and the SF-36 generic QOL instrument. The total score of our instrument correlated significantly with all SF-36 dimensions in the whole sample and the diagnostic subgroups, with the exception of the total score in TTH that was not correlated with SF-36's social functioning domain. CHQQ's three dimensions had significant correlations with the majority of SF-36's domains. Most correlations were of moderate strength (0.3 to 0.5) in the whole sample and migraine group, while there was a high number of strong (>0.5) correlations between CHQQ scores and SF-36 domains in the TTH group. Correlation coefficients were higher in the TTH group (0.374–0.778) than in the migraine group (0.179–0.487). The strength of correlations was again similar to those found in previous validation studies. In the MSQOL validation study convergent validity was measured by calculating the correlations of MSQOL with the SF-36

domains: mostly moderate correlations were found with the exception of a strong (0.53) correlation with the mental health domain (52). The validation study of the MSQ2.1 reported low-to-modest correlations between MSQ dimensions and the two component scores of the SF-36 (79). The fact that most correlations were moderate may be explained by three factors. First, SF-36 gathers data about the 4 preceding weeks, while the CHQQ asked questions about the last 2 weeks. Second, there are important differences between the items in the two instruments. The CHQQ asks questions about sleep, intrafamiliar relations, sex life and leisure activities, while these are not included in the SF-36. Furthermore, it is important to stress that the CHQQ explicitly asks about the way headaches influence the various areas, so limitations caused by other conditions were probably not taken into account by the patients, whereas SF-36, as a generic QOL measure, gathers information about the effect of one's health in general (including the headaches) on QOL. The same three factors may also explain the lack of significant correlation between SF-36's social functioning domain and CHQQ's total score in TTH patients.

Confronting the diagnostic subgroups' headache specific QOL (discriminative or known group validity) lent further support to the validity of the instrument. It is important to stress that, as we had expected, migraine patients had numerically lower scores (worse QOL) for all items, dimensions and the total score, and that the difference was significant in most (with the exception of seven items). It therefore seemed that the CHQQ was able to disclose the differential effect of headache types on QOL. In this regard it is worth noting that in the present study the SF-36 questionnaire found a significantly different QOL between migraine and TTH only in four of its eight dimensions, and in two of them TTH sufferers had worse QOL, which is not consistent with the widespread notion of migraine being a more severe condition.

We started developing the CHQQ with the intention of producing an instrument that examines the QOL of headache patients in detail. It was expected that the underlying factor structure would be complex. The analysis of the item–dimension correlations confirmed the hypothesized structure of the instrument. With the exception of one item, all the items showed the highest correlation with their intended dimensions.

An obvious issue with our study was the method of patient selection. As patients presenting at a tertiary center were involved, patients suffering from more severe headaches may have been over-represented in the sample. In fact, patients with more severe limitations may be more motivated to seek medical help in a specialized headache center. An indirect proof of this possibility may be the fact that migraineurs outnumbered TTH sufferers in this study, in spite of TTH being much more prevalent in the general population. A further limitation of our study was that most of the patients had migraine. This was due to the fact that we had chosen to enroll all consecutive outpatients who fulfilled the diagnostic criteria of migraine or TTH. Although the TTH group was much smaller, the reliability and validity measurements in this subgroup also showed that the psychometric properties of the instrument were adequate. This was further underscored by the fact that the instrument showed significant differences between the migraine and TTH groups, with TTH patients having better QOL. In this respect it is also worth noting that there were significant differences in the clinical characteristics of headache in the two groups, with migraineurs reporting higher values of disease duration, length of attacks (average, minimum and maximum), and severity of the attacks. Intriguingly, those clinical characteristics that were higher in the TTH group (signifying bigger disease load), i.e. attack frequency and number of days with headache, were the ones that showed fewer correlations with CHQQ's items, dimensions and total score. A more precise assessment of the instrument's usability would require samples drawn from the general population.

Comparing the new instrument with previously developed headache-specific measures could have added further evidence about the validity of the instrument and may have yielded important data about its usability. However, due to a lack of validated Hungarian translations of headache-specific QOL instruments, this approach was not possible (the validation study of the Hungarian version of the MSQOL was only published in 2011 (59), after the enrollment to the present study had been terminated). Although the HIT-6 has been validated in Hungarian (101), due to the small sample size (only 35 Hungarian migraineurs diagnosed by their primary care physician were studied) and to the fact that, in a strict sense, HIT-6 is not a QOL instrument, we decided not to use it.

Regardless of these limitations, this study has provided sufficient evidence that the CHQQ was a reliable and valid instrument to measure QOL in episodic migraine and TTH.

6.2.2. Validation in medication overuse headache

We evaluated the psychometric properties of the Comprehensive Headache-related QOL Questionnaire in patients suffering from medication overuse headache. The majority of patients (81%) were overusing simple or combined NSAIDs, while only 15% were triptan-overusers. The infrequent overuse of triptans was due to financial issues (the local health system covers only 30% of its price). The reliability of the questionnaire was adequate. Criterion validity results of the instrument showed negative correlations between the clinical data and CHQQ scores. Convergent validity results showed that the dimensions of the questionnaire have positive and almost always significant correlations with the SF-36 domains. During the examination of discriminative validity, we compared the CHQQ values of MOH patients to those of chronic tension type headache patients with no medication overuse, who had a similar headache frequency. We decided not to use patients with chronic migraine as a control group, as there was a huge overlap (from 65.5% to 73%) between chronic migraine and medication overuse in previous studies (104, 105) and also, 75% of our patients' headaches met the IHS criteria for chronic migraine. While this consideration would not be relevant during assessment of an individual's QOL, using clearly distinctive clinical groups are necessary for the purposes of a validation study. On the other hand, further studies are necessary to assess the validity of CHQQ in chronic migraine.

A further limitation of this study is the relatively small sample size, therefore our results should be considered as preliminary, and they should be verified on a larger sample, preferably drawn from the general population. Nonetheless, such a validation study is important to confirm that the CHQQ's psychometric properties in MOH are adequate for further testing.

6.2.3 Examination of responsivity in medication overuse headache

This pilot study was conducted to evaluate the feasibility of using the Comprehensive Headache-related QOL Questionnaire as an outcome measure in a prophylactic treatment trial of medication overuse headache. At baseline, patients were found to have low headache-related quality of life that was comparable to the QOL of EM patients. Acute medication withdrawal and prophylactic treatment resulted in the improvement of the headache characteristics and also the QOL of patients. The highly significant changes in QOL indicate that the Comprehensive Headache-related Quality of life Questionnaire may be useful in monitoring the QOL in MOH patients undergoing headache prophylaxis.

In this study, the baseline QOL of MOH patients was not significantly different from the QOL of a large group of patients with EM. This is in contrast with previous studies where MOH patients had lower generic QOL values than EM (103). Our findings might be explained partly by the limited number of MOH patients (ie. it is not sure whether the sample was representative of Hungarian MOH patients). Another plausible explanation is that during the chronification of the headache, the severity of pain and the accompanying symptoms usually decrease; moreover patients with frequent migraines tend to use abortive treatments in the early phase of attacks when the pain and accompanying symptoms are usually mild (91) and therefore their direct effect on QOL may be less robust.

We observed highly significant improvements of both the clinical data/external measures of headache and headache-specific QOL after the treatment. This is not a common finding. A PubMed search on 30th January 2014 identified 53 papers using the keywords ‘medication overuse headache’ and ‘quality of life’. Only six of these used QOL instruments as clinical endpoints in determining the effect of withdrawal treatment; headache-specific instruments were used in just three studies. Of these three studies, one did not find any significant effect of the treatment on QOL (111). So, to our knowledge this is the 3rd study where the clinical improvement was paralleled by significant improvements of headache-specific QOL. Condition-specific QOL instruments are developed to better reflect the effect of a certain condition and its

treatment on QOL. The present study, showing that the CHQQ reflected the expected changes in QOL as the external measures of headache improved, is a small but important step about exploring the feasibility of using CHQQ in clinical trials.

We found mild to moderate, but nonsignificant correlations between measures of clinical improvement and QOL improvement. The chance of finding significant correlations in any given study depends heavily on the number of subjects. While significant correlations would certainly lend further support to the criterion validity of the CHQQ, it was very unlikely that they would be encountered in such a small sample. The present study provides further evidence for the discriminative validity of the CHQQ, as there were significant differences between the pre-, and post-treatment values (dimensions, total score and also the majority of items). As the number of patients was small, most of the correlations between the changes in CHQQ values and headache characteristics were not significant. Nevertheless, the fact that in most patients the improvement of headache-related QOL was paralleled by a similar improvement of clinical variables may provide further evidence for the criterion validity of the CHQQ.

This study had a number of limitations, such as the small sample size, the lack of psychological profile of the patients, the short data collection period and lack of follow-up information. Because of the small number of patients the study was not able to answer whether in-, or outpatient withdrawal is more feasible, or the various prophylactic drugs we used are equally effective. Due to the lack of a longer follow-up period this study was not suited to examine whether the promising results we obtained remain stable over time. On the other hand, the present study confirmed the CHQQ's ability to discern the improvement of MOH patients' quality of life after successful treatment and therefore may be useful as an endpoint in headache trials. This study also corroborated our previous hypothesis (113) about the possibility of successfully using CHQQ to measure QOL in headaches other than migraine or episodic tension type headache. Formal validation studies in MOH and other headaches are necessary to clarify this issue (114).

DOI:10.14753/SE.2016.1860

7. Conclusion

Primary headaches constitute a public health problem, affecting 46% of the adult population globally, causing a significant amount of disability and poor health related quality of life. Health-related QOL reflects the patient's perspective of the way medical conditions and their treatment influence their position in life. Measuring QOL can give a unique insight into the patient's condition as the doctor's evaluation of the effect of illness can be markedly different from the patient's perspective. Along with other patient reported outcomes that measure disability, illness intrusiveness or other consequences of health problems, measuring QOL has become an important means of assessing the burden of disease and the efficacy of therapeutic interventions.

The aim of our studies was to assess the impact of common headache types on HRQoL. Our first study investigated quality of life in cluster headache. After that, we set out to develop a new comprehensive headache-specific questionnaire, which would assess several aspects of QOL. We then examined the psychometrical properties of our new questionnaire, called Comprehensive Headache-related QOL Questionnaire, in several headache types.

Our first study investigated the health-related and condition-specific quality of life in episodic cluster headache. Although there had been sporadic studies measuring generic QOL in CH, headache-related QOL had previously not been studied. In our study, generic and headache-specific HRQoL were found to be seriously impaired during the cluster period. This impairment was at least as severe as in migraineurs for most HRQoL domains; bodily pain and social functioning were significantly worse in CH. After the termination of the cluster period the HRQoL of patients was similar to that of headache-free controls. MSQ2.1 and SF-36 were not sensitive enough to the difference between the QOL profiles of CH patients and migraineurs, so it was concluded that these two instruments may not capture some essential aspects of CH. Among others, these observations also motivated us to develop a new headache specific HRQoL instrument.

In our next study, we developed a new headache-specific HRQoL questionnaire, called Comprehensive Headache-related Quality of life Questionnaire, which aims to assess the patients' HRQoL in a more detailed fashion. The development of the questionnaire consisted of the following steps: relevant item identification, development of a draft version, psychometric testing of the draft version and development of the final version. The psychometric properties of the item scores, dimension scores and total score of the draft version were tested in a group of 117 migraineurs. After omitting 2 questions, we confirmed that the resulting 23-item questionnaire was adequate for further testing.

We then validated the new questionnaire in three main headache types (migraine, tension-type headache and medication overuse headache). According to the internationally accepted recommendations, we investigated the reliability and validity (criterion, convergent and discriminative validity) of the questionnaire during the psychometric testing.

We calculated the internal consistency to assess the reliability of the questionnaire. Cronbach's alpha was adequate in all the diagnostic subgroups, and in several subgroups its value exceeded the very conservative level of 0.9, which represents an excellent reliability.

When assessing the criterion validity of the questionnaire, the clinical data of patients showed negative correlations with the QOL scores, as expected. In all diagnostic subgroups QOL scores correlated mostly and strongest with pain intensity. This confirms the finding, which had been observed by other working groups, too, that pain intensity is the main determinant of QOL in headache. Surprisingly, QOL scores showed less correlations with headache and attack frequency. The strength of the correlations we observed (weak to moderate) was comparable to those found in other validation studies, and can be explained by the conception of QOL, which is based on the patients' subjective interpretation, while the clinical data are considered more objective. In our studies, clinical data were gathered from the patients' headache diaries. In the field of headache research, by a general consensus, the headache diary is considered to be objective. It is worth noting, that the SF-36 domains showed a smaller

number of weaker correlations with clinical data, and in the subgroup of MOH patients, we found significant positive correlations between disease duration and 4 of the 8 SF-36 domains (higher quality of life with longer disease duration), which is contrary to the clinical expectations. This suggests, that according to our original intentions, the CHQQ may be more sensitive to the clinical characteristics of headaches than the generic instrument SF-36.

While assessing the convergent validity we examined the correlations of the different patient subgroups' quality of life scores with the domains of the SF-36. Most correlations were of weak to moderate strength, which was similar to those found in previous validation studies and studies using validated questionnaires, including our own earlier study.

The fact that most correlations were moderate may be explained by the fact that although the two questionnaires measure similar constructs, there are several differences on the level of items; moreover, the CHQQ investigates also such domains (e.g. sleep, leisure activities), which are not included in SF-36.

While assessing the discriminative validity we found that the questionnaire was able to disclose the differential effect of different headache types on quality of life. Confronting the diagnostic subgroups' headache specific quality of life (migraine versus tension type headache and medication overuse headache versus chronic tension type headache) significant differences were measured by our questionnaire. As expected, QOL was significant worse in migraineurs than in TTH patients and also in MOH patients than in chronic TTH patients. It is worth noting, that in our earlier studies, the difference of QOL scores between CH patients and migraineurs was significant only in 2 of the 8 SF-36 domains, and similarly the difference between the SF-36 scores of migraineurs and TTH patients was only significant in 4 domains (in two of which migraineurs had better QOL, which was contrary to our expectations). It is also important, that limitations measured by MSQ caused by CH were not significantly different than than those of migraineurs. These findings suggest that the discriminative validity of CHQQ is adequate, and it may be able to detect differences between the impact of different headache types better than previously used questionnaires.

Further we observed that the responsivity of our questionnaire was adequate. In a pilot study the complex treatment of medication overuse headache patients resulted in a significant improvement of the headache characteristics and simultaneously in highly significant changes of quality of life. This is an important finding as only a few similar studies in MOH have been done as yet, and the applied methods have not measured QOL improvement in all cases.

The length and ease of use of a questionnaire are important aspects of its usability. In our studies the questionnaire did not present any difficulty for the patients and we observed a high response rate, which indicated that the length of this questionnaire would probably not be a significant limiting aspect of its clinical use.

In summary, the psychometric properties of the new questionnaire were adequate in all diagnostic subgroups. The reliability and validity of CHQQ were appropriate; the questionnaire was capable to specify and follow the impact of headache on QOL and it was useful in monitoring the effectiveness of headache therapy. To the best of our knowledge, CHQQ is the first among the quality of life questionnaires used in headache research to have been formally validated in the most important headache types, ie. migraine, TTH and MOH. The aim of our working group is encouraging the widespread use of the new questionnaire in clinical practice as well as in headache research. In our current studies the new questionnaire is being validated in other languages (English, Farsi and Serbian). Furthermore, we already have preliminary data for a validation study in cluster headache. Our studies were performed on patients from specialized headache centers, where patients with more serious headaches are probably overrepresented. Therefore, for a more accurate assessment of the questionnaire's usefulness, we are preparing a study which will investigate a sample of the general population. We are also planning studies which would evaluate the effect of prophylactic and acute headache treatment on QOL.

DOI:10.14753/SE.2016.1860

The new results generated by our studies are the following:

1. We investigated the quality of life in cluster headache in details. During the active period of CH, patients had significantly lower generic and headache-specific HRQoL than healthy controls. The impact of CH on HRQoL was comparable with that of migraineurs; some domains were more affected than in migraineurs. After the termination of the cluster period the HRQoL of patients was similar to that of headache-free controls. Our study was the first, which investigated condition specific HRQoL in CH.

2. We developed a new headache-specific HRQoL questionnaire, called Comprehensive Headache-related Quality of life Questionnaire, which aims to assess the patients' HRQoL in a more detailed fashion.

3. We examined the psychometric properties of CHQQ in the two most common and important primary headache types, ie. migraine and tension-type headache. The reliability and validity of the questionnaire were adequate in these headache types. The questionnaire detected significant differences in the effect of migraine and TTH on HRQoL. This difference was in accordance with the clinical experience, as migraineurs had lower scores than TTH patients.

4. We performed a validation study of the questionnaire in patients suffering from medication overuse headache. Again, the reliability and validity of the questionnaire were adequate in this headache type.

5. In a pilot study, we studied the responsiveness of the questionnaire in a group of MOH patients. The complex treatment of these patients resulted in the improvement of the headache characteristics and simultaneously in highly significant improvement in the QOL as measured by the new questionnaire.

6. Our results indicate that the questionnaire may be useful in assessing the QOL of patients suffering from different forms of primary and secondary headaches, and also in monitoring the effect of headache treatments on QOL.

DOI:10.14753/SE.2016.1860

8. Summary

Measuring health-related quality of life (HRQoL) is one of the most commonly used patient-reported outcomes. We examined HRQoL in different headache disorders using generic and headache-specific questionnaires.

First we investigated the quality of life (QOL) in cluster headache (CH) in details. During the active period of CH, patients had significantly lower generic and headache-specific HRQoL than healthy controls. The impact of CH on HRQoL was comparable with that of migraineurs; some domains were more affected than in migraineurs. After the termination of the cluster period the HRQoL of patients was similar to that of headache-free controls. Our study was the first, which investigated condition specific HRQoL in CH.

After that, we developed a new headache-specific HRQoL questionnaire, called Comprehensive Headache-related Quality of life Questionnaire (CHQQ), which aims to assess the patients' HRQoL in a more detailed fashion.

We examined the psychometric properties of CHQQ in the two most common and important primary headache types, ie. migraine and tension-type headache (TTH). The reliability and validity of the questionnaire were adequate in these headache types. The questionnaire detected significant differences in the effect of migraine and TTH on HRQoL. This difference was in accordance with the clinical experience, as migraineurs had lower scores than TTH patients.

We then performed a validation study of the questionnaire in patients suffering from medication overuse headache (MOH). Again, the reliability and validity of the questionnaire were adequate in this headache type.

In a pilot study, we studied the responsiveness of the questionnaire in a group of MOH patients. The complex treatment of these patients resulted in the improvement of the headache characteristics and simultaneously in highly significant improvement in the QOL as measured by the new questionnaire.

Taken together, our results indicate that the questionnaire may be useful in assessing the QOL of patients suffering from different forms of primary and secondary headaches, and also in monitoring the effect of headache treatments on QOL.

DOI:10.14753/SE.2016.1860

Összefoglalás

Az egészségfüggő életminőség (HRQoL) mérése az egyik leggyakrabban alkalmazott, a beteg beszámolóján alapuló mérés. Kutatásaink során a HRQoL-t vizsgáltuk különböző fejfájás betegségekben, általános és betegség-specifikus életminőség-kérdőívek felhasználásával.

Elsőként cluster fejfájós (CF) betegek életminőségét vizsgáltuk részletesen. Vizsgálatunkkal megállapítottuk, hogy a CF aktív szakában, a cluster periódus alatt mind az általános, mind a fejfájás-specifikus életminőség szignifikánsan alacsonyabb, mint az egészséges kontrolloké. A CF életminőséget rontó hatása a migrénével összemérhető volt; egyes területekre a CF erősebb hatással volt, mint a migrén. A CF periódus megszűnte után az életminőség a fejfájásmentes kontrollokétól nem különbözött. A CF betegség-specifikus életminőségre gyakorolt hatását korábban nem vizsgálták.

Ezt követően kifejlesztettünk egy új fejfájás-specifikus kérdőívet, a Fejfájással Kapcsolatos Átfogó Életminőség-Kérdőívet, melynek célja a betegek életminőségének a korábbiaknál részletesebb vizsgálata. A Fejfájással Kapcsolatos Átfogó Életminőség-Kérdőív pszichometriai tulajdonságait a két leggyakoribb és legjelentősebb fejfájás kórképben, migrénben és tenziós fejfájásban (TF) vizsgáltuk. A kérdőív megbízhatósága és érvényessége megfelelőnek bizonyult ezen kórképekben. A kérdőív a migrén és a TF életminőségre kifejtett hatása között szignifikáns különbséget mért. A klinikai tapasztalatnak megfelelően, a migrénesek életminősége rosszabb volt, mint a TF-ban szenvedőké.

Következő vizsgálatunkban a kérdőív validálálását gyógyszer-túlhasználathoz társuló fejfájás (GyTTF) miatt kezelt betegek körében végeztük el. Ebben a kórképben szintén megfelelő volt a kérdőív megbízhatósága és érvényessége.

Egy próbavizsgálatban a kérdőív érzékenységét vizsgáltuk GyTTF miatt kezelt betegcsoportban. A fejfájás komplex kezelése javulást eredményezett a klinikai végpontokban, melyet a kérdőívvel mért életminőség szignifikáns javulása kísért.

Összefoglalva, eredményeink alapján a kérdőív alkalmas az életminőség mérésére az elsődleges és másodlagos fejfájás betegségek különböző formáiban, valamint felhasználható a fejfájás kezelésének hatékonyságának követésére.

9. References

1. World Health Organization. (1946) WHO definition of Health. Official Records of the World Health Organization, 2:100.

2. Schipper H. J. (1983) Why measure quality of life? Can Med Assoc, 128:1367–1370.

3. WHOQOL. (1993) Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument. Group Qual Life Res, 2:153-159.

4. Ware JE. Jr. (1991) Conceptualizing and measuring generic health outcomes. Cancer, 67(3):774-779.

5. Schrag A.(2006) Quality of life and depression in Parkinson's disease. J Neurol Sci, 248:151-157.

6. Solari A, Filippini G, Mendozzi L, Ghezzi A, Cifani S, Barbieri E, Baldini S, Salmaggi A, Mantia LL, Farinotti M, Caputo D, Mosconi P. (1999) Validation of Italian multiple sclerosis quality of life 54 questionnaire. J Neurol Neurosurg Psychiatry, 67:158-162.

7. Lopez Revuelta K, Garcia Lopez FJ, de Alvaro Moreno F, Alonso J. (2004) Perceived mental health at the start of dialysis as a predictor of morbidity and mortality in patients with end-stage renal disease (CALVIDIA Study). Nephrol Dial Transplant, 19:2347-2353.

8. Lis CG, Gupta D, Grutsch JF. (2006) Patient satisfaction with quality of life as a predictor of survival in pancreatic cancer. Int J Gastrointest Cancer, 37:35-44.

9. Mathews WC, May S. (2007) EuroQol (EQ-5D) measure of quality of life predicts mortality, emergency department utilization, and hospital discharge rates in HIV-infected adults under care. Health Qual Life Outcomes, 5:5.

10. Guyatt GH, Feeny DH, Patrick DL. (1993) Measuring health related quality of life. Ann Intern Med, 118:622-629.

11. Ware Jr. JE. (2000) SF-36 Health Survey update. Spine, 25:3130-3139.

12. Mathews WC, May S.(2007) EuroQol (EQ-5D) measure of quality of life predicts mortality, emergency department utilization, and hospital discharge rates in HIV-infected adults under care. Health Qual Life Outcomes, 25:5.

13. Szende A, Németh R. (2003) Health-related quality of life of the Hungarian population. Orv. Hetilap, 144:1667-1674.

14. Lund E, Gram IT. (1988) Response rate according to title and length of questionnaire. Scand J Soc Med, 26:154-160.

15. Jepson C, Asch DA, Hershey JC, Ubel PA. (2005) In a mailed physician survey, questionnaire length had a threshold effect on response rate. J Clin Epidemiol, 58:103-105.

16. Crocker LM, Algina J. Introduction to Classical and Modern Test Theory. Holt, Rinehart and Winston Publishing Company, New York. 1986

17. McCauley C, Bremer BA. (1991) Subjective quality of life measures for evaluating medical intervention. Evaluation and The Health Professions, 14:371-387.

18. Anastasi A. Psychological Testing. MacMillan Publishing Company, New York. 1990

19. Bland JM, Altman GA. (1997) Statistics notes: Cronbach's alpha. BMJ, 314:572.

20. Terwee CB , Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC. (2007) Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol, 60:34-42.

21. Lohr KN , Aaronson NK, Alonso J, Burnam MA, Patrick DL, Perrin EB, Roberts JS. (1996) Evaluating quality-of-life and health status instruments: development of scientific review criteria. Clin Ther, 18:979-992.

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

23. Headache Classification Subcommittee of the International Headache Society. (2004) The International Classification of Headache Disorders: 2nd edition. 24(1):9-160.

24. Tovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton RB, Scher Al, Steiner TJ, Zwart J-A. (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia, 27(3):193-210.

25. Russell MB. (2004) Epidemiology and genetics of cluster headache. Lancet Neurology, 3(5):279-283.

26. Westergaard ML, Hansen EH, Glümer C, Olesen J, Jensen RH. (2014) Definitions of medication-overuse headache in population-based studies and their implications on prevalence estimates: A systematic review. Cephalalgia, 34(6):409-425.

27. Jensen R, Bendtsen L. (2008) Medication overuse headache in Scandinavia. Cephalalgia, 28:1237-1239.

28. Olesen J, Gustavsson A, Svensson M, Wittchen H.-U, Jönsson B. (2012) The economic cost of brain disorders in Europe. European Journal of Neurology, 19:155-162.

29. Manhalter N, Palásti Á, Bozsik G, Áfra J, Ertsey C. (2010) Examining the psychometric properties of a new quality of life questionnaire in migraineurs Ideggyogy Sz, 63:305-313.

30. Ertsey C. (2009) Az elsődleges fejfájások klasszifikációja, A migrén epidemiológiája, A fejfájásban szenvedő betegek kivizsgálási stratégiája, Az elsődleges fejfájások kezelési protokollja, A fejfájás centrumok kritériumai 2. Kiadás. Cephalalgia Hungarica, 9.

31. Ertsey C. (2010) A fejfájás centrumok helyzete Magyarországon. Cephalalgia Hungarica, 20:7.

32. Bussone G, Usai S, Grazzi L, Rigamonti A, Solari A, D'Amico D (2004) Disability and quality of life in different primary headaches: results from Italian studies. Neurol Sci, 25(3):105-107.

33. Ertsey C , Manhalter N, Bozsik G, Afra J, Jelencsik I. (2004) Health-related and condition-specific quality of life in episodic cluster headache. Cephalalgia, 24:188-196.

34. D'Amico D, Rigamonti A, Solari A, Leone M, Usai S, Grazzi L, Bussone G. (2002) Health-related quality of life in patients with cluster headache during active periods. Cephalalgia, 22:818-821.

35. Holroyd KA, Stensland M, Lipchik GL, Hill KR, O'Donnell FS, Cordingley G. (2000) Psychosocial correlates and impact of chronic tension-type headaches. Headache, 40:3-16.

36. Guitera V , Muñoz P, Castillo J, Pascual J. Quality of life in chronic daily headache: a study in a general population. (2002) Neurology, 58:1062-1065.

37. Osterhaus JT, Townsend RJ, Gandek B, Ware JE. (1994) Measuring the functional status and well-being of patients with migraine headache. Headache, 34:337-343.

38. Solomon GD, Skobieranda FG, Gragg LA. (1933) Quality of life and well-being of headache patients: measurement by the medical outcomes study instrument. Headache, 33:351-358.

39. Wells KB , Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J. The functioning and well-being of depressed patients (1989) Results from the Medical Outcomes Study. JAMA, 262:914-919.

40. Cole JC, Lin P, Rupnow MFT. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. Quality of Life Research, 16:1231-1237.

41. Garcia-Monco JC , Foncea N, Bilbao A, Ruiz de Velasco I, Gomez-Beldarrain M. (2007) Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients. Cephalalgia, 27:920-928.

42. Dahlöf C , Loder E, Diamond M, Rupnow M, Papadopoulos G, Mao L. (2007) The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. Health Qual Life Outcomes, 4:5-56.

43. Santanello NC , Polis AB, Hartmaier SL, Kramer MS, Block GA, Silberstein SD. Improvement in migraine-specific quality of life in a clinical trial of rizatriptan. Cephalalgia, 17:867-872.

44. Géraud G, Valette C. (2000) Sumatriptan nasal spray 20 mg: Efficacy, tolerance and quality of life in migraine patients. Revue Neurologique, 156:646-653.

45. Solomon GD, Skobieranda FG, Gragg LA. Does quality of life differ among headache diagnoses? Analysis using the medical outcomes study instrument. (1994) Headache, 34:143-147.

46. Ware J E Jr, Sherbourne C D. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. (1992) Medical Care, 30(6):473-483.

47. Stewart AL, Ware JE. Measuring functioning and wellbeing: the medical outcomes study approach. Duke University Press, Durham, NC. 1992:6

48. Ware J Jr. (2003) SF-36 Health Survey update. [WWW document]. URL http://www.sf-36.org/tools/SF36bookchapter.shtml.

49. Stewart AL, Hays RD, Ware JE Jr. (1988) The MOS short-form general health survey. Reliability and validity in a patient population. Med Care, 26:724-735.

50. Ware JE, Kosinski M. Improvements in the content and scoring of the SF-36 Health Survey Version 2. SF-36 Users Site at http://www.SF-36.com/news/SF36–20.html.

51. Jhingran P, Osterhaus JT, Miller DW. Development and validation of the migraine-specific quality of life questionnaire. (1998) Headache, 38:295-302.

52. Wagner TH , Patrick DL, Galer BS, Berzon RA. (1996) . A new instrument to assess the long-term quality of life effects from migraine: Development and psychometric testing of the MSQOL. Headache, 36:484-492.

53. Santanello NC, Hartmaier SL, Epstein RS, Silberstein SD. (1995)Validation of a new quality of life questionnaire for acute migraine headache. Headache, 35:330-337.

54. Richard A , Henry P, Chazot G, Massiou H, Tison S, Marconnet R, Chicoye A, d'Allens H. (1993) Qualite´ de vie et migraine. Validation du questionnaire QVM en consultation hospitaliere et en medecine generale. Therapie, 48:89-96.

55. Kosinski M, Bayliss MS, Bjorner JB W, Ware Jr JE, Garber WH, Batenhorst A, Cady R, Dahlöf CGH, Dowson A, Tepper S. (2003) A six-item short-form survey for measuring headache impact: The HIT-6™. Quality of Life Research, 12:963-974.

56. Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner A, Liberman JN, Sawyer J. (1999) An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology, 53:988-994.

57. Bagley CL , Rendas-Baum R, Maglinte GA, Yang M, Varon SF, Lee J, Kosinski M. (2012). Validating Migraine-Specific Quality of life questionnaire v2.1 in episodic and chronic migraine. Headache, 52:409-421.

58. Patrick DL, Hurst BC, Hughes J. Further development and testing of the Migraine-Specific Quality of Life (MSQOL) measure. (2000) Headache, 40:550-560.

59. Berghammer R, Zsombok T. Examination of the quality of life of migraineurs and tension headache patients in connection with impulsivity, empathy, depression, and vital exhaustion. (2011) Mentalhigiene es Pszichoszomatika, 12:173-189.

60. Pini LA, Cicero A F G, Sandrini M. (2001) Long-term followup of patients treated for chronic headache with analgesic overuse. Cephalalgia, 21:878-883.

61. Duru G, Auray JP, Gaudin AF, Dartigues JF, Henry P, Lantéri-Minet M, Lucas C, Pradalier A, Chazot G, El Hasnaoui A (2004) Impact of headache on quality

of life in a general population survey in France (GRIM2000 Study). Headache, 44:571-580.

62. Simić S, Slankamenac P, Kopitović A, Jovin Z, Banić-Horvat S. (2008) Quality of life research in patients suffering from tension type headache. Med Pregl, 61:215-221.

63. Yang M, Rendas-Baum R, Varon SF, Kosinski M. (2011) Validation of the Headache Impact Test (HIT-6TM) across episodic and chronic migraine. Cephalalgia, 31:357-367.

64. Coeytaux RR, Linville JC. (2007) Chronic daily headache in a primary care population: prevalence and Headache Impact Test scores. Headache, 47:7-12.

65. Abbott RB, Hui KK, Hays RD, Li MD, Pan T. (2007) A randomized controlled trial of tai chi for tension headaches. Evid Based Complement Alternat Med, 4:107-113.

66. Gesztelyi G, Bereczki D. (2004) Primary headaches in an outpatient neurology headache clinic in East Hungary. Eur J Neurol, 11:389-395.

67. Czimbalmos A; Nagy Z; Varga Z; Husztik P. (1999) Measuring patient satisfaction with the SF-36 questionnaire: determining the Hungarian normal values. Népegészségügy, 1:4-19.

68. Dodick D W, Rozen T D, Goadsby P J, Silberstein S D. (2000) Cluster headache. Cephalalgia, 20:787-803.

69. Anonymous. Introduction. [WWW document]. URL http://www.clusterheadaches.com/index.html2003.

70. Santanello NC, Davies G, Allen C, Kramer M, Lipton R. (2002) Determinants of migraine-specific quality of life. Cephalalgia, 22:680-685.

71. Bahra A, May A, Goadsby PJ. (2002) Cluster headache. A prospective clinical study with diagnostic implications. Neurology 58:354-561.

72. Slevin ML , Plant H, Lynch D, Drinkwater J, Gregory WM. (1988) Who should measure quality of life, the doctor or the patient? Br J Cancer, 57:109-112.

73. Failde I, Ramos I J. Validity and reliability of the SF-36 Health Survey Questionnaire in patients with coronary artery disease. (2000) J Clin Epidemiol, 55:359-365.

74. Scheingraber S, Kurz T, Dralle H. (2002) Short- and long-term outcome and health-related quality of life after severe peritonitis. World J Surg, 26:667-671.

75. Soderman P, Malchau H. Validity and reliability of Swedish WOMAC osteoarthritis index: a self-administered disease-specific questionnaire (WOMAC) versus generic instruments (SF-36 and NHP). (2000) Acta Orthop Scand, 71:39-46.

76. de Graaff JC, Ubbink DT, Kools EI, Chamuleau SA, Jacobs MJ. (2002) The impact of peripheral and coronary artery disease on health-related quality of life. Ann Vasc Surg, 16:495-500.

77. Aaronson NK , Acquadro C, Alonso J, Apolone G, Bucquet D, Bullinger M, Bungay K, Fukuhara S, Gandek B, Keller S. (1992) International Quality of Life Assessment (IQOLA) project. Qual Life Res, 1:349-351.

78. Dahlöf C, Bouchard J, Cortelli P, Heywood J, Jansen JP, Pham S, Hirsch J, Adams J, Miller DW. (1997) A multinational investigation of the impact of subcutaneous sumatriptan. II: Health-related quality of life. Pharmacoeconomics, 1(11):24-34.

79. Martin BC , Pathak DS, Sharfman MI, Adelman JU, Taylor F, Kwong WJ, Jhingran P. (2000) Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). Headache, 40:204-215.

80. Adelman J, Sharfman J, Johnson R, Miller D, Clements B, Pait G, Gutterman D, Batenhorst A. (1996) Impact of oral sumatriptan on workplace productivity, health-related quality of life, healthcare use and patient satisfaction with medication in nurses with migraine. Am J Managed Care, 2:1407-1416.

81. Gross M L P, Dowson A J, Deavy L, Duthie T. (1996) Impact of oral sumatriptan 50 mg on work productivity and quality of life in migraineurs. Br J Med Economics, 10:231-246.

82. D'Alessandro R, Gamberini G, Benassi G, Morganti G, Cortelli P, Lugaresi E. (1986) Cluster headache in the Republic of San Marino. Cephalalgia, 6:159-162.

83. Jürgens TP, Gaul C, Lindwurm A, Dresler T, Paelecke-Habermann Y, Schmidt-Wilcke T, Lürding R, Henkel K, Leinisch E. (2011) Impairment in episodic and chronic cluster headache. Cephalalgia, 31(6):671-782.

84. Jensen RM, Lyngberg A, Jensen R H. (2007) Burden of cluster headache. Cephalalgia, 27(6):535-541.

85. Dahlhof C G. (1995) Health-related quality of life under six months' treatment of migraine – an open clinic-based longitudinal study. Cephalalgia, 15:414-422.

86. Bozsik Gy, Manhalter N, Ertsey C. (2005) Quality of life determinants in cluster headache and migraine. Cephalalgia, 22:654.

87. Manhalter N, Bozsik Gy, Ertsey C. (2006) Which quality of life domains are most affected by migraine. (2006) J Headache Pain. 7(1):30.

88. C Ertsey, A Palasti, G Bozsik, J Afra, N Manhalter. (2007) Item response modeling in the development of a new headache-specific quality of life instrument. Cephalalgia, 27:1193.

89. Jacobson GP , Ramadan NM, Aggarwal SK, Newman CW. (1994) The Henry Ford Hospital Headache Disability Inventory (HDI). Neurology. 44:837-842.

90. Holroyd KA , Malinoski P, Davis MK, Lipchik GL. (1999) The three dimensions of headache impact: pain, disability and affective distress. Pain, 83:571-578.

91. Silberstein SD, Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Göbel H, Lainez MJ, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Steiner TJ; International Headache Society. (2005) The International Classification of Headache Disorders, 2nd Edition (ICHD-II) – revision of criteria for 8.2 Medication-overuse headache. Cephalalgia, 25:460-465.

92. Burdine JN, Felix MR, Abel AL, Wiltraut CJ, Musselman YJ. (2000) The SF-12 as a population health measure: an exploratory examination of potential for application. Health Serv Res, 35:885-904.

93. Guyatt G H, Feeny D H, Patrick D L. (1993) Measuring health related quality of life. Ann Intern Med, 118:622-629.

94. Osoba D. (2007) Translating the science of patient-reported outcomes assessment into clinical practice. J Natl Cancer Inst Monog, 37:5-11.

95. Fayers PM, Hand DJ, Bjordal K, Groenvold M. (1997) Causal indicators in quality of life research. Qual Life Res, 6:393-406.

96. Davies G M, Santanello N, Lipton R. (2000) Determinants of patient satisfaction with migraine therapy. Cephalalgia, 20:554-60.

97. Silberstein S D. (1995) Migraine symptoms: results of a survey of self-reported migraineurs. Headache, 35:387-396.

98. Bigal ME , Bigal JM, Betti M, Bordini CA, Speciali JG. (2001) Evaluation of the impact of migraine and episodic tension-type headache on the quality of life and performance of a university student population. Headache, 41:710-719.

99. Peñacoba-Puente C , Fernández-de-Las-Peñas C, González-Gutierrez JL, Miangolarra-Page JC, Pareja JA. (2008) Interaction between anxiety, depression, quality of life and clinical parameters in chronic tension-type headache. Eur J Pain, 12:886-894.

100. Hoppe A, Weidenhammer W, Wagenpfeil S, Melchart D, Linde K. (2009) Correlations of headache diary parameters, quality of life and disability scales. Headache, 49:868-878.

101. Martin M , Blaisdell B, Kwong JW, Bjorner JB. (2004) The Short-Form Headache Impact Test (HIT-6) was psychometrically equivalent in nine languages. J Clin Epidemiol, 57:1271-1278.

102. Headache Classification Committee of the International Headache Society (1998) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia, 8(7):1-96.

103. Lantéri-Minet M, Duru G, Mudge M, Cottrell S. (2011) Quality of lifeimpairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. Cephalalgia, 31(7):837-850.

104. Silberstein SD , Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, Aurora SK, Sirimanne M, DeGryse RE, Turkel CC, Dodick DW. (2013) Onabotulinumtoxin A for treatment of chronicmigraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci, 331(1-2):48-56.

105. Mathew N T. (1993) Chronic refractory headache. Neurology, 43:26-33.

106. Evers S, Jensen R. (2011) Treatment of medication overuse headache - guideline of the EFNS headache panel. Eur J Neurol, 18:1115-1121.

107. Sandrini G , Perrotta A, Tassorelli C, Torelli P, Brighina F, Sances G, Nappi G. (2011) Botulinum toxin type-A in the prophylactic treatment ofmedication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. J Headache Pain, 12(4):427-433.

108. D'Amico D, Usai S, Grazzi L, Rigamonti A, Solari A, Leone M, Bussone G. (2003) Quality of life and disability in primary chronic daily headaches. Neurol Sci, 24(2):97-100.

109. Zebenholzer K, Thamer M, Wöber C.(2012) Quality of life, depression,and anxiety 6 months after inpatient withdrawal in patients with medication overuse headache: an observational study. Clin J Pain, 28(4):284-290.

110. Bøe MG, Salvesen R, Mygland A. (2009) Chronic daily headache with medication overuse: predictors of outcome 1 year after withdrawal therapy. Eur J Neurol, 16(6):705-712.

111. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, TOPMAT-MIG-201(TOP-CHROME) Study Group. (2007)Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia, 27(7):814-823.

112. Pini LA , Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, Ciccarese M, Zappaterra M. (2012) Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain, 13(8):677-684.

113. Manhalter N, Bozsik Gy, Palásti Á, Csépány É, Ertsey C. The validation of a new comprehensive headache-specific quality of life questionnaire. Cephalalgia, 32(9):668-682.

114. Gyüre T, Csépány É, Hajnal B, Kellermann I, Balogh E, Nagy Zs, Manhalter N, Bozsik Gy, Ertsey C. (2014) The Comprehensive Headache-related Quality of Life Questionnaire shows significant improvement after withdrawal treatment in medication overuse headache: a pilot study. Ideggyogy Sz, 67(5–6):169-176.

DOI:10.14753/SE.2016.1860

10. Publications

Articles related to the thesis

Gyüre T, Csépány É, Hajnal B, Kellermann I, Balogh E, Nagy Zs, Manhalter N, Bozsik Gy, Ertsey C. (2014) The Comprehensive Headache-related Quality of Life Questionnaire shows significant improvement after withdrawal treatment in medication overuse headache: a pilot study. Ideggyogy Sz, 67(5–6):169-176.

Ertsey C, Palasti A, Bozsik G, Csepany E, Manhalter N. Perspectives for the Comprehensive Headache-Specific Quality of Life Questionnaire (CHQQ). (2013) A response to the Editorial 'Assessing the quality of health-related quality of life measures' by Lipton et al. Cephalalgia, 33(12):1063-1064.

Manhalter N, Bozsik Gy, Palasti A, Csepany E, Ertsey C. (2012) The validation of a new comprehensive headache-specific quality of life questionnaire. Cephalalgia, 32(9):668-682.

Manhalter N, Palasti A, Bozsik Gy, Afra J, Ertsey C. (2010) Új életminőség-kérdőív pszichometriai tulajdonságainak vizsgálata migrénes betegek esetében. Ideggyógyászati szemle / Clinical neuroscience, 63(9-10):305-313.

Ertsey C, Manhalter N, Bozsik Gy, Afra J, Jelencsik I. (2004) Health-related and condition-specific quality of life in episodic cluster headache. Cephalalgia, 24(3):188-196.

Other, relevant publications

Ertsey C, Vesza Z, Bango M, Varga T, Nagyidei D, Manhalter N, Bozsik Gy (2012) A cluster fejfájás klinikumának prospektiv vizsgálata [Prospective study of the clinical features of cluster headache]. Ideggyógyászati szemle / Clinical neuroscience, 65(9-10):307-314.

Vesza Z, Varallyay G, Szoke K, Bozsik Gy, Manhalter N, Bereczki D, Ertsey C (2010) Trigemino-autonomic headache related to Gasperini syndrome. Journal of Headache an Pain, 11(6):535-538.

DOI:10.14753/SE.2016.1860

11. Acknowledgments

First of all I am grateful to my thesis advisor, Dr. Csaba Ertsey, who granted me the privilege to get involved in the activities of the Headache Workgroup at the Department of Neurology of the Semmelweis University, in Budapest when I was yet a medical student of the University.

My work and the whole set of underlying publications have been completed under his supervision. Dr. Ertsey offered indispensable help to each phase of research, publishing results and the writing of this dissertation.

I am particularly indebted to Dr. Magdolna Bokor, Head of Dept. of Neurology at Nyírő Gyula Hospital, in Budapest who gave her consent and persistent help for my post-graduate studies, even amongst the daily realities of a general hospital.

I wish to express my gratitude to Prof. Imre Szirmai for his decision to launch this research project and thanks to his successor, Prof. Dániel Bereczki, Head of the Department of Neurology of the Semmelweis University, in Budapest for the wide support he gave for carrying on with the commenced researches.

I owe with gratitude to Univ. Docent Josef Spatt, Head of Neur. Rehab. Zentrum, in Wien, for his consent to sustain my commenced research works.

Thanks to my patients, who amongst the pains of headache tolerated the burdens of the examinations.

And finally, special thanks should go to my husband and daughter, for their patience and help.

DOI:10.14753/SE.2016.1860

12. Appendix

12.1 Comprehensive Headache-related QOL Questionnaire

This questionnaire was designed to investigate the impact of headaches. It can help us considerably in learning more about your headache and general health, and thus in the planning of further investigations and treatment. Your identity will not be revealed to third parties and the information you give us will only be used for research purposes. As you can see, this questionnaire consists of two separate parts. The first part starts at the bottom of this page with a question about the intensity of pain. The second part starts on the following page with five possible responses to each question. The questions relate to the impact of headaches in many areas of life. It is important that you answer all questions.

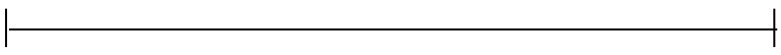
Thank you for taking part in this survey.

Part 1

In this part, we would like to learn how strong your headache is. Please indicate on the line below the intensity of your headache by placing a mark between “no pain” and “the worst pain a person could ever have ”. “The worst pain a person could ever have” is defined as the strongest possible pain, which you may not have necessarily experienced. For example, if you had renal colic before and it was worse than your headache, then the headache cannot be “the worst pain a person could ever have”. Also, do not mark “the worst pain a person could ever have ” if you had no other painful conditions apart from headaches, but you think that others may have experienced stronger pain than you have due to a headache or other conditions.

If you have different types of headaches with different intensities, you can mark them with an explanatory note (e.g. migraine, milder headache).

Intensity of the headache attack:



No pain

The worst pain a person could ever have

DOI:10.14753/SE.2016.1860

Part 2 The following questions relate to the past four weeks. In your answer, please make an "average" of the past 4 weeks.

1. How much did your headache impair your ability to work?

□Not at all □Slightly □Moderately □Significantly □Prevented me from working

2. How much did your headache impair your ability to perform household tasks (cleaning up, washing, cooking, gardening, minor repairs, etc.)?

□Not at all □Slightly □Moderately □Significantly □Prevented me from working

3. How much did your headache interfere with your social life (e.g. going to the movie theater, theater, concert, pub, excursion, visiting friends, etc.)?

□Not at all □Slightly □Moderately □Very much □Unable to do

4. How much did your headache interfere with how you spend your leisure time (reading, listening to music, hobbies, etc.)?

□Not at all □Slightly □Moderately □Very much □Unable to do

5. How much did your headache interfere with the planning of longer leisure programs (such as weekend, outings)? (E.g., did you have to cancel or postpone something because of the headache?)

□Not at all □Slightly □Moderately □Very much □Unable to do

6. How much did your headache affect your physical health (condition)? (E.g., in doing sports or heavy manual work?)

□Not at all □Slightly □Moderately □Significantly □Extremely

DOI:10.14753/SE.2016.1860

7. How much did your headache affect your physical appearance (looks)? (Is your appearance worse because of the headache?)

☐Not at all ☐Slightly ☐Moderately ☐Significantly ☐Extremely

8. How much did your headache interfere with the relationship to your family members (persons living in the same household as you)?

☐Not at all ☐Slightly ☐Moderately ☐Very much ☐Awfully

9. How much did your headache interfere with your sex life?

☐Not at all ☐Slightly ☐Moderately ☐Very much ☐Awfully

10. How much did your headache interfere with your sleep?

☐Not at all ☐Slightly ☐Moderately ☐Very much ☐Awfully

11. How exhausted were you because of your headache? (How much was your energy reduced because of your headache?)

☐Not at all ☐Slightly ☐Moderately ☐Very much ☐Awfully

12. How much did your headache influence your mood? (Were you depressed because of your heaache?)

☐Not at all ☐Slightly ☐Moderately ☐Very much ☐Awfully

13. How much did your headache impair your memory? (Did you become more forgetful because of your headache?)

☐Not at all ☐Slightly ☐Moderately ☐Very much ☐Awfully

DOI:10.14753/SE.2016.1860

14. How much did your headache impair your concentration? (Did your headache make it difficult to concentrate on what your were doing?)

Not at all Slightly Moderately Very much Unable to do

15. How much did your headache affect your thinking?

Not at all Slightly Moderately Very much Unable to do

16. In general, how much did your headache impair your health?

Not at all Slightly Moderately Very much Awfully

17. Did you become irritable because of your headache? (Did you lose your temper more easily as compared to times when you have no headache?)

Not at all Slightly Moderately Very much Awfully

18. Are you more anxious and/or nervous because of your headache?

Not at all Slightly Moderately Very much Awfully

19. Do you use painkillers or other medications to stop your headache?

Not at all Very rarely Sometimes Often Very often

20. How much does your headache affect your financial situation? (Due to costs of medicine, loss of working hours, sick leave, etc.?)

Not at all Slightly Moderately Very much Extremely

21. Do you feel ashamed of your headache or because of your headache?

Not at all Slightly Moderately Very much Extremely

DOI:10.14753/SE.2016.1860

22. How much do you worry because of your headache?

□Not at all □Slightly □Moderately □Very much □Extremely

23. How much does your headache interfere with your enjoyment of the good things in life or of life in general?

□Not at all □Slightly □Moderately □Very much □Completely

DOI:10.14753/SE.2016.1860

12.2 Fejfájással Kapcsolatos Átfogó Életminőség-Kérdőív

Tisztelt Betegünk!

Ez a kérdőív a fejfájás hatásainak felmérésére szolgál. Nagy segítséget jelenthet ahhoz, hogy fejfájásáról és általános egészségi állapotáról még többet megtudjunk, és ezen keresztül segíti a további vizsgálatok és kezelés megtervezését. A kérdőív két önálló részből áll. Az első része itt a lap alján kezdődik, a fájdalom erősségére vonatkozó kérdéssel. Ha lapoz egyet, a következő oldalon kezdődik a második rész, ahol minden kérdésre öt lehetséges választ adhat. Ezek a kérdések a fejfájásnak az élet különböző területeire gyakorolt hatásáról szólnak. Ennek a résznek a végén felteszünk pár kérdést azokról a gyógyszerekről, amelyeket pillanatnyilag a fejfájás kezelésére használ. Nagyon fontos, hogy minden kérdésre válaszoljon.

Segítségét köszönjük.

1. rész

Itt azt szeretnénk megtudni, hogy fejfájása mennyire erős. Kérjük, a lenti vonalon jelölje be a fejfájás erősségét, a „nincs fájdalom” és a „maximális fájdalom” között. Maximális fájdalomnak az elképzelhető legerősebb fájdalmat tekintjük (nem biztos, hogy Ön átélt ilyet). Ha például volt már veseköves rohama, és az rosszabb volt bármelyik fejfájásánál, akkor a fejfájás nem lehet „maximális fájdalom”. Akkor se jelölje be a „maximális fájdalmat”, ha a fejfájáson kívül nem volt más fájdalmas betegsége, de úgy gondolja, hogy mások át szoktak élni az önénél erősebb fájdalmat fejfájás vagy más betegség miatt.

Ha különböző típusú és erősségű fejfájásai is szoktak lenni, akkor ezeket különböző magyarázattal jelölheti meg (pl: migrénes fejfájás, enyhébb fejfájás).

A fejfájás roham erőssége:

nincs fájdalom maximális fájdalom

DOI:10.14753/SE.2016.1860

2. rész. A következő kérdések az elmúlt négy hétre vonatkoznak. Kérjük, próbáljon a négy hét "átlaga" alapján válaszolni

1. Mennyire zavarta a fejfájás a munkájának (munkahelyi tevékenységének) elvégzésében?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

2. Mennyire zavarta a fejfájás a házimunka (takarítás, főzés, mosás, kerti munkák, kisebb javítások stb) elvégzésében?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

3. Mennyire zavarta a fejfájás barátokkal stb. közös programjait (vendégség, mozi, színház, koncert, szórakozóhelyek, kirándulások stb.)?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

4. Mennyire zavarta a fejfájás szabadidő eltöltésében (olvasás, zenehallgatás, hobbi stb)?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

5. Mennyire akadályozta a fejfájás hosszabb programok (pl. hétvégék, utazások) tervezését? (Előfordult-e például olyan, hogy le kellett mondania vagy el kellett halasztania egy programot a fejfájás miatt?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

6. Mennyire befolyásolta a fejfájás az ön fizikai egészségét (erőnlétét)? (Például a sportolás vagy nehéz fizikai munka kapcsán?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

DOI:10.14753/SE.2016.1860

7. Mennyire befolyásolta a fejfájás az ön külsejét, megjelenését? (Azaz rosszabbul néz-e ki a fejfájás miatt?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

8. Mennyire zavarta a fejfájás a családtagokkal (azaz az önnel közös háztartásban élőkkel) való kapcsolatát?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

9. Mennyire zavarta a fejfájás az ön szexuális életét?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

10. Mennyire zavarta a fejfájás az alvásban?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

11. Mennyire érezte magát kimerültnek a fejfájás miatt? (Mennyire csökkentette a fejfájás az ön energiáját?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

12. Mennyire befolyásolta a fejfájás az ön hangulatát? (Rosszabb lett-e a hangulata, kedve a fejfájás miatt?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

13. Mennyire befolyásolta a fejfájás az ön emlékezőtehetségét? (Feledékenyebb lett-e a fejfájás miatt?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

DOI:10.14753/SE.2016.1860

14. Mennyire zavarta a fejfájás az összpontosításban? (Mennyire zavarta a fejfájás abban, hogy arra koncentráljon, amit éppen csinált?)

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

15. Mennyire zavarta a fejfájás a gondolkodásban?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

16. Mennyire rontotta a fejfájás az ön egészségi állapotát általában véve?

Egyáltalán nem Kicsit Közepesen Nagyon Lehetetlenné tette

17. Ingerlékenyebbé vált a fejfájás miatt? (Könnyebben elveszti az önuralmát, ahhoz képest, amikor nem fáj a feje?)

Egyáltalán nem Kicsit Közepesen Nagyon Borzasztóan

18. Feszültebb, idegesebb a fejfájások miatt?

Egyáltalán nem Kicsit Közepesen Nagyon Borzasztóan

19. Használ-e fájdalomcsillapítót vagy más gyógyszert a fejfájás elmulasztására?

Egyáltalán nem Kicsit Közepesen Gyakran Nagyon gyakran

20. Mennyire befolyásolja a fejfájás az ön anyagi (pénzügyi) helyzetét? (A gyógyszerek árának, a kiesett munkaóráknak, betegszabadságnak, stb. köszönhetően)

Egyáltalán nem Kicsit Közepesen Nagyon Borzasztóan

21. Mennyire szégyenli a fejfájását, mennyire szégyenkezik a fejfájás miatt?

Egyáltalán nem Kicsit Közepesen Nagyon Borzasztóan

DOI:10.14753/SE.2016.1860

22. Mennyire aggódik a fejfájás miatt?

Egyáltalán nem Kicsit Közepesen Nagyon Borzasztóan

23. Mennyire zavarja a fejfájás abban, hogy az élet jó dolgainak örüljön, az életet élvezze?

Egyáltalán nem Kicsit Közepesen Nagyon Borzasztóan