Headache
Series Editors: Paolo Martelletti · Rigmor Jensen

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Pharmacological Management of Headaches

Springer

Headache

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The huge importance of headache in public health arises from its causal association with personal and societal burdens of pain, disability, damaged quality of life, and financial costs. Headache disorders are in fact common and ubiquitous. They have a neurological basis, but rarely they are due to serious underlying illness. The primary headache disorders – migraine, tension-type headache, and cluster headache – are easily seen by family physicians or GPs; however, a relatively small number of secondary headache disorders could also be encountered in primary care. It is important that they are recognized and treated in the most appropriate way because of their potentially dangerous underlying causes; moreover, mismanagement and overuse of medications to treat acute headache are major risk factors for disease aggravation. Purpose of this Series, endorsed by the European Headache Federation – EHF, is to provide a detailed description of all aspects of headache disorders that are common and relevant both in primary care and in hospital setting.

More information about this series at http://www.springer.com/series/11801

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Pharmacological Management of Headaches

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ISSN 2197-652X ISSN 2197-6538 (electronic)
Headache
ISBN 978-3-319-19910-8 ISBN 978-3-319-19911-5 (eBook)
DOI 10.1007/978-3-319-19911-5

Library of Congress Control Number: 2015947611

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Foreword

The European Headache Federation project on Headache Series has consolidated its structure and travels now at cruising speed. This is the third volume and has been conceived in order to produce a cushy main street for the therapeutic management of headache disorders and facial pains. The completeness of the single chapters is the natural consequence of the chosen *All Stars* expert team.

We can now testify that the challenge underneath this project has been won as the initial reluctances have vanished in front of the enthusiasm of the readers for this series.

The volume faces the insidious corners of primary headache therapy slipping on solid rails between the risks of multi-pharmacological approaches that often lead to an interaction on the metabolic pathways afoot of inefficacy or – even worse – side effects.

For this sterling volume we thank the authors, and a special *plaudit* goes to the two editors, Koen Paemeleire and Dimos-Dimitrios Mitsikostas, who have built and directed this fine cultural product with special care.

This step is over; we are getting ready for the next ones.

Rome, Italy — Paolo Martelletti
København, Denmark — Rigmor Høiland Jensen

Preface

We are very excited to present the third book in the *Headache* Series, conceived and endorsed by the European Headache Federation. The EHF was founded as a non-profit organisation in 1992 to improve the life of those affected by headache in Europe. Educational activities, including publication of guidelines and books, are important means for EHF to achieve its goals.

We want to express our sincere gratitude to all co-authors of this book, who have devoted their precious time to this project. We are proud to have received contributions from renowned headache experts, both friends and colleagues, from Austria, Belgium, Denmark, Germany, Greece, Italy, Russia, Spain, Sweden, Turkey and the United Kingdom.

We also like to thank Roberto Garbero and Angela Schulze-Thomin, and all those involved at the publisher Springer, for their professionalism in managing this publication.

While acute treatment and prevention of migraine, tension-type headache and cluster headache receive particular attention, we have tried to keep the scope of the book as wide as possible. As such, we have sought unique input from our colleagues working in facial pain. We have also included separate chapters on pharmacotherapy in special populations, including the elderly, children and pregnant or lactating women. Pharmacotherapy for selected secondary headache disorders is presented.

EHF acknowledges that optimal management of headache and facial pain often requires a multifaceted and sometimes even a multidisciplinary approach. The focus of this book on pharmacotherapy should therefore be interpreted as part of a continuum in the *Headache* Series, in which further volumes will be devoted to comorbidities and multidisciplinary management.

The authors have exerted every effort to ensure that drug selection and dosage set forth in this publication are correct. The reader is, however, urged to consult a local national formulary to corroborate any recommendations made.

We hope the information in this book will meet the daily practice needs of medical students, general physicians, neurologists in training and general neurologists.

Ghent, Belgium — Koen Paemeleire
Athens, Greece — Dimos D. Mitsikostas

Contents

Headache Classification

1

Vera V. Osipova

The "golden standard" of the diagnosis of any headache type is the *International Classification of Headache Disorders (ICHD)*. The present version – *ICHD-3 beta* – was approved by the International Headache Society (IHS) in 2013 and became the third one after two previous successful editions in 1988 and 2004. The complete version of the ICHD-3 beta was published in *Cephalalgia* and could be found on the website www.ihs-headache.org (3). Unlike previous editions, which were mostly based on the opinions of experts this edition is leaned on a substantial body of evidence [1–3].

1.1 On the Way to ICHD-3: Conformity of ICHD-3 and ICD-11 Codes

ICHD-3 beta has been published ahead of the final version – *ICHD-3 beta* – that is expected to be finalized in a few years. The main reason for the publication of preliminary ICHD-3 beta version was to synchronize the future ICHD-3 beta with the World Health Organization's next revision (11th edition) of the International Classification of Diseases (ICD-11). The IHS classification committee headed by devoted and enthusiastic *chairman Prof. Jes Olesen* made their best not only to secure a very good representation of headache within ICD-11 but also to ensure congruence between ICD-11 and ICHD-3 beta. The ICD-11 now entered a phase of field trials, and it was recommended that the ICHD-3 beta should do the same. Such a test period will allow identification and correction of mistakes and enable a broad input from the members of the IHS. ICD-11 diagnostic codes will be finalized in 2

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_1

or 3 years from now, and it would be a major advantage for ICHD-3 beta to be able to include these codes along with its own. Field-testing will continue for 2–3 years and some amendments will be made both to ICHD-3 beta and to the ICD-11 diagnostic codes before the final ICHD-3 beta version will be published. ICHD-3 beta is published only in English but it is highly recommended that the final ICHD-3 beta version should be translated into as many languages as possible.

To ensure the quality and accuracy of the future final ICHD-3 beta edition, the IHS classification committee encourages all practitioners to study ICHD-3 beta very closely and comment on any inconsistencies they may come across. Comments should be sent to the chairmen of the relevant working groups (names and email addresses are found on the IHS website).

1.2 How to Use the ICHD-3 Beta?

As recommended by the HIS classification committee, clinicians and researchers *should start using the ICHD-3 beta criteria immediately which means that the previous ICHD-2 version should no longer be used in scientific and clinical work*. It is not necessary to learn the ICHD-3 beta by heart; it should be consulted from time to time when needed. Unlike general practitioners (GPs) and neurologists, the headache experts do not need the classification for the obvious cases of migraine or tension-type headache, but it is useful when the diagnosis is uncertain or if the rare headache type is suspected. For research purposes, the classification is indispensable which assumes that every headache patient enrolled into a research project or clinical trial must be coded in accordance with ICHD-3 beta diagnostic criteria.

ICHD-3 beta is structured in a *hierarchical way* and this assumes that there could be several diagnostic levels ranging from the rough to more detailed. For example:

1. *Migraine*
   - 1.1 Migraine without aura
   - 1.2 Migraine with aura
     - 1.2.1 Migraine with typical aura
       - 1.2.1.1 Typical aura with headache
       - 1.2.1.2 Typical aura without headache
     - 1.2.2 Migraine with brainstem aura…

GPs should be able to get an approximate idea about which group the patient belongs to and could use the first- or second-digit diagnoses. For example, *1. Migraine*, *2. Tension-type headache* or *5. Headache attributed to the head trauma*. In specialist practice and headache centers, a more detailed diagnosis is appropriate. For example, *1.2.1.2 Typical aura without headache*, *2.1.1 Infrequent episodic tension-type headache associated with pericranial tenderness* or *5.1.2 Acute headache attributed to mild traumatic injury to the head.* It is recommended that for most purposes, patients receive *a diagnosis according to the headache phenotype that they currently present*, or that they *have presented within the last year*. For genetic and some other purposes, occurrence during the whole lifetime is used.

Since a patient may suffer from more than one headache type, *each distinct type, subtype or subform of headache must be separately diagnosed* and coded. Thus, *a patient may receive several diagnoses* and codes, for instance: *2.1 Infrequent episodic tension-type headache* and *11.3.1 Headache attributed to acute glaucoma* or *1.3 Chronic migraine* and *8.2.2 Triptan-overuse headache*. In case a patient receives more than one diagnosis, these should be listed in the order of importance to the patient. If *not all diagnostic criteria are fulfilled*, a clinician could use the diagnosis of "*Probable headache*".

It often happens in the routine practice that *one type of headache in a particular patient fulfils two different sets of diagnostic criteria.* If it is the case, other available information should be used to define more precisely which of the alternatives is the more likely diagnosis? This could include the family and longitudinal headache history (how and when did the headache start?), menstrual relationship, the impact of pregnancy and alcohol, trigger factors, the effect of drugs, etc.

Another clinical reality is when *two headache types are present in one patient*. If headache No. 1 meets one set of criteria, whereas headache No. 2 meets another one, diagnoses of both headaches should be considered. A patient whose headache fulfils criteria for both probable headache (e.g., *1.5 Probable migraine*) and let say, *2.1 Infrequent episodic tension-type headache* should be coded to the latter (to more likely type).

When a patient is having more than one headache type or subtype, it is highly recommended that a patient fill out a *diagnostic headache diary* in which the important characteristics for each headache episode are recorded: headache severity, frequency, duration, accompanying symptoms, number of painkillers, etc. Such a diary not only improves diagnostic accuracy and allows a more precise count of medication consumption but also teaches the patient how to distinguish between different headache types if there are more than two clinical subforms.

In many cases to receive a particular headache diagnosis, *the patient must experience a minimum number of attacks of (or days with) that headache.* This number is specified in the diagnostic criteria for the headache type, subtype or subform. For example, criterion A for 1.1 Migraine without aura reads as: *A. At least five attacks fulfilling criteria B–D*, for 2.3 Chronic tension-type headache – *A. Headache occurring on ≥15 days per month on average for >3 months (≥180 days per year), fulfilling criteria B–D*.

Further, *the headache must fulfill a number of other requirements described within the criteria under separate letter headings*: A, B, C etc. Some letter headings are *monothetic* (they express a single requirement). For example, criterion B for 2.2 Frequent episodic TTH reads as: *B. Headache lasting from 30 min to 7 days*. Other letter headings are *polythetic*, requiring for example any two out of four listed characteristics. For example, criterion C for 3.1 Cluster headache: *Either or both of the following:*

1. At least one of the following symptoms or signs, ipsilateral to the headache:
   (a) Conjunctival injection and/or lacrimation
   (b) Nasal congestion and/or rhinorrhoea
   (c) Eyelid edema

(d) Forehead and facial sweating
(e) Forehead and facial flushing
(f) Sensation of fullness in the ear
(g) Miosis and/or ptosis
2. A sense of restlessness or agitation

For the primary headache disorders, the frequency of pain episodes can vary from every 1 to 2 years to daily attacks; the severity of attacks also varies. *ICHD-3 beta does not generally provide a possibility to code for headache frequency or severity*, but recommends that these clinical features are specified in free text.

For almost every headache disorder, the last criterion reads as *"Not better accounted for by another ICHD- 3 diagnosis"*. This criterion is a reminder always to consider/exclude other diagnoses that might better explain the headache.

1.3 The Structure of ICHD-3 Beta: Primary and Secondary Headache Disorders

One of the main ICHD principles is the division of headache disorders into *primary* and *secondary. Primary headache* variants present the *genuine* ones and are not attributed to any disorder of the brain, cerebral and vertebral vessels or abnormalities of any structures located within the head and the neck (eyes, ears, nose, sinuses, mouth, teeth, etc.). Primary headaches are listed in Part I of the ICHD-3 beta (Chaps. 1, 2, 3, and 4) and include:

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

Secondary (symptomatic) headaches are defined in the ICHD-3 beta as follows: *"When a new headache occurs for the first time in close temporal relation to another disorder that is known to cause headache, or fulfils other criteria for causation by that disorder, the new headache is coded as a secondary headache attributed to the causative disorder"*. A secondary headache can be definitely diagnosed only when solid evidence exists from published scientific studies that the disorder specified in criterion B below is capable of causing headache.

A great advantage of ICHD-3 beta vs ICHD-2 (2004) is the *revision of the diagnostic criteria for secondary headaches* (Table 1.1). The new diagnostic criteria for secondary headaches may be applied as soon as the underlying disorder is confirmed. *Criterion A* is the presence of the headache, *criterion B* is the presence of the causative disorder and *criterion C* is the evidence of causation. Moreover, the *new criteria no longer require "remission or substantial improvement of the underlying causative disorder before the headache diagnosis can be made"*.

Table 1.1 General diagnostic criteria for secondary headaches (ICHD-3 beta, 2013)

A. Any headache (H) fulfilling criterion C
B. Another disorder scientifically documented to be able to cause H has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
1. H has developed in temporal relation to the onset of the presumed causative disorder
2. One or both of the following:
(a) H has significantly worsened in parallel with worsening of the presumed causative disorder
(b) H has significantly improved in parallel with improvement of the presumed causative disorder
3. H has characteristics typical for the causative disorder 3
4. Other evidence exists of causation
D. Not better accounted for by another ICHD-3 diagnosis

For example, if a patient develops headache for the first time (or a new headache type appears), and at the same time a brain tumor is diagnosed, it could be logically concluded that headache is secondary to the tumor. In this case, one headache diagnosis shall be given: *7.4 Headache attributed to intracranial neoplasia*. In other words, *"a de novo headache occurring with another disorder recognized to be capable of causing a headache is always diagnosed as secondary"*.

Important to mention that this remains true even when the headache has the characteristics of a primary headache (migraine, TTH, etc.). It could happen in clinical practice that a *pre-existing primary headache worsens or becomes chronic in close temporal relation to an acute causative disorder.* In this case, both the diagnoses of primary and secondary headache should be given, provided that there is good evidence that the disorder can cause headache. For example, *2.3.2 Chronic TTH not associated with pericranial tenderness* and *10.3.4 Headache attributed to pre-eclampsia or eclampsia*.

Secondary headaches are listed in Part II of the ICHD-3 beta (Chaps. 5, 6, 7, 8, 9, 10, 11, and 12) and include:

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder

In each chapter, the most well-known and well-established causes are mentioned and criteria for these are given. However, in many chapters, for example, *9. Headache attributed to infection*, there are huge number of possible causes. In order

to avoid a very long list, only the most important are mentioned. More rare or less determined cases could be assigned to *9.2.3 Headache attributed to other systemic infection*. The same system is used in the other chapters on secondary headaches.

In acute conditions, a close temporal relation between onset of headache and onset of the presumed causative disorder is often sufficient to establish causation, whereas less acute conditions usually require more evidence of causation. In all cases, the last criterion must be applied as a check: "Not better accounted for by another ICHD-3 beta disorder".

Some secondary headaches are being *transformed to a persistent/chronic form*. It happens when headache that was initially caused by another disorder fails to remit after that disorder has resolved. In such cases, the diagnosis changes from the acute subform to the persistent subform after a specified time interval (usually 3 months). For example, *5.1 Acute headache attributed to traumatic head injury* to *5.2 Persistent headache attributed to traumatic head injury*. Most of such diagnoses are in the *Appendix* because of insufficient evidence for their existence.

Part III of the ICHD-3 beta comprises Chap. 13. *Painful cranial neuropathies, other facial pains* (with 12 clinical subforms) and Chap. 14. *Other headaches* (not elsewhere classified and unspecified).

The ICHD-3 beta is concluded by the *Appendix* which was developed for research purposes. The Appendix comprises the forms, types and sub-types of headaches which do not still have enough body of evidence. After a certain trial period, these orphan entities could either be transferred to the main body of the classification or be irretrievably deleted.

Being the main tool for the diagnosis of any headache type, the latest but not last edition of the International Classification of Headache Disorders – *ICHD-3 beta* – serves as a guarantor of uniformity and quality of headache diagnosis all over the world.

> "ICHD-3 beta is published. Use it immediately" (Jes Olesen, Chairman, 1st, 2nd and 3rd Headache Classification Committee)

References

1. Headache Classification Subcommittee of the International Headache Society: classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain (1988) Cephalalgia 8(Suppl 7):1–96
2. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd ed. Cephalalgia 24(Suppl 1):1–232
3. Headache Classification Subcommittee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808

Epidemiology of Headache

2

Ugur Uygunoglu and Aksel Siva

2.1 Introduction

On the WHO's ranking of causes of disability, headache disorders is listed among the 10 most disabling conditions for the two genders, and into the five most disabling for women. But despite being the most common neurological symptom, the diagnosis and treatment approaches for headache disorders are not globally established and their burden of disease is underestimated.

Epidemiology is defined as "the study of distribution and determinants of disease frequency in human populations" [1]. Epidemiological studies in headache disorders are mainly performed for evaluating the prevalence and incidence and determining the burden of disease to raise awareness for this common health problem [2]. "*Prevalence"* answers the question "how common a disease is?" and is expressed by the proportion of a given population that has a disease over a defined period of time. "*Incidence"* is a measure of the probability of occurrence of a given medical condition in a population within a specified period of time. *"Incidence proportion"* is the number of new cases within a specified time period divided by the size of the population initially at risk [3]. The other aims of epidemiological studies are to examine the sociodemographic, familial, and environmental risk factors, which may help to identify high-risk groups for headache and provide a better understanding on the pathogenesis of disease and improve treatment strategies [4].

Due to methodological issues, many papers regarding epidemiological studies show discrepancies. The main challenge in all studies is that the diagnosis depends on subjective experiences rather than standard criteria. To eliminate these differences, International Headache Society (IHS) has published criteria of headache disorders subtypes firstly in 1988, revised in 2004, and recently, preliminary form

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_2

named as beta was published in 2013 [5–7]. The International Classification of Headache Disorders, 2nd edition (ICHD-II) and The International Classification of Headache Disorders, 3rd edition (beta version) have provided improved definitions to reduce problems in methodological studies. However, personal interview and neurological examination are still the "gold standards" used in headache epidemiology studies. This methodology, which provides an improved clinical headache diagnosis is difficult to carry out, as they should involve large populations, which in turn requires a high cost. Therefore, such studies have been carried out only in a limited number of studies [8]. Another and probably more important issue is the lack of diagnostic biomarkers or other study tools that may provide an accurate diagnosis of primary headaches!

Headache prevalence usually corresponds to the sum of "primary headaches," mainly of migraine and tension-type headache prevalence. The overall headache prevalence rates in one year vary between 29 and 77 % in adults, which is more frequent in women (40–83 % vs. 19–69 %). Lifetime prevalence was found 35–96 % in European countries. As a summary of six European studies, it showed 50.5 % headache prevalence in one year, which is more common in women (57.6 vs. 41 %) [9].

2.2 Epidemiology of Migraine

2.2.1 Incidence of Migraine

Although there are a large number of migraine prevalence studies, the incidence studies are limited. The high variability of incidence rates among age groups and some migraine definition-related issues have resulted in having only a few reliable, large population-based incidence studies in migraine. In order to obtain exact incidence rates in migraine, large cohorts need to be followed in long periods.

Incidence studies show significant differences, which may be explained by various study populations and methodology. A population-based study using estimated onset age of migraine was conducted by Stewart et al. in 1991. Telephone interviews were done randomly with 10,619 participants between ages 12 and 29. Three hundred and ninety-two men and 1018 women with migraine were evaluated. *Onset age for* migraine with aura peaked between ages 12 and 13 (adjusted incidence rate: 14.1/1000) and migraine without aura between 14 and 17 years among females. *Incidence* of migraine with aura peaked in 5 years (6.6/1000) and without aura between 10 and 11 years (adjusted incidence rate: 10/1000) in men. They emphasized that the incidence rate of migraine with aura peaks 3–5 years earlier than migraine without aura. One of the limitation study was the lack of the participants older than 30 [10].

In 1996, Breslau et al. conducted a prospective study in migraine. The cohort comprised 1007 individuals between 21 and 30 ages. Follow-up interviews were carried out at 3.5 and 5.5 years later in 972 patients. At the end of the study, the cumulative incidence of migraine was estimated to be 8.4 % (71/848). The rate of

incidence was 6 per 1000 person-years for men, and 24 per 1000 person-years for women. The major limitation of the study was the narrow age group of the study population [11].

The Danish 12-year follow-up incidence study, which was conducted by Lyngberg in 2005, showed similar results with Breslau et al. The annual incidence rate was 8.1/1000 person-years, with a male-to-female ratio of 1:6. The study population was between 25 and 64 ages and incidence rates were higher in the 25–34 years group and decreased markedly by age in both genders afterward (25–34 years: 13.8/1000; 35–44 years: 7.0/1000; 45–54 years: 6.7/1000; 55–64 years: 2.6/1000). Young age, female gender, no vocational education, familial disposition, a high workload, and having frequent tension-type headaches were found to be risk factors for developing migraine. Forty percent of migraine patients described aura [12].

A follow-up study regarding the incidence of migraine was conducted in 2008 by Stewart et al. Cumulative lifetime migraine incidence in women and men was assessed. Data was obtained from the American Migraine Prevalence and Prevention study, in which a mailed survey was sent to 120,000 US households. Cumulative incidence of 43 % was found in women and 18 % in men by age 85. Median age of onset was 25 years among women and 24 years among men [13].

In a Turkish incidence study using ICHD-II criteria, which was conducted by Ertas et al., 2563 people who did not have migraine in the original Turkish Headache Epidemiology study [14] were reached by a headache specialist through a telephone interview after 5 years. This study has shown a yearly incidence of 2.38 % (females 2.98 %; males 1.93 %) (Ertas et al., poster presentation at the American Headache Association Meeting, San Diego, 2014).

2.2.2 Prevalence of Migraine

Prevalence studies in migraine are numerous. However, different results were found among studies because of variations in case definitions and demographic features of the study groups.

The range of migraine prevalence varies between 3 and 35 % in these studies. Results in European countries and North America show similarities. Most studies in the adult population give rates of 5–9 % for men and 12–25 % for women. Stovner and Andree published a review paper in 2010 as a part of the Eurolight projects, including all headache prevalence studies until 2009. The prevalence of migraine in adults was found to be 14.7 % (8 % in man and 17.6 % in woman) in more than 170,000 participants [15].

The first comprehensive migraine prevalence study in the United States was conducted by The American Migraine Study group in 1989 using a case definition based on the International Headache Society (IHS) criteria [4, 5]. Migraine prevalence was found to be 18 % for women and 6 % for men varying with age (highest in the 35–45 years range), household income (highest in lowest income), and race (highest in whites than in blacks) [16]. Ten years after the first study, The American Migraine Study II was conducted. The one-year prevalence of migraine was found

18.2 % among females and 6.5 % among males, which was similar to the reported results in the first study [4, 16]. The prevalence of migraine in the United States remained constant from the American Migraine Study I to the American Migraine Study II, which were conducted 10 years apart [4, 16]. However, according to the US Centers for Disease Control, the self-reported migraine prevalence in the United States increased by 60 %, from 25.8 per 1000 person-years to 41 per 1000 person-years between 1981 and 1989 [17].

The Turkish primary headache prevalence studies showed similar results with other reported studies. The migraine prevalence rates in 1998, 2008, and 2013, were 16.4 %, 16.4 %, and 16.7 %, respectively [14]. The frequency of migraine in females was almost three times higher than men.

In the Turkish Headache epidemiology 5-year follow-up study, 10.2 % of participants without a primary headache in 2008 were diagnosed as having definite migraine in 2013. Interestingly, 14.7 % of definite TTH, their diagnosis changed to definite migraine 5 years later (Ertas et al., in preparation).

In children within 36,000 participants, the migraine prevalence was 9.2 % (5.2 % for boys, 9.1 % for girls) [15]. Migraine prevalence in children ranges from 3.2 to 14.5 % in other studies. One of the main reasons of difference among studies is the use of various definitions of migraine in pediatric population. Of note, 60–77.5 % of children with migraine report family history, which shows higher frequency than adults and the debate is still going on to put family history in the criteria of pediatric migraine to better distinguish from TTH [18].

A large epidemiological study among 5562 children between ages 8 and 16 was conducted by Ozge et al. in Mersin, a Mediterranean city of Turkey. The migraine prevalence was found to be 10.4 % with a similar distribution in both genders (52.6 % were girls; 47.4 % were boys) and emphasized that "*severity of pain"* was the most sensitive headache characteristic for migraine [19]. Interestingly, when this population was restudied 6 years later, the prevalence of migraine increased to 18.6 % and episodic-TTH prevalence increased from 22.6 to 57.5 %, respectively [20].

2.2.3 Age, Gender, Genetics, and Environmental Factors in Migraine

Migraine prevalence rates vary by age and gender. Migraine prevalence is more common in boys than in girls before puberty and the prevalence ratio inverses in favor of girls following puberty. In women, prevalence increases throughout childhood and in early adult life until approximately age of 40, after which it declines [17]. Prevalence is highest between ages 25 and 55, and more specifically between ages 35 and 45, which corresponds to the peak productivity years of men and women. These findings emphasize the magnitude of the burden of migraine in economic productivity [21].

Although genetics in migraine is complex and multifactorial, prevalence studies showed significant increase among the first-degree relatives of migraine patients. Russell et al. reported a 1.9-fold increased risk in first-degree relatives and 1.5 in the

spouses of migraineurs without aura, which indicates the importance of both genetic and environmental factors in migraine without aura. In contrast to migraine without aura, the risk was 3.8 in first-degree relatives and no risk for spouses in migraine with aura, which highlights the major role of genetic factors in migraine with aura [22]. Twin studies also support the contribution of genetic factors on migraine [23, 24]. Migraine may also be a part of the clinical symptomatology of some genetic disorders, such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes), RVCL (retinal vasculopathy and cerebral leukodystrophy), COL4A1 (retinal arteriolar tortuosity and leukoencephalopathy), and FASPS (familial anticipated sleep phase syndrome).

In addition to the above genetic disorders with migraine features, autosomal dominant transmission of the ion transportation genes CACNA1A, ATP1A2, and SCN1A can cause the familial hemiplegic migraine (FHM). Overlap of idiopathic migraine and FHM more than a chance may support the common pathway among two disorders [25]. Consequently, after the evaluation of both family and twin studies, approximately 50 % of patients have a first-degree relative affected from migraine. However, whether in these genetic disorders, having a headache with migrainous features should be accepted as this headache being "migraine" and therefore related to a common migraine gene needs to be further evaluated!

Due to limited studies, the effect of race in headache is still controversial. American Migraine Study I-II and the AMPP, which are the largest population-based studies revealed similar migraine prevalence among Blacks and Whites and Baltimore County Study also did not show significant prevalence differences among races (Whites 29 %, Blacks 23.4 %) [4, 15, 26].

ARIC (Atherosclerosis Risk in Communities) study was mainly designed to estimate the lifetime course of atherosclerosis in the US population. However, at the third clinic examination, they intended to determine the lifetime prevalence of migraine and other headaches lasting than 4 h. When we compare the differences among races in this study, the age-adjusted prevalence of migraine without aura was highest in white women (4.5 %), followed by African American women (2.0 %), white man (1.1 %), and African American men (0.5 %). The rate of migraine without aura was also common in white women (9.0 %) than other groups (white men 2.7 %, African American women 2.2 %, African American men 0.5 %) [27].

In the National Health Interview Survey (NHIS), which was conducted by the National Center for Health Statistics, overall prevalence was estimated as 14.3 % in Whites, 14.0 % in Blacks, 9.2 % in Asians, 12.9 % in Hispanics, 11.9 % in Mexican Americans, and 17.7 % in Native Americans [28].

When we evaluate all studies regarding the migraine prevalence among races in the United States, all of the prevalence studies except ARIC showed similar ratios in both races.

Geographic diversity is another controversial issue regarding the headache epidemiology. The prevalence of migraine is higher in European and North American studies and slightly lower in Asia. In Asia, the estimated one-year prevalence of primary headache disorders was 9.1 % for migraine, 16.2 % for TTH, and 2.9 % for CDH [29].

In contrast to other continents reports, African studies show very low frequency, which may support the effect of environmental factors on migraine. In a review of 21 community-based studies, including 137,277 people, migraine prevalence was found to be 5.61 % in the general population [30]. A recent study that was conducted in Enugu, the southeast part of Nigeria the prevalence of migraine and TTH were 6.4 % and 13.8%, respectively [31]. Further well-designed studies must be carried out in Africa to reveal the prevalence and impact of headache.

2.2.4 Chronification of Migraine

Chronification of migraine is one the major issues that affects the quality of life and causes lower productivity in patients. Chronic migraine was not recognized as a distinct entity in ICHD-I and later as an emerging concept, it was subclassified as a complication of migraine in ICHD-II. Finally, in ICHD, 3rd edition (beta version) chronic migraine was added as a distinct disorder to reduce the underestimation of such a disabling disorder and to create awareness for new treatment strategies.

Chronic migraine, which is defined as at least 15 days (more than 4 h/day) of headache each month, including at least eight of these days, the headache having migrainous features in the ICHD 3rd edition (beta version). It was shown that 2.5–3.0 % of people with episodic migraine will transform to chronic migraine every year [32]. High frequency of headaches at baseline, medication overuse, obesity, sleep disorders, excessive caffeine intake, psychiatric comorbidities, female sex, lower socioeconomic status, comorbid pain disorders, history of head or neck injury, and presence of cutaneous allodynia are the risk factors for chronification [32]. However, in 2 years, 26 % of these patients with chronic migraine, also will remit back to episodic migraine [33].

According to 12 reported studies regarding chronic migraine, the overall prevalence of CM ranges from 0 to 5.1 % [34]. The major reason of various results among studies was the usage of different criteria for CM. The largest study, which was conducted by Buse et al. in the US population, the prevalence of CM was found to be 0.91 % (1.29 % of females and 0.48 % of males) and the prevalence increased throughout adolescence, peaked in midlife, and declined after age 50 in both genders. The proportion of CM among all migraine patients was 7.68 % in this study (7.45 % – among females with migraine; 8.47 % – among males with migraine [35].

In The Turkish primary headache prevalence study, the prevalence of chronic migraine was found to be 1.7 %. Three-fourths of CM patients reported medication overuse. CM was seen in 10.7 % of the migraineurs [14].

2.3 Tension-type Headache (TTH)

There are relatively few studies regarding the epidemiology of tension-type headache (TTH) in comparison with migraine. Most of the studies show different results probably due to methodological differences including case definition and demographic factors. The first study with episodic TTH prevalence using IHS criteria was conducted in Denmark. One thousand men and women aged 25–64 years were randomly drawn from the Danish National Central Person Registry and invited for a general health examination, and 740 people participated in the study. The lifetime prevalence of TTH was 69 % in men and 88 % in women. Prevalence of TTH in the previous year was 63 % in man and 86 % in woman. They also reported increased prevalence by age [8].

The second large-scale population study was carried out in the United States by collecting data through a telephone interview. The one-year prevalence rate was found to be 38.3 %, which is lower than the Danish study. The prevalence of episodic TTH peaked in fourth decade and decreased afterward [36].

Stovner et al. evaluated 107 publications consistent with headache epidemiology. In this study, the adult population with tension-type headache (TTH) was found to be 42 %. Headache in general is most prevalent in the youngest age group whereas TTH is most prevalent in adolescents. This is probably due to few studies of TTH among children. TTH appears to be much more common in Europe (80 %) than in Asia or the Americas (20–30 %). The headache-related disability of tension-type headache was larger than migraine because of higher prevalence [37].

According to published 19 reports, Stovner and Andree estimated that the prevalence of TTH was 62.6 % among >66,000 adults. In children and young adolescent group, the estimated prevalence was lower at 15.9 % among 25,000 children [15].

In contrast to other published reports, in Turkish study the rate of TTH was very low (14.5 %; with probable TTH being 9.5 % and definite TTH being 5 %). The significant difference in comparison to other studies may be explained by some probable methodological issues. In the Turkish study, a diagnosis of TTH was made only if participants were not diagnosed with “definite” or “probable” migraine and fulfilled all TTH criteria. This could have been caused by overlapping the groups of probable TTH and probable migraine. One other issue to be considered is that “true” TTH is likely to be less than all cases diagnosed with TTH, as most of them would turn out to be not primary, but having headaches secondary to somatization or other psychogenic causes, or due to head-neck postural changes. Such an approach would be more selective and detect lower rates of TTH [14]. This issue is discussed in more details elsewhere [38] (Table 2.1).

Table 2.1 The prevalence of headache, migraine, and TTH in some European countries

	References	Number of participants	Period	Age	Headache	Migraine	TTH
Eurolight Project (2014)	Steiner et al. [39]	8271 (9 countries)	1 year (unadjusted)	18–65	79.6 %	22.2 % (definite)	30.8 % (definite)
Turkey (2008)	Ertas et al. [14]	5323	1 year	18–65	44.6 %	16.4 %	14.5 %
Greece (1995)	Mitsikostas et al. [40]	3501	1 year	15–65	29 %	NA	NA
Germany (2009)	Pfaffenrath et al. [41]	7417	6 months	≥20	49.5 %	11.4 %	31.5 %
Austria (2003)	Lampl et al. [42]	997	1 year	≥15	49.4 %	10.2 %	NA
Denmark (2006)	Russell et al. [43]	28,195	1 year	12–41	NA	19.1 %	86 %
Spain (2010)	Matías-Guiu et al. [44]	5668	1 year	18–65	NA	12.6 %	NA
Russia (2012)	Ayzenberg et al. [45]	2025	1 year	18–65	62.9 %	20.8 %	30.8 %

2.4 Chronic Daily Headache (CDH)

The definition of chronic headache still remains controversial. There is no agreement on how many days per month the headache must be present, the obligatory time from initiation of headache and the type of headache. Although a lot of studies have been done, only two of them used the same criteria.

Global prevalence of CDH was found in 3 %. CDH is less prevalent among children and adolescents. It is more common in Central/South America (5 %) than Africa (1.7 %). Medication-overuse headache (MOH), a potentially treatable and preventable headache type, is common among those with CDH. Possible MOH was found to occur in about 1 % [15].

In the Turkish study, chronic daily headache was found to be 3.3 %, of which 1.8 % had a diagnosis of chronic migraine (0.4 % for those without medication overuse and 1.3 % for those with medication overuse) and 0.2 % for chronic TTH.

2.5 Trigeminal Autonomic Cephalalgias

Trigeminal autonomic cephalalgias consists of cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/short lasting neuralgiform headache attacks with cranial autonomic features (SUNA), and hemicrania continua (HC).

Because of the low frequency of TACs, there are few available data on epidemiology.

In the Vågå study, 1838 people between 18 and 65 years were studied; two were diagnosed as having SUNCT and in 18 individuals (11 females and 7 males), the symptoms were consistent with hemicrania continua. For paroxysmal hemicrania, the one-year prevalence rate was estimated to be 0.5 per 1000 [46].

Epidemiological studies with CH are more common than the other TACs. Vågå study is the most comprehensive study estimating the prevalence of CH [47].

The study was conducted in Norwegian rural community among 1838 participants by face-to-face interviews. Prevalence of CH was found to be 326 per 100,000 in the total population (106 per 100,000 for females, and 558 per 100,000 for males).

In an Italian study similar to the Norwegian study, the prevalence was found to be 279/100,000 among >10,000 patients [48]. D'Alessandro et al. found the prevalence of CH 69/100,000 in Republic of San Marino [49]. Rasmussen et al. and Monteiro et al. showed similar prevalences (100/100,000) [50, 51]. In Germany, the one-year prevalence of CH was estimated to be 119/100,000 [52]. Ekbom et al. reported the lifetime prevalence and concordance risk of cluster headache in the Swedish twin population in 2006. They found the prevalence as 1 per 500 of the general population [53].

However, when considering the clinical practice, the number of cluster patients seems to be lower than these prevalence studies (personal comment: Rigmor Jensen)

2.6 Impact of Headache

Global Burden of Disease (GBD) Study 2010 revealed that TTH and migraine are, respectively, the second and third most common prevalent diseases after dental caries and migraine is ranked as the seventh highest cause of disability in the world. The main disadvantage of GBD 2010 is the lack of data regarding the interictal impairment in migraine and medication overuse headache [54].

The societal impact of headache consists of direct and indirect costs. Direct costs correspond to the sum of diagnostic investigations and treatment costs. Indirect costs, which include loss of productivity due to absenteeism and reduced performance, are the major leading causes of cost when compared with direct costs of headache. The cost of migraine in Europe is estimated at € 27 billion annually. Although there are many epidemiological studies with the prevalence of headache, migraine, TTH, the data on impact of headache is rare. The most comprehensive study evaluating the impact of headache was conducted by Eurolight project. In this study, personal impact of headache was assessed by seven questions to show headache-attributed lost work, housework, and social days in preceding three months. Eurolight project emphasized that the common headache disorders have very high personal impact [55]. However, much more studies with applicable questionnaires have to be done to indicate the impact of headache, which will provide awareness among physicians.

References

1. Hennekens CH, Buring JE (1987) Epidemiology in medicine. Lippincott, Williams & Wilkins, Philadelphia
2. Andlin-Sobocki P, Jönsson B, Wittchen HU et al (2005) Cost of disorders of the brain in Europe. Eur J Neurol 12:1–27
3. Rothman KJ, Lash TL, Greenland S (2008) Modern epidemiology, 3rd edn. Lippincot Williams & Wilkins, Philadelphia, pp 33–48
4. Stewart WF, Lipton RB, Celentano DD et al (1992) Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA 267(1):64–69
5. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society (1988) Cephalalgia 8(Suppl 7):1–96
6. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders, 2nd edn. Cephalalgia 24(Suppl 1):1–150
7. Headache Classification Committee of the International Headache Society (IHS) (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808
8. Rasmussen BK, Jensen R, Schroll M et al (1991) Epidemiology of headache in a general population–a prevalence study. J Clin Epidemiol 44(11):1147–1157
9. Stovner LJ, Zwart JA, Hagen K et al (2006) Epidemiology of headache in Europe. Eur J Neurol 13(4):333–345
10. Stewart WF, Linet MS, Celentano DD et al (1991) Age- and sex-specific incidence rates of migraine with and without visual aura. Am J Epidemiol 134(10):1111–1120

11. Breslau N, Chilcoat HD, Andreski P (1996) Further evidence on the link between migraine and neuroticism. Neurology 47(3):663–667
12. Lyngberg AC, Rasmussen BK, Jorgensen T et al (2005) Incidence of primary headache: a Danish epidemiologic follow-up study. Am J Epidemiol 161(11):1066–1073
13. Stewart WF, Wood C, Reed ML et al (2008) Cumulative lifetime migraine incidence in women and men. Cephalalgia 28(11):1170–1178
14. Ertas M, Baykan B, Orhan EK et al (2012) One-year prevalence and the impact of migraine and tension-type headache in Turkey: a nationwide home-based study in adults. J Headache Pain 13(2):147–157
15. Stovner LJ, Andree C (2010) Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain 11(4):289–299
16. Lipton RB, Stewart WF, Diamond S et al (2001) Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 41(7):646–657
17. Scher AI, Stewart WF, Lipton RB (1999) Migraine and headache: a meta-analytic approach. In: Crombie IK (ed) Epidemiology of pain. IASP Press, Seattle, pp 159–170
18. Ozge A, Termine C, Antonaci F et al (2011) Overview of diagnosis and management of paediatric headache. Part I: diagnosis. J Headache Pain 12(1):13–23
19. Ozge A, Bugdayci R, Saşmaz T et al (2003) The sensitivity and specificity of the case definition criteria in diagnosis of headache: a school-based epidemiological study of 5562 children in Mersin. Cephalalgia 23(2):138–145
20. Ozge A, Sasmaz T, Cakmak SE et al (2010) Epidemiological-based childhood headache natural history study: after an interval of six years. Cephalalgia 30(6):703–712
21. Bigal ME, Lipton RB (2009) The epidemiology, burden, and comorbidities of migraine. Neurol Clin 27(2):321–334
22. Russell MB, Iselius L, Olesen J (1996) Migraine without aura and migraine with aura are inherited disorders. Cephalalgia 16(5):305–309
23. Ulrich V, Gervil M, Kyvik KO et al (1999) The inheritance of migraine with aura estimated by means of structural equation modelling. J Med Genet 36:225–227
24. Russell MB, Ulrich V, Gervil M et al (2002) Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. Headache 42:332–336
25. Persico AM, Verdecchia M, Pinzone V et al (2015) Migraine genetics: current findings and future lines of research. Neurogenetics 16(2):77–95
26. Stewart WF, Lipton RB, Liberman J (1996) Variation in migraine prevalence by race. Neurology 47:52–59
27. Perry Carson AL, Rose KM, Sanford CP et al (2004) Lifetime prevalence of migraine and other headaches lasting 4 or more hours: the Atherosclerosis Risk in Communities (ARIC) study. Headache 44:20–28
28. National Health Interview Survey website. http://www.cdc.gov/nchs/nhis.htm. Accessed 29 July 2014
29. Peng KP, Wang SJ (2014) Epidemiology of headache disorders in the Asia-pacific region. Headache 54(4):610–618
30. Woldeamanuel YW, Andreou AP, Cowan RP (2014) Prevalence of migraine headache and its weight on neurological burden in Africa: a 43-year systematic review and meta-analysis of community-based studies. J Neurol Sci 342(1–2):1–15
31. Ezeala-Adikaibe BA, Onyekonwu C, Okudo G et al (2014) Prevalence of primary headaches in an urban slum in Enugu South East Nigeria: a door-to-door survey. Headache 54(10):1601–1610
32. Bigal ME, Serrano D, Buse D et al (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–1168
33. Manack A, Buse DC, Serrano D et al (2011) Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. Neurology 76(8):711–718
34. Natoli JL, Manack A, Dean B et al (2010) Global prevalence of chronic migraine: a systematic review. Cephalalgia 30:599–609

35. Buse DC, Manack AN, Fanning KM et al (2012) Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache 52:1456–1470
36. Schwartz BS, Stewart WF, Simon D et al (1998) Epidemiology of tension-type headache. JAMA 279(5):381–383
37. Stovner LJ, Hagen K, Jensen R et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 27(3):193–210
38. Uygunoglu U, Siva A (2014) Headache attributed to somatization disorders: is it tension-type headache, is it "somatization headache," or both? In: Siva A, Lampl C (eds) Case-based diagnosis and management of headache disorders. Springer, Cham, pp 259–265
39. Steiner TJ, Stovner LJ, Katsarava Z et al (2014) The impact of headache in Europe: principal results of the Eurolight project. J Headache Pain 15:31
40. Mitsikostas DD, Tsaklakidou D, Athanasiadis N et al (1996) The prevalence of headache in Greece: correlations to latitude and climatological factors. Headache 36(3):168–173
41. Pfaffenrath V, Fendrich K, Vennemann M et al (2009) Regional variations in the prevalence of migraine and tension-type headache applying the new IHS criteria: the German DMKG Headache Study. Cephalalgia 29(1):48–57
42. Lampl C, Buzath A, Baumhackl U et al (2003) One-year prevalence of migraine in Austria: a nation-wide survey. Cephalalgia 23(4):280–286
43. Russell MB, Levi N, Saltyte-Benth J et al (2006) Tension type headache in adolescents and adults: a population based study of 33,764 twins. Eur J Epidemiol 21(2):153–160
44. Matías-Guiu J, Porta-Etessam J, Mateos V et al (2011) One-year prevalence of migraine in Spain: a nationwide population-based survey. Cephalalgia 31(4):463–470
45. Ayzenberg I, Katsarava Z, Sborowski A et al (2012) The prevalence of primary headache disorders in Russia: a countrywide survey. Cephalalgia 32(5):373–381
46. Sjaastad O, Bakketeig LS (2007) The rare, unilateral headaches. Vågå study of headache epidemiology. J Headache Pain 8(1):19–27
47. Sjaastad O, Bakketeig LS (2003) Cluster headache prevalence. Vågå study of headache epidemiology. Cephalalgia 23(7):528–533
48. Torelli P, Beghi E, Manzoni GC (2005) Cluster headache prevalence in the Italian general population. Neurology 64(3):469–474
49. D'Alessandro R, Gamerini G, Benassi G et al (1986) Cluster headache in the Republic of San Marino. Cephalalgia 6:159–162
50. Rasmussen BK (1994) Epidemiology of headache. Thesis, Köbenhavns Universitet, Copenhagen
51. Pereira Monteiro JM (1995) Cefaleias. Estudo epidemiologico e clinico de uma população urbana. Thesis, Porto
52. Katsarava Z, Obermann M, Yoon MS et al (2007) Prevalence of cluster headache in a population-based sample in Germany. Cephalalgia 27(9):1014–1019
53. Ekbom K, Svensson DA, Pedersen NL et al (2006) Lifetime prevalence and concordance risk of cluster headache in the Swedish twin population. Neurology 67(5):798–803
54. Vos T, Flaxman AD, Naghavi M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2163–2196
55. Stovner LJ, Andree C, Eurolight Steering Committee (2008) Impact of headache in Europe: a review for the Eurolight project. J Headache Pain 9(3):139–146

General Principles of Pharmacotherapy for Headache Disorders

3

Luana Lionetto, Andrea Negro, and Paolo Martelletti

The Headache Classification Subcommittee of the International Headache Society [1] recognizes three main primary headaches: migraine, tension-type headache (TTH), and the trigeminal autonomic cephalalgias (TACs). The huge public health importance of primary headache arises from their causal association with personal and societal burdens of pain, disability, damaged quality of life, and financial cost [2].

Cure is rarely a realistic aim in primary headache disorders and the expectations of people disabled by headache could not be achieved even with optimum management.

The purpose of pharmacotherapy of primary headache is mostly to control symptoms in order to minimize the impact of the disorder on each individual patient's life and lifestyle.

This requires an individual approach, and patients with two or more coexisting headache disorders are likely to require separate plans for each disorder.

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_3

3.1 Migraine

The management of migraine is divided into acute and/or symptomatic strategies (to relieve headache attack) and preventative strategies (to reduce frequency, duration, and intensity of the attacks).

The decision of the drug to use to stop a migraine attack should be in function of the severity of illness and match the patient's needs to the characteristics of the attack (severity, frequency, disability, symptoms, and time to peak).

Acute therapies are generally divided into two categories. The first category includes nonspecific treatments, such as paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), opioids and combinations of analgesics, alone or in combination with antiemetics. These are usually the first choice for the treatment of mild or moderate migraine attacks. The second category includes specific anti-migraine treatments, such as ergotamine and triptans, which are usually first-line drugs for the treatment of severe migraine attacks. It can happen that the resolution of symptoms and functions fully returning within 2 h is not attainable by everyone with the drugs currently available.

When the best acute therapy is inadequate to control the symptom, it can be supplemented with prophylactic medication. The aim is to reduce frequency, duration, or severity of attacks and conversely increase the effect of acute treatment.

The different pharmacological classes of prophylactic anti-migraine drugs are β -blockers, antiepileptic drugs, calcium channel antagonists, tricyclic antidepressants, and serotonin antagonists.

More recently, onabotulintoxinA (Botox®) [3] has been approved for the prevention of chronic migraine and it is the only treatment to have that indication so far.

3.2 Pharmacological Treatment

Several drugs are available for both acute/symptomatic and preventative pharmacological treatment of migraine. Experts defined four levels of recommendation on the basis of levels and scientific strength of the evidence and clinical effectiveness. Specifically, level of recommendation I refers to compounds whose efficacy is high and supported by statistically significant data (evidence of at least two controlled, randomized studies versus placebo or drugs of proven efficacy) or with high clinical benefit and no severe adverse effects for patients. Level of recommendation II includes drugs with lower efficacy compared to drugs of group I, with less clinical benefit for patients and without severe adverse effects. Drugs labeled with level of recommendation III show statistical but no clinical evidences of efficacy. These drugs are divided into two subgroups: (a) drugs with no severe adverse effects and (b) unsafe drugs with important pharmacological interactions. Level of recommendation IV includes effective drugs with frequent and severe adverse effects and drugs whose clinical patient benefit or efficacy has not been demonstrated (contrasting or unavailable data).

Concluding, this chapter will focus mostly on levels of recommendation I and II that include drugs with high levels of efficacy (from $p<0.0001$ to $p<0.05$), occasional and not severe adverse effects. Moreover, considering the clinical effectiveness of these drugs, more than 60 % of the patients referred partial or total relief from headache and more than 30 % were pain free.

3.3 Acute Treatment

Symptomatic treatment of migraine attacks is recommended when attacks are not severe or, if disabling, they occur for less than 4 days per month. Drugs for acute treatment of migraine include triptans, analgesics (NSAIDs), ergot derivatives, and antiemetics.

3.3.1 Triptans

Triptans are indicated for the treatment of moderate-severe attacks. Triptans are specific serotonin (5-HT) receptor agonists, selective for 5-HT1. In particular, sumatriptan binds to 5-HT1D receptors, zolmitriptan, rizatriptan, naratriptan, almotriptan; frovatriptan binds to 5-HT1B/1D; and eletriptan binds to 5-HT1B/1D/1 F receptors. Triptans are members of the tryptamine-based drugs family, derivatives of indole with substitutions at positions 3 and 5. The chemical structure of triptans is shown in Fig. 3.1.

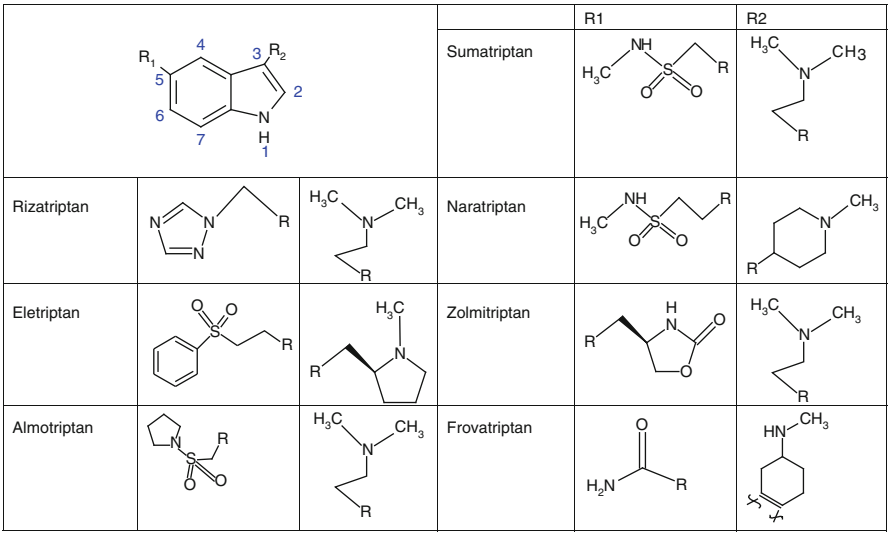

Fig. 3.1 Chemical structure of triptans

The indole structure of triptans is identical to the neurotransmitter 5-HT. Triptan structure contains side chain on the indole ring. The main structural difference of triptans is the presence of the sulfonamide with a different side chain attached to it at position 5 and the presence of a nitrogen-alkyl chain at position 3. Rizatriptan, zolmitriptan, and frovatriptan have, respectively, a 2-oxazolidone and an amide instead of a sulfonamide, a triazole. In the chemical structure of eletriptan, the nitrogen-alkyl chain connected to the indole ring is replaced with a dimethyl-pyrrolidine, and in naratriptan with a 1-methyl-piperidine ring. Triptans are characterized by three main mechanisms of action, all contributing to their anti-migraine effects. These effects include: (i) the peripheral inhibition of the vasoactive peptides release from trigeminal nociceptive afferents; (ii) the cranial vasoconstriction; and (iii) the inhibition of the second-order neurons transmission through the trigemino-cervical complex. There is also evidence that they may be acting in other brainstem nuclei and the thalamus [4–6].

Nowadays, triptans are considered the first-line option in the acute treatment of moderate–severe migraine attacks. Cardiovascular and cerebrovascular diseases represent the main contraindication for the prescription of triptans, although the clinical significance of triptan vasoconstriction is unclear and still being debated.

3.3.2 NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of molecules that have analgesic, antipyretic and, in higher doses, anti-inflammatory effects. Chemically, most NSAIDs are organic acids with low pKa values. This feature favors their accumulation at inflammation sites, considering that these areas often exhibit low pH values. Moreover, low pKa values are also related to short half-lives. Most NSAIDs can be classified into two groups based on their chemical structure: carboxylic acid and enolic acid derivatives (Table 3.1). Carboxylic acid subgroups include the salicylates, arylpropionic acids, anthranilic acids, and phenylacetic acids. The main subgroups of enolic acids are pyrazolones and oxicams. NSAIDs can be classified on chemical structure or mechanism of action. Newer molecules are frequently classified by mechanism of action.

The term NSAID is used for compounds that inhibit the metabolism of arachidonic acid (AA). NSAIDs inhibit the synthesis of prostaglandins and thromboxanes, modifying the activity of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which catalyzes the formation of prostaglandins responsible for pain and inflammation. Experts believe that the inhibition of COX-2 leads to the anti-inflammatory, analgesic, and antipyretic effects and that those NSAIDs, inhibiting also COX-1 and particularly aspirin, may cause gastrointestinal bleeding and ulcers [7]. Most of selective COX-2 inhibitors are diarylheterocycles. NSAIDs that inhibit prostaglandin E2 synthesis are effective in treating acute migraine attacks. Ibuprofen, paracetamol, acetylsalicylic acid, lysine acetylsalicylate, naproxen sodium, diclofenac sodium, and potassium and ketorolac have the highest efficacy in migraine treatment, whereas the evidence of efficacy for other NSAIDs is more limited.

Table 3.1 Classification of NSAIDs

Carboxylic acids	Arylpropionic acids		Flurbiprofen, ketoprofen, oxaproxin, ibuprofen, naproxen, fenoprofen
	Salicylic acids		Aspirin, difunisal, trisalicylate salsalate, sodium salicylate, olsalazine, sulfasalazine
	Anthranilic acids		Mefenamic acid, meclofenamic acid
	Acetic acids	Indole and indene acids	Etodolac, indomethacin, sulindac, tolmetin, ketorolac
		Phenylacetic	Diclofenac
Enolic acids	Pyrazolones		Phenylbutazone
	Oxicams		Piroxicam, meloxicam
Nonacidic compounds	Nabumetone		
COX-2 selective inhibitors (Coxibs)	Colecoxib, rofecoxib, meloxicam, nimesulide, paracoxib		Etodolac, lumiracoxib, valdecoxib, deracoxib, etoricoxib

Ibuprofen is a nonselective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway, but its exact mechanism of action is yet unknown. It is administered as a racemic mixture. The R-enantiomer goes through interconversion to the S-enantiomer in vivo. It is believed that the S-enantiomer is the more pharmacologically active enantiomer. Its pharmacological effects might be due to inhibition of cyclooxygenase-2 (COX-2), which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Side effects of ibuprofen, such as GI ulceration, are due to its inhibition of COX-1.

Paracetamol is an analgesic antipyretic derivative of acetanilide and it has weak anti-inflammatory properties. It is the drug of choice for adult patients when salicylates or other NSAIDs are contraindicated. The lack of significant anti-inflammatory activity of paracetamol implies a mode of action distinct from that of NSAIDs; yet, despite years of use and research, the mechanisms of action of paracetamol are not fully understood even if it is now being considered as a selective COX-2 inhibitor.

3.3.3 Ergot Derivatives

Ergotamine and dihydroergotamine activate 5-HT1B receptors located on intracranial blood vessels, leading to vasoconstriction correlated with the relief of migraine headache; they also act on the inhibition of pro-inflammatory neuropeptide release by activating 5-HT1D receptors on sensory nerve endings of the trigeminal system [8]. Ergot derivatives have a potential risk of abuse; therefore, their use should be restricted to low-frequency severe attacks unresponsive to other treatments. The ergot alkaloids were found in ergot fungi (*genus Claviceps*) and, in their chemical structure, they present the basic compound *ergoline*, the structural skeleton of several alkaloids (Fig. 3.2a).

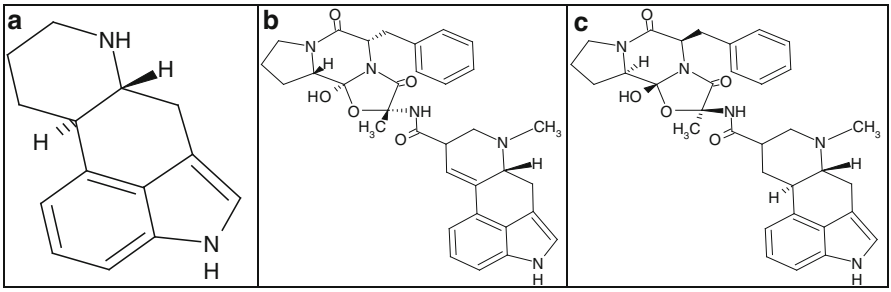

Fig. 3.2 Chemical structure of ergot alkaloids. (**a**) Ergoline; (**b**) ergotamine; (**c**) dihydroergotamine

In particular, ergotamine is an ergopeptine and dihydroergotamine is a 9,10 alpha-dihydro derivative of ergotamine (Fig 3.2b, c). They have a complex mechanism of action due to the interaction with several receptors. In fact, both ergotamine and dihydroergotamine demonstrate affinities for 5-hydroxytryptamine, dopamine, and noradrenaline receptors since they have a structure similar to these neurotransmitters.

3.3.4 Antiemetics

Antiemetics, including metoclopramide, prochlorperazine, and chlorpromazine, are effective treatment options for migraine independently from their ability to control nausea and vomiting. They are considered primary options for treating acute migraine in the emergency department setting. They are to be considered adjuvants in the treatment of migraine attacks, especially when nausea or vomiting is prominent: the efficacy of analgesics is reduced in many migraineurs because of impaired gastrointestinal motility, which is associated with nausea, and the nonabsorption of the drugs due to vomiting. For instance, NSAIDs are often combined with an antiemetic for migraine pain treatment to reduce associated nausea and vomiting [9]. It is also true that the dopamine antagonist properties of metoclopramide might make it effective as single treatment for acute migraine. Metoclopramide belongs to the salicylamides, carboxamide derivatives of salicylic acid. Other dopamine antagonists such as prochlorperazine and chlorpromazine have also shown effectiveness in migraine (Fig. 3.3). These polycyclic aromatic compounds belong to the chemical class of phenothiazine, which is a linear tricyclic system that consists of two benzene rings united by a para-thiazine ring.

Prochlorperazine and chlorpromazine are considered dopamine receptors antagonist (subtypes D1, D2, D3, and D4), even if their antiemetic effects are due to the antagonism on histaminergic receptors (H1).

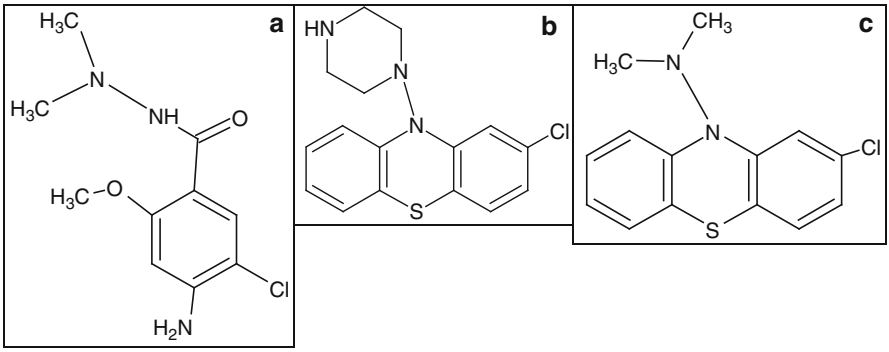

Fig. 3.3 Chemical structure of antiemetics. (**a**) Metoclopramide; (**b**) prochlorperazine; (**c**) chlorpromazine

3.4 Preventative Treatment

A preventative treatment is recommended when migraine attacks are disabling and last more than 4 days per month or, if less, in case of poor response to acute treatment. Preventative drugs include beta-blockers, calcium channel antagonists, antidepressants, antiepileptic drugs, dihydroergotamine, and botulinum toxin A.

3.4.1 β-Blockers

Beta-blockers such as propranolol, metoprolol, and nadolol are considered preventative treatment options for migraine. They are effective especially for patients with frequent migraines and periods of headache freedom. Moreover, β-blockers are considered first-line drugs in case of hypertension or tachycardia. The structural activity relationship (SAR) for β-blockers is shown in Fig. 3.4.

A common feature in the chemical structure of β-blockers is that there is at least one aromatic ring structure linked to a side alkyl chain with a secondary hydroxyl and amine functional group (β-ethanolamine). The aromatic ring must either be benzoheterocyclic (such as indol) or heterocyclic (such as thiadiazole), while the side chains can be different. The X part of the side chain can either be directly linked to the aromatic ring or linked through a -OCH_2- group. When X is -CH_2CH_2-, -CH=CH-, -SCH_2- or -NCH_2-, there is little or no activity. Each of the available beta-blockers has one or more chiral centers directly attached to a hydroxyl group.

There are different mechanisms of action of β-blockers in migraine prophylactic treatment, such as the blockade of beta-adrenergic receptors that results in the inhibition of arterial dilatation. They may also help to activate a central mechanism of action in the brain, which "turns off" the generators that cause migraine [10].

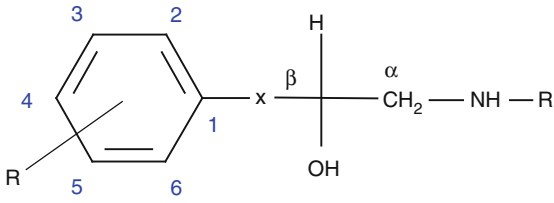

Fig. 3.4 Structural activity relationship for β-blockers

3.4.2 Antiepileptic Drugs

Several drugs used in the treatment of epilepsy have been found to be helpful also in the preventative treatment of migraine. Following the hypothesis that migraine and epilepsy have some pathogenic mechanisms, such as an abnormal activation of voltage-gated sodium channels, the administration of sodium-channel blockers was extended to the preventative treatment of migraine. In fact, one of the main mechanisms in the pathophysiology of migraine is the abnormal Na+-dependent discharge and, in particular, the persistent Na+conductance in the trigeminovascular system due to the neurogenic inflammation. However, apart from sodium valproate and topiramate, not all anticonvulsants have this dual role. Other helpful anticonvulsants are gabapentin and pregabalin, while lamotrigine, levetiracetam, and zonisamide may be tried but their use is not supported by clinical evidence.

The main mechanism of action of valproic acid (VPA, di-n-propylacetic acid) is the inhibition of voltage-sensitive sodium channels, leading to the suppression of repetitive neuronal firing. It also reduces the excitatory transmission through the increase of brain GABA levels, the main inhibitory neurotransmitter in the CNS [11]. Chemically, VPA is one of the simplest molecule in the therapeutic armamentarium also approved for the treatment of migraine prophylaxis and bipolar disorder.

Differently from valproic acid, the exact mechanism of action of topiramate is unknown; however, studies showed several topiramate sites of action. Topiramate blocks sodium and calcium channels. Additionally, it shows antagonism of the AMPA/kainate glutamate receptors and also increases GABA concentrations.

Lamotrigine and zonisamide seem to inhibit voltage-sensitive sodium channels leading to the inhibition of glutamate release and to the suppression of neuronal depolarization. This mechanism of action may contribute to the management of migraine since the release of glutamate is involved in the propagation of cortical spreading depression.

3.4.3 Calcium Channel Blockers

Calcium channel antagonists are particularly recommended for the treatment of migraineurs suffering from anxiety and insomnia. They may be also useful in patients with severe aura symptoms, including hemiplegic migraine [9]. Cinnarizine and flunarizine, respectively, classified as antihistamine and calcium channel

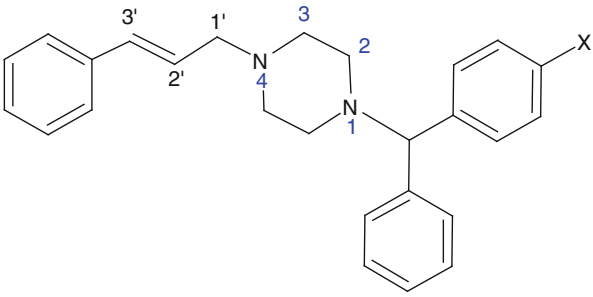

Fig. 3.5 Chemical structure of cinnarizine and flunarizine

blocker, are derivatives of piperazine. Drugs of different pharmacological actions have been developed by mono- or di-substitution of the two nitrogen atoms present on the piperazine structure. In particular, cinnarizine and flunarizine are di-substituted derivatives of piperazine, grouped under the class diphenylmethyl piperazines of piperazine.

Both nitrogen atoms in these molecules are aliphatic, displaying similar basicities. In order to reach maximum activity, the terminal N-atom should be a tertiary amine. The main differences among these compounds involve the para aromatic ring substituent (X = H or F) and the nature of the terminal nitrogen substituent (Fig. 3.5). Cinnarizine blocks L-type and T-type voltage-gated calcium channels thus inhibiting the contractions of vascular smooth muscle cells. It also binds to dopamine D2, histamine H1, and muscarinic acetylcholine receptors. Flunarizine physically plugs the channel, inhibiting the influx of extracellular calcium through myocardial and vascular membrane pores. Flunarizine may be particularly useful in patients with severe aura symptoms, including hemiplegic migraine.

3.4.4 Antidepressants

The use of tricyclic antidepressants has become a preventative migraine treatment option, since serotonin (5-HT) and norepinephrine (NE) are involved in migraine pathophysiology. Antidepressants such as amitriptyline, nortriptiline, or dosulepin are therefore commonly used for headaches and neuropathic pain, even if the doses used are generally much lower in migraine than in depression [12]. Amitriptyline is the prototypical tricyclic antidepressant with high efficacy in pain and migraine. It has mixed serotoninergic and noradrenergic reuptake inhibitor (SNRI) properties, which enhances the activity of diffuse noxious inhibitory control. Their chemical structure contains three rings of atoms; in particular, there are two phenyl rings in a 6-7-6 ring system. The central ring, formed by 7 or 8 atoms shaping an angled or twisted conformation, is responsible for the tricyclic drugs activity. The amine group may be either tertiary or secondary. The tertiary amines seem to inhibit the reuptake of serotonin, while the secondary amines the norepinephrine one. However, the potency and selectivity for the inhibition of the uptake of norepinephrine, serotonin, and dopamine vary greatly among the molecules. Nevertheless, although the

entire class is considered useful in prophylaxis, tertiary amines such as amitriptyline are more effective than the secondary amines, such as nortriptyline. These agents are effective in the preventative treatment of migraines, and patients' response is typically more rapid (within 4 weeks) than with β-blockers.

3.4.5 Onabotulintoxin A

Botulinum toxin is a protein and neurotoxin produced by the bacterium *Clostridium botulinum*. Botulinumtoxin-type A (BT-A) injection therapy was approved in 2010 by the Federal Drug Administration for the preventative treatment of chronic migraine (CM). The pharmacological profile of BT-A makes it a valid option for CM patients. Its long duration of action (3 months on average) and the high tolerability profile makes it a privileged alternative for patients who have showed low tolerance or poor compliance with oral preventative drugs. BT-A preventative treatment significantly decreases costs related to acute headache medication use, suggesting BT-A as a cost-reasonable option for medication offsets alone, especially in chronic headache patients with a acute medication overuse [13]. The still open issue on this therapy is if and when it should be discontinued.

Conclusions

This short overview has been conceived as an introductive practical guide to the various pharmacological classes actually used in the treatment of headaches. Details on dosage and side effects are widely reported in other dedicated chapters. The knowledge of medical pharmacology is essential for the clinician who faces this painful pathology every day.

The basics regarding chemical structures and consequently the mechanism of action of the examined drugs must not be considered other than clinical practice, particularly in the management of migraine since most of the drugs used were developed for different disorders. The selective and targeted use of a drug belonging to a wide class must be selected starting from its chemical structure, which primarily determines its efficacy and the presence of side effects.

Moreover, the evident comorbidities with migraine impose the co-administration of different drug classes and therefore the necessity of a thorough knowledge of the possible pharmacological and metabolic interactions.

A headache expert must also be a fine pharmacologist.

Acknowledgments The authors wish to thank Dr. Matilde Capi for her contribution in the figures and Dr. Valerio De Angelis for his help in the revision of the proofs.

References

1. Headache Classification Subcommittee of the International Headache Society (2013) The International Classification of Headache Disorders: 3rd edition (beta version). Cephalalgia 33(9):629–808

2. Martelletti P, Birbeck GL, Katsarava Z, Jensen RH, Stovner LJ, Steiner TJ (2013) The Global Burden of Disease survey 2010, Lifting The Burden and thinking outside-the-box on headache disorders. J Headache Pain 14(1):13
3. Martelletti P (2011) Dispute settlement understanding on the use of Botox in chronic migraine. J Headache Pain 12(1):1–2
4. Lionetto L, Casolla B, Mastropietri F et al (2012) Pharmacokinetic evaluation of zolmitriptan for the treatment of migraines. Expert Opin Drug Metab Toxicol 8:1043–1050
5. Bartsch T, Knight YE, Goadsby PJ (2004) Activation of 5-HT(1B/1D) receptor in the periaqueductal gray inhibits nociception. Ann Neurol 56:371–381
6. Shields KG, Goadsby PJ (2006) Serotonin receptors modulate trigeminovascular responses in ventroposteromedial nucleus of thalamus: a migraine target? Neurobiol Dis 23:491–501
7. Silberstein SD, Stirpe JC (2014) COX inhibitors for the treatment of migraine. Expert Opin Pharmacother 15(13):1863–1874
8. Tfelt-Hansen P, Saxena PR, Dahlöf C, Pascual J, Láinez M, Henry P, Diener H, Schoenen J, Ferrari MD, Goadsby PJ (2000) Ergotamine in the acute treatment of migraine: a review and european consensus. Brain 123:9–18
9. Sarchielli P, Granella F, Prudenzano MP, Pini LA, Guidetti V, Bono G, Pinessi L, Alessandri M, Antonaci F, Fanciullacci M, Ferrari A, Guazzelli M, Nappi G, Sances G, Sandrini G, Savi L, Tassorelli C, Zanchin G (2012) Italian guidelines for primary headaches: 2012 revised version. J Headache Pain 13(Suppl 2):S31–S70
10. Shamliyan TA, Choi JY, Ramakrishnan R, Miller JB, Wang SY, Taylor FR, Kane RL (2013) Preventive pharmacologic treatments for episodic migraine in adults. J Gen Intern Med 28(9):1225–1237
11. Mulleners WM, McCrory DC, Linde M (2015) Antiepileptics in migraine prophylaxis: an updated Cochrane review. Cephalalgia 35(1):51–62
12. Mercier A, Auger-Aubin I, Lebeau JP, Schuers M, Boulet P, Hermil JL, Van Royen P, Peremans L (2013) Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. BMC Fam Pract 14:55
13. Lionetto L, Negro A, Palmisani S, Gentile G, Del Fiore MR, Mercieri M, Simmaco M, Smith T, Al-Kaisy A, Arcioni R, Martelletti P (2012) Emerging treatment for chronic migraine and refractory chronic migraine. Expert Opin Emerg Drugs 17(3):393–406

Placebo and Nocebo Effects

4

Dimos D. Mitsikostas and Christina I. Deligianni

4.1 Introduction

Since millennia, once man realized himself as a social being, medicine is based in placebo. In old times, magicians or chaplains used to treat people by using the positive expectation and the will to heal. Even today, medicine would be almost inefficient or very poor after extracting placebo. Although will power alone is not enough to overcome the disease, it is indispensable. Having no volition there is no improvement or cure. On the contrary, negative expectations limit or even destroy treatment's improvement, not only by increasing the magnitude of adverse events (AEs), but also by decreasing the impact of improving itself. Data from randomized placebo-controlled studies (RCTs) allow to measure both placebo and nocebo effects precisely. But the impact in clinical practice remains uncertain and individualized. The physician's role is essential to increase placebo and limit nocebo in order to maximize the effect of treatment. Although much has been said for placebo in headache management, as in all medical situations, little is known for nocebo, the real negative factor that has to be battled in real life. In this chapter, the size of placebo and nocebo in RCTs for primary headache disorders will be summarized after a short overview of potential pathogenetic mechanisms for each phenomenon.

4.2 Placebos

In the article "Lessons from placebo effects in migraine treatment," Antonaci and colleagues [1] report that the word "placebo," which literally means "I shall please," derives from the Latin *Placebo domino in regione vivorum* ("I shall please the Lord

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_4

in the land of the living"). It was first used in the fourteenth century in reference to hired professional mourners at funerals and thus had associations with the ideas of depreciation and substitution [2]. Around the same time, Chaucer in *The Canterbury Tales* (The Merchant's Tale) depicts a wicked, parasitic, and sycophantic character, whom he calls Placebo [3]. Much later, placebo came to mean a substance that can be given to humor or gratify a patient rather than to exert a genuine pharmacological effect. The first recorded medical dictionary definition of placebo refers to "a commonplace method or medicine," commonplace meaning common and pedestrian. Indeed, in Motherby's 1795 dictionary, placebo was defined as "a commonplace method or medicine calculated to amuse for a time, rather than for any other purpose" [4]. This definition was maintained until 1937, when *Taber's Digest of Medical Terms* [5] defined placebo as an "inactive substance" and a "substitute for medicine given to deceive the patient." This introduction is placed as it is in their article [1], without changing the syntax, because the authors describe the origin of the term in the best way it could be found.

4.2.1 Mechanisms of Placebo

Placebo effects illustrate the power of the human brain [6]. Placebo in pain conditions has great importance. All mechanisms involved were classified into psychological and biological, but all fall into brain's activity. Simply expecting an improvement can alter pain processing and produce analgesia. There is evidence that placebo analgesia and hyperhedonia associated with pain relief are mediated by activation of shared emotion appraisal neurocircuitry, which regulates early sensory processing, depending on whether the expectation is reduced pain or increased pleasure. Placebo responses are associated with similar patterns of activation increase in circuitry involved in emotion appraisal, including the pregenual anterior cingulate, medial orbitofrontal cortex, amygdala, accumbens, and midbrain structures [6]. Both opioid and non-opioid systems are involved. Opioid antagonists such as naloxone [7] and cholecystokinin [8] attenuate placebo responses, while dopamine improves [9]. From the psychological point of view, a multitude of mechanisms contribute to placebo effects. These include expectations, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, past experiences and social observation, and meaning. While there is a growing amount of research into these mechanisms, two principal mechanisms are well supported: expectancy and conditioning [10].

4.2.2 Placebo in RCTs for Primary Headache Disorders

Because placebo is widely variable and high enough, International Headache Society guidelines for randomized controlled studies in primary headache disorders recommend the use of placebo, although there are effective treatments. Placebo varies not only among studies, but seems to be related to the primary headache disorder and to the nature of treatment (acute vs. chronic, route of drug administration,

pharmaceutical vs. nonpharmaceutical, etc.). Interventional treatments show higher placebo effect, like acupuncture, surgery, or botulin toxin type A. Children and adolescents have greater placebo rates than adults.

4.2.2.1 Placebo in Migraine Trials

In clinical trials for acute migraine treatments, placebo response ranges from 6 to 47 % generally. The mean placebo effect for RCTs used analgesics was estimated at 30 %, but variability was large (7–50 %). The primary outcome was the headache response defined as a proportion of attacks that decreased in pain severity from moderate–severe to mild or no headache within 2 h post treatment. When the primary outcome was pain free 2 h post treatment, the mean placebo was only 9 %, and the variability much lower (7–17 %), suggesting that this outcome measure is more vigorous [11]. In another meta-analysis, mean placebo response in RCTs for symptomatic treatment that used triptans was estimated at 28.5 ± 8.7 % (range 15–50 %) when the primary outcome was headache response, and 6.1 ± 4.4 % (range 5–17 %) when the primary outcome was pain free 2 h post treatment [12], mirroring the results of the previous review [11]. Placebo response in children and adolescents with migraine varied from 37 to 53 % of patients treated with placebo analgesics/non-steroidal anti-inflammatory drugs (NSAIDs), and from 28 to 65 % of those treated with placebo triptans [13], partly explaining why most trials investigating the efficacy of triptans in children and adolescents showed limited efficacy of the drug investigated.

In phase II RCTs using novel symptomatic antimigraine drugs (anti-CGRP, anti-HT1F, anti-AMPA compounds), placebo effect for pain free 2 h post treatment varies from 4.0 to 16.0 % [14–18] as in RCTs for analgesics and triptans. For symptomatic treatment of migraine using transcranial magnetic stimulation (TMS) however, placebo (sham stimulation) was much higher up to 67 % of treated patients (55 out of 82), when the outcome was no or mild pain 2 h post stimulation vs. 72 % patients in the treatment group (72 out of 82, $P = 0.498$ only) [19].

In a meta-analysis for migraine prophylaxis, the mean placebo effect for responders (those who report at least 50 % reduction in headache days after treatment) estimated at 23.5 ± 8 % (95 % CI 18.3–28.8 %) vs. 45.5 ± 15.5 % (95 % CI 37.4–53.6 %) in the active groups. A reduction in migraine attacks of 16.8 ± 12.7 % (95 % CI 10.9–22.6 %) was observed in the placebo groups and 41.8 ± 11.7 % (95 % CI 36.9–46.6 %) in the active groups. The authors of the meta-analysis concluded that only if the percentage of responders in an open-label prophylactic trial in migraine is above 35–40 %, or if a reduction in migraine attack frequency is found of 40 % or more, further studies are needed to determine the prophylactic activity of the drug [20]. Since these meta-analysis studies for topiramate and botulin toxin A have been published showing that placebo falls within the same limits (16 % for topiramate [21]) with the exception of botulin toxin A that showed significantly increased placebo effect up to 35 % vs. 23.5 ± 8 % (95 % CI 18.3–28.8 %) in oral treatments [20, 22]. Interestingly, therapeutic techniques with limited documentation such as acupuncture and surgery show increased placebo effect compared to oral pharmaceutical interventions. In a recent meta-analysis of 102 eligible trials, sham acupuncture (proportion of responders,

38 % [95 % CI 30–47 %]) and sham surgery (58 % [37–77 %]) were associated with a more pronounced reduction of migraine frequency than oral pharmacological placebos (22 % [17–28 %]) and were the only significant predictors of response in placebo groups in multivariable analyses ($P=0.005$ and $P=0.001$, respectively). Network meta-analysis confirmed that more patients reported response in sham acupuncture groups than in oral pharmacological placebo groups (odds ratio, 1.88 [95 % CI 1.30–2.72]) [23]. Thus, the overall placebo effect in RCTs for migraine prevention varies from 22 to 23 % [20, 23]. In trials with botulin toxin, acupuncture, and surgery, the placebo effect is significantly increased, almost double. Clinicians who treat patients with migraine should be aware, therefore, that a relevant part of the overall effect they observe in practice might be due to nonspecific effects and that the size of such effects might differ between treatment modalities [23].

In phase II RCTs for migraine prevention using with monoclonal anti-CGRP antibodies, placebo effect varied from 33 to 45 % (responders rate) [24, 25], while trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med., Herstal, Belgium) in migraine prevention showed only a 12.1 % efficacy in sham group vs. 38.1 % in the active group (50 % responders rate) [26]. Placebo effect was similar in another controlled study using an implanted device for stimulation of the occipital nerve (responders defined as patients that achieved a ≥50 % reduction in mean daily visual analog scale scores): 13.5 % in the sham group vs. 17.1 % in the active group (difference not significant) [27].

In conclusion, for symptomatic treatment of migraine, placebo effect defined as pain free 2 h post treatment varies from 6 to 9 % in oral treatments (one out of 13 treated patients approximately). In children, this effect seems to be much higher, as in trials with neurostimulation (one out of three, approximately). In preventive oral treatments, placebo effect defined as ≥50 % reduction in headache days per month varies from 20 to 25 % (one out of five treated). Treatments with botulin toxin A, acupuncture, and surgery show higher placebo effects (up to 60 % for surgery), as in novel anti-CGRP monoclonal antibodies treatments. Neurostimulation for the prevention of migraine shares the same size of placebo effect in oral treatments in the published studies so far.

4.2.2.2 Placebo in Tension-Type Headache and Cluster Headache

Placebo effect (defined as pain free 2 h post treatment) in symptomatic treatment of tension-type headache (TTH) seems to be higher than in trials for migraine (12–51 %) [28]. In RCTs for prevention of TTH the placebo effect for the proportion of responders (defined as ≥ 50 % reduction in headache days per month) varies from 15.4 % to 28 % [29, 30]. In a meta-analysis for preventive treatment of TTH with acupuncture, placebo effect (sham acupuncture) was estimated at 41 % however [31].

In acute symptomatic treatment of cluster headache with triptans, placebo effect varies from 3 to 17 % (pain free 15 min post treatment) [32]. Treatment with oxygen was effective (same criterion) in 20 % of patients treated with air [33]. Interestingly, in one study for prevention of cluster headache with verapamil, placebo effect was zero (no headache attacks) vs. 80 % in the treatment group [34]; 54.5 % of patients

Table 4.1 Placebos in primary headache disorders

Condition	Placebo	Placebo in children
1. Migraine		
1.1 Symptomatic treatment[a]		
Analgesics	9 % (7–17)	37–53 %
Triptans	6.1 ± 84.4 % (5–17)	28–65 %
TMS	67 %	
1.2. Prophylactic treatment[b]		
All drugs	23.5 ± 8 % (95 % CI 18.3–28.8)	NA
Botulin toxin A	35 %	NA
Acupuncture	38 % (95 % CI 30–47)	NA
Surgery	58 % (37–77)	NA
Anti-CGRP antibodies	33–45 %	NA
Neurostimulation[c]	12.1–13.5 %	NA
2. Tension-type headache		
2.1 Symptomatic treatment[a]		
All drugs	12–51 %	NA
2.2 Prophylactic treatment[b]		
Venlafaxine and mirtazapine	15.4–28 %	NA
Acupuncture	41 %	NA
3. Cluster headache		
3.1 Symptomatic treatment[d]		
Triptans	3–17 %	NA
Oxygen	20 %	NA
3.3 Prophylactic treatment[e]		
Steroid suboccipital injections	54.5 %	NA

[a]Primary outcome pain free 2 h post treatment
[b]Primary outcome ≥50 % reduction in days with headache per month
[c]Supraorbital transcutaneous stimulator and stimulation of the occipital nerve
[d]Primary outcome pain free 15 min post treatment
[e]Primary outcome reduction in daily attacks to <2 per day
TMS transcranial magnetic stimulation

treated with suboccipital injections with normal saline responded to treatment (reduction in daily attacks to <2 per day) vs. 95.2 % in patients treated with suboccipital injections of steroids [35].

In conclusion, there are limited data for both TTH and cluster headache compared to migraine. In symptomatic treatment of TTH, placebo seems to be higher than in migraine (one out of four approximately). In cluster headache, the pattern looks similar to migraine (one out 10) on the other hand. In chronic prophylactic treatment of TTH, placebo is similar to migraine trials, whereas in cluster headache there are not enough data to draw a conclusion. As in migraine, interventional treatments tend to much increase placebo in both TTH and cluster headache prevention (Table 4.1).

4.3 Nocebos

Nocebo refers to adverse events (AEs) related to patient's negative expectations that medical treatment will likely harm instead of heal [36]. Other relevant mechanisms contain prior conditioning and suggestions. Nocebo submits more to the intervention than to the outcome and includes expected AEs or, less frequently, nonspecific effects that cannot be substantiated referring to pharmacological action of the treatment [36, 37]. The term nocebo ("I shall harm") was introduced in contraposition to the term placebo ("I shall please"), by Kennedy in the early 1960s to distinguish the noxious from the pleasing effects of placebo [1, 38]. Nocebo is related to lower adherence in therapy as well as with high rates of dropouts and significant difficulty in assessing the efficacy and the safety profile of a drug in clinical trials [39, 40]. It has been suggested that dopaminergic, cyclooxygenase/prostaglandins and opioid brain pathways reward circuitries, and decision-making processes play a crucial role in the mechanisms that underlie nocebo [40–43]. Reports from clinicians indicate that the nocebo effects are very prevalent, but the exact magnitude remains elusive [44]. Information disclosure for potential side effects can itself contribute to producing AEs, or detailed and extensive information by physicians can also trigger nocebo AEs. Nocebo adversely influences quality of life and therapy adherence, emphasizing the need for minimizing these responses to the extent possible. Definitively, the content and the way information are presented to patients in clinical trials in both the placebo and active treatment conditions influence nocebo. Evidence further indicates that the informed consent process in clinical trials may also induce nocebo [45]. Like placebo, nocebo shares key functions in pain conditions. Two recent systemic meta-analyses searched for nocebo in trials for prevention of migraine and tension-type headache and revealed that 1 out of 20 patients treated with placebo withdraw treatment due to adverse effects. Additionally, adverse events in placebo groups mirrored the adverse events expected of the active medication studied, confirming that pretrial suggestions induce the adverse events in placebo-treated patients. Therefore, nocebo reduces the study population by 10 % and limits the treatment outcomes in randomized controlled trials for primary headaches. The potential implications of this substantial nocebo effect for both trial designing and clinical practice are discussed below [46].

4.3.1 Nocebo in Migraine RCTs

Reuter and colleagues [47] first investigated nocebo in randomized placebo-controlled trials (RCTs) and found that up to one third of migraineurs treated with placebo experience AEs. In trials for symptomatic migraine treatment that tested the therapeutic efficacy of triptans, 21.9 % of control patients reported at least one AE although treated with placebo. Symptoms were grouped into three categories: migraine-related (symptoms such as nausea, photophobia, and phonophobia), drug-related (symptoms typical of the experimental compound such as chest pressure in response to triptans), and nonspecific or coincidental (symptoms such as sleep

disturbance). Thus, symptoms in the placebo group were related to the drug under study and to the symptomatology of migraine, whereas some others had no obvious relation to the condition or treatment [47]. In another review aimed at estimating the placebo response in migraineurs treated with oral triptans, it was found that 23.40–14.05 % of participants treated with placebo reported AEs. Fascinatingly, studies performed in North America showed a higher nocebo frequency than those conducted in Europe [12]. Amanzion and colleagues [37] published an extensive systematic review of nocebo in clinical trials for migraine. This was the first attempt to intensely investigate migraine-related nocebo effects. They investigated the AEs after placebo in RCTs testing NSAIDs, triptans, or anticonvulsants. Their major finding was that nocebo AEs mirrored the AEs expected of the active medication studied precisely. For example, anorexia and memory difficulties, which are typical AEs of anticonvulsants, were present only in the placebo arm of these trials. In other words, nocebo in migraine trials arose from patients' distrust [37]. However, this important meta-analysis aimed to investigate mechanisms of nocebo in particular, rather than to investigate the magnitude of nocebo in RCTs for migraine. Migraine most likely was used as a vehicle pain condition in this study. For instance, the investigators searched RCTs for migraine trials, both symptomatic and preventive, only if specific anti-migraine agents were tested. Undoubtedly, the results of this meta-analysis confirmed their findings derived from experimental human studies that expectations modulate both nocebo and placebo (the expectation theory of placebo and nocebo) [37].

In another more recent meta-analysis of RCTs for all primary headache disorders, 56 RCTs published in the last decade were analyzed to estimate the frequency of patients treated with placebo who experience any AE (nocebo AE ratio) or discontinued treatment due to AE (nocebo dropout ratio) [36]. In this meta-analysis, all RCTs using any compound, either for acute or for chronic treatment, were included. The aim was to estimate the magnitude of nocebo in headaches in the most clinically relevant manner for both the clinicians and trial designers. In symptomatic treatments (STs) nocebo dropout ratio was limited (0.33 %), but in chronic preventive treatments was increased up to 5 %, showing that 1 out of 20 patients treated for migraine prophylaxis discontinues treatment due to nocebo AEs. Practitioners should be aware of this fundamental nocebo effect, trial designers as well [48].

Stratified analyses in migraine studies revealed that (1) nocebo AEs and nocebo dropout ratios were higher in preventive trials than in symptomatic trials ($P<0.001$); (2) nocebo AE ratio varied by year of publication in trials for ST of migraine, decreasing from 22.05 % (95 % CI 16.46–28.21 %) for trials published within 1998–2004 to 14.39 % (95 % CI 10.81–18.39 %) for trials published within 2005–2009 ($P<0.001$); (3) nocebo did not change with route of drug administration; (4) no differences were found between studies performed in North America compared with Europe; (5) dropout ratio was lower in the placebo group than in the active drug group (mean difference, 7.09 %; 95 % CI 4.1–10.1 %; $P<0.0001$); (6) nocebo rates did not vary with the drug tested, with headache type, or by continent, with one exception. In studies with botulin toxin type A, the dropout ratio was significantly lower than in any other preventive drug (0.92 % vs. 4.75 %); and (7) dropout rates

Table 4.2 Nocebos in primary headache disorders

Condition	Nocebo AE ratio	Nocebo AE dropout ratio
1. Symptomatic treatment		
Migraine	18.4 % (15–22.2)	0.3 % (0.2–0.5)
Cluster headache	18.7 % (1.6–28.3)	NA
2. Prophylactic treatment		
Migraine	42.8 % (34.7–51.4)	4.7 % (3.3–6.5)
Tension-type headache	24 % (4.6–52.2)	5.4 % (1.3–12.1)

Nocebo AE ratio: percentage of patients experienced any adverse event in the placebo-treated group; nocebo AE dropout ratio: percentage of patients discontinued treatment in placebo group because of severe adverse event

were strongly associated in both treatment groups ($r = 0.824$; $P < 0.0001$) [36]. These correlations indicate that the safer a drug is, the less nocebo is induced. These correlations indicate that the safer a drug is, the less nocebo is induced and the less potential AEs the concept form describes in RCTs, the less nocebo is caused. This principal finding is in line with other meta-analyses and with the expectation theory of placebo and nocebo [36, 37].

Another key finding concerns the low nocebo dropout ratio in trials for symptomatic migraine treatment. Even the nocebo AE ratio was limited in STs, compared with nocebo AE ratio in preventive antimigraine treatments, implying that the duration of a pharmaceutical treatment may be essential for nocebo. What makes botulin toxin A to have lower dropout nocebo ratio compared to other anti-migraine treatments remains unclear. The route and the frequency of drug administration, or even a positive expectation related to this particular treatment, may account for this variation. It seems that the frequency and the study protocol for the drug administration may be more important for this variation (every 3 months injections in the head and neck). Notably, placebo responder rate was increased (35.1 % vs. 47.1 %) [22]. Conversely, as noted above, the pooled analysis revealed a positive relation between nocebo and placebo rates [36]. Thus, a high positive expectation for the treatment outcome may also explain the low nocebo dropout rate in botulin toxin type A trials (Table 4.2).

4.3.2 Nocebo in Tension-Type Headache and Cluster Headache

Like chronic migraine, chronic TTH results in a variety of negative repercussions both on individuals and on society at large [49]. There is no more than one meta-analysis available for nocebo in trials for TTH [36]. Unfortunately, only four RCTs for prophylactic TTH treatments fulfilling the search criteria were found for pooled data analysis. Nocebo AE (24 %, 95 % CI 4.6–52.2 %) and nocebo dropout rates (5.44 %, 95 % CI 1.3–12.1 %) were similar to those estimated in RCTs for migraine prophylaxis, but the limited number of RCTs included in this analysis did not allow extensive meta-regression analyses to reveal specific TTH-related nocebo manipulating cofactors [36]. Unlike TTH and migraine, cluster headache is a rare primary

headache disorder affecting more men than women [50]. Only data from two RCTs were analyzed [36]. Like in migraine, the pooled estimate for nocebo AE ratio in RCTs for ST of cluster headache was 18.6 % (95 % CI 1.6–28.3 %). But no good data to estimate the nocebo dropout rate in these RCTs were found [36]. In summary, both TTH and cluster headache share similar size nocebo with migraine in prophylactic treatments (one out of five treated patients) (Table 4.2).

4.4 Clinical Implications

4.4.1 Placebo

Because the placebo effect is part of the overall treatment effect, placebos – even powerful placebos – should not replace treatments [51]. Patients will benefit if physicians exploit relatively powerful placebos either alone or as part of a therapeutic regime. A clear case where placebos might be used for clinical benefit is pain, where placebo effects are almost similar in magnitude to treatment effects [51, 52]. But this is not the case for headache. All available treatments showed significant higher effect compared to placebo, although placebo size was large enough. Along these lines, presented numbers needed to treat, a common outcome measurement in meta-analyses, does not represent the actual power of treatments because the placebo effect is extracted. Apparently, this measurement helps to make cross trial comparisons. But in daily practice both the physician and the patient may modify the treatment power individually. All patients share a motivation to overcome the disease. When the physician understands and manages the patients' needs and expectations he may improve the disease outcome by triggering this motivation. The skill to touch and amplify the positive patients' expectations varies substantially among physicians. Eventually, the ancient magician's spirit to stimulate, motivate, and convince patients is needed to be added into the scientific education in order to better control a medical condition. And because pain perception varies considerably by individuals, this skill becomes more important in the case of headache. In this context, comorbidity with somatoform and mood disorders [53] is also important in headache management. Non-pharmaceutical treatments and alternative treatments show higher placebo effects, together with botulin toxin A. Neurostimulation and treatments with monoclonal antibodies may follow this pattern, but more studies are needed to draw clear conclusions in this matter. Children and adolescents tend to express higher placebo effects as well, indicating that physician may control them easier than adults, as expected (Table 4.1).

4.4.2 Nocebo

Clinicians should be aware that drug intolerance and treatment failure might be caused by nocebo. In clinical practice, nocebo may be more prevalent than in RCTs.

Patients who are reluctant to receive novel medical treatments due to anxiety or general mistrust might avoid participating in clinical trials completely. For this reason, a nocebo effect, whereby patients experience AEs seemingly unrelated to the pharmacologic activity of the medication, may be common. Both migraine and TTH share the same risk for nocebo that includes drug-related AEs mainly, not general or unexpected ones. Thus, the proper delivery of drug safety information to patients is crucial and clinicians should use tailored strategies to prevent patients' negative expectations and increase positive ones for the suggested treatment. Comorbidity with anxiety and depressive disorders typically increases nocebo. Previous repetitive treatment failures or discontinuation due to AEs is a strong predictive finding for nocebo behaviors, as well as experience with alternative medicine techniques and treatments. Altered awareness in these cases is needed. Because nocebo is associated with the safety profile of the active drug, one should expect more nocebo AEs when administrating drugs with poor safety profiles. Reading the drug brochures or Internet information on drug safety without proper reassurance from the physician may increase nocebo. Discussing the likely risk for nocebo and explaining the phenomenon to the patient may help. In addition, face-to-face follow-up may help to minimize patients' fears and maximize their understanding of the pharmacotherapy benefits [36, 37, 46]. Patients with nocebo behaviors may use as first choice alternative treatments and only if these interventions fail, they ask for medical management. To pre-scan patients for potential nocebo behaviors, a specific 4-item self-fulfilled questionnaire (Q-No) was developed [54] in order to help physicians to prevent the phenomenon. Q-No score $\geq$15 predicts nocebo with 71.7 % specificity, 67.5 % sensitivity, and 42.5 % positive predictive value and may serve as a useful tool to predict nocebo in outpatients seeking neurological consultation [54].

Although nocebo has been recognized as an important cofactor for patients' compliance and treatment adherence, little progress has been made in translating this knowledge into improvement of clinical outcomes. Evidence from recent meta-analyses on RCTs for migraine and TTH prevention revealed that almost 1 out of 20 patients treated with placebo stop treatment due to AEs. The frequencies of AEs were similar in both active drug and placebo treated patients. Additionally, the AEs in placebo groups mirrored the AEs of the active drugs, indicating that nocebo is mainly powered by verbal pretrial negative suggestions. These fundamental nocebo effects share significant implications for both clinical science and practice. Trial designers should be aware that nocebo may decrease the study population by up to 10 % in RCTs for prophylaxis of migraine or TTH and should develop techniques to limit it. In this context, modification of informed concepts may be needed together with individualized strategies targeting patients' compliance. Future clinical research is warranted to establish predictive factors for nocebo. In real life, nocebo may be more prevalent than in RCTs. Thus, in the field of clinical practice, physicians treating headache sufferers should also acknowledge nocebo as a significant cofactor for treatment adherence and failure and plan techniques to border nocebo, such as patients' education and close follow-up. Positive suggestions and continuous support increase patient's compliance and decrease the nocebo response [46].

References

1. Antonaci F, Chimento P, Diener H-C, Sances G, Bono G (2007) Lessons from placebo effects in migraine treatment. J Headache Pain 8:63–6
2. Shapiro AK (1964) A historic and heuristic definition of the placebo. Psychiatry 27:52–8
3. de Craen AJM (1999) Placebos and placebo effects in medicine: historical overview. J R Soc Med 92:511–5
4. Motherby G (1795) A new medical dictionary or general repository of physics, 4th edn. J. Johnson, London
5. Taber CW (1937) Taber's digest of medical terms. F.A. Davis, Philadelphia
6. Ellingsen D-M, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H, Leknes S (2013) Placebo improves pleasure and pain through opposite modulation of sensory processing. Proc Natl Acad Sci U S A 110(44):17993–8
7. Colloca L, Benedetti F (2005) Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci 6:545–52
8. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubeita JK (2005) Neurobiological mechanisms of the placebo effect. J Neurosci 25:10390–402
9. Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L (2004) Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. Nat Neurosci 7(6):587–8
10. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F (2010) Placebo effects: biological, clinical and ethical advances. Lancet 375(9715):686–95
11. Bendtsen L, Mattsson P, Zwart JA, Lipton RB (2003) Placebo response in clinical randomized trials of analgesics in migraine. Cephalalgia 23:487–90
12. Loder E, Goldstein R, Biondi D (2005) Placebo effects in oral triptan trials: the scientific and ethical rationale for continued use of placebo controls. Cephalalgia 25:124–31
13. Lewis DW, Winner P, Wasiewski W (2005) The placebo responder rate in children and adolescents. Headache 45:232–9
14. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ (2014) BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 34(2):114–25
15. Diener HC, Barbanti P, Dahlöf C, Reuter U, Habeck J, Podhorna J (2011) BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia 31(5):573–84
16. Färkkilä M, Diener HC, Géraud G, Láinez M, Schoenen J, Harner N, Pilgrim A, Reuter U, COL MIG-202 study group (2012) Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. Lancet Neurol 11(5):405–13
17. Goldstein DJ, Roon KI, Offen WW, Ramadan NM, Phebus LA, Johnson KW, Schaus JM, Ferrari MD (2001) Selective seratonin 1F (5-HT(1F)) receptor agonist LY334370 for acute migraine: a randomised controlled trial. Lancet 358(9289):1230–4
18. Gomez-Mancilla B, Brand R, Jürgens TP, Göbel H, Sommer C, Straube A, Evers S, Sommer M, Campos V, Kalkman HO, Hariry S, Pezous N, Johns D, Diener HC, BGG492 Study Group (2014) Randomized, multicenter trial to assess the efficacy, safety and tolerability of a single dose of a novel AMPA receptor antagonist BGG492 for the treatment of acute migraine attacks. Cephalalgia 34(2):103–13
19. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Fischell RE, Ruppel PL, Goadsby PJ (2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomized, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 9(4):373–80
20. van der Kuy P-HM, Lohman JJHM (2002) A quantification of the placebo response in migraine prophylaxis. Cephalalgia 22:265–70
21. Linde M, Mulleners WM, Chronicle EP, McCrory DC (2013) Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev (6):CD010610

22. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF, PREEMPT Chronic Migraine Study Group (2010) Onabotulinumtoxin A for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50(6):921–36
23. Meissner K, Fässler M, Rücker G, Kleijnen J, Hróbjartsson A, Schneider A, Antes G, Linde K (2013) Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern Med 173(21):1941–51
24. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J, ALD403 study investigators (2014) Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 13(11):1100–7
25. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS (2014) Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 13(9):885–92
26. Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, Magis D (2013) Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 80(8):697–704
27. Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, Reed K, Narouze S, Mogilner A, Goldstein J, Trentman T, Vaisman J, Ordia J, Weber P, Deer T, Levy R, Diaz RL, Washburn SN, Mekhail N (2012) Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia 32(16):1165–79
28. Moore RA, Derry S, Wiffen PJ, Straube S, Bendtsen L (2014) Evidence for efficacy of acute treatment of episodic tension-type headache: Methodological critique of randomised trials for oral treatments. Pain 155(11):2220–8
29. Zissis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, Karageorgiou K (2007) A randomized, double-blind, placebo-controlled study of venlafaxine XR in outpatients with tension-type headache. Cephalalgia 27(4):315–24
30. Bendtsen L, Jensen R (2004) Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. Neurology 62(10):1706–11
31. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR (2009) Acupuncture for tension-type headache. Cochrane Database Syst Rev (1):CD007587
32. Law S, Derry S, Moore RA (2013) Triptans for acute cluster headache. Cochrane Database Syst Rev (7):CD008042
33. Cohen AS, Burns B, Goadsby PJ (2009) High-flow oxygen for treatment of cluster headache: a randomized trial. JAMA 302(22):2451–7
34. Leone M, D'Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A, Bussone G (2000) Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology 54(6):1382–5
35. Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C, Ducros A (2011) Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 10(10):891–7
36. Mitsikostas DD, Mantonakis LI, Chalarakis NG (2011) Nocebo is the enemy, not placebo. A meta-analysis of reported side effects after placebo treatment in headaches. Cephalalgia 31:550–61
37. Amanzion M, Corazzini LL, Vase L, Benedetti F (2009) A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain 146:261–9
38. Kennedy WP (1961) The nocebo reaction. Med World 95:203–5
39. Barsky AJ, Saintfort R, Barsky AJ, Saintfort R, Rogers MP, Borus JF (2002) Nonspecific medication side effects and the nocebo phenomenon. JAMA 287:622–7
40. Enck P, Benedetti F, Schedlowski M (2008) New insights into the placebo and nocebo responces. Neuron 59:195–206

41. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2008) Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry 65:220–31
42. Benedetti F, Lanotte M, Lopiano L, Colloca L (2007) When words are painful: unraveling the mechanisms of the nocebo effect. Neuroscience 147(2):260–71
43. Benedetti F, Durando J, Vighetti S (2014) Nocebo and placebo modulation of hypobaric hypoxia headache involves the cyclooxygenase-prostaglandins pathway. Pain 155(5):921–8
44. Evans WR (2003) Headaches and the nocebo effect. Headache 43:1111–5
45. Colloca L, Miller FG (2011) The nocebo effect and its relevance for clinical practice. Psychosom Med 73(7):598–603
46. Mitsikostas DD (2012) Nocebo in headaches: implications for clinical practice and trial design. Curr Neurol Neurosci Rep 12(2):132–7
47. Reuter U, Sanchez del Rio M, Carpay JA et al (2003) GSK headache masters program: placebo adverse events in headache trials: headache as an adverse event of placebo. Cephalalgia 23:496–503
48. Amanzio M (2011) Do we need a new procedure for the assessment of adverse events in anti-migraine clinical trials? Recent Pat CNS Drug Discov 6:41–7
49. Manzoni GC, Torelli P (2010) Epidemiological classification and social impact of chronic headache. Intern Emerg Med 5(Suppl 1):S1–5
50. Stovner LJ, Andree C (2010) Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain 11:289–99
51. Howick J, Friedemann C, Tsakok M, Watson R, Tsakok T, Thomas J, Perera R, Fleming S, Heneghan C (2013) Are treatments more effective than placebos? A systematic review and meta-analysis. PLoS One 8(5), e62599
52. Benedetti F (2014) Placebo effects: from the neurobiological paradigm to translational implications. Neuron 84(3):623–37
53. Deligianni CI, Vikelis M, Mitsikostas DD (2012) Depression in headaches: chronification. Curr Opin Neurol 25(3):277–83
54. Mitsikostas DD, Deligianni CI (2014) Q-No: a questionnaire to predict nocebo in outpatients seeking neurological consultation. Neurol Sci 2015;36(3):379–81

Review of Existing Guidelines

5

Stefan Evers

5.1 Introduction

This chapter reviews the guidelines for the pharmacological treatment of headache disorders. It focuses on Europe and on those guidelines available at present for the public community and created according to evidence-based medicine. There are several so-called guidelines published by single persons or scientific societies, which are not part of the International Headache Society; these will not be considered.

Since it would be a major opus to compare all single treatment recommendations for all headache disorders in these dozens of published guidelines, this chapter will mainly discuss the structure of and the systematic differences between these guidelines.

Although the topic of this book includes only pharmacological treatment of headaches, many guidelines also consider non-pharmacological treatment such as different types of psychotherapy, physiotherapy, and interventional treatment.

5.2 Historical Remarks

Guidelines on headache treatment have been published since antiquity. Systematic treatment recommendations for headaches have been given by Aretaios of Cappadocia (80/81 to 130/138) and by Galen (129/131 to 199/215) in particular. For the Islamic world, Avicenna (980 to 1037) published treatment guidelines on headache, which were later introduced in the European medical writings.

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_5

In the neurological textbooks (the first by Jason Pratensis (1486–1558), De cerebri morbis) until the nineteenth century, the treatment of headache was described but no systematic recommendations were given. Even in the famous textbooks on headache such as "On megrim, sick-headache and some allied disorders" (1873) by Edward Liveing or "Wolff's headache" (1948) by Harold G. Wolff, no systematic treatment descriptions are mentioned.

The first modern, officially published treatment guideline for headache was probably the guideline by the Italian Headache Society SISC in 1993 based on a wide revision of the existing literature and a consensus conference of Italian headache experts [14]. The method of this guideline was not what we call nowadays evidence-based medicine, but it was already the same principle: reviewing the literature and finding an expert consensus. This first guideline on adults was followed in 1996 by a guideline on children and adolescents published by the same society [18]. After this, several European countries and finally the European Federation of Neurological Societies (EFNS) published different guidelines, which are available until now. All modern guidelines use the International Classification of Headache Disorders (3rd edition) for their recommendations, and only guidelines with this background should be considered in daily practice.

5.3 Systematic Remarks

Guidelines on headache treatment can be classified with respect to several different levels. First, we differentiate between so-called cross-sectional guidelines and diagnosis-related guidelines. Cross-sectional guidelines do not focus on a specific headache diagnosis but on a specific patient group or situation. Among these, we can find guidelines on headache treatment in different age groups (e.g., children and elderly people), guidelines on specific situations (e.g., pregnancy, lactation, headache as emergency; even headache in sports had been addressed), guidelines on specific legal situation (e.g., expert testimony in cases with headache). It is also of particular interest to know who is addressed by the guideline. The details of recommendation might differ with respect to the addressed healthcare workers, there are guidelines addressing general practitioners, addressing emergency physicians, addressing neurologists, addressing headache experts, and addressing nonphysicians such as nurses or chirotherapists.

Another level of differentiation is the source of guideline. Most of the guidelines have been written by a collective of authors appointed by the national scientific headache society. But there are also guidelines created by other scientific societies such as the society for general medicine (General Practitioner guidelines) and others created by legal institutions or health authorities. The latter ones can be in concurrence to scientific society guidelines. As an example, the British Association for the Study of Headache (BASH) published a guideline on the treatment of migraine; in parallel, there is a guideline by the National Institute for Health and Care Excellence (NICE) on headache in adults, including migraine. This refers also to the applicability and relevance of the guidelines. In some countries, such as in Germany and Switzerland, the national guidelines are only recommendations for

the physicians (and related professions) but are not regular documents of the authorities. Therefore, physicians do not have to stick to these guidelines, and reimbursement of treatment does not necessarily depend on these guidelines. In other countries such as Belgium or the United Kingdom, physicians are not independent in their decision to treat headache but have to stick to the guidelines developed by the authorities. In particular, reimbursement of treatment costs by the national health system is restricted to those procedures listed in such guidelines.

Further, the regional level can be different for guidelines. Normally, guidelines are published by a national scientific society dealing with headache. Most countries have their own national headache society; in some countries, this is part of the national neurological society. The only exception in Europe is the United Kingdom where we have the BASH guideline and the NICE guideline for England (see above) and separately the guideline on headache by the Scottish Intercollegiate Guidelines Network (SIGN). There are some examples for supranational, but not European guidelines; the German-speaking countries have created common guidelines in the same language for all three countries (Austria, Germany, and Switzerland), with some final specific remarks only valid for the health system of one of these countries.

On the European level, the EFNS started its guideline program with the European Handbook of Neurological Management in 2006. This also included guidelines on the treatment of migraine and of cluster headache. Since then, more new and revisions of older guidelines in the field of headache have been published by the EFNS. The International Headache Society (IHS) as the global scientific society for headache has explicitly waived the idea to publish treatment guidelines for headache disorders, although this was a controversial debate. This decision was based on the fact that, particularly in headache treatment, the national health systems have a major impact on the medical pathways and that these systems are very different all over the world. So, international treatment guidelines might cause more problems than solving problems in countries with no national guidelines. A specific role is played by the Cochrane library, which does not publish treatment guidelines as such but which publishes recommendations for different treatment procedures in the field of headache, which can be used for treatment guidelines. These Cochrane recommendations are purely evidence-based and do not consider national health system restrictions.

Furthermore, the grade of evidence is also different between some guidelines. We have different systems of evaluating the evidence in the scientific literature, and according to these different methods, we have different grading systems for the level of evidence. The system introduced by the EFNS is the most often used one, but it is not applicable to all systems.

5.4 Comparison of Guidelines

In Table 5.1, all available treatment guidelines for headache disorders published by the responsible national scientific societies are presented; the EFNS guidelines are also included.

Table 5.1 Guidelines on headache treatment published by the national scientific headache societies and the EFNS in the Internet or in scientific journals

Austria	See also Germany
Belgium	Guideline for migraine treatment in primary care (Internet)
	Guideline for the management of chronic migraine [22]
Croatia	Evidence-based guidelines for treatment of primary headaches [27]
Denmark	Guideline for diagnosis and treatment of headache disorders and facial pain [3]
Finland	Guideline on migraine treatment – Migreenin käypä hoito (internet)
France	Revised French guidelines for the diagnosis and management of migraine in adults and children [16]
	Chronic migraine and chronic daily headache [17]
Germany	Treatment of headache in pregnancy and lactation [4]
	Treatment of migraine [7]
	Treatment of headaches in children and adolescents [8]
	Self-medication in migraine and tension-type headache [12]
	Treatment of chronic headache including tension-type headache [26]
	Treatment of rare idiopathic headache disorders [6]
	Treatment of cluster headache [19]
	Treatment of trigeminal neuralgia [23]
Italy	Italian guidelines for primary headaches: 2012 revised version [24]
Hungary	Guideline on headache treatment (Internet)
Netherlands	Diagnostic and therapeutic guideline on chronic headache without neurological abnormalities (internet)
Portugal	Therapeutic recommendations for headache [21]
Spain	Manual book on diagnosis and treatment of headache [13]
Switzerland	Therapeutic recommendations for primary headaches 2014 (Internet)
	See also Germany
UK	Guidelines for All Healthcare Professionals in the Diagnosis and Management of Headache Disorders (Internet)
	Headache in sports [15]
EFNS	Treatment of migraine [9]
	Treatment of cluster headache [20]
	Treatment of tension-type headache [2]
	Treatment of trigeminal neuralgia [5]
	Treatment of rare idiopathic headache disorders [10]
	Treatment of medication-overuse headache [11]

In general, the recommendations in all guidelines are very similar both for acute and for prophylactic drug treatment. All guidelines recommend the use of NSAIDs and of triptans in acute migraine treatment. Ergotamine derivatives are not drugs of first choice any more in the guidelines after the year 2010. For the prophylactic drug treatment, beta-blockers and anticonvulsant drugs (valproic acid and topiramate) are first choice in all guidelines. There is a considerable difference in some countries with respect to antidepressants in migraine prophylactic treatment. This has

also been noticed in previous comparisons of migraine guidelines [1], and this is also a major difference to the US American guideline on migraine prevention [25].

Systematic comparisons for the treatment of other headache disorders cannot be made since in many countries only migraine guidelines exist. For tension-type headache and for cluster headache, the available evidence on drug treatment is poor and only very few trials exist. Therefore, evidence-based treatment guidelines are difficult to create. For other primary headache disorders, only one guideline could be identified [6]; the available evidence for drug treatment in this group is even poorer. There are no guidelines on the treatment of secondary headaches and only a few on the treatment of trigeminal neuralgia and facial pain.

With respect to cross-sectional guidelines, only children and adolescents have been addressed in more than one guideline. Often, all age groups were included in one guideline but discussed separately in different chapters. Since specific trials on different patient groups in headache treatment are rare, good evidence is hard to obtain for cross-sectional guidelines.

According to a previous analysis of guidelines [1], guidelines are developed to assist the physician in making appropriate choices in the treatment of headache patients. To ensure their optimal use, guidelines need to be kept up to date; they should encompass the most recent published evidence and therapeutic strategies. Because guidelines are needed to set recognizable and acceptable standards of good practice, their adoption in primary care should be encouraged. This has, however, not been the case in most guidelines published in Europe.

5.5 Critical Remarks

After a boom in the years between 2000 and 2010, many guidelines have not been updated and almost no new guidelines have been published. It might be that there was a period with enthusiasm on evidence-based medicine, which has now gone down. However, it is important to update guidelines regularly. The quality of guidelines even depends on a regular update, which should be dated in the prior guideline. Another problem might be that human and financial resources are more limited nowadays to create a guideline. This is even more a problem since the requirements to write an accepted guideline have increased.

Another problem is that in most countries, only guidelines on the treatment of migraine exist. Guidelines on other primary headaches can be found only infrequently and guidelines on secondary headaches do not exist (with the exception of medication-overuse headache). The basic principles of migraine treatment are well known and presented in several neurological textbooks. However, the treatment of rare idiopathic headache disorders is a major problem even for neurologists and some guidance would be of benefit. In tension-type headache, several recommendations which are not evidence-based exist in the literature and it would be important for GP and even neurologists to be informed about which recommendation is evidence-based and which is not. With respect to secondary headaches, treatment recommendations are often restricted to the treatment of the underlying disorder.

This is, however, not always appropriate. It should be considered that some secondary headaches are primarily seen by headache specialists such as headaches associated with changes in intracranial pressure. For these headache disorders, evidence-based treatment guidelines are warranted.

The question arises whether it would be sufficient to have only one European headache guideline for the different headache disorders rather than several national guidelines that are nearly identical. There is of course a major benefit for the headache community if only one guideline exists, which is updated regularly and supervised by the most accepted headache experts. On the other hand, such a guideline could not consider the impacts of the national health systems on treatment decisions. The availability of drugs, the reimbursement of pharmacological treatment, the procedures of outpatient and inpatient vary considerably between the different European countries. In addition, there are also cultural aspects that should be integrated in treatment guidelines (e.g., willingness of a population to take drugs for pain or to give children drugs for pain). A solution could be that a guideline manual is created, which encompasses several drug profiles and the evidence of these drugs for specific headache disorders, and which is complemented by specific national recommendations.

Finally, a problem is that only a few European guidelines are published internationally. Internet publications of guidelines are mainly written in the native language and can therefore not be discussed in the scientific community and cannot be understood by others who are in the process of writing guidelines. Guidelines published in scientific journals should be written both in the native language to attract as many physicians as possible and in English to allow a scientific debate on these guidelines.

References

1. Antonaci F, Dumitrache C, De Cillis I, Allena M (2010) A review of current European treatment guidelines for migraine. J Headache Pain 11:13–19
2. Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J, EFNS (2010) EFNS guideline on the treatment of tension-type headache – report of an EFNS task force. Eur J Neurol 17:1318–1325
3. Bendtsen L, Birk S, Kasch H, Aegidius K, Sørensen PS, Thomsen LL, Poulsen L, Rasmussen MJ, Kruuse C, Jensen R, Danish Headache Society (2012) Reference programme: diagnosis and treatment of headache disorders and facial pain. Danish Headache Society, 2nd Edition, 2012. J Headache Pain 13(Suppl 1):S1–S29
4. Bingel U, Evers S, Reister FA, Ebinger F, Paulus W (2009) Behandlung der Migräne und idiopathischer Kopfschmerzsyndrome in Schwangerschaft und Stillzeit. Nervenheilkunde 28:896–906
5. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM, American Academy of Neurology Society, European Federation of Neurological Society (2008) AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 15:1013–1028
6. Evers S, Frese A, May A, Sixt G, Straube A (2005) Therapie seltener idiopathischer Kopfschmerzerkrankungen. Nervenheilkunde 24:217–226

7. Evers S, May A, Fritsche G, Kropp P, Lampl C, Limmroth V, Malzacher V, Sandor P, Straube A, Diener HC (2008) Akuttherapie und Prophylaxe der Migräne. Nervenheilkunde 27:933–949
8. Evers S, Kropp P, Pothmann R, Heinen F, Ebinger F (2008) Therapie idiopathischer Kopfschmerzen im Kindes- und Jugendalter. Nervenheilkunde 27:1127–1137
9. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS, European Federation of Neurological Societies (2009) EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. Eur J Neurol 16:968–981
10. Evers S, Goadsby P, Jensen R, May A, Pascual J, Sixt G, EFNS task force (2011) Treatment of miscellaneous idiopathic headache disorders (Group 4 of the IHS classification) – report of an EFNS task force. Eur J Neurol 18:803–812
11. Evers S, Jensen R, European Federation of Neurological Societies (2011) Treatment of medication overuse headache – guideline of the EFNS headache panel. Eur J Neurol 18:1115–1121
12. Haag G, Diener HC, May A, Meyer C, Morck H, Straube A, Wessely P, Evers S, DMKG, DGN, OKSG, SKG (2011) Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG). J Headache Pain 12:201–217
13. Insa SD (ed) (2011) Guia official de la sociedad Espanola de neurologia para el diagnostic y tratamiento de las cefaleas. Thomson Reuters, New york
14. Italian Society for the Study of Headache (SISC) (1993) Guidelines and recommendations for the treatment of migraine. Funct Neurol 8:441–446
15. Kernick DP, Goadsby PJ, Royal College of General Practitioners, British Association for the Study of Headache (2011) Guidance for the management of headache in sport on behalf of The Royal College of General Practitioners and The British Association for the Study of Headache. Cephalalgia 31:106–111
16. Lanteri-Minet M, Valade D, Geraud G, Lucas C, Donnet A (2014) Revised French guidelines for the diagnosis and management of migraine in adults and children. J Headache Pain 15:2
17. Lantéri-Minet M, Demarquay G, Alchaar H, Bonnin J, Cornet P, Douay X, Dousset V, Géraud G, Guillouf V, Navez M, Radat F, Radenne S, Revol A, Valade D, Donnet A (2014) Démarche diagnostique générale devant une céphalée chronique quotidienne (CCQ) – Prise en charge d'une CCQ chez le migraineux : céphalée par abus médicamenteux et migraine chronique/ Recommandations de la SFEMC, ANLLF et SFETD. Rev Neurol 170:162–176
18. Lanzi G, Balottin U, Zambrino CA, Cernibori A, Del Bene E, Gallai V, Guidetti V, Sorge F (1996) Guidelines and recommendations for the treatment of migraine in paediatric and adolescent patients. Italian Society for the Study of Headache. Funct Neurol 11:269–275
19. May A, Evers S, Straube A, Pfaffenrath V, Diener HC (2004) Therapie und Prophylaxe von Clusterkopfschmerzen und anderen trigemino-autonomen Kopfschmerzen. Nervenheilkunde 23:478–490
20. May A, Leone M, Afra J, Linde M, Sándor PS, Evers S, Goadsby PJ, EFNS Task Force (2006) EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 13:1066–1077
21. Monteiro JM, Fontes Ribeiro CA, dos Santos Luzeiro IM, de Araujo Sousa Fernandes Machado MG, Ferreira Lopes Esperansa PM (2009) Recomendacoes terapeuticas para cefaleias. Sinapse 9(Suppl 1):1–36
22. Paemeleire K, Louis P, Magis D, Vandenheede M, Versijpt J, Vandersmissen B, Schoenen J (2014) Diagnosis, pathophysiology and management of chronic migraine: a proposal of the Belgian Headache Society. Acta Neurol Belg. doi:10.1007/s13760-014-0313-z
23. Paulus W, Evers S, May A, Steude U, Wolowski A, Pfaffenrath V (2002) Therapie und Prophylaxe von Gesichtsneuralgien und andere Formen der Gesichtsschmerzen. Nervenheilkunde 21:255–268
24. Sarchielli P, Granella F, Prudenzano MP, Pini LA, Guidetti V, Bono G, Pinessi L, Alessandri M, Antonaci F, Fanciullacci M, Ferrari A, Guazzelli M, Nappi G, Sances G, Sandrini G, Savi

L, Tassorelli C, Zanchin G (2012) Italian guidelines for primary headaches: 2012 revised version. J Headache Pain 13(Suppl 2):S31–S70
25. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E, Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society (2012) Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 78:1337–1345
26. Straube A, May A, Kropp P, Katsarava Z, Haag G, Lampl C, Sándor PS, Diener HC, Evers S (2007) Therapie primärer chronischer Kopfschmerzen: Chronische Migräne, chronischer Kopfschmerz vom Spannungstyp und andere chronische tägliche Kopfschmerzen. Nervenheilkunde 26:186–199
27. Vuković Cvetković V, Kes VB, Serić V, Solter VV, Demarin V, Janculjak D, Petravić D, Lakusić DM, Hajnsek S, Lusić I, Bielen I, Basić S, Sporis D, Soldo SB, Antoncić I, Croatian Society for Neurovascular Disorders, Croatian Medical Association (2012) Evidence based guidelines for treatment of primary headaches – 2012 update. Acta Clin Croat 51:323–378

Treatment of Acute Migraine Attacks

6

Lars Edvinsson

6.1 Introduction

Headache conditions are among the ten most costly diseases in Europe and one in every three subjects in the Western World has seen a physician at some point in their lives due to a headache [1]. In general practice in the EU, more than 10 % of patients have migraine and more than 5 % suffer from a chronic, often incapacitating, headache. In the USA prevalence of migraine headaches is high, affecting roughly 1 out of every 6 adult Americans annually [2]. Due to the high occurrence, the overall socioeconomic cost derived from headaches is substantial and cause 20 % of the overall sickness absence recorded in the total EU workforce [3]. The quality of life of patients who suffer from headaches is also considerably reduced. Consumption of medication has an increasing trend, and the introduction of novel specific migraine medications and novel prophylactic pharmaceuticals contributes to a considerable need to establish systematic and updated treatment strategy in the EU. There is an overwhelming majority of subjects who suffer from headaches regularly. At present they are being treated in primary health care and should continue to do so. Further, it has been indicated that there is a growing need for clear guidelines on referral and organization of specialist treatment of the more severe and rare headache conditions.

International general recommendations on the treatment of migraine and other primary headache disorders are now in place, and there is a substantial need to implement such guidelines in the EU context as it has recently been suggested for USA [4] and Denmark [5].

The European Headache Federation (EHF) consisting of member societies aims to help the individual countries within the EU to provide the specialists and the

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_6

general practitioners with guidelines which may assist in providing as good as possible understanding and therapy for its subjects. Here the acute treatment of migraine is addressed, which represents the largest group of the primary headaches. The aim is to help our colleagues and to offer an updated view on direction of acute therapy in a field that is moving on with novel therapies.

6.2 What Is Migraine?

Migraine is a painful and often disabling condition and is one of the primary headache disorders. It occurs sometimes secondarily to a number of other conditions. A wide range of headache types have been classified in detail by the International Headache Society (IHS) [6]. The most common of these are tension-type headache (TTH), migraine, cluster headache and chronic daily headache syndromes. Further, migraine is a primary headache disorder that has often a genetic basis but environmental factors play an important role in the expression of the disease. It may start at young age, being more frequent in puberty (or lost) and have its highest prevalence in the age group 20–45 years. After this age period the attacks are reduced and eventually diminish to a very low level. The migraine attacks may sometimes persist in seniors but is rare. It has been argued that the pain disappears but not the underlying attack. This view is not shared by all researchers in the field but is an interesting hypothesis. At the moment, it is considered by many that migraine starts in the CNS and involves diencephalic and brainstem regions and mechanisms [7, 8]. In fact recent work has revealed that there are even premonitory alterations in the CNS prior to the aura and pain phases of migraine attacks [9]. The trigeminovascular system is of importance for the sensitization at peripheral and central sites, and plays a key role in the generation of pain caused during the migraine attack [7].

6.3 Diagnosis of Migraine

During a long time the classification of migraine was up to the different physicians and their respective centers, this made it difficult to compare study results, analyze data in depth, and to perform international studies. In conjunction with the appearance of the first triptan, sumatriptan, the development of mentioned drug stimulated more careful characterization of the condition and stimulated work to find a common view on the disease group. The IHS produced the first international classification in 1998, revised it in 2004 as the second classification, and in 2014 the beta-version of the third classification appeared [6]. This work clarified diagnostic criteria and emphasized the need for solid data and information gathering that is now the basis for the diagnosis (see Table 6.1). At present there are still no reliable diagnostic tests. The medical history should reveal any warning signs indicating the presence of a serious secondary headache.

Physical and neurological examinations should be performed to exclude or confirm any secondary headache. The physical examination would generally produce

Table 6.1 Classification of migraine without aura and typical aura with migraine headache [6]

Migraine without aura	Indicators
Migraine without aura and its indicators, 1.1 [G43.0/N89] *Migraine without aura*	
A	At least five attacks fulfilling criteria B–D
B	Headache attacks lasting 4–72 h
C	Headache has at least one of the following characteristics
	Unilateral localization
	Pulsating quality
	Moderate or severe pain intensity
	Aggravation by/or causing avoidance of routine physical activity
D	During headache at least one of the following happens
	Nausea and/or vomiting
	Phono- and photophobia

Aura with migraine headache	Indicators
Aura with migraine headache, 1.2.1 [G43.10/N89] *Typical aura with migraine headache*	
A	At least five attacks fulfilling criteria B–D
B	Aura consisting of at least one of the following, but no motor weakness
	Fully reversible visual symptoms including positive features and/or negative properties
	Fully reversible sensory symptoms including positive features and/or negative features
	Fully reversible dysphasic speech disturbance
C	At least two of the following
	Homonymous visual symptoms and/or unilateral sensory symptoms
	At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over period of ≥5 min
	Each symptom lasts ≥5 and ≤60 min
D	Headache fulfilling criteria B–D in 1.1 Migraine without aura begins during the aura or follows aura within 60 min

normal findings in case of a primary headache. Attacks of cluster headache will produce physical findings including lacrimation, redness of the eyes, ptosis, and similar symptoms. In trigeminal neuralgia, pain trigger points can often be identified. Blood pressure and pulse should always be measured due to acute hypertension associated with headache. Computer tomography/magnetic resonance imaging (CT/MRI) scans are rarely indicative, but should be performed where the history or physical examination raise suspicion of a secondary condition.

Once a serious secondary headache has been excluded, the use of a headache diary for a minimum of 4 weeks and a headache calendar for a few months is highly recommended [5]. Two most frequently occurring types of migraine are migraine with aura and migraine without aura. Many patients have both types. Migraine without aura presents itself as attacks lasting from 4 to 72 h and the typical characteristics are throbbing unilateral headaches of moderate to severe intensity with aggravation by routine physical activity. These headaches are typically accompanied by nausea, vomiting, and phono- and/or photophobia (see Table 6.1). Patients are symptom-free between attacks. The lifetime prevalence of migraine is considered 16 %; this is based on the fulfillment of diagnostic criteria of five attacks of clear migraine without aura or two documented attacks of migraine with aura [2].

Various imaging studies have revealed not only changes in brain blood flow and metabolism but they are highly localized and related to the different symptoms during the attacks [8]. Recently, it has been shown that there are changes in the CNS during prodromal phase of an induced migraine attack [9] that provide more support to its origin in the CNS.

Approximately one-fourth of migraine patients have migraine with aura. The aura phase consists of lateralized, reversible symptoms from the vision and tactile senses, such as flickering scotomas and sensory disturbances [6].

Transitory aphasia may also occur. Typically, symptoms develop gradually over minutes, every aura symptom has duration of 5–60 min and several types of symptoms follow in a sequence (see Table 6.1). If aura includes motor weakness, the condition may be classified as hemiplegic migraine. In migraine with aura, the headache phase frequently meets the criteria for migraine without aura and is then classified as typical aura with migraine headache (see Table 6.1). It should be noted that aura is not necessarily followed by headache, and that such headache does not necessarily meet the criteria for migraine without aura. In these cases, the migraine is diagnosed as typical aura with non-migraine headache or as typical aura with no headache.

Warning signals that should attract physicians' attention in particular and suggest in-depth examination are:

- Thunderclap headache (severe headache with sudden onset)
- Headache with atypical aura (lasting more than 1 h or including motor symptoms)
- Newly presenting headache in a cancer patient
- Headache/facial pain accompanied by fever or neurological symptoms
- Progressive headache that lasts for weeks
- Newly presenting headache in patients below the age of 10 years or above 45 years

6.4 Clinical Assessment and Special Assessment Program

Use of a headache diary is essential to reach the correct diagnosis, particularly to distinguish between mild migraine attacks and tension-type headaches, and to exclude medication overuse headache (see specific chapters elsewhere).

Comorbidity, e.g., hypertension, asthma, severe obesity and depression, should be diagnosed and managed. If these conditions are properly managed the migraine may in many cases be markedly reduced. Comorbid conditions are essential for the choice of prophylactic medication. Migraine for centuries been known to be a benign condition, however frequent monthly attacks of migraine with aura are at increased risk of stroke, even though absolute risk is small.

6.5 Non-pharmacological Treatment

Generally, there is only limited evidence to support the effect of non-pharmacological treatment on migraine. In some patients, the following factors have a positive effect:

- Information about the causes of migraine and about treatment options
- A thorough examination allowing the patient to feel that he/she is safe, and does not need to fear life-threatening disease
- Making the patient feel that he/she is being taken seriously

Identify and reduce, if possible, any predisposing factors such as stress and depression/anxiety. Identify and eliminate, if possible, any trigger factors, e.g., irregular lifestyle, poor sleep pattern or irregular food intake and consumption of triggering foods such as red wine and some cheeses (if applicable).

Physiotherapy should primarily comprise instruction on how to maintain a correct work posture. Correcting posture and instruction allows the patient to perform active exercises at home might be beneficial. Biofeedback therapy has a documented effect on migraine in some cases. Behavioral therapy and cognitive therapies (stress and pain management) are probably effective, but offer help only to a limited extent. Controlled trials of the effect of acupuncture have yielded a wide array of results.

6.6 Pharmacological Treatment of Acute Migraine Attacks

General Guidelines

- No certain difference has been demonstrated between simple analgesics (paracetamol, NSAID, and acetylsalicylic acid) alone or in combination with antiemetics and triptans [10]. Simple analgesics, i.e., in combination with antiemetics, are therefore first-line treatment [11]. Many of the patients who experience an insufficient effect of simple analgesics have good effect from triptans [11].
- Stepwise treatment is recommended in which each step comprises three treatments before progressing to the next step. Hereby, the most effective and inexpensive treatment is achieved [11].
  - The first step consists of simple analgesics and antiemetics, if needed.
  - The second step consists of triptans.
- Treatment should be initiated as early as possible during the attack [12]; triptans, however, should not be initiated until after any aura phase has subsided.

- Pharmaceutical treatment often has a better effect when combined with rest and/or sleep. If the patient has difficulty relaxing, benzodiazepine may be given, e.g., 5 mg diazepam or another benzodiazepine.

6.6.1 Simple Analgesics and Antiemetics

- It is known for decades that the following drugs have effect on migraine attacks:
  - Paracetamol
  - Acetylsalicylic acid
  - Various NSAIDs [11]
- In case of accompanying nausea, simple analgesics may be given in conjunction with antiemetics to manage the vegetative symptoms and to increase resorption of the analgesics [13]. The following may be used:
  - Metoclopramide 20 mg suppository (or tablet 10–20 mg in case of aversion against suppositories)
  - Tablet domperidone 10–20 mg (this last drug is frequently used in younger patients owing to its low risk of extrapyramidal side effects)
- The use of simple analgesics should not exceed 14 days/month in order to avoid medication overuse headache (Table 6.2).

Table 6.2 Acute migraine treatment, first step: simple analgesic and antiemetic with demonstrated effect in migraine attack treatment using the recommended initial doses [11]

Analgesic	Initial dose (mg)
Acute migraine treatment with analgesic, 1st step (These medications can typically be taken two to three times a day)	
Acetylsalicylic acid	1000
Ibuprofen	400–600
Naproxen	500–750
Diclofenac	50–100
Tolfenamicacid	200
Paracetamol	1000
Antiemetic	**Initial dose (mg)**
Acute migraine treatment with antiemetic 1st step (These medications can typically be taken two to three times a day)	
Metoclopramide	10.0–20.0
Domperidone	20

6.6.2 Triptans

- The triptans are often thought to be all generally alike with regard to effect and side effects [14], but the response of the individual patient to the various triptans may vary considerably [11]. The different triptans have different potencies at the receptor sites, vary in uptake and are treated differently by the p-glycoprotein pump; hence they differ in pharmacokinetics and pharmacodynamics. Patients who have no effect from one triptan may experience effect from another. To exclude any unwanted effect of triptans, the patient should, as a general rule of thumb, have tried three different triptans, each during three different attacks.
- Price differences between triptans are considerable but more recently reduced with generics on the market.
- There is no evidence that the effect of orally disintegrating tablets or rapidly soluble tablets is any quicker than that of standard tablets. Nasal spray and subcutaneous injection act more rapidly than tablets.
- Triptans should be taken early in the attack (while the pain is mild) [15], but not during the aura phase, as they are ineffective in this particular phase [12]. To avoid overuse of triptans, it is essential that the patient is able to distinguish between migraine and tension-type headache. The latter does not respond to triptans.
- Some studies seem to indicate that a combination of a triptan and a NSAID is superior to each of the pharmaceuticals alone [16].
- Oral triptans may, in case of severe nausea/vomiting, be combined with an antiemetic such as metoclopramide [17] or domperidone; in some cases, non-oral administration is to be preferred (nasal spray, suppository or subcutaneous injection).
- Approximately, 20–50 % of patients experience migraine relapse within 24–48 h. An additional dose of triptan is normally effective in these cases. Migraine relapse may also be managed with NSAID.
- In case of lacking effect from triptans, repetition of the treatment during the same attack is usually ineffective.
- Use of triptans should not exceed 9 days/month to avoid medication overuse headache [18].
- Common side effects include a sensation of pressure on the chest, nausea, distal paresthesia and fatigue.
- Triptans are contraindicated in cases with uncontrolled hypertension, ischemic heart conditions, previous cerebral infarctions, and peripheral vascular diseases. Caution should be exercised when treating patients <18 and >65 years. However, sumatriptan nasal spray 10 mg is approved for use in adolescents aged 12–17 years (Table 6.3).

Table 6.3 Acute migraine treatment, second step: triptans available in the EU

Triptan	Formulation	Comments
Acute migraine treatment, 2nd step (An additional dose may be administered after a minimum of 2 h if the first dose has an effect and the headache returns. Generally, a maximum of two doses per day)		
Sumatriptan	Tablets 50 and 100 mg Nasal spray 10 and 20 mg Suppositories 25 mg Subcutaneous injection 6 mg	
Zolmitriptan	Tablets 2.5 and 5 mg	
Naratriptan	Tablets 2.5 mg	Less effective than sumatriptan
Almotriptan	Tablets 12.5 mg	Possibly less side effects than sumatriptan
Rizatriptan	Tablets 10 mg	5 mg when used in combination with propranolol treatment
Eletriptan	Tablets 40 mg	80 mg allowed if 40 mg is inefficient
Frovatriptan	Tablets 2.5 mg	Possibly less effective, fewer side effects and a longer duration of effect than sumatriptan

6.7 Suggestion in Some Specific Situations

6.7.1 Emergency Situation

Patients with a severe migraine attack in an emergency situation have often already tried oral medication (in several doses) without success. Treatment of first choice in this situation is the intravenous application of 1000 mg of acetylsalicylic acid (ASA) with or without metoclopramide [19]. Alternatively, 6 mg subcutaneous sumatriptan can be given. For the treatment of a status migrainosus, 50–100 mg prednisone or 10 mg dexamethasone is recommended by expert consensus. In placebo-controlled trials, however, there is no consistent efficacy of this procedure in the acute treatment of migraine attacks [20–22].

6.7.2 Migraine in Children and Adolescents

The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen 10 mg per kg body weight and paracetamol 15 mg per kg body weight [23]. The only antiemetics licensed for the use in children up to 12 years is domperidone. Sumatriptan nasal spray 5–20 mg is the only triptan with positive placebo-controlled trials in the acute migraine treatment of children and adolescents, the recommended dose for adolescents from the age of 12 is 10 mg [24–26]. Oral triptans did not show significant efficacy in the first placebo-controlled childhood and adolescents' studies [27]. This was in particular because of high placebo responses of 50 % in this age group. In post hoc analyses, however,

2.5–5 mg zolmitriptan were effective in adolescents from the age of 12 to 17 [28, 29]. In trials, oral zolmitriptan 2.5 mg [30], nasal zolmitriptan 5 mg [31], and oral rizatriptan 5–10 mg [32] have been superior to placebo in acute migraine treatment.

6.8 Final Comments

Migraine is the most frequent of the neurological disorders and carries high morbidity and suffering to the individual. The present overview of the acute treatment of migraine is based on current literature and clinical experience within Europe. My experience is that there exist minor variations when comparing several local sites but this publication provides some useful comments on how to treat the subjects that come to the clinic in an acute situation and they have often tried several remedies already.

References

1. Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA (2006) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 27:193–210
2. Burch RC, Loder S, Loder E, Smitherman TA (2015) The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache 55:21–34
3. Linde M, Gustavsson A, Stovner LJ, Steiner TJ, Barré J, Katxarava Z, Lainez JM, Lampl C, Lantéri-Minet M, Rastenyte D, Ruiz de la Torre E, Tassorelli C, Andrée C (2012) The cost of headache disorders in Europe: the Eurolight project. Eur J Neurol 19:703.e43
4. Marmura MJ, Silberstein SD, Schwedt TJ (2015) The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache 55:3–20
5. Bendtsen L, Birk S, Kasch H, Aegidius K, Schmidt Sorensen P, Thomsen LL, Poulsen L, Rasmussen MJ, Kruuse C, Jensen R (2012) Reference programme: diagnosis and treatment of headache disorders and facial pain. Danish headache society, 2nd edition, 2012. J Headache Pain 13(Suppl 1):S1–S29
6. Headache Classification of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:627–808
7. Ackerman S, Holland PR, Goadsby PJ (2011) Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 12:570–584
8. Lakhan SE, Avramut M, Tepper SJ (2013) Structural and functional neuroimaging in migraine: insights from 3 decades of research. Headache 53:46–66
9. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ (2014) Brain activation in the premonitory phase of nitroglycerine-triggered migraine attacks. Brain 137:232–241
10. Tfelt-Hansen P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G (1995) The effectiveness of combined oral lysine acetylsalicylate and metoclopraminde compared with oral sumatriptan for migraine. Lancet 346:923–926
11. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandon PS (2009) EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. Eur J Neurol 16:968–981
12. Olesen J, Diener CH, Schoenen J, Hettiarachchi J (2004) No effect of eletriptan administration during the aura phase of migraine. Eur J Neurol 11:671–677

13. Azzopardi TD, Brooks NA (2008) Oral metoclopramide as an adjunct to analgesics for the outpatient treatment of acute migraine. Ann Pharmacother 42:397–402
14. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ (2001) Oral triptans (serotonin 5-HT (1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 358:1668–1675
15. Scholpp J, Schellenberg R, Moeckesch B, Banik N (2004) Early treatment of a migraine attack while pain is still mild increases the efficacy of sumatriptan. Cephalalgia 24:925–933
16. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ (2005) Sumatriptan and naproxen sodium for the acute treatment of migraine. Headache 45:983–991
17. Schulman EA, Dermott KF (2003) Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. Headache 43:729–733
18. Katsarava Z, Jensen R (2007) Medication-overuse headache: where are we now? Curr Opin Neurol 20:326–330
19. Diener HC, for the ASASUMAMIG Study Group (1999) Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multi-centre, parallel group study. Cephalalgia 19:581–588
20. Friedman BW, Greenwald P, Bania TC, Esses D, Hochberg M, Solorzano C, Corbo J, Chu J, Chew E, Cheung P, Fearon S, Paternoster J, Baccellieri A, Clark S, Bijur PE, Lipton RB, Gallagher EJ (2007) Randomized trial of IV dexamethasone for acute migraine in the emergency department. Neurology 69:2038–2044
21. Donaldson D, Sundermann R, Jackson R, Bastani A (2008) Intravenous dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a multicenter, double-blinded, placebo-controlled randomized clinical trial. Am J Emerg Med 26:124–130
22. Rowe BH, Colman I, Edmonds ML, Blitz S, Walker A, Wiens S (2008) Randomized controlled trial of intravenous dexamethasone to prevent relapse in acute migraine headache. Headache 48:333–340
23. Evers S, Kropp P, Pothmann R, Heinen F, Ebinger F (2008) Therapie idiopathischer – Kopfschmerzen im Kindes- und Jugendalter. Nervenheilkunde 27:1127–1137
24. Uberall MA, Wenzel D (1999) Intranasal sumatriptan for the acute treatment of migraine in children. Neurology 52:1507–1510
25. Winner P, Rothner AD, Saper J, Nett R, Asgharnejad M, Laurenza A, Austin R, Peykamian M (2000) A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. Pediatrics 106:989–997
26. Ahonen K, Hamalained M, Rantala H, Hoppu K (2004) Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. Neurology 62:883–887
27. Evers S (1999) Drug treatment of migraine in children. A comparative review. Paediatr Drugs 1:7–18
28. Solomon GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM (1997) Clinical efficacy and tolerability of 2,5 mg zolmitriptan for the acute treatment of migraine. Neurology 49:1219–1225
29. Tepper SJ, Donnan GA, Dowson AJ, Bomhof MA, Elkind A, Meloche J, Fletcher PE, Millson DS (1999) A long-term study to maximize migraine relief with zolmitriptan. Curr Med Res Opin 15:254–271
30. Evers S, Rahmann A, Kraemer C, Kurlemann G, Debus O, Husstedt IW, Freze A (2006) Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. Neurology 67:497–499
31. Lewis DW, Winner P, Hershey AD, Wasiewski WW, Adolescent Migraine Steering Committee (2007) Efficacy of zolmitriptan nasal spray in adolescent migraine. Pediatrics 120:390–396
32. Ahonen K, Hamalainen ML, Eerola M, Hoppu K (2006) A randomized trial of rizatriptan in migraine attacks in children. Neurology 67:1135–1140

Preventive Episodic Migraine Treatment

7

Anna Ambrosini and Jean Schoenen

7.1 Introduction

Migraine headache sufferers may benefit from acute (abortive or symptomatic) or preventive (prophylactic) treatments. Patients with frequent and severe headaches often require both interventions. Preventive treatments aim at reducing the global burden of the disorder, i.e. frequency, duration and severity of attacks, but they can also enhance the response to acute treatments [1] and result in health care cost reductions [2]. For clinical trials, however, attack frequency is the primary outcome measure according to international guidelines [3], as a prophylactic anti-migraine treatment is considered successful if it reduces the number of migraine attacks by at least 50 %. Although there is no uniform consensus on the circumstances that might warrant preventive treatment, usually these include: recurring migraine attacks that significantly interfere with the patient's quality of life and daily routine activities despite acute treatment, three or more attacks per month, the minimum of attacks required to initiate prophylactic treatment varying between National Guidelines, absence of response or contraindication to or troublesome side effects from acute medications, and frequent, very long and/or uncomfortable auras [4, 5]. In practice, the decision to start and to select a preventive treatment has to be discussed with each individual patient.

Only about 13 % of migraine patients are currently treated with preventive drugs [4] although at least 38.8 % of them should be considered for (13.1 %) or offered

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_7

(25.7 %) a prophylactic treatment according to the American Migraine Prevalence and Prevention (AMPP) study [6].

Drugs from numerous pharmacological classes can be used for the prevention of episodic migraine [7]. They include ß-adrenergic blockers, anticonvulsants, antidepressants, calcium channel antagonists, serotonin antagonists, non-steroidal anti-inflammatory drugs and others (including riboflavin, magnesium and petasites). Recently, neurostimulation methods, such as transcutaneous supraorbital neurostimulation, were also found beneficial. When a prophylactic treatment is advisable, in principle one of the first-order categories of medications should be chosen according to the drug's efficacy in large, double-blind placebo-controlled trials, its possible side effects and the patient's comorbid conditions [7]. However, in practice, the patient's preference must also be taken into account. In this chapter, we will review all pharmacological and non-pharmacological preventative treatments for episodic migraine that were evaluated in randomized controlled trials.

7.2 Pharmacological Treatments for Episodic Migraine

7.2.1 ß-Adrenergic Blockers

The most used drugs in prophylactic migraine treatment are ß-blockers. They show effectiveness in about 50 % of migraineurs. The more effective beta-blockers in preventing migraine are the non-selective ß-blocker propranolol [8–16] and the selective ß1-blocker metoprolol [17–20]. Atenolol [21], bisoprolol [22], nadolol [10, 23, 24] and timolol [15, 25] are also effective, while β-blockers that have intrinsic sympathomimetic activity, such as acebutolol, alprenolol, oxprenolol and pindolol have no preventive effect. The recommended daily dose of propranolol ranges from 120 to 240 mg, but no clear-cut correlation was found between dose and efficacy. Long-acting formulations of propranolol are available in most countries and allow a q.d. regimen with somewhat less side effects. The ß1-selective and less lipophilic agents metoprolol and bisoprolol may have fewer central adverse effects.

The precise mechanisms of action of ß-blockers in migraine are not known. They may act by inhibiting central ß-adrenoreceptors that are involved in the vigilance-enhancing adrenergic pathways, by interacting with 5HT receptors and/or by cross-modulating the serotonin system [3]. That they can act centrally is supported by neurophysiological data before and after treatment in migraine patients. The deficit in habituation of cortical evoked potentials found in migraineurs between attacks normalizes indeed after treatment with beta-blockers [26–28].

All ß-blockers are relatively or absolutely contraindicated in patients suffering from asthma, chronic obstructive lung disease, Raynaud's disease or atrioventricular conduction defects, congestive heart failure and diabetes. Common adverse effects that may lead to treatment interruption are drowsiness, orthostatic hypotension, bradycardia, decreased exercise tolerance, lethargy, sleep disorders, depression, hallucinations and erectile dysfunction.

7.2.2 Anticonvulsants

Two anticonvulsants have FDA approval for migraine prevention and are among the best-studied preventive drugs: sodium valproate and, even more so, topiramate. They are thus recommended in most guidelines although their overall efficacy rate hardly exceeds 50–60 % and their side effect profile is not favourable.

Efficacy and safety of *topiramate* in migraine prevention was proven in two large, pivotal, multicenter, randomized, double-blind, placebo-controlled trials with doses ranging from 50 to 200 mg/day. In the first trial, the 200 mg/day dosage reduced monthly migraine frequency in 52 % of patients ($P<0.001$); the 100 mg/day dosage in 54 % ($P<0.001$); the 50 mg/day dosage in 36 % ($P=0.039$) and placebo in 23 % [29]. In the second pivotal trial [30] a 50 % or greater reduction in mean monthly migraines was obtained in 39 % of patients with 50 mg/day ($P=0.009$), 49 % with 100 mg/day ($P=0.001$) and 47 % with 200 mg/day ($P=0.001$). In both trials the 200 mg and the 100 mg doses had similar effectiveness, but side effects were more frequent with the 200 mg dose.

In a third randomized, double-blind, parallel-group, multicenter trial [31] two doses of topiramate (100 mg/day or 200 mg/day) were compared to placebo or propranolol (160 mg/day). Topiramate 100 mg/day was superior to placebo and similar to propranolol in reducing average monthly migraine periods. Respective to placebo, it was also more effective in reducing mean monthly migraine days, rescue medication use, and with regard to responder rate.

The most common AEs from topiramate are paresthesias, fatigue, decreased appetite and weight loss, nausea, taste perversion, hypoesthesia and abdominal pain. Very common side effects are also mood disorders, anxiety, somnolence, insomnia, memory difficulties and language or concentration problems. Nephrolithiasis may occur during topiramate treatments because of the decrease in urine pH that can be corrected partially with potassium citrate. Less common side effects are acute myopia associated with secondary angle closure glaucoma, visual field modifications, hair loss, oligohidrosis and erectile dysfunction. In an analysis of pooled from available placebo-controlled trials of 100 mg topiramate in migraine, 50 % of patients reported adverse events and one out of four dropped out of the trials because of unbearable side effects [32]. Slow titration is necessary to minimize AEs.

Sodium valproate was effective in a small double-blind, randomized, crossover study [33] in 86.2 % of 29 patients. Their attacks were lowered from 15.6 to 8.8 per month. A triple-blind, placebo- and dose-controlled, crossover study of slow-release sodium valproate [34] confirmed its efficacy compared to placebo in 43 migraineurs without aura with an overall reduction of migraine frequency by 50 % or more for the verum group compared to 18 % for placebo. These results were confirmed in many subsequent randomized, placebo-controlled studies in which responder rates ranged between 43 and 48 % [35–38] and dosages used between 500 and 1500 mg/day. The extended release formulation of divalproex sodium was equally effective for migraine prevention, but had a better side effect profile [39].

The most common side effects of sodium valproate are nausea, vomiting and gastrointestinal disorders; intention tremor and alopecia are also common as well as increased appetite and craving for sweets. By contrast, valproate has little effect on cognitive functions; it can have a favourable effect on mood. Rare, unpredictable and idiosyncratic [40] reactions to valproate are hepatitis and pancreatitis, reported chiefly in children and when other antiepileptic medications are used in association. Valproate is teratogenic and should thus be avoided in fertile women without effective contraception. It is also contraindicated in case of hyperandrogenism, ovarian cysts, severe obesity, a history of pancreatitis or hepatic disorder, thrombocytopenia, pancytopenia and bleeding disorders [37]. Slow titration is recommended, as well as periodic monitoring of serum levels of ammonia and valproic acid.

Several open-label studies have suggested that *lamotrigine*, an anticonvulsant that blocks voltage-sensitive sodium channels and inhibits neuronal glutamate release, may be an option for the preventative treatment of migraine with aura, but no placebo-controlled studies are available. By contrast, in migraine without aura lamotrigine was not superior to placebo in a double-blind, randomized, placebo-controlled trial [41]. Similarly, a crossover trial comparing lamotrigine 50 mg/day to placebo or topiramate 50 mg/day in a mixed group of migraineurs (30 % of them with aura) found no superiority of lamotrigine over placebo for responder rate (>50 % reduction in monthly migraine attack frequency) but a slight superiority for monthly headache frequency [42].

The most common side effect of lamotrigine is a cutaneous rash that can be partly avoided with slow titration.

Gabapentin has been tested in only one placebo-controlled, double-blind trial with a modified intent-to-treat analysis, at a dose ranging from 1800 to 2400 mg/daily. It was said efficacious with a 50 % attack frequency reduction in about one-third of patients [43]. Reported side effects were dizziness or giddiness and drowsiness. A recent updated Cochrane review of anticonvulsants in migraine prevention concluded, however, that there was insufficient evidence to further support the use of gabapentin [44]. There is no evidence that *carbamazepine* is useful in preventive migraine treatment, as the only placebo-controlled trial suggesting a possible benefit on migraine prevention suffered from several important methodological issues [45]. In a recent small (85 patients) RCT comparing *levetiracetam* (500 mg/day), sodium valproate (500 mg/day) and placebo, the 50 % responder rates for headache frequency after 6 months were respectively 63 %, 65.6 % and 15.4 % [46]. Larger placebo-controlled trials are necessary to assess the utility of levetiracetam in migraine prophylaxis.

7.2.3 Antidepressants

Among antidepressants, only *amitriptyline*, a tricyclic antidepressant (TCA), has been found useful in migraine prophylaxis [9]. The useful dose range is wide and needs to be individualized, by starting with a low dose at bedtime (usually 10 mg), and increasing the dose according to the patient's tolerance and the benefits obtained.

Common AEs are dry mouth, metallic taste, epigastric distress, weight gain, constipation, tachycardia, palpitations, increased parasomnias, blurred vision, urinary retention, dizziness, orthostatic hypotension and mental confusion. Attention has to be paid to bipolar patients, where depression may turn into hypomania or frank mania, and to older patients, who are more prone to become confused [47] and to develop cardiac conduction abnormalities.

Poor evidence for efficacy of *selective serotonin reuptake inhibitors* (SSRI) in migraine prevention is available. Effectiveness of fluoxetine in doses between 10 and 40 mg was suggested in three out of four small placebo-controlled trials [48–51], and sertraline was not effective. Common AEs are anxiety, nervousness, insomnia, tremor, anorexia, nausea, vomiting, sexual dysfunctions, drowsiness, fatigue, sweating and dizziness or light-headedness.

Among the *selective serotonin and noradrenaline reuptake inhibitors* (SNRIs), venlafaxine was found effective in a double-blind, placebo-controlled trial [52] and in a separate placebo- and amitriptyline-controlled trial [53]. In clinical practice, however, venlafaxine has limited efficacy, but it is an alternative in patients who do not tolerate tricyclics. The usual dose of 150 mg/daily is reached by slow titration. Its most common side effects are insomnia, nervousness, mydriasis, palpitations and seizures.

The mechanism by which antidepressants may act in preventing migraine headache is not known, but it may involve an action on the aminergic systems. Their effect seems not to be due to an improvement of latent depression. They are also used to manage other chronic pain conditions, including headache, and their benefit on pain occurs sooner than the expected antidepressant effect [54, 55].

7.2.4 Calcium Channel Antagonists

Flunarizine, a calcium channel antagonist with antidopaminergic properties, was found beneficial in migraine prevention in several randomized clinical trials [56–65]. The effective dose may range from 5 to 10 mg at night, and the most common side effects include weight gain, somnolence, dry mouth, dizziness, hypotension, exacerbation or induction of depression in the young patients and extrapyramidal symptoms in the old ones.

Flunarizine is not available in the USA, where *verapamil* is the recommended calcium-channel antagonist. It was more effective than placebo in two out of three trials [66]. Both trials with positive outcomes were very small and had high dropout rates casting doubts on its real utility in migraine prevention.

Cinnarizine, a compound chemically close to flunarizine, may also have a preventive effect in migraine. It has been studied in three randomized trials by the same Iranian group: versus placebo in childhood migraine, versus valproate in migraineurs not sufficiently ameliorated by beta-blockers or tricyclics, and versus topiramate in childhood migraine. In a fourth RCT conducted by another Iranian group, cinnarizine was compared to valproate. In the placebo-controlled trial in children and adolescents ($n=62$), cinnarizine (1.5 mg/kg/day) was associated after 12 weeks with a

50 % responder rate of 60 %, compared to 31.3 % for placebo [67]. In the comparative trial with topiramate in a similar patients group ($n=40$), the responder rate for cinnarizine was as high as 85 % compared to 65 % for topiramate (50 mg/day) [68]. In the study of "refractory" migraineurs ($n=125$) there was a high drop-out rate of 37 %. Nonetheless, responder rates were reported to be 61 % for cinnarizine (75 mg/day) and 63 % for valproate (600 mg/day) [69]. Finally, the comparative trial between cinnarizine and valproate in adult migraineurs ($n=140$) yielded a clearly higher responder rate of 66.7 % for valproate than for cinnarizine (32 %), but dosing was low for both, respectively, 200 mg and 25 mg per day [70]. Further, RCT trials of cinnarizine in migraine prophylaxis might thus be worthwhile. At present, however, it is not clear what its possible advantages over flunarizine might be, the more so that cinnarizine has a similar AE profile as flunarizine, including fatigue, somnolence, depressive mood, weight gain and parkinsonian symptoms in the elderly.

Nimodipine, nicardipine, diltiazem and cyclandelate, other non-selective calcium-channel antagonists, were not found superior to placebo in well-designed clinical trials.

The mode of action of the calcium channel antagonists in preventing migraine is not completely known. It has been suggested that their possible targets are inhibition of 5HT release, neurovascular inflammation, or initiation and propagation of cortical spreading depression [71].

7.2.5 Other Drugs

Methysergide, active on several serotonin receptors subtypes, is one of the rare drugs specifically designed more than 50 years ago for preventive migraine treatment. Unfortunately, available trials have insufficient methodological quality to sustain clear evidence of its efficacy, but clinical practice suggests that it is remarkably effective. The most frequent AEs are abdominal and leg pains, appetite increase, nausea and fatigue. It is contraindicated in patients with cardiovascular disorders. Unfortunately, as other ergot derivatives after long-term use at a high dose, it may occasionally cause fibrosis that can be prevented by a 1-month drug holiday after every 6-month treatment period. Because of this rare, though potentially serious, complication the European Medicines Agency has recommended its withdrawal from the market so that it is not available anymore in most European countries.

Among drugs acting on the angiotensin system, the best studied is the angiotensin II receptor blocker *candesartan*. In a randomized, double-blind, placebo-controlled, crossover study at a 16 mg/day dose [72], the mean number of headache days in a period of 12 weeks was 18.5 with placebo vs 13.6 with candesartan ($P=0.001$) and the number of 50 % candesartan responders was 18 of 57 (31.6 %) for days with headache and 23 of 57 (40.4 %) for days with migraine. The effect size with candesartan was thus significant, though rather small, but its tolerability profile was comparable to that of placebo. In a recent larger randomized, blinded, placebo-controlled, double crossover trial of candesartan and propranolol in both episodic and chronic migraineurs [73], the 50 % responder rate for candesartan

16 mg/day (43 %) was higher than that in the previous trial, but similar to propranolol 160 mg/day (40 %) and superior to placebo (23 %).

An advantage of the sartans is thus their good tolerance, although migraineurs may be sensitive to their hypotensive effect requiring slow titration.

Lisinopril, an angiotensin-converting enzyme inhibitor, was tested in a double-blind, placebo-controlled, crossover study for migraine prevention in 47 patients [74]. Days with migraine were reduced by at least 50 % in 30 % of participants in the lisinopril treatment period compared to the placebo period and in 36 % of subjects compared to the run-in period. The effect size may thus be lower than with candesartan and ACE inhibitor-induced cough is a frequent reason for treatment interruption.

Several *NSAIDs* are possibly effective in migraine prevention, such as ibuprofen, aspirin, fenoprofen, ketoprofen or naproxen [20, 75, 76], but their daily use increases the risk for vascular events and gastric ulcer. In some patients they may also chronify headache and induce medication overuse headache (ICHD-3 beta 8.2), although this complication is much more frequent with analgesics, ergotamine and triptans. Aspirin is an option for the prevention of migraine attacks with aura [77], but no controlled trial is available.

In two randomized, double-blinded, placebo-controlled studies [78, 79] *frovatriptan* was superior to placebo as short-term prophylaxis for menstrually associated attacks when 2.5 mg were taken twice daily for 6 days starting 2 days before the anticipated start of the menstrual attack.

Several *vitamins, minerals and herbal extracts* have been tested as preventative anti-migraine treatments.

Riboflavin (400 mg) was effective in a placebo-controlled, double-blind trial. Over half of the patients were 50 % responders for attack frequency after 3 months [80]. It is overall well tolerated; the most common side effect is flavinuria, rarely it induces gastrointestinal disturbances, and exceptionally an allergic cutaneous rash. Interestingly, riboflavin is the only preventive treatment for which there is a pharmacogenetic correlation. Di Lorenzo et al. [81] found indeed in a study of polymorphisms in the non-coding portion of mitochondrial DNA that patients responding to riboflavin belonged at majority to the non-H haplogroups supposed to have a less performant OXPHOS metabolism. A patented dispersion of well characterized very small nanoparticles containing *Coenzyme Q10* (Sanomit° 100 mg tid) was significantly superior to placebo in reducing attack frequency from baseline to the 4th month of treatment [82]. In a recent placebo-controlled trial, a combination of riboflavin (400 mg), magnesium (600 mg), co-enzyme Q10, minute quantities of vitamins and trace elements (Migravent,° Europe; Dolovent,°USA) was found to reduce migraine days by 29 % after 3 months, which was not significantly different from placebo, contrary to the reductions in migraine intensity and HIT-6 score that were significant [83].

Among *herbal extracts*, feverfew (*Tanacetum parthenium*) was tested as a CO(2)-extract (MIG-99) in a double-blind, placebo-controlled, multicentre, parallel-group study [84] that demonstrated its superiority over placebo in reducing migraine frequency, with an excellent tolerability profile. Feverfew is available in some

countries in different preparations containing various concentrations of parthenolide, the active component of Tanacetum Parthenium. Among adverse effects, the most frequent are mouth ulcerations and oral inflammation with loss of taste.

Two double-blind, placebo-controlled studies [85–87] found that *Petasites hybridus* root (butterbur), a perennial shrub, used as a standardized extract at the dosage of 75 mg bid was effective in migraine prevention. A common AE of butterbur is belching.

Finally, a small Class II study [88] reported a reduction of menstrual migraine attack frequency by using standardized components of soy isoflavones, dong quai and black cohosh when compared to placebo.

Unfortunately, the concentration and bioavailability of the active compound in many commercialized, particularly herbal, products may greatly differ between the various available preparations, so that results from trials should always be interpreted with caution.

Magnesium was studied in two placebo-controlled trials in adult migraineurs. Trimagnesium dicitrate 600 mg daily (24 mmol Mg^{++}) was superior to placebo in reducing attack frequency after a 12-week period (41.6 % vs 15.8 %) [89] but when a lower dosage was used (10 mmol Mg^{++}) there was no significant difference with placebo [90]. The most common AEs are diarrhoea and gastric irritation.

7.3 Non-pharmacological Treatments for Episodic Migraine

According to several RCTs, homeopathy is not superior to placebo for migraine prevention. Physical therapy and various behavioural therapies are claimed to be effective for migraine prevention. Evidence from placebo-controlled trials is, however, usually lacking.

Holroyd et al. [91] published a pivotal trial on *cognitive-behavioural management* in episodic migraine that compared outcome at 10 and up to 16 months of adding to optimized acute treatment a beta-blocker, propranolol or nadolol ($n=53$), a placebo ($n=55$), individualized behavioural management (psycho-education, relaxation, stress management and temperature biofeedback in various combination) plus placebo ($n=55$) or behavioural management plus beta-blocker ($n=69$). There was no significant difference in outcome at 10 or 16 months between placebo, beta-blocker or behavioural management plus placebo, although beta-blockers were numerically slightly superior reducing monthly migraine days by 5, compared to 4 in the other treatment groups. The major finding, however, was that the only group that significantly improved with respect to the three others was the combination of a beta-blocker and behavioural migraine management.

Reports on the preventive effect of *acupuncture* in episodic migraine are controversial. Some studies have shown that traditional acupuncture is not superior to sham acupuncture [92].

Non-invasive neurostimulation methods were recently developed for the preventive treatment of migraine. *Transcranial* magnetic (TMS) or direct current (tDCS) stimulation allows modifying excitability of the underlying cerebral cortex that is

supposed to be abnormal interictally in migraine. Cathodal, i.e. inhibitory, tDCS of the visual cortex was tested in two sham-controlled studies: it was superior to sham only for intensity of pain in one [93], for headache frequency and duration in the other [94]. In a proof-of-concept study based on the rationale that the visual cortex in migraineurs between attacks is hyperresponsive, but not hyperexcitable, occipital anodal, i.e. excitatory, tDCS was highly effective on frequency, duration and intensity of migraine attacks [95].

A single pulse of TMS over the occipital cortex delivered within 1 h of the appearance of an aura was able to prevent the subsequent headache in 39 % of patients compared to 22 % in the sham group [96]. Low-frequency repetitive TMS applied at the vertex was not superior to placebo in a sham-controlled trial of episodic migraineurs [97].

Larger sham-controlled studies are clearly needed for transcranial neurostimulation methods to determine their usefulness in the preventive treatment of migraine.

The hitherto only randomized double-blind sham-controlled trial of *transcutaneous* peripheral nerve stimulation in episodic migraine was performed with the supraorbital stimulator Cefaly® [98]. After 3 months of once daily 20-min session, the 50 % responder rate was 38 % in the active group, compared to 12 % in the sham group. Tolerance is excellent since in a large survey of 2313 patients using the device, the only cumbersome adverse effects were local pain from the electrical stimulation reported by 1.25 % of patients and an allergic skin reaction to the electrode gel in 0.09 % of them [99]. Pushing the "on" button of the device to interrupt the increment of the stimulus intensity can attenuate the former; an anergic gel is available for the latter.

Lifestyle changes can positively influence the migraine burden. In a RCT daily *aerobic exercise* on a bicycle was as effective in migraine prevention as relaxation and topiramate [100], but this has not been replicated yet. A very *low calorie ketogenic diet* was found superior in reducing monthly headache frequency, headache days and symptomatic drug consumption in overweighted migrainous women when compared to a standard low calorie diet [101].

7.4 Perspectives

Pharmacological interventions targeting CGRP, a major actor in the trigeminovascular pathway, were initially developed to treat migraine attacks. The so-called gepants, non-peptide antagonists of the CGRP receptor, are the pioneering pharmacological agents found to be as effective as triptans for migraine attacks, but lacking cardiovascular adverse effects. Although one of them, telcagepant, was superior to placebo also in a RCT for migraine prevention [102], development of the gepants is at present halted because of liver toxicity.

Monoclonal antibodies against CGRP or its receptor that are very promising in migraine prevention because of their long duration of action follow them up. Phase II studies were recently published for two humanized anti-CGRP Mabs, LY2951742 (subcutaneous injection once every 2 weeks for 12 weeks) [103] and ALD403

(a single intravenous injection) [104]. They showed excellent tolerability as well as a decrease of 4.2 monthly migraine days at 12 weeks for LY2951742 (versus 3.0 for placebo) and a decrease of 5.6 migraine days at 8 weeks for ALD403 (versus 4.6 for placebo). Despite the large placebo response, the efficacy results are extremely encouraging because of their long persistence and the results of ongoing phase III trials are eagerly awaited.

7.5 Issues in Preventative Treatments

7.5.1 Adherence and Persistence

In an Internet survey of subjects in the general population renting the tSNS Cefaly® device before deciding to buy it or not [99], a majority (54.4 %) of 2313 subjects declared to be satisfied and to keep the device (average testing period: 58.2 days). Among the unsatisfied patients (46.6 %) who sent back the device, the in-built software monitoring the time it was turned on showed poor compliance, as only 48.6 % of subjects used the device for the recommended time and 4.46 % of them did not even switch it on.

Poor adherence on the long term is also an issue in migraineurs with pharmacological preventive treatments. In a recent systematic review of 33 articles, Hepp et al. [105] found that adherence ranged from 21 to 80 % at 6 months, from 35 to 56 % at 12 months for observational studies, while pooled persistence from RCTs at 16–26 weeks was 77 % for propranolol, 55 % for amitriptyline and 57 % for topiramate.

7.5.2 Comorbidities and Their Management

Coexistent diseases play a key role for migraine preventative treatment, as on the one hand they provide therapeutic opportunities – one single drug to treat both migraine and a second illness – but on the other hand they may impose crucial therapeutic limitations. Most drugs used for migraine prevention have been initially employed for other indications, thus it is common that they have effects on other disorders comorbid with migraine. Some drugs may help to control several different conditions at the same time, such as beta-blockers, useful for arterial hypertension and anxiety, topiramate and valproate, which should be preferred to other anticonvulsants in migraineurs with comorbid epilepsy, antidepressants, that may be the first choice of preventive anti-migraine drugs in a migraine patient with depression, anxiety and insomnia. Vice versa certain preventive migraine drugs can have adverse effects that are harmful for certain comorbid disorders, like flunarizine in case of depression or obesity, valproate in obese patients, beta-blockers or sartans in hypotensive patients, or topiramate in case of recurrent renal lithiasis. By contrast, the metabolic enhancers, such as riboflavin, coenzyme Q10, as well as the non-invasive

neurostimulation methods can be used without consideration of comorbidities and combined with all other pharmacological classes of preventive drugs.

In clinical practice, frequently a patient is already treated for a disorder other than migraine. It is thus mandatory that different medical specialists communicate and cooperate in order to coordinate the respective specific treatments, and the reciprocal influence of migraine and comorbidity therapies has to be taken into account [106].

7.5.3 Treatment Duration and Discontinuation

Treatments for migraine prevention are often recommended for short periods (usually only 6–9 months), but few RCTs are available to support this. Diener et al. [107] assessed the effects of treatment discontinuation or not in 818 migraine patients after 6 months of treatment with topiramate. After a 6-month open-phase treatment with topiramate patients were randomly assigned to continue the drug ($n=255$) or to switch to placebo ($n=259$) for a 26-week, double-blind phase. The number of monthly migraine days increased during the randomized phase in the placebo group (1.19 days; $P<0.001$) but not in the topiramate group (0.10 day; $P=0.5756$). Sustained benefit was found in a number of patients after topiramate discontinuation: 49 % of patients receiving placebo rated the treatment as good or very good, compared to 69 % of those receiving topiramate. As far as topiramate is concerned, these findings confirm that after 6 months of efficacious treatment, patients may be offered treatment discontinuation, but at least 20 % of them will lose all or part of their previous benefit.

7.6 Conclusions and General Recommendations

The preventive anti-migraine treatments are aimed at reducing frequency, duration and severity of attacks. They may also improve responsiveness to acute attack drugs, and reduce migraine-related disability. A wide range of prophylactic medications is available, so that it may be difficult to select the most appropriate for the individual patient as soon as the first visit. Several National Headache Societies have established guidelines for their use. Unfortunately, they often differ with respect to the criteria used for assessing the methodological quality of clinical trials, the impact of so-called “expert consensus” and local drug marketing and reimbursement policies. No clinical data can predict efficacy of the various therapeutic options with the possible exception of mitochondrial DNA haplotypes that may predict therapeutic response to riboflavin [80]. The preventative treatments with the best-documented efficacy are beta-blockers, divalproex/sodium valproate and topiramate. Metabolic enhancers and transcutaneous supraorbital neurostimulation with the Cefaly® device are somewhat less effective, but are quasi devoid of adverse events so that they may suffice in the less disabled patients and can be combined with the other treatments. Behavioural migraine management enhances on the long

term the efficacy of preventive drugs, but does not seem to be sufficient on its own. The choice of a preventive treatment is made based on the patient's preferences and headache profile, presence or absence of coexisting disorders, evidence-based efficacy, adverse effect profile and the treating physician's experience [5].

Preventive treatments play a crucial role in migraine management. They can result in reduced health care resource utilization and improved quality of life, as well as prevent migraine chronification. Only a small percentage of migraine patients is or have been effectively treated for migraine prevention, although epidemiological data suggest that many of them should receive such treatment.

The following can be used as general guidelines in managing patients:

- Except for metabolic enhancers, for all other drug treatments, go "low and slow" to avoid AEs and find the minimal efficient dose.
- Each treatment should be tried for an adequate period. Some drugs may show their clinical benefit not before 3 months of treatment, and this effect latency is longer for nutraceuticals, and possibly for non-invasive neurostimulation.
- When a preventative treatment is started, realistic and appropriate goals have to be set: reduction in attack frequency higher than 50 %, decrease in attack duration and severity, and an improved response to acute medications.
- Inform clearly about possible AEs and possible ways to avoid or minimize them. Most are self-limited and dose-dependent; patients should be encouraged to tolerate the early AEs.
- Prevent acute headache medication overuse by informing the patient and giving the preference to NSAIDs over analgesics.
- Identify comorbidities and be aware of the possible favourable or deleterious effects on migraine or the comorbid condition of the drugs taken.
- Reevaluate therapy periodically, and, try to taper or discontinue the treatment after a sustained period of remission (6–9 months).
- Knowing that pregnancy improves migraine without aura in 80 % of women, be sure that a woman of childbearing potential is aware of any potential risks and choose the medication that has no teratogenic potential.
- It is important that patients are involved in their own care, and their preferences are taken into account in order to maximize their compliance,
- Since combining drugs also combines their AEs, combine preferably a drug with known AEs with a nutraceutical, behavioural management or non-invasive neurostimulation.

References

1. Lipton RB, Silberstein SD (1994) Why study the comorbidity of migraine? Neurology 44:4–5
2. Silberstein SD, Winner PK, Chmiel JJ (2003) Migraine preventive medication reduces resource utilization. Headache 43:171–178

3. Tfelt-Hansen P, Pascual J, Ramadan N et al; International Headache Society Clinical Trials Subcommittee (2012) Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia 32:6–38
4. Lipton RB, Diamond M, Freitag F et al (2005) Migraine prevention patterns in a community sample: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 45:792–793 (Abstract)
5. Silberstein SD, Latsko M, Schoenen J (2012) Preventive antimigraine drugs. In: Fernandez-de-las-Penas C, Chaitow L, Schoenen J (eds) Multidisciplinary management of migraine. Jones & Bartlett Learning, Burlington, pp 91–102
6. Silberstein S, Diamond S, Loder E et al (2005) Prevalence of migraine sufferers who are candidates for preventive therapy: results from the American migraine study (AMPP) study. Headache 45:770–771 (Abstract)
7. Tfelt-Hansen P (2000) Prioritizing acute pharmacotherapy of migraine. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches. Lippincott Williams & Wilkins, New York, pp 453–456
8. Gray RN, Goslin RE, McCrory DC et al (1999) Drug treatments for the prevention of migraine headache. Prepared for the Agency for Health Care Policy and Research, Contract No. 290-94-2025. Available from the National Technical Information Service Accession 1999; No. 127953
9. Silberstein SD (2000) Practice Parameter–Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology for the United States Headache Consortium. Neurology 55:754–762
10. Ryan RE (1984) Comparative study of nadolol and propranolol in prophylactic treatment of migraine. Am Heart J 108:1156–1159
11. Cortelli P, Sacquegna T, Albani F, Baldrati A, D'Alessandro R, Baruzi A, Lugaresi E et al (1985) Propranolol plasma levels and relief of migraine. Arch Neurol 42:46–48
12. Koella WP (1985) CNS-related side-effects of b-blockers with special reference to mechanisms of action. Eur J Clin Pharmacol 28:55–63
13. Andersson K, Vinge E (1990) Beta-adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. Drugs 39:355–373
14. Ramadan NM (2004) Prophylactic migraine therapy: mechanisms and evidence. Curr Pain Headache Rep 8:91–95
15. Tfelt-Hansen P, Standnes B, Kangasniemi P et al (1984) Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial. Acta Neurol Scand 69:1–8
16. Sudilovsky A, Elkind AH, Ryan RE et al (1987) Comparative efficacy of nadolol and propranolol in the management of migraine. Headache 27:421–426
17. Andersson PG, Dahl S, Hansen JH et al (1983) Prophylactic treatment of classical and non-classical migraine with metoprolol–a comparison with placebo. Cephalalgia 3:207–212
18. Kangasniemi P, Hedman C (1984) Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. Cephalalgia 4:91–96
19. Olsson JE, Behring HC, Forssman B et al (1984) Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study. Acta Neurol Scand 70:160–168
20. Diener HC, Hartung E, Chrubasik J et al (2001) A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia 21:120–128
21. Johannsson V, Nilsson LR, Widelius T et al (1987) Atenolol in migraine prophylaxis a double-blind cross-over multicentre study. Headache 27:372–374
22. van de Ven LL, Franke CL, Koehler PJ (1997) Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. Cephalalgia 17:596–599
23. Ryan RE, Sudilovsky A (1983) Nadolol: its use in the prophylactic treatment of migraine. Headache 23:26–31
24. Sudilovsky A, Stern MA, Meyer JH (1986) Nadolol: the benefits of adequate trial duration in the prophylaxis of migraine. Headache 26:325

25. Stellar S, Ahrens SP, Meibohm AR et al (1984) Migraine prevention with timolol. A double-blind crossover study. JAMA 252:2576–2580
26. Schoenen J, Maertens de Noordhout A, Timsit-Berthier M et al (1986) Contingent negative variation and efficacy of beta-blocking agents in migraine. Cephalalgia 6:229–233
27. Maertens de Noordhout A, Timsit-Berthier M, Timsit M et al (1987) Effects of beta blockade on contingent negative variation in migraine. Ann Neurol 21:111–112
28. Sándor PS, Áfra J, Ambrosini A et al (2000) Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache 40:30–35
29. Silberstein SD, Neto W, Schmitt J et al (2004) Topiramate in the prevention of migraine headache: a randomized, double-blind, placebo-controlled, multiple-dose study. For the MIGR-001 Study Group. Arch Neurol 61:490–495
30. Brandes JL, Saper JR, Diamond M et al (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291:965–973
31. Diener HC, Tfelt-Hansen P, Dahlof C et al (2004) Topiramate in migraine prophylaxis–results from a placebo-controlled trial with propranolol as an active control. J Neurol 251:943–950
32. Bussone G, Diener HC, Pfeil J et al (2005) Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomized controlled trials. Int J Clin Pract 59:961–968
33. Hering R, Kuritzky A (1992) Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 12:81–84
34. Jensen R, Brinck T, Olesen J (1994) Sodium valproate has prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 44:241–244
35. Freitag FG, Collins SD, Carlson HA et al (2003) A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. For the Depakote ER Migraine Study Group. Neurology 58:1652–1659
36. Klapper JA (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 17:103–108
37. Silberstein SD (1996) Divalproex sodium in headache–literature review and clinical guidelines. Headache 36:547–555
38. Mathew NT, Saper JR, Silberstein SD et al (1995) Migraine prophylaxis with divalproex. Arch Neurol 52:281–286
39. Mathew NT, Saper JR, Silberstein SD et al (1995) Prophylaxis of migraine headaches with divalproex sodium. Arch Neurol 52:281–286
40. Pellock JM, Willmore LJ (1991) A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. Neurology 41:961–964
41. Steiner TJ, Findley LJ, Yuen AW (1997) Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 17:109–112
42. Gupta P, Singh S, Goyal V et al (2007) Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp Study). Headache 47:402–412
43. Mathew NT, Rapoport A, Saper J et al (2001) Efficacy of gabapentin in migraine prophylaxis. Headache 41:119–128
44. Mulleners WM, McCrory DC, Linde M (2015) Antiepileptics in migraine prophylaxis: an updated Cochrane review. Cephalalgia 35:51–62
45. Rompel H, Bauermeister PW (1970) Aetiology of migraine and prevention with carbamazepine (Tegretol). S Afr Med J 44:75–80
46. Sadeghian H, Motiei-Langroudi R (2015) Comparison of Levetiracetam and sodium Valproate in migraine prophylaxis: a randomized placebo-controlled study. Ann Indian Acad Neurol 18:45–48
47. Baldessarini RJ (1990) Drugs and the treatment of psychiatric disorders. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds) The pharmacological basis of therapeutics. Pergamon, New York, pp 383–435
48. d'Amato CC, Pizza V, Marmolo T et al (1999) Fluoxetine for migraine prophylaxis: a double-blind trial. Headache 39:716–719

49. Steiner TJ, Ahmed F, Findley LJ et al (1998) S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia 18:283–286
50. Saper JR, Silberstein SD, Lake AE 3rd et al (1994) Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 34:497–502
51. Saper JR, Silberstein SD, Lake AE 3rd (1995) Fluoxetine and migraine: comparison of double-blind trials. Headache 35:233
52. Ozyalcin SN, Talu GK, Kiziltan E et al (2005) The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache 45:144–152
53. Bulut S, Berilgen MS, Baran A et al (2004) Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. Clin Neurol Neurosurg 107:44–48
54. Kishore-Kumar R, Max MB, Schafer SC et al (1990) Desipramine relieves post-herpetic neuralgia. Clin Pharmacol Ther 47:305–312
55. Panerai AE, Monza G, Movilia P et al (1990) A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. Acta Neurol Scand 82:34–38
56. Frenken CW, Nuijten ST (1984) Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo. Clin Neurol Neurosurg 86:17–20
57. Mendenopoulos G, Manafi T, Logothetis I et al (1985) Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. Cephalalgia 5:31–37
58. Cerbo R, Casacchia M, Formisano R et al (1986) Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis. Cephalalgia 6:15–18
59. Lücking CH, Oestreich W, Schmidt R et al (1988) Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. Cephalalgia 8(Suppl 8):21–26
60. Sørensen PS, Larsen BH, Rasmussen MJ et al (1991) Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. Headache 31:650–657
61. Gawel MJ, Kreeft J, Nelson RF et al (1992) Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. Can J Neural Sci 19:340–345
62. Mitsikostas DD, Polychronidis I (1997) Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. Funct Neurol 12:267–276
63. Bordini CA, Arruda MA, Ciciarelli MC et al (1997) Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. Arq Neuropsiquiatr 55:536–541
64. Diener HC, Matias-Guiu J, Hartung E et al (2002) Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. Cephalalgia 22:209–221. Erratum in. Cephalalgia 22(6):488
65. Luo N, Di W, Zhang A et al (2012) A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. Pain Med 13:80–86
66. Solomon GD (1989) Verapamil in migraine prophylaxis–a five-year review. Headache 29: 425–427. Review
67. Ashrafi MR, Salehi S, Malamiri RA et al (2014) Efficacy and safety of cinnarizine in the prophylaxis of migraine in children: a double-blind placebo-controlled randomized trial. Pediatr Neurol 51:503–508
68. Ashrafi MR, Najafi Z, Shafiei M et al (2014) Cinnarizine versus Topiramate in Prophylaxis of Migraines among Children and Adolescents: a Randomized, Double-Blind Clinical Trial. Iran J Child Neurol 8:18–27
69. Togha M, Rahmat Jirde M, Nilavari K et al (2008) Cinnarizine in refractory migraine prophylaxis: efficacy and tolerability. A comparison with sodium valproate. J Headache Pain 9:77–82
70. Bostani A, Rajabi A, Moradian N et al (2013) The effects of cinnarizine versus sodium valproate in migraine prophylaxis. Int J Neurosci 123:487–493

71. Wauquier A, Ashton D, Marranes R (1985) The effects of flunarizine in experimental models related to the pathogenesis of migraine. Cephalalgia 5:119–120
72. Tronvik E, Stovner LJ, Helde G et al (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 289:65–69
73. Stovner LJ, Linde M, Gravdahl GB et al (2013) A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomized, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 34:523–532
74. Schrader H, Stovner LJ, Helde G et al (2001) Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomized, placebo-controlled, crossover study. Br Med J 322:19–22
75. Pradalier A, Clapin A, Dry J (1988) Treatment review: nonsteroid antiinflammatory drugs in the treatment and long-term prevention of migraine attacks. Headache 28:550–557
76. Bensenor IM, Cook NR, Lee IM et al (2001) Low-dose aspirin for migraine prophylaxis in women. Cephalalgia 21:175–183
77. Massiou H (2000) Prophylactic treatments of migraine. Rev Neurol (Paris) 156(Suppl 4):4S79–4S86. [Article in French]
78. Brandes JL, Ac P, Kallela M et al (2009) Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. Cephalalgia 29:1133–1148
79. Silberstein SD, Elkind AH, Schreiber C et al (2004) A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology 63:261–269
80. Schoenen J, Jacquy J, Lenaerts M (1998) Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 50:466–470
81. Di Lorenzo C, Pierelli F, Coppola G et al (2009) Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. Neurology 72:1588–1594
82. Sandor PS, Di CL, Coppola G et al (2005) Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 64:713–715
83. Gaul C, Diener HC, Danesch U, Migravent® Study Group (2015) Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. J Head Pain 2015:16–32
84. Diener HC, Pfaffenrath V, Schnitker J et al (2005) Efficacy and safety of 6.25 mg t.i.d. feverfew CO2-extract (MIG-99) in migraine prevention–a randomized, double-blind, multicentre, placebo-controlled study. Cephalalgia 25:1031–1041
85. Grossmann M, Schmidramsl H (2000) An extract of Petasites hybridus is effective in the prophylaxis of migraine. Internat J Clin Pharmacol Therapeut 38:430–435
86. Lipton RB, Gobel H, Wilks K et al (2002) Efficacy of petasites (an extract from petasites rhizone) 50 and 75 mg for prophylaxis of migraine: results of a randomized, double-blind, placebo-controlled study. Neurology 58:A472
87. Lipton RB, Gobel H, Einhaupl KM et al (2004) Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. Neurology 63:2240–2244
88. Burke BE, Olson RD, Cusack BJ (2002) Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. Biomed Pharmacother 56:283–288
89. Peikert A, Wilimzig C, Köhne-Volland R (1996) Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 16:257–263
90. Pfaffenrath V, Wessely P, Meyer C et al (1996) Magnesium in the prophylaxis of migraine—a double-blind placebo-controlled study. Cephalalgia 6:436–440
91. Holroyd KA, Cottrell CK, O'Donnell FJ et al (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomized controlled trial. BMJ 341:c4871
92. Diener HC (2013) Acupuncture prophylaxis of migraine no better than sham acupuncture for decreasing frequency of headaches. Evid Based Med 18:33–34
93. Antal A, Kriener N, Lang N et al (2011) Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia 31:820–828

94. Rocha S, Melo L, Boudoux C et al (2015) Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: a pilot randomized controlled trial. J Neurol Sci 349:33–39
95. Vigano A, Sasso d'Elia T, Sava SL et al (2013) Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. J Head Pain 14:23–31
96. Lipton RB, Dodick DW, Silberstein SD et al (2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomized, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 9:373–380
97. Teepker M, Hötzel J, Timmesfeld N et al (2010) Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia 30:137–144
98. Schoenen J, Vandersmissen B, Jeangette S et al (2013) Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 80:697–704
99. Magis D, Sava S, d'Elia TS et al (2013) Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly(R) device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain 14:95
100. Varkey E, Cider A, Carlsson J et al (2011) Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. Cephalalgia 31:1428–1438
101. Di Lorenzo C, Coppola G, Sirianni G et al (2015) Migraine improvement during short lasting ketogenesis: a proof-of-concept study. Eur J Neurol 22:170–177
102. Ho TW, Connor KM, Zhang Y et al (2014) Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology 83:958–966
103. Dodick DW, Goadsby PJ, Spierings EL et al (2014) Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomized, double-blind, placebo-controlled study. Lancet Neurol 13:885–892
104. Dodick DW, Goadsby PJ, Silberstein SD et al (2014) Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomized, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 13:1100–1107
105. Hepp Z, Bloudek LM, Varon SF (2014) Systematic review of migraine prophylaxis adherence and persistence. J Manag Care Pharm 20:22–33. Review
106. Sándor PS, Dodick DW, Schoenen J (2011) Optimal management of migraine taking into account comorbidities and "positive side effects". In: Schoenen J, Dodick DW, Sándor PS (eds) Comorbidity in migraine. Wiley-Blackwell Publishing Ltd, Oxford, pp 132–138
107. Diener HC, Agosti R, Allais G et al (2007) Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomized, double-blind, placebo-controlled trial. Lancet Neurol 6:1054–1062

Drug Treatment for Chronic Migraine

8

Hans-Christoph Diener

8.1 Introduction

Chronic migraine (CM) is a disabling illness that has substantial impact on the patient's ability to perform routine daily activities and on productivity in the workplace [1, 2]. Management of chronic migraine requires identifying and managing risk factors, establishing limits on the use acute pain and migraine medications to minimize the effects of overuse, initiating non-pharmacologic treatment, and treating neuropsychiatric disorders (e.g., depression, anxiety) and other comorbid conditions (e.g., obesity) that may contribute to increased attack frequency. All these therapeutic recommendations are based on clinical experiences and not on the results of randomized, placebo controlled trials. The primary goals of preventive therapy in subjects with chronic migraine are to reduce the frequency and severity of attacks, to reduce reliance on acute medications, and to improve quality of life.

Until recently, evidence regarding the efficacy and safety of migraine preventive medications for the treatment of chronic migraine has been limited to case studies, and open-label and small randomized trials. However, recent randomized, controlled medication trials have been conducted in the chronic migraine population. Most of the drugs used for the prevention of episodic migraine have not been investigated for chronic migraine [3, 4]. Their use might be justified in patients who do not respond and cannot tolerate the drugs mentioned below.

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_8

8.1.1 Topiramate

The results of a small placebo-controlled trial with topiramate [5] prompted further investigation of efficacy of topiramate in chronic migraine patients in larger, controlled studies (Table 8.1). Two separate studies in Europe and the USA showed that topiramate was effective in the preventive therapy of chronic migraine [6, 7].

There was a key difference between the US and EU trials: patients were allowed to take acute rescue medication as usual during the EU trial, but not during the US trial. Remarkably, the benefits of topiramate extended to the subgroup of patients overusing acute medications, as demonstrated by significant reductions in mean monthly migraine days over placebo (−3.5 days for topiramate vs. +0.2 days for

Table 8.1 Studies of treatment with topiramate in patients with chronic migraine

Study	Study design	Population and treatment	Results
Topiramate			
Silvestrini et al. [5]	Double-blind, randomized, placebo-controlled, parallel group trial	Low dose treatment (50 mg/day), 28 patients with chronic migraine and medication overuse, 9-week treatment phase	Baseline headache frequency 20.8 days. 28-day headache frequency 8.1 ± 8.1 with topiramate versus 20.6 ± 3.4 for placebo ($P < 0.0007$),
Silber-stein et al. [6]	Double-blind, randomized, placebo-controlled, parallel group, multicenter trial	306 patients (intent-to-treat population) with chronic migraine,[a] and without medication overuse 153 in treatment group and 153 given placebo, 16 weeks treatment (4-week titration period, 12-week maintenance phase)	Topiramate, 6.4 ± 5.8 days (baseline frequency 17.1 days) Placebo, 4.7 ± 6.1 days (baseline frequency 17.0 days) Significant reduction in mean number of migraine days per month, $P = 0.01$:
Diener et al. [7]	Double-blind, randomized, placebo-controlled, parallel-group, multicenter trial	59 patients (intent-to-treat population) with chronic migraine,[b] most of whom had medication overuse with triptans 32 in treatment group and 27 given placebo, 16 weeks treatment[c]	Significant reduction from baseline in the mean number of migraine days per month, $P = 0.02$ Topiramate, baseline frequency 15.5 ± 4.6, reduction 3.5 ± 6.3 days Placebo, baseline 16.4 ± 4.4, reduction 0.2 ± 4.7 days

Modified from Diener et al. [8]

[a]Chronic migraine defined as ≥15 headache days per 28 days, of which at least 50 % were migraine headache

[b]Chronic migraine defined as ≥15 monthly migraine days for ≥3 months prior to trial entry, regardless of acute medication overuse

[c]Patients included if they had ≥12 migraine days during the 28 days baseline phase

placebo). Topiramate decreased the number of days per month with acute medication intake versus placebo (reduction of 3 days/month for topiramate vs 0.7 days/month for placebo). The difference, however, was not statistically significant. Adverse events of topiramate were consistent with those observed in previous clinical trials: paresthesia and nausea. A particular finding in the European study was the absence of a placebo response, considering the fact that patients continued to overuse acute headache medications throughout the study. Both trials demonstrated the efficacy and safety of topiramate in chronic migraine patient populations, and the efficacy was maintained regardless of the presence or absence of medication overuse [9].

Combination therapy of topiramate plus propranolol versus topiramate alone was investigated in a randomized, double blind trial in 171 patients with CM [10]. Combination therapy was not superior to monotherapy and therefore cannot be recommended [4].

8.1.2 Onabotulinum Toxin Type A

Onabotulinum toxin type A has been reported to relieve pain associated with a variety of conditions [11–14], and is approved for use as prophylactic therapy in patients with chronic migraine. Unlike its function at the neuromuscular junction, the mechanism of action of onabotulinum toxin type A in migraine relief is at present not understood. A number of placebo-controlled trials in episodic migraine and chronic daily headache failed to show the efficacy of onabotulinum toxin type A [15–20]. Post-hoc analyses indicated that perhaps migraine patients with frequent headache might benefit from this treatment [21]. Therefore, the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program evaluated the efficacy and safety of onabotulinum toxin type A as a prophylactic treatment for adults with chronic migraine. Two phase 3, multicenter studies (PREEMPT 1 and 2) were conducted. A total of 1384 patients with chronic migraine were enrolled across both trials [22, 23]. Patients were randomized (1:1) to either onabotulinum toxin type A or placebo injections and stratified based on whether they were overusing acute headache medication at baseline. The minimum dose of onabotulinum toxin type A was 155 U, administered to 31 sites in seven head and neck muscles [24]. PREEMPT 1 failed its primary endpoint, which was reduction in headache episodes. A statistically significant improvement from baseline in frequency of headache episodes was greater for onabotulinum toxin type A than for placebo in PREEMPT 2, although this was not the primary endpoint, which was changed prior to breaking the blind to headache days. Statistically significant reductions from baseline in frequency of headache days were observed after onabotulinum toxin type A treatment compared with placebo treatment in both PREEMPT 1 and 2. In the pooled analysis, the reduction in headache days after 6 months was 8.4 days from a baseline frequency of 19.9 days for onabotulinum toxin type A and 6.6 days from baseline 19.8 days for placebo with a therapeutic gain of ±11 % [24]. In a study in Spain, the long-term efficacy of onabotulinum toxin type A was investigated in 132 patients with chronic

migraine. Efficacy was achieved in 82 % after 1 year. Treatment beyond 1 year results in failure in 14 out of 108 patients [25]. This indicates that onabotulinum toxin type A shows the efficacy beyond the time period studies in randomized trials. In an open study in the UK with 254 patients with CM, onabotulinum toxin type A significantly reduced the number of headache and migraine days [26]. Onabotulinum toxin type A is the only drug approved for the treatment of chronic migraine by the FDA (Table 8.2)

Table 8.2 Results from phase III trials of onabotulinum toxin type A

Study site	End points	Results
PREEMPT 1 [22]		
56 sites in the USA	Primary: change in frequency of headache episodes at week 24 compared with baseline Secondary: change in frequency of headache days at week 24 compared with baseline	No significant improvement in frequency of headache episodes Significant reduction in frequency of headache days, $P=0.006$
PREEMPT 2 [23]		
50 sites in the USA and 16 sites in Europe	Primary: change in frequency of headache days at week 24 compared with baseline Secondary: change in frequency of headache episodes at week 24 compared with baseline	Significant reduction in frequency of headache days, $P<0.001$ Significant improvement in frequency of headache episodes
Pooled analysis of results from PREEMPT 1 and 2 [24]		
NA	NA	Significant reduction in headache days after 6 months in treatment vs placebo groups, $P<0.001$: Treatment, 8.4 days (baseline frequency 19.9 days) Placebo, 6.6 days (baseline frequency 19.8 days) with a therapeutic gain of ±11 %. Significant difference in other efficacy variables, favoring treatment, including: frequency of migraine episodes, migraine days, and severe headache days; cumulative hours of headache/day; proportion of patients with severe disability. Intake of medication to treat acute migraine attacks was not different between placebo and treatment groups (however, in post hoc analysis, intake of triptans was significantly reduced in treatment group)

Modified from Diener et al. [8]
Similar study designs in both trials: 24 week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase
Abbreviation: *NA* not applicable

8.1.3 Other Drugs

The efficacy of sodium valproate in the treatment of chronic daily headache was assessed in a small study with 29 patients with chronic migraine [27]. The study showed that sodium valproate was superior to placebo for a number of outcome parameters. Another small study investigated topiramate and valproic acid (750 mg/day) in patients with chronic migraine and found a significant reduction in headache frequency for both drugs [28]. Larger randomized placebo-controlled trials are required for further evaluation of chronic migraine treatment with sodium valproate. Additional small studies reported the efficacy of gabapentin (400–600 mg bid) [29] and amitriptyline [30, 31]. Gabapentin (2400 mg) was studied in 95 participants, 22 of which had chronic migraine. Results for the subgroup of patients with CM were not reported separately [29]. All of these studies were underpowered or lacked a placebo group.

Levetiracetam was studied in a multicenter, randomized placebo-controlled crossover study of patients with both chronic migraine and chronic-tension type headache. Seventy-three of ninety-six recruited patients had chronic migraine. The study failed its primary endpoint, although some secondary endpoints were positive [32]. As the data stand, it is not possible to recommend the use of levetiracetam in chronic migraine. Several drugs were studies in open-label and uncontrolled trials. These include pregabalin (up to 150 mg/day) [33], zonisamide in patients refractory to topiramate [34], and memantine [35].

8.2 Practical Recommendations

Patients with chronic migraine and medication overuse need advice and support to discontinue their medication overuse. Simultaneously or after a drug free period, they as well as non-overusing patients need to be treated by an interdisciplinary approach [36]. In addition to education, behavioral therapy and exercise migraine prevention by drug treatment has to be considered as in patients with episodic migraine [37–39]. Most patients with chronic migraine contact tertiary headache centers because they failed migraine prevention with beta-blockers, anticonvulsants, flunarizine, or amitriptyline. Migraine prevention with topiramate or onabotulinum toxin type A should be offered to patients with chronic migraine. Due to cost considerations, prevention should start with topiramate and onabotulinum toxin type A should be offered to patients in whom topiramate is not effective, not tolerated or in case of contraindications.

In patients with chronic migraine and medication overuse, counseling is recommended about the role of acute migraine medication in the transition from episodic to chronic migraine. Patients who are not able to reduce the intake days of specific migraine mediations below 10 days/month are offered treatment with either topiramate or onabotulinum toxin type A. If this approach also fails, then patients have to undergo a detoxification program [37, 40, 41].

References

1. D'Amico D, Usai S, Grazzi L, Rigamonti A, Solari A, Leone M et al (2003) Quality of life and disability in primary chronic daily headaches. Neurol Sci 24(Suppl 2):S97–S100
2. Wiendels NJ, van Haestregt A, Knuistingh Neven A, Spinhoven P, Zitman FG, Assendelft WJ et al (2006) Chronic frequent headache in the general population: comorbidity and quality of life. Cephalalgia 26(12):1443–1450
3. Evans RW (2013) A rational approach to the management of chronic migraine. Headache 53(1):168–176
4. Schwedt TJ (2014) Chronic migraine. BMJ 348:g1416
5. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L (2003) Topiramate in the treatment of chronic migraine. Cephalalgia 23:820–824
6. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache 47(2):170–180
7. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 27(7):814–823
8. Diener HC, Dodick DW, Goadsby PJ, Lipton RB, Olesen J, Silberstein SD (2011) Chronic migraine–classification, characteristics and treatment. Nat Rev Neurol 8(3):162–171
9. Diener HC, Dodick DW, Goadsby PJ, Bigal ME, Bussone G, Silberstein SD et al (2009) Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse. Cephalalgia 29(10):1021–1027
10. Silberstein SD, Dodick DW, Lindblad AS, Holroyd K, Harrington M, Mathew NT et al (2012) Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology 78(13):976–984
11. Foster L, Clapp L, Erickson M, Jabbari B (2001) Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology 56(10):1290–1293
12. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C (2005) Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 45(4):293–307
13. Ranoux D, Attal N, Morain F, Bouhassira D (2008) Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol 64(3):274–283
14. Freitag FG, Diamond S, Diamond M, Urban G (2008) Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache 48(2):201–209
15. Silberstein S, Mathew N, Saper J, Jenkins S, BOTOX Migraine Clinical Research Group (2000) Botulinum toxin type A as a migraine preventive treatment. Headache 40:445–450
16. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt I-W, Frese A (2004) Botulinum toxin A in the prophylactic treatment of migraine–a randomized, double-blind, placebo-controlled study. Cephalalgia 24:838–843
17. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo ClinProc 80(9):1126–1137
18. Aurora SK, Gawel M, Brandes JL, Pokta S, Vandenburgh AM (2007) Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache 47(4):486–499
19. Saper JR, Mathew NT, Loder EW, DeGryse R, VanDenburgh AM (2007) A double-blind, randomized, placebo-controlled comparison of botulinum toxin type a injection sites and doses in the prevention of episodic migraine. Pain Med 8(6):478–485
20. Vo AH, Satori R, Jabbari B, Green J, Killgore WD, Labutta R et al (2007) Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviat Space Environ Med 78(5 Suppl):B113–B118
21. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD (2005) Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache 45(4):315–324

22. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 30(7):793–803
23. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 30(7):804–814
24. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50(6):921–936
25. Cernuda-Morollon E, Ramon C, Larrosa D, Alvarez R, Riesco N, Pascual J (2014) Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: what happens after one year? Cephalalgia, PMID 25431141
26. Khalil M, Zafar HW, Quarshie V, Ahmed F (2014) Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U.K. J Headache Pain 15:54
27. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F (2008) The effect of sodium valproate on chronic daily headache and its subgroups. JHeadache Pain 9(1):37–41
28. Bartolini M, Silvestrini M, Taffi R, Lanciotti C, Luconi R, Capecci M et al (2005) Efficacy of topiramate and valproate in chronic migraine. Clin Neuropharmacol 28(6):277–279
29. Spira P, Beran R, Australian Gabapentin Chronic Daily Headache Group (2003) Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. Neurology 61:1753–1759
30. Krymchantowski AV, Silva MT, Barbosa JS, Alves LA (2002) Amitriptyline versus amitriptyline combined with fluoxetine in the preventative treatment of transformed migraine: a double-blind study. Headache 42(6):510–514
31. Couch JR (2010) Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache 51(1):33–51
32. Beran RG, Spira PJ (2011) Levetiracetam in chronic daily headache: a double-blind, randomised placebo-controlled study: (The Australian KEPPRA Headache Trial [AUS-KHT]). Cephalalgia 31(5):530–536
33. Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, Rodriguez-Lopez CM (2010) Pregabalin in the treatment of chronic migraine: an open-label study. Clin Neuropharmacol 33(1):35–39
34. Bermejo PE, Dorado R (2009) Zonisamide for migraine prophylaxis in patients refractory to topiramate. Clin Neuropharmacol 32(2):103–106
35. Bigal M, Rapoport A, Sheftell F, Tepper D, Tepper S (2008) Memantine in the preventive treatment of refractory migraine. Headache 48(9):1337–1342
36. Diener HC, Gaul C, Jensen R, Gobel H, Heinze A, Silberstein S (2011) Integrated headache care. Cephalalgia 31(9):1039–1047
37. Evers S, Jensen R (2011) Treatment of medication overuse headache – guideline of the EFNS headache panel. Eur J Neurol 18(9):1115–1121
38. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A et al (2006) EFNS guideline on the drug treatment of migraine – report of an EFNS task force. Eur J Neurol 13(6):560–572
39. Orr SL, Aube M, Becker WJ, Davenport WJ, Dilli E, Dodick D et al (2014) Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia 35(3):271–284
40. Zeeberg P, Olesen J, Jensen R (2009) Medication overuse headache and chronic migraine in a specialized headache centre: field-testing proposed new appendix criteria. Cephalalgia 29(2):214–220
41. Diener HC, Holle D, Dodick D (2011) Treatment of chronic migraine. Curr Pain Headache Rep 15(1):64–69

Drug Treatment for Episodic and Chronic Tension-Type Headache

9

Lars Bendtsen and Sait Ashina

9.1 Introduction

Tension-type headache (TTH) is the second most prevalent disorder in this world [1], but still remains poorly understood and inadequately managed [2]. A review of the global prevalence and burden of headaches [3] showed that the disability of TTH as a burden of society was greater than that of migraine, which indicates that the overall cost of TTH is greater than that of migraine.

TTH is classified into three subtypes according to headache frequency: infrequent episodic TTH, frequent episodic TTH and chronic TTH [4]. This division may seem artificial but has proved to be highly relevant for several reasons. First, impact on quality of life differs considerably between the subtypes. A person having headache every day from the time of waking, persisting until bedtime, month in and month out, is disabled. At the other extreme, a mild headache once every other month has very little impact on health or functional ability and needs little if any medical attention. Thus, while infrequent episodic TTH may be trivial, frequent episodic and chronic TTH is clinically relevant. Second, the pathophysiological mechanisms may differ significantly between the subtypes; peripheral mechanisms are probably more important in episodic TTH [5], whereas central pain mechanisms are pivotal in chronic TTH [6–8]. Third, treatment differs between the subtypes, with symptomatic and prophylactic treatments being more appropriate for episodic and chronic TTH, respectively [9].

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_9

9.2 Principles of Treatment in Tension-Type Headache

A correct diagnosis is essential for successful management. The diagnosis of TTH is based on the typical patient's history and a normal neurological examination and should be assured by means of a headache diary [10] recorded over at least 4 consecutive weeks. The diagnostic problem most often encountered is to discriminate between TTH and mild migraine, since patients with frequent headaches often suffer from both disorders. We find it important to treat each disorder separately, although other experts have questioned whether TTH and migraine can be distinguished in patients with frequent headaches [11]. The diary may also reveal triggers and acute medication overuse, and it will establish the baseline against which to measure the efficacy of treatments. Identification of a high intake of analgesics is important because medication overuse requires specific treatment [12, 13]. Paraclinical investigations, in particular brain imaging, is necessary if secondary headache is suspected (e.g., the headache characteristics are untypical), if the course of headache attacks changes, or if persistent neurological or psychopathological abnormalities are present. Significant co-morbidity, e.g., anxiety or depression, should be identified and treated concomitantly as these conditions are associated with increased headache frequency. It should be explained to the patient that frequent TTH cannot be cured, but that a meaningful improvement often can be obtained with the combination of drug and non-drug treatments and that it often improves with age [9].

European guidelines for the treatment of TTH have been published by a task force of the European Federation of Neurological Societies (EFNS) [9]. In general, non-pharmacological management should always be considered in TTH [9]. When it comes to pharmacological management, the general rule is that patients with episodic TTH are treated with symptomatic (acute) drugs, while prophylactic drugs should be considered in patients with very frequent episodic TTH and in patients with chronic TTH. Analgesics are often ineffective in patients with chronic TTH. Furthermore, their frequent use produces risk of medication-overuse headache (MOH) [13] as well as systemic side effects and toxicity. The topic of this review is pharmacological management, which will be described in the following.

9.3 Acute Pharmacotherapy

Acute drug therapy refers to the treatment of individual attacks of headache in patients with episodic and chronic TTH. Most headaches in patients with episodic TTH are mild to moderate and the patients often can self-manage by using simple analgesics (paracetamol or non-steroidal anti-inflammatory drugs [NSAIDs including aspirin]). The efficacy of simple analgesics tends to decrease with increasing frequency of the headaches. In patients with chronic TTH, the headaches are often associated with stress, anxiety and depression, and simple analgesics are usually ineffective and should be used with caution because of the risk of medication-overuse headache at a regular intake of simple analgesics above 14 days a month or

combination analgesics or triptans in case of co-existent migraine above 9 days a month [14]. Other interventions such as non-drug treatments and prophylactic pharmacotherapy should be considered.

The effect of acute drugs in TTH has been examined in many studies, and these have used many different methods for measurement of efficacy. This makes comparison of results between studies difficult.

9.3.1 Simple Analgesics

Paracetamol 1000 mg was significantly more effective than placebo in most [15–21] but not all [22, 23] trials, while three trials found no significant effect of paracetamol 500–650 mg compared with placebo [15, 22, 24].

Aspirin has consistently been reported more effective than placebo in doses of 1000 mg [15, 25, 26], 500–650 mg [15, 26–28] and 250 mg [26]. One study found no difference in efficacy between solid and effervescent aspirin [28].

Ibuprofen 800 mg [27], 400 mg [18, 19, 27, 29, 30] and 200 mg [31] are more effective than placebo, as are ketoprofen 50 mg [22, 31], 25 mg [21, 23, 31] and 12.5 mg [23]. One study could not demonstrate a significant effect of ketoprofen 25 mg possibly due to a low number of patients [22]. Diclofenac 25 mg and 12.5 mg have been reported effective [29], while there are no trials of the higher doses of 50–100 mg proved effective in migraine. Naproxen 375 mg [20] and 550 mg [24, 32] and metamizole 500 and 1000 mg [25] have also been demonstrated effective. The latter drug is not available in many countries including USA and UK, because it carries a minimal (if at all) risk of causing agranulocytosis. Treatment with intramuscular injection of ketorolac 60 mg in an emergency department has been reported effective [33]. A recent systematic review examined any intervention for treating acute TTH where trials were randomised and double blind; it included 55 such trials with 12,143 patients [34]. Numbers needed to treat (NNT) values for being pain free at 2 h compared with placebo were 8.7 (95 % CI 6.2–15) for paracetamol 1000 mg, 8.9 (5.9–18) for ibuprofen 400 mg and 9.8 (5.1–146) for ketoprofen 25 mg. Lower (better) NNTs (3.5–8.4) were calculated for the outcomes of mild or no pain at 2 h, and patient global assessment. It was likely that aspirin, naproxen and diclofenac were also more effective than placebo, but there were insufficient data to be sure.

Optimal Dose There are only few studies investigating the ideal dose for drugs used for the acute treatment of TTH. One study demonstrated a significant dose-response relationship of aspirin with 1000 mg being superior to 500 and 500 mg being superior to 250 mg [26]. Ketoprofen 25 mg tended to be more effective than 12.5 mg [23], while another study found very similar effects of ketoprofen 25 and 50 mg [31]. Paracetamol 1000 mg seems to be superior to 500 mg, since only the former dose has been demonstrated effective. In lack of evidence, the most effective dose of a drug well tolerated by a patient should be chosen. Suggested doses are presented in Fig. 9.1.

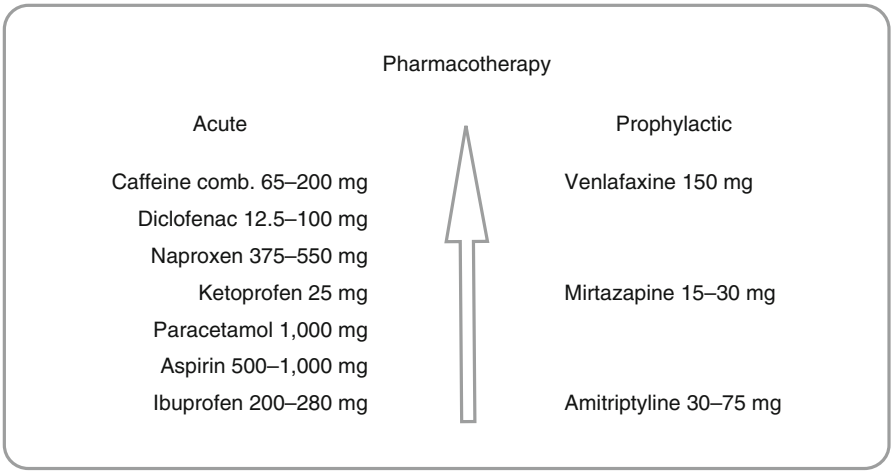

Fig. 9.1 Pharmacological treatment paradigm for tension-type headache

Comparison of Simple Analgesics Five studies reported NSAIDs to be significantly more effective than paracetamol [18, 19, 22–24], while three studies could not demonstrate a difference [15, 20, 21]. Five studies have compared efficacy of different NSAIDs, and it has not be possible to clearly demonstrate superiority of any particular drug [25, 27, 29, 31, 35].

Adverse Events A thorough review of the acute drug treatment of TTH could not detect any difference in adverse events between paracetamol and NSAIDs or between these drugs and placebo [36]. Among the NSAIDs, ibuprofen seems to have the most favourable side-effect profile [36].

9.3.2 Combination Analgesics

The efficacy of simple analgesics and NSAIDs is increased by combination with caffeine 64–200 mg [16, 17, 37–40]. There are no comparative studies examining the efficacy of combination with codeine. It is clinically well known that caffeine withdrawal can cause headache, and chronic daily headache has been reported associated with use of over-the-counter caffeine combination products [41]. Therefore, it is probable that combinations of simple analgesics or NSAIDs with caffeine are more likely to induce MOH than simple analgesics or NSAIDs alone. Until otherwise proven, we therefore recommend that simple analgesics or NSAIDs are drugs of first choice, and that combinations of one of these drugs with caffeine are drugs of second choice for the acute treatment of TTH. Combinations of simple analgesics with codeine or barbiturates should not be used, because use of the latter drugs increases the risk of developing medication-overuse headache [41, 42].

9.3.3 Triptans and Muscle Relaxants

Triptans have been reported effective for the treatment of interval headaches [43], which were most likely mild migraines [44], in patients with migraine comorbid with TTH. Triptans most likely do not have a clinically relevant effect in patients with TTH [45, 46] and cannot be recommended. Muscle relaxants have not been demonstrated effective in episodic TTH [47]. Use of opioids increases the risk of developing medication-overuse headache [41]. Opioids are not recommended for the treatment of TTH.

9.3.4 Conclusions

Simple analgesics are the mainstays in the acute therapy of TTH (Fig. 9.1). Ibuprofen 200–800 mg, ketoprofen 25 mg, aspirin 500–1000 mg, naproxen 375–550 mg, diclofenac 12.5–100 mg and paracetamol 1000 mg can be recommended [9]. Ibuprofen 400 mg may be recommended as drug of choice among the NSAIDs because of a favourable gastrointestinal side-effect profile compared with other NSAIDs [48]. Paracetamol 1000 mg is probably less effective than the NSAIDs. Combination analgesics containing caffeine are more effective than simple analgesics or NSAIDs alone but are regarded by some experts [49] to more likely induce medication-overuse headache. Physicians should be aware of the risk of developing medication-overuse headache as a result of frequent and excessive use of all types of analgesics in acute therapy [13]. Triptans, muscle relaxants and opioids do not play a role in the treatment of TTH.

9.4 Prophylactic Pharmacotherapy

Prophylactic pharmacotherapy should be considered in patients with chronic TTH, and it can be considered in patients with very frequent episodic TTH. Comorbid disorders or conditions, e.g., overweight or depression should be taken into account. For many years, the tricyclic antidepressant amitriptyline has been used. More lately other antidepressants, NSAIDs, muscle relaxants, anticonvulsants and botulinum toxin have been tested in chronic TTH. The effect of prophylactic drugs in TTH has been examined in surprisingly few placebo-controlled studies, which have used different methods for measurement of efficacy. The guidelines for drug trials in TTH from the International Headache Society recommend days with TTH or area-under-the-headache curve (AUC) to be used as primary efficacy measure [50]. These parameters have been used in some studies, while other studies have used other efficacy measures such as pain reduction from baseline, headache intensity, etc. This makes comparison of results between studies difficult.

9.4.1 Amitriptyline

Lance and Curran [51] reported amitriptyline 10–25 mg three times daily to be effective, while Diamond and Baltes [52] found amitriptyline 10 mg/day but not 60 mg/day to be effective. Amitriptyline 75 mg/day was reported to reduce headache duration in the last week of a 6-week study [53], while no difference in effect size between amitriptyline 50–75 mg/day or amitriptylinoxide 60–90 mg/day and placebo was found in one study [54]. However, also the frequencies of side effects were similar on amitriptyline and placebo in the latter study. The inability to detect the well-known side effects of amitriptyline suggests insensitivity of the trial for reasons which remain obscure. Bendtsen et al. [55] found that amitriptyline 75 mg daily reduced the area-under-the-headache curve (calculated as headache duration times headache intensity) by 30 % compared with placebo, which was highly significant. Holroyd and colleagues [56] treated patients with antidepressants (83 % took amitriptyline median dose 75 mg daily and 17 % took nortriptyline median dose 50 mg daily) and compared this with stress management therapy and with a combination of stress management and antidepressant treatment. After 6 months, all three treatments reduced headache index with approximately 30 % more than placebo, which was highly significant. The effect tended to be greatest in the combined treatment group.

9.4.2 Other Antidepressants

The tricyclic antidepressant clomipramine 75–150 mg daily [57] and the tetracyclic antidepressants maprotiline 75 mg daily [58] and mianserin 30–60 mg daily [57] have been reported more effective than placebo. Interestingly, some of the newer more selective antidepressants with action on serotonin and noradrenaline seem to be as effective as amitriptyline with the advantage that they are tolerated in doses needed for the treatment of a concomitant depression. Thus, the noradrenergic and specific serotonergic antidepressant mirtazapine 30 mg/day reduced headache index by 34 % more than placebo in difficult to treat patients without depression including patients who had not responded to amitriptyline [59]. The efficacy of mirtazapine was comparable to that of amitriptyline reported by the same group [55]. A systematic review concluded that the two treatments may be equally effective for the treatment of chronic TTH [60]. The serotonin and noradrenaline reuptake inhibitor venlafaxine 150 mg/day [61] reduced headache days from 15 to 12 per month in a mixed group of patients with either frequent episodic or chronic TTH. Low-dose mirtazapine 4.5 mg/day alone or in combination with ibuprofen 400 mg/day was not effective in chronic TTH. The selective serotonin reuptake inhibitors (SSRIs) citalopram [55] and sertraline [62] have not been found more effective than placebo. SSRIs have been compared with other antidepressants in six studies. These studies were reviewed in a Cochrane analysis that concluded that SSRIs are less efficacious than tricyclic antidepressants for the treatment of chronic TTH [63].

9.4.3 Miscellaneous Agents

There have been conflicting results for treatment with the muscle relaxant tizanidine [58, 64], while the NMDA-antagonist memantine was not effective [65]. Botulinum toxin has been extensively studied [66–76]. It was concluded in a systematic review that botulinum toxin is likely to be ineffective or harmful for the treatment of chronic TTH [60]. The prophylactic effect of daily intake of simple analgesics has not been studied in trials that had this as the primary efficacy parameter, but explanatory analyses indicated that ibuprofen 400 mg/day was not effective in one study [77]. On the contrary, ibuprofen increased headache compared with placebo indicating a possible early onset of medication-overuse headache [77]. Topiramate [78] and buspirone [79] have been reported effective in open-label studies.

9.4.4 Conclusions

Amitriptyline has a clinically relevant prophylactic effect in patients with chronic TTH and should be drug of first choice (Fig. 9.1). Mirtazapine or venlafaxine are probably effective, while the older tricyclic and tetracyclic antidepressants clomipramine, maprotiline and mianserin may be effective. A recent systematic review [60] concluded that amitriptyline and mirtazapine are the only forms of treatment that can be considered proven beneficial for the treatment of chronic TTH. However, the last search was performed in 2007 before publication of the study on venlafaxine [61].

Amitriptyline should be started at low dosages (10–25 mg/day) and titrated by 10–25 mg weekly until the patient has either good therapeutic effect or side effects are encountered. It is important that patients are informed that this is an antidepressant agent but has an independent action on pain. The maintenance dose is usually 30–75 mg daily administered 1–2 h before bedtime to help to circumvent any sedative adverse effects. The effect is not related to the presence of depression [55]. A significant effect of amitriptyline may be observed already in the first week on the therapeutic dose [55]. It is therefore advisable to change to other prophylactic therapy, if the patient does not respond after 4–8 weeks on maintenance dose. The side effects of amitriptyline include dry mouth, drowsiness, dizziness, obstipation and weight gain. Mirtazapine, of which the major side effects are drowsiness and weight gain, or venlafaxine, of which the major side effects are vomiting, nausea, dizziness and loss of libido, should be considered if amitriptyline is not effective or not tolerated. Discontinuation should be attempted every 6–12 months. The physician should keep in mind that the efficacy of preventive drug therapy in TTH is often modest, and that the efficacy should outweigh the side effects.

Amitriptyline is drug of first choice for the prophylactic treatment of chronic TTH. Mirtazapine and venlafaxine are drugs of second choice.

Declaration of Interests Lars Bendtsen has received honoraria for lectures from MSD, Allergan and Pfizer, serves on the scientific advisory board for Berlin-Chemie, has been a consultant to

Reckitt Benckiser and been on Reckitt Benckiser speaker panels and has been principal investigator for Convergence Pharmaceuticals.

Sait Ashina received honoraria for lecturing from Allergan, Nautilus Neurosciences and NeurogesX and served as a consultant for Depomed.

References

1. Vos T, Flaxman AD, Naghavi M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2163–2196
2. Schwartz BS, Stewart WF, Lipton RB (1997) Lost workdays and decreased work effectiveness associated with headache in the workplace. J Occup Environ Med 39:320–327
3. Stovner L, Hagen K, Jensen R et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 27:193–210
4. Headache Classification Subcommittee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:629–808
5. Bendtsen L, Fernandez-de-la-Penas C (2011) The role of muscles in tension-type headache. Curr Pain Headache Rep 15:451–458
6. Bezov D, Ashina S, Jensen R, Bendtsen L (2011) Pain perception studies in tension-type headache. Headache 51:262–271
7. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R (2008) Increased pain sensitivity is not a risk factor but a consequence of frequent headache: a population-based follow-up study. Pain 137:623–630
8. Bendtsen L (2000) Central sensitization in tension-type headache – possible pathophysiological mechanisms. Cephalalgia 20:486–508
9. Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J (2010) EFNS guideline on the treatment of tension-type headache – report of an EFNS task force. Eur J Neurol 17:1318–1325
10. Russell MB, Rasmussen BK, Brennum J, Iversen HK, Jensen R, Olesen J (1992) Presentation of a new instrument: the diagnostic headache diary. Cephalalgia 12:369–374
11. Manzoni GC, Torelli P (2009) Chronic migraine and chronic tension-type headache: are they the same or different? Neurol Sci 30(Suppl 1):S81–S84
12. Bendtsen L, Munksgaard S, Tassorelli C et al (2014) Disability, anxiety and depression associated with medication-overuse headache can be considerably reduced by detoxification and prophylactic treatment. Results from a multicentre, multinational study (COMOESTAS project). Cephalalgia 34:426–433
13. Katsarava Z, Jensen R (2007) Medication-overuse headache: where are we now? Curr Opin Neurol 20:326–330
14. Olesen J, Bousser MG, Diener HC et al (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
15. Steiner TJ, Lange R, Voelker M (2003) Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. Cephalalgia 23:59–66
16. Schachtel BP, Thoden WR, Konerman JP, Brown A, Chaing DS (1991) Headache pain model for assessing and comparing the efficacy of over-the-counter analgesic agents. Clin Pharmacol Ther 50:322–329
17. Migliardi JR, Armellino JJ, Friedman M, Gillings DB, Beaver WT (1994) Caffeine as an analgesic adjuvant in tension headache. Clin Pharmacol Ther 56:576–586
18. Schachtel BP, Furey SA, Thoden WR (1996) Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. J Clin Pharmacol 36:1120–1125
19. Packman B, Packman E, Doyle G et al (2000) Solubilized ibuprofen: evaluation of onset, relief, and safety of a novel formulation in the treatment of episodic tension-type headache. Headache 40:561–567

20. Prior MJ, Cooper KM, May LG, Bowen DL (2002) Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial. Cephalalgia 22:740–748
21. Steiner TJ, Lange R (1998) Ketoprofen (25 mg) in the symptomatic treatment of episodic tension-type headache: double-blind placebo-controlled comparison with acetaminophen (1000 mg). Cephalalgia 18:38–43
22. Dahlöf CGH, Jacobs LD (1996) Ketoprofen, paracetamol and placebo in the treatment of episodic tension-type headache. Cephalalgia 16:117–123
23. Mehlisch DR, Weaver M, Fladung B (1998) Ketoprofen, acetaminophen, and placebo in the treatment of tension headache. Headache 38:579–589
24. Miller DS, Talbot CA, Simpson W, Korey A (1987) A comparison of naproxen sodium, acetaminophen and placebo in the treatment of muscle contraction headache. Headache 27:392–396
25. Martinez-Martin P, Raffaelli E Jr, Titus F et al (2001) Efficacy and safety of metamizol vs. acetylsalicylic acid in patients with moderate episodic tension-type headache: a randomized, double-blind, placebo- and active-controlled, multicentre study. Cephalalgia 21: 604–610
26. Von Graffenried B, Nuesch E (1980) Non-migrainous headache for the evaluation of oral analgesics. Br J Clin Pharmacol 10(Suppl 2):225S–231S
27. Diamond S (1983) Ibuprofen versus aspirin and placebo in the treatment of muscle contraction headache. Headache 23:206–210
28. Langemark M, Olesen J (1987) Effervescent ASA versus solid ASA in the treatment of tension headache. A double-blind, placebo controlled study. Headache 27:90–95
29. Kubitzek F, Ziegler G, Gold MS, Liu JM, Ionescu E (2003) Low-dose diclofenac potassium in the treatment of episodic tension-type headache. Eur J Pain 7:155–162
30. Schachtel BP, Thoden WR (1988) Onset of action of ibuprofen in the treatment of muscle-contraction headache. Headache 28:471–474
31. van Gerven JM, Schoemaker RC, Jacobs LD et al (1996) Self-medication of a single headache episode with ketoprofen, ibuprofen or placebo, home-monitored with an electronic patient diary. Br J Clin Pharmacol 42:475–481
32. Pini LA, Del BE, Zanchin G et al (2008) Tolerability and efficacy of a combination of paracetamol and caffeine in the treatment of tension-type headache: a randomised, double-blind, double-dummy, cross-over study versus placebo and naproxen sodium. J Headache Pain 9:367–373
33. Harden RN, Rogers D, Fink K, Gracely RH (1998) Controlled trial of ketorolac in tension-type headache. Neurology 50:507–509
34. Moore RA, Derry S, Wiffen PJ, Straube S, Bendtsen L (2014) Evidence for efficacy of acute treatment of episodic tension-type headache: methodological critique of randomised trials for oral treatments. Pain 155:2220–2228
35. Lange R, Lentz R (1995) Comparison ketoprofen, ibuprofen and naproxen sodium in the treatment of tension-type headache. Drugs Exp Clin Res 21:89–96
36. Verhagen AP, Damen L, Berger MY, Passchier J, Merlijn V, Koes BW (2006) Is any one analgesic superior for episodic tension-type headache? J Fam Pract 55:1064–1072
37. Ward N, Whitney C, Avery D, Dunner D (1991) The analgesic effects of caffeine in headache. Pain 44:151–155
38. Diamond S, Balm TK, Freitag FG (2000) Ibuprofen plus caffeine in the treatment of tension-type headache. Clin Pharmacol Ther 68:312–319
39. Diener HC, Pfaffenrath V, Pageler L, Peil H, Aicher B (2005) The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 25:776–787
40. Cerbo R, Centonze V, Grazioli I et al (2005) Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine in the treatment of episodic tension-type headache: a double-blind, randomized, nimesulide-controlled, parallel group, multicentre trial. Eur J Neurol 12:759–767

41. Scher AI, Lipton RB, Stewart WF, Bigal M (2010) Patterns of medication use by chronic and episodic headache sufferers in the general population: results from the frequent headache epidemiology study. Cephalalgia 30:321–328
42. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–1168
43. Cady RK, Gutterman D, Saiers JA, Beach ME (1997) Responsiveness of non-IHS migraine and tension-type headache to sumatriptan. Cephalalgia 17:588–590
44. Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C (2002) Diagnostic lessons from the spectrum study. Neurology 58:S27–S31
45. Brennum J, Brinck T, Schriver L et al (1996) Sumatriptan has no clinically relevant effect in the treatment of episodic tension-type headache. Eur J Neurol 3:23–28
46. Brennum J, Kjeldsen M, Olesen J (1992) The 5-HT1-like agonist sumatriptan has a significant effect in chronic tension-type headache. Cephalalgia 12:375–379
47. Mathew N, Ashina M (2005) Acute pharmacotherapy of tension-type headaches. In: Olesen J, Goadsby PJ, Ramadan N, Tfelt-Hansen P, Welch KM (eds) The headaches, 3rd edn. Lippincott Williams Wilkins, Philadelphia, pp 727–733
48. Langman MJ, Weil J, Wainwright P et al (1994) Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 343:1075–1078
49. Bigal ME, Lipton RB (2009) Overuse of acute migraine medications and migraine chronification. Curr Pain Headache Rep 13:301–307
50. Bendtsen L, Bigal ME, Cerbo R et al (2010) Guidelines for controlled trials of drugs in tension-type headache: second edition. Cephalalgia 30:1–16
51. Lance JW, Curran DA (1964) Treatment of chronic tension headache. Lancet 1:1236–1239
52. Diamond S, Baltes BJ (1971) Chronic tension headache – treated with amitriptyline – a double-blind study. Headache 11:110–116
53. Göbel H, Hamouz V, Hansen C et al (1994) Chronic tension-type headache: amitriptyline reduces clinical headache-duration and experimental pain sensitivity but does not alter pericranial muscle activity readings. Pain 59:241–249
54. Pfaffenrath V, Diener HC, Isler H et al (1994) Efficacy and tolerability of amitriptylinoxide in the treatment of chronic tension-type headache: a multi-centre controlled study. Cephalalgia 14:149–155
55. Bendtsen L, Jensen R, Olesen J (1996) A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry 61:285–290
56. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW (2001) Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. JAMA 285:2208–2215
57. Langemark M, Loldrup D, Bech P, Olesen J (1990) Clomipramine and mianserin in the treatment of chronic tension headache. A double-blind, controlled study. Headache 30:118–121
58. Fogelholm R, Murros K (1992) Tizanidine in chronic tension-type headache: a placebo controlled double-blind cross-over study. Headache 32:509–513
59. Bendtsen L, Jensen R (2004) Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. Neurology 62:1706–1711
60. Krishnan A, Silver N (2009) Headache (chronic tension-type). BMJ Clin Evid pii: 1205
61. Zissis N, Harmoussi S, Vlaikidis N et al (2007) A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. Cephalalgia 27:315–324
62. Singh NN, Misra S (2002) Sertraline in chronic tension-type headache. J Assoc Physicians India 50:873–878

63. Moja PL, Cusi C, Sterzi RR, Canepari C (2005) Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Cochrane Database Syst Rev (3):CD002919
64. Murros K, Kataja M, Hedman C et al (2000) Modified-release formulation of tizanidine in chronic tension-type headache. Headache 40:633–637
65. Lindelof K, Bendtsen L (2009) Memantine for prophylaxis of chronic tension-type headache–a double-blind, randomized, crossover clinical trial. Cephalalgia 29:314–321
66. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL (2004) Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia 24:675–680
67. Relja M, Telarovic S (2004) Botulinum toxin in tension-type headache. J Neurol 251(Suppl 1):12–14
68. Rollnik JD, Tanneberger O, Schubert M, Schneider U, Dengler R (2000) Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. Headache 40:300–305
69. Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM (2001) Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 41:658–664
70. Schulte-Mattler WJ, Krack P, BoNTTH Study Group (2004) Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. Pain 109:110–114
71. Smuts JA, Baker MK, Smuts HM (1999) Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. Eur J Neurol 6(Suppl):S99–S102
72. Göbel H, Lindner V, Krack PK (1999) Treatment of chronic tension-type headache with botulinum toxin, a double blind, placebo-controlled clinical trial. Cephalalgia 19:455
73. Silberstein SD, Gobel H, Jensen R et al (2006) Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 26:790–800
74. Kokoska MS, Glaser DA, Burch CM, Hollenbeak CS (2004) Botulinum toxin injections for the treatment of frontal tension headache. J Headache Pain 5:103–109
75. Harden RN, Cottrill J, Gagnon CM et al (2009) Botulinum toxin a in the treatment of chronic tension-type headache with cervical myofascial trigger points: a randomized, double-blind, placebo-controlled pilot study. Headache 49:732–743
76. Straube A, Empl M, Ceballos-Baumann A, Tolle T, Stefenelli U, Pfaffenrath V (2008) Pericranial injection of botulinum toxin type A (Dysport) for tension-type headache – a multicentre, double-blind, randomized, placebo-controlled study. Eur J Neurol 15:205–213
77. Bendtsen L, Buchgreitz L, Ashina S, Jensen R (2007) Combination of low-dose mirtazapine and ibuprofen for prophylaxis of chronic tension-type headache. Eur J Neurol 14:187–193
78. Lampl C, Marecek S, May A, Bendtsen L (2006) A prospective, open-label, long-term study of the efficacy and tolerability of topiramate in the prophylaxis of chronic tension-type headache. Cephalalgia 26:1203–1208
79. Mitsikostas DD, Gatzonis S, Thomas A, Ilias A (1997) Buspirone vs amitriptyline in the treatment of chronic tension-type headache. Acta Neurol Scand 96:247–251

Cluster Headache: Acute and Transitional Treatment

10

Peter J. Goadsby

10.1 Introduction

Cluster headache is a member of the broad family of primary headache disorders known as trigeminal autonomic cephalalgias (TACs) [1]. These disorders are characterized by unilateral head pain occurring in association with prominent ipsilateral cranial autonomic features, such as lacrimation, conjunctival injection or nasal symptoms [1]. The other TACs are paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA), and hemicrania continua [2]. These will not be further considered.

10.2 Clinical Background

Cluster headache is the most common of the TACs with a 1-year prevalence of 0.1 % [3]. It is perhaps the most painful condition for humans; of the more than 1000 patients the author has seen, not a single one has had a more painful experience, including childbirth, multiple fractures of the limbs or renal stones. Its treatment principles fall around prevention, covered elsewhere in this volume, and acute/transitional therapy. Given the very considerable suffering of patients, acute therapy must be rapid, reliable and effective. It is imperative that any patient with cluster headache has appropriate access to treatment of their acute attacks (Table 10.1).

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_10

Table 10.1 Diagnostic criteria for cluster headache (after ICHD-3, 2)

3.1 Diagnostic criteria:
A. At least 5 attacks fulfilling B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min if untreated
C. Headache is accompanied by at least one of the following:
1. Ipsilateral conjunctival injection and/or lacrimation
2. Ipsilateral nasal congestion and/or rhinorrhoea
3. Forehead and facial sweating
4. Ipsilateral eyelid oedema
5. Ipsilateral forehead and facial sweating
6. Ipsilateral miosis and/or ptosis
7. A sense of restlessness or agitation
D. Attacks have a frequency from 1 every other day to 8/day
E. Not attributed to another disorder
3.1.1 Episodic cluster headache
Description: Occurs in periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or more
Diagnostic criteria:
A. All fulfilling criteria A–E of 3.1
B. At least 2 cluster periods lasting from 7 to 365 days and separated by pain-free remissions of ≥1 month
3.1.2 Chronic cluster headache
Description: Attacks occur for more than 1 year without remission or with remissions lasting less than 1 month
Diagnostic criteria:
A. All alphabetical headings of 3.1
B. Attacks recur over >1 year without remission periods or with remission periods <1 month

Core features of cluster headache are its periodicity, be it circadian or in terms of active and inactive bouts over weeks and months, and the lateralization of the pain. The typical cluster headache patient is male, with a 3:1 predominance, who has bouts of one to two attacks of relatively short duration unilateral pain every day for 8–10 weeks a year [4]. They are generally perfectly well between times. Patients with cluster headache tend to move about during attacks, pacing, rocking or even rubbing their head for relief. The pain is usually retro-orbital boring and very severe. It is associated with ipsilateral symptoms of cranial (parasympathetic) autonomic activation: a red or watering eye, the nose running or blocking, or cranial sympathetic dysfunction: eyelid droop. Cluster headache is likely to be a disorder involving neurons in or around the central pacemaker regions of the posterior hypothalamic grey matter [5, 6]. While cluster headache patients may also experience nausea, photophobia and phonophobia, the latter particularly photophobia tends to be ipsilateral to the pain in TACs [7].

10.3 Oxygen for Acute Cluster Headache

Treatment of acute cluster headache with 100 % oxygen was first suggested in the early 1950s [8]; interestingly it is not clear what the basis for the suggestion was [9]. Janks [10] set the use out very clearly as a sufferer himself, contributing the need for a rate of 10 L/min. Kudrow [11] reported the first series using 100 % oxygen at 7 L/min noting three-quarters of patients responded. He also reported oxygen to be better than sublingual ergotamine.

The scientific study of oxygen in cluster headache began with Fogan [12] who reported 19 patients in whom he compared air and oxygen, at 6 L/min, in a crossover study. Eleven patients completed the crossover. Oxygen was more effective than air.

The only substantial, well-powered study of oxygen in cluster headache used a double-blind, placebo (air)-controlled crossover design to treat four attacks in a balanced allocation. Oxygen 100 % at 12 L/min for 15 min rendered 78 % of patients pain free at 15 min while air rendered 20 % of patients pain free; the difference was highly significant with 78 subjects treating 298 attacks [13]. Oxygen reduced associated features and was extremely well tolerated. A proportion of patients have a rebound effect after the oxygen is stopped with the attacks returning; there is no large database to estimate this with although experience suggests it happens in up to one-third of patients. It can be responsible for a perception that attack frequency has been increased [14].

Hyperbaric oxygen offers no advantages [15–17] and very considerable logistical challenges such that it cannot be recommended.

10.4 Triptans-Serotonin 5-$HT_{1B/1D}$ Receptor Agonists

Triptans were primarily developed by Humphrey and colleagues [18] for the acute treatment of migraine. The broad pharmacology of the triptans is similar [19], while there are some differences in pharmacokinetics and thus far only sumatriptan is available as an injection.

10.4.1 Sumatriptan by Injection

Sumatriptan 6 mg s/c was first shown to be effective in a randomized, double-blind, placebo-controlled crossover study in acute cluster headache where with a 10 % placebo response rate compared to a 46 % pain-free response for sumatriptan at 15 min. Thirteen per cent of the sumatriptan arm went on to use rescue oxygen while 49 % of the placebo arm rescued with oxygen [20]. In a dose-ranging study, sumatriptan 6 mg had a 75 % response rate at 15 min while 12 mg had a response rate of 80 % with overlapping confidence intervals [21]. Absent meaningful differences, the 6 mg was licensed. There is no attenuation of the effect even with very long bouts or in patients with chronic cluster headache [22, 23]. Sumatriptan 6 mg s/c is very fairly regarded as a gold-standard treatment of acute cluster headache [24].

10.4.2 Triptans – Intranasal

Sumatriptan 20 mg nasal spray was compared to placebo in a randomized placebo-controlled, two-attack crossover study. At 30 min, 47 % of patients using sumatriptan and 18 % using placebo were pain free, with a clear and significant benefit for active treatment [25]. While clearly not as effective in population terms as the injection, an important group of patients can derive benefit from the nasal spray. Having shown zolmitriptan 10 mg orally could be helpful in cluster headache [26], zolmitriptan 5 and 10 mg nasal spray were compared to placebo in two randomized double-blind, placebo-controlled three-attack crossover studies. In the European study, the pain-free rate at 30 min was 28 % for zolmitriptan 5 mg and 16 % for placebo [27]. In the US study, the pain-free rate at 15 min was 39 % for zolmitriptan 5 mg and 20 % for placebo [28]. Both the sumatriptan and zolmitriptan studies included patients with episodic and chronic cluster headache, as well as male and female patients, and neither of these variables predicted outcome. While slower in onset, and being useful for less number of patients, there are those who certainly find nasal sprays useful.

10.5 Dihydroergotamine

Parenteral dihydroergotamine (DHE) has been considered to be an effective abortive agent for cluster headaches for some time [8, 29]. There are no controlled trials of injectable DHE; however, clinical experience has demonstrated that intravenous administration can be helpful even when attacks have been resistant to other treatments [30]. DHE nasal spray 1 mg in a double-blind, placebo-controlled, crossover trial in 25 patients demonstrated a significant reduction in pain intensity in acute cluster headache [31]. The development of new, inhaled formulation thus far studied in migraine may be very useful and should certainly be tested in the cluster headache [32].

10.6 Lidocaine – Intranasal

Lidocaine (10 %) was reported to be effective at aborting nitroglycerin-induced cluster attacks in a double-blind, placebo-controlled study in nine patients [33]. Lidocaine or saline was applied for 5 min using a cotton swab in the area corresponding to the pterygopalatine fossa, under anterior rhinoscopy. The onset of effect was slow and the method not applicable to most patients. Based on this evidence, and our experience of a modest adjunctive effect, lidocaine solution 20–60 mg, given as nasal drops (4–6 % lidocaine solution) is prescribed, and applied bilaterally in the region of the pterygopalatine fossa. To ensure that the solution reaches the pterygopalatine foramen, the patient should be instructed to lie down horizontally as early as possible during an attack, with the head extending out of the bed, bent downwards 30–45° and rotated 20–30° towards the side of the headache. The tip of

the dropper is inserted above the rostral end of the inferior turbinate and pushed inwards as deep as possible before dripping. The patient should be asked to maintain the position for about 2–5 min. It is certainly a cumbersome approach so that few patients find it useful in the medium term.

10.7 Octreotide by Injection

Octreotide is a somatostatin SST2 receptor agonist [34]. A link between pituitary tumour-headache clinical presentations and trigeminal autonomic cephalalgias [35] led to octreotide's exploration in an initial proof-of-principle study. In a double-blind, placebo-controlled two-attack crossover study, octreotide 100 mcg was compared to placebo. At 15 min after injection 33 % of patients treated with octreotide and 13 % treated with placebo were pain free [36]. The treatment was well tolerated, and although not practical for cost reasons, and possible rebound headache [37], the possibility of other SST receptor agonists being developed is an important prospect for the future.

10.8 Transitional Treatments

The use of transitional treatments is advised in cluster headache where this means a strategy to bridge the patient in a bout to reduce attack frequency quickly.

10.8.1 Greater Occipital Nerve (GON) Injection

Anthony [38] described the successful use of local anaesthetic and corticosteroid injections around the greater occipital nerve (GON) homolateral to the pain. Open-label experience suggests this effect is seen in two-thirds of patients for 6–8 weeks [39]. In a randomized double-blind placebo controlled study, GON injection aborted attacks in both episodic and chronic cluster headache [40]. Furthermore, it has been shown that three repeated injections with corticosteroids alone is superior to placebo as an add-on when starting verapamil in the sub-acute setting [41]. The effect is stable and reproducible over time [42].

10.8.2 Corticosteroids

The use of corticosteroids in cluster headache was established in a double-blind trial by Jammes [43]. Soon after Couch and Ziegler [44] reported that prednisolone (prednisone) 10–80 mg/day employed in 19 cluster headache patients (9 episodic, 10 chronic) provided greater than 50 % relief in 14 patients. Kudrow [45] reported that, of 77 episodic cluster patients unresponsive to methysergide, prednisolone (prednisone) relieved 77 %.

The use of corticosteroids is contraindicated by a past history of the tuberculosis or psychotic disturbance. Caution should be exercised because of the potential for serious side effects. Bone problems with steroid use have been reviewed, and the shortest course of prednisolone (prednisone) reported to be associated with osteonecrosis of the femoral head is a 30-day course. Furthermore, courses of adrenocorticotropic hormone have produced osteonecrosis after 16 days, and dexamethasone after 7 days [46]. Thus, a tapering course of prednisolone (prednisone) for 21 days is prudent, with an excess risk for bone problems occurring if more than two courses are administered per year [46]. The author starts patients on oral prednisolone (prednisone) 1 mg/kg, to a maximum of 60 mg daily for 5 days and thereafter decreases the dose by 10 mg every 3 days. Unfortunately, relapse almost invariably occurs as the dose is tapered, so this must be truly regarded in most patients as a transitional approach to longer lasting preventives.

References

1. Goadsby PJ, Lipton RB (1997) A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic features, including new cases. Brain 120:193–209
2. Headache Classification Committee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:629–808
3. Olesen J, Tfelt-Hansen P, Ramadan N, Goadsby PJ, Welch KMA (2005) The headaches. Lippincott, Williams & Wilkins, Philadelphia
4. Nesbitt AD, Goadsby PJ (2012) Cluster headache. Br Med J 344, e2407
5. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ (1998) Hypothalamic activation in cluster headache attacks. Lancet 352:275–278
6. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RSJ et al (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5:836–838
7. Irimia P, Cittadini E, Paemeleire K, Cohen AS, Goadsby PJ (2008) Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia 28:626–630
8. Horton BT (1952) Histaminic cephalgia. J Lancet 72:92–98
9. Haane DY, Dirkx TH, Koehler PJ (2012) The history of oxygen inhalation as a treatment for cluster headache. Cephalalgia 32(12):932–939
10. Janks J (1978) Oxygen for cluster headaches. JAMA 239:191
11. Kudrow L (1981) Response of cluster headache attacks to oxygen inhalation. Headache 21:1–4
12. Fogan L (1985) Treatment of cluster headache: a double blind comparison of oxygen vs air inhalation. Arch Neurol 42:362–363
13. Cohen AS, Burns B, Goadsby PJ (2009) High flow oxygen for treatment of cluster headache. A randomized trial. JAMA 302:2451–2457
14. Geerlings RP, Haane DY, Koehler PJ (2011) Rebound following oxygen therapy in cluster headache. Cephalalgia 31:1145–1149
15. Weiss LD (1989) Treatment of a cluster headache patient in a hyperbaric chamber. Headache 29:109–110
16. Di Sabato F, Fusco BM, Pelaia P, Giacovazzo M (1993) Hyperbaric oxygen therapy in cluster headache. Pain 52:243–245

17. Nilsson Remahl AIM, Ansjon R, Lind F, Waldenlind E (2002) Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. Cephalalgia 22:730–739
18. Humphrey PPA, Feniuk W, Perren MJ, Beresford IJM, Skingle M, Whalley ET (1990) Serotonin and migraine. Ann N Y Acad Sci 600:587–598
19. Goadsby PJ (2000) The pharmacology of headache. Prog Neurobiol 62:509–525
20. The Sumatriptan Cluster Headache Study Group (1991) Treatment of acute cluster headache with sumatriptan. N Engl J Med 325:322–326
21. Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D (1993) Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. Acta Neurol Scand 88:63–69
22. Ekbom K, Krabbe A, Micelli G, Prusinski A, Cole JA, Pilgrim AJ et al (1995) Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). Cephalalgia 15:230–236
23. Ekbom K, Waldenlind E, Cole JA, Pilgrim AJ, Kirkham A (1992) Sumatriptan in chronic cluster headache: results of continuous treatment for eleven months. Cephalalgia 12:254–256
24. Goadsby PJ (1994) Cluster headache and the clinical profile of sumatriptan. Eur Neurol 34(Suppl 2):35–39
25. van Vliet JA, Bahra A, Martin V, Aurora SK, Mathew NT, Ferrari MD et al (2003) Intranasal sumatriptan in cluster headache- randomized placebo-controlled double-blind study. Neurology 60:630–633
26. Bahra A, Gawel MJ, Hardebo J-E, Millson D, Brean SA, Goadsby PJ (2000) Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology 54:1832–1839
27. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ (2006) Effectiveness of intranasal zolmitriptan in acute cluster headache. A randomized, placebo-controlled, double-blind crossover study. Arch Neurol 63:1537–1542
28. Rapoport AM, Mathew NT, Silberstein SD, Dodick D, Tepper SJ, Sheftell FD et al (2007) Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. Neurology 69:821–826
29. Friedman AP, Mikropoulos HE (1958) Cluster headache. Neurology (Minneapolis) 8:653–663
30. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ (2011) Intravenous dihydroergotamine (DHE) for inpatient management of refractory primary headaches. Neurology 77:1827–1832
31. Andersson PG, Jespersen LT (1986) Dihydroergotamine nasal spray in the treatment of attacks of cluster headache. Cephalalgia 6:51–54
32. Aurora SK, Silberstein SD, Kori SH, Tepper SJ, Borland SW, Wang M et al (2011) MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. Headache 51:507–517
33. Costa A, Pucci E, Antonaci F, Sances G, Granella F, Broich G et al (2000) The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. Cephalalgia 20:85–91
34. Lesche S, Lehmann D, Nagel F, Schmid HA, Schulz S (2009) Differential effects of octreotide and pasireotide on somatostatin receptor internalization and trafficking in vitro. J Clin Endocrinol Metab 94(2):654–661
35. Levy M, Matharu MS, Meeran K, Powell M, Goadsby PJ (2005) The clinical characteristics of headache in patients with pituitary tumours. Brain 128:1921–1930
36. Matharu MS, Levy MJ, Meeran K, Goadsby PJ (2004) Subcutaneous octreotide in cluster headache- randomized placebo-controlled double-blind cross-over study. Ann Neurol 56:488–494
37. Levy MJ, Barakat M, Bejon P, Goadsby PJ, Meeran K (2003) Acromegaly: a unique human headache model? Headache 43:794–797
38. Anthony M (1985) Arrest of attacks of cluster headache by local steroid injection of the occipital nerve. In: Rose FC (ed) Migraine: clinical and research advances. Karger, London, pp 169–173

39. Afridi SK, Shields KG, Bhola R, Goadsby PJ (2006) Greater occipital nerve injection in primary headache syndromes- prolonged effects from a single injection. Pain 122:126–129
40. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F et al (2005) Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 118:92–96
41. Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C et al (2011) Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 10:891–897
42. Gantenbein AR, Lutz NJ, Riederer F, Sandor PS (2012) Efficacy and safety of 121 injections of the greater occipital nerve in episodic and chronic cluster headache. Cephalalgia 32:630–634
43. Jammes JL (1975) The treatment of cluster headaches with prednisone. Dis Nerv Syst 36:375–376
44. Couch JR, Ziegler DK (1978) Prednisone therapy for cluster headache. Headache 18:219–221
45. Kudrow L (1980) Cluster headache: mechanisms and management. Oxford University Press, Oxford
46. Mirzai R, Chang C, Greenspan A, Gershwin ME (1999) The pathogenesis of osteonecrosis and the relationships to corticosteroids. J Asthma 36:77–95

Cluster Headache: Preventative Treatment

11

Sarah Miller and Manjit S. Matharu

11.1 Introduction

Cluster headaches (CH) consist of attacks of severe, strictly unilateral pain occurring in the orbital, supraorbital, and temporal regions, lasting from 15 to 180 min and occurring from once every other day to eight times daily [1]. These attacks are associated with ipsilateral autonomic features and restlessness or agitation. It is important to standardize the terminology used by clinicians in CH. A cluster attack is the individual episode of pain lasting minutes to hours. The cluster bout or period is used to refer to the duration of time over which recurrent cluster attacks are occurring, usually lasting weeks to months. A remission is the period of time that is pain free between cluster bouts. About 80–90 % of patients have episodic cluster headache (ECH), which is diagnosed when cluster attacks occur in periods lasting from 7 days to 1 year and are separated by pain-free periods of at least 1 month [1, 2]. The remaining 10–20 % have chronic cluster headache (CCH) where there is either no remission periods within 1 year or the remissions last for less than 1 month [1, 2].

11.2 Transitional Treatments for Cluster Headache

Transitional treatments are fast acting treatments that provide short-term prophylaxis. As preventative medications often take weeks to exert their effect, ECH patients with short bouts (e.g., under 5 weeks) or patients where one wishes to control attack frequency quickly may benefit from such transitional treatments. These

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_11

interventions are not suitable for long-term use and so patients will often require concurrent treatment with more traditional preventatives. Greater occipital nerve blocks (GONB), corticosteroids and dihydroergotamine infusions can all be useful transitional treatments.

11.2.1 Greater Occipital Nerve Blocks

Anesthetic blockade of the greater occipital nerve has shown therapeutic efficacy in both ECH and CCH in a number of open-label and a randomized studies [3–7]. A randomized control trial (RCT) in 43 CH patients (28 ECH and 15 CCH) found that a GONB resulted in a significant reduction in daily attacks over a 15-day period compared to placebo [7]. In open-label series, response rates of around 50 % are reported again with sustained benefit for at least 4 weeks [4–6]. Adverse event data is positive, although there are isolated reports of alopecia and cutaneous atrophy secondary to the steroid component of the blockade [8–10].

11.2.2 Corticosteroids

Corticosteroids are highly efficacious and can act rapidly to control attacks. There are no adequate placebo-controlled trials on the use of corticosteroids in CH. One small, low-quality crossover RCT of low doses of prednisolone versus placebo in 19 CH patients reported a significant reduction in attack frequency in the prednisolone group [11]. Treatment should be limited to a short course of 2–3 weeks in tapering doses due to the risks of potential side effects. The authors use a regime of oral prednisolone started at a maximum of 60 mg (1 mg/kg) once daily for 5 days and then reduced by 10 mg every 3 days. As the dose decreases, the attacks invariably recur. Therefore, another long-term preventative should be started alongside the corticosteroids.

11.2.3 Dihydroergotamine

Intravenous dihydroergotamine (IV DHE) can be useful in CH refractory to other transitional or preventative measures. Open-label series from a number of centers report that between 73 and 100 % of ECH and 46–100 % of CCH patients will be rendered pain free on an infusion on IV DHE [12–14]. Benefit is often at its peak while on the infusion, but one series reported a mean of 66 days for attacks to return to pretreatment frequency [14]. Although IV DHE may have a role in the management of refractory CH, its side effect profile includes vasospastic angina, and more recently, cases of neuralgiform headache attacks developing while on treatment have been reported [15]. Due to the potential risks, the use of this drug is best reserved for specialist units only.

11.3 Preventative Treatment

Long-term preventative treatments are used to suppress the attacks for the anticipated duration of the cluster period. Agents should be started as soon as possible at the start of the bout and the dose titrated to the maximum therapeutic dose tolerated. In ECH, preventative medications should be continued until the patient is out of a bout and has been pain free for at least 2 weeks. In CCH, patients often need to stay on preventatives indefinitely.

Current European Federation of Neurological Societies guidelines give verapamil, lithium, methysergide, topiramate, valproate, melatonin, and baclofen as first-line treatments [16]. Other treatments that may prove useful in CH include gabapentin, candesartan, levetiracetam, and neuromodulation techniques.

11.3.1 Verapamil

Verapamil is the first choice drug in the prophylaxis of episode and chronic CH. One RCT evaluated the efficacy of 360 mg daily of verapamil in ECH versus placebo [17]. A statistically significant difference was seen in responder rate of treated (80 %) versus placebo (0 %) groups. Open label series have shown verapamil to be effective in reducing attack frequency in between 69 and 79 % of patients receiving 160–600 mg/daily [18, 19]

Clinical experience has demonstrated that higher doses than those used in cardiological indications are needed. Daily doses of 240–960 mg in divided doses are commonly employed. Verapamil can cause heart block and therefore electrocardiograms (ECGs) must be used to monitor PR intervals for potential prolongation or heart block. Our local policy is to conduct a baseline ECG on all patients and to then start on 120 mg two times daily, increasing by 120 mg daily increments every 14 days in a three times daily regime. An ECG is performed prior to every increment. Doses are increased until the attacks are suppressed, side effects become intolerable or the maximum dose of 960 mg/daily is achieved. Although unproven, it is our clinical experience that standard preparations of verapamil are more effective than modified-release formulations. Adverse effects with verapamil include constipation, peripheral edema, bradycardia, gastrointestinal discomfort, gingival hyperplasia, and worsening of migraine headache. Beta-blockers must not be used concurrently with verapamil.

11.3.2 Lithium

The efficacy of lithium in psychiatric disorders with a cyclical nature, such as bipolar disorder, led to the drug being tested in CH. Ekbom first used the drug in five patients (3 CCH and 2 ECH) with immediate improvement in CCH patients. Lithium has been evaluated in two randomized, double-blind trials. One failed to show the

superiority of sustained-relief lithium over placebo, and the other, a crossover RCT comparing lithium with verapamil found equivalent effects in 24 CCH patients [20, 21]. In the second RCT, both lithium and verapamil were shown to be superior to placebo [21]. A review of unblinded trials of lithium by Ekbom in 1981 identified 28 clinical trials involving 468 patients [22]. Excellent responses were found in 78 % of the 304 CCH treated but efficacy appeared less robust in ECH with 63 % of 164 ECH reporting a good response. The long-term efficacy of lithium was examined by Manzoni et al. and reported to show continued efficacy for up to 4 years on treatment [23].

Most patients benefit from dosages between 600 and 1200 mg daily. Renal and thyroid function should be measured prior to initiating treatment. The authors start patients on 300 mg twice daily of lithium and the dose is increased until the attacks are suppressed, side effects intervene or the serum lithium level is within therapeutic range. Lithium has the potential for numerous side effects and must be monitored carefully. Lithium levels should be measured 12-h after the last dose. A serum lithium level in the upper part of the therapeutic range (0.8–1.0 mEq/l) is desirable. Adverse effects include weakness, nausea, thirst, tremor, slurred speech, and blurred vision. Clinical manifestations of toxic levels of lithium are vomiting, anorexia, diarrhea, confusion, delirium, nystagmus, ataxia, extrapyramidal signs, and seizures. Hypothyroidism and polyuria (nephrogenic diabetes insipidus) can occur with long-term exposure and thus renal and thyroid function must be monitored during treatment. Lithium should not be used in conjunction with NSAIDs, diuretics, or carbamazepine.

11.3.3 Methysergide

Methysergide is a serotonergic antagonist that has been shown in a number of open-label series to be a potent agent in the treatment of CH [24–27]. Currently, it is unavailable in the United States and Europe. Methysergide was first reported effective in CH in the 1950s by Sicuteri [24]. Reviews of open-label data from the 1960s suggested that methysergide used in doses of 3–12 mg daily was effective in 73 % of the 451 CH patients studied [25]. Krabbe reported a more limited benefit in his prospective series of 42 patients (16 ECH, 26 CCH). Benefit without side effects was seen in only 26 % of 42 patients [27].

Doses up to 12 mg daily can be used if tolerated. Patients should be started on a low dose to minimize side effects. Prolonged treatment has been associated with fibrotic reactions (retroperitoneal, pulmonary, cardiac, and pleural) although these appear to be rare [28]. If prolonged use is undertaken, then it is believed that fibrotic reactions are minimized by ensuring that patients are given a 1-month drug holiday for every 6 months of therapy. In such cases, yearly checks for pulmonary, cardiac, renal or abdominal pathology should be undertaken to monitor for signs of visceral fibrosis. Patients on methysergide must remain under the supervision of the treating physician. Other side effects of methysergide include nausea, vomiting, dizziness, muscle cramps, abdominal pain, and peripheral edema. Occasionally, patients can complain of symptoms of cardiac or peripheral arterial insufficiency due to

drug-related vasoconstriction. Methysergide should not be used in patients with a history or at high risk of coronary artery disease, atherosclerosis or peripheral vascular disease, valvular heart disease, fibrotic disorders, lung disease, and known hepatic or renal dysfunction or in pregnancy. It should not be given alongside other ergot derivatives and all other vasoconstrictive agents must be used with caution.

11.3.4 Topiramate

Several open-label studies have indicated that topiramate at a dose of 100–200 mg daily may be useful in CH [29, 30]. In one study, 10 CH patients (2 CH, 8 ECH) showed rapid improvements with topiramate treatment [29]. Cluster bout duration reduced in nine patients and remission was induced in two CCH patients. Only three patients reported mild side effects. Another open-label study in five CH patients (2 ECH, 3 CCH) showed an effect in three patients. In two patients taking the drug at doses of 125 and 200 mg daily, the drug caused intolerable side effects [30].

We start topiramate at low doses (25 mg daily) and make increases of 25–50 mg every 7 days to a maximum of 400 mg daily. The usefulness of topiramate is often limited by its side-effect profile. Paresthesia, somnolence, dizziness, cognitive slowing, speech disturbance, mood changes, psychosis, and weight loss are all commonly reported. Glaucoma and nephrolithiasis have also been reported.

11.3.5 Valproic Acid

Valproic acid or valproate has an uncertain place in the treatment of CH. Although open-label series reported it to have a positive effect in between 50 and 70 % of patients, a placebo-controlled study of 96 patients failed to show any difference between valproate and placebo groups [31–33]. However, it should be noted that the placebo response in this study was unusually high. Although this was likely due to spontaneous remission, it means no valid conclusions can be drawn on the efficacy of valproate at this time. If it is to be tried, the authors recommend starting on a dose of 200 mg twice daily and increase the dosage in steps of 200 mgs twice daily every 1–2 weeks until a maximum of 1 g twice daily is reached or side effects intervene. Common adverse events on valproate include dizziness, fatigue, nausea, abdominal pain, and weight gain. Rarely, patients will develop alopecia, hepatotoxicity, or blood dyscrasias. Therefore, liver function tests and full blood counts should be monitored monthly during the titration period. Valproate should be used with caution in women of childbearing age due to the known risk of teratogenic effects.

11.3.6 Melatonin

Melatonin was tried in CH due to the observation of circadian periodicity and the importance of the hypothalamus in the pathophysiology of the disorder [34]. Results of placebo-controlled trials have been contradictory; however, this may have been

due to the relatively low doses used in the negative study [35, 36]. Our practice is to use doses of up to 15 mg daily taken at night.

11.3.7 Baclofen

Baclofen has proven useful in a variety of pain conditions. Small open-label series have appeared to show its efficacy in CH [37]. The drug should be started at a low dose of 5 mg three times daily and increased by 5 mg per dose every 7 days. Maximum therapeutic dose is 30 mg three times daily. Side effects of baclofen include nausea, vomiting, diarrhea, fatigue, drowsiness, and insomnia. Although no published evidence exists, in our experience, tizanadine, an alpha-2 antagonist, has similar properties to baclofen but tends to be better tolerated.

11.3.8 Gabapentin

Gabapentin is a medication widely used in the treatment of pain. Although it has been trialed in CH, the highly positive data from open-label series does not seem to be mirrored in clinic practice [38, 39]. It is relevant to note that although previously considered beneficial for migraine, recent RCTs and Cochrane reviews have found no evidence for its efficacy [40]. Our practice is to use a dose of up to 1200 mg three times daily when used for CH prevention. Possible side effects include dizziness, fatigue, peripheral edema, nausea, ataxia, and weight gain.

11.3.9 Candesartan

Candesartan was investigated for its efficacy in CH by Tronvik et al. in a placebo-controlled study [41]. Although the initial trial was negative, post-hoc analysis showed a reduction in attack frequency in the treatment group. Candesartan can be a useful drug, although larger scale trials are obviously needed. Candesartan can be started at a dose of 4 mg twice daily and increased weekly to a maximum of 16 mg twice daily. Renal function blood tests and full blood count should be performed around a month after reaching a stable dose. Side effects include dizziness, symptomatic hypotension, and a low white cell count.

11.3.10 Levetiracetam

Levetiracetam has low-quality evidence for its efficacy in neuropathic pain and migraine. Recently, open-label evidence has emerged for its use in CH [42]. Although published evidence is limited to five patients, our local experience is positive. We start the drug at a dose of 250 mg twice daily and increase by 250 mg per dose every 7 days until the maximum of 1.5 g twice daily is reached or side effects

intervene. The most common side effects reported are agitation, low mood, dizziness, tremor, insomnia, nausea, and anorexia and muscle pain.

11.4 Neurostimulation

Neurostimulation involves using electrical pulses to modulate the activity of the pain system. Invasive and noninvasive techniques are now available. Where possible, noninvasive techniques should be employed before attempting invasive treatments.

11.4.1 Noninvasive Neurostimulation

11.4.1.1 Vagal Nerve Stimulation

Following reports of CH improving in patients implanted with vagus nerve stimulators for epilepsy, a noninvasive vagal nerve stimulator, the gammaCore device, was developed [43]. The device can be used both as an acute treatment, where it is applied at the start of an attack, and a preventative, where it is used three times daily for at least 3 months. An initial open-label cohort series of 19 patients reported an average improvement of 48 % in 15 patients [44]. Prophylactic use resulted in a substantial reduction in daily attack frequency.

11.4.2 Invasive Neurostimulation

Due to the invasive nature of the surgery and the potential risks involved with these treatments, they should only be considered in medically refractory patients [45]. Recent data seems to support the concept that adverse event profiles of these procedures are much more favorable when a smaller number of highly experienced centers offer the surgery [46]. The European Headache Society has released an international consensus regarding the use of neuromodulation in chronic headache emphasizing these issues [47].

11.4.2.1 Sphenopalatine Ganglion (SPG) Stimulation

The SPG is an extracranial structure lying in the pterygopalatine fossa (PPF), containing parasympathetic and sympathetic neurons. It has connections to the trigeminovascular system, the superior salivatory nucleus, and the hypothalamus. A recent multicenter sham-controlled trial of on-demand SPG stimulation reported a significant difference in the number of resolved attacks in the treated group [48]. Pain relief was achieved in 67 % of treated attacks compared to 7 % of sham-treated attacks. Adverse events were mild and only 5 of the 28 patients required repeat surgery for hardware-related complications. Although used as an acute treatment, almost half of the patients reported a more than 50 % reduction in attack frequency with continued use implying that SPG stimulation can have a prophylactic effect also. Further work into the prophylactic efficacy is underway.

11.4.2.2 Occipital Nerve Stimulation (ONS)

The occipital nerves are a target for neurostimulation due to the anatomical overlap of trigeminal and cervical afferents in the trigeminocervical complex. This convergence means that stimulation of the occipital nerves modulates pain in the territories innervated by the occipital nerves and the trigeminal nerves. From the open-label data available, ONS appears to be a safe and efficacious treatment for refractory CCH with around 70 % of patients reporting at least a 50 % reduction in attack frequency [49–55]. The most frequent hardware-related adverse events, such as lead migration, electrode fracture, or infection, are dependent on surgical experience and can be limited by ensuring that a small number of specialist centers with experienced surgeons implant the devices [46]. A number of series report side-shift of attacks if unilateral stimulation is employed and we therefore recommend bilateral stimulation as the standard procedure. A time lag of around 2–3 months is observed before treatment effects emerge. It is important to explain this to patients to avoid unnecessary adjustments in the early stages of treatment. Once the ONS is implanted, patients need to be under the follow-up of physicians skilled in the use of neuromodulation for headache as the device will need adjusted over time to treat any residual attacks.

11.4.2.3 Deep Brain Stimulation (DBS)

Functional neuroimaging showed that the posterior hypothalamic area was overactive in cluster attacks. This led to Leone et al. implanting a DBS electrode in the ipsilateral posterior hypothalamic area in a CCH patient with good results [56]. There are now over 60 published cases [57–66]. The overall success rate is around 66 % (mean follow-up of 2 years) [49]. Again, there is a delay to clinical effect of around 2 months. Since the initial implant, further imaging and anatomical work has localized the area of implantation to the ventral tegmental area and not the posterior hypothalamus [67]. DBS is not without serious risk. Although the risk for serious hemorrhage is within the same range as that for movement disorders (3 %), one CH patient has died from a postoperative intracerebral hemorrhage [65]. As with ONS, it is important that this procedure is carried out in specialist centers and that patients continue under the care of a physician trained in the use of neuromodulation for headache.

Conclusion

Cluster headache is an excruciatingly painful condition and every effort must be made to control attacks quickly and with minimal side effects. Transitional treatments can be used to control attacks quickly but they must be used in conjunction with preventative treatments to cover longer bouts. In CCH, patients will often need to remain on preventatives for prolonged time periods. In ECH, the preventative should only be given when a patient is in a bout and should be weaned off once the patient is pain free.

Verapamil should be considered the first-line treatment option but if a patient fails to respond to this drug, then other options should be chosen depending on the patient, their comorbidities, and the experience of the treating physician.

Preventatives should be started at low dose and titrated over a number of weeks to maximum therapeutic levels. Although most patients will respond to oral medications, there will be a small but highly disabled group of CCH patients that will prove refractory and that may benefit from neurostimulation.

In CH, as in other primary headache conditions, the evidence base for the preventatives used is often of low quality. Therefore, the medications used are currently chosen on the basis of clinical experience. In the future, larger quality trials into CH treatments may enable a more evidence-based treatment plan to be constructed.

References

1. Headache Classification Committee of the International Headache S (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808
2. Russell MB (2004) Epidemiology and genetics of cluster headache. Lancet Neurol 3(5):279–283
3. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F et al (2005) Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 118(1–2):92–96
4. Afridi SK, Shields KG, Bhola R, Goadsby PJ (2006) Greater occipital nerve injection in primary headache syndromes–prolonged effects from a single injection. Pain 122(1–2):126–129
5. Peres MF, Stiles MA, Siow HC, Rozen TD, Young WB, Silberstein SD (2002) Greater occipital nerve blockade for cluster headache. Cephalalgia 22(7):520–522
6. Lambru G, Abu Bakar N, Stahlhut L, McCulloch S, Miller S, Shanahan P et al (2014) Greater occipital nerve blocks in chronic cluster headache: a prospective open-label study. Eur J Neurol 21(2):338–343
7. Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C et al (2011) Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 10(10):891–897
8. Shields KG, Levy MJ, Goadsby PJ (2004) Alopecia and cutaneous atrophy after greater occipital nerve infiltration with corticosteroid. Neurology 63(11):2193–2194
9. Louis DS, Hankin FM, Eckenrode JF (1986) Cutaneous atrophy after corticosteroid injection. Am Fam Physician 33(1):183–186
10. Jacobs MB (1986) Local subcutaneous atrophy after corticosteroid injection. Postgrad Med 80(4):159–160
11. Jammes JL (1975) The treatment of cluster headaches with prednisone. Dis Nerv Syst 36(7):375–376
12. Mather PJ, Silberstein SD, Schulman EA, Hopkins MM (1991) The treatment of cluster headache with repetitive intravenous dihydroergotamine. Headache 31(8):525–532
13. Magnoux E, Zlotnik G (2004) Outpatient intravenous dihydroergotamine for refractory cluster headache. Headache 44(3):249–255
14. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ (2011) Intravenous dihydroergotamine for inpatient management of refractory primary headaches. Neurology 77(20):1827–1832
15. Lambru G, Shanahan P, Matharu M (2015) Exacerbation of SUNCT and SUNA syndromes during intravenous dihydroergotamine treatment: a case series. Cephalalgia doi:10.1177/0333102415570495
16. May A, Leone M, Afra J, Linde M, Sandor PS, Evers S et al (2006) EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 13(10):1066–1077
17. Leone M, D'Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A et al (2000) Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology 54(6):1382–1385

18. Gabai IJ, Spierings EL (1989) Prophylactic treatment of cluster headache with verapamil. Headache 29(3):167–168
19. Jonsdottir M, Meyer JS, Rogers RL (1987) Efficacy, side effects and tolerance compared during headache treatment with three different calcium blockers. Headache 27(7):364–369
20. Bussone G, Leone M, Peccarisi C, Micieli G, Granella F, Magri M et al (1990) Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache 30(7):411–417
21. Steiner TJ, Hering R, Couturier EG, Davies PT, Whitmarsh TE (1997) Double-blind placebo-controlled trial of lithium in episodic cluster headache. Cephalalgia 17(6):673–675
22. Ekbom K (1981) Lithium for cluster headache: review of the literature and preliminary results of long-term treatment. Headache 21(4):132–139
23. Manzoni GC, Bono G, Lanfranchi M, Micieli G, Terzano MG, Nappi G (1983) Lithium carbonate in cluster headache: assessment of its short- and long-term therapeutic efficacy. Cephalalgia 3(2):109–114
24. Sicuteri F (1959) Prophylactic and therapeutic properties of 1-methyl-lysergic acid butanolamide in migraine. Int Arch Allergy Appl Immunol 15:300–307
25. Curran DA, Hinterberger H, Lance JW (1967) Methysergide. Res Clin Stud Headache 1:74–122
26. Kudrow L (1980) Cluster headache: mechanisms and management. Oxford University Press, Oxford/New York
27. Krabbe A (1989) Limited efficacy of methysergide in cluster headache. A clinical experience. Cephalalagia 9(Suppl 10):404–405
28. Graham JR, Suby HI, LeCompte PR, Sadowsky NL (1966) Fibrotic disorders associated with methysergide therapy for headache. N Engl J Med 274(7):359–368
29. Wheeler SD, Carrazana EJ (1999) Topiramate-treated cluster headache. Neurology 53(1):234–236
30. Forderreuther S, Mayer M, Straube A (2002) Treatment of cluster headache with topiramate: effects and side-effects in five patients. Cephalalgia 22(3):186–189
31. Hering R, Kuritzky A (1989) Sodium valproate in the treatment of cluster headache: an open clinical trial. Cephalalgia 9(3):195–198
32. Gallagher RM, Mueller LL, Freitag FG (2002) Divalproex sodium in the treatment of migraine and cluster headaches. J Am Osteopath Assoc 102(2):92–94
33. El Amrani M, Massiou H, Bousser MG (2002) A negative trial of sodium valproate in cluster headache: methodological issues. Cephalalgia 22(3):205–208
34. Goadsby PJ (2002) Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. Lancet Neurol 1(4):251–257
35. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G (1996) Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia 16(7):494–496
36. Pringsheim T, Magnoux E, Dobson CF, Hamel E, Aube M (2002) Melatonin as adjunctive therapy in the prophylaxis of cluster headache: a pilot study. Headache 42(8):787–792
37. Hering-Hanit R, Gadoth N (2001) The use of baclofen in cluster headache. Curr Pain Headache Rep 5(1):79–82
38. Leandri M, Luzzani M, Cruccu G et al (2001) Drug-resistant cluster headache responding to gabapentin: a pilot study. Cephalalagia 21:744–746
39. Schuh-Hofer S, Israel H, Neeb L, Reuter U, Arnold G (2007) The use of gabapentin in chronic cluster headache patients refractory to first-line therapy. Eur J Neurol 14(6):694–696
40. Silberstein S, Goode-Sellers S, Twomey C, Saiers J, Ascher J (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33(2):101–111
41. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 289(1):65–69

42. Palermo A, Giglia G, Cosentino G, Raieli V, Brighina F, Fierro B (2013) Two cases of cluster headache effectively treated with levetiracetam. Funct Neurol 28(1):63–64
43. Mauskop A (2005) Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia 25(2):82–86
44. Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ (2015) Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology 84(12):1249–1253
45. Goadsby PJ, Schoenen J, Ferrari MD, Silberstein SD, Dodick D (2006) Towards a definition of intractable headache for use in clinical practice and trials. Cephalalgia 26:1168–1170
46. Sharan A, Huh B, Narouze S, Trentman T, Mogilner A, Vaisman J et al (2014) Analysis of adverse events in the management of chronic migraine by peripheral nerve stimulation. Neuromodulation. doi:10.1111/ner.12243
47. Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, de Tommaso M et al (2013) Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain 14(1):86
48. Schoenen J, Jensen RH, Lanteri-Minet M, Lainez MJ, Gaul C, Goodman AM et al (2013) Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 33:816–830
49. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11(8):708–719
50. Schwedt TJ, Dodick DW, Trentman TL, Zimmerman RS (2006) Occipital nerve stimulation for chronic cluster headache and hemicrania continua: pain relief and persistence of autonomic features. Cephalalgia 26(8):1025–1027
51. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J (2007) Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol 6(4):314–321
52. Magis D, Gerardy PY, Remacle JM, Schoenen J (2011) Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. Headache 51(8):1191–1201
53. Mueller OM, Gaul C, Katsarava Z, Diener HC, Sure U, Gasser T (2011) Occipital nerve stimulation for the treatment of chronic cluster headache – lessons learned from 18 months experience. Cen Eur Neurosurg 72(2):84–89
54. Burns B, Watkins L, Goadsby PJ (2007) Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet 369(9567):1099–1106
55. Burns B, Watkins L, Goadsby PJ (2009) Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. Neurology 72(4):341–345
56. Leone M, Franzini A, Bussone G (2001) Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 345:1428–1429
57. Bartsch T, Pinsker MO, Rasche D et al (2008) Hypothalamic deep brain stimulation for cluster headache: experience from a new multicase series. Cephalalgia 28:285–295
58. Fontaine D, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N et al (2010) Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. J Headache Pain 11(1):23–31
59. Fontaine D, Christophe Sol J, Raoul S, Fabre N, Geraud G, Magne C et al (2011) Treatment of refractory chronic cluster headache by chronic occipital nerve stimulation. Cephalalgia 31(10):1101–1105
60. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52(5):1095–1099; discussion 9–101
61. Leone M, Franzini A, Broggi G, Cecchini AP, Bussone G (2012) Success, failure and putative mechanisms in hypothalamic stimulation for drug-resistant chronic cluster headache. Pain 154:89–94

62. Leone M, Proietti Cecchini A, Franzini A, Broggi G, Cortelli P, Montagna P et al (2008) Lessons from 8 years' experience of hypothalamic stimulation in cluster headache. Cephalalgia 28(7):789–797; discussion 98
63. Leone M, Franzini A, Proietti Cecchini A, Bussone G (2013) Success, failure, and putative mechanisms in hypothalamic stimulation for drug-resistant chronic cluster headache. Pain 154(1):89–94
64. Pinsker MO, Bartsch T, Falk D, Volkmann J, Herzog J, Steigerwald F et al (2008) Failure of deep brain stimulation of the posterior inferior hypothalamus in chronic cluster headache – report of two cases and review of the literature. Zentralbl Neurochir 69(2):76–79
65. Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M et al (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128(Pt 4):940–947
66. Starr PA, Barbaro NM, Raskin NH, Ostrem JL (2007) Chronic stimulation of the posterior hypothalamus region for cluster headache: technique and 1-year results in four patients. J Neurosurg 106:999–1005
67. Matharu MS, Zrinzo L (2010) Deep brain stimulation in cluster headache: hypothalamus or midbrain tegmentum? Curr Pain Headache Rep 14(2):151–159

Pharmacotherapy for Other Primary Headache Disorders

12

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12.1 Introduction

Chapter 4 in the current International Classification of Headache Disorders (ICHD-IIIβ) includes a number of primary headache disorders that are clinically heterogeneous [1]. In general, their pathogenesis is still poorly understood and their treatments are suggested on the basis of anecdotal reports or uncontrolled trials. The chapter includes some clinical entities, such as primary stabbing headache or hypnic headache, that are primary in most cases, together with, for instance, primary thunderclap headache or primary cough headache, entities where our efforts must be directed to rule out a secondary origin. Two headache disorders which appeared in Chap. 13 in the previous Classification have now been moved to this chapter: cold stimulus headache and external-pressure headache, while hemicrania continua has been now moved to Chap. 3 as evidence indicates that it rightly belongs to trigeminal autonomic cephalalgias [1].

12.2 Primary Cough Headache

12.2.1 Epidemiology, Pathophysiology and Clinical Features

Headaches related to exertion can be brought on by Valsalva manoeuvres ("cough headache"), prolonged exercise ("exercise headache") and sexual excitation ("sexual headache") [1]. These conditions are a challenging diagnostic problem. They can be primary or secondary and as their aetiologies differ depending on the

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_12

headache type. Historically, cough headache has been included in the broader context of exercise-induced headache, but clinical features of cough headache are clearly different from those of exertional and sexual headaches which do have many properties in common. It was not until modern neuroimaging techniques became available that these activity-related headaches were clinically differentiated [2, 3].

Cough headache has been classically considered a rare entity. However, Rasmussen and Olesen have shown that the lifetime prevalence of cough headache is 1 % (95 % CI 0–2 %) [4]. Over 10 years, of the 6.412 patients who attended a general neurology department, 68 (1,6 %) consulted because of cough headache [5].

Headache precipitated by cough can be either a primary benign condition or secondary to structural cranial disease. From case series prior to CT and MRI it was concluded that about 20 % of patients with cough headache had structural lesions, most of them a Chiari type I deformity [6–8]. However, with modern neuroimaging techniques it is clear that about 40 % of cough headache patients have secondary cough headache due to tonsillar descent or, more rarely, to other space-occupying lesions in the posterior fossa/foramen magnum area [2, 3]. Up to one-third of patients with Chiari type I malformation experience headache aggravated by Valsalva manoeuvres, mainly cough [9]. Therefore, it can be concluded that about 60 % of the patients with cough headache will show no demonstrable etiology, while 40 % will be secondary to structural lesions, mostly at the foramen magnum level.

In contrast to secondary cough headache, the pathophysiology of primary cough headache is not known. The possibility of a sudden increase in venous pressure being sufficient itself to cause headache due to an increase in brain volume has been proposed [10]. There should be other contributing factors, however, such as a hypersensitivity of some receptors, sensitive to pressure and hypothetically localised on the venous vessels [11]. One of the potential etiologies for this transient receptor sensitisation could be a hidden or previous infection. Interestingly, Chen and coworkers have found that patients with primary cough headache are associated with a more crowded posterior cranial fossa, which may be a further contributing factor for the pathogenesis of this headache syndrome [12].

Primary cough headache is defined as that head pain precipitated by coughing or other Valsalva manoeuvres in the absence of any intracranial disorder. According to the ICHD-IIIβ diagnostic criteria, primary cough headache is a sudden onset headache lasting from 1 s to 120 min, brought on by and occurring only in association with coughing, straining and/or Valsalva manoeuvres, in the absence of any intracranial disorder [1].

The clinical picture of primary cough headache is somewhat characteristic, which should allow its differentiation from secondary cases. It usually affects subjects over the age of 40 years; with a mean age in patient series above 60 years of age. There is a slight male predominance. The pain begins immediately or within seconds of the precipitants. Such precipitants include coughing, sneezing, nose blowing, laughing, crying, singing, lifting a weight, straining at stool, and stooping. Prolonged physical exercise is not a precipitating factor for primary cough headache, which is moderate to severe in intensity, with a sharp, stabbing, splitting, or even explosive quality. The headache is usually bilateral but can be unilateral.

The pain is most often in the occipital region but may also be in the frontotemporal regions. Primary cough headache is not associated with other clinical manifestations, not even nausea or vomiting, photo- and phonophobia. Primary cough headache is an episodic disease, ranging from 2 months to a maximum of 2 years in our experience [2, 3].

12.2.2 Treatment

Symptomatic treatment is not practical because of the short duration and multiplicity of cough headaches. Potential precipitants, for instance lung infections or cough-inducing medications, such as angiotensin-converting enzymes inhibitors, must be treated or withdrawn. Most patients with primary cough headache respond to indomethacin, given prophylactically at doses usually ranging from 25 to 150 mg daily [2, 3, 11, 13, 14, 15]. The mechanism of action of this drug is unknown, but could include a decrease in intracranial pressure. This would explain the benefits seen with lumbar puncture or acetazolamide in some patients with primary cough headache [11, 16]. There is no consensus on treatment duration with indomethacin, though in general, after a good response to indomethacin, the recommendation is to continue the treatment for about 6 months [2, 3].

12.3 Primary Exertional and Sexual Headache

12.3.1 Epidemiology, Pathophysiology and Clinical Features

These two headaches will be considered together in this chapter as they share many points in common, including treatment approach. Sexual activity is in fact a kind of exercise and many patients with primary exertional headaches also experience headaches precipitated by sexual activity [2, 3, 17]. According to the ICHD-IIIβ, primary exertional headache is precipitated by any form of prolonged exercise and lasts less than 48 h. Primary headache associated with sexual activity is precipitated by sexual activity, which can star as a dull bilateral headache as sexual excitement increases and/or suddenly becomes intense at orgasm and lasts from 1 min to a maximum of 72 h [1].

Even though these headaches are not a frequent reason for neurological consultation, it seems that they are not rare in the general population. In a wide (1838 participants) epidemiological survey in Norway, 12.3 % referred to exertional headache [18], while in a further survey in Taiwan carried out in 1963 adolescents the prevalence of exertional headache was as high as 30.4 % [19]. Primary exertional and sexual headaches appear to be more frequent in men and in young people [2, 3, 6, 8, 20, 21].

The pathophysiology of these headaches remains speculative. The development of headache after sustained exertion, particularly after a hot day, is more likely caused by arterial dilatation [22], but objective evidence is lacking. Exertional headache in this respect may resemble headaches associated with high altitude and fever. It has been suggested that, in some patients, primary exertional headache could be a

venous disease, as the prevalence of jugular valve incompetence (leading to transient increased of intracranial pressure during exertion) has been shown to be higher than expected [23].

12.3.2 Treatment

For non-incapacitating cases or for those with a low exercise or sexual activity frequency, the first, and sometimes the only recommendation should be transient exercise moderation or sexual abstinence. There is no absolute evidence of the value of pharmacological treatments in the management of primary exertional or sexual headaches. In general, however, anti-migraine preventive medications show benefit [2, 3, 21]. For most patients, beta-blockers at the usual anti-migraine doses seem useful. There are well-documented cases with exertional headache who did not improve or could not tolerate beta-blockers. Some of these cases seem to improve on indomethacin in doses varying from 25 to 150 mg a day. There is no consensus on the treatment duration in these cases. Primary exertional and sexual headaches are usually transient, lasting less than 3 months and rarely longer than 6 months. Therefore, we recommend stopping the preventive treatment after 3–6 months to check for headache recurrence.

Acute therapy, immediately before physical exercise, may be a reasonable alternative for some patients. Simple analgesics and nonsteroidal anti-inflammatory drugs do not seem to prevent the development of these headaches. Ergotamine may be useful and the efficacy of triptans taken prior to headache intercourse in preventing the development of this headache has also been reported [24, 25].

12.4 Primary Thunderclap Headache

12.4.1 Epidemiology, Pathophysiology and Clinical Features

Thunderclap headache is an uncommon type of headache, but recognition and diagnosis are crucial because of the possibility of a serious brain disorder. Primary thunderclap headache is defined in the ICHD-IIIβ as a high-intensity headache of abrupt onset, reaching maximum intensity in <1 min and lasting at least 5 min, mimicking that of ruptured cerebral aneurysm, in the absence of intracranial pathology [1]. Evidence that thunderclap headache exists as a primary headache disorder is poor, therefore the search for an underlying cause should be expedited and exhaustive. Thunderclap headache is frequently associated with serious vascular intracranial disorders, particularly subarachnoid haemorrhage. It is mandatory to exclude this and a range of other such conditions including intracerebral haemorrhage, cerebral vein thrombosis, unruptured vascular malformation, arterial dissection, pituitary apoplexy, meningitis, colloid cyst of the third ventricle, low cerebrospinal pressure, acute sinusitis and reversible vasoconstriction syndrome, which probably explains a relevant proportion of cases diagnosed as primary thunderclap headache [26, 27].

12.4.2 Treatment

Primary thunderclap headache is a self-limited syndrome and treatment consists of symptomatic analgesics if necessary. As sudden headaches tend to recur in the majority of patients during the first 2 weeks (up to 1 month), nimodipine, which has been shown to be clinically efficacious in an open fashion in a well-documented series of cases, can be prophylactically administered during this period. Because thunderclap headache has been associated with serotonergic drugs and reversible cerebral vasospasm, the safety of serotonin agonists (triptans or ergots) in this group of patients has not been evaluated and should be avoided. Because of the potential for recurrence patients must be cautioned to avoid sympathomimetic drugs and vigorous physical activity during 1 month. Most do not experience recurrent headaches and are not at increased risk for serious neurologic events over months or years; therefore, patients can and should be reassured [26, 27].

12.5 Cold Stimulus Headache and External-Pressure Headache

These two headaches were among secondary headaches in the previous version of the IHS Classification. They have been moved to this chapter because they seem more likely to be primary headache disorders in that they are brought on by physiological (non-damaging) stimuli [1]. Their treatment consists of avoidance of these triggering factors in predisposed patients.

12.6 Primary Stabbing Headache

12.6.1 Epidemiology, Pathophysiology and Clinical Features

This headache is characterised by non-provoked, ultrashort stabs of pain, localised in the head. ICHD-IIIβ criteria for primary stabbing headache are illustrated in Table 12.1 [1]. Primary stabbing headache is a fairly frequent complaint. In a large study in Norway primary stabbing headache was verified in 35.2 % of the examined adult population [28]. Primary stabbing headache is more prevalent in subjects with other primary headaches and particularly in migraine.

Table 12.1 ICHD-IIIβ diagnostic criteria for primary stabbing headache [1]

A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D
B. Each stab lasts for up to a few seconds
C. Stabs recur with irregular frequency, from one to many per day
D. No cranial autonomic symptoms
E. Not better accounted for by another ICHD-III diagnosis

Primary stabbing headache is a frequent condition, but the frequency of the stabs varies from 1 per year to more than 50 daily [26, 29]. The ultrashort duration and lack of cranial autonomic features distinguish this disorder form short-lasting unilateral neuralgiform pain with conjunctival injection and tearing (SUNCT) syndrome. The presence of triggers, duration of a few seconds and occurrence of pain in the second and third trigeminal branches are characteristics of trigeminal neuralgia, other condition which primary stabbing headache can be confused.

12.6.2 Treatment

Treatment is rarely necessary. Symptomatic, acute treatment of primary stabbing headache is not feasible given its ultrashort duration and repetitive nature. When attacks occur with a frequency that warrants preventive treatment, indomethacin is usually the treatment of choice [13, 26, 29]. Indomethacin provides complete or partial improvement in about two-thirds of patients. The usual effective dose ranges from 25 to 150 mg per day. The erratic temporal pattern of this condition and the potentially ominous adverse events of indomethacin must be taken into account when indomethacin therapy is considered for this condition. Gabapentin, nifedipine, melatonin and celecoxib have shown efficacy in a few patients and could be used as potential alternatives [26].

12.7 Nummular Headache

12.7.1 Epidemiology, Pathophysiology and Clinical Features

Nummular headache is a primary headache disorder and therefore it has been moved from the Appendix to Chap. 4 in the ICHD-IIIβ [1]. Since defined by Pareja et al. in 2002 [30], more than 200 cases have been reported. This coin-shaped cephalalgia was first described as a chronic, mild–moderate, pressure-like pain that is felt exclusively in a circumscribed area with a diameter of 2–6 cm, in the absence of any underlying lesions of the head. Current diagnostic criteria are summarised in Table 12.2. Primary nummular headache is considered a rare entity, though its exact

Table 12.2 ICHD-IIIβ diagnostic criteria for primary nummular headache [1]

A. Continuous head pain fulfilling criteria B–C
B. Felt exclusively in an area of the scalp, with all of the following four characteristics:
1. Sharply-contoured
2. Fixed in size and shape
3. Round or elliptical
4. 1–6 cm in diameter
C. Not better accounted for by another ICHD-III diagnosis

prevalence is uncertain. Nummular headache accounts for about 1 % of headaches attending a general neurology outpatient office and up to 5 % of headaches in a specialised clinic [31].

12.7.2 Treatment

There is no specific treatment for primary nummular headache. Anti-epileptics have been tried in most reported patients, with gabapentin being effective in around half of cases [32]. Local botulinum toxin type A has been injected in a few patients and proved to be effective in some of them [33]. Local nerve blocks showed effectiveness in only one quarter of patients [31].

12.8 Hypnic Headache

12.8.1 Epidemiology, Pathophysiology and Clinical Features

Hypnic headache is a rare, recurrent, sleep-related, primary headache disorder, which usually begins after 50 years of age. Pain tends to be bilateral and mild to moderate, develops only during sleep, and usually lasts from 15 to 180 min. Most cases are persistent, with daily or near daily headaches, but an episodic subform (on <15 days/month) has been described [1]. The exact pathophysiological mechanisms of hypnic headache have not been elucidated; a disturbance of the suprachiasmatic nucleus, as mammalian pacemaker, dysregulation of melatonin and a disorder of REM sleep have been some of the postulated mechanisms [34].

12.8.2 Treatment

Several different treatments have been tried in hypnic headache. Lithium remains the most indicated treatment for hypnic headache [35]. Treatment should be started with low doses (300 mg) of lithium carbonate at bedtime, which can be increased up to 600 mg at bedtime if necessary. Lithium should be tapered after 3–4 months. If headache recurs during tapering, a longer duration therapy may be needed. Renal and thyroid function as well as serum lithium levels must be assessed periodically to avoid toxicity. Usual side effects include tremor, diarrhoea, increased thirst and polyuria and not infrequently make lithium poorly tolerated by hypnic headache patients, which are usually elderly people. Other agents that have been reported to effectively treat hypnic headache in small observational series include bedtime doses of caffeine (40–60 mg tablet, or as a cup of coffee), melatonin (2 mg), flunarizine (5 mg) or indomethacin (25–75 mg) [34–37]. Indomethacin appears to be more useful when attacks are strictly unilateral. Due to the poor tolerability of lithium and indomethacin and even though they seem to be the most efficacious preventive

treatment for hypnic headache, we usually try first melatonin and flunarizine. In anecdotal reports, other drugs, such as topiramate, gabapentin, pregabalin, acetazolamide, pizotifen, acetylsalicylic acid, prednisone or verapamil have apparently been useful in preventing attack recurrence. Options, such as beta-blockers, tryciclic antidepressants, oxygen or subcutaneous sumatriptan have afforded no benefit [34].

12.9 New Daily Persistent Headache

12.9.1 Epidemiology, Pathophysiology and Clinical Features

New daily persistent headache is defined as persistent headache, daily from its onset which is clearly remembered. In the new ICHD-IIIβ it is clarified that the pain can be migraine-like or tension-type-like (Table 12.3). New daily persistent headache is unique in that the headache is daily from onset, typically occurring in individuals with no prior headache history. Patients with this disorder invariably recall and can accurately describe such an onset; if they cannot do so, another diagnosis should be made. New daily persistent headache has two clinical subforms: a self-limiting one that resolved within several months without therapy, in which an infectious origin has been hypothesised, and a refractory form that is resistant to aggressive treatment regimens [1].

12.9.2 Treatment

At present no specific treatment strategy can be suggested for primary new daily persistent headache based on clinical evidence. Leaving the self-limiting subform aside, this headache can continue for years to decades after onset and can be extremely disabling to the patient. Patients with new daily persistent headache will fail every possible class of acute and preventive medications. Most patients with this condition receive all preventatives used for migraine or tension-type headache, including botulinum toxin type A, antidepressants and nerve or facet blocks without success [38, 39]. Rozen presented five patients who responded to gabapentin or topiramate, but these agents do not work in the majority of cases [40]. New daily persistent headache is, therefore, overall unresponsive to conventional preventive headache treatment. As a result of this, these patients overuse analgesics, but unlike chronic migraine with medication overuse headache, getting these patients out of analgesic rebound typically does nothing to help in relieving their pain [41].

Table 12.3 ICHD-IIIβ diagnostic criteria for new daily persistent headache [1]

A. Persistent headache fulfilling criteria B–C
B. Each stab lasts for up to a few seconds
C. Stabs recur with irregular frequency, from one to many per day
D. No cranial autonomic symptoms
E. Not better accounted for by another ICHD-III diagnosis

With this negative scenario treatment or new daily persistent headache must be individualised. Some of the preventatives, such as botulinum toxin of nerve block, can be considered, though we must take into account that condition may not remit for decades and none of these treatments should be chronically prescribed if there is no clear response. For these patients a judicious planning of their symptomatic treatment is all we can and should do.

References

1. Headache Classification Committee of the International Headache Society (2013) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 33:629–808
2. Pascual J, Iglesias F, Oterino A et al (1996) Cough, exertional, and sexual headaches. An analysis of 72 benign and symptomatic cases. Neurology 46:1520–1524
3. Pascual J, González-Mandly A, Martín R et al (2008) Headaches precipitated by cough, prolonged exercise or sexual activity: a prospective etiological and clinical study. J Headache Pain 9:259–266
4. Rasmussen BK, Olesen J (1992) Symptomatic and nonsymptomatic headaches in a general population. Neurology 42:1225–1231
5. Pascual J, Combarros O, Leno C et al (1995) Distribución por diagnósticos del dolor de cabeza como motivo de consulta neurológica. Med Clin (Barc) 104:161–164
6. Rooke ED (1968) Benign exertional headache. Med Clin North Am 52:801–808
7. Sands GH, Newman L, Lipton R (1991) Cough, exertional and other miscellaneous headaches. Med Clin North Am 75:733–747
8. Symonds C (1956) Cough headache. Brain 79:557–568
9. Pascual J, Oterino A, Berciano J (1992) Headache in type I Chiari malformation. Neurology 42:1519–1521
10. Wang SJ, Fuh JL, Lu SR (2000) Benign cough headache is responsive to acetazolamide. Neurology 55:149–150
11. Raskin NH (1995) The cough headache syndrome: treatment. Neurology 45:1784
12. Chen YY, Lirng JF, Fuh JL et al (2004) Primary cough headache is associated with posterior fossa crowdedness: a morphometric MRI study. Cephalalgia 24:694–699
13. Diamond S, Medina JL (1979) Benign exertional headache: successful treatment with indomethacin. Headache 19:249
14. Diamond S (1982) Prolonged benign exertional headache: its clinical characteristics and response to indomethacin. Headache 22:96–98
15. Pascual J (2005) Primary cough headache. Curr Pan Headache Rep 9:272–276
16. Boes CJ, Matharu MS, Goadsby PJ (2002) Benign cough headache. Cephalalgia 22:772–779
17. Silbert PL, Edis RH, Stewart-Wynne EG et al (1991) Benign vascular sexual headache and exertional headache: interrelationships and long term prognosis. J Neurol Neurosurg Psychiatry 54:417–421
18. Sjaastad O, Bakketeig LS (2002) Exertional headache. I. Vaga study of headache epidemiology. Cephalalgia 22:784–790
19. Chen SP, Fuh JL, Lu SR et al (2009) Exertional headache-a survey of 1963 adolescents. Cephalalgia 29:401–407
20. Frese A, Eikermann A, Frese K, Schwaag S et al (2003) Headache associated with sexual activity: demographics, clinical features, and comorbidity. Neurology 23:796–800
21. Evers S, Lance JW (2006) Primary headache attributed to sexual activity. In: Olesen J, Goadsby PJ, Tfelt-Hansen P, Welch KMA (eds) The headaches, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 841–845
22. Evers S, Schmidt O, Frese A et al (2003) The cerebral hemodynamics of headache associated with sexual activity. Pain 102:73–78

23. Donnet A, Dufour H, Levrier O, Metellus P (2008) Exertional headache: a new venous disease. Cephalalgia 28:1201–1203
24. Frese A, Gantenbein A, Marziniak M et al (2006) Triptans in orgasmic headache. Cephalalgia 26:1458–1461
25. Doepp F, Valdueza JM, Schreiber SJ (2007) Incompetence of internal jugular valve in patients with primary exertional headache: a risk factor? Cephalalgia 28:182–185
26. Dodick D, Pascual J (2006) Primary stabbing, cough, exertional, and thunderclap headaches. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds) The headaches, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 831–839
27. Linn FHH (2011) Primary thunderclap headache. In: Nappi G, Moskowitz MA (eds) Headache, vol 97, Handbook of clinical neurology. Elsevier, Amsterdam, pp 473–481
28. Sjaastad O, Pettersen H, Bakketeig LS (2001) The Vaga study: epidemiology of headache I: the prevalence of ultrashort paroxysms. Cephalalgia 21:207–215
29. Pareja JA, Ruiz J, de Isla C et al (1996) Idiopathic stabbing headache (jabs and jolts syndrome). Cephalalgia 16:93–96
30. Pareja JA, Caminero AB, Serra J et al (2002) Nummular headache: a coin-shaped cephalgia. Neurology 58:1678–1679
31. Dai WD, Yu S, Liang J et al (2013) Nummular headache: peripheral or central? One case with reappearance of nummular headache after focal scalp was removed, and literature review. Cephalalgia 33:390–397
32. Cortijo E, Guerrero-Peral AL, Herrero-Velázquez S et al (2011) Nummular headache: clinical features and therapeutic experience in a series of 30 new cases. Rev Neurol 52:72–80
33. Linde M, Hagen K, Stovner LJ (2011) Botulinum toxin treatment of secondary headaches and cranial neuralgias. A review of evidence. Aca Neurol Scand Suppl 191:50–55
34. Newman LC, Mosek A (2006) Hypnic headaches. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds) The headaches, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 847–850
35. Evers S, Goadsby PJ (2003) Hypnic headache: clinical features, pathophysiology, and treatment. Neurology 60:905–909
36. Dodick D, Mosek AC, Campbell JK (1998) The hypnic ("alarm clock") headache syndrome. Cephalalgia 18:152–156
37. Dodick D, Jones JM, Capobianco DJ (2000) Hypnic headache: another indomethacin-response headache syndrome? Headache 40:830–835
38. Rozen TD, Jensen R (2006) New daily persistent headache. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds) The headaches, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 855–857
39. Rozen TD (2011) New daily persistent headache. In: Nappi G, Moskowitz MA (eds) Headache, vol 97, Handbook of clinical neurology. Elsevier, Amsterdam, pp 489–494
40. Rozen TD (2002) Succesful treatment of new daily persistent headache with gabapentin and topiramate. Headache 42:433
41. Takase Y, Nakano M, Tatsumi C et al (2004) Clinical features, effectiveness of drug based treatment and prognosis of new daily persistent headache: thirty cases in Japan. Cephalalgia 24:955–959

Acute Treatment for Primary Headache Disorders in Children

13

Çiçek Wöber-Bingöl

13.1 Introduction

Headache and migraine are highly prevalent in children and adolescents. The estimated overall mean prevalence of headache is 54 % and the mean prevalence of migraine is 9 % in these age groups [1]. Headache and migraine cause considerable burden and reduced quality of life [2–4]. Accordingly, adequate management of headache disorders in children and adolescents is essential. Dealing with primary headaches requires to: (1) establish the correct diagnosis bearing in mind that the characteristics of migraine differ from those in adults, (2) consider somatic and psychiatric comorbidities, (3) ask for trigger factors, (4) assess the degree of disability, (5) educate the patient, the parents, and other caregivers, (6) establish an appropriate therapy, (7) prescribe acute medication if needed and advise how to use it, (8) discuss prophylactic therapy, (9) instruct the patients to keep a headache diary, and (10) provide information about realistic expectations regarding the efficacy of treatment [5–7]. Based on expert opinion, therapy comprises lifestyle modification such as regular meals, sufficient fluid intake, physical exercise, regular sleep, advice on how to cope with trigger factors, non-pharmacological and pharmacological management of the acute attack, and in the case of frequent attacks prophylactic interventions [5–7].

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_13

13.2 Acute Treatment of Migraine

Acute treatment must be tailored to the individual needs of the patients. The goal of treatment should be a quick response with return to normal activity and without relapse. Several key concepts should be emphasized to help guide the patients. Acute medication should not be used for mild headaches, for headaches easing with sleep and for moderate or severe migraines lasting less than 2 h. Furthermore, medication use must be limited to avoid medication-overuse headache. It is important that an appropriate dose is used. Medications should be taken shortly after onset of migraine headache to optimize the effect. The medication should be available to the patients also at school [5, 6].

13.2.1 Analgesics and NSAIDs

In children and adolescents, data are available for acetaminophen and ibuprofen. Acetaminophen was examined in only one crossover study including 88 patients aged 4–16 years [8]. Ibuprofen was examined in three studies including a total of 201 patients aged 4–18 years (Table 13.1) [8–10]. In the acetaminophen trial, patients treated 3 attacks, 1 with acetaminophen, 1 with ibuprofen and 1 with placebo. The efficacy analysis included 66 patients. One hour postdose, acetaminophen was superior to placebo with regard to headache relief (OR 3.3, 95 % CI 1.4–11.0) and made the children headache-free (OR 3.3, 95 % CI 1.0–11.1), but there was no difference observed after ibuprofen. Two hours postdose, acetaminophen was not superior to placebo and it was inferior to ibuprofen (OR 2.2. 95 % CI 1.1–4.0 for ibuprofen vs acetaminophen). In the intent-to-treat analysis, acetaminophen as well as ibuprofen was twice as effective as placebo and the active drugs did not differ from each other.

Ibuprofen was examined in the study already mentioned [8] – one parallel group study and another crossover study [9, 10]. In the crossover study comparing acetaminophen, ibuprofen and placebo [8], ibuprofen was superior to placebo at 1 h as well as at 2 h for headache relief (OR 3.4, 95 % CI 1.2–10.2 and OR 2.9, 95 % CI 1.0–8.1) and pain-free response (OR 3.1, 95 % CI 1.0–9.9 and OR 3.5, 95 % CI 1.0–11.9), as well as superior to acetaminophen in aborting migraine within 2 h (OR 2.2,. 95 % CI 1.1–4.0).

In the parallel group study [9], patients had to treat one moderate or severe migraine headache under adult supervision. Ibuprofen was superior to placebo in relieving headache 2 h postdose, and with respect to the median pain score, absence of nausea and need for rescue medication, but not in making the children headache-free and stopping other autonomic symptoms at 2 h. Analyzing boys and girls separately, significantly higher response rates was observed for ibuprofen compared to placebo in boys, but no difference whatsoever was noticed in girls.

The second crossover study compared ibuprofen, zolmitriptan and placebo [10]. Ibuprofen was superior to placebo with respect to pain relief at 1, 2 and 4 h, pain-free at 2 and 4 h, sustained pain free as well as absence of nausea and photophobia/phonophobia at 1 and 2 h. Response rates in boys and girls did not differ from each other.

Table 13.1 Randomized, double-blind, placebo-controlled studies on drugs for acute migraine attacks in children and adolescents

Pain relief[a]					Pain-free[a]				
Drug	Dose	Age (ys.)	Active drug (%)	Placebo (%)	*P*-value	Active drug (%)	Placebo (%)	*P*-value	Reference
Acetaminophen	15 mg/kg	4–16	54	37	–	39	28	–	[8]
Ibuprofen	10 mg/kg	4–16	68	37	–	60	28	–	[8]
	7.5 mg/kg	6–12	76	53	.006	44	25	NS	[9]
	200/400 mg[b]	6–18	69	28	<.05	48	7	<.01	[10]
Dihydroergotamine	20/40 µg/kg	5–15	58	17	–	–	–	–	[11]
Sumatriptan oral	50/100 mg[c]	8–16	30	22	NS	22	9	NS	[12]
	25/50 mg	10–17	31	39	NS	24	29	NS	[13]
Sumatriptan nasal	20 mg	6–10	86	43	.03	64	14	.02	[14]
	5/10/20 mg	12–17	63[d]	53	NS	36[d]	25	<.05	[15]
	5/20 mg	12–17	58[d]	68	.046	44[d]	30	<.001	[16]
	10/20 mg[c]	8–17	64	39	.003	31	19	NS	[17]
Zolmitriptan oral	2,5 mg	6–18	62	28	<.05	45	7	<.01	[10]
	2,5/5/10 mg	12–17	53–58[e]	54	NS	19–23[e]	25	NS	[18]
Zolmitriptan nasal	5 mg[f]	12–17	66	54	NS	39	19	<.01	[19]
Rizatriptan	5 mg	12–17	66	56	NS	32	28	NS	[20]
	5 mg	12-17	68	69	NS	39	31	NS	[21]
	5/10 mg[c]	6–17	74+73[g]	36	<.001	35+31[g]	18	.02+.04	[22]
	5/10 mg[c,h]	6–17	58	53	NS	33	24	<.05	[23]
Almotriptan	6.25/12,5 /25 mg	12–12	67[i]	55	.02	40[i]	34	NS	[24]
Eletriptan	40 mg	12–17	57	57	NS	22	15	NS	[25]
Sumatriptan+Naproxen	10/60, 30/180, 85/500 mg	12–17	–	–	–	24–29	10	.003	[26]

[a]2 h postdose
[b]Age-dependent
[c]Dependent on body weight
[d]20 mg
[e]2.5 mg, 5 mg, 10 mg
[f]Single-blind placebo challenge
[g]Separate data for first and second dose
[h]Double-blind stage 1 run-in with 20:1 randomiziation of placebo:rizatriptan
[i]25 mg

With respect to adverse events (AE) of acetaminophen and ibuprofen, the authors of a systematic review conclude that ibuprofen, acetaminophen and placebo have similar tolerability and safety profiles in terms of gastrointestinal symptoms, asthma and renal AE [27]. Another review also concluded that both acetaminophen and ibuprofen "appear to be exceptionally safe", but the authors point out the controversy regarding the role of acetaminophen in the development of asthma [28].

Acetaminophen and ibuprofen appear to be safe and well tolerated in children and adolescents. Regarding their efficacy for treating acute migraine attacks, there is limited evidence for ibuprofen and poor evidence for acetaminophen.

13.2.2 Ergotamines

Only one very small crossover study on oral dihydroergotamine (DHE) in 13 patients has been published (Table 13.1) [11]. Treatment with oral dihydroergotamine is limited by its low bioavailability. In addition, it is no longer on the market in many countries. DHE nasal spray, orally inhaled and intravenous DHE have not been examined in randomized placebo-controlled studies in children and adolescents up till now.

Oral dihydroergotamine seems not to be useful for the treatment of acute migraine attacks in children and adolescents.

13.2.3 Triptans

There are a total of 16 full-paper, randomized, placebo-controlled studies on triptans for acute migraine attacks in children and adolescents (Table 13.1). Oral sumatriptan was used in two studies and sumatriptan nasal spray in four studies. Zolmitriptan was examined in three studies (2 oral, 1 nasal), rizatriptan in four studies and almotriptan as well as eletriptan in one study each. In addition, a fixed combination of oral sumatriptan and naproxen was used in one study. In most studies, triptan efficacy rates were comparable to those in adults; however placebo rates were much higher. Therefore, several studies failed to demonstrate superiority over placebo.

For adolescents aged 12–17 years, nasal sumatriptan and nasal zolmitriptan have been approved in several European countries and almotriptan has been approved by the Food and Drug Administration (FDA). Furthermore, rizatriptan has been licensed for patients aged 6–17 years by the FDA. In children and adolescents, use of oral sumatriptan, oral zolmitriptan, eletriptan, naratriptan, frovatriptan as well as sumatriptan-naproxen fixed combination is off-label both in Europe and the US. In addition, use of almotriptan and rizatriptan is off-label in Europe and use of nasal sumatriptan and nasal zolmitriptan is off-label in the US.

13.2.3.1 Sumatriptan

Oral sumatriptan was not superior to placebo in a small single-center study including 23 patients from Finland as well as in a multicenter study from Japan including 178 patients [12, 13].

In contrast, there is good evidence for nasal sumatriptan, even though it was not consistently superior to placebo in four available studies (Table 13.1) [14–17]. A small study in 14 children with migraine refractory to "commonly used antimigraine drugs" was the first suggesting efficacy of nasal sumatriptan in young migraineurs [14]. Apart from the small patient number, the study has several other limitations [29]. Considering that 2 of the other studies on sumatriptan nasal spray—including only adolescents aged 12–17 years and the third study including patients between 8 and 17 years—did not provide separate analyses for children, the evidence for nasal sumatriptan in patients below the age of 12 years is poor.

In a large parallel group study [15], 510 patients aged 12–17 years were analyzed. Patients were treated for 1 moderate or severe migraine attack with sumatriptan 5, 10, 20 mg, or placebo. The endpoints comprised headache relief (i.e. reduction in pain severity from severe or moderate to mild or none), complete relief and associated symptoms 15, 30, 60, 90 and 120 min postdose as well as headache recurrence (i.e. worsening of pain from no/mild 2 h postdose to moderate or severe 2–24 h postdose) and use of rescue medication. The primary endpoint was headache relief at 2 h postdose. Compared to placebo, headache relief was achieved significantly more often with sumatriptan 10 and 20 mg 1 h postdose and with sumatriptan 5 mg (but not 20 mg) 2 h postdose in the intention-to-treat population. In the per-protocol population, sumatriptan 20 mg was superior to placebo with respect to pain relief 2 h postdose. Complete relief was achieved significantly more often with sumatriptan 20 mg than with placebo 2 h postdose (Table 13.1). Further statistically significant results comprised the prevalence of photophobia 2 h postdose for sumatriptan 20 mg and the prevalence of phonophobia for sumatriptan 5 mg 2 h postdose and for sumatriptan 20 mg at 30 min, 60 min and 2 h. Nausea, vomiting, headache recurrence and rescue medication did not differ between sumatriptan 5 mg, 10 mg or 20 mg and placebo at any time point.

In another study by the same first author [16], including 738 patients, sumatriptan 5 and 20 mg were compared to placebo. The study design was very similar. Primary endpoints were headache relief at 1 h and sustained relief from 1 to 24 h (i.e. no additional use of medication and no recurrence of moderate or severe pain within 1–24 h postdose). Comparing sumatriptan 5 mg to placebo revealed no statistically significant differences except for phonophobia 2 h postdose. Sumatriptan 20 mg was superior to placebo with respect to headache relief at 30 min and 2 h, pain-free rates at 2 h, photophobia and photophobia plus phonophobia at 2 h and freedom from migraine (i.e. pain and all associated symptoms) at 2 h postdose. The proportions of patients with sustained relief, use of rescue medication and recurrence of headache pain did not differ between sumatriptan 20 mg and placebo.

Finally, in a Finnish crossover study [17], a dose of 10-mg sumatriptan nasal spray was used in patients with a body weight of 20–39 kg and a dose of 20 mg in those with a body weight of ≥40 mg. The Finnish study is the only one using sumatriptan nasal spray providing detailed data on patients falling asleep within 2 h after using study medication. If a child fell asleep and was pain-free upon awakening, the treatment was classified as successful. Sumatriptan nasal spray differed statistically significantly with respect to headache relief at 2 h as well as at 1, 3, and 4 h postdose. More children preferred sumatriptan than placebo, and rescue medication was

used less often after sumatriptan. In contrast, pain-free responses did not differ between sumatriptan and placebo. Age, gender and puberty stage had no effect on the response to sumatriptan. The proportion of children who fell asleep within 2 h of treatment was 13 % after sumatriptan and 12 % after placebo and all were pain-free upon awakening.

Regarding safety, there were no serious AE in any of the five studies on sumatriptan, with the exception of 1 placebo patient experiencing exacerbation of migraine symptoms which required treatment in an emergency department. The prevalence of AE was lowest in the placebo groups (8–18 %) and increased with increasing doses of sumatriptan reaching 33–44 % for nasal sumatriptan 20 mg. The most common AE in the studies on sumatriptan nasal spray were taste disturbances reported by 19–30 % of the patients after sumatriptan and by 2–3 % after placebo [15–17].

In summary, there is no evidence supporting the efficacy of oral sumatriptan for treating acute migraine attacks in children and adolescents. There is no clear evidence for nasal sumatriptan in children below the age of 12 years, whereas sumatriptan nasal spray was superior to placebo in adolescents. In detail, this was true for headache relief and pain-freedom in three studies each, but not for sustained pain-free. Published data on safety and AE do not raise concerns regarding the use of sumatriptan nasal spray in adolescents. Accordingly, there is sufficient evidence supporting the safety and short-term efficacy of sumatriptan nasal spray 20 mg for treating migraine attacks in adolescents. Further studies in children are needed.

13.2.3.2 Zolmitriptan

Zolmitriptan was examined in a total of three studies (2 with oral, 1 with nasal zolmitriptan), applying different study designs (Table 13.1). One oral study was crossover, comparing zolmitriptan 2.5 mg and ibuprofen to placebo, and has already been mentioned above [10]. The other was a parallel group study comparing zolmitriptan 2.5, 5 and 10 mg to placebo [18]. To control the high placebo-response rates in adolescent migraineurs, the trial on zolmitriptan nasal spray applied a novel study design [19]. The protocol included a single-blind placebo challenge for each migraine attack and patients who had achieved a response within 15 min did not use additional medication.

In the crossover study with ibuprofen [10], zolmitriptan was superior to placebo with respect to pain relief and pain-freedom at 1, 2 and 4 h, sustained pain-free response and rescue medication as well as with respect to nausea at 1, 2, and 4 h and photophobia/phonophobia at 1 and 2 h. Zolmitriptan was also superior to placebo in 11 patients under the age of 13 years. Response rates in boys and girls did not differ from each other. The placebo-response rate was extremely low.

In the other oral zolmitriptan study [18], 696 patients treated a single migraine attack either with zolmitriptan 2.5 mg, 5 mg or 10 mg or with placebo. Patients included had to have migraine headache duration of ≥4 h in all of their untreated attacks and study medication had to be taken not later than 1 h after the start of the attack or the time the patient first became aware of it. The proportions of patients with headache relief and pain-free response were similar for zolmitriptan 10 mg and

placebo. Because a step-down approach was taken, statistical analyses were not performed for zolmitriptan 5 and 2.5 mg.

Considering the high placebo-response rates the novel approach of a single blind placebo challenge was used for the first time in the study on zolmitriptan nasal spray [19]. In a crossover design, adolescent migraineurs had to be treated for two moderate to severe migraine attacks. Each attack was first treated with placebo. If headache relief (i.e. improvement from moderate or severe pain intensity to mild or none) was achieved within 15 min, no more medication was to be taken. If pain intensity remained moderate or severe, the patients used zolmitriptan 5 mg or placebo. Outcome parameters were similar to previous studies on sumatriptan [15, 16]. Primary endpoint was the headache relief at 1 h after intake of study medication. Twelve patients showed a response to placebo challenge in both attacks and 22 showed a response in 1 attack. Out of 248 patients included, 171 placebo-challenge non-responders treated at least one attack with zolmitriptan or placebo. Zolmitriptan 5-mg nasal spray was statistically significantly superior to placebo with respect to headache relief at 15 min, 30 min and 1 h (but not at 1.5 and 2 h) as well as to 2-h sustained headache relief (defined as response at 1–2 h postdose without use of escape medication), pain-free response at 1, 1.5 and 2 h, photophobia and phonophobia at 30 min and return to normal activity at 45 min and 1 h postdose. Finally, the use of escape medication was lower in attacks treated with zolmitriptan.

Data on safety and AE in these studies do not give any cause for concern. There was one serious AE, i.e. prolonged headache. The incidence of any AE was 34–44 % for zolmitriptan and 13–19 % for placebo. However, long-term safety data for children and adolescents are not available.

In summary, the efficacy of oral zolmitriptan is controversial with a small crossover study suggesting superiority over placebo and a large parallel group study which showed similar efficacy rates for zolmitriptan and placebo. Nasal zolmitriptan was effective in adolescent migraineurs in a single placebo-controlled study applying a novel placebo-challenge design. Even though evidence from placebo-controlled studies is limited to a single trial, and pharmacokinetic data are only available for oral administration, nasal zolmitriptan is an alternative for treating migraine in adolescents, particularly in countries (such as Austria) where sumatriptan nasal spray is no longer available. Further studies including patients below the age of 12 are needed.

13.2.3.3 Rizatriptan

There are four studies on rizatriptan for migraine in children and adolescents, one crossover study and three parallel group studies (Table. 13.1) [20–23]. The latest of these [23] excluded patients responding within 15 min after taking an initial dose of study medication similar to the zolmitriptan nasal spray trial [19].

The first study on rizatriptan [20] included 360 adolescents 12–17 years of age. The design of this parallel group study was similar to studies on sumatriptan and zolmitriptan [15, 16, 18]. The study failed the primary endpoint, i.e. pain-free at 2 h. In addition, there was no difference between rizatriptan and placebo with respect to pain-free response at all other time points, pain relief at all time points except 3 h

postdose and associated symptoms at all time with the exception of nausea at 1, 1.5 and 4 h postdose. Phonophobia was reported more often by patients in the rizatriptan group at 30 min and by patients in the placebo group at 4 h postdose. Regarding normal functioning, rizatriptan was superior to placebo at 1 and 1.5 h postdose. The need for additional medication and recurrence rates did not differ in the two study groups. A post hoc analysis revealed differences between weekdays and weekend. In detail, the placebo-response rate was lower on weekends and rizatriptan 5 mg showed a statistically significant benefit over placebo on weekends, but not on weekdays.

In a subsequent parallel group study [21], the authors instructed the patients to restrict the intake of study medication "to days that they were not attending school or camp". They expected that the majority will treat attacks during the weekend, but in fact this was the case in only 30 %. This time, pain relief at 2 h was the primary endpoint. However, the proportion of patients who achieved this endpoint was exactly the same (68.2 % on rizatriptan 5 mg and 68.8 % on placebo). Two-hour pain-free response favored numerically rizatriptan, but the difference just did not reach statistical significance ($p = 0.053$). Separate analyses of weekdays and weekends confirmed the finding of the first rizatriptan study [20]. On weekends, rizatriptan was statistically significantly superior to placebo with respect to pain relief (but not with respect to pain-freedom).

The findings of the crossover trial [22] demonstrating clear superiority of rizatriptan over placebo with regard to pain relief as well as pain-free response suggest that the study design may play an important role, as the two negative trials discussed above were parallel group studies. The study design followed that of the nasal sumatriptan trial of the same group [17]. Patients aged 6–17 years treated three migraine attacks – two with rizatriptan 5 mg (body weight 20–39 kg) or 10 mg (body weight ≥ 40 kg) and one with placebo. The primary efficacy endpoint – headache relief by at least 2 grades on a 5-point scale at 2 h – was reached significantly more often with rizatriptan than with placebo. Rizatriptan was superior to placebo with respect to headache relief also at 1, 3 and 4 h postdose and the effect at 2 h remained statistically significant after classifying sleeping as treatment failure. The proportion of patients who were pain-free at 2 h was higher and the use of rescue medication was lower with rizatriptan than with placebo. Similar results were found in the intention-to-treat analysis, except for the pain-free response at 1 h which did not differ between active treatment and placebo. Rizatriptan was superior to placebo irrespective of age.

Most recently, a large parallel group study [23] in children and adolescents aged 6–17 years was published using an "adaptive enrichment" design, i.e. an initial double-blind run-in phase. In contrast to the single blind run-in phase in the nasal zolmitriptan trial [19], the run-in phase in the rizatriptan trial was double-blind and patients were randomized to placebo or rizatriptan in a ratio of 20:1. Patients with mild or no pain after 15 min did not take more study medication and patients with moderate or severe pain took further medication. Those who initially had taken placebo were randomized to rizatriptan or placebo in a ratio of 1:1, whereas those who had taken rizatriptan were allocated to placebo. Both in the run-in phase and in

stage 2, randomization was stratified by age, differentiating patients 6–11 and 12–17 years of age and making sure to include similar numbers of subjects aged 12–14 and 15–17 years. At stage 2, patients were additionally randomized by headache intensity, i.e. moderate or severe. The rizatriptan dose was 5 mg or 10 mg depending on the patient's body weight. The primary endpoint was freedom from pain in 12–17-year olds, secondary endpoints were pain relief in this age group as well as pain freedom and pain relief in the entire group of patients. In addition there were several exploratory endpoints. Rizatriptan was superior to placebo with respect to the primary endpoint, i.e. 2-h pain freedom in patients aged 12–17, whereas 2-h pain relief did not differ between rizatriptan and placebo in this age group. Furthermore, rizatriptan was superior to placebo for 2-h pain-freedom in 6–17-year olds, and it was superior in 12–17-year olds as well as in 6–17-year olds with respect to 2-h pain relief according to the definition in the Finnish crossover study [22], 2–24- and 2–48 h sustained pain freedom, nausea and "as usual" function. In addition, absence of vomiting was seen more often after rizatriptan than after placebo in 12–17-year olds. However, in the group of 6–11-year olds not one endpoint showed a statistically significant difference between active drug and placebo.

Safety data for rizatriptan are available from the placebo-controlled studies as well as from open-label and long-term studies. In the placebo-controlled trials, the proportion of patients reporting any AE was highest in the two conventional parallel group studies [20, 21] (rizatriptan 34 %, placebo 30–35 %) – a little bit lower in the 2-stage parallel group study excluding early responders [23] (rizatriptan 23–25 %, placebo 22–30 %), and lowest in the crossover study [22] (rizatriptan 9–14 %, placebo 2 %). In a long-term open-label safety study [30], 606 patients treated 20 attacks on average. Four hundred of them (66 %) reported any AE, 14 (2.3 %) discontinued due to an AE and 16 (2.6 %) had a serious AE. Among the latter, 3 were considered drug-related and all of them were classified as serious, because they were associated with an overdose, i.e. more than 1 dose of study medication within a 24-h period.

Recently, a randomized, double-blind, placebo-controlled study on pharmacokinetics in 31 children and adolescents with migraine has been published [31]. Patients with a body weight of <40 kg received 5 mg rizatriptan oral disintegrating tablets or placebo, and those with a body weight of ≥40 kg received 10 mg rizatriptan or placebo. Rizatriptan plasma concentrations with the weight-based dosing scheme were similar to those observed previously in adults, thus supporting this approach.

Rizatriptan is the only triptan with placebo-controlled pharmacokinetic data in children and adolescents. Furthermore, safety data are available from single-attack as well as long-term studies including way above 2000 subjects in total. The published data suggest that the use of rizatriptan in children and adolescents with migraine seems to be safe. Regarding efficacy, placebo-response rates of up to 69 % explain why rizatriptan was not superior over placebo in several primary and secondary endpoints. It might be useful to perform a further study using the "adaptive enrichment" design within a crossover study, in order to provide more evidence for the efficacy of rizatriptan in childhood as well as in adolescence migraine.

13.2.3.4 Almotriptan

There is one placebo-controlled parallel group study comparing 6.25, 12.5 and 25 mg almotriptan to placebo in adolescents aged 12–17 years (Table 13.1) [24]. The primary endpoint was headache relief at 2 h postdose. Other endpoints were headache relief at other time points, nausea, photophobia, phonophobia and sustained pain relief as well as sustained pain-free response. Efficacy analysis included data of 714 patients. Two-hour headache relief was seen significantly more often in patients who had received almotriptan 25 mg than in those who had received placebo and this was true for analysis with and without adjustment for baseline pain severity. Two-hour pain relief rates were significantly higher for almotriptan 12.5 mg at 1.5 and 2 h postdose and for almotriptan 6.25 mg at 2 h postdose. Furthermore, almotriptan 6.25, 12.5 and 25 mg were superior to placebo for sustained pain relief, almotriptan 25 mg for nausea at 1 h and almotriptan 12.5 mg for phonophobia at 1.5 h postdose. Pain-free response rates of the three almotriptan doses did not differ from placebo at any time point. A subgroup analysis of 12–14-year olds and 15–17-year olds showed statistically significant differences between placebo and almotriptan 6.25, 12.5 and 25 mg only for the older, but not for the younger group.

The proportion of patients reporting at least 1 AE was 18.6 % for placebo and increased with increasing doses of almotriptan from 15 to 25.8 %. Treatment-related AE were found in 6.7, 12.1 and 12.4 % of the patients who had received almotriptan 6.25, 12.5 and 25 mg and 5.8 % in those who had received placebo. There were no serious AE, no discontinuations due to an AE and no relevant changes in laboratory tests, electrocardiogram and vital signs. Safety data for almotriptan 12.5 mg are also available from a 12-month open-label study in 420 adolescents showing that 67.1 % of the patients reported at least one AE, 7.6 % had a treatment-related AE, 2.4 % discontinued because of an AE, and 1.9 % reported a serious AE. Very similar percentages were reported for rizatriptan [30].

The use of almotriptan for treatment of migraine in adolescents 12–17 years of age is supported by one randomized, placebo-controlled study and a long-term open-label safety study. Further efficacy studies, preferably with a crossover design as well as studies in patients below the age of 12 are needed.

13.2.3.5 Eletriptan

In 1997 and 1998, a study on eletriptan for the acute treatment of migraine in adolescents was performed and the negative results were published in 2007 [25]. This double-blind placebo-controlled parallel-group study included 274 patients who treated a single moderate or severe migraine attack within 4 h of headache onset. Not one primary, secondary or exploratory endpoint showed a statistically significant difference between eletriptan and placebo. The proportion of patients reporting any AE was 33–42 % for eletriptan and 28 % for placebo, thus, being comparable to studies on other triptans in children and adolescents.

Based on these findings and the lack of pharmacokinetic and further safety data, eletriptan is not indicated for the treatment of migraine in children and adolescents.

13.2.3.6 Sumatriptan and Naproxen Combination

Following trials, providing evidence for the efficacy of this combination in adults [32], a study in adolescents has been published [26]. This parallel group study compared sumatriptan/naproxen 10/60, 30/180 and 85/500 mg to placebo in 589 adolescents. Similar to the nasal zolmitriptan and the most recent rizatriptan trial, there was a run-in phase (in this study with single-blind administration of placebo) and patients reporting headache 2 h postdose were included in the double-blind phase. The primary endpoint was pain-free at 2 h postdose. Of 865 patients enrolled, 683 entered the run-in phase and 589 were randomized to 1 of the 4 treatment arms. The proportion of 2-h pain-free patients was 10, 29, 27 and 24 % with placebo, sumatriptan/naproxen 10/60, 30/180 and 85/500 mg and the difference between all sumatriptan/naproxen doses and placebo was statistically significant. In addition, the 3 sumatriptan/naproxen doses were superior to placebo with respect to most of 10 secondary endpoints. After correction for multiple testing, however, only 3 secondary endpoints for sumatriptan/naproxen 85/500 mg remained statistically significant: sustained pain-free, photophobia-free at 2 h and phonophobia-free at 2 h.

The incidence of treatment emergent AE was similar for active treatment and placebo and ranged between 8 and 13 %. AE within 72 h and drug-related AE were dose dependent. Further safety data are available from an open long-term study [33]. Analyses of more than 12,000 exposures to sumatriptan/naproxen revealed no new or clinically significant findings as compared to the individual components or to the AE profile in adults. Seven percent of the patients discontinued participation in the study because of an AE and 4 subjects had 5 serious AE not related to sumatriptan/naproxen.

Sumatriptan/naproxen may be an alternative for adolescents with migraine attacks refractory to triptan monotherapy. The optimal dose remains to be determined considering treatment response to the lowest dose and dose dependent AE.

13.3 Acute Treatment of Tension-Type Headache

Searching Medline for randomized controlled trials on pharmacological acute treatment of tension-type headache, revealed not one study. Acetaminophen or ibuprofen may be used restrictively for severe episodes of tension-type headache, but in general non-pharmacological preventive treatments should be favored [34]. In chronic tension-type headache the use of analgesics must be restrictive to prevent medication-overuse headache [34].

13.4 Acute Treatment of Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache is extremely rare during childhood, but may start during adolescents. For treatment of acute attacks of cluster headache, oxygen is the treatment of first choice, even though no studies in young patients are available. Zolmitriptan

nasal spray may be used (off-label) supported by controlled studies in adults with cluster headache and good tolerability in adolescent migraine.

Conclusion

With respect to the pharmacological acute therapy of migraine in the young, evidence in children is very poor and evidence for adolescents is better but still limited with high placebo-response rates as the major problem. In clinical practice, acetaminophen and ibuprofen are the first-line drugs because of their excellent safety profile. Adolescents and children not responding to these compounds (or to other analgesics and NSAIDs) may be treated with triptans, i.e. nasal sumatriptan, nasal zolmitriptan, rizatriptan and almotriptan licensed at least in some countries [35]. With respect to the acute treatment of tension-type headache and cluster headache, randomized controlled trials are not available.

References

1. Wöber-Bingöl Ç (2013) Epidemiology of migraine and headache in children and adolescents. Curr Pain Headache Rep 17(6):341
2. Karwautz A, Wöber C, Lang T et al (1999) Psychosocial factors in children and adolescents with migraine and tension-type headache: a controlled study and review of the literature. Cephalalgia 19(1):32–43
3. Kernick D, Reinhold D, Campbell JL (2009) Impact of headache on young people in a school population. Br J Gen Pract 59(566):678–681
4. Wöber-Bingöl Ç, Wöber C, Uluduz D et al (2014) The global burden of headache in children and adolescents – developing a questionnaire and methodology for a global study. J Headache Pain 15:86
5. Wöber-Bingöl Ç, Martin IP (2011) Managing headache in young people. In: Martelletti P, Steiner TJ (eds) Handbook of headache. Practical management. Springer, Berlin, Germany, pp 565–578
6. Termine C, Özge A, Antonaci F et al (2011) Overview of diagnosis and management of paediatric headache. Part II: therapeutic management. J Headache Pain 12(1):25–34
7. Wöber-Bingöl Ç, Hershey A (2011) Migraine co-morbidities in children. In: Schoenen J, Sandor P, Dodick D (eds) Co-morbidity in migraine – clinical aspects, prevalence, mechanisms and management. Wiley-Blackwell, West Sussex, UK, pp 122–132
8. Hämäläinen ML, Hoppu K, Valkeila E et al (1997) Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology 48(1):102–107
9. Lewis DW, Kellstein D, Dahl G et al (2002) Children's ibuprofen suspension for the acute treatment of pediatric migraine headache. Headache 42(8):780–786
10. Evers S, Rahmann A, Kraemer C et al (2006) Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. Neurology 67(3):497–499
11. Hämäläinen H, Hoppu K, Santavuori P (1997) Oral dihydroergotamine for therapy-resistant migraine attacks in children. Pediatr Neurol 16(2):114–117
12. Hämäläinen M, Hoppu K, Santavuori P (1997) Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine respond to oral sumatriptan differently than adults? Neurology 48(4):1100–1103
13. Fujita M, Sato K, Nishioka H et al (2014) Oral sumatriptan for migraine in children and adolescents: a randomized, multicenter, placebo-controlled, parallel group study. Cephalalgia 34(5):365–375

14. Uebarall MA (1999) Intranasal sumatriptan for the acute treatment of migraine in children. Neurology 52(7):1507–1510
15. Winner P, Rothner AD, Saper J et al (2000) A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. Pediatrics 106(5):989–997
16. Winner P, Rothner AD, Wooten JD et al (2006) Sumatriptan nasal spray in adolescent migraineurs: a randomized, double-blind, placebo-controlled, acute study. Headache 46(2): 212–222
17. Ahonen K, Hämäläinen ML, Rantala H et al (2004) Nasal sumatriptan is effective in the treatment of migraine attacks in children. Neurology 62(6):883–887
18. Rothner AD, Wasiewski W, Winner P et al (2006) Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents. Headache 46(1):101–109
19. Lewis DW, Winner P, Hershey AD et al (2007) Efficacy of zolmitriptan nasal spray in adolescent migraine. Pediatrics 120(2):390–396
20. Winner P, Lewis D, Visser WH, Rizatriptan Adolescent Study Group et al (2002) Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind placebo-controlled study. Headache 42(1):49–55
21. Visser WH, Winner P, Strohmaier K, Rizatriptan Protocol 059 and 061 Study Groups et al (2004) Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double-blind, single-attack study and two open-label, multiple-attack studies. Headache 44(9): 891–899
22. Ahonen K, Hämäläinen ML, Eerola M et al (2006) A randomized trial of rizatriptan in migraine attacks in children. Neurology 67(7):1135–1140
23. Ho TW, Pearlman E, Lewis D et al (2012) Efficacy and tolerability of rizatriptan in pediatric migraineurs: results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design. Cephalalgia 32(10):750–765
24. Linder SL, Mathew NT, Cady RK et al (2008) Efficacy and tolerability of almotriptan in adolescents: a randomized, double-blind, placebo-controlled trial. Headache 48(9):1326–1336
25. Winner P, Linder SL, Lipton RB et al (2007) Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo-controlled trial. Headache 47(4):511–518
26. Derosier FJ, Lewis D, Hershey AD et al (2012) Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine. Pediatrics 129(6):e1411–e1420
27. Southey ER, Soares-Weiser K, Kleijnen J (2009) Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. Curr Med Res Opin 25(9):2207–2222
28. Bárzaga Arencibia Z, Choonara I (2012) Balancing the risks and benefits of the use of over-the-counter pain medications in children. Drug Saf 35(12):1119–1125
29. Wöber C, Wöber-Bingöl Ç (2000) Intranasal sumatriptan for the acute treatment of migraine in children. (Letter). Neurology 54(5):1209–1210
30. Hewitt DJ, Pearlman E, Hämäläinen M et al (2013) Long-term open-label safety study of rizatriptan acute treatment in pediatric migraineurs. Headache 53(1):104–117
31. Fraser IP, Han L, Han TH et al (2012) Pharmacokinetics and tolerability of rizatriptan in pediatric migraineurs in a randomized study. Headache 52(4):625–635
32. Khoury CK, Couch JR (2010) Sumatriptan-naproxen fixed combination for acute treatment of migraine: a critical appraisal. Drug Des Devel Ther 4:9–17
33. McDonald SA, Hershey AD, Pearlman E et al (2011) Long-term evaluation of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescents. Headache 51(9):1374–1387
34. Wöber-Bingöl Ç (2013) Tension-type headache. In: Abu-Arafeh I (ed) Childhood headache, 2nd edn. Mac Keith Press, London, UK, pp 166–172
35. Wöber-Bingöl Ç (2013) Pharmacological treatment of acute migraine in adolescents and children. Paediatr Drugs 15(3):235–246

Pharmacological Strategies in the Prevention of Migraine in Children

14

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Preventative treatment of migraine is not only based on drugs. A balanced, flexible and individual treatment must include both non-pharmacological methods, such as bio-behavioral strategies as well as pharmacological measures [1].

The basic bio-behavioral strategies for patients and families include regulation of sleep, institution of a regular exercise program, stress management, dietary precautions and lifestyle modification to cope with identified triggers [2, 3].

The use of a pharmacological treatment to prevent migraine attacks is recommended if a severe impairment has been valuated in the daily life of a patient and non-pharmacological preventive treatment has not been successful; if the frequency of the headache episodes is more than 2 per month lasting for quite a long period; and if they are associated with other phenomena such as auras [4]. Moreover, preventive medications are recommended if the headache attacks do not respond to acute drug treatment and further to avoid excessive acute migraine medication.

A good response to prophylactic treatment, assessed for at least 3 months, is obtained if there is about 50 % reduction in the frequency and severity of migraine attacks and a significant improvement in the quality of life is reached. Maintaining a migraine diary is necessary to evaluate the trend of the prophylactic treatment, to underline residual crisis or to establish side effects. Criteria for terminating preventive migraine treatment are not clearly established. The frequency of therapy has to be gradually decreased in order to avoid "rebound" effects. Suspension of the preventive treatment is further recommended, after an ongoing period of 3 months – with a period free from drugs before a subsequent cycle of treatment.

The choice between a preventive drug or any other is also determined on the basis of the type of migraine itself, by the comorbidity with other pathologies,

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_14

privileging drugs with efficacy in both the cases (i.e. flunarizine in migraine associated with anxiety; amitriptyline in the comorbidity with depression; valproate in case of epilepsy) and by avoiding medications that can worsen the associated pathology (i.e. flunarizine for migraine and depression; propranolol in case of asthma; amitriptyline for comorbidity with epilepsy) [5].

During child development, the migraine preventive treatment has to consider two basic matters: the different efficacy of drugs between adults and children and the relevance of a placebo effect in preventive therapy particularly in childhood.

Indeed, the response to drugs can markedly differ during development because of many differences in pathophysiology, in the variants of disease, in pharmacodynamics, in the host response and in adverse reactions. It is important to consider the particular pharmacokinetics presented during the development due to several differences in children metabolisms, such as limited binding proteins, immature renal functions in infants, slower gastrointestinal absorption and a faster intra-muscle, and larger brain/body weight ratio and higher blood brain barrier permeability in younger children.

Placebo has been found to be statistically efficient in children because the expectancy and the conditioning in the pharmacological treatment is linked with psychological component of the chronic headache [6–8].

Finally patient treatment compliance is basilar for the outcome of the therapy. It is needed to ensure patient's choice for more comfortable therapy, considering the compliance is inversely proportional to the duration of the treatment and to the number of daily doses. Moreover, it is important to explore the child and his parents' expectation and record their inputs so that medication can be directed that will decrease the frequency, the number and the intensity of migraine attacks.

14.1 Calcium-Channel Blockers

In migraine prevention, calcium-channel blockers are thought to exert their effects through selective inhibition of vasoactive substances on cerebrovascular smooth muscle. Calcium-channel blockers have been extensively studied for migraine prophylaxis in adults, but evidence is still lacking in children and adolescents, with exception of flunarizine [2].

14.1.1 Flunarizine

Flunarizine is a calcium-channel blocker that has been evaluated in several controlled trials in adults [4]. Flunarizine has been investigated for the preventive migraine treatment in children as well as in a controlled trial and in an open-label study, showing good efficacy and safety [8, 9]. Further data are necessary for recommending treatment in children. Currently, flunarizine is an off-label drug in childhood, prescribed in Europe but not licensed in UK or USA [4, 10]. It can be consumed once a day, preferably as a single bedtime dose – dosage 5–10 mg – for

3 months to be effective, and dosage is to be reduced with decrease in headache frequency and headache duration. The possible side effects of this therapy are the main limiting factors in the prescription. In fact, it may determine depression, extrapyramidal symptoms, drowsiness and weight gain.

14.2 Antiepileptic Agents

Antiepileptic drugs such as topiramate and valproate have expanding roles for pediatric migraine. Indeed, anticonvulsants represent an intriguing and unclarified role, because of the current views of the pathophysiology of migraine, that suggested a primary neuronal initiation and propagation through cortical excitation and, later, "spreading depression" [10, 11]. Topiramate and valproate are approved by the FDA for migraine prevention in adult patients, and topiramate was recently approved in adolescents of 12 years for migraine prevention.

14.2.1 Topiramate

Topiramate is an antiepileptic drug with an uncertain mechanism of modulation of pain. Its property acts by interacting with GABA-receptors and increasing the availability of GABA. Indeed, Topiramate, blocking sodium and calcium channels inhibits AMPA receptors and also presents a partial activity on the positive modulation of GABA A receptors. Furthermore, topiramate causes an inhibition of the carbonic anhydrase. Topiramate was found to be superior to placebo in double-blind placebo-controlled trials both in children [12, 13] and in adolescents [14]. The dosage of topiramate is 1.4 mg/kg/day with a starting dose of 25 mg per day and increasing doses every 2 weeks, to a maximum of 2 mg/kg/day. Side effects included hypohidrosis, hyperthermia, nephrolithiasis, cognitive changes with impairments in verbal fluency, weight loss and sensory symptoms.

14.2.2 Sodium Valproate

Sodium Valproate is an antiepileptic drug that showed an efficacy in the prevention of migraine in adults. Uptil now, few studies about preventive treatment with valproate have been conducted in children and adolescents. Open-label and retrospective studies seem to confirm the findings in adults [14, 17]. The mechanism of action of valproate in migraine is due to the ability to increase the GABA activity. Caruso et al. [14] conducted an open clinical observational study to evaluate the efficacy of valproate at the dose of 45 mg/kg in 42 patients aged between 7 and 16 years. After 6 months of ongoing therapy, 78 % decrease in headache was noted in 50 % of patients, and 9 % reported absence of headache. These data were also confirmed by a retrospective study on a sample of 207 migraine patients [18] and by an open-label study on a sample of 20 patients [19]. The prescribed dosage of valproate in

children is between 15 and 45 mg/kg/day with a reasonable safety profile [15]. Side effects of this drug include sleepiness, tremor, cutaneous rash, alopecia, anorexia and weight gain. In addition, it may cause hepatotoxicity, especially in children <10 years old, and a decrease in the number of platelets. Thus, it is not recommended in case of liver disease or decreased bone marrow function.

14.3 Antidepressants

Antidepressants have become a basilar strategy of migraine prophylaxis. However, while considerable literature is present on the study of efficacy of antidepressants for adult migraine, there is no equal data available in childhood category [20, 21].

14.3.1 Amitriptyline

Amitriptyline is a first generation antidepressant, belonging to the pharmacological category of tricyclics. It is also used in the therapy of migraine prevention and in neuropathic pain because of its pain modulating properties. Amitriptyline, particularly, is the first-choice drug in patients with comorbid anxiety and depression, with problems such as sleeping the whole night with concomitant tension-type headache. Amitriptyline acts primarily as a serotonin-norepinephrine reuptake inhibitor, but it also has an interaction with muscarinic receptors, H1-istaminergic receptors, beta and alpha 2-adrenergic receptors. Because of this partial receptor selectivity, the chronic treatment with amitriptyline can produce several side effects and interactions. Side effects are represented by sedation, confusion, blurry vision, xerostomia for muscarinic receptors' inhibition, or cardio-vascular side effects with hypotension, arrhythmia, cardiac conduction alteration for the interaction with H1-istaminergic and adrenergic receptors. Moreover, it should be emphasized that the severe interaction with MAO inhibitors can cause hyperthermia, seizures and exitus. Amitriptyline dosage is 1 mg/kg per day, starting from a single bedtime dose of 5–10 mg to 25–50 mg [10]. At these low doses, side effects are occasional and not severe.

14.4 Beta-Blockers

Beta-blockers are often considered one of the first-line agents in childhood migraine prevention.

14.4.1 Propranolol

Propranolol is the most used non-selective beta-blocker working on Beta-1 and Beta-2 Receptors. Propranolol has been mostly studied in adult patients for the

prevention of migraine, and placebo-controlled trials have shown a better efficacy of propranolol than the placebo. In children, conflicting results were identified in comparison to propranolol with placebo. Ludviggson et al. [22] showed that in 32 children aged 7–16 years propranolol (60–120 mg) produced a significant increase in the perception of benefit compared to placebo. In contrast, the other two open-label studies failed to show efficacy of propranolol over placebo [23, 24]. It may be used on a single daily dose basis with a starting dose of 1–2 mg/kg/day to be gradually increased to 3 mg/kg/day as can be tolerated, with dosing adjustments made every 2–3 weeks.

The selective beta-blockers – *atenolol*, *metoprolol* and *nadolol* – may be the alternative choices, although controlled data is lacking to advise any relative advantage. The use of beta-blockers is contraindicated in reactive airway disease, diabetes mellitus, orthostatic hypotension, certain cardiac disorders associated with bradyarrhythmias and psoriasis. It is also described as an interaction between propranolol and rizatriptan. When prescribing rizatriptan for acute treatment of migraine in patients receiving propranolol for prophylaxis, the 5-mg dose of rizatriptan is recommended. Indeed, propranolol seems to increase plasma concentrations of rizatriptan by inhibiting monoamine oxidase-A. Administration with other beta-adrenoceptor blockers does not require consideration of dose adjustment [25].

14.5 Pizotifen

Pizotifen is especially used for the prevention of migraine and cluster headache. Even if pizotifen is reasonably effective, it is usually not the first choice medication for preventing migraines because of its side effects, e.g. drowsiness and weight gain in particular. Pizotifen acts by inhibiting 5-hydroxytryptamine-2B and 2C receptors in the vascular endothelium and blocking the production of nitric oxide. In clinical trials, pizotifen was found to be more effective than placebo in the prevention of migraine in adults, but randomized placebo-controlled trials in children are not sufficient [26]. The daily dose can vary from 0.5 to 1.5 mg, up to 3.5 mg used particularly in abdominal migraine [27]. Although it is used in some European countries but it is not licensed in USA.

14.6 Riboflavin

An alteration in the brain metabolism has been found in migraine patients. Indeed, one of the hypotheses for migraine attacks is that a mitochondrial defect may reduce the threshold for increasing neuronal excitability and may determine a hyperresponsiveness of the brain to triggering stimuli [28, 29]. Because riboflavin is a major co-factor in oxidative metabolism, it may play an important role in overcoming this metabolic impairment, improving brain energy metabolism. Studies in adults confirmed the safety and effectiveness of riboflavin in migraine prophylaxis, but evidence in children is very limited and controversial. One retrospective study

reported decreased migraine frequency and intensity with dosage of 200–400 mg/die of riboflavin [30]. Two randomized double-blind placebo-controlled trials showed no reduction of migraines with use of riboflavin, with daily dosages between 50 and 200 mg [31, 32]. The suggested pediatric dosage of riboflavin is 100–400 mg per day.

Riboflavin was safe and well tolerated in all the studies mentioned above. The side effects described in both adults and children were a few cases of vomiting, diarrhea, and orange-colored urine.

14.7 Coenzyme Q10

Several studies in adults demonstrated the efficacy of Coenzyme Q10 (CoQ10) supplementation in migraine prevention [33]. The role of CoQ10 is essential for the energy production of the cells; it is also an electron transporter in the mitochondrial respiratory chain. CoQ10 seems to act both in improving the mitochondrial function and in the inflammatory changes occurring in recurrent migraine attacks. Pertaining to the above, deficit of CoQ10 may influence the clinical characteristics of migraine attacks and can modulate the response to an acute or chronic migraine treatment.

The efficiency of CoQ10 in pediatric migraine has had controversial results [33, 34] and it has not been largely investigated in children and adolescents; indeed further studies are needed.

14.8 Magnesium

Low levels of magnesium seem to be associated also with the sequence of events that may trigger migraine [35, 36]. Results about supplementation of magnesium to prevent migraine attacks are dichotomous. Despite conflicting results, many clinicians believe that magnesium can be useful, mostly in young migraine patients [35, 37].

14.9 Botulinum Toxin

In adults, botulinum toxin type A (BoNT-A) was superior to placebo in chronic migraine, but not in episodic migraine [38]. According to the PREEMPT trials a total of 155–195 units of BoNT-A are injected in the pericranial muscles following a fixed site, fixed dose scheme and applying 5 U at each site [38]. Treatment is repeated every 3 months. Recently it was shown that a meaningful proportion of those who did not respond to the first treatment cycle responded in the second and third cycles of treatment [39]. Adverse effects comprise neck pain, facial paresis, eyelid ptosis and blurred vision. In 2010, BoNT-A was approved by the US Food and Drug Administration for the use of chronic migraine in adults. Data on effectiveness and tolerability in the pediatric population are very limited.

Botox is recommended to any pediatric patient for chronic headache refractory to two or more oral medications used for prophylaxis. Study in children and adolescents showed a major change in the frequency of the headache with a statistical difference in the improvement of headache days per month. A drop in the pediatric disability scoring was also observed between first injection and follow-up injection with a change from severe disability to moderate disability [40, 41].

14.10 Pharmacological Strategies in the Prevention of Tension-Type Headache

Not many studies are concerned with tension-type headache in childhood; trials often involved adults in particular [42]. For preventing tension-type headache, antidepressants are still the first-choice drugs [43]. Moreover, emphasis should be on non-pharmacological measures such as nutraceuticals (e.g. melatonin), behavioral therapies (e.g. relaxation training, cognitive-behavioral therapy) and lifestyle factors, especially adequate sleep hygiene and strategies to cope with anxiety.

14.11 Pharmacological Strategies in the Prevention of Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Recommendations for cluster headache preventive treatments by European Federation of Neurological Society [44] included, as first choice medication, verapamil (Level A), while as second choices (Level B), lithium and antiepileptic agents, such as, topiramate and gabapentin. Valproate is a third choice (Level C) although it is indicated as second choice in the American Academy of Neurology [45].

Verapamil, in pediatric prevention therapies for chronic cluster headache, is reported at the dosage of 120–240 mg [46, 47], with a starting dose of 40–80 mg daily. Electrocardiography is advised in the monitoring of potential development of heart block.

14.12 Preventive Treatment: Conclusion

In high-frequency migraine management a combined program needs to be considered. Indeed, bio-behavioral strategies (i.e. diet, sleep) are a mainstay in the treatment of these conditions together with a pharmacological approach. First-line drugs for children and adolescents are flunarizine, propranolol and antiepileptic drugs such as topiramate. Valproate is a second-line medication. Data evidence is still lacking and use of third-line drugs in children and adolescents is still debatable (Table 14.1).

Table 14.1 It is reported the different drug evidence level with dosage and dose frequency

Drug	Evidence level	Dosage	Study design	References	Dose frequency
Flunazine	A	5–10 mg	DBPC; OL	[8, 9]	Once per die
Topiramate	A	1–2 mg/kg	BDPC	[12–14]	Once per die
Valproate	B	15–45 mg/kg	OL; DBPC; rDBPC	[15–17, 19]	Once/twice per die
Amitriptyline	C	0.25–1 mg/kg	RR, OL	[20, 21]	Once per die
Propanolol	C	1–2 mg/kg	DBPC	[22–24]	Once per die
Pizotifen	C	0.5–1.5 mg/kg	DBPCCO	[26]	Once per die

Literature references and study designs are also reported: DBPC double-blind placebo-controlled, DBPCCO double-blind placebo-controlled crossover, rDBPC randomized double-blind placebo controlled, OL open-label, RR retrospective review

References

1. Brenner M, Lewis D (2008) The treatment of migraine headaches in children and adolescents. J Pediatr Pharmacol Ther 13(1):17–24
2. O'Brien HL, Kabbouche MA, Kacperski J et al (2015) Treatment of pediatric migraine. Curr Treat Options Neurol 17(1):326
3. Silberstein SD (2000) Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55(6):754–762
4. Evers S, Afra J, Frese A et al (2006) EFNS guideline on the drug treatment of migraine – report of an EFNS task force. Eur J Neurol 13(6):560–572
5. Lanzi G, Balottin U, Zambrino CA et al (1996) Guidelines and recommendations for the treatment of migraine in paediatric and adolescent patients. Italian Society for the Study of Headache. Funct Neurol 11(5):269–275
6. El-Chammas K, Keyes J, Thompson N et al (2013) Pharmacologic treatment of pediatric headaches: a meta-analysis. JAMA Pediatr 167(3):250–258
7. Autret A, Valade D, Debiais S (2012) Placebo and other psychological interactions in headache treatment. J Headache Pain 13(3):191–198
8. Sorge F, De Simone R, Marano E et al (1988) Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. Cephalalgia 8(1):1–6
9. Guidetti V, Moscato D, Ottaviano S et al (1987) Flunarizine and migraine in childhood. An evaluation of endocrine function. Cephalalgia 7(4):263–266
10. Lewis DW, Winner P (2006) The pharmacological treatment options for pediatric migraine: an evidence-based appraisal. NeuroRx 3(2):181–191
11. Oakley CB, Kossoff EH (2014) Migraine and epilepsy in the pediatric population. Curr Pain Headache Rep 18(3):402
12. Winner P, Pearlman EM, Linder SL, Topiramate Pediatric Migraine Study Investigators et al (2005) Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 45(10):1304–1312
13. Lakshmi CV, Singhi P, Malhi P et al (2007) Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. J Child Neurol 22(7):829–835
14. Lewis D (2009) Pediatric migraine. Neurol Clin 27:481–501
15. Caruso JM, Brown WD, Exil G et al (2000) The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. Headache 40(8):672–676

16. Apostol G, Cady RK, Laforet GA et al (2008) Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache 48(7):1012–1025
17. Serdaroglu G, Erhan E, Tekgul H et al (2002) Sodium valproate prophylaxis in childhood migraine. Headache 42(8):819–822
18. Moore KL (1992) Valproate in the treatment of refractory recurrent headaches: a retrospective analysis of 207 patients. Headache Q 3/3:323–325
19. Pakalnis A, Greenberg G, Drake ME Jr et al (2001) Pediatric migraine prophylaxis with divalproex. J Child Neurol 16(10):731–734
20. Lewis D, Diamond S, Scott D et al (2004) Prophylactic treatment of pediatric migraine. Headache 44:230–237
21. Hershey AD, Powers SW, Bentti AL et al (2000) Effectiveness of amitriptyline in the prophylactic management of childhood headaches. Headache 40:539–549
22. Ludvigsson J (1974) Propranolol used in prophylaxis of migraine in children. Acta Neurol 50:109–115
23. Damen L, Bruijn JK, Verhagen AP et al (2005) Symptomatic treatment of migraine in children: a systematic review of medication trials. Pediatrics 116(2):e295–e302
24. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S (2004) Practise parameter: pharmacological treatment of migraine headache in children and adolescents: children and adolescents report of the American Academy of Neurology Qualitee Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology 63:2215–2224
25. Goldberg MR, Sciberras D, De Smet M et al (2001) Influence of beta-adrenoceptor antagonists on the pharmacokinetics of rizatriptan, a 5-HT1B/1D agonist: differential effects of propranolol, nadolol and metoprolol. Br J Clin Pharmacol 52(1):69–76
26. Gillies D, Sills M, Forsythe I (1986) Pizotifen (Sanomigran) in childhood migraine. A double-blind controlled trial. Eur Neurol 25:32–35
27. Salmon MA (1985) Pizotifen in the prophylaxis of childhood migraine. Cephalalgia 5(suppl 3):178
28. Yorns WR Jr, Hardison HH (2013) Mitochondrial dysfunction in migraine. Semin Pediatr Neurol 20(3):188–193
29. Colombo B, Saraceno L, Comi G (2014) Riboflavin and migraine: the bridge over troubled mitochondria. Neurol Sci 35(Suppl 1):141–144
30. Condò M, Posar A, Arbizzani A et al (2009) A Riboflavin prophylaxis in pediatric and adolescent migraine. J Headache Pain 10(5):361–365
31. MacLennan SC, Wade FM, Forrest KM et al (2008) High-dose riboflavin for migraine prophylaxis in children: a double-blind, randomized, placebo-controlled trial. J Child Neurol 23(11):1300–1304
32. Bruijn J, Duivenvoorden H, Passchier J et al (2010) Medium-dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomised, double-blind, cross-over trial. Cephalalgia 30(12):1426–1434
33. Slater SK, Nelson TD, Kabbouche MA et al (2010) A randomized, double-blinded, placebo-controlled, crossover, add on study of coenzyme Q10 in the prevention of pediatric and adolescent migraine. Cephalalgia 31(8):897–905
34. Hershey AD, Powers SW, Vockell AL et al (2007) Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache 47(1):73–80
35. Bigal ME, Rapoport AM, Sheftell FD et al (2002) New migraine preventive options: an update with pathophysiological considerations. Rev Hosp Clin Fac Med Sao Paulo 57(6):293–298
36. Peikert A, Wilimzig C, Kohne-Volland R (1996) Prophylaxis of migraine with oral magnesium: results from a prospective, multicenter, placebo-controlled and double-blind randomized study. Cephalalgia 16:257–263
37. Pfaffenrath V, Ostreich W, Haase W (1996) Magnesium in the prophylaxis of migraine – a double-blind, placebo- controlled study. Cephalalgia 16:436–440
38. Dodick DW, Turkel CC, DeGryse RE et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50(6):921–936

39. Silberstein SD, Dodick DW, Aurora SK et al (2014) Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. J Neurol Neurosurg Psychiatry doi:10.1136
40. Kabbouche M, O'Brien H, Hershey AD (2012) OnabotulinumtoxinA in pediatric chronic daily headache. Curr Neurol Neurosci Rep 12(2):114–117
41. Chan VW, McCabe EJ, MacGregor DL (2009) Botox treatment for migraine and chronic daily headache in adolescents. Tossina BotulinicaJ Neurosci Nurs 41(5):235–243
42. Barbanti P, Egeo G, Aurilia C et al (2014) Treatment of tension-type headache: from old myths to modern concepts. Neurol Sci 35(1 Suppl):17–21
43. Pinchefsky E, Dubrovsky AS, Friedman D et al (2015) Part II-Management of pediatric post-traumatic headaches. Pediatr Neurol 52(3):270–280. doi:10.1016/j.pediatrneurol.2014.10.015
44. May A, Leone M, Afra J et al (2006) EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 13(10):1066–1077
45. Francis GJ, Becker WJ, Pringsheim TM (2010) Acute and preventive pharmacologic treatment of cluster headache. Neurology 75(5):463–473
46. McNabb S, Whitehouse W (1999) Cluster headache-like disorder in childhood. Arch Dis Child 81(6):511–512
47. Gallai B, Mazzotta G, Floridi F et al (2003) Cluster headache in childhood and adolescence: one-year prevalence in an out-patient population. J Headache Pain 4:132–137

Pharmacological Management of Migraine in Pregnancy

15

E. Anne MacGregor

15.1 Introduction

Over 40 % of women will experience migraine at some time in their lives, with peak incidence between the ages of 20 and 24 years [1]. The majority of women require medication to control the symptoms of migraine effectively and some may need additional prophylactic drugs if attacks are frequent. Drugs have their greatest effects on the fetus during the first trimester so the increasing unintended birth rate is of particular concern [2]. Although migraine typically improves during pregnancy, this is not usually until the second trimester. Most drugs used for migraine management do not have adverse effects on the outcome of pregnancy and inadvertent use of medication is rarely an indication for termination of pregnancy. When a woman is planning pregnancy or finds herself pregnant, all medication should be carefully reviewed with respect to appropriate use, including over-the-counter drugs, vitamins, and herbal treatments. Nondrug strategies may be appropriate but medication should not be withheld if attacks are poorly controlled. Breastfeeding maintains the benefits of migraine on pregnancy but medication needs further review at this time due to the potential transfer of drugs in breast milk.

15.2 The Effect of Pregnancy and Lactation on Migraine

Retrospective and prospective studies suggest that around 60 % of women with migraine report improvement of migraine during pregnancy and 20 % report complete relief (Figs. 15.1 and 15.2) [3–13]. Relief from migraine is more likely in women with a history of menstrual migraine (Table 15.1).

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_15

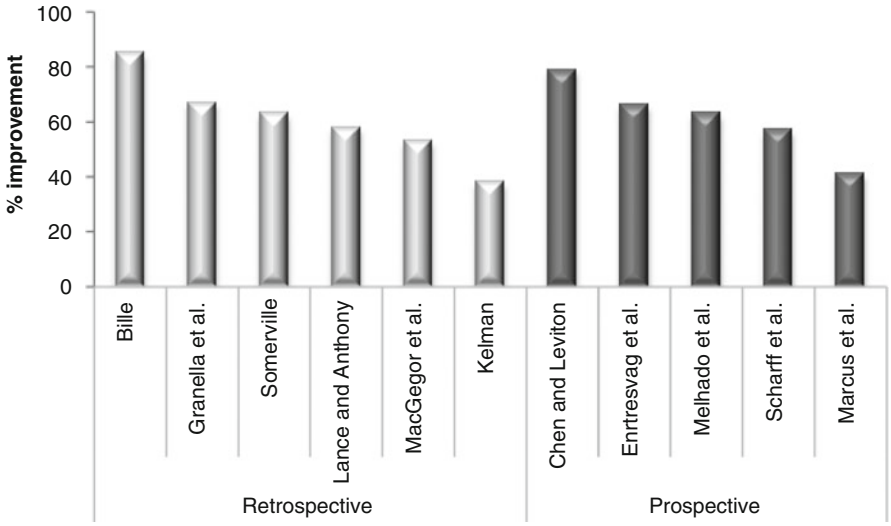
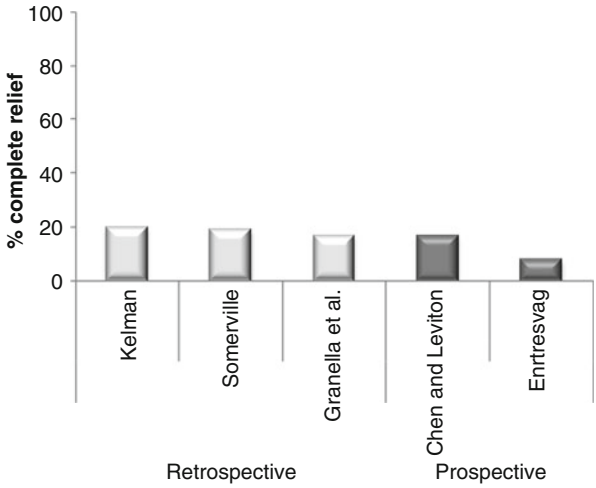


Fig. 15.1 Improvement in migraine during pregnancy: outcomes of retrospective and prospective studies

Fig. 15.2 Complete relief of migraine during pregnancy: outcomes of retrospective and prospective studies



Migraine can be troublesome in early pregnancy but usually improves by the end of the first trimester; if it is still troublesome early in the second trimester migraine, it is likely to persist throughout pregnancy [14]. Aura can occur for the first time during pregnancy and requires specific assessment if the symptoms are atypical [15, 16]. A careful history is imperative to differentiate migraine aura from other

Table 15.1 Effect of pregnancy on women with prior history of menstrual vs nonmenstrual headaches

Study	Sample size	Improvement	
		Hx menstrual headache (%)	Hx nonmenstrual headaches (%)
Melhado et al. [11]	933	78	55
MacGregor et al. [7]	30	71	31
Lance and Anthony [6]	120	64	48
Granella et al. [4]	571	22.7	16.8

transient neurological disorders [17]. The differential diagnosis of atypical aura or persistent headache in pregnancy is thrombocytopenia, cerebral venous sinus thrombosis, or imminent eclampsia.

Postpartum is also a time of increased risk of migraine, typically occurring a couple of days following delivery [14, 18, 19]. Breastfeeding should be encouraged, where possible, as it sustains the benefits of pregnancy on migraine until menstruation returns [14].

15.3 Effect of Migraine and Lactation on Pregnancy

Migraine itself has no significant adverse effects on the outcome of pregnancy [20, 21]. However, large case-control studies confirm a 1.4-fold increased risk of preeclampsia in pregnancy women with migraine [21, 22].

Migraine is also a recognized risk factor for pregnancy-related ischemic stroke (OR range 7.9–30.7 versus nonmigraineurs) [23].

Although it has not been established if the type of migraine is important with respect to risk of preeclampsia and stroke during pregnancy, there is an increasing body of evidence to support that the risk is associated with migraine with aura and not migraine without aura [24].

15.4 Investigations

Unnecessary investigations can be avoided by taking a careful history. Pregnancy should not affect the decision to investigate; the indications for investigation of the pregnant women with headache are the same as for a nonpregnant woman. MRI is preferred to X-ray exposure and is considered to be safe during pregnancy [25]. Gadolinium can be used if contrast imaging is indicated provided that the lowest risk and lowest dose required of gadolinium is used; high-risk gadolinium-based contrast agents and iodinated contrast media should be avoided [26, 27].

15.5 Management

15.5.1 Nonpharmacological

Where possible, trigger identification and management, small and frequent meals, keeping hydrated, taking regular exercise, and a regular sleep schedule can reduce the frequency of attacks and minimize the need for medication.

When an attack starts, a sweet fizzy drink, resting in a quiet and darkened room, cold and/or hot compresses, and gentle massage can help to ease symptoms.

15.5.2 Pharmacological

Recommendations for the safety of drugs during pregnancy are based on the US Food and Drug Administration (FDA) pregnancy labeling, which has five categories: A, B, C, D, and X (Table 15.2). Safety of drugs during lactation is based on data from the National Library of Medicine Drugs and Lactation Database (LactMed). Evidence of efficacy in migraine management is based on recommendations from the American Academy of Neurology, American Headache Society, and the European Federation of Neurological Sciences [28–30].

15.6 Acute Treatment

Most drugs used for acute treatment of migraine can be safely continued during pregnancy and lactation, with the exception of ergots (Tables 15.3 and 15.4). However, as drugs are not licensed for use in pregnancy and lactation they should

Table 15.2 FDA pregnancy categories

Category A Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
Category B Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
Category C Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category D There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category X Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

Table 15.3 Drugs used for acute treatment during pregnancy

		Level of evidence of efficacy[a]
FDA category B: No evidence of harm		
Aspirin plus paracetamol plus caffeine	1st and 2nd trimesters only. Contraindicated in 3rd trimester	A
Diclofenac	1st and 2nd trimesters only. Contraindicated in 3rd trimester	A
Ibuprofen	First line NSAID. 1st and 2nd trimesters only Contraindicated in 3rd trimester	A
Naproxen	1st and 2nd trimesters only Contraindicated in 3rd trimester	A
Tolfenamic acid	More commonly used NSAIDs preferred	B
Metoclopramide		B
Paracetamol	First-line analgesic of choice throughout pregnancy	C
FDA category C: Benefits outweigh risks		
Aspirin	1st and 2nd trimesters only Contraindicated in 3rd trimester	A
Almotriptan		A
Eletriptan		A
Frovatriptan		A
Naratriptan		A
Rizatriptan		A
Sumatriptan	First-line triptan	A
Zolmitriptan		A
Domperidone		B
Prochlorperazine		B
Prednisolone		U
FDA category X: Contraindicated		
Dihydroergotamine		A

[a]*A* Medications with established efficacy (>2 Class I trials), *B* Medications are probably effective (1 Class I or 2 Class II studies), *C* Medications are possibly effective (1 Class II study), *U* Inadequate or conflicting data to support or refute medication use

only be considered if nondrug treatments have failed and the potential benefits to the individual woman outweigh the potential risks to the fetus.

Paracetamol is the analgesic of choice for symptomatic treatment of mild-to-moderate pain during pregnancy and lactation.

Aspirin can be taken during the first and second trimesters but should be avoided after 30 weeks of pregnancy because of increased risk premature closure of the fetal ductus arteriosus, prolonged labor, postpartum hemorrhage, and neonatal bleeding. Standard doses of aspirin are contraindicated during lactation as the drug is excreted in breast milk, increasing the risk of Reye's syndrome and impaired platelet function in susceptible infants.

Table 15.4 Drugs used for acute treatment during lactation

		Level of evidence of efficacy[a]
Minimal risk		
Diclofenac		A
Eletriptan		A
Ibuprofen	First-line NSAID	A
Sumatriptan	First-line triptan. Consider for severe unresponsive attacks.	A
Domperidone	Increases milk production	B
Prochlorperazine		B
Tolfenamic Acid	More commonly used NSAIDs preferred	B
Paracetamol	First-line analgesic of choice	C
Magnesium sulfate		U
Prednisolone	Doses up to 50 mg daily unlikely to cause any adverse effects	U
Benefits likely to outweigh risks		
Naproxen	Drugs with short half-life preferred	A
Metoclopramide	Increases milk production Avoid use in women with a history of major depression	B
Risks likely to outweigh benefits		
Aspirin		A
Aspirin plus paracetamol plus caffeine		A
Insufficient data		
Almotriptan		A
Frovatriptan	Long half-life; drugs with short half-life preferred	A
Naratriptan		A
Rizatriptan		A
Zolmitriptan		A
Contraindicated		
Dihydroergotamine		A

[a]*A* Medications with established efficacy (>2 Class I trials), *B* Medications are probably effective (1 Class I or 2 Class II studies), *C* Medications are possibly effective (1 Class II study), *U* Inadequate or conflicting data to support or refute medication use

NSAIDS are safe for use during the first and second trimesters but, as with aspirin, should be avoided after 30 weeks of pregnancy because of increased risk of premature closure of the ductus arteriosus and oligohydramnios. NSAIDs can be taken during breastfeeding and the amount of drug in breast milk is very low. Ibuprofen is the NSAID of choice during both pregnancy and lactation.

Opioids are not indicated for migraine as they exacerbate gastric stasis and nausea. Further, their use has been associated with a twofold increased risk of neural tube defects [31].

Antiemetics metoclopramide and prochlorperazine can be taken during pregnancy and lactation. Metoclopramide has additional prokinetic activity that may help to reverse gastric stasis during migraine and enhance absorption of oral medication. As it stimulates prolactin release it has been used "off-label" to increase milk production during lactation.

There are limited data regarding the safety of triptans, with the exception of sumatriptan, which may be used during pregnancy and breastfeeding if attacks fail to respond to the above strategies. Although no trials have been undertaken during pregnancy, data collected over 25 years for the Sumatriptan/Naratriptan/Treximet Pregnancy Registry did not find any adverse outcomes associated with inadvertent exposure to sumatriptan during pregnancy [32]. Eletriptan can be used during lactation.

15.7 Prophylaxis

The options for drug prophylaxis are shown in Tables 15.5 and 15.6.

Table 15.5 Drugs used for prophylaxis during pregnancy

		Level of evidence of efficacy[a]
FDA category C: Benefits outweigh risks		
Metoprolol		A
Propranolol	Beta-blocker of choice	A
Naproxen		B
Amitriptyline		B
Venlafaxine		B
Aspirin	Doses up to 150 mg daily	U
Bisoprolol		U
Gabapentin		U
Nortriptyline		U
FDA category D: Risks outweigh benefits		
Topiramate		A
Atenolol	Propranolol or metoprolol preferred	B
Candesartan	Category C in 1st trimester	B
Magnesium		B
Lisinopril	Category C in 1st trimester	C
FDA category X: Contraindicated		
Valproic acid	Teratogenic	A
FDA category N: not classified by the FDA		
Flunarizine		

[a]*A* Medications with established efficacy (>2 Class I trials), *B* Medications are probably effective (1 Class I or 2 Class II studies), *C* Medications are possibly effective (1 Class II study), *U* Inadequate or conflicting data to support or refute medication use

Table 15.6 Drugs used for prophylaxis during lactation

		Level of evidence of efficacy[a]
Minimal risk		
Flunarizine		A
Metoprolol	Propranolol preferred	A
Propranolol	First-line prophylaxis	A
Amitriptyline	Nortriptyline preferred	B
Magnesium		B
Naproxen		B
Aspirin	Doses up to 150 mg daily unlikely to cause any adverse effects Avoid breastfeeding for 1–2 h after a dose	U
Nortriptyline	First-line prophylaxis	U
Risks likely to outweigh benefits		
Topiramate	Doses up to 200 mg daily unlikely to cause any adverse effects	A
Valproic acid	Low levels in infant serum. Theoretical risk of infant liver toxicity	A
Atenolol	Propranolol or metoprolol preferred	B
Venlafaxine		B
Gabapentin	Doses up to 2.1 g daily unlikely to cause any adverse effects	U
Insufficient data to make a recommendation		
Candesartan		B
Lisinopril		C
Bisoprolol	Propranolol or metoprolol preferred	U

[a]*A* Medications with established efficacy (>2 Class I trials), *B* Medications are probably effective (1 Class I or 2 Class II studies), *C* Medications are possibly effective (1 Class II study), *U* Inadequate or conflicting data to support or refute medication use

The beta-blocker propranolol is the drug of choice for prophylaxis during pregnancy and lactation, given in the lowest effective doses. Due to the risk fetal bradycardia and decreased uterine contraction it should be discontinued 2–3 days before delivery. The neonate should be monitored for bradycardia, hypotension, and hypoglycemia.

Amitriptyline 10–25 mg daily is an alternative option during pregnancy and lactation. Limb deformities have been reported following high dose but not with doses less than 50 mg taken during pregnancy. Tapering the dose 3–4 weeks before delivery can prevent neonatal drowsiness, jitteriness, hyperexcitability, and suckling problems.

Sodium valproate is contraindicated during pregnancy because of the increased risk of neural tube defects in the fetus. An increased risk of neurodevelopmental

Table 15.7 Supplements and herbal medication

	Pregnancy	Lactation	Level of evidence for efficacy[a]
Suitable			
Riboflavin (vitamin B2)[b]	Compatible with pregnancy in doses within RDA	Compatible with breast feeding in doses within RDA	B
Coenzyme Q10	Compatible with pregnancy; may prevent preeclampsia	Compatible with breast feeding	C
Unsuitable			
Petasites	Insufficient data: avoid	Insufficient data: avoid	A
Tanacetum Parthenium	Insufficient data: avoid	Insufficient data: avoid	B

[a]*A* Medications with established efficacy (>2 Class I trials), *B* Medications are probably effective (1 Class I or 2 Class II studies), *C* Medications are possibly effective (1 Class II study)
[b]Use of megadose vitamin regimens should be avoided

delay and autism spectrum disorders has also been identified in children exposed to sodium valproate in utero.

Some supplements are safe during pregnancy and lactation but herbal treatments should be avoided (Table 15.7). Coenzyme Q10 has the additional benefit of reducing the risk of preeclampsia [33].

Nonpharmacologic preventives such as acupuncture and biofeedback are safe and effective during pregnancy [34–37].

For status migrainosus or short-term prophylaxis of frequent treatment-refractory migraine, there is some evidence to support the safety and efficacy of peripheral nerve blocks [38].

15.7.1 Devices

Transcranial magnetic stimulation (TMS) is a noninvasive method by which weak electrical currents are induced in the brain by a rapidly changing magnetic field. A review of the evidence for the safety of TMS identified that experience with TMS during pregnancy is limited but the extremely low-frequency magnetic fields are unlikely to have any effect on pregnancy outcome [39].

The safety and effectiveness of implantable devices during pregnancy has not been established although there is one case report of implantable vagal nerve stimulation successfully used for seizure control and depression without adverse effects on the pregnancies [40].

If indicated, botulinum toxin A does not appear to cross the placenta during pregnancy, and amounts ingested by the infant from breast milk are expected to be insignificant and not cause any adverse effects [41].

15.7.2 Emergency Treatment

Severe attacks that risk dehydration can be aborted with prochlorperazine 10 mg or chlorpromazine 25–50 mg by intramuscular injection together with IV fluids. Intravenous magnesium sulfate 1 g given over 15 min is an alternative either alone or with intravenous prochlorperazine 10 mg [42]. Treatment with magnesium sulfate for more than 5–7 days should be avoided due to increased risk of fetal osteopenia [43].

Conclusions

Pregnancy and lactation are both associated with improvement in migraine with up to 20 % of women experiencing complete relief. Women with a history of menstrual migraine benefit most whereas women with migraine with aura are less likely to report improvement and may experience aura for the first time during pregnancy. Atypical aura may warrant assessment to exclude preeclampsia but a careful history can prevent unnecessary investigation. Investigations, if indicated, are the same as for the nonpregnant women, although routine investigations should be deferred until postpartum.

First-line acute treatment during pregnancy and breastfeeding is with simple analgesics and antiemetics. Sumatriptan may be indicated for severe attacks that do not respond to first-line treatment. Prochlorperazine and magnesium sulfate can be used to abort attacks when standard treatment fails. The lowest effective dose of propranolol or amitriptyline is safe for prophylaxis during pregnancy and lactation.

Useful Websites

National Library of Medicine Drugs and Lactation Database (LactMed): http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Organization of Teratology Information Specialists (OTIS): http://www.mothertobaby.org/fact-sheets-s13037

References

1. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB (2008) Cumulative lifetime migraine incidence in women and men. Cephalalgia 28:1170–1178
2. Finer LB, Zolna MR (2011) Unintended pregnancy in the United States: incidence and disparities, 2006. Contraception 84:478–485
3. Bille B (1997) A 40-year follow-up of school children with migraine. Cephalalgia 17:488–491
4. Granella F, Sances G, Zanferrari C, Costa A, Martignoni E et al (1993) Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. Headache 33:385–389
5. Somerville BW (1972) A study of migraine in pregnancy. Neurology 22:824–828
6. Lance J, Anthony M (1966) Some clinical aspects of migraine. Arch Neurol 15:356–361
7. MacGregor EA, Igarashi H, Wilkinson M (1997) Headaches and hormones: subjective versus objective assessment. Headache Quart 8:126–136

8. Kelman L (2004) Women's issues of migraine in tertiary care. Headache 44:2–7
9. Chen TC, Leviton A (1994) Headache recurrence in pregnant women with migraine. Headache 34:107–110
10. Ertresvag JM, Zwart JA, Helde G, Johnsen HJ, Bovim G (2005) Headache and transient focal neurological symptoms during pregnancy, a prospective cohort. Acta Neurol Scand 111:233–237
11. Melhado E, Maciel JA Jr, Guerreiro CA (2005) Headaches during pregnancy in women with a prior history of menstrual headaches. Arq Neuropsiquiatr 63:934–940
12. Scharff L, Marcus DA, Turk DC (1997) Headache during pregnancy and in the postpartum: a prospective study. Headache 37:203–210
13. Marcus DA, Scharff L, Turk D (1999) Longitudinal prospective study of headache during pregnancy and postpartum. Headache 39:625–632
14. Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N et al (2003) Course of migraine during pregnancy and postpartum: a prospective study. Cephalalgia 23:197–205
15. Chancellor AM, Wroe SJ, Cull RE (1990) Migraine occurring for the first time in pregnancy. Headache 30:224–227
16. Cupini LM, Matteis M, Troisi E, Calabresi P, Bernardi G et al (1995) Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. Cephalalgia 15:140–144
17. Ertresvag JM, Stovner LJ, Kvavik LE, Johnsen HJ, Zwart JA et al (2007) Migraine aura or transient ischemic attacks? A five-year follow-up case-control study of women with transient central nervous system disorders in pregnancy. BMC Med 5:19
18. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M (2011) Headache and migraine during pregnancy and puerperium: the MIGRA-study. J Headache Pain 12:443–451
19. Goldszmidt E, Kern R, Chaput A, Macarthur A (2005) The incidence and etiology of postpartum headaches: a prospective cohort study. Can J Anaesth 52:971–977
20. Wainscott G, Sullivan M, Volans G, Wilkinson M (1978) The outcome of pregnancy in women suffering from migraine. Postgrad Med 54:98–102
21. Banhidy F, Acs N, Horvath-Puho E, Czeizel AE (2007) Pregnancy complications and delivery outcomes in pregnant women with severe migraine. Eur J Obstet Gynecol Reprod Biol 134:157–163
22. Chen HM, Chen SF, Chen YH, Lin HC (2010) Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. Cephalalgia 30:433–438
23. Wabnitz A, Bushnell C (2014) Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. Cephalalgia 35:132–139
24. Kurth T, Chabriat H, Bousser MG (2012) Migraine and stroke: a complex association with clinical implications. Lancet Neurol 11:92–100
25. ACOG (2004) ACOG Committee opinion #299: guidelines for diagnostic imaging during pregnancy. Obstet Gynecol 104:647
26. Webb JA, Thomsen HS (2013) Gadolinium contrast media during pregnancy and lactation. Acta Radiol 54:599–600
27. Webb JA, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital R (2005) The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol 15:1234–1240
28. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C et al (2012) Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 78:1337–1345
29. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C et al (2012) Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 78:1346–1353
30. Evers S, Afra J, Frese A, Goadsby PJ, Linde M et al (2009) EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol 16:968–981

31. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM (2013) Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol 122:838–844
32. GlaxoSmithKline (2012) The Sumatriptan/Naratriptan/Treximet Pregnancy Registry. Interim Report 1 January 1996 through 31 October 2011. http://pregnancyregistry.gsk.com/sumatriptan.html. Accessed 19 Nov 2014
33. Teran E, Hernandez I, Nieto B, Tavara R, Ocampo JE et al (2009) Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. Int J Gynaecol Obstet 105:43–45
34. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A et al (2009) Acupuncture for migraine prophylaxis. Cochrane Database Syst Rev (1):CD001218
35. Park J, Sohn Y, White AR, Lee H (2014) The safety of acupuncture during pregnancy: a systematic review. Acupunct Med 32:257–266
36. Marcus DA, Scharff L, Turk DC (1995) Nonpharmacological management of headaches during pregnancy. Psychosom Med 57:527–535
37. Scharff L, Marcus DA, Turk DC (1996) Maintenance of effects in the nonmedical treatment of headaches during pregnancy. Headache 36:285–290
38. Govindappagari S, Grossman TB, Dayal AK, Grosberg BM, Vollbracht S et al (2014) Peripheral nerve blocks in the treatment of migraine in pregnancy. Obstet Gynecol 124(6):1169–74. doi:10.1097/AOG.0000000000000555
39. Dodick DW, Schembri CT, Helmuth M, Aurora SK (2010) Transcranial magnetic stimulation for migraine: a safety review. Headache 50:1153–1163
40. Houser MV, Hennessy MD, Howard BC (2010) Vagal nerve stimulator use during pregnancy for treatment of refractory seizure disorder. Obstet Gynecol 115:417–419. doi:10.1097/AOG.1090b1013e3181bd1091a1098b.
41. Tan M, Kim E, Koren G, Bozzo P (2013) Botulinum toxin type A in pregnancy. Can Fam Physician 59:1183–1184
42. Demirkaya S, Vural O, Dora B, Topcuoglu MA (2001) Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache 41:171–177
43. FDA (2013) FDA recommends against prolonged use of magnesium sulfate to stop preterm labor due to bone changes in exposed babies. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM353335.pdf. Accessed 19 Nov 2014

Pharmacotherapy for Primary Headache Disorders in the Elderly

16

Andreas Straube

16.1 Definition of an Elderly Patient

There is no generally accepted definition of the age at which a patient should be classified as elderly. Most authors distinguish between older patients (older than 65 years) and elderly in the more restricted sense for patients older than 75 years. Due to improved health care, better working and living conditions, and improved nutrition, a larger percentage of society is living to more than 65 or even 80 years. Demographic developments estimate that in 2037 about 45 % of the German population will be older than 65 years and that by 2050 the percentage of those over 80 years old will be three times higher [5]. Age alone is not a health disorder, but with increasing age the percentage of patients with more than one health complaint increases, resulting in an increase in the number of patients receiving multiple pharmaceutical treatments. Furthermore, with increasing age the number of patients with cognitive decline and/or functional impairment also increases and it has been shown that a poor cognitive status is correlated with less frequent reporting of pain and, in contrast, a reduced functional status with more reporting of pain [45]. The review will focus on some general aspects of medical treatment in elderly patients and will discuss the consequences of this for the treatment of those headache syndromes which are more common in the elderly.

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_16

16.2 General Aspects of Pharmacotherapy in the Older Patient

With increasing age there is also a strong increase in some chronic disorders like arterial hypertension, diabetes mellitus, renal insufficiency, and cognitive decline (as a result of neurodegenerative diseases or cerebrovascular disorders). Consequently, the number of patients who receive more than one medical drug treatment rapidly increases, and as a result the risk of unforeseen pharmacokinetic or pharmacodynamic interactions also increases. The reduced clearance rate of the kidneys is especially critical, since nonsteroidal antiphlogistics influence the filtration rate of the kidneys and some opioids as well as calcium channel modulators are eliminated renally. A decline of gastric and intestinal peristalsis affects the resorption of oral medication and increases the vulnerability of the gastric mucosa to nonsteroidal antiphlogistic drugs. In addition, cognitive impairment also means that the patients will be more vulnerable to centrally acting substances and the fast increase of serum levels of such substances. This is also the cause of an increased numbers of falls in these patients and consequently increased anxiety with less physical activity, which again has a negative effect on the pain (for further comments: [14, 42]). Another point is that most of the phase III pharmacological studies excluded patients older than 65 years and therefore the scientific evidence for treatment recommendations in older patients is rather weak. The general recommendations for starting a pharmacological therapy are therefore:

1. start low and go slow
2. stay low

This means that the smallest dosage sufficient to decrease the headache symptoms should be used and that the dosage should be increased starting from a very low level only very slowly to a higher dosage (Table 16.1).

Table 16.1 Age-dependent side effects of specific drugs

Analgesics:	
Ibuprofen/diclofenac/ indomethacin:	Reduction of the renal blood flow, intestinal bleeding, arterial hypertension, interaction with anticoagulants; confusion
Triptans:	Slight increase in blood pressure, no permission for patients >65 years, theoretical risk of vasoconstriction of cardiac arteries
Opioids:	obstipation, falls, cognition, accumulation, sedation
Prophylactic drugs	
Beta-blockers	Cave: prolonged PQ time
Amitriptyline	Mouth dryness, bladder function, cognition accommodation impairment Cardiac dysrhythmia, drowsiness, falls
Flunaricine	Parkinson's syndrome, sedation, depression
Topiramate	Cognitive impairment, kidney stones, depression paraesthesias
Cortisone	Osteoporosis, glaucoma, diabetes mellitus, hypertension, psychosis

16.2.1 General Aspects of Headaches in Older Patients

Age is not an analgesic and headaches are still a frequently reported complaint, but the overall prevalence of primary headaches decreases with increasing age and the proportion of secondary headaches increases with age. Otherwise the first manifestation of migraine headache above the age of 50 is not so rare and some authors report that about 19 % of women with migraine had an onset later [32]. But a new onset of migrainous headache after the age of 60 always needs to be diagnosed carefully [13]. In the older population, 50 % of females and males still report headaches with a tendency to less frequent headache with increasing age [29]. In a population-based investigation, 44.5 % of the older population complained about tension-type headache, 11 % about migraine, and 2.2 % about symptomatic headache (12-month prevalence). Females were affected twice as often as males [29]. The DMKG epidemiological study in Germany found a 6-month prevalence in the group of the 65–75-year-olds of about 3.5 % for migraine and of about 12.5 % for tension-type headache. Females were again affected 1.5–2 times more often than males [28]. Subjects who complain about headaches for the first time after the age of 64 have an elevated risk of having symptomatic headache (about 15.3 %) compared to the general population with 7–8 % [29, 33]. In another population-based study, the prevalence of migraine after the 75th year was 2.7 % for males and 7.6 % for females [35]. In general, headache prevalence in Asia seems to be lower than in western countries. A Japanese questionnaire-based survey found a 1-year prevalence for 60–69-year-olds of 1.4 % (males) and 5.3 % (females) for migraine, of 14.8 and 20.3 % for episodic tension-type headache, and of 1.9 and 4.3 % for chronic tension-type headache [39]. A Chinese study, using an interview due to a neurological assessment, reported a prevalence of chronic daily headache of 1.8 % for males older than 65 years and 5.6 % for females [43].

16.2.2 Primary Headaches in Older Patients

16.2.2.1 Migraine (IHS 1.1, 1.2, and 1.3)

With regard to the symptoms present in the different headache disorders, the IHS classification does not differentiate in terms of the age of the patients, even it is known and also generally accepted that migraine symptoms in children are quite different to those in adolescents. In general, migraine attacks in the elderly are less often accompanied by vomiting or strong nausea, the headache has a less pulsating character [48], and also the character is more tension type like (unpublished own observation). In this sense, aggravation of the headache by physical activity is also reported less often [48]. Acute medication seems to influence the attacks better than in younger patients [18]. Aura symptoms with headache but also without accompanying headache seem to occur more often in the elderly; in the group of 18–29-year-olds about 15.2 % have auras compared to 41 % of the patients aged 70 years and older [3, 18, 49]. It has not been investigated whether the increased proportion of elderly patients with aura symptoms is due to the fact that migraine with aura more often persists in older age than migraine without aura or really

reflects new onset auras. Diagnostic problems can be that aura-like phenomena can also be triggered by cortical ischemia and therefore diagnostic tests may be necessary in each patient with aura for the first time or with changes in the symptoms of the aura compared to previous one. In the Framingham study, slightly more than 1 % of all subjects reported on visual migraine symptoms, mostly starting after the age of 50 years [46]. A clinical manifestation of migraine that has been discussed more often in recent years is so-called vestibular migraine. These patients report on spells of vertigo/dizziness with durations of seconds to days which are regularly accompanied by migraine-like headache in some patients. Vestibular migraine can occur in all age groups but on average the patients seem to be older than the typical migraine patient [26].

Since auras in particular are caused by a temporary dysfunction of cortical neurons it is speculated that migraine patients should be more prone to cognitive decline in old age than nonmigraine patients. But in contrast most studies do not show an age-related more rapid decline in cognitive functions in migraine patients [13, 20].

The mean age of patients with chronic migraine is about 41 years [1]; it has not been investigated if the proportion of patients over 65 years is larger in chronic migraine than in episodic migraine, but the available data suggest that older patients with migraine on average have headache on more days (41 % on 10–14 days/month) [3, 23]. In contrast, in the general German population only 15.5 % of migraine patients have headache on more than 6 days [37]. In general, the incidence of migraine strongly declines with increasing age, as does the male-to-female ratio which declines from 1:3 to 1:2 after the menopause [13].

Based on the data from a population-based study in Northern Italy, it is estimated that about 20 % of female migraine patients lose their migraine with every 10 years of lifetime after the menopause [35].

Concerning the acute attack treatment, the EFNS and the DMKG recommend the usual self-medication in older patients as well [10, 12]. Acetaminophen or the fixed-dose combination of acetaminophen, acetylsalicylic acid, and caffeine are the first choice in acute attack treatment, if there are no cardiac contraindications triptans can also be prescribed [13]. Preventive treatment is less often prescribed in the elderly but most of the regularly used drugs can be given. Tricyclic antidepressants should be avoided since the anticholinergic action of them may influence cognition, bladder function, and may cause cardiac arrhythmia. Flunaricine should also be avoided because of the risk of pharmacologically induced Parkinson syndrome. Topiramate and ß-blockers, candesartan, as well as onabotulinumtoxinA have no special risk in older patients. Nonpharmacological treatment options should be considered, especially in older patients with multimorbidity. Beside psychological relaxation techniques, aerobic training therapy and acupuncture are both useful. For acupuncture a Cochrane review found that the available studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment [21, 22], but no subgroup analysis was done for older patients.

16.2.3 Primary Headaches in Older Patients

16.2.3.1 Tension-Type Headache (IHS 2.1 and 2.3)

The prevalence of tension-type headache also declines with increasing age. In an epidemiological study in South Tyrol, the 12-month prevalence of episodic tension-type headache was 35.8 % and that of chronic tension-type headache was 2.1 % in patients older than 55 years [35]. Compared to the prevalence of migraine the decline in the prevalence with age is less in tension-type headache [16, 17] but it is not clear if that is due to a change in the clinical representation of migraine toward a more tension type-like headache with the consequence that some patients with migraine could be diagnosed as having tension-type headache. The clinical characteristics of tension-type headache in older patients do not differ from those in younger patients. It can also be problematic that most secondary headaches can be confused with tension-type headache. A consequence of this is that the diagnosis of primary tension-type headache in the elderly can only be established after exclusion of secondary headaches, such as medication overuse headache, idiopathic intracranial hypertension, and sleep apnea-associated headache. Sleep-associated apneas, in particular, are much more prevalent in the elderly. Prevalence rates of up to 30–80 % are reported in subjects older than 65 years (compared to 2–4 % in the general population) [19]. Clinically apnea-associated headache is characterized by a morning headache with a dull character strongly resembling tension-type headache [31]. It is estimated that about 30 % of all patients with sleep apnea report on such a morning headache. For the acute treatment of tension-type headache, the same recommendations as for migraine attacks can be made [12]. Acetaminophen or the fixed-dose combination of acetaminophen, acetylsalicylic acid, and caffeine is the first choice. There is no indication for the use of triptans and opioids. In the case of chronic tension-type headache, preventive treatment can be helpful. Nonpharmacological options, such as relaxation training, biofeedback, and aerobic training, should be tried first. Pharmacological options are tricyclic antidepressants (e.g., amitriptyline) and the selective serotonin and noradrenalin reuptake inhibitor venlafaxine; the side-effect profile is better for venlafaxine but more studies are reported for amitriptyline. Other less established options are mirtazapine and tizanidine [37]. No studies focusing on older patients have been published. A recent Cochrane review stated that acupuncture could be a valuable nonpharmacological tool in patients with frequent episodic or chronic tension-type headaches [21, 22].

16.2.4 Primary Headaches in Older Patients

16.2.4.1 Cluster Headache (IHS 3.1)

In general, cluster headache can first manifest at any age and there are several reports with first clinical manifestation above the age of 65 years [11]. No studies concerning the clinical symptoms or treatment in the elderly have been published. The clinical manifestation does not seem to be different in older patients. One

problem is that the most effective acute treatment sumatriptan 6 mg subcutaneously or zolmitriptan 5 mg nasally has not been tested in older patients and is not approved for patients older than 65 years. In about 70 % of the patients breathing 100 % oxygen, 8–10 l per minute, reduces the headache significantly in 5–20 min [24]. No efficacy and safety data for older patients have been published for preventive treatment. Most guidelines recommend verapramil in a dosage of 240–480 mg (if necessary even 720 mg or more), but, especially in older patients, this treatment has to be monitored very carefully because of the cardiac side effects of verapramil. Another substance used is lithium (serum level 0.6–0.8 mmol/l), which is useful in chronic and probably also in episodic cluster headache [38]. Careful monitoring of the kidney and thyroid function is important. The use of topiramate is less well documented, although some experience in older patients with seizures is available for this substance and the side-effect profile in older patients is not very different to that in younger patients.

16.2.4.2 Hypnic Headache (HIS 4.9)

Hypnic headache (IHS 4.9) is a primary headache which normally occurs almost only in patients older than 50 years. The reason for this is not known.

On average several years elapse before the diagnosis is established (average age 61 years) [8, 9]. Clinically the headache is characterized by headache attacks which occur out of sleep with a bifrontal pain of a moderate intensity and no autonomic signs. The headache lasts about 60 min and in some patients onset is associated with REM sleep. No changes in clinical characteristics with increasing age are reported. The pathophysiology is not clear. No randomized treatment studies have been published; most authors recommend caffeine (e.g., 200 mg at bedtime) or alternatively a single dosage of verapramil 40–80 mg or 50–150 mg indomethacin at bedtime) [10].

16.3 Secondary Headaches in Older Patients

As mentioned before, the incidence of secondary headaches increases with age since most of the causes of secondary headaches like vascular diseases, tumors, degenerative spine disorder, obstructive sleep apnea, and inflammations are more prevalent in older patients [32, 33]. It is important to note that further diagnostics should always be initiated in the case of suddenly changing characteristics of headaches or the first occurrence of otherwise unknown headaches.

16.3.1 Brain Tumors

Gliomas have a maximum incidence between the age of 40 and 70 years and headache is one of the first complaints in about 60 % of the patients; however, in only 2 % of the patients the headaches are the sole symptom of the tumor [34]. Interestingly, patients with a history of primary headaches report headaches significantly more often than patients without such a history. This might be an indication that the pathophysiology which is responsible for the pain in primary headaches is

also involved in the pathophysiology of secondary headaches [34]. The general therapy of such headaches is no different in the elderly to that in younger patients.

16.3.2 Sleep Apnea

It has become increasingly evident that recurrent headaches are often related to sleep disorders and especially to obstructive sleep apnea syndrome. Clinically the headache is characterized by a mild-to-moderate holocephalic dull headache, which is present directly after the waking in the morning and which subsides over the course of the day. The average age of onset of sleep apnea is between 50 and 70 years and about 2 % of all females and 4 % of all males may be affected [30]. Typically, in addition to the headache, the patients also report daytime sleepiness and they are often but not always obese and have arterial hypertension. The diagnostic gold standard is polysomnographic registration of the sleep apnea, associated hypoxia, and arousal on EEG. The therapy of choice is nasal continuous positive airway pressure treatment of the sleep apnea (CPAP) which will improve the daytime sleepiness as well as the headaches.

16.3.3 Vasculitis

Cerebral vasculitis is generally a rare disease. The most frequent form of cranial vasculitis by far is giant cell arteritis. Typically all patients with such a form of cranial vasculitis are older than 50 years and females are affected 3–4 times more often than males. The main clinical symptoms are pain and general sickness with increased sweating, fatigue, loss of appetite, and weight. The prevalence is 70–133/100,000 [4]. The headache is described as dull and holocephalic with a moderate intensity, sometimes there is also an increased painfulness of the temporal arteries and increasing pain during chewing [44]. Since there is always the risk of an irreversible loss of vision if giant cell arteritis is not treated, therapy has to be started even in the case of suspected but still not proven giant vasculitis. A typical clinical history and severely elevated markers of a systemic inflammation (CRP, IL-2, etc.) are suggestive for the diagnosis and the prompt response to cortisone (1 mg prednisolone per kg body weight) establishes the diagnosis clinically. Further diagnostic tests can be the ultrasound examination of the temporal artery (“halo sign”), FDG-PET (increased uptake in the inflamed vessels), and a biopsy to obtain histological proof (although the biopsy can provide a false negative due to the fact that the inflammation is manifest only segmentally). It is important to monitor the cortisone therapy on a regular basis in order to reduce the dose to the minimum effective dose and also not to stop the treatment too early.

16.3.4 Substance-Induced Headaches

Due to the increasing polypharmacy with increasing age in combination with an increased susceptibility, substance-induced headaches should always be ruled out in

elderly patients reporting about new headaches. Drugs which quite regularly induce headache are phosphodiesterase inhibitors, NO donors, calcium antagonists, calcineurin inhibitors, immunoglobulins, some biologics, and others. It is therefore important to ask the patients specifically about medication they may have started taking at the time of headache onset.

16.3.5 Degenerative Cervical Spine Disorder

The prevalence of degenerative spine disorders increases proportionally with increasing age. Nevertheless, the prevalence of headaches in the elderly is lower than that in the younger population. This shows that there is no clear correlation between degenerative cervical spine disorder and headaches. No epidemiological data have been published on the prevalence of headaches attributed to disorders of the neck. For cervicogenic headache, a subgroup of headaches attributed to disorders of the neck, Sjaastad and Bakketeig [36] found a prevalence of 4.1 % in the age group of 18–65 years in Norway; older subjects were not investigated and they used the "Sjaastad criteria" which are different to the IHS criteria. The age at onset of the cervicogenic headache was 32.7 years. In another study from Australia, which was not population based, the age of onset was 49.5 years compared to 34.7 years in a migrainous group [2]. A further problem in the diagnosis of neck-related headaches is that musculoskeletal dysfunction can also be found in patients with headaches classifiable as migraine or tension-type headache, but more of these symptoms (impaired range of motion, tenderness of the neck muscles, cervical joint dysfunction, muscle strength, etc.) can be found in patients with cervicogenic headache in the more restricted sense [41]. There are also no specific MRI or CT findings which can be attributed to neck pain [27]. No differences in the symptoms of the headache were seen between a group of patients with radiologically proven cervical spondylosis and a group without spondylosis. Furthermore, the overall incidence of headache in the patients with spondylosis was low [15]. In conclusion, the attribution of headache to the neck is still difficult due to the lack of specific symptoms, specific clinical findings, specific radiological findings, clear diagnostic criteria, and the unspecific effect of therapeutic interventions. The combination of stretching the cervical muscles and endurance and strength training may be the best therapy recommendation [50]. Often tricyclic antidepressants or ca-channel modulators are also given.

16.3.6 Arterial Hypertension

Arterial hypertension is quite common and can be found in about 50 % of patients over 50 [47]. There is no clear relationship between arterial hypertension and headache. Headache is one of the most prevalent signs of an acute hypertensive crisis [7]. It is not completely clear whether headaches are more frequent in patients with only mildly to moderately elevated arterial pressure. Some studies reported an increased

prevalence [6], in other studies there was no significant increase [25, 32, 33, 40]. Independent of the relationship to headaches even a mild arterial hypertension has to be treated in accordance with the guidelines since hypertension is the most important risk factor for stroke.

Literature

1. Adams AM, Serrano D, Buse DC, Reed ML, Marske V, Fanning KM, Lipton RB (2015) The impact of chronic migraine: the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia 35(7):563–78
2. Anthony M (2000) Cervicogenic headache: prevalence and response to local steroid therapy. Clin Exp Rheumatol 18(2 Suppl 19):S59–S64
3. Bigal ME, Libermann JN, Lipton RB (2006) Age-dependent prevalence and clinical features of migraine. Neurology 67:246–251
4. Boesen P, Sorensen SF (1987) Giant cell arteritis, temporal arteritis, and polymyalgia rheumatica in a Danish county. A prospective investigation, 1982–1985. Arthritis Rheum 30:294–299
5. Bräuninger M, Sattler C, Kriedel N, Völpel H, Straubhaar T (2007) Gesundheitsentwicklung in Deutschland bis 2037 – Eine volkswirtschaftliche Kostensimulation. Hamburgisches Weltwirtschaftsinstitut HWWI, Hamburg
6. Bulpitt CJ, Dollery CT, Carne S (1976) Change in symptoms of hypertensive patients after referral to hospital clinic. Br Heart J 38(2):121–128
7. Cortelli P, Grimaldi D, Guaraldi P, Pierangeli G (2004) Headache and hypertension. Neurol Sci Suppl 3:S132–S134
8. Donnet A, Lantéri-Minet M (2009) A consecutive series of 22 cases of hypnic headache in France. Cephalalgia 29(9):928–934
9. Evers S, Goadsby PJ (2003) Hypnic headache: clinical features, pathophysiology, and treatment. Neurology 60:905–909
10. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS, European Federation of Neurological Societies (2009) EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol 16(9):968–981
11. Fischera M, Anneken K, Evers S (2005) Old age of onset in cluster-headache patients. Headache 45(5):615
12. Haag G, Diener HC, May A, Meyer C, Morck H, Straube A, Wessely P, Evers S (2011) Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG). J Headache Pain 12(2):201–217
13. Haan J, Hollander J, Ferrari M (2007) Migraine in the elderly: a review. Cephalalgia 27(2):97–106
14. Heckenbach K, Ostermann T, Schad F, Kröz M, Matthes H (2014) Medication and falls in elderly outpatients: an epidemiological study from a German Pharmacovigilance Network. Springerplus 3:483
15. Iansek R, Heywood J, Karnaghan J, Balla JI (1987) Cervical spondylosis and headaches. Clin Exp Neurol 23:175–178
16. Kaniecki RG (2006) Tension-type headache in the elderly. Curr Pain Headache Rep 10:448–453
17. Kaniecki RG (2007) Tension-type headache in the elderly. Curr Treat Options Neurol 9:31–37
18. Kelman L (2006) Migraine changes with age: impact on migraine classification. Headache 46:1161–1171

19. Kleisiaris CF, Kritsotakis EI, Daniil Z, Tzanakis N, Papaioannou A, Gourgoulianis KI (2014) The prevalence of obstructive sleep apnea-hypopnea syndrome-related symptoms and their relation to airflow limitation in an elderly population receiving home care. Int J Chron Obstruct Pulmon Dist 9:1111–1117
20. Jelicic M, van Boxtel MP, Houx PJ, Jolles J (2000) Does migraine headache affect cognitive function in the elderly? Report from the Maastricht Aging Study (MAAS). Headache 40(9):715–719
21. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR (2009) Acupuncture for migraine prophylaxis. Cochrane Database Syst Rev (1):CD001218
22. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR (2009) Acupuncture for tension-type headache. Cochrane Database Syst Rev (1):CD007587
23. Martins KM, Bordini CA, Bigal ME, Speciali JG (2006) Migraine in the elderly: a comparison with migraine in young adults. Headache 46:312–316
24. May A, Leone M, Afra J, Linde M, Sándor PS, Evers S, Goadsby PJ, EFNS Task Force (2006) EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 13(10):1066–1077
25. Muiesan ML, Padovani A, Salvetti M, Monteduro C, Poisa P, Bonzi B, Paini A, Cottini E, Agosti C, Castellano M, Rizzoni D, Vignolo A, Agabiti-Rosei E (2006) Headache: prevalence and relationship with office or ambulatory blood pressure in a general population sample (the Vobarno Study). Blood Press 15(1):14–19
26. Neuhauser HK, Radtke A, von Brevern M, Feldmann M, Lezius F, Ziese T, Lempert T (2006) Migrainous vertigo: prevalence and impact on quality of life. Neurology 67(6):1028–1033
27. Nordin M, Carragee EJ, Hogg-Johnson S, Weiner SS, Hurwitz EL, Peloso PM, Guzman J, van der Velde G, Carroll LJ, Holm LW, Côté P, Cassidy JD, Haldeman S (2009) Assessment of neck pain and its associated disorders: results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. J Manipulative Physiol Ther 32(2 Suppl):S117–S140
28. Pfaffenrath V, Fendrich K, Vennemann M, Meisinger C, Ladwig KH, Evers S, Straube A, Hoffmann W, Berger K (2009) Regional variations in the prevalence of migraine and tension-type headache applying the new IHS criteria: the German DMKG Headache Study. Cephalalgia 29(1):48–57
29. Prencipe M, Casini AR, Ferretti C, Santini M, Pezzella F, Scaldaferri N, Culasso F (2001) Prevalence of headache in an elderly population: attack frequency, disability, and use of medication. J Neurol Neurosurg Psychiatry 70:377–381
30. Provini F, Vetrugno R, Lugaresi E, Montagna P (2006) Sleep-related breathing disorders and headache. Neurol Sci Suppl 2:S149–S152
31. Rains JC, Poceta JS (2006) Headache and sleep disorders: review and clinical implications for headache management. Headache 46(9):1344–1363
32. Rasmussen BK, Olesen J (1992) Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 12:221–228
33. Rasmussen BK, Olesen J (1992) Symptomatic and nonsymptomatic headaches in a general population. Neurology 42:1225–1231
34. Schankin CJ, Ferrari U, Reinisch VM, Birnbaum T, Goldbrunner R, Straube A (2007) Characteristics of brain tumour-associated headache. Cephalalgia 27(8):904–911
35. Schwaiger J, Kiechl S, Seppi K, Sawires M, Stockner H, Erlacher T, Mairhofer ML, Niederkofler H, Rungger G, Gasperi A, Poewe W, Willeit J (2009) Prevalence of primary headaches and cranial neuralgias in men and women aged 55–94 years (Bruneck Study). Cephalalgia 29(2):179–187
36. Sjaastad O, Bakketeig LS (2008) Prevalence of cervicogenic headache: Vågå study of headache epidemiology. Acta Neurol Scand 117(3):173–180
37. Straube A, Pfaffenrath V, Ladwig KH, Meisinger C, Hoffmann W, Fendrich K, Vennemann M, Berger K (2010) Prevalence of chronic migraine and medication overuse headache in Germany–the German DMKG headache study. Cephalalgia 30(2):207–213

38. Stochino ME, Deidda A, Asuni C, Cherchi A, Manchia M, Del Zompo M (2012) Evaluation of lithium response in episodic cluster headache: a retrospective case series. Headache 52:1171–1175
39. Takeshima T, Ishizaki K, Fukuhara Y, Ijiri T, Kusumi M, Wakutani Y, Mori M, Kawashima M, Kowa H, Adachi Y, Urakami K, Nakashima K (2004) Population-based door-to-door survey of migraine in Japan: the Daisen study. Headache 44(1):8–19
40. Tronvik E, Stovner LJ, Hagen K, Holmen J, Zwart JA (2008) High pulse pressure protects against headache: prospective and cross-sectional data (HUNT study). Neurology 70(16):1329–1336
41. Uthaikhup S, Sterling M, Jull G (2009) Cervical musculoskeletal impairment is common in elders with headache. Man Ther 14(6):636–641
42. Veal FC, Bereznicki LR, Thompson AJ, Peterson GM (2014) Pharmacological management of pain in Australian Aged Care Facilities. Age Ageing 43(6):851–856
43. Wang SJ, Liu HC, Fuh JL, Liu CJ, Wang PN, Lu SR (1999) Comorbidity of headaches and depression in the elderly. Pain 82:239–243
44. Ward TN, Levin M (2005) Headache in giant cell arteritis and other arteritides. Neurol Sci 26:134–137
45. Westerbotn M, Hilleråas P, Fastbom J, Agüero-Torres H (2008) Pain reporting by very old Swedish community dwellers: the role of cognition and function. Aging Clin Exp Res 20(1):40–46
46. Wijman CA, Wolf PA, Kase CS, Kelly-Hayes M, Beiser AS (1998) Migrainous visual accompaniments are not rare in late life: the Framingham Study. Stroke 29(8):1539–1543
47. Wittchen HU, Krause P, Hofler M, Pfister H, Ritz E, Goke B, Lehnert H, Tschope D, Kirch W, Pittrow D, Sharma AM, Bramlage P, Kupper B, Unger T (2003) Hypertension, diabetes mellitus and comorbidity in primary care. Fortschr Med Orig 27:19–27
48. Wöber-Bingöl C, Wöber C, Karwautz A, Auterith A, Serim M, Zebenholzer K, Aydinkoc K, Kienbacher C, Wanner C, Wessely P (2004) Clinical features of migraine: a cross-sectional study in patients aged three to sixty-nine. Cephalalgia 24(1):12–17
49. Wöber C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P, Wober-Bingol C (2007) Prospective analysis of factors related to migraine attacks: the PAMINA study. Cephalagia 27:304–314
50. Ylinen J, Nikander R, Nykänen M, Kautiainen H, Häkkinen A (2010) Effect of neck exercises on cervicogenic headache: a randomized controlled trial. J Rehabil Med 42(4):344–349

Pharmacological Treatment of Acute and Chronic Post-traumatic Headache

17

Rigmor Højland Jensen

17.1 Introduction

Post-traumatic headache (PTH) attributed to head trauma is now well defined in The International Classification of Headache Disorders (ICHD-3 beta), but the treatment still remains a significant enigma for headache experts. Despite a high prevalence and significant disease burden the underlying mechanisms are widely unknown and management is not evidence-based and complicated. This chapter aims to cover the diagnostic challenges and the existing treatment strategies for both the acute and persistent PTH.

17.2 Definitions

PTH is defined as a secondary headache in the ICHD-3 beta (Table 17.1). Until more evidence is provided, the diagnostic criteria are the same in children and adults.

When a new headache occurs for the first time in close temporal relation to a known trauma, it is classified as a secondary headache attributed to the trauma. In the PTH, there has to be a close temporal relationship to the trauma. Thus, PTH has to begin within 7 days after injury to the head or after regaining consciousness. The 7-day interval is somewhat arbitrary and further research is needed to assess whether or not a different interval would be more appropriate. In the meantime, the ICHD-3 has also created appendix criteria for when the interval between injury and headache onset is greater than 7 days (delayed-onset headache attributed to traumatic injury to the head).

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_17

Table 17.1 Classification. The ICHD-3 beta classifies acute and persistent post-traumatic headache attributed to traumatic head injury (Criteria 5.1 and 5.2). Criteria for PTH attributed to the standard definition of mild concussion (Criteria B below) are also presented (Criteria 5.1.2 and 5.2.2)

5.1 Acute headache attributed to traumatic injury to the head
Diagnostic criteria:
A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head1 has occurred
C. Headache is reported to have developed within 7 days after one of the following:
1. The injury to the head
2. Regaining of consciousness following the injury to the head
3. Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head
D. Either of the following:
1. Headache has resolved within 3 months after the injury to the head
2. Headache has not yet resolved but 3 months have not yet passed since the injury to the head
E. Not better accounted for by another ICHD-3 diagnosis
5.1.2 Acute post-traumatic headache attributed to mild traumatic injury to the head
Diagnostic criteria:
A. Headache fulfilling criteria for 5.1 Acute headache attributed to traumatic injury to the head
B. Any headache fulfilling criteria C and D
C. Injury to the head fulfilling both of the following:
1. Associated with none of the following:
(a) Loss of consciousness for >30 min
(b) Glasgow Coma Scale (GCS) score <13
(c) Post-traumatic amnesia lasting >24 h
(d) Altered level of awareness for >24 h
(e) Imaging evidence of a traumatic head injury such as intracranial haemorrhage and/or brain contusion
2. Associated, immediately following the head injury, with one or more of the following symptoms and/or signs:
(a) Transient confusion, disorientation or impaired consciousness
(b) Loss of memory for events immediately before or after the head injury
(c) Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness and/or vertigo, impaired memory and/or concentration
D. Headache is reported to have developed within 7 days after one of the following:
1. The injury to the head
2. Regaining of consciousness following the injury to the head
3. Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head
E. Either of the following:
1. Headache has resolved within 3 months after the injury to the head
2. Headache has not yet resolved but 3 months have not yet passed since the injury to the head

Table 17.1 (continued)

F. Not better accounted for by another ICHD-3 diagnosis
5.2. Persistent headache attributed to traumatic injury to the head
Diagnostic criteria:
A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head 1 has occurred
C. Headache is reported to have developed within 7 days after one of the following:
1. The injury to the head
2. Regaining of consciousness following the injury to the head
3. Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head
D. Headache persists for >3 months after the injury to the head
E. Not better accounted for by another ICHD-3 diagnosis.
5.2.2 Persistent headache attributed to mild traumatic injury to the head
A. Headache fulfilling criteria for 5.2 Persistent headache attributed to traumatic injury to the head
B. Head injury fulfilling both of the following:
1. Associated with none of the following:
(a) Loss of consciousness for >30 min
(b) Glasgow Coma Scale (GCS) score <13
(c) Post-traumatic amnesia lasting >24 h
(d) Altered level of awareness for >24 h
(e) Imaging evidence of a traumatic head injury such as intracranial haemorrhage and/or brain contusion
2. Associated, immediately following the head injury, with one or more of the following symptoms and/or signs:
(a) Transient confusion, disorientation or impaired consciousness
(b) Loss of memory for events immediately before or after the head injury
(c) Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness and/or vertigo, impaired memory and/or concentration

PTH is further divided into an acute and a persistent (previously called chronic) PTH. Acute PTH is defined as resolving within 3 months after the injury. Persistent PTH is defined as headache lasting more than 3 months after the injury (Table 17.1).

Both the acute and the persistent PTHs are then classified based upon the severity of the initial trauma in mild versus moderate and severe. There is no consensus about what characterizes the trauma that causes PTH except for the severity and the level of consciousness in the acute stage measured at the Glasgow Coma Scale. Within the trauma literature, multiple terms such as traumatic brain injury (TBI), head trauma, closed head injury, minor or minimal head injury, commotion or concussion have been applied and there is no clear consensus on the best term and definition. Still, there is also no evidence for an underlying brain injury after a mild injury to the head so the more descriptive term “head trauma” is consequently used

in the following as in the opinion to the author we only have the history of a trauma to the head. For a clear debate and research strategy, the head trauma and the applied terms have to be clearly defined in the scientific community. More than 90 % of head trauma is classified as mild and the main body of literature is focused on PTH after a mild trauma.

The reason for these subdivisions is mainly practical as the underlying mechanisms most likely are different in the acute or persistent subforms. It seems also obvious for both patients and the society that a moderate or severe head trauma can cause headache whereas it is mystifying that a mild trauma, even without unconsciousness, can give rise to a debilitating persistent PTH. Several studies confirm the inverse relation between trauma severity and persistent PTH as patients with moderate to severe head trauma only rarely report persistent PTH.

17.3 Epidemiology and Disease Course

The prior controversies around the diagnostic criteria of PTH and the various definitions of head trauma had complicated the epidemiological research. In recent years, more reliable data have however been provided. In the USA at least 1.7 mio TBIs are annually reported and hereof 75 % are classified as concussions or mild head trauma. Internationally, similar incidences are reported with predominance in children, adolescents and young adults due to accidents, falls, combats and sport activities. Some patients may not even seek medical attention, and it is estimated that 20–40 % of people who have mild head injuries in the USA have not seeked treatment.

The vast majority resolve spontaneously over weeks most often with minimal or no treatment, so the exact number of mild head trauma and/or acute PTH is actually unknown.

In the military, it is estimated that more than 350,000 returning service members have sustained mild head injuries. The absolute prevalence of headache is unknown, but amongst those reporting blast injuries, greater than 90 % have headaches, mostly of the migraine type. Of all traumatic brain injuries (TBI) – causalities from Operation Enduring Freedom/Operation Iraqi Freedom up to 98 % report headaches in the acute phase, and 37 % still had headaches after 3 months observation period. In such combat situations, the circumstances and the intensities of the trauma may also be very different than in civil life so data are difficult to compare directly.

In the civilian populations, a prospective study by Kuczynski et al. in 670 children reported PTH in 11 % after 16 days and 7.8 % after 3 months. Others report acute PTH incidences at 1 month ranging from 31 to 90 %; at 3 months from 47 to 78 %; and at 1 year from 8.4 to 35 %. Twenty-four percent of patients have persisting headaches at 4 years in another study.

In the large Akershus population study from Norway, among 30–44 years old, persistent PTH occurred in 0.15–0.2 % after mild head injury in the general population.

In clinical populations from tertiary headache centers such as the Danish Headache Center, the prevalence of CPTH is up to 10 % of all new patients. The exact prevalence in a less selected clinical population is yet unknown.

17.4 Clinical Presentation

Among a multitude of symptoms such as fatigue, phonophobia, sleep problems and difficulties with cognition and memory, headache is the cardinal symptom. In this chapter, only the therapy of headache is covered. Phenotypically, the acute PTH presents most often as a tension-type (TTH)-like headache, pressing diffuse and dull but can occasionally be associated with migraine features as aggravation by physical activity, phonophobia and nausea. In a recent study of 90 patients with persistent PTH, the phenotype was a constant featureless background headache fulfilling the main criteria for chronic TTH in 97%, and 36 % suffered also from other types of headache, i.e. 26 % with attacks of migraine without aura and only 2 % with migraine with aura. PTH can also be complicated by medication overuse headache (MOH), varying from 13 to 42 % in the Danish clinical populations to more than 70 % in a group of 104 adolescents studied 3–12 months after the incident. After discontinuation of overused drugs, 68.5 % had complete resolution of their headaches in this latter study. Such transformation into MOH should be carefully addressed and preventive initiatives against medication overuse should be included very early in the management programme.

17.5 Burden

Beside PTH the concussive patient may also present a wide range of emotional, cognitive and other somatic symptoms in relation to their trauma. These symptoms are, however, often unspecific, difficult to measure and frequently reported among the general population, too. In the Eurolight project, the per-person annual overall cost of headache disorders is estimated to €3561 for MOH, €1222 for migraine and €303 for tension-type headache. To our knowledge no cost studies have been made on PTH alone, but a study by Leibson et al. reported that patients with a concussion had significant higher medical costs than a control group even when adjusted for medical cost before the trauma. The concussive patient had medical annual cost for 11,725 $ for the period 1–5 years after trauma. The study also showed that the medical cost of concussion may not become apparent until 1 year post-injury.

17.6 Pathophysiology

The aetiology of PTH is not clarified and multiple hypotheses have been proposed. Both structural injuries and disruptions of functional network as well as release of excitatory transmitters, oxidative stress and inflammatory mediators are likely to occur during the trauma, also in the mild head trauma. Probably, genetic predisposing factors and eventual comorbidities can be both positive and negative indicators for the disease course but none of these are yet properly identified. Several animal models for TBI have been developed but an ideal model is still lacking and headache is really difficult to assess in an animal model. In one experimental animal

study, the behavioural effect of simple analgesics was studied. Actually none of the applied analgesics appeared to have any effect on the animals but still they are used liberally in humans. Further, mechanism-based studies are needed for development of more specific and better treatment strategies.

17.7 Treatment

There is little research and still no evidence-based guidelines on which to base treatment as head trauma and PTH typically is an exclusion criterion for studies examining headache treatments in the general population.

In the acute phase, symptomatic treatment with relaxation, sleep, fluid and simple analgesics are recommended. To our knowledge, no randomized controlled trials have yet been published. But according to https://clinicaltrials.gov, several interesting studies of both acute and preventive therapy mainly in CPTH are on their way.

In most reports, the acute PTH usually resolve spontaneously over time in the vast majority of patients (70–80 %) and the prognosis is regarded as favourable, probably better in children than in adults. A spontaneous remission over 2–8 weeks is to be expected and the general rule in clinical recommendations is rest and relaxation as well as informed expectation of a good outcome. The length of remission phase appears to be independent of pharmacological treatment and also of the variety of non-pharmacological strategies but proper randomized studies are missing.

Due to the fairly good prognosis for spontaneous remission, there is a general consensus that there is no need and no evidence for preventive therapy in the acute stage, unless it is a very severe debilitating headache. The benefits of preventive treatment should be weighed against the possible side effects as the concussive brain is highly sensitive for all internal and external stimuli including pharmacological compounds.

Based on the clinical experience and the published observational studies, a treatment paradigm for the various stages of PTH is presented in Fig. 17.1.

One retrospective analysis of treatment in active duty service members with mild TBI and post-traumatic headaches found that migraine-like headaches were most prevalent. Here triptans were the most effective abortive medication, and topiramate was the most effective prophylactic medication. However, this was not a controlled study, and it had a small number of participants. Other similar publications observed the effectiveness of multiple medications in small convenient samples. Literature reviews and expert opinions have recommended treating post-traumatic headaches in a manner consistent with the primary headache guidelines.

In an observational study of 670 Canadian children with mild TBI, patients were advised to take simple analgesics as Acetaminophen and Ibuprofen in the acute phase for a maximum of 3 days/week. If the headache persisted after the acute phase, preventive medication was initiated. Melatonin was started with 3 mg and increased to a maximum of 10 mg and/or amitriptyline with 5 mg in slowly increasing doses to 1 mg/kg. Likewise topiramate was used, if obesity was comorbid.

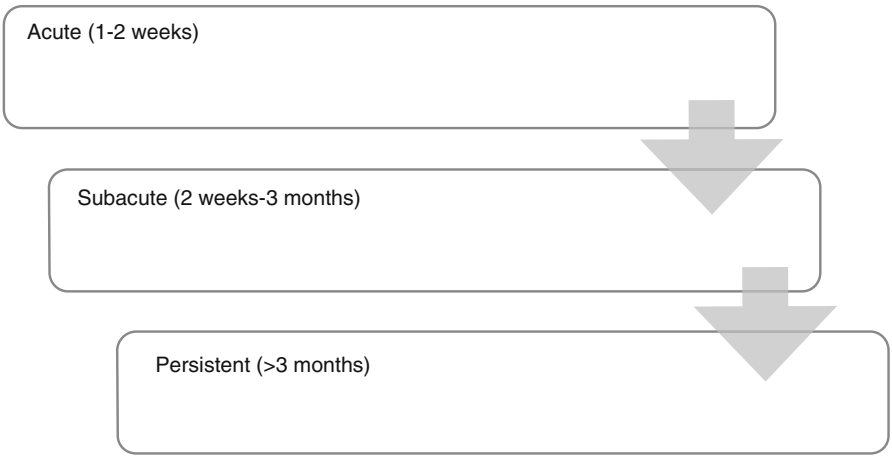

Fig. 17.1 Treatment paradigm and recommendations for the acute, subacute and persistent stages of post-traumatic headache after mild head trauma

Overall, 64 % responded to preventive treatment, defined as at least 50 % frequency reduction and melatonin was reported to be the most effective in 9/12 children and 13/18 patients responded to amitriptyline. The effect of simple analgesics was not reported.

An observational study of 167 adults admitted to an American level 1 trauma hospital due to a mild TBI and with a 1 year follow-up reported that more than 70 % occasionally took simple pain killers independent of the present phenotype. At 1 year follow-up less than 10 % used preventive medication and overall they tended only to have a periodic use of pain killers. Triptans was only used by 8 % despite they presented with a migraine phenotype. In total, only 26 % of those with migraine-like headache reported complete relief by pain medication. Of those with TTH-like presentation only a small subset used pain medication but in those 17 patients with TTH-like headache that took pain medication, 70 % reported complete relief. The authors concluded that the medical treatment was very unspecific and that there was a significant unmet need for treatment of PTH, especially they recommended triptans for the migraine phenotype, simple analgesics for TTH phenotype and conventional preventive strategies as used in primary headaches.

In management of persistent PTH the first important step is therefore to identify the phenotype of their headache by means of a headache diary for at least 1 month. If there is a medication overuse, a detoxification should first be initiated. Whether it should be gradually or abrupt is widely dependent on the type and quantity of overused drugs as well as patient compliance and available treatment support. In overuse of simple analgesics, NSAIDS and/or triptans abrupt withdrawal is safe and very effective. In case of overuse of opioids and/or barbiturates, a gradual tapering over weeks is recommended unless relevant in-patient facilities are available.

If the phenotypical presentation of persistent PTH is migraine, the recommended treatment for the migraine-like attack is triptans, oral or parenterally administered

depending on availabilities as early as possible in the attack. The general rule to administer triptans at a maximum of 2 days per week is also important for PTH patients in order to avoid the frequent complication with MOH. Regular use of antiemetics is also advisable both to minimize the associated nausea that often follow PTH and to promote gastric absorption of oral triptan during the headache phase. If the migraine-like headache occur more than three times a month and continues on a regular basis, migraine preventives should be offered to the patient. In the absence of evidence for treatment of PTH, the international treatment guidelines for primary headaches can be followed with beta-blockers, topiramate, valproate, candersatan and/or sibelium as the most frequently recommended preventives for migraine. As in genuine migraine, the drug of choice is dependent on previous experience, side effects and eventual comorbidities. In PTH the clinicians should even be more alert to the well-known side effects, especially regarding the cognitive side effects and the fatigue from Topiramate and beta-blockers. Such symptoms are highly prevalent in these PTH patients probably due to an overall increased central sensitivity after the trauma and the coexisting symptoms in their underlying post-traumatic brain syndrome.

If the phenotype of PTH is more like chronic TTH, the treatment of the headache episode is still simple analgesics with acetaminophens or NSAIDS, but here also in restricted doses at a maximum of 3 days a week to avoid MOH. In most of these cases, where a daily headache is the rule and where medical treatment is needed, a strong focus on preventives is needed. In TTH-like PTH amitriptyline, nortriptyline or gabapentin are the drugs of choice, starting with very low doses. Amitriptyline or Nortriptyline can be started with 10 mg daily at bedtime and then gradually increasing very slowly with 10 mg per week to a daily dose of 70–100 mg per day. Gabapentin can be started at 300 mg BID and then over a period of 4–6 weeks increased to 2400–3600 mg per day divided on 3–4 doses per day.

Preventive treatment is probably only indicated in the persistent PTH and in a subset of patients with constant headaches of moderate to severe intensity. If the headache is mild in intensity most patients (and doctors) tend to avoid preventive medication as they fear that the pharmacological side-effects may overshadow the beneficial effect although cultural differences in practice may occur.

In case of no effect or intolerable side effects of the preventative treatment non-pharmacological treatment strategies should be considered, either instead of pharmacological treatment or as an add-on treatment. Although the scientific evidence also is scarce, there are several possibilities for non-pharmacological strategies (please see Pinchefsky et al.; Vargas et al.; Kjeldgaard et al.). A recent randomized controlled study of cognitive behavioural therapy in persistent PTH, however, turned out to be negative. The controls that received no active treatment and only standard of care had a similar and in some points even better outcome.

In conclusion, it is still unclear how post-traumatic headaches can best be treated. It is unknown whether typical headache treatments work as effectively for post-traumatic headaches as for primary headaches. The present 3 months subdivision of the PTHs in acute PTH and persistent PTH is found to be rational and practical as

the vast majority resolve within the acute stages. A subset, however, continues and progress to a more constant headache, for yet unknown reasons. In clinical practice, the persistent PTHs are difficult to manage and there are no existing specific pharmacological substances on the market. In the acute stage, only simple pain killers and/or triptans can be recommended whereas in the persistent PTH stages, preventive therapies dedicated to the presenting phenotype are recommended. Development of MOH is also prevalent in PTH and this complication can and should be avoided by careful information to patients and their caretakers. To reduce the unmet need and major burden of PTH, more dedicated research into the pathophysiology and the treatment of PTH are highly warranted.

Suggested Reading

1. Aaseth K, Grande RB, Kvaerner KJ, Gulbrandsen P, Lundqvist C, Russell MB (2008) Prevalence of secondary chronic headaches in a population-based sample of 30-44-year-old persons. The Akershus study of chronic headache. Cephalalgia 28(7):705–713
2. Baandrup L, Jensen R (2005) Chronic post-traumatic headache- a clinical analysis in relation to the International Headache Classification 2nd Edition. Cephalalgia 25(2):132–138
3. Costa PT Jr, Herbst JH, McCrae RR, Siegler IC (2000) Personality at midlife: stability, intrinsic maturation, and response to life events. Assessment 7(4):365–378
4. Evans RW (2004) Post-traumatic headaches. Neurol Clin 22(1):237–249, viii
5. Evans RW (2010) Persistent post-traumatic headache, postconcussion syndrome, and whiplash injuries: the evidence for a non-traumatic basis with an historical review. Headache J Head Face Pain 50(4):716–724
6. Haas DC (1996) Chronic post-traumatic headaches classified and compared with natural headaches. Cephalalgia (Wiley-Blackwell) 16(7):486–493
7. Harrison JL, Rowe RK, O'Hara BF, Adelson PD, Lifshitz J (2014) Acute over-the-counter pharmacological intervention does not adversely affect behavioral outcome following diffuse traumatic brain injury in the mouse. Exp Brain Res 232(9):2709–2719
8. Heyer GL, Idris SA (2014) Does analgesic overuse contribute to chronic post-traumatic headaches in adolescent concussion patients? Pediatr Neurol 50(5):464–468
9. Jensen R, Tassorelli C, Rossi P, Allena M, Osipova V, Steiner T et al (2011) A basic diagnostic headache diary (BDHD) is well accepted and useful in the diagnosis of headache. A multicentre European and Latin American study. Cephalalgia 31(15):1549–1560
10. Keidel M et al (1998) Treatment of post-traumatic headaches. Recommendations of the German Migraine and Headache Society. Med Monatsschr Pharm 21(6):166–72
11. Kjeldgaard D et al (2014) Cognitive behavioural treatment for the chronic post-traumatic headache patient: a randomized controlled trial. J Headache Pain 15:81
12. Kjeldgaard D, Forchhammer H, Teasdale TW, Jensen R (2014) Chronic post-traumatic headache after mild head injury: a descriptive study. Cephalalgia 34(3):191–200
13. Kozminski M (2010) Combat-related posttraumatic headache: diagnosis, mechanisms of injury, and challenges to treatment. J Am Osteopath Assoc 110(9):514–519
14. Leibson CL, Brown AW, Hall LK, Ransom JE, Mandrekar J, Osler TM et al (2012) Medical care costs associated with traumatic brain injury over the full spectrum of disease: a controlled population-based study. J Neurotrauma 29(11):2038–2049
15. Linde M, Gustavsson A, Stovner LJ, Steiner TJ, Barre J, Katsarava Z et al (2012) The cost of headache disorders in Europe: the Eurolight project. Eur J Neurol 19(5):703–711
16. Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S (2012) Characterization of headache after traumatic brain injury. Cephalalgia 32(8):600–606

17. Marcus DA (2003) Disability and chronic posttraumatic headache. Headache 43(2):117–121
18. Obermann M, Keidel M, Diener HC (2010) Post-traumatic headache: is it for real? Crossfire debates on headache: pro. Headache J Head Face Pain 50(4):710–715
19. Packard RC (1999) Epidemiology and pathogenesis of posttraumatic headache. J Head Trauma Rehabil 14(1):9–21
20. Pinchefsky E, Dubrovsky AS, Friedman D, Shevell M (2014) Part II-Management of pediatric posttraumatic headaches. Pediatr Neurol 52(3):270–280
21. Russell MB, Rasmussen BK, Brennum J, Iversen HK, Jensen RA, Olesen J (1992) Presentation of a new instrument: the diagnostic headache diary. Cephalalgia 12(6):369–374
22. Seifert TD, Evans RW (2010) Posttraumatic headache: a review. Curr Pain Headache Rep 14(4):292–298
23. Sigurdardottir S, Andelic N, Roe C, Jerstad T, Schanke AK (2009) Post-concussion symptoms after traumatic brain injury at 3 and 12 months post-injury: a prospective study. Brain Inj 23(6):489–497
24. Vargas BB, Dodick DW (2012) Posttraumatic headache. Curr Opin Neurol 25(3):284–289
25. Headache Classification Committee of the International Headache Society (IHS) (2013) The International Classification of Headache Disorders: 3nd edition beta. Cephalalgia 33(9):629–808
26. Zasler NDM (2011) Pharmacotherapy and posttraumatic cephalalgia. J Head Trauma Rehabil 26(5):397–399
27. Zeeberg P, Olesen J, Jensen R (2005) Efficacy of multidisciplinary treatment in a tertiary referral headache centre. Cephalalgia 25(12):1159–1167

Headache Attributed to Intracranial Hypertension and Hypotension

18

Jan Hoffmann

18.1 Introduction

Intracranial pressure (ICP) of cerebrospinal fluid (CSF) is regulated by a delicate equilibrium of its production and absorption. Alterations of this regulatory system may quickly affect ICP and result in intracranial hyper- or hypotension, both of which commonly induce headache. While an elevation of ICP is frequently secondary to a space-occupying process resulting from a neoplastic, hemorrhagic, or infectious process, the most common cause that induces a decrease of ICP is a medical intervention such as a lumbar puncture.

In contrast, the underlying causes of spontaneous alterations of ICP, idiopathic intracranial hypertension (IIH), and spontaneous (idiopathic) intracranial hypotension (SIH) are largely unknown. The following chapter will focus on these idiopathic variations of ICP and review the clinical picture, current pathophysiological understanding, and treatment of these rare but probably underdiagnosed disorders.

18.2 Idiopathic Intracranial Hypertension

The clinical syndrome of increased intracranial pressure of unknown etiology underwent several changes in its terminology. The German neurologist Max Nonne defined the condition in 1904 as pseudotumor cerebri (PTC). Due to the fact that in some patients a cause of the disorder can be identified during the course of the disease or as a result of an improvement of the pathophysiological understanding, the term PTC syndrome is now used as an umbrella term that encompasses the primary

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_18

form with no identifiable cause, idiopathic intracranial hypertension (IIH), as well as the secondary form induced by cerebral venous abnormalities, medications, or other medical conditions.

IIH typically affects obese young women of childbearing age. The annual incidence of this rare disorder has been estimated at 0.9 cases per 100,000, its prevalence at 8.6 cases per 100,000 of the general population. While in prepubertal children no sex predilection has been observed, in adults around 90 % of IIH patients are women [1–3].

The clinical syndrome is characterized by a rather unspecific headache which may be accompanied by a visual impairment that, if untreated, can lead to complete visual loss. The syndrome has initially been defined by the criteria established by Walter Dandy [4] which over the years underwent several modifications [5–7] to take into account novel diagnostic imaging techniques. Today, IIH is defined by the criteria established by the International Headache Society (IHS) [8] (Table 18.1).

18.2.1 Pathophysiology

Over the past decades, several mechanisms that ultimately lead to an alteration in CSF hydrodynamics have been proposed. However, despite a substantial amount of studies that aimed at elucidating the causes of the elevation of ICP, the detailed mechanisms that lead to the known structural abnormalities and clinical symptoms remain largely unknown [9–12]. ICP is normally kept at a relatively constant level due to an equilibrium between CSF production and absorption. Several studies have therefore investigated if a CSF overproduction may be the underlying cause of the elevated ICP in IIH. However, this hypothesis could neither be confirmed in an experimental in vivo study [13] nor in clinical studies [14, 15] including a long-term study [16].

Research efforts have therefore focused recently on venous outflow and CSF absorption abnormalities as the possible mechanism behind IIH. In this context it is hypothesized that an obstruction in venous outflow elevates cerebral venous

Table 18.1 Diagnostic criteria for Idiopathic Intracranial Hypertension (IIH) Established by the International Headache Society (ICHD-3 beta) (*Cephalalgia* 2013; 33(9): 629–808)

A. Any headache fulfilling criterion C
B. Idiopathic intracranial hypertension (IIH) has been diagnosed, with CSF pressure >250 mm CSF (measured by lumbar puncture performed in the lateral decubitus position, without sedative medications, or by epidural or intraventricular monitoring)
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to IIH, or led to its discovery
2. Headache is relieved by reducing intracranial hypertension
3. Headache is aggravated in temporal relation to increase in intracranial pressure
D. Not better accounted for by another ICHD-3 diagnosis

pressure affecting the rate of CSF absorption. The hypothesis is fueled by the strong association between IIH and obesity, which is present in up to 80 % of adult IIH patients [17–19] with clinical studies indicating a direct correlation between the body mass index (BMI) and CSF opening pressure [19–21]. The proposed rationale behind this association suggests that the obesity-related increase in intra-abdominal and intra-thoracic pressure may lead to an increase in cerebral venous pressure, a decrease in CSF absorption and finally an elevation in ICP [22]. The fact that a weight reduction reduces CSF opening pressure as well as clinical symptoms proves the pathophysiological importance of obesity in IIH [23–30]. In this context is has been suggested that the effect of acetazolamide in the treatment of IIH may be, at least in part, the result of the associated weight loss [31].

However, despite the clear relationship between obesity and IIH, the proposed mechanistic rationale behind this association has been questioned as it does neither explain female preponderance nor the fact that IIH patients tend to be obese in lower parts of the body rather than in abdominal parts [32, 33]. The distinct body fat distribution in IIH is even more pronounced in women than in men [33]. Therefore, other factors such as hormonal influences may contribute to the relationship between obesity and IIH [34]. Clinical data suggest that substances secreted by adipose tissue may be involved in the pathogenesis of IIH. For example, aromatase has been discussed in this context as aromatase is involved in the production of estrogens from androstenedione and its distribution correlates with the female distribution of body fat [35]. Recently, vitamin A has also been associated with IIH. It is converted in adipose tissue to retinoic acid, its active metabolite. The exact mechanism of action that relates retinol to increased ICP remains largely unknown. However, studies indicate that excessive vitamin A concentrations in plasma and CSF, which have been demonstrated in IIH [36–38], may impair CSF absorption. However, as vitamin A may induce the synthesis of progesterone and activate the mineralocorticoid receptor [39], the functional basis of the relationship of vitamin A and elevated ICP may be much more complex than initially suspected. The fact that hypovitaminosis may also increase ICP adds to the complexity of the association [40]. Further research is needed to elucidate further the mechanisms behind the association between vitamin A and ICP.

Beside the mechanistic hypothesis that suggests an outflow reduction resulting from an increase in an obesity-related elevation of intra-abdominal pressure and the hormonal hypothesis that suggests a reduced CSF absorption which may be based on structural changes in the arachnoid villi [41], stenotic transverse sinuses (TSS) have been proposed to play a significant role in impairing CSF absorption as they can be observed in up to 90 % of IIH patients [42]. However, if the observed TSS are cause or consequence of the elevated ICP in IIH has not been entirely clarified [10, 43, 44]. In this context, it has been hypothesized that a primary TSS may impair venous outflow affecting the pressure gradient over the arachnoid granulations and thereby reducing CSF absorption [43]. Another hypothesis suggests that the observed TSS are secondary to increased ICP [43, 44]. This rationale is supported

by the observations that high ICP may lead to a collapsing of the transverse sinuses causing an additional increase in venous pressure in the superior sagittal sinus and that CSF diversion procedures may reverse previously identified TSS [44–50]. Regardless of the question if observed TSS are primary or secondary, the location and degree of the TSS does not seem to affect the clinical course of IIH [51].

Data obtained in an in vivo study suggest that the hemodynamic consequences of a unilateral TSS do not suffice to affect CSF absorption while a bilateral TSS does lead to an elevation of ICP [52]. Clinical, in particular interventional studies, have therefore aimed at investigating the consequences of an endovascular treatment in patients that show bilateral TSS in MR imaging. Based on existing data it seems clear that endovascular treatment can be effective in alleviating IIH-associated symptoms in most patients with bilateral TSS [45, 53–60] supporting a causality between TSS in IIH, at least in some patients. However, this observation does still not clarify whether bilateral TSS are primary or secondary as a beneficial effect on elevated ICP is feasible in both cases.

Taken together, based on the available literature it seems unlikely that the commonly observed IIH-associated TSS are primary stenoses as this mechanism would not explain the observed female preponderance and the fact that TSS are common in the general population [42, 61, 62]. The uni- and bilateral TSS rather appear to be secondary to the elevated ICP triggering a vicious cycle that further increases ICP due to a reduced venous outflow and consecutively reduced CSF absorption.

18.2.2 Clinical Syndrome and Diagnosis

The headache associated with IIH lacks of any specific features and may vary substantially in its clinical presentation. It is commonly described as a daily occurring diffuse headache with a frontal, retro-orbital localization that may be aggravated by physical activity and even be accompanied by nausea. IIH-associated headache can occasionally even show similarities to primary headaches including migraine [63–65] and tension-type headache [66] that may hamper its clinical distinction to these syndromes, in particular if IIH presents without an accompanying papilledema or visual abnormalities. Despite the fact that headache is usually the symptom that leads affected patients to seek medical advice, cases of probable IIH without headache have been described [67].

Visual disturbances described in IIH include a reduction in visual acuity, visual field losses, and photopsia [2]. Ophthalmoscopic examination reveals a papilledema in 40–95 % of patients [11, 63, 68] which occasionally may be asymmetric or even unilateral [69, 70]. Ophthalmoscopic examination is therefore mandatory if IIH is suspected. Nevertheless, the presence and extent of an observed papilledema does not correlate with headache frequency and intensity [68]. Horizontal diplopia occurs in about one-third of IIH patients and is in most cases a result of a sixth nerve palsy [3].

In addition to headache and visual disturbances, olfactory disturbances and a pulse-synchronous tinnitus are commonly observed in IIH [71, 72].

In contrast to its clinical features, IIH is associated with characteristic structural abnormalities that can be identified using magnetic resonance imaging (MRI) techniques [11, 71, 73–75]. The most reliable signs observed in MRI scans are the morphometric changes of the pituitary gland (partial or complete empty sella) and the

optic nerve sheath (ONS) [11, 73–76]. The commonly observed posterior flattening of the optic globe is highly specific for the presence of IIH but its low sensitivity limits its use as a diagnostic criterion for the initial diagnosis of IIH. In contrast, the size of the lateral ventricles is not affected in IIH [73, 76, 77]. In addition to the described structural abnormalities, uni- or bilateral stenoses of the transverse sinuses (TSS) are commonly observed in IIH with reported prevalence rates of up to 90 % [42, 78]. Therefore, the diagnostic workup should always include a MR venography to exclude a venous sinus thrombosis and to identify the presence of a uni- or bilateral TSS.

Nevertheless, due to their variability as well as their specificity and sensitivity with respect to IIH, imaging abnormalities observed in MRI can only serve as supportive for the diagnosis of intracranial hypertension in IIH. Lumbar puncture with a measurement of CSF opening pressure is therefore still required for the initial diagnosis and the evaluation of treatment effects. According to the criteria established by the IHS, an elevated CSF opening pressure is diagnosed if pressure exceeds 250 mm CSF [8]. Occasionally the elevation of ICP may occur intermittently, hampering the diagnosis of the syndrome, in particular in cases of IIH without accompanying papilledema. In this case continuous monitoring of CSF pressure by lumbar catheter may be considered if IIH is suspected but CSF opening pressure remains within normal range.

18.2.3 Treatment

The principal aim in the treatment of IIH is the preservation of visual acuity followed by the relief of the associated headache. An appropriate treatment strategy should therefore include a consequent reduction of body weight, complemented by an adequate pharmacological treatment. Invasive interventions such as endovascular treatments, CSF diversion procedures, and optic nerve sheath fenestration should be reserved exclusively for treatment refractory cases with a high risk of partial or complete visual loss.

18.2.3.1 Weight Reduction

The consequent reduction of body weight in obese patients has been demonstrated to reduce ICP, papilledema, and consecutive visual loss as well as the IIH-associated headache [23, 79]. Even minor weight losses of about 6 % have been demonstrated to be effective [26, 28]. A weight gain should be avoided, even after successful treatment, as it increases the risk of recurrence [80] and may even increase the risk of IIH in non-obese individuals highlighting the importance of weight reduction and maintenance of a normal BMI in the treatment of IIH [17, 72, 81, 82]. If an effective weight reduction is not achieved, bariatric surgery may represent an effective treatment strategy in these exceptional cases [29, 30].

18.2.3.2 Lumbar Puncture

Repeated therapeutic lumbar punctures may provide a treatment option for a short period of time. The withdrawal of CSF through a lumbar puncture probably improves IIH-associated headache although no trials exist to confirm this hypothesis [83, 84]. Since ICP is restored within hours, it remains unclear why the relief of IIH-associated symptoms, in particular the headache, may persist for a prolonged

time [15]. It may be speculated that the transient reduction in ICP reduces secondary TSS improving venous outflow and CSF absorption restoring a stable equilibrium with adequate CSF dynamics [12, 85–87].

18.2.3.3 Pharmacological Treatment

The pharmacological treatment of IIH is mainly based on the use of carbonic anhydrase inhibitors. The carbonic anhydrase plays a significant role in the production of CSF as it regulates the synthesis of hydrogen carbonate (HCO_3^-) [88–91]. The enzyme is located in epithelial cells of the choroid plexus. In addition to the cytosolic form, extracellular membrane-associated isoforms exist [92]. Carbonic anhydrase inhibitors such as acetazolamide may inhibit CSF secretion [93–95] and reduce ICP [96, 97]. If this effect is mediated through an action on the intra- or extracellular isoforms of carbonic anhydrase or both, has not been entirely clarified.

Acetazolamide represents the most widely used carbonic anhydrase inhibitor for the pharmacological treatment of IIH. It is generally used in a dose ranging between 500 and 2000 mg per day. Despite the widespread use of acetazolamide, until recently evidence on its clinical efficacy was scarce and mainly based on small open-label studies [98, 99]. A randomized controlled trial that was conducted in 2011 did not show a convincing efficacy, probably due to the small number of participants and the high discontinuation rate of acetazolamide. In addition, this trial did not include a placebo group [98]. In 2014, the NORDIC Idiopathic Intracranial Hypertension Study Group published data from the first multicenter, randomized, double-masked, placebo-controlled study of acetazolamide with 165 participants which demonstrate that acetazolamide is effective in improving visual function, papilledema, and headache disability [100]. Interestingly, participants also experienced a significant weight reduction that may have contributed to the clinical efficacy of this pharmacological approach [31, 100]. In the trial participants were treated with up to 4 g of acetazolamide per day. The most commonly observed unwanted side effects were fatigue and gastrointestinal symptoms including diarrhea, dyspepsia, nausea, and vomiting.

The anticonvulsant topiramate is increasingly used for the treatment of IIH, in particular in cases in which the effect of acetazolamide does not suffice to normalize ICP and stop the progression of visual deficits or in which acetazolamide has to be discontinued due to intolerable side effects. Topiramate is commonly used in a dose ranging between 50 and 200 mg per day. Treatment with topiramate is frequently accompanied by unwanted side effects that may include dysesthesias, mood changes, and decline in cognitive abilities [101]. The effect of topiramate is thought to be based on its ability to inhibit carbonic anhydrase and the reduction of body weight. Despite its common use in clinical routine, up to date no randomized, placebo-controlled trial has been conducted to verify its efficacy in treating IIH. In an open-label study, topiramate has been demonstrated to be as effective in improving visual field grades as acetazolamide [99]. Another small study conducted by Shah et al. largely confirmed the findings [102] but results have to be taken with caution as the study was based on an open-label design and did not include a control group. As in the case of acetazolamide, it is not entirely clear if the beneficial effect

is mainly the result of topiramate-induced weight loss, rather than an effect on carbonic anhydrase [28]. Further studies, in particular a randomized, placebo-controlled trial, are required to clarify if topiramate is beneficial in the treatment of IIH and which mechanism is responsible for its efficacy.

The use of diuretic substances for the treatment of IIH has been debated since Jefferson et al demonstrated beneficial effects for several diuretic compounds [103]. In this context, furosemide has been demonstrated to inhibit carbonic anhydrase [104–108] and to lower ICP [109]. Given its widespread use in clinical routine, the effect on carbonic anhydrase led to its increasing use for the treatment of IIH. For the relief of IIH-associated symptoms it is generally used in a dose ranging between 30 and 80 mg per day. However, up to date no randomized placebo-controlled trials exist that may demonstrate its efficacy in IIH.

Steroids have been used for the treatment of IIH in the past [110]. Due to their significant side effects, which may include a substantial weight gain, long-term treatment of IIH with steroids has become obsolete. In addition to the substantial side effects, long-term treatment with steroids bear the risk of a rebound when treatment is terminated. However, in exceptional cases with an imminent risk of a complete visual loss, short-term treatment may be considered to bridge a preoperative period prior to a CSF diversion procedure.

18.2.3.4 Endovascular Treatment

Endovascular treatment has been shown to be effective in the treatment of IIH in the majority of patients with TSS [45, 53–60, 111]. The mechanism behind this beneficial effect is believed to be based on an improvement of venous outflow that leads to an improved CSF absorption and a decrease in ICP [43, 112]. However, endovascular treatment may be accompanied by severe complications which include an in-stent thrombosis, stent migration, sinus perforation, and subdural hemorrhage. Due to the potential complications that may arise in the context or as a consequence of endovascular treatment, the lack of studies investigating the long-term efficacy and safety of this treatment in IIH and the fact that most patients benefit significantly from weight loss and pharmacological treatments, the procedure remains controversial and is currently not recommended for the routine treatment of IIH [113].

18.2.3.5 Surgical Treatment

CSF diversion procedures include the surgical implantation of a ventriculoperitoneal or lumboperitoneal shunt [114]. Clinical data suggest, that ventriculoperitoneal shunts should be preferred in contrast to lumboperitoneal shunts as the latter are associated with a higher risk of complications that require surgical shunt revision [115]. Studies that address the long-term efficacy and safety of these procedures remain scarce [54]. Given the lack of conclusive data and due to the fact that these procedures may suffer complications such as a shunt infection, shunt failure, or over-shunting, that may occasionally require a surgical shunt revision, these interventions should only be considered in treatment refractory cases or in case of an imminent risk of complete visual loss [116].

18.2.3.6 Optic Nerve Sheath Fenestration

Optic nerve sheath fenestration should be considered if papilledema and visual disturbances represent the primary symptom or if pharmacological treatment has not been effective in preventing visual deterioration. The intervention is performed through an incision in the meninges surrounding the optic nerve. The technique is highly effective in stabilizing and improving papilledema and visual loss [117–121]. Nevertheless, as with endovascular treatment options and CSF diversion procedures, future studies will need to clarify long-term efficacy and safety as current studies still provide inconclusive results [118, 121].

A recommendation on which interventional technique, CSF diversion procedure or optic nerve sheath fenestration, should be preferred if surgical treatment is indicated is currently not possible based on the existing literature [113].

18.3 Spontaneous Intracranial Hypotension

Spontaneous intracranial hypertension (SIH) is a rare headache syndrome with an estimated annual incidence of 5 cases per 100,000 people and a prevalence of 1 case per 50,000. Although it may occur at any age, the typical age of incidence ranges between 40 and 60 years. The syndrome shows a female sex predilection with a female to male ratio of 2:1 [122].

The clinical syndrome has been initially described by Schaltenbrand in 1938 [123] and is now defined in the IHS classification [8] (Table 18.2). It is characterized by an orthostatic headache that is usually the result of a spontaneous CSF leak. The underlying cause of the CSF leaks, in particular the reasons for the observed age distribution and sex predilection, remain largely unknown.

18.3.1 Pathophysiology

In contrast to earlier hypotheses that suggested a decrease in CSF production or an increase in CSF absorption [124], clinical evidence indicates that SIH is the result of a spontaneous CSF leak which causes a reduction of CSF pressure. Most of the CSF leaks causing SIH are located in the cervicothoracic junction or along the thoracic spine and occasionally multiple simultaneous CSF leaks may be observed

Table 18.2 Diagnostic criteria for Idiopathic Intracranial Hypertension (IIH) Established by the International Headache Society (ICHD-3 beta) (*Cephalalgia* 2013; 33(9): 629–808)

A. Any headache fulfilling criterion C
B. Low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging
C. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
D. Not better accounted for by another ICHD-3 diagnosis

[122]. In contrast, cranial leaks are not associated with the clinical syndrome of SIH [125]. The underlying cause of the development of CSF leaks has not been entirely clarified. Clinical evidence suggests that traumatic events which may include trivial increases in ICP during coughing or physical exercise, as well as a genetic predisposition that may induce tissue abnormalities increasing the likelihood of spontaneous dural ruptures and CSF leaks, have been hypothesized [8, 126–130]. While evidence for traumatic events can be identified in about one-third of SIH patients, evidence for an underlying generalized connective tissue disorder, which among others may include Marfan [131–134] and Ehlers-Danlos [135] syndromes, can be observed in up to two-thirds of SIH patients [130, 135–139]. These associated connective tissue disorders may be underdiagnosed as their clinical manifestations may be subtle [135].

The cause of SIH-induced headache is believed to be the result of a downward displacement of the brain causing traction on pain-sensitive intracranial structures, in particular the dura mater [122, 140]. Spinal manifestations of SIH such as radiculopathy and myelopathy are caused by spinal cord or nerve root compression induced by extrathecal CSF collections [141].

18.3.2 Clinical Syndrome and Diagnosis

The clinical picture is characterized by an orthostatic headache that initiates or worsens in upright position as intracranial CSF pressure falls due to gravitation-induced downward flow. The brain consequently suffers a downward displacement with painful traction on the dura mater. Worsening after assuming upright position and relief after lying down generally occur within 15 min but the time frame may well range between seconds and several hours [8, 122, 142–144]. The commonly bilateral headache can be of throbbing quality and may vary substantially in its intensity ranging from mild to severe. Headache initiates and worsens gradually but in rare cases an acute onset can be observed. It is usually accompanied by neck stiffness and occasionally even subjective hearing symptoms and tinnitus. Nausea, photophobia, and phonophobia may also occur [8]. In exceptional cases spinal symptoms such as radiculopathy or myelopathy, which follow no orthostatic pattern, may be observed [141].

Diagnosis of SIH is largely based on neuroimaging techniques as the clinical picture may vary substantially and even the orthostatic component of the headache may be completely absent [143]. In general, cranial MRI is used to identify specific signs of reduced ICP. Prominent MRI signs of SIH include supra- and infratentorial pachymeningeal enhancement resulting from the dilation of subdural blood vessels [145, 146], subdural fluid collections as a compensatory fluid accumulation due to the CSF leak and the resulting downward displacement of the brain [122, 147, 148], effacement of perichiasmatic and prepontine cisterns with flattening of the pons against the clivus, descent of cerebellar tonsils and in exceptional cases ventricular

collapse [10, 122, 146], pituitary hyperemia and enlargement as well as engorgement of venous structures [149–153]. Occasionally, in particular in cases of an extensive reduction of ICP, a rupture of the bridging veins may occur leading to the appearance of subdural hematomas.

However, in up to 20 % of SIH patients no MRI abnormalities can be observed [122, 154, 155]. Myelography and in particular radionuclide cisternography should be reserved for cases in which the identification of a CSF leak is not possible by the use of MRI and in which the clinical picture does not remit spontaneously requiring further interventions. In this context, it has to be considered that in about one-third of SIH patients a CSF leak is not identified even if radionuclide cisternography is used [122]. If results from imaging techniques remain inconclusive, which is the case in 25 % of SIH patients [148], a lumbar puncture may be considered to identify a reduced CSF opening pressure (<6 cm CSF). However, the risk of a new CSF leak induced by the procedure should be considered when evaluating the potential diagnostic benefit. In contrast to previous diagnostic criteria, the efficacy of an epidural blood patch is no longer required for the diagnosis of SIH as it is not effective in about 25 % of SIH patients [156, 157].

18.3.3 Treatment

Given the underlying pathophysiological mechanism of the clinical syndrome it is highly likely that in a large number of SIH patients the syndrome remits without any kind of treatment. Therefore, it can be assumed that the condition is largely underdiagnosed as many patients may not seek medical advice if headache is mild and remits within a short period of time. If the clinical symptoms are disabling or the condition does not remit spontaneously, pharmacological or interventional treatment may become necessary. However, available treatment options are limited and no randomized, placebo-controlled trials exist to demonstrate their efficacy.

The most pragmatic approach consists in starting treatment with conservative measures including strict bed rest and adequate hydration. It has been suggested that the additional administration of caffeine, theophylline, and steroids may be useful as they are thought to increase CSF production [158], but in clinical practice the effect appears to be limited and no trials exist to confirm their utility. In case further treatment is required, an epidural blood patch is the treatment of choice. During the procedure, 10–20 ml of autologous blood is injected into the epidural space [156, 157]. The first epidural blood patch is successful in 30–50 % of cases [122, 156, 157]. If the treatment fails to seal the CSF leak, the procedure can be repeated with a larger blood volume. In case epidural blood patches do not achieve the desired sealing effect, the use of fibrin sealant may be considered [159, 160]. In contrast to the epidural blood patch, the procedure requires the identification of the exact site of the CSF leak. Together with the fact that anaphylactic reactions have been observed in the context of fibrin sealant use [161], the use of this technique should be limited to SIH patients in which the epidural blood patch was unsuccessful and would therefore require a surgical intervention. In this group of patients, the use of

the percutaneously applied fibrin sealant is successful in about one-third of SIH patients [159].

If conservative methods and the described sealing techniques fail to achieve closure of the CSF leak and remission of the SIH-associated symptoms or if anatomical abnormalities are responsible for the leakage, surgical intervention at the site of the leak may become necessary [162–165].

Conflicts of Interest Dr. Jan Hoffmann reports no conflict of interest.

References

1. Bruce BB, Kedar S, Van Stavern GP et al (2009) Idiopathic intracranial hypertension in men. Neurology 72:304–309
2. Wall M (2010) Idiopathic intracranial hypertension. Neurol Clin 28:593–617
3. Wall M, George D (1991) Idiopathic intracranial hypertension. A prospective study of 50 patients. Brain 114(Pt 1A):155–180
4. Dandy WE (1937) Intracranial pressure without brain tumor: diagnosis and treatment. Ann Surg 106:492–513
5. Smith JL (1985) Whence pseudotumor cerebri? J Clin Neuroophthalmol 5:55–56
6. Friedman DI, Jacobson DM (2002) Diagnostic criteria for idiopathic intracranial hypertension. Neurology 59:1492–1495
7. Friedman DI, Liu GT, Digre KB (2013) Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology 81:1159–1165
8. Headache Classification Committee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:629–808
9. Walker RW (2001) Idiopathic intracranial hypertension: any light on the mechanism of the raised pressure? J Neurol Neurosurg Psychiatry 71:1–5
10. Hoffmann J, Goadsby PJ (2013) Update on intracranial hypertension and hypotension. Curr Opin Neurol 26:240–247
11. Degnan AJ, Levy LM (2011) Pseudotumor cerebri: brief review of clinical syndrome and imaging findings. AJNR Am J Neuroradiol 32:1986–1993
12. Biousse V, Bruce BB, Newman NJ (2012) Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 83:488–494
13. Rekate HL, Erwood S, Brodkey JA et al (1985) Etiology of ventriculomegaly in choroid plexus papilloma. Pediatr Neurosci 12:196–201
14. Fishman RA (1984) The pathophysiology of pseudotumor cerebri. An unsolved puzzle. Arch Neurol 41:257–258
15. Johnston I, Paterson A (1974) Benign intracranial hypertension. II. CSF pressure and circulation. Brain 97:301–312
16. Malm J, Kristensen B, Markgren P, Ekstedt J (1992) CSF hydrodynamics in idiopathic intracranial hypertension: a long-term study. Neurology 42:851–858
17. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE (1993) Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci 116:18–28
18. Galvin JA, Van Stavern GP (2004) Clinical characterization of idiopathic intracranial hypertension at the Detroit Medical Center. J Neurol Sci 223:157–160
19. Pollak L, Zohar E, Glovinsky Y, Huna-Baron R (2013) Reevaluation of presentation and course of idiopathic intracranial hypertension – a large cohort comprehensive study. Acta Neurol Scand 127:406–412

20. Whiteley W, Al-Shahi R, Warlow CP, Zeidler M, Lueck CJ (2006) CSF opening pressure: reference interval and the effect of body mass index. Neurology 67:1690–1691
21. Avery RA, Shah SS, Licht DJ et al (2010) Reference range for cerebrospinal fluid opening pressure in children. N Engl J Med 363:891–893
22. Sugerman HJ, DeMaria EJ, Felton WL 3rd, Nakatsuka M, Sismanis A (1997) Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. Neurology 49:507–511
23. Sinclair AJ, Burdon MA, Nightingale PG et al (2010) Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ 341:c2701
24. Sugerman HJ, Felton WL 3rd, Salvant JB Jr, Sismanis A, Kellum JM (1995) Effects of surgically induced weight loss on idiopathic intracranial hypertension in morbid obesity. Neurology 45:1655–1659
25. Nadkarni T, Rekate HL, Wallace D (2004) Resolution of pseudotumor cerebri after bariatric surgery for related obesity. J Neurosurg 101:878–880
26. Newborg B (1974) Pseudotumor cerebri treated: by rice-reduction diet. Arch Intern Med 133:802–807
27. Kupersmith MJ, Gamell L, Turbin R, Peck V, Spiegel P, Wall M (1998) Effects of weight loss on the course of idiopathic intracranial hypertension in women. Neurology 50:1094–1098
28. Johnson LN, Krohel GB, Madsen RW, March GA Jr (1998) The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). Ophthalmology 105:2313–2317
29. Egan RJ, Meredith HE, Coulston JE, Bennetto L, Morgan JD, Norton SA (2011) The effects of laparoscopic adjustable gastric banding on idiopathic intracranial hypertension. Obes Surg 21:161–166
30. Fridley J, Foroozan R, Sherman V, Brandt ML, Yoshor D (2011) Bariatric surgery for the treatment of idiopathic intracranial hypertension. J Neurosurg 114:34–39
31. Sinclair AJ, Woolley R, Mollan SP (2014) Idiopathic intracranial hypertension. JAMA 312:1059–1060
32. Kesler A, Kliper E, Shenkerman G, Stern N (2010) Idiopathic intracranial hypertension is associated with lower body adiposity. Ophthalmology 117:169–174
33. Schwartz R, Kliper E, Stern N, Dotan G, Berliner S, Kesler A (2013) The obesity pattern of idiopathic intracranial hypertension in men. Graefes Arch Clin Exp Ophthalmol 251:2643–2646
34. McGeeney BE, Friedman DI (2014) Pseudotumor cerebri pathophysiology. Headache J Head Face Pain 54:445–458
35. Mendelson CR, Simpson ER (1987) Regulation of estrogen biosynthesis by human adipose cells in vitro. Mol Cell Endocrinol 52:169–176
36. Jacobson DM, Berg R, Wall M, Digre KB, Corbett JJ, Ellefson RD (1999) Serum vitamin A concentration is elevated in idiopathic intracranial hypertension. Neurology 53:1114–1118
37. Warner JE, Larson AJ, Bhosale P et al (2007) Retinol-binding protein and retinol analysis in cerebrospinal fluid and serum of patients with and without idiopathic intracranial hypertension. J Neuroophthalmol 27:258–262
38. Warner JE, Bernstein PS, Yemelyanov A, Alder SC, Farnsworth ST, Digre KB (2002) Vitamin A in the cerebrospinal fluid of patients with and without idiopathic intracranial hypertension. Ann Neurol 52:647–650
39. Kushida A, Tamura H (2009) Retinoic acids induce neurosteroid biosynthesis in human glial GI-1 Cells via the induction of steroidogenic genes. J Biochem 146:917–923
40. Calhoun MC, Hurt HD, Eaton HD, Rousseau JE Jr, Hall RC Jr (1967) Rates of formation and absorption of cerebrospinal fluid in bovine hypovitaminosis A. J Dairy Sci 50:1489–1494
41. Hayes KC, McCombs HL, Faherty TP (1971) The fine structure of vitamin A deficiency. II. Arachnoid granulations and CSF pressure. Brain 94:213–224
42. Farb RI, Vanek I, Scott JN et al (2003) Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology 60:1418–1424

43. Owler BK, Parker G, Halmagyi GM et al (2005) Cranial venous outflow obstruction and pseudotumor Cerebri syndrome. Adv Tech Stand Neurosurg 30:107–174
44. Pickard JD, Czosnyka Z, Czosnyka M, Owler B, Higgins JN (2008) Coupling of sagittal sinus pressure and cerebrospinal fluid pressure in idiopathic intracranial hypertension–a preliminary report. Acta Neurochir Suppl 102:283–285
45. Ahmed R, Friedman DI, Halmagyi GM (2011) Stenting of the transverse sinuses in idiopathic intracranial hypertension. J Neuroophthalmol 31:374–380
46. Stienen A, Weinzierl M, Ludolph A, Tibussek D, Hausler M (2008) Obstruction of cerebral venous sinus secondary to idiopathic intracranial hypertension. Eur J Neurol 15:1416–1418
47. Higgins JN, Pickard JD (2004) Lateral sinus stenoses in idiopathic intracranial hypertension resolving after CSF diversion. Neurology 62:1907–1908
48. Lee SW, Gates P, Morris P, Whan A, Riddington L (2009) Idiopathic intracranial hypertension; immediate resolution of venous sinus "obstruction" after reducing cerebrospinal fluid pressure to < 10cmH(2)O. J Clin Neurosci 16:1690–1692
49. Corbett JJ, Digre K (2002) Idiopathic intracranial hypertension: an answer to, "the chicken or the egg?". Neurology 58:5–6
50. Osterholm JL (1970) Reaction of the cerebral venous sinus system to acute intracranial hypertension. J Neurosurg 32:654–659
51. Riggeal BD, Bruce BB, Saindane AM et al (2013) Clinical course of idiopathic intracranial hypertension with transverse sinus stenosis. Neurology 80:289–295
52. Bedford THB (1935) The effect of increased intracranial venous pressure on the pressure of the cerebrospinal fluid. Brain 58(4):427–447.
53. Ahmed RM, Wilkinson M, Parker GD et al (2011) Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. AJNR Am J Neuroradiol 32:1408–1414
54. Fields JD, Javedani PP, Falardeau J et al (2013) Dural venous sinus angioplasty and stenting for the treatment of idiopathic intracranial hypertension. J Neurointerv Surg 5:62–68
55. Higgins JN, Cousins C, Owler BK, Sarkies N, Pickard JD (2003) Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. J Neurol Neurosurg Psychiatry 74:1662–1666
56. Higgins JN, Owler BK, Cousins C, Pickard JD (2002) Venous sinus stenting for refractory benign intracranial hypertension. Lancet 359:228–230
57. Albuquerque FC, Dashti SR, Hu YC et al (2011) Intracranial venous sinus stenting for benign intracranial hypertension: clinical indications, technique, and preliminary results. World Neurosurg 75:648–652; discussion 592–645
58. Bussiere M, Falero R, Nicolle D, Proulx A, Patel V, Pelz D (2010) Unilateral transverse sinus stenting of patients with idiopathic intracranial hypertension. AJNR Am J Neuroradiol 31:645–650
59. Arac A, Lee M, Steinberg GK, Marcellus M, Marks MP (2009) Efficacy of endovascular stenting in dural venous sinus stenosis for the treatment of idiopathic intracranial hypertension. Neurosurg Focus 27, E14
60. Donnet A, Metellus P, Levrier O et al (2008) Endovascular treatment of idiopathic intracranial hypertension: clinical and radiologic outcome of 10 consecutive patients. Neurology 70:641–647
61. Alper F, Kantarci M, Dane S, Gumustekin K, Onbas O, Durur I (2004) Importance of anatomical asymmetries of transverse sinuses: an MR venographic study. Cerebrovasc Dis 18:236–239
62. Friedman DI (2006) Cerebral venous pressure, intra-abdominal pressure, and dural venous sinus stenting in idiopathic intracranial hypertension. J Neuroophthalmol 26:61–64
63. Mathew NT, Ravishankar K, Sanin LC (1996) Coexistence of migraine and idiopathic intracranial hypertension without papilledema. Neurology 46:1226–1230
64. Bono F, Messina D, Giliberto C et al (2006) Bilateral transverse sinus stenosis predicts IIH without papilledema in patients with migraine. Neurology 67:419–423
65. Vieira DS, Masruha MR, Goncalves AL et al (2008) Idiopathic intracranial hypertension with and without papilloedema in a consecutive series of patients with chronic migraine. Cephalalgia 28:609–613

66. Bono F, Messina D, Giliberto C et al (2008) Bilateral transverse sinus stenosis and idiopathic intracranial hypertension without papilledema in chronic tension-type headache. J Neurol 255:807–812
67. Bruce BB, Kedar S, Van Stavern GP, Corbett JJ, Newman NJ, Biousse V (2010) Atypical idiopathic intracranial hypertension: normal BMI and older patients. Neurology 74:1827–1832
68. Digre KB, Nakamoto BK, Warner JE, Langeberg WJ, Baggaley SK, Katz BJ (2009) A comparison of idiopathic intracranial hypertension with and without papilledema. Headache 49:185–193
69. Maxner CE, Freedman MI, Corbett JJ (1987) Asymmetric papilledema and visual loss in pseudotumour cerebri. Can J Neurol Sci 14:593–596
70. Lepore FE (1992) Unilateral and highly asymmetric papilledema in pseudotumor cerebri. Neurology 42:676–678
71. Schmidt C, Wiener E, Hoffmann J et al (2012) Structural olfactory nerve changes in patients suffering from idiopathic intracranial hypertension. PLoS One 7, e35221
72. Giuseffi V, Wall M, Siegel PZ, Rojas PB (1991) Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. Neurology 41:239
73. Hoffmann J, Huppertz HJ, Schmidt C et al (2013) Morphometric and volumetric MRI changes in idiopathic intracranial hypertension. Cephalalgia 33:1075–1084
74. Hoffmann J, Schmidt C, Kunte H et al (2014) Volumetric assessment of optic nerve sheath and hypophysis in idiopathic intracranial hypertension. AJNR Am J Neuroradiol 35:513–518
75. Degnan AJ, Levy LM (2011) Narrowing of Meckel's cave and cavernous sinus and enlargement of the optic nerve sheath in Pseudotumor Cerebri. J Comput Assist Tomogr 35:308–312
76. Agid R, Farb RI, Willinsky RA, Mikulis DJ, Tomlinson G (2006) Idiopathic intracranial hypertension: the validity of cross-sectional neuroimaging signs. Neuroradiology 48:521–527
77. Jacobson DM, Karanjia PN, Olson KA, Warner JJ (1990) Computed tomography ventricular size has no predictive value in diagnosing pseudotumor cerebri. Neurology 40:1454–1455
78. Higgins JN, Gillard JH, Owler BK, Harkness K, Pickard JD (2004) MR venography in idiopathic intracranial hypertension: unappreciated and misunderstood. J Neurol Neurosurg Psychiatry 75:621–625
79. Wong R, Madill SA, Pandey P, Riordan-Eva P (2007) Idiopathic intracranial hypertension: the association between weight loss and the requirement for systemic treatment. BMC Ophthalmol 7:15
80. Ko MW, Chang SC, Ridha MA et al (2011) Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study. Neurology 76:1564–1567
81. Daniels AB, Liu GT, Volpe NJ et al (2007) Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). Am J Ophthalmol 143:635–641
82. Ireland B, Corbett JJ, Wallace RB (1990) The search for causes of idiopathic intracranial hypertension. A preliminary case-control study. Arch Neurol 47:315–320
83. Ball AK, Clarke CE (2006) Idiopathic intracranial hypertension. Lancet Neurol 5:433–442
84. Johnston I, Paterson A (1974) Benign intracranial hypertension: I. Diagnosis and prognosis. Brain 97:289–300
85. Scoffings DJ, Pickard JD, Higgins JN (2007) Resolution of transverse sinus stenoses immediately after CSF withdrawal in idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 78:911–912
86. Bateman GA, Stevens SA, Stimpson J (2009) A mathematical model of idiopathic intracranial hypertension incorporating increased arterial inflow and variable venous outflow collapsibility. J Neurosurg 110:446–456
87. De Simone R, Marano E, Fiorillo C et al (2005) Sudden re-opening of collapsed transverse sinuses and longstanding clinical remission after a single lumbar puncture in a case of idiopathic intracranial hypertension. Pathogenetic implications. Neurol Sci 25:342–344
88. Maren TH (1988) The kinetics of HCO3- synthesis related to fluid secretion, pH control, and CO2 elimination. Annu Rev Physiol 50:695–717
89. Praetorius J (2007) Water and solute secretion by the choroid plexus. Pflugers Arch (Eur J Physiol) 454:1–18

90. Damkier HH, Brown PD, Praetorius J (2013) Cerebrospinal fluid secretion by the choroid plexus. Physiol Rev 93:1847–1892
91. Speake T, Whitwell C, Kajita H, Majid A, Brown PD (2001) Mechanisms of CSF secretion by the choroid plexus. Microsc Res Tech 52:49–59
92. Kallio H, Pastorekova S, Pastorek J et al (2006) Expression of carbonic anhydrases IX and XII during mouse embryonic development. BMC Dev Biol 6:22
93. Vogh BP, Godman DR, Maren TH (1987) Effect of AlCl3 and other acids on cerebrospinal fluid production: a correction. J Pharmacol Exp Ther 243:35–39
94. Ames A 3rd, Higashi K, Nesbett FB (1965) Effects of Pco2 acetazolamide and ouabain on volume and composition of choroid-plexus fluid. J Physiol 181:516–524
95. Rubin RC, Henderson ES, Ommaya AK, Walker MD, Rall DP (1966) The production of cerebrospinal fluid in man and its modification by acetazolamide. J Neurosurg 25:430–436
96. Cowan F, Whitelaw A (1991) Acute effects of acetazolamide on cerebral blood flow velocity and pCO2 in the newborn infant. Acta Paediatr Scand 80:22–27
97. Gucer G, Viernstein L (1978) Long-term intracranial pressure recording in the management of pseudotumor cerebri. J Neurosurg 49:256–263
98. Ball AK, Howman A, Wheatley K et al (2011) A randomised controlled trial of treatment for idiopathic intracranial hypertension. J Neurol 258:874–881
99. Celebisoy N, Gokcay F, Sirin H, Akyurekli O (2007) Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study. Acta Neurol Scand 116:322–327
100. Wall M, McDermott MP, Kieburtz KD et al (2014) Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA 311:1641–1651
101. Loring DW, Williamson DJ, Meador KJ, Wiegand F, Hulihan J (2011) Topiramate dose effects on cognition: a randomized double-blind study. Neurology 76:131–137
102. Shah VA, Fung S, Shahbaz R, Taktakishvili O, Wall M, Lee AG (2007) Idiopathic intracranial hypertension. Ophthalmology 114:617
103. Jefferson A, Clark J (1976) Treatment of benign intracranial hypertension by dehydrating agents with particular reference to the measurement of the blind spot area as a means of recording improvement. J Neurol Neurosurg Psychiatry 39:627–639
104. McCarthy KD, Reed DJ (1974) The effect of acetazolamide and furosemide on cerebrospinal fluid production and choroid plexus carbonic anhydrase activity. J Pharmacol Exp Ther 189:194–201
105. Melby JM, Miner LC, Reed DJ (1982) Effect of acetazolamide and furosemide on the production and composition of cerebrospinal fluid from the cat choroid plexus. Can J Physiol Pharmacol 60:405–409
106. Reed DJ (1969) The effect of furosemide on cerebrospinal fluid flow in rabbits. Arch Int Pharmacodyn Ther 178:324–330
107. Carta F, Supuran CT (2013) Diuretics with carbonic anhydrase inhibitory action: a patent and literature review (2005–2013). Expert Opin Ther Pat 23:681–691
108. Temperini C, Cecchi A, Scozzafava A, Supuran CT (2009) Carbonic anhydrase inhibitors. Comparison of chlorthalidone, indapamide, trichloromethiazide, and furosemide X-ray crystal structures in adducts with isozyme II, when several water molecules make the difference. Bioorg Med Chem 17:1214–1221
109. Pollay M, Fullenwider C, Roberts PA, Stevens FA (1983) Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure. J Neurosurg 59:945–950
110. Paterson R, Depasquale N, Mann S (1961) Pseudotumor cerebri. Medicine (Baltimore) 40:85–99
111. Elder BD, Rory Goodwin C, Kosztowski TA et al (2015) Venous sinus stenting is a valuable treatment for fulminant idiopathic intracranial hypertension. J Clin Neurosci. http://dx.doi.org/10.1016/j.jocn.2014.10.012
112. Owler BK, Parker G, Halmagyi GM et al (2003) Pseudotumor cerebri syndrome: venous sinus obstruction and its treatment with stent placement. J Neurosurg 98:1045–1055
113. Lueck C, McIlwaine G (2005) Interventions for idiopathic intracranial hypertension. Cochrane Database Syst Rev (3):CD003434
114. Rosenberg ML, Corbett JJ, Smith C et al (1993) Cerebrospinal fluid diversion procedures in pseudotumor cerebri. Neurology 43:1071–1072

115. Menger RP, Connor DE Jr, Thakur JD et al (2014) A comparison of lumboperitoneal and ventriculoperitoneal shunting for idiopathic intracranial hypertension: an analysis of economic impact and complications using the Nationwide Inpatient Sample. Neurosurg Focus 37, E4
116. Sinclair AJ, Kuruvath S, Sen D, Nightingale PG, Burdon MA, Flint G (2011) Is cerebrospinal fluid shunting in idiopathic intracranial hypertension worthwhile? A 10-year review. Cephalalgia 31:1627–1633
117. Kelman SE, Heaps R, Wolf A, Elman MJ (1992) Optic nerve decompression surgery improves visual function in patients with pseudotumor cerebri. Neurosurgery 30:391–395
118. Sergott RC, Savino PJ, Bosley TM (1988) Modified optic nerve sheath decompression provides long-term visual improvement for pseudotumor cerebri. Arch Ophthalmol 106:1384–1390
119. Corbett JJ, Nerad JA, Tse DT, Anderson RL (1988) Results of optic nerve sheath fenestration for pseudotumor cerebri. The lateral orbitotomy approach. Arch Ophthalmol 106:1391–1397
120. Goh KY, Schatz NJ, Glaser JS (1997) Optic nerve sheath fenestration for pseudotumor cerebri. J Neuroophthalmol 17:86–91
121. Spoor TC, McHenry JG (1993) Long-term effectiveness of optic nerve sheath decompression for pseudotumor cerebri. Arch Ophthalmol 111:632–635
122. Schievink WI (2006) Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. JAMA 295:2286–2296
123. Schaltenbrand G (1938) Neuere Anschauungen zur Pathophysiologie der Liquorzirkulation. Zentralbl Neurochir 3:290–300
124. Schaltenbrand G (1953) Normal and pathological physiology of the cerebrospinal fluid circulation. Lancet 1:805–808
125. Schievink WI, Schwartz MS, Maya MM, Moser FG, Rozen TD (2012) Lack of causal association between spontaneous intracranial hypotension and cranial cerebrospinal fluid leaks. J Neurosurg 116:749–754
126. Nosik WA (1955) Intracranial hypotension secondary to lumbar nerve sleeve tear. J Am Med Assoc 157:1110–1111
127. Schievink WI, Ebersold MJ, Atkinson JL (1996) Roller-coaster headache due to spinal cerebrospinal fluid leak. Lancet 347:1409
128. Schievink WI (2000) Spontaneous spinal cerebrospinal fluid leaks: a review. Neurosurg Focus 9, e8
129. Schievink WI, Louy C (2007) Precipitating factors of spontaneous spinal CSF leaks and intracranial hypotension. Neurology 69:700–702
130. Mokri B, Maher CO, Sencakova D (2002) Spontaneous CSF leaks: underlying disorder of connective tissue. Neurology 58:814–816
131. Davenport RJ, Chataway SJ, Warlow CP (1995) Spontaneous intracranial hypotension from a CSF leak in a patient with Marfan's syndrome. J Neurol Neurosurg Psychiatry 59:516–519
132. Fukutake T, Sakakibara R, Mori M, Araki M, Hattori T (1997) Chronic intractable headache in a patient with Marfan's syndrome. Headache 37:291–295
133. Rosser T, Finkel J, Vezina G, Majd M (2005) Postural headache in a child with Marfan syndrome: case report and review of the literature. J Child Neurol 20:153–155
134. Milledge JT, Ades LC, Cooper MG, Jaumees A, Onikul E (2005) Severe spontaneous intracranial hypotension and Marfan syndrome in an adolescent. J Paediatr Child Health 41:68–71
135. Schievink WI, Gordon OK, Tourje J (2004) Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: a prospective study. Neurosurgery 54:65–70
136. Schievink WI, Meyer FB, Atkinson JL, Mokri B (1996) Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. J Neurosurg 84:598–605
137. Reinstein E, Pariani M, Bannykh S, Rimoin DL, Schievink WI (2013) Connective tissue spectrum abnormalities associated with spontaneous cerebrospinal fluid leaks: a prospective study. Eur J Hum Genet 21(4):386–90
138. Schievink WI, Meyer F, Schrijver I, Francke U (1998) A syndrome of spontaneous spinal cerebrospinal fluid leaks and skeletal features of Marfan syndrome. Ann Neurol 44:458
139. Schrijver I, Schievink WI, Godfrey M, Meyer FB, Francke U (2002) Spontaneous spinal cerebrospinal fluid leaks and minor skeletal features of Marfan syndrome: a microfibrillopathy. J Neurosurg 96:483–489

140. Mea E, Franzini A, D'Amico D et al (2011) Treatment of alterations in CSF dynamics. Neurol Sci 32(Suppl 1):S117–S120
141. Schievink WI, Chu RM, Maya MM, Johnson JP, Cohen HC (2013) Spinal manifestations of spontaneous intracranial hypotension. J Neurosurg Spine 18:96–101
142. Mokri B, Posner JB (2000) Spontaneous intracranial hypotension: the broadening clinical and imaging spectrum of CSF leaks. Neurology 55:1771–1772
143. Schievink WI, Dodick DW, Mokri B, Silberstein S, Bousser MG, Goadsby PJ (2011) Diagnostic criteria for headache due to spontaneous intracranial hypotension: a perspective. Headache 51:1442–1444
144. Mea E, Chiapparini L, Savoiardo M et al (2009) Application of IHS criteria to headache attributed to spontaneous intracranial hypotension in a large population. Cephalalgia 29:418–422
145. Mokri B, Piepgras DG, Miller GM (1997) Syndrome of orthostatic headaches and diffuse pachymeningeal gadolinium enhancement. Mayo Clin Proc 72:400–413
146. Fishman RA, Dillon WP (1993) Dural enhancement and cerebral displacement secondary to intracranial hypotension. Neurology 43:609–611
147. Schievink WI, Maya MM, Moser FG, Tourje J (2005) Spectrum of subdural fluid collections in spontaneous intracranial hypotension. J Neurosurg 103:608–613
148. Schievink WI, Maya MM, Louy C, Moser FG, Tourje J (2008) Diagnostic criteria for spontaneous spinal CSF leaks and intracranial hypotension. AJNR Am J Neuroradiol 29:853–856
149. Koss SA, Ulmer JL, Hacein-Bey L (2003) Angiographic features of spontaneous intracranial hypotension. AJNR Am J Neuroradiol 24:704–706
150. Roll JD, Larson TC 3rd, Soriano MM (2003) Cerebral angiographic findings of spontaneous intracranial hypotension. AJNR Am J Neuroradiol 24:707–708
151. Baryshnik DB, Farb RI (2004) Changes in the appearance of venous sinuses after treatment of disordered intracranial pressure. Neurology 62:1445–1446
152. Alvarez-Linera J, Escribano J, Benito-Leon J, Porta-Etessam J, Rovira A (2000) Pituitary enlargement in patients with intracranial hypotension syndrome. Neurology 55:1895–1897
153. Mokri B, Atkinson JL (2000) False pituitary tumor in CSF leaks. Neurology 55:573–575
154. Schoffer KL, Benstead TJ, Grant I (2002) Spontaneous intracranial hypotension in the absence of magnetic resonance imaging abnormalities. Can J Neurol Sci 29:253–257
155. Schievink WI, Tourje J (2000) Intracranial hypotension without meningeal enhancement on magnetic resonance imaging. J Neurosurg 92:475–477
156. Sencakova D, Mokri B, McClelland RL (2001) The efficacy of epidural blood patch in spontaneous CSF leaks. Neurology 57:1921–1923
157. Berroir S, Loisel B, Ducros A et al (2004) Early epidural blood patch in spontaneous intracranial hypotension. Neurology 63:1950–1951
158. Han M-E, Kim H-J, Lee Y-S et al (2009) Regulation of cerebrospinal fluid production by caffeine consumption. BMC Neurosci 10:110
159. Schievink WI, Maya MM, Moser FM (2004) Treatment of spontaneous intracranial hypotension with percutaneous placement of a fibrin sealant. Report of four cases. J Neurosurg 100:1098–1100
160. Gladstone JP, Nelson K, Patel N, Dodick DW (2005) Spontaneous CSF leak treated with percutaneous CT-guided fibrin glue. Neurology 64:1818–1819
161. Schievink WI, Georganos SA, Maya MM, Moser FG, Bladyka M (2008) Anaphylactic reactions to fibrin sealant injection for spontaneous spinal CSF leaks. Neurology 70:885–887
162. Schievink WI, Morreale VM, Atkinson JL, Meyer FB, Piepgras DG, Ebersold MJ (1998) Surgical treatment of spontaneous spinal cerebrospinal fluid leaks. J Neurosurg 88: 243–246
163. Schievink WI, Reimer R, Folger WN (1994) Surgical treatment of spontaneous intracranial hypotension associated with a spinal arachnoid diverticulum. Case report. J Neurosurg 80:736–739
164. Schievink WI, Jacques L (2003) Recurrent spontaneous spinal cerebrospinal fluid leak associated with "nude nerve root" syndrome: case report. Neurosurgery 53:1216–1219. 1210.1227/1201.NEU.0000089483.0000030857.0000089411
165. Schievink WI, Moser FG, Maya MM (2014) CSF–venous fistula in spontaneous intracranial hypotension. Neurology 83:472–473

Medication-Overuse Headache (MOH)

19

Zaza Katsarava

19.1 Historical Note and Nomenclature

Chronic headache following overuse of acute migraine drugs was described first by Horton and Peters. They reported 52 patients with migraine who took ergotamine daily, developed daily headache, and noted improvement after the ergotamine was withdrawn [48].

The International Headache Society originally defined *drug-induced headache* as chronic headache occurring on 15 or more days a month following overuse of any kind of acute headache drugs [46]. This, however, was based on experience with overuse of analgesics and ergots only and did not cover the triptan-induced medication-overuse headache. After triptans were introduced, it became clear that they can also lead to medication-overuse headache [52, 57, 58]. The revised second edition of the classification criteria of the International Headache Society introduced the term *"medication-overuse headache,"* which replaced previous terms such as "drug-induced headache," "analgesic-induced headache," and "rebound headache." It further differentiated between medication-overuse headaches induced by analgesics, ergots, triptans, and opioids [65]. In 2006, an expert board consensus paper introduced of broader concept of medication-overuse headache in which the diagnosis of medication-overuse headache is based on the headache frequency (equal to or greater than 15 days/month) and overuse of headache medication but does not require the headache to improve after withdrawal [64]. In 2013, the International Headache Society published a beta version of the third version of the classification criteria. Here the medication-overuse headache (MOH) is defined in chapter 8 under section 8.2. It has eight subforms: MOH induced by ergotamine, triptans, analgesics

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_19

Table 19.1 8.2 Medication-overuse headache

Diagnostic criteria:
A. Headache occurring on ≥15 days per month in a patient with a preexisting headache disorder
B. Regular overuse for ≥3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Not better accounted for by another ICHD-3 diagnosis

Table 19.2 Subentities of MOH

8.2 Medication-overuse headache
8.2.1 Ergotamine-overuse headache
8.2.2 Triptan-overuse headache
8.2.3 Analgesic-overuse headache
8.2.3.1 Paracetamol (acetaminophen)-overuse headache
8.2.3.2 Acetylsalicylic acid-overuse headache
8.2.3.3 Other nonsteroidal anti-inflammatory drug (NSAID)-overuse headache
8.2.4 Opioid-overuse headache
8.2.5 Combination analgesic-overuse headache
8.2.6 Medication-overuse headache attributed to multiple drug classes not individually overused
8.2.7 Medication-overuse headache attributed to unverified overuse of multiple drug classes
8.2.8 Medication-overuse headache attributed to other medication
8.3 Headache attributed to substance withdrawal
8.3.1 Caffeine-withdrawal headache
8.3.2 Opioid-withdrawal headache
8.3.3 Estrogen-withdrawal headache
8.3.4 Headache attributed to withdrawal from chronic use of other substance

(simple and combined), opioids, undefined multiple drug classes, and others. The authors of the third version stressed the importance of the pharmacological properties of the overused medication and divided simple analgesics into paracetamol, aspirin, and other nonsteroidals. New is also section 8.3 defining withdrawal headache due to withdrawal from opioids, caffeine, estrogens, and other substances.

In general, MOH is defined as headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped. Patients with a preexisting primary headache who, in association with medication overuse, develop a new type of headache or a marked worsening of their preexisting headache that, in either case, meets the criteria for 8.2 Medication-overuse headache (or one of its subtypes), should be given both this diagnosis and the diagnosis of the preexisting headache. Patients who meet criteria for both chronic migraine and 8.2 Medication-overuse headaches should be given both diagnoses [47] (Tables 19.1 and 19.2).

19.2 Clinical Manifestations

Patients with medication-overuse headache are mostly women, on average 40–45 years old. Most of them have migraine, some of them have tension-type headache, or combination of both. On average they suffer from primary headache for 20 years and overuse medication for about 5 years. Simple analgesics or their combination with caffeine is the most frequently overused drug, followed by triptans. In the recant decade, use and overuse of ergots decreased significantly all over the world. In Europe very few patients overuse combination of analgesics with barbiturates, which is much more frequent in the USA [10, 26, 106].

Clinical features of medication-overuse headache seem to depend on the pharmacology of the overused substances. For example, unlike patients who suffer from medication-overuse headaches following ergot or analgesic overuse, migraine patients (but not patients with tension-type headache) who overused triptans did not describe the typical tension-type daily headache but rather a migraine-like daily headache (a unilateral, pulsating headache with autonomic disturbances) or a significant increase in migraine frequency (see the International Headache Society criteria for triptan-induced medication-overuse headache). The delay between the frequent medication intake and the development of daily headache is shortest for triptans (1.7 years), longer for ergots (2.7 years), and longest for analgesics (4.8 years). Hence, triptans do not only cause a different spectrum of clinical features but are able to cause medication-overuse headache faster and with lower dosages than other substance groups [17, 58].

19.3 Epidemiology

Epidemiological studies on the consumption of analgesics in the general population clearly indicate that antiheadache drugs are widely overused all over the world, in developed as well as developing countries. According to these surveys, between 1 and 3 % of the general population take analgesics on a daily basis, and up to 7 % take them at least once a week [43, 85].

Population-based prevalence studies demonstrate that about 1–2 % of the general population suffer from chronic daily headache combined with overuse of headache medication [13, 15, 56, 59, 69, 73, 92]. Studies in Post-Soviet countries reported a significantly higher prevalence of chronic headache of 10 % and of chronic headache with medication overuse of 6 % [5]. A further study in a population of elderly (65 years or older) Chinese subjects revealed a prevalence of 1.3 % of chronic daily headache in combination with analgesic overuse [100].

Single or combined analgesics are the most frequently overused (71 %) headache drugs all over the world.

Meskunas and colleagues performed a retrospective analysis in order to evaluate the overuse of acute headache drugs in a United States center over the past 15 years. The proportion of subjects with a diagnosis of medication-overuse headache remained stable over the years, varying from 64 % of all cases seen in the center in 1990 to 59.3 %

in 2005. The authors found a significant decrease in the relative frequency of probable ergotamine-overuse headache (from 18.6 to 0 %) and in probable combination analgesic-overuse headache (from 42.2 to 13.6 %). The relative frequency increased significantly for the triptans (from 0 to 21.6 %), for simple analgesics (from 8.8 to 31.8 %), and for combinations of acute medications (from 9.8 to 22.7 %). These data indicated that medication-overuse headache remained an important problem in tertiary headache care but that the profile of medication overuse has dramatically changed [60].

Several studies addressed the prevalence of chronic headache in adolescents. One Taiwanese study revealed a prevalence of chronic daily headache in a population of adolescents (12–14 years of age) of 1.5 %. Only 20 % of them overused headache medication, confirming previous findings that medication overuse is less important in children and adolescents [101]. A study from Canada reported a clinical analysis of 1669 children with headache seen in a neurology outpatient clinic. The prevalence of chronic headache was 3 %. The prevalence of medication overuse, however, was significantly higher, about 52 % [61]. Some recent studies report in contrast higher prevalence of pediatric MOH both in GP headache clinic and tertiary headache institutions [71].

19.4 Etiology

The incidence of developing chronic headache for people with episodic headache is about 2–3 % in 1 year [82]. This number, however, is not entirely correct because most of cases resolve spontaneously.

According to the current knowledge, the following risk factors lead to the development of MOH:

19.4.1 Migraine and TTH as Primary Headache

Most headache experts agree that mainly patients with migraine and tension-type headaches have a higher risk to develop medication-overuse headache than patients with no primary headache using analgesics for other diseases. For example, patients who were consuming fairly large amounts of analgesics regularly for arthritis did not show an increased incidence of headache [6, 55]. However, clinical series reported medication-overuse headache in patients with cluster headache [67] and shunted hydrocephalus [23, 105], interestingly in those patients with a positive family history of migraine. In both observations, frequency and intensity of headache decreased after reducing analgesic intake.

19.4.2 Overuse of Any Kind of Acute Headache Medication

A Norwegian study evaluated analgesic use by 32,067 adults in 1984 and again 11 years later. Those who used analgesics daily or weekly at baseline had a higher

risk of developing chronic migraine (RR = 13.3), of chronic nonmigraine headache (RR = 6.2), and of chronic neck pain (RR = 2.4) at follow-up [109]. In a subsequent follow-up 10 years later (HEAD HUNT III), the authors were able to estimate the incidence of MOH to be 0.72 per 1000 person-years (95 % confidence interval 0.62–0.81) and the overuse of tranquilizers [odds ratio 5.2 (3.0–9.0)], or a combination of chronic musculoskeletal complaints, gastrointestinal complaints, and Anxiety and Depression [odds ratio 4.7 (2.4–9.0)], Smoking and physical inactivity as the most important risk factors [45]. A population-based study in the USA identified higher headache frequency at baseline and medication overuse as risk factors for developing of chronic headache [82]. A Danish study investigated a population-based sample of 740 people in 1989 and in 2001 and found that daily intake of analgesics and coexistence of migraine and TTH were associated with frequent headache [1]. The incidence of de novo chronic headache was significantly higher (14 %) in a patient population of a specialized headache clinic in Germany. Patients who used acute headache medication frequently (more than 10 days per month) had a 20-fold increased risk for chronic headache than patients who used acute headache medication fewer than 5 days per month. The risk increased to twofold in patients who used two or more different headache drugs simultaneously [50].

A very important question whether use of specific classes of acute headache drugs bears a higher risk for development of MOH was addressed recently in the American Migraine Prevalence and Prevention (AMPP) Study. Of 8219 individuals with episodic migraine, 209 developed chronic headache during the following year. Thus, the incidence of de novo chronic headache was 2.5 %. People using medication containing barbiturates or opiates had a twofold higher risk to develop chronic headache than those using single analgesics or triptans [10]. A large, population-based, case-control study revealed caffeine consumption to be a modest risk factor for chronic daily headache development [81].

19.4.3 Socioeconomic Status and Obesity

Low socioeconomic status is associated with chronic headache and medication-overuse headache in Norway [44, 102] and was even more prominent in countries in transition, e.g., Russia, Republic of Georgia [5, 51]. This observation was supported in immigrant studies. Wiendels and colleagues found a threefold higher prevalence of chronic headache in immigrants than in a Dutch general population [103]. Kavuk and colleagues observed a sevenfold higher prevalence of chronic headache (21 %) in first-generation Turkish immigrants in Germany than in German natives (3.1 %). Interestingly, prevalence of medication-overuse headache in Turkish immigrants of the second generation (i.e., born in Germany) was 3.6 %. This study clearly demonstrated that poor utilization of adequate medical care in first-generation Turkish immigrants in Germany was a major factor leading to high prevalence of medication-overuse headache [53].

Obesity could be another important risk factor for headache chronification. In a longitudinal 1-year population study, Scher et al. demonstrated that obese

individuals were five times more likely to develop chronic headache than people with normal weight [82]. Another US study found a significant association of obesity with chronic headache [9].

19.4.4 Psychiatric and Other Comorbidities

Several studies dealt with family history and comorbidities of patients' MOH. Depression seems to increase the risk of developing chronic headache by 50 % [2]. It seems that patients' MOH more frequently have a positive family history chronic headache and of substance abuse [14]. Insomnia [80], temporomandibular disorders [20], mood disorders, dependency like behavior [39], or use of psychoactive substances are more frequent in patients with MOH [74], especially in those with preexisting episodic tension-type headache [3].

19.5 Pathogenesis and Pathophysiology

The pathophysiology of medication-overuse headache is unknown. Until now, clarification of the underlying pathophysiology was hampered by the lack of experimental research or suitable animal models. During recent years, however, the number of animal studies has increased significantly demonstrating complex changes in central nervous system following chronic administration of triptans. Reuter and colleagues demonstrated that chronic exposure of triptans causes a downregulation of receptors in trigeminal ganglion and, subsequently, a reduction of receptor function [76]. Chronic administration of sumatriptan and zolmitriptan caused a decrease of the 5-HT synthesis in the dorsal raphe nuclei of the brainstem [30, 97]. Finally, triptan given daily resulted in a sensitization of trigeminal nociception, possibly due to increased expression of neuronal nitric oxide synthase in dural afferents [21]. Chronic application of analgesics resulted in upregulation of pronociceptive 5HT2A receptors of platelets in humans [90], in a significant decrease in the maximum number of 5-HT2A binding sites, and an increase in the maximum number of 5-HT transporter binding sites in the CNS of rats [91].

Genetic studies on medication-overuse headache are ambiguous. Park and colleagues reported an association of a serotonin transporter protein gene polymorphism (short allele) with medication overuse in chronic tension-type headache [68]. In contrast, a recent Italian study did not found significant associations between MOH risk and 5HT2A gene polymorphisms [94]. Another study suggested a possible role of Wolframin His611Arg (WFS1) polymorphism in medication overuse and subsequent medication-overuse headache. Homozygous or compound heterozygous mutations in WFS1 (chromosome 4p16.1) determine Wolfram syndrome, a neurodegenerative disorder associated with diabetes mellitus, diabetes insipidus, hearing loss, progressive blindness, and a heterogenous combination of psychiatric disorders. Heterozygous Wolfram syndrome carriers are prone to develop psychiatric illness or behavioral problems such as impulse control, alcohol, or illicit drug abuse [24].

There is a growing evidence that central sensitization may play an important role in the pathophysiology of chronic headache. A series of investigations using psychophysical and electrophysiological techniques clearly demonstrated a facilitation of trigeminal pain processing in patients with chronic headache. Decreased pain thresholds have been found in patients with chronic tension-type headache [8]. These findings have been confirmed by demonstrating increased amplitudes of laser-evoked cortical potentials in patients with chronic tension-type headache [22]. Ayzenberg and colleagues used a novel technique of simultaneous recording of blink reflex and nociceptive cortical potentials following nociceptive trigeminal stimulation. The authors were able to demonstrate a temporary facilitation of the trigeminal nociceptive system at a supraspinal level that normalized again after withdrawal [4]. Using transcranial magnetic stimulation Curra et al. demonstrated an increase of cortical inhibitory mechanisms in NSAID-induced headache but not in patients overusing triptans [19].

Imaging studies provide further insights into the pathophysiology of medication-overuse headache. The studies are however rather small and findings in details are inconsistent. Overall the available data suggest both structural [77, 83] and functional [32, 36] changes in the pain matrix of the brain. Psychological factors include the reinforcing properties of pain relief by drug consumption, a powerful component of positive conditioning. Many patients report that they take migraine drugs prophylactically because they are worried about missing work or an important social event or they fear an imminent headache. They are often instructed by physicians or by the instructions supplied with the medication to take the migraine drug as early as possible at the start of either the aura or the headache phase of a migraine attack.

Withdrawal headache is an additional factor. When the patient tries to stop or reduce the medication, the preexisting headache worsens. Barbiturates that are contained in drugs used to treat tension-type headache have a high potency for addiction. The stimulating action of analgesics or migraine drugs and their psychotropic side effects, such as sedation or mild euphoria, may lead to drug dependency. Barbiturates, codeine, other opioids, and caffeine are most likely to have this effect. Caffeine increases vigilance, relieves fatigue, and improves performance and mood [41, 42]. The typical symptoms of caffeine withdrawal such as irritability, nervousness, restlessness, and "caffeine-withdrawal headache" [89, 99], which may last for several days, encourage patients to continue their abuse. Despite the fact that caffeine may enhance the analgesic action of acetylsalicylic acid and acetaminophen, caffeine-containing combinations should not be used. Similarly, caffeine and meprobamate, the main metabolite of carisoprodol, should be removed from ergotamine-containing formulations.

Headache patients can develop physical dependence on codeine and other opioids [33, 108]. Although some headache patients have been on codeine for as long as 10 years, no studies have investigated the effects of codeine intake over this time period. It should be remembered that up to 10 % of codeine is metabolized to morphine.

19.6 Differential Diagnosis

All conditions that lead to more than 10–12 headache days per month must be considered in the differential diagnosis of medication-overuse headache. Chronic tension-type headache is a diffuse, dull, nonlocalized headache with or without minimal autonomic features. Headache intensity is lower than that of migraine. Patients find it difficult to describe the character of pain. Sometimes it is described as a feeling of a metal band around the head or a feeling of increased pressure. Many patients with chronic tension-type headache complain of mild autonomic disturbances such as nausea, photophobia, or phonophobia. Chronic tension-type headache with medication overuse can be differentiated from chronic tension-type headache without medication overuse only after drug withdrawal or a drug holiday. If the headache persists, responsibility for chronic headache cannot be attributed to the analgesic intake.

Patients with chronic migraine have a history of episodic migraine attacks that increase in frequency over time. Chronic migraine is diagnosed if patients have daily or almost-daily headaches with migrainous features (e.g., unilateral throbbing pain, nausea or vomiting, photo- and phonophobia, and headache intensity that is increased by physical activity). The majority of patients are women, 90 % of whom have a history of migraine without aura. Chronic migraine has to be distinguished from combination headache, in which patients suffer from chronic tension-type headache along with the daily, pressing, tightening, and bilateral headache from intermittent migraine attacks. It is sometimes impossible to separate migraine from tension-type headache. In these cases, treating at least three headache days with a triptan is recommended. If the headache responds to the triptan, headache prophylaxis is performed as if a migraine exists [28, 38, 95]. The other patients are treated for chronic tension-type headache.

Hemicrania continua patients suffer from daily headache of moderate intensity. Superimposed exacerbation of severe headache with ipsilateral autonomic features such as ptosis, miosis, tearing, and sweating [62, 63] may occur. Some patients have photo- and phonophobia or nausea. In some cases, the head pain alternates sides. Hemicrania continua is differentiated from cluster headache and chronic paroxysmal hemicrania by its continuous pain character; furthermore, the autonomic symptoms during acute pain exacerbations are less pronounced compared with cluster headache or chronic paroxysmal hemicrania.

Patients with new daily persistent headache abruptly develop chronic headache without remission. Many patients remember the exact day the headache started. These patients did not have a previous history of migraine or episodic tension-type headache. In some patients a viral infection was suspected to cause this form of headache [25]. The headache usually does not respond to ergots, triptans, or simple analgesics.

19.7 Prevention

The most important preventive measure is proper instruction and appropriate surveillance of patients. Migraine patients at risk often have a mixture of migraine and tension-type headaches and should be carefully instructed to use specific

antimigraine drugs for migraine attacks only. This point was already stressed in 1951 by Peters and Horton concerning ergotamine abuse. For example, complications can be avoided if enough time is taken to properly instruct the patient, so that he or she can distinguish between vasodilating and nondilating headache [70].

Restricting the number of doses of any kind of acute headache and migraine drugs to ten doses per month can be effective to avoid medication overuse. Migraine drugs that contain barbiturates, caffeine, codeine, or tranquilizers, as well as mixed analgesics, should be avoided at all. Patients who take nonprescription medication should be advised to avoid caffeine combinations. Early migraine prophylaxis, either by medical or behavioral treatment, can be a preventive measure to avoid chronic headache.

19.8 Management

Management of MOH should be performed using multimodal approach (e.g., involving psychologists and physiotherapists), which results in significant improvement of headache, improvement of well-being, and a reduction of the illness-related costs. On average about 70 % of patients improve significantly. The medication-related costs decrease by 25 %, in patients overusing triptans by 43 % [86].

Abrupt drug withdrawal is the treatment of choice for medication-overuse headache. The typical withdrawal symptoms last for 2–10 days (average 3.5 days) and include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness. The withdrawal phase is much shorter when patients are abusing only triptans. Seizures or hallucinations were only rarely observed, even in patients who were abusing barbiturate-containing migraine drugs.

Drug withdrawal is performed differently. A consensus paper by the German Neurological Society recommends outpatient withdrawal for patients who do not take barbiturates or tranquilizers with their analgesics and are highly motivated [29]. Patients who take tranquilizers, codeine, or barbiturates and who failed to withdraw the drugs as outpatients or who have a high depression score should have inpatient treatment. The decision of withdrawal setting, however, differs and depends on the political and economic circumstances in different countries. The medical evidence is scarce. Several studies compared the efficacy of inpatient versus outpatient withdrawal and reported no differences between the two settings [18, 78, 93]. Another recent study demonstrated that psychological education alone is equally effective as cognitive behavioral contact program [35]. Therefore, we suggest an outpatient withdrawal in the first instance in uncomplicated patients with MOH. Patients with psychiatric or psychological comorbidities should be treated using multidisciplinary treatment approach [37]. Italian headache group from Pavia established a stratified approach for MOH patients with and without comorbidities. They were able to show that simple MOH can be treated equally successfully using in- and outpatient approach, while more complicated patients (e.g., psychiatric comorbidities or overuse of benzodiazepines or barbiturates) should be admitted to the hospital [79].

Treatment recommendations for the acute phase of drug withdrawal vary considerably between studies. They include fluid replacement, analgesics, tranquilizers, neuroleptics, amitriptyline, valproate, intravenous dihydroergotamine, oxygen, and electrical stimulation. Studies on cortisone to reduce withdrawal headache are ambiguous. The first open trial showed that cortisone effectively reduced withdrawal symptoms, including rebound headache [54]. A small pilot placebo controlled study in Germany demonstrated the superiority of oral prednisone 100 mg toward placebo [66]. Larger studies from Norway and Germany, however, were negative ([11]; Rabe et al, 201).

When evaluating chronic headache patients, it is necessary to take a careful history. These patients frequently take several different substances daily despite the fact that their effect is negligible. This behavior is merely an attempt to avoid a disabling withdrawal headache. Patients should record their present and prior use of prescription drugs and nonprescription compounds and caffeine intake. Many patients also abuse other substances, such as tranquilizers, opioids, decongestants, and laxatives. It is often helpful for patients to keep a diagnostic headache diary for 1 month in order to actually record headache patterns and drug use. History and examination should also search for possible complications of regular drug intake, such as recurrent gastric ulcers, anemia, and ergotism. A good indicator is the number of physicians the patient has consulted and the number of previous unsuccessful therapies. One study showed that headache patients had consulted an average of 5.5 physicians who had prescribed 8.6 different therapies [27].

A short hospital stay is recommended if medication-overuse headache has lasted more than 5 years when additional tranquilizer, barbiturate, or opioid intake exists. It is further indicated for patients who have failed outpatient withdrawal or have concomitant depression or anxiety disorder. In the hospital, all pain or headache medication is stopped abruptly. Fluids should be replaced by infusion if frequent vomiting occurs. Vomiting can be treated with antiemetics (e.g., metoclopramide or domperidone). The withdrawal headache can be treated with nonsteroidal antiinflammatory drugs (e.g., naproxen 500 mg twice daily). In some countries, aspirin is available in injectable form and 1000 mg are given every 8–12 h. If the headache has migrainous features and the patient has not abused ergotamine, intravenous dihydroergotamine 1–2 mg every 8 h is given [75, 87, 88]. Prednisone 100 mg on the first day, tapering by 20 mg for the next days, is highly effective. Symptoms of opioid withdrawal can be treated with clonidine. The initial dose is 0.1–0.2 mg three times daily, and this is titrated up or down based on withdrawal symptoms (tachycardia, tremor, sleeping disturbances). Some patients may require anxiolytic medication; this should be given for no longer than a week. Patients need the support of treating physicians and nurses as well as encouragement from family and friends. Behavioral techniques such as relaxation therapy and stress management should be initiated as soon as the withdrawal symptoms fade.

Outpatient treatment is advised for patients who take monosubstances or analgesic mixtures not containing barbiturates or codeine. Patients whose original headache is migraine can start prophylactic medication 4 weeks before withdrawal.

Beta-blockers will improve withdrawal symptoms such as restlessness, tachycardia, or tremor. Patients who have chronic tension-type headache may be started on a tricyclic antidepressant 4 weeks prior to detoxification (e.g., amitriptyline 10 mg increasing to 25–75 mg at nighttime). Ergots, triptans, and nonopioid drugs should be stopped abruptly. Opioids and barbiturates should be withdrawn more slowly depending on the dose and duration of intake. Withdrawal headache after ergots and triptans can be treated with oral or parenteral nonsteroidal anti-inflammatory drugs (e.g., 500 mg naproxen three times daily for 5–7 days).

If a patient experiences more than three migraine attacks a month after withdrawal, medical and behavioral prophylaxis should be initiated. Clinical experience shows that many patients respond to prophylactic treatment with beta-blockers, flunarizine, or valproic acid after drug withdrawal despite the fact that these drugs had been unsuccessful before [16]. Ergotamine, triptans, and possibly analgesics counteract the action of prophylactic therapy and will not improve drug-induced headache. The same phenomenon can be observed for the action of amitriptyline and behavioral therapy in patients with tension-type headache.

19.9 Prognosis and Complications

Several studies have dealt with the long-term outcome of patients with medication-overuse headache after successful withdrawal therapy. Success is defined as no headache at all or an improvement of more than 50 % in terms of headache days. The success rate of withdrawal therapy within a time window of the first year months is about 70 % [7, 12, 27, 40, 84, 104, 107]. Studies with longer observation time up 6 years reported relapse rates between 40 and 50 % [31, 34, 72, 84, 98]. Predictors for relapses after successful withdrawal therapy remain difficult to analyze. Two aspects appear to be important: the type of primary headache (patients with tension-type headache or cooccurrence of migraine and tension-type headache have a higher relapse risk) [27, 31, 49, 84] and a longer duration of regular drug intake [72, 96].

References

1. Ashina S, Lyngberg A, Jensen R (2010) Headache characteristics and chronification of migraine and tension-type headache: a population-based study. Cephalalgia 30:943–952
2. Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC, Reed ML, Buse DC (2012) Depression and risk of transformation of episodic to chronic migraine. J Headache Pain 13:615–624
3. Atasoy HT, Atasoy N, Unal AE, Emre U, Sumer M (2005) Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. Eur J Pain 9:285–291
4. Ayzenberg I, Obermann M, Nyhuis P et al (2006) Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures. Cephalalgia 26:1106–1114

5. Ayzenberg I, Katsarava Z, Sborowski A, Chernysh M, Osipova V, Tabeeva G, Yakhno N, Steiner TJ (2012) Lifting the Burden. The prevalence of primary headache disorders in Russia: a countrywide survey. Cephalalgia 32:373–381
6. Bahra A, Walsh M, Menon S, Goadsby PJ (2003) Does chronic daily headache arise de novo in association with regular analgesic use? Headache 43:179–190
7. Baumgartner C, Wessely P, Bingol C, Maly J, Holzner F (1989) Long-term prognosis of analgesic withdrawal in patients with drug-induced headaches. Headache 29:510–514
8. Bendtsen L, Jensen R, Olesen J (1996) Decreased pain detection and tolerance thresholds in chronic tension-type headache. Arch Neurol 53:373–376
9. Bigal ME, Liberman JN, Lipton RB (2006) Obesity and migraine. A population study. Neurology 66:545–550
10. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population based study. Headache 48:1157–1168
11. Boe MG, Mygland A, Salvesen R (2007) Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. Neurology 69:26–31
12. Boe MG, Salvesen R, Mygland A (2009) Chronic daily headache with medication overuse: predictors of outcome 1 year after withdrawal therapy. Eur J Neurol 16:705–712
13. Castillo J, Munoz P, Guitera V, Pascual J (1999) Epidemiology of chronic daily headache in the general population. Headache 39:190–196
14. Cevoli S, Sancisi E, Grimaldi D, Pierangeli G, Zangini S, Nicodemo M, Cortelli P, Montagna P (2009) Family history for chronic headache and drug overuse as a risk factor for headache chronification. Headache 49:412–418
15. Colas R, Munoz P, Temprano R, Gomez C, Pascual J (2004) Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology 27:1338–1342
16. Coskun O, Ucler S, Cavdar L, Inan LE (2007) Effect of valproic acid on withdrawal therapy in patients with overuse of chronic daily headache medications. J Clin Neurosci 14:334–339
17. Creac'h C, Radat F, Mick G, Guegan-Massardier E, Giraud P, Guy N, Fabre N, Nachit-Quinekh F, Lanteri-Minet M (2009) One or several types of triptan overuse headaches? Headache 49:519–528
18. Créac'h C, Frappe P, Cancade M, Laurent B, Peyron R, Demarquay G, Navez M (2011) In-patient versus out-patient withdrawal programmes for medication overuse headache: a 2-year randomized trial. Cephalalgia 31:1189–1198
19. Currà A, Coppola G, Gorini M, Porretta E, Bracaglia M, Di Lorenzo C, Schoenen J, Pierelli F (2011) Drug induced changes in cortical inhibition in medication overuse headache. Cephalalgia 31:1282–1290
20. da Silva JA, Costa EC, Gomes JB, Leite FM, Gomez RS, Vasconcelos LP, Krymchantowski A, Moreira P, Teixeira AL (2010) Chronic headache and comorbibities: a two-phase, population-based, cross-sectional study. Headache 50:1306–1312
21. De Felice M, Ossipov MH, Wang R, Dussor G, Lai J, Meng ID, Chichorro J, Andrews JS, Rakhit S, Maddaford S, Dodick D, Porreca F (2010) Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. Brain 133:2475–2488
22. de Tommaso M, Libro G, Guido M, Sciruicchio V, Losito L, Puca F (2003) Heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in chronic tension-type headache. Pain 104:111–119
23. deSouza RM, Toma A, Watkins L (2014) Medication overuse headache – an under-diagnosed problem in shunted idiopathic intracranial hypertension patients. Br J Neurosurg 19:1–5
24. Di Lorenzo C, Sances G, Di Lorenzo G, Rengo C, Ghiotto N, Guaschino E, Perrotta A, Santorelli FM, Grieco GS, Troisi A, Siracusano A, Pierelli F, Nappi G, Casali C (2007) The Wolframin His 611Arg polymorphism influences medication overuse headache. Neurosci Lett 424:179–184
25. Diaz-Mitoma F, Vanast WJ, Tyrrell DL (1987) Increased frequency of Epstein-Barr-virus excretion in patients with new daily persistent headaches. Lancet 1:411–414

26. Diener HC, Dahlof CG (1999) Headache associated with chronic use of substances. In: Olesen J, Tfelt-Hansen P, Welch KM (eds) The headaches, 2nd edn. Lippincott, Williams & Wilkins, Philadelphia, pp 871–878
27. Diener HC, Dichgans J, Scholz E, Geiselhart S, Gerber WD, Bille A (1989) Analgesic-induced chronic headache: long-term results of withdrawal therapy. J Neurol 236:9–14
28. Diener HC, Wilkinson M (1988) Drug-induced headache. Springer, New-York
29. Diener HC, Evers S, Fritsche G, Katsarava Z, Kropp P, Limmroth V, May A, Meyer U, Pfaffenrath V. Medication overuse headache. In: Diener HC (ed) Guidelines of the German Society of neurology. Thieme Verlag 2009.
30. Dobson CF, Tohyama Y, Diksic M, Hamel E (2004) Effects of acute or chronic administration of anti-migraine drugs sumatriptan and zolmitriptan on serotonin synthesis in the rat brain. Cephalalgia 24:2–11
31. Evers S, Suhr B, Bauer B, Grotemeyer KH, Husstedt IW (1999) A retrospective long-term analysis of the epidemiology and features of drug-induced headache. J Neurol 246:802–809
32. Ferraro S, Grazzi L, Mandelli ML, Aquino D, Di Fiore D, Usai S, Bruzzone MG, Di Salle F, Bussone G, Chiapparini L (2012) Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) Study. Pain Med 13:255–262
33. Fisher MA, Glass S (1997) Butorphanol (Stadol): a study in problems of current drug information and control. Neurology 48:1156–1160
34. Fritsche G, Eberl A, Katsarava Z, Limmroth V, Diener HC (2001) Drug-induced headache: long-term follow-up of withdrawal therapy and persistence of drug misuse. Eur Neurol 45:229–235
35. Fritsche G, Frettlooh J, Hüppe M, Dlugaj M, Matatko N, Gaul C, Diener HC (2010) Prevention of medication overuse in patients with migraine. Pain 151:404–413
36. Fumal A, Laureys S, Di Clemente L et al (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain 129:543–550
37. Gaul C, van Doorn C, Webering N, Dlugaj M, Katsarava Z, Diener HC, Fritsche G (2011) Clinical outcome of a headache-specific multidisciplinary treatment program and adherence to treatment recommendations in a tertiary headache center: an observational study. J Headache Pain 12:475–483
38. Goadsby PJ (1997) How do the currently used prophylactic agents work in migraine? Cephalalgia 17:85–92
39. Grande RB, Aaseth K, Saltyte-Benth J, Gulbrandsen P, Russel MB, Lundquist C (2009) The severity of Dependence Scale detects people with medication overuse: Akershus study of chronic headache. J Neurol Neurosurg Psychiatry 80:784–789
40. Grazzi L, Andrasik F, D'Amico D et al (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. Headache 42:483–490
41. Griffiths RR, Woodson PP (1988) Caffeine physical dependence: a review of human and laboratory animal studies. Psychopharmacology (Berl) 94:437–451
42. Griffiths RR, Woodson PP (1988) Reinforcing properties of caffeine: studies in humans and laboratory animals. Pharmacol Biochem Behav 29:419–427
43. Gutzwiller F, Zemp E (1986) Der Analgetikakonsum in der Bevölkerung und socioökonomische Aspekte des Analgetikaabusus. In: Mihatsch MJ (ed) Das Analgetikasyndrom. Thieme, Stutgart, p 197
44. Hagen K, Vatten L, Stovner LJ et al (2002) Low socio-economic status is associated with increased risk of frequent headache: a prospective study of 22718 adults in Norway. Cephalalgia 22:672–679
45. Hagen K, Linde M, Steiner TJ, Stovner LJ, Zwart JA (2012) Risk factors for medication-overuse headache: an 11-year follow-up study. The Nord-Trøndelag Health Studies. Pain 153:56–61
46. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8(Suppl 7):1–93

47. Headache Classification Committee of the International Headache Society (2013) The international classification of headache disorders 3rd edition (beta version). Cephalalgia 33(9):629–808
48. Horton BT, Peters GA (1963) Clinical manifestations of excessive use of ergotamine preparations and management of withdrawal effect: report of 52 cases. Headache 3:214–226
49. Katsarava Z, Limmroth V, Finke M, Diener HC, Fritsche G (2003) Rates and predictors for relapse in medication overuse headache: a 1-year prospective study. Neurology 60: 1682–1683
50. Katsarava Z, Schneeweiss S, Kurth T et al (2004) Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 62:788–790
51. Katsarava Z, Dzagnidze A, Kukava M, Mirvelashvili E, Djibuti M, Janelidze M, Jensen R, Stovner LJ, Steiner TJ (2009) Primary headache disorders in the Republic of Georgia: prevalence and risk factors. Neurology 73:1796–1803
52. Kaube H, May A, Diener HC, Pfaffenrath V (1994) Sumatriptan misuse in daily chronic headache. BMJ 308:1573
53. Kavuk I, Weimar C, Kim BT et al (2006) One-year prevalence and socio-cultural aspects of chronic headache in Turkish immigrants and German natives. Cephalalgia 26:1177–1181
54. Krymchantowski AV, Barbosa JS (2000) Prednisone as initial treatment of analgesic-induced daily headache. Cephalalgia 20:107–113
55. Lance F, Parkes C, Wilkinson M (1988) Does analgesic abuse cause headache de novo? Headache 38:61–62
56. Lanteri-Minet M, Auray JP, El Hasnaoui A et al (2003) Prevalence and description of chronic daily headache in the general population in France. Pain 102:143–149
57. Limmroth V, Kazarawa S, Fritsche G, Diener HC (1999) Headache after frequent use of new 5-HT agonists zolmitriptan and naratriptan. Lancet 353:378
58. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC (2002) Features of medication overuse headache following overuse of different acute headache drugs. Neurology 59: 1011–1014
59. Lu SR, Fuh JL, Chen WT, Juang KD, Wang SJ (2001) Chronic daily headache in Taipei, Taiwan: prevalence, follow-up and outcome predictors. Cephalalgia 21:980–986
60. Meskunas CA, Tepper SJ, Rapoport AM et al (2006) Medications associated with probable medication overuse headache reported in a tertiary care headache center over a 15-year period. Headache 46:766–772
61. Moore AJ, Shevell M (2004) Chronic daily headaches in pediatric neurology practice. J Child Neurol 19:925–929
62. Newman LC, Lipton RB, Russell M, Solomon S (1992) Hemicrania continua: attacks may alternate sides. Headache 32:237–238
63. Newman LC, Lipton RB, Solomon S (1993) Hemicrania continua: 7 new cases and a literature review. Headache 32:267
64. Olesen J, Bousser MG, Diener HC et al (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
65. Olesen J, Lipton RB (2004) Headache classification update 2004. Curr Opin Neurol 17: 275–282
66. Pageler L, Katsarava Z, Diener HC, Limmroth V (2008) Prednisone vs. placebo in withdrawal therapy following medication overuse headache. Cephalalgia 28:152–156
67. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ (2006) Medication-overuse headache in patients with cluster headache. Neurology 67:109–113
68. Park JW, Kim JS, Kim YI, Lee KS (2005) Serotonergic activity contributes to analgesic overuse in chronic tension-type headache. Headache 45:1229–1235
69. Park JW, Moon HS, Kim JM, Lee KS, Chu MK (2014) Chronic daily headache in Korea: prevalence, clinical characteristics, medical consultation and management. J Clin Neurol 10:236–243
70. Peters GA, Horton BT (1951) Headache: with special reference to the excessive use of ergotamine preparations and withdrawal effects. Proc Staff Meet Mayo Clin 26:153–161

71. Piazza F, Chiappedi M, Maffioletti E, Galli F, Balottin U (2012) Medication overuse headache in school-aged children: more common than expected? Headache 52:1506–1510
72. Pini LA, Cicero AF, Sandrini M (2001) Long-term follow-up of patients treated for chronic headache with analgesic overuse. Cephalalgia 21:878–883
73. Prencipe M, Casini AR, Ferretti C et al (2001) Prevalence of headache in an elderly population: attack frequency, disability, and use of medication. J Neurol Neurosurg Psychiatry 70:377–381
74. Radat F, Creac'h C, Swendsen JD et al (2005) Psychiatric comorbidity in the evolution from migraine to medication overuse headache. Cephalalgia 25:519–522
75. Raskin NH (1986) Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology 36:995–997
76. Reuter U, Salomone S, Ickstein GW, Waeber C (2004) Effects of chronic sumatriptan and zolmitriptan treatment on 5-HAT receptor expression and function in rats. Cephalalgia 24:398–407
77. Riederer F, Marti M, Luechinger R, Lanzenberger R, von Meyenburg J, Gantenbein AR, Pirrotta R, Gaul C, Kollias S, Sándor PS (2012) Grey matter changes associated with medication-overuse headache: correlations with disease related disability and anxiety. World J Biol Psychiatry 13:517–525
78. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G (2006) Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. Cephalalgia 26:1097–1105
79. Rossi P, Faroni JV, Tassorelli C, Nappi G (2013) Advice alone versus structured detoxification programmes for complicated medication overuse headache (MOH): a prospective, randomized, open-label trial. J Headache Pain 14:10
80. Sancisi E, Cevoli S, Vignatelli L, Nicodemo M, Pierangeli G, Zanigni S, Grimaldi D, Cortelli P, Montagna P (2010) Increased prevalence of sleep disorders in chronic headache: a case-control study. Headache 50:1464–1472
81. Scher AI, Stewart WF, Lipton RB (2004) Caffeine as a risk factor for chronic daily headache: a population-based study. Neurology 63:2022–2027
82. Scher AI, Stewart WF, Ricci JA, Lipton RB (2003) Factors associated with the onset and remission of chronic daily headache in a population–based study. Pain 106:81–89
83. Schmidt-Wilcke T, Leinisch E, Straube A et al (2005) Gray matter decrease in patients with chronic tension type headache. Neurology 65:1483–1486
84. Schnider P, Aull S, Baumgartner C et al (1996) Long-term outcome of patients with headache and drug abuse after inpatient withdrawal: five year follow-up. Cephalalgia 16:481–485
85. Schwarz A, Farber U, Glaeske G (1985) Daten zu Analgetikakonsum und Analgetikanephropathie in der Bundesrepublik. Öffent Gesundheitswes 47:298
86. Shah AM, Bendtsen L, Zeeberg P, Jensen RH (2013) Reduction of medication costs after detoxification for medication-overuse headache. Headache 53:665–672
87. Silberstein SD, Schulman EA, McFaden Hopkins M (1990) Repetitive intravenous DHE in the treatment of refractory headache. Headache 30:334–339
88. Silberstein SD, Silberstein JR (1992) Chronic daily headache: long-term prognosis following inpatient treatment with repetitive intravenous DHE. Headache 32:439–445
89. Silverman K, Evans SM, Strain EC, Griffiths RR (1992) Withdrawal syndrome after the double-blind cessation of caffeine consumption. N Engl J Med 327:1109–1114
90. Srikiatkhachorn A, Anthony M (1996) Platelet serotonin in patients with analgesic-induced headache. Cephalalgia 16:423–426
91. Srikiatkhachorn A, Tarasub N, Govitrapong P (2000) Effect of chronic analgesic exposure on the central serotonin system: a possible mechanism of analgesic abuse headache. Headache 40:343–350
92. Straube A, Pfaffenrath V, Ladwig KH, Meisinger C, Hoffmann W, Fendrich K, Vennemann M, Berger K (2010) Prevalence of chronic migraine and medication overuse headache in Germany – the German DMKG headache study. Cephalalgia 30:207–213

93. Suhr B, Evers S, Bauer B, Gralow I, Grotemeyer KH, Husstedt IW (1999) Drug-induced headache: long-term results of stationary versus ambulatory withdrawal therapy. Cephalalgia 19:44–49
94. Terrazzino S, Sances G, Balsamo F, Viana M, Monaco F, Bellomo G, Martignoni E, Tassorelli C, Nappi G, Canonico PL, Genazzani AA (2010) Role of 2 common variants of 5HT2A gene in medication overuse headache. Headache 50:1587–1596
95. Tfelt-Hansen P (1995) Prophylactic treatment of migraine: evaluation of clinical trials and choice among drugs. Cephalalgia S15:29–32
96. Tfelt-Hansen P, Krabbe AA (1981) Ergotamine abuse: do patients benefit from withdrawal? Cephalalgia 1:29–31
97. Tohyama Y, Yamane F, Fikre Merid M, Blier P, Diksic M (2002) Effects of serotonin receptor agonists, TFMPP and CGS12066B, on regional serotonin synthesis in the rat brain: an autoradiographic study. J Neurochem 80:788–798
98. Tribl GG, Schnider P, Wober C et al (2001) Are there predictive factors for long-term outcome after withdrawal in drug-induced chronic daily headache? Cephalalgia 21:691–696
99. van Dusseldorp M, Katan MB (1990) Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. Br Med J 300:1558–1559
100. Wang SJ, Fuh JL, Lu SR et al (2000) Chronic daily headache in Chinese elderly: prevalence, risk factors, and biannual follow-up. Neurology 54:314–319
101. Wang SJ, Fuh JL, Lu SR, Juang KD (2006) Chronic daily headache in adolescents. Prevalence, impact, and medication overuse. Neurology 66:193–197
102. Westergaard ML, Glümer C, Hansen EH, Jensen RH (2014) Prevalence of chronic headache with and without medication overuse: associations with socioeconomic position and physical and mental health status. Pain 11:S0304–S3959
103. Wiendels NJ, Knuistingh Neven A, Rosendaal FR et al (2006) Chronic frequent headache in the general population: prevalence and associated factors. Cephalalgia 26:1434–1442
104. Williams DR, Stark RJ (2003) Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia 23:963–971
105. Willer L, Jensen RH, Juhler M (2010) Medication overuse as a cause of chronic headache in shunted hydrocephalus patients. J Neurol Neurosurg Psychiatry 81:1261–1264
106. Zeeberg P, Olesen J, Jensen R (2006) Probable medication-overuse headache: the effect of a 2-month drug-free period. Neurology 66:1894–1898
107. Zidverc-Trajkovic J, Pekmezovic T, Jovanovic Z, Pavlovic A, Mijajlovic M, Radojicic A, Sternic N (2007) Medication overuse headache: clinical features predicting treatment outcome at 1-year follow-up. Cephalalgia 27:1219–1225
108. Ziegler DK (1994) Opiate and opioid use in patients with refractory headache. Cephalalgia 14:5–10
109. Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J (2003) Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT Study. Neurology 61:160–164

Painful Cranial Neuropathies

20

Joanna M. Zakrzewska

20.1 Introduction

20.1.1 General Principles

The cranial neuropathies in the area of the face are relatively rare and so there are few high-quality randomised controlled trials (RCTs) on which to put forward guidance. In some areas, e.g. glossopharyngeal neuralgia there are none. In those cases results are extrapolated, e.g. post-herpetic neuralgia of the trigeminal divisions is managed according to the general guidelines for post-herpetic neuralgia. Often drugs are used off licence and this makes for more difficulties when primary care physicians are asked to continue prescriptions. It is also important to remember that in the pain field a 50 % reduction in pain is considered a successful treatment. If RCTs have been done then it is often possible to calculate the so-called number needed to treat (NNT) and the lower this is the better the medication. There is a number needed to harm (NNH) and if this is low then the incidence of side effects will be high. There is an increasing tendency to add medications but rarely are medication reviews done to exclude drugs that are no longer effective [39]. There is virtually no evidence for the use of polypharmacy in any of the conditions covered in this chapter and yet many patients are on polypharmacy including opioids when referred to specialist centres.

Care needs to be taken when prescribing medications and providing written information, and personalised schedules go a long way in helping patients optimise drug regimes. Clinical nurse specialists with prescribing rights can provide invaluable help. Medications should be carefully reviewed and some forms of more objective measures are used. In our unit we use the Brief Pain Inventory – Facial

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_20

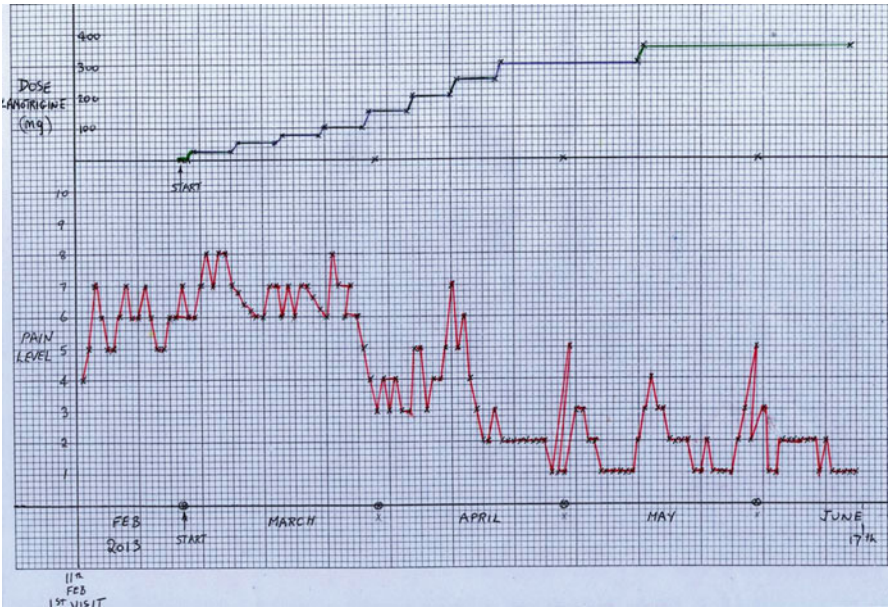

Fig. 20.1 Diary of patient reporting severity of pain on a scale of 0–10 and drug dosage (lamotrigine) over time

[24] which not only provides details of pain levels but also quality of life which can be affected not just by pain but also by the side effects of drugs. We use the Adverse Events Profile questionnaire [4] which has enabled us to evaluate the adverse effects of carbamazepine and oxcarbazepine [9].

Patients should be encouraged to keep pain diaries to evaluate outcomes which can be the ones they devised themselves or from various apps available on the Internet. Figure 20.1 illustrates such a one made by the patient and clearly shows the advantage of changing from carbamazepine to lamotrigine. It is important that these diaries are not kept continuously but at points in time when changes are occurring. These can be extremely useful in review consultations to determine not only dosages but also schedules. Many new patients with trigeminal neuralgia will not be aware that they should take their medications before a meal in order to be able to eat a meal, as this can be a major trigger factor if drug levels have fallen. Patients can therefore take control and be prescribed medications on a sliding scale especially for conditions like trigeminal neuralgia which vary considerably in pain intensity.

Medications will only provide partial relief, so combining them with psychological strategies can lead to significant improvement in outcomes. Systematic reviews have shown that cognitive behaviour techniques for chronic pain can have a significant impact on quality of life and hence patients' abilities to cope with their pain [31]. There is less evidence for their use in orofacial pain [1]. These are often delivered face to face but online ones are also available [29]. Allaying patients' fears and changing beliefs about their pain will have a marked impact on their ability to respond to further management with both medications and psychology [6].

20.1.2 Clinical Trials in Trigeminal Neuropathies

There are a variety of reasons for why there are so few trials in this area. The conditions are rare and so one centre will not be able to recruit enough patients for an adequately powered study. A recent trial of a new drug for trigeminal neuralgia needed 11 countries and 27 centres in order to recruit 30 to the full trial [43]. There are no biomarkers for any of these conditions and so diagnosis is based solely on history and examination and will be dependent on the expertise of the clinician and patients' ability to recall details. The changes in the diagnostic criteria seen between different versions of the IHCH classification [2, 3], are ample evidence of the difficulties in agreeing on criteria. These need to be very precise in clinical trials. Patients with rare conditions are often reluctant to volunteer for RCTs as they are concerned that they will be allocated to placebo or the current best drug rather than the new one [22]. RCTs are often of short duration which may not provide sufficient time for the effects of the drug to be noted nor for their adverse effects to become evident. Many of these conditions are very severe and so designs with placebo controls cannot be used. An active control may not be possible due to drug interactions as is found in trials in trigeminal neuralgia (TN) [43]. Another major concern in trials in TN is that spontaneous remissions are common especially in the early stages of the disease. Thus, recruiting patients with a short duration of the disease may bias towards a favourable outcome as may have occurred in one study in the field of trigeminal neuralgia [25]. These factors have recently been considered by the NeupSig group and shown how significantly they can affect outcomes [13].

20.2 Trigeminal Neuralgia, Classical, with Concomitant Pain

Trigeminal Neuralgia TN is defined by the Headache Classification Committee of the International Headache Society as "A disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. There may or may not be, additionally, persistent background facial pain of moderate intensity" [2].

Patients with classical-type TN do not have any background pain whereas the patients with some background pain are described as classical trigeminal neuralgia with concomitant persistent facial pain. The background pain may be continuous or only be present for several hours [28]. None of the current trials are specific about this distinction and yet Maarbjerg et al. [28] suggest that those with background pain have a poorer response to anti-epileptic drugs (AEDs). There is also a general consensus that patients with multiple sclerosis (MS) have reduced efficacy and tolerability to AEDs when used to manage their TN.

The first drug to be shown to have a significant impact on TN was phenytoin in 1942 and then in 1962 the landmark paper by Blom established carbamazepine as a very effective drug [8]. Baclofen, valproate and clonazepam were the next series of drugs used and except for baclofen the reports were all case series. Subsequently

Table 20.1 Commonest drugs in use for trigeminal neuralgia to gain 50 % pain relief

Drug/therapy	Daily dose range	Efficacy	Side effects/comments
Evidence from RCT			
Baclofen	50–80 mg used as four times a day	Good	Ataxia, lethargy, fatigue, nausea, vomiting, beware of rapid withdrawal, useful in MS
Carbamazepine	300–1000 mg used as four times a day	Excellent number needed to treat 2	Drowsiness, ataxia, cognitive impairment, gastrointestinal, diplopia, rash, introduce slowly, drug interactions common, regular monitoring
Lamotrigine	200–400 mg used as twice a day	Good when added to other anti-epileptics	Dizziness, drowsiness, cognitive impairment, constipation, ataxia, diplopia, irritability, rapid dose escalation leads to rashes
Gabapentin	1800–3600 mg used as three times a day	Good	Drowsiness, cognitive impairment, ataxia, oedema, weight gain
Oxcarbazepine	300–1200 mg used as four times a day	Excellent	Fatigue, dizziness, cognitive impairment, nausea, hyponatraemia in high doses, no major drug interactions
Case series only			
Phenytoin	200–300 mg used as three times a day	Good	Drowsiness, ataxia, cognitive impairment, gastrointestinal, diplopia, easy to overdose
Pregablin	300–600 mg used as twice a day	Good	Drowsiness, cognitive impairment, ataxia, gastrointestinal, oedema

numerous other drugs have been trailed, some in RCTs but others as open label. The most recent is CNV 1014802 [43] which shows promise. There has recently been published an update on trigeminal neuralgia in Clinical Evidence and this will be used for individual drug results [41, 42]. Although there are now a vast array of drugs available to manage TN, it is important to ensure that a neurosurgical opinion is sought early on so that if patients develop severe pain they know that there are options other than drugs available [41, 42].

Carbamazepine The gold standard drug is carbamazepine and three RCTs, cross-over design of poor quality in a total of 208 patients have been reported as well as a systematic review. The NNT is 2 with 95 % CI 1–2 [41, 42]. There is very little literature on effectiveness over time and one study suggests that over a 16-year period efficacy is reduced [37]. This however could also have been due to progression of the disorder itself. Although highly effective the side effects of carbamazepine are significant and there are reported deaths but it is not clear if carbamazepine was the direct cause. Allergies to carbamazepine occur and there is a risk of Stevens-Johnson syndrome in people with the allele HLA-B1502. Side effects are listed in Table 20.1 and recent review of side effects using a psychometrically tested questionnaire AEP shows that cognitive side effects are the most prominent [9]. Drug interactions are also common and this becomes a substantial problem in the elderly who are on

polypharmacy. To reduce side effects the drug needs to be slowly escalated and equally slowly withdrawn. Due to its pharmacokinetics it is important to monitor haematinics, electrolytes, liver enzymes on a regular basis if high doses are used and especially at the start of therapy. NICE [33] suggests that vitamin D and calcium levels need to be checked if the drug is used long term. It remains the first-line drug of choice in the UK [34].

Oxcarbazepine This drug is closely related to carbamazepine but as it does not use the liver enzyme system for metabolism and has fewer drug interactions. RCTs have been done and compared to carbamazepine but the only data available is in poster presented at a conference and then quoted in Beydoun's paper [5]. Its efficacy was the same as for carbamazepine but there are insufficient data to report an NNT. The data also suggest that tolerability of oxcarbazepine was better but no further details are provided. The drug reduces in efficacy over time [44], [11]. One of its major side effects is hyponatraemia which is dose-related [44]. There is general consensus among clinicians that oxcarbazepine is the preferred drug and in some countries it is the first-line drug [10].

Lamotrigine This has only been used in combination with either carbamazepine or phenytoin in a small crossover RCT. It is therefore not possible to provide an NNT. It needs to be very slowly escalated due to its propensity to cause rashes when the dose is escalated too rapidly. It remains a useful drug when allergy to carbamazepine or oxcarbazepine occurs and it has been reported to be useful in SUNA (short unilateral neuralgiform pain with autonomic features) [23]. Otherwise, its side effect profile is similar to other AEDs.

Baclofen As this is a drug often used in patients with MS to improve spasticity, many clinicians will use the drug in this group of patients. There is a reported RCT but its quality is too poor to make any recommendations or provide an NNT. It is probably better used in combination with carbamazepine rather than on its own. It can cause sedation and its withdrawal must be slow as it can result in hallucinations.

Gabapentin A newer AED which has been used in a small RCT comparing its action to supplementation with injection of ropivicane into trigger zones [25]. Although an effective drug in other neuropathic pains, its effectiveness in this study was low.

Botulinum Injections of botulinum toxin type A have been reported in RCTs but many are of poor quality and recent systematic reviews suggest that there is insufficient evidence for its use [17, 27].

Other RCTs These have been very small trials of drugs in facial neuralgia, dextromethorphan [16] and topiramate [15]. There are older drugs such as pimozide, tizanidine, tocainide and proparacaine eye drops that have been reported in small poor quality RCTs which showed no positive efficacy and are not in use [40].

Pregablin Obermann et al. [36] reported a prospective open label study of variable doses of pregablin over a period of 1 year in 53 patients. Significant pain reductions were noted and the most significant side effects were cognitive, i.e. dizziness, tiredness and headaches.

Leviteracetam Two small open-label studies have provided conflicting results as to its efficacy [18, 30] and no further studies have been reported.

Lidocaine Patches These have been reported for use in post-herpetic neuralgia but their use in TN is not indicated based on some case reports [21].

Table 20.1 summarises the dosages of the most commonly used drugs.

20.2.1 Acute Management of TN

It is well recognised that some patients with TN will get severe prolonged attacks of pain which result in them going to emergency departments. Inevitably, they are given opioids which do little to relieve the pain. There are two RCTs reporting the use of sumatripan subcutaneous [19] or intranasal lidocaine [20] which give relief for a few hours. This would support clinicians, especially dental surgeons, impressions that lidocaine injection into trigger points can provide immediate pain relief that is often prolonged beyond the effect of the drug. There is a report of intravenous fosphenytoin injection but this necessitates admission for cardiac monitoring [7].

20.3 TN and Multiple Sclerosis

Baclofen is often the preferred drug in this group of patients if they are already using it. There are small case reports of drugs used specifically in MS, e.g. topiramate doses of 200–300 mg [45], misoprostol 600 μg daily [12] which suggest that both provide 50 % pain relief.

20.4 Glossopharyngeal Neuralgia

This is defined as "A severe, transient, stabbing, unilateral pain experienced in the ear, base of the tongue, tonsillar fossa and/or beneath the angle of the jaw. It is commonly provoked by swallowing, talking and/or coughing, and may remit and relapse in the fashion of classical trigeminal neuralgia" [2].

There have not been any RCTs of drugs specifically for this condition. Due to its similarity to TN all the same drugs are used.

20.5 Nervus Intermedius (Facial Nerve) Neuralgia

This is defined as "A rare disorder characterized by brief paroxysms of pain felt deeply in the auditory canal, sometimes radiating to the parieto-occipital region. It may develop without apparent cause or as a complication of Herpes zoster" [2].

There are no RCTs in relation to this condition and drugs used for post-herpetic neuralgia are used.

20.6 Post-herpetic Trigeminal Neuropathy, Post-herpetic Neuralgia

This is defined as "Unilateral head and/or facial pain persisting or recurring for at least 3 months in the distribution of one or more branches of the trigeminal nerve, with variable sensory changes, caused by Herpes zoster" [2].

There are no specific RCTs for trigeminal post-herpetic neuralgia (PHN) but most of the drugs used in the generic trials can be used in these patients. Care however needs to be taken with topical agents especially if the ophthalmic division is involved.

The recently updated NICE guidelines have suggested that all the drugs have similar NNTs so no hierarchies are suggested [34]. There are a number of international guidelines whose recommendations are very similar [35]. There is some recent evidence to suggest that combination therapies using lower dosages can reduce side effects. One such trial is by Gilron et al. [14] who showed in an RCT that gabapentin and nortriptyline can be effective when used in lower doses. A recent review of the literature for drug therapy of neuropathic pain suggests that previous RCTs and systematic reviews have been overoptimistic about outcomes because they have not taken into account large placebo responses, poor phenotyping and heterogeneous diagnostic criteria [13].

Gabapentin This drug's efficacy has been shown in several RCTs and it improves pain after 7–8 weeks, NNT 4, 95 % CI 3–6 [38]. Side effects include tiredness 27–17 %, dizziness: 24–20 %, ataxia: 7 % and peripheral oedema in around 10 % [38]. Maximum doses suggested are 3600 mg used as a three times a day dosage and trailed for 10 weeks [35].

Pregablin Numerous RCTs and a systematic review have confirmed that pregablin in adequate doses 300 mg and over is effective in PHN [31]. The 19 studies involved 7003 participants a scale never seen in trials for TN. The NNT for 600 mg pregablin daily compared with placebo is 3.9 (95 % confidence interval 3.1–5.1). As with all AEDs cognitive side effects are common tiredness in 15–25 % and dizziness reported between 27 and 46 %. It has an overall NNH of 6.1 (95 % CI 5.1–7.7) which is only slightly affected by dosage. It is recommended that it is used at maximum dosage of 600 mg as a twice daily schedule for 4 weeks [35].

Antidepressants There is no evidence that serotonin-noradrenaline reuptake inhibitors are helpful. On the other hand, the tricyclic antidepressants may be more effective at reducing pain in people after 3–8 weeks, NNT 3, 95 % CI 2–4 [38]. Dry mouth is a significant problem especially with amitriptyline, up to 62 % with sedation being the other major side effect and they are dose-dependent. Nortriptyline may be a better option if using this class of drug NICE [34]. Lower doses are used than for treating depression. Care needs to be taken when using these drugs and they are not recommended in the presence of severe or recent myocardial injury or arrhythmia or for older men with prostatism because of possible anticholinergic aggravation of urinary retention. Nortriptyline can be used up to 150 mg daily for 10 weeks although at this high dose side effects could be substantial [35].

Opioids These include tramadol, oxycodone, morphine and methadone, can provide some pain relief but the evidence is of poor quality. The adverse effects outweigh their usefulness in PHN [38]. If used should only be for a trial of 4 weeks [35].

Topical Treatments (Lidocaine Patches) There is moderate evidence that these 5 % lidocaine-medicated plasters can relieve pain. One RCT reported an NNT 2, 95 % CI 1–3, but this was not replicated in other studies [38]. They are well tolerated

and they are recommended in the old or those who cannot take systemic drugs, in others they may be a useful adjunct. It is difficult to use them on the face during the day but if they have significant allodynia that prevents sleep then used at night they can be helpful [21]. Liedgens et al. [26] have shown that in Europe these patches are cost-effective when compared to pregablin and have a much higher safety profile. Patches can be used three times a day for a maximum of 12–18 h. If no effect is noted at 3 weeks they are unlikely to be helpful [35].

Capsaicin patches have some evidence for efficacy but currently are not licensed for use on the face.

Conclusions

AEDs are the main drugs of value in this group of disorders. They have been shown to be effective but result in significant side effects such that patients stop using them. It is important to consider stopping the drugs if no efficacy is noted after a few months.

References

1. Aggarwal VR, Lovell K, Peters S, Javidi H, Joughin A, Goldthorpe J (2011) Psychosocial interventions for the management of chronic orofacial pain. Cochrane Database Syst Rev (11):CD008456. Available from: PM:22071849
2. Anon (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808. Available from: PM:23771276
3. Anonymous (2004) The international classification of headache disorders: 2nd edition. Cephalalgia 24 Suppl 1:9–160. Available from: PM:14979299
4. Baker GA, Frances P, Middleton E (1994) Initial development, reliability, and validity of a patient-based adverse event scale. Epilepsia 35(Suppl 7):80
5. Beydoun A, Schmidt D, D'Souza J (2002) Oxcarbazepine versus carbamazepine in trigeminal neuralgia: a meta-anlaysis of three double blind comparative trials. Neurology 58(Suppl 3):p02.083, Ref Type: Abstract
6. Bonathan CJ, Zakrzewska JM, Love J, Williams AC (2014) Beliefs and distress about orofacial pain: patient journey through a specialist pain consultation. J Oral Facial Pain Headache 28(3):223–232. Available from: PM:25068216
7. Cheshire WP (2001) Fosphenytoin: an intravenous option for the management of acute trigeminal neuralgia crisis. J Pain Symptom Manage 21(6):506–510. Available from: PM:11397609
8. Cole CD, Liu JK, Apfelbaum RI (2005) Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. Neurosurg Focus 18(5):E4. Available from: PM:15913280
9. Cregg R, Besi E, Boniface B, Zakrzewska J (2014) EHMTI-0355 comparison of carbamazepine and oxcarbazepine tolerability in patients with trigeminal neuralgia. J Headache Pain 15(Suppl 1):12
10. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM (2008) AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 15(10):1013–1028. Available from: PM:18721143
11. Di Stefano G, La CS, Truini A, Cruccu G (2014) Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. J Headache Pain 15:34. Available from: PM:24912658
12. DMKG Study Group (2003) Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis. J Neurol 250(5):542–545. Available from: PM:12736732
13. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M,

Sena E, Siddall P, Smith BH, Wallace M (2015) Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 14:162–173. Available from: PM:25575710
14. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL (2009) Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 374(9697):1252–1261. Available from: PM:19796802
15. Gilron I, Booher SL, Rowan JS, Max MB (2001) Topiramate in trigeminal neuralgia: a randomized, placebo-controlled multiple crossover pilot study. Clin Neuropharmacol 24(2):109–112. Available from: PM:11307048
16. Gilron I, Booher SL, Rowan MS, Smoller MS, Max MB (2000) A randomized, controlled trial of high-dose dextromethorphan in facial neuralgias. Neurology 55(7):964–971. Available from: PM:11061252
17. Hu Y, Guan X, Fan L, Li M, Liao Y, Nie Z, Jin L (2013) Therapeutic efficacy and safety of botulinum toxin type A in trigeminal neuralgia: a systematic review. J Headache Pain 14:72. Available from: PM:23964790
18. Jorns TP, Johnston A, Zakrzewska JM (2009) Pilot study to evaluate the efficacy and tolerability of leviteracetam (keppra) in the treatment of patients with trigeminal neuralgia. Eur J Neurol 16:740–744
19. Kanai A, Saito M, Hoka S (2006) Subcutaneous sumatriptan for refractory trigeminal neuralgia. Headache 46(4):577–582. Available from: PM:16643550
20. Kanai A, Suzuki A, Kobayashi M, Hoka S (2006) Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. Br J Anaesth 97(4):559–563. Available from: PM:16882684
21. Kern KU, Nalamachu S, Brasseur L, Zakrzewska JM (2013) Can treatment success with 5% lidocaine medicated plaster be predicted in cancer pain with neuropathic components or trigeminal neuropathic pain? J Pain Res 6:261–280. Available from: PM:23630431
22. Kesselheim AS, McGraw S, Thompson L, O'Keefe K, Gagne JJ (2015) Development and use of new therapeutics for rare diseases: views from patients, caregivers, and advocates. Patient 8(1):75–84
23. Lambru G, Matharu MS (2013) SUNCT and SUNA: medical and surgical treatments. Neurol Sci 34(Suppl 1):S75–S81. Available from: PM:23695051
24. Lee JY, Chen HI, Urban C, Hojat A, Church E, Xie SX, Farrar JT (2010) Development of and psychometric testing for the Brief Pain Inventory-Facial in patients with facial pain syndromes. J Neurosurg 113(3):516–523. Available from: PM:20151778
25. Lemos L, Flores S, Oliveira P, Almeida A (2008) Gabapentin supplemented with ropivacain block of trigger points improves pain control and quality of life in trigeminal neuralgia patients when compared with gabapentin alone. Clin J Pain 24(1):64–75. Available from: PM:18180639
26. Liedgens H, Obradovic M, Nuijten M (2013) Health economic evidence of 5% lidocaine medicated plaster in post herpetic neuralgia. Clin Econ Outcomes Res 5:597–609
27. Linde M, Hagen K, Stovner LJ (2011) Botulinum toxin treatment of secondary headaches and cranial neuralgias: a review of evidence. Acta Neurol Scand Suppl 124(191):50–55. Available from: PM:21711257
28. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L (2014) Concomitant persistent pain in classical trigeminal neuralgia–evidence for different subtypes. Headache 54(7):1173–1183. Available from: PM:24842632
29. Macea DD, Gajos K, Daglia Calil YA, Fregni F (2010) The efficacy of Web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. J Pain 11(10):917–929. Available from: PM:20650691
30. Mitsikostas DD, Pantes GV, Avramidis TG, Karageorgiou KE, Gatzonis SD, Stathis PG, Fili VA, Siatouni AD, Vikelis M (2010) An observational trial to investigate the efficacy and tolerability of levetiracetam in trigeminal neuralgia. Headache 50(8):1371–1377. Available from: PM:21044281
31. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ (2014) Pregablin for acute and chronic pain in adults. Cochrane Database Syst Rev (3):CD007076
32. Morley S, Eccleston C, Williams A (1999) Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 80(1–2):1–13. Available from: PM:10204712

33. NICE (2012) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care pp 1–636
34. NICE (2013) Neuropathic pain -pharmacological management NICE Guideline. stand alone document 173:2.
35. O'Connor AB, Dworkin RH (2009) Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 122(10 Suppl):S22–S32. Available from: PM:19801049
36. Obermann M, Yoon MS, Sensen K, Maschke M, Diener HC, Katsarava Z (2008) Efficacy of pregabalin in the treatment of trigeminal neuralgia. Cephalalgia 28(2):174–181. Available from: PM:18039340
37. Taylor JC, Brauer S, Espir MLE (1981) Long-term treatment of trigeminal neuralgia. Postgrad Med J 57:16–18
38. Watson PN (2010) Postherpetic neuralgia. BMJ Clin Evid pii: 0905. Available from: PM: 21418680
39. Wise J (2013) Polypharmacy: a necessary evil. BMJ 347:f7033. Available from: PM:24286985
40. Zakrzewska JM (2002) Trigeminal neuralgia. In: Zakrzewska JM, Harrison SD (eds) Assessment and management of orofacial pain, 1st edn. Elsevier Sciences, Amsterdam, pp 267–370
41. Zakrzewska JM, Linskey ME (2014) Trigeminal neuralgia. BMJ Clin Evid pii: 1207. Available from: PM:25299564
42. Zakrzewska JM, Linskey ME (2014) Trigeminal neuralgia. BMJ 348:g474. Available from: PM:24534115
43. Zakrzewska JM, Palmer J, Ettlin DA, Obermann M, Giblin GM, Morisset V, Tate S, Gunn K (2013) Novel design for a phase IIa placebo-controlled, double-blind randomized withdrawal study to evaluate the safety and efficacy of CNV1014802 in patients with trigeminal neuralgia. Trials 14:402. Available from: PM:24267010
44. Zakrzewska JM, Patsalos PN (2002) Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia. Pain 95(3):259–266. Available from: PM:11839425
45. Zvartau-Hind M, Din MU, Gilani A, Lisak RP, Khan OA (2000) Topiramate relieves refractory trigeminal neuralgia in MS patients. Neurology 55(10):1587–1588. Available from: PM:11094125

Dental and Musculoskeletal Pain

21

Antoon De Laat and Tara Renton

21.1 Pain Originating from Teeth and Periodontal Structures

Dental and periapical periodontal (dental abscess) pain is reported by 12–14 % of the population in the last 1–6 months [20]. Interestingly, periodontal disease and gingivitis are painless. Consequently, a thorough dental examination is essential in every patient presenting with orofacial pain in order to exclude dental pathology. Since the patterns of radiating pain can be very puzzling, acute pulpitis has often been confused with typical or atypical forms of trigeminal neuralgia and other orofacial pains. Response to anti-inflammatories and antibiotics may indicate this pathology rather than neuropathic pain. Improved technical investigations including electrical pulp testing, pulpal blood flow assessments, and cone-beam CT-scans assist in investigating teeth for cracks, fractures, or extra roots/pulpal canals, which allowed to decrease the group of patients previously classified as "persistent idiopathic facial pain" or "atypical odontalgia." Management of dental and periapical pain primarily needs local treatment by the dentist including removal of carious dentine and enamel and restoration, pulpal extirpation with root canal treatment or dental extraction. Pharmacological management of the pain, mostly NSAIDs and paracetamol, is only indicated in the short term prior to or subsequent to surgery. Antibiotic prophylaxis should only be installed in case of abscess or in case of medically compromised patients.

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_21

21.2 Pain Associated with Jaw Muscles and Temporomandibular Joints

Pain associated with temporomandibular disorders (TMD) has the highest prevalence in the orofacial region next to dental pain [20] and can clinically be expressed as masticatory muscle pain (MMP), arthritides, and/or TMJ-arthralgia [1]. Joint function and loading of the masticatory system usually aggravates the pain. Often, the pain is also expressed as a (tension-type) headache in the frontal or temporal regions. In part of the patients, limitation of jaw movement, interference during movement, or locking of the TMJ may accompany the pain.

TMD pain is very common: it has been reported in 4–12 % of the general population (especially in the 20–40 years of age range) with a female-to-male ratio of 2:1 [8, 12, 18]. TMD has a benign natural course: the symptoms remit in 33–49 % of cases over a 5-year period [31] and progression to severe and/or chronic pain is rare [21].

Many aspects of the etiology of TMD are unclear. Based upon the biopsychosocial model for pain, Diatchenko et al. [7] proposed a model in which TMD and its associated symptoms would be influenced by the interaction of two sets of intermediate phenotypes: psychosocial distress and pain amplification. Each of these phenotypes was influenced in itself by multiple potential risk factors, that again depend on genetic regulation and are influenced by environmental contributions [37]. The Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study [22, 38] tested this model. Several genetic associations with TMD were confirmed [39], offering promising potential biomarkers. Patients and controls could clearly be discriminated on the basis of pain pressure thresholds and cutaneous mechanical thresholds [16]. In addition, psychometric instruments elucidated higher levels of affective distress, somatic awareness, and pain catastrophizing [11]. TMD appeared also associated with several biological measures illustrative for autonomic dysregulation [23]. These recent findings reinforce the shift from morphological causes like dental occlusion in favor of the biopsychological and multifactorial background [15].

Specifically for MMP, parafunctions like tooth clenching and bruxism have been implicated in the etiology (for review see Lavigne et al. [19]). Strikingly, daytime (low-level) tooth clenching was identified as a risk factor [3, 10]. In TMJ-arthralgia, some kind of trauma or overload of the joint system overrules its adaptive capacity [43] possibly also after whiplash injury (for review see [17]), or in case of intrinsic overloading of the TMJ [26]. As in MMP, genetic factors and gender differences have been identified also in osteoarthritis, [14]. Smoking proved a significant risk factor for the development of TMD in subjects under 30 years of age [32].

MMP is reported as a dull regional pain that aches especially in the jaw closing muscles and around the ear. Some patients report more pain in the morning or the evening [6] but the pattern may be variable [13]. The intensity is rated 3–7/10 on a VAS [42]. The specific relation between MMP and (tension-type) headache is unclear and a cause-effect relationship has not been established. MMP may be part of widespread musculoskeletal pain and there appears to be a significant overlap with fibromyalgia [40].

TMJ-arthralgia appears as a dull or sharp pain of moderate intensity, typically more localized in or around the joint, and irradiating into the ear. Loading, movements of the joint, and stretching of the joint capsule during maximal mouth opening may aggravate the pain. Mouth opening and joint function may be limited as a result of the pain or as a result of articular disk dysfunction (internal derangement of the joint with clicking and locking).

Osteoarthritis of the TMJ is sometimes part of a general arthritis. Where acute phases of arthritis typically are associated with increased pain, it is striking that a "settled" osteoarthrosis of the TMJ, even with significant radiological degeneration of the joint surfaces, often is only characterized by increased crepitation but without pain complaints.

In case chronic TMD pain develops, both MMP and TMJ-arthralgia may be accompanied by central sensitization and psychological problems such as depression, somatization, and anxiety [2].

For the most common subgroups of TMD, research diagnostic criteria (RDC-TMD) were established [9] and soon translated into a clinical classification [41]. Recently, the diagnostic criteria have been refined [34, 35]. Details and decision trees for these diagnoses, as well as numerous translations of the questionnaires and examination sheets, can be readily accessed at the RDC-TMD website (http://www.rdc-tmdinternational.org/).

In view of their self-limiting and benign character, management of these problems aims at providing optimal circumstances for the body to adapt and heal. Most treatment approaches are reversible and fit into the biopsychosocial approach:

- Correct information regarding the benign natural course of TMD is a primary and very important step. Patients have to be instructed in avoiding overload of the system, as in tooth clenching, and in active self-care, using warmth application and massage [25].
- Systematic review did not find a particular method in physical therapy to be superior [24]. And recent RCTs have indicated that, while in the initial phase physical therapy results in decrease of pain and improved jaw movement there is no specific therapy effect after 1 year [4, 5].
- The clinical efficacy on pain of intraoral occlusal appliances, widely used in the management of TMD, is poorly documented. They should be designed in order to avoid irreversible changes in the dental occlusion.
- Pain medication (analgesics, NSAIDs) can be needed to overcome acute pain, and this is for a limited period of time [27].
- Arthrocentesis of the joint might be considered in patients with persistent TMJ-arthralgia [29]. TMJ-surgery, however, did not prove to be superior to medical management or conservative therapy in case of internal derangement with locking [33, 36].

In patients with chronic TMD pain, these therapies must be accompanied by psychological support, e.g., cognitive behavioral therapy and relaxation therapy

[30]. Low-dose tricyclic antidepressants or selective serotonin reuptake inhibitors can be considered, as in other chronic pain syndromes [28].

References

1. Benoliel R, Sharav Y (2008) Masticatory myofascial pain, tension-type and chronic daily headache. In: Sharav Y, Benoliel R (eds) Orofacial pain and headache. Elsevier, London, pp 109–128
2. Carlson CR (2008) Psychological considerations for chronic orofacial pain. Oral Maxillofac Surg Clin North Am 20:185–195
3. Chen CY, Palla S, Erni S, Sieber M, Gallo LM (2007) Nonfunctional tooth contact in healthy controls and patients with myogenous facial pain. J Orofac Pain 21:185–193
4. Craane B, Dijkstra PU, Stappaerts K, De Laat A (2011) One-year evaluation of the effect of physical therapy for masticatory muscle pain: a randomized controlled trial. Eur J Pain 16:737–747
5. Craane B, Dijkstra PU, Stappaerts K, De Laat A (2012) Randomised controlled trial on physical therapy for TMJ closed lock. J Dent Res 91:364–369
6. Dao TT, Lund JP, Lavigne GJ (1994) Comparison of pain and quality of life in bruxers and patients with myofascial pain of the masticatory muscles. J Orofac Pain 8:350–356
7. Diatchenko L, Nackley EG, Slade GD, Fillingim RB, Maixner W (2006) Idiopathic pain disorders – pathways of vulnerability. Pain 123:226–230
8. Drangsholt M, LeResche L (1999) Temporomandibular disorder pain. In: Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korff M (eds) Epidemiology of pain. IASP Press, Seattle, pp 203–233
9. Dworkin SF, LeResche L (1992) Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 6:301–355
10. Farella M, Soneda K, Vilmann A, Thomsen CE, Bakke M (2010) Jaw muscle soreness after tooth-clenching depends on force level. J Dent Res 89:717–721
11. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Dubner R, Bair E, Baraian C, Slade GD, Maixner W (2011) Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 12(suppl 3):T46–T60
12. Gesch D, Bernhardt O, Alte D, Schwahn C, Kocher T, John U, Hensel E (2004) Prevalence of signs and symptoms of temporomandibular disorders in an urban and rural German population: results of a population-based Study of Health in Pomerania. Quintessence Int 35: 143–150
13. Glaros AG, Williams K, Lausten L (2008) Diurnal variation in pain reports in temporomandibular disorder patients and control subjects. J Orofac Pain 22:115–121
14. Goldring MB, Goldring SR (2007) Osteoarthritis. J Cell Physiol 213:626–634
15. Greene CS (2006) Concepts of TMD etiology: effects on diagnosis and treatment. In: Laskin DM, Greene CS, Hylander WL (eds) TMDs, an evidence-based approach to diagnosis and treatment. Quintessence Publ Co, Chicago, pp 219–228
16. Greenspan JD, Salde GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, Knott C, Mulkey F, Rothwell R, Maixner W (2011) Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. J Pain 12(suppl 3):T61–T74
17. Häggman-Henrikson B, List T, Westergren HT, Axelsson SH (2013) Temporomandibular disorder pain after whiplash trauma: a systematic review. J Orofac Pain 27:217–226
18. Isong U, Gansky SA, Plesh O (2008) Temporomandibular joint and muscle disorder-type pain in U.S. adults: the National Health Interview Survey. J Orofac Pain 22:317–322

19. Lavigne GJ, Khoury S, Abe S, Yamaguchi T, Raphael K (2008) Bruxism physiology and pathology: an overview for clinicians. J Oral Rehabil 35:476–494
20. Lipton JA, Ship JA, Larach-Robinson D (1993) Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 124:115–121
21. Magnusson T, Egermark I, Carlsson GE (2005) A prospective investigation over two decades on signs and symptoms of temporomandibular disorders and associated variables. A final summary. Acta Odontol Scand 63:99–109
22. Maixner W, Diatchenko L, Dubner R, Fillingim RB, Greenspan JD, Knott C, Ohrbach R, Weir B, Slade G (2011) Orofacial pain prospective evaluation and risk assessment study – the OPPERA study. J Pain 12(suppl 3):T4–T11
23. Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V, Knott C, Slade GD, Ohrbach R, Diatchenko L, Fillingim RB (2011) Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 12(suppl 3):T75–T91
24. Medlicott MS, Harris SR (2006) A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. Phys Ther 86:955–973
25. Michelotti A, de Wijer A, Steenks M, Farella M (2005) Home-exercise regimes for the management of non-specific temporomandibular disorders. J Oral Rehabil 32:779–785
26. Milam SB (2005) Pathogenesis of degenerative temporomandibular joint arthritides. Odontology 93:7–15
27. Mujakperuo HR, Watson M, Morrison R, Macfarlane TV (2010) Pharmacological interventions for pain in patients with temporomandibular disorders. Cochrane Database Syst Rev (10):CD004715. doi:10.1002/14651858.CD004715
28. Nijs J, Meeus M, Van Oosterwijck J, Roussel N, De Kooning M, Ickmans K, Matic M (2011) Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have? Expert Opin Pharmacother 12:1087–1098
29. Onder ME, Tüz HH, Koçyiğit D, Kişnişci RS (2009) Long-term results of arthrocentesis in degenerative temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 107:e1–e5
30. Orlando B, Manfredini D, Salvetti G, Bosco M (2007) Evaluation of the effectiveness of biobehavioral therapy in the treatment of temporomandibular disorders: a literature review. Behav Med 33:101–118
31. Rammelsberg P, LeResche L, Dworkin SF, Mancl L (2003) Longitudinal outcome of temporomandibular disorders: a 5-year epidemiologic study of muscle disorders defined by research diagnostic criteria for temporomandibular disorders. J Orofac Pain 17:9–20
32. Sanders AE, Maixner W, Nackley AG, Diatchenko L, By K, Miller VE, Slade GD (2012) Excess risk of temporomandibular disorder associated with cigarette smoking in young adults. J Pain 13:21–31
33. Schiffman EL, Look JO, Hodges JS, Swift JQ, Decker KL, Hathaway KM, Templeton RB, Fricton JR (2007) Randomized effectiveness study of four therapeutic strategies for TMJ closed lock. J Dent Res 86:58–63
34. Schiffman EL, Truelove EL, Ohrbach R, Anderson GC, John MT, List T, Look JO (2010) The Research Diagnostic Criteria for Temporomandibular Disorders. I: overview and methodology for assessment of validity. J Orofac Pain 24:7–24
35. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF (2014) Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache 28:6–27

36. Schiffman E, Velly AM, Look JO, Hodges JS, Swift JQ, Decker KL, Anderson QN, Templeton RB, Lenton PA, Kang W, Fricton JR (2014) Effects of four treatment strategies for temporomandibular joint closed lock. Int J Oral Maxillofac Surg 43:217–226
37. Slade GD, Bair E, Greenspan JD, Dubner R, Fillingim RB, Diatchenko L, Maixner W, Knott C, Ohrbach R (2013) Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study. J Pain 14(Suppl):T20–T32
38. Slade GD, Fillingim RB, Sanders AE, Bair E, Greenspan JD, Ohrbach R, Dubner R, Diatchenko L, Smith SB, Knott C, Maixner W (2013) Summary of findings from the OPPERA prospective cohort study of incidence of first-onset temporomandibular disorder: implications and future directions. J Pain 14(Suppl):T116–T124
39. Smith SB, Maixner DW, Greenspan JD, Dubner R, Fillingim RB, Ohrbach R, Knott C, Slade G, Bair E, Gibson DG, Zaykin DV, Weir BS, Maixner W, Diatchenko L (2011) Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. J Pain 12 –Suppl 3:T92–T101
40. Solberg-Nes L, Carlson CR, Crofford LJ, Leeuw RD, Segerstrom SC (2010) Self-regulatory deficits in fibromyalgia and temporomandibular disorders. Pain 151:37–44
41. Truelove EL, Sommers EE, LeResche L, Dworkin SF, Von Korff M (1992) Clinical diagnostic criteria for TMD. New classification permits multiple diagnoses. J Am Dent Assoc 123:47–54
42. Von Korff M, Dworkin SF, LeResche L, Kruger A (1988) An epidemiologic comparison of pain complaints. Pain 32:173–183
43. Yun PY, Kim YK (2005) The role of facial trauma as a possible etiologic factor in temporomandibular joint disorder. J Oral Maxillofac Surg 63(11):1576–1583

Post-traumatic Neuropathy and Burning Mouth Syndrome

22

Tara Renton and Antoon De Laat

22.1 Post-traumatic Trigeminal Nerve Neuropathy

The trigeminal nerve is the largest sensory nerve in the body supplying the orofacial region. Iatrogenic (caused by doctors or dentists) trigeminal nerve injuries (TNI) result in pain in 70 % of patients [38] resulting in interference with speaking, eating, kissing, shaving, applying makeup, tooth brushing and drinking, and consequently a significant negative effect on the patient's self-image, quality of life and psychology [38, 39].

Causes of trigeminal alveolar nerve injury include local anaesthetic injections, third molar surgery, implants, endodontics, ablative surgery, trauma and orthognathic surgery. The inferior alveolar nerve (IAN) neuropathy related to third molar surgery or inferior alveolar block injections is usually temporary but can persist and become permanent (at 3 months). There are rare reports of resolution of implant-related IAN neuropathies at over 4 years [12] but these do not comply with normal reports of peripheral sensory nerve injuries [24]. Many authors recommend referral of injuries after 6 months [16] but this may be too late for many peripheral sensory nerve injuries to recover. We now understand that many dentally induced nerve injuries require intervention immediately, within 30 h or within 3 months, to optimise resolution from injury and prevent the permanent central and peripheral changes within the nervous system [48].

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D.D. Mitsikostas, K. Paemeleire (eds.), *Pharmacological Management of Headaches*, Headache, DOI 10.1007/978-3-319-19911-5_22

Nerve damage is likely to result from preoperative factors including poor preoperative planning, resulting in inaccurate measurements and selection of implant site and type (width and length). Any protrusion into the inferior dental canal (IDC) or breech of the IDC will result in acute and often severe neuralgic-type pain intra-operatively [23] and it is imperative that the clinician uses an appropriate LA protocol to allow the patient to indicate proximity of the surgical instruments to the IDC.

The most significant issue with implant-related nerve injuries is that they are entirely avoidable as this is elective surgery and potentially permanent with or without surgical intervention [2, 34].

22.1.1 Prevention

22.1.1.1 Local Anaesthetic-Related Nerve Injuries

Nerve injury due to LA may be physical (needle, compression due to epineural or perineural haemorrhage) or chemical (haemorrhage or LA contents). Thus the resultant nerve injury may be a combination of peri-, epi- and intra-neural trauma causing subsequent haemorrhage, inflammation and scarring resulting in demyelination [30]. Only 1.3–8.6 % of patients get an 'electric shock'-type sensation on application of an IAN block and 57 % of patients suffer from prolonged neuropathy having not experienced the discomfort on injection, thus this is not a specific sign. Routine practice in Europe and USA includes warning patients of potential nerve injury in relation to dental injections.

Thus prevention of LA nerve injuries is possible and some simple steps may minimise LA-related nerve injuries:

- Avoid high concentration LA for ID blocks (use 2 % Lidocaine as standard). There is increasing evidence that higher concentration agents are more neurotoxic thus more likely to cause persistent inferior dental block (IDB)-related neuropathy [33].
- Avoid multiple blocks where possible.
- Avoid IAN blocks by using high concentration agents (Articaine), infiltrations only. Infiltration dentistry avoids the use of IDBs, thus prevent LA-related nerve injury, for which there is no cure. A recent report highlights that the prevalence of IDB-related nerve injuries in UK General dental practice is 1:14,000 blocks, of which 25 % are permanent [33, 37].

22.1.2 Third Molar Surgery (TMS)

Worldwide, surgical removal of mandibular third molars is the most common oral surgical procedure. Previous studies report that TMS-related IANIs occur in up to 3.6 % of cases permanently and 8 % of cases temporarily [40]. Factors associated

with IAN injury include age, difficulty of surgery and proximity of the tooth to the IAN canal [31].

Only lingual nerve injuries in association with lingual access third molar surgery are mainly temporary with 88 % of lingual nerve injuries resolving in the first 10 weeks post-surgery [15, 26]. In contrast, the IAN is at more risk from a variety of dental procedures and the IAN is contained within a bony canal predisposing it to ischaemic trauma and subsequent injury.

Patient safety and prevention of trigeminal nerve injury in relation to third molar surgery is maximised by:

- Preoperative radiographic assessment of inferior alveolar nerve risk based upon plain films and additional Cone Beam CT scanning if M3M at high risk of inferior alveolar nerve injury.
- Consider coronectomy procedure if M3M is at high risk of IAN injury (in high-risk vital tooth, healthy compliant consenting patient [32]), confirmed using cone beam CT radiographic assessment [25, 29, 34, 36].
- Use of buccal approach without lingual flap elevation and retraction optimises the prevention of lingual nerve injury avoiding high concentration inferior dental blocks when possible using buccal infiltration techniques and/or routine 2 % concentration local anaesthetic agents [10, 28].

22.1.3 Dental Implant-Related Nerve Injuries

The incidence of implant-related IANIs varies from 0 to 40 % [21]. More recently, two studies have raised the issue of persistent neuropathic pain due to implant-related nerve injuries [14, 34].

Based upon literature prevention, diagnosis and management of nerve injuries in relation to dental implants, the cause of permanent implant-related nerve injury can be attributed to direct damage to the inferior dental canal (IDC). Adequate preoperative assessment and planning as well as surgical procedure are important [1].

A. Inadequate preoperative assessment and planning may be due to:
   - Lack of knowledge/inexperience
   - Inadequate informed consent-all options provided and related risk benefit for each
   - Lack of identification of existing presurgical neuropathy
   - Inadequate planning in positioning the implant
     - Bone assessment quality and quantity –
     - Know where the nerve is. Nerve localisation, risk factors when assessing IAN position (Mental loop, characteristics of IAN position in various sites of mandible). The parasymphyseal zone is a high risk zone. The necessary accuracy of estimating the position of the IDC based on plain films or CT scans is mandatory.

- Safety zone – Risk perforation of a canal surrounding IDC or, even direct perforation and damage to the nerve.
- Selection of implants (short implants <8 mm to simplify the procedure and minimise morbidity)

B. Surgical procedure should include the execution of:
- Local anaesthesia (see previous section)
- Flap design
- Use surgical guides [45]
- Using intraoperative radiographs
- Drill stops.

C. Postoperative care should attend to:
- Early postoperative recognition of neuropathy (HOMECHECK)
- Prompt management of neuropathy (removal of implant if indicated)
  - Acute phase
  - Late phase
- Early or late postoperative infection

22.1.4 Assessment of Trigeminal Neuropathy

Our studies highlight the need for a more holistic approach for patients with nerve injury [38]. Features of iatrogenic trigeminal nerve injury worthy of assessment include

- Focal sensory neuropathy (not always present). There is almost always an area of abnormal sensation (neuropathy with the exception in Trigeminal neuralgia) and the patient's maximum pain is associated with the area of sensory deficit (i.e. suffering from a mixture of pain, numbness and altered sensation). This is an important diagnostic feature for sensory nerve neuropathy.
- Pain discomfort, altered sensation, numbness (anaesthesia). Neuropathic pain is commonly experienced by 50–70 % of patients, either spontaneous ongoing pain, which often had a burning character, and spontaneous shooting, electric shock-like sensations (neuralgia). Patients experiencing evoked pain due to touch or cold often have difficulties with daily function, such as kissing, socialising, speech, eating and drinking. Consequently, patients were often anxious, tearful and had psychological repercussions of surgery. These symptoms were often compounded by the lack of informed consent, which was given by only 30 % of patients, most of whom were not specifically warned about potential nerve injury.
- Functional implications (eating, speaking, drinking, kissing, tooth brushing and avoidance)
- Psychological (personality traits, anxiety, stress, post-traumatic stress disorder, anger, etc.)

Table 22.1 Permanent neuropathy rates

Procedure	Recovery rate	Reference
Third molar surgery	IANI – 67 %; LNI – 72 % Buccal access TMS LIN – lingual access TMS 88 %	[8] [26] (90 %) [6])
Mandibular fractures	IANI – 91 %	[3]
Orthognathic surgery	IANI – 97 % BSSO IANI (patients are quoted 8–20 %)	[17]
Local anaesthesia inferior dental block (mainly Lidocaine)	25 %	[35]
Implant-related IANI	Complete recovery – 50 % Partial recovery – 44 % No change – 6 %	[19]

A review of common operations such as groin hernia repair, breast and thoracic surgery, leg amputation, and coronary artery bypass surgery found an incidence of chronic post-surgical pain in 10–50 % of patients [20]

22.1.5 Prognosis

It is the author's opinion that it is not possible to classify the degree and prognosis of sensory nerve injury based on clinical findings early post-injury. Just as a phantom limb patient may express non-existence or existence of a 'normal feeling' limb (after amputation; the most catastrophic nerve injury) with or without pain, numbness or altered sensation. Thus in order to evaluate the outcome of nerve injury the patient must be reassessed and/or treated if indicated. The type and related permanency of trigeminal nerve injuries is summarised in Table 22.1.

22.1.6 Management of Iatrogenic Trigeminal Nerve Damage

The management will depend on the mechanism (Table 22.2) and the duration of the nerve injury and the patients' complaints. Many injuries have limited benefit from surgical intervention and should be managed symptomatically. Earlier intervention is required for endodontic, implant and third molar-related nerve injuries as discussed.

If there is a persistent large neuropathic area (>40 % dermatome) then a severe nerve injury is present. If pain and/or hypersensitivity are present these will often be the main precipitating factors of difficulty with daily function. These symptoms may not be best treated using surgical intervention, however the patient's inability to cope with disability and pain, is often the driving factor.

Prevention is the key as no management strategy guarantees resolution of nerve injury in relation to implants. Timing of intervention is summarised in Table 22.2.

Table 22.2 Timing and management of trigeminal nerve injury

Event	Duration
Endo	<24–48 h surgery
Implant	<24–48 h surgery
Wisdom teeth – Inferior alveolar nerve injury	<2 weeks surgery
Wisdom teeth – Lingual nerve injury	>3–months surgery
Local anaesthetic nerve injuries (LN or IAN)	Therapeutic management only
Orthognathic nerve injuries	Therapeutic management only
Mandibular fracture nerve injuries	Therapeutic management only

A known or suspected sectioned/damaged nerve should undergo immediate exploration repair

Management of LA, orthognathic surgery and trauma-related injuries is essentially by counselling and medication for pain if present; however, prevention is better than cure. Valid consent will ensure that the patient understands the surgical risks and consequences when nerve injury occurs. Reassurance of the patient and giving them realistic expectations of recovery is suggested. Iatrogenic nerve injuries will require treatment in the

- Acute phase (within 30 h)
- Or Late phase

22.1.6.1 Acute Phase

There may be a limited window to maximise inferior alveolar nerve injury resolution in relation to dental implants, endodontics and mandibular wisdom teeth. A report illustrated that early removal of implants (within 30 h) may maximise neuropathy resolution, however the evidence remains weak [21].

The suggested protocol based upon available evidence includes:

- HOMECHECK – The treating clinician must contact the patient between 6 and 24 h after surgery (Homecheck) to establish any persistent neuropathy after LA has resolved. (This builds on the relationship of the clinician with the patient that will be premised upon good consent process.)
- Confirm the presence of neuropathy. If the neuropathy affects most of the dermatome +/– associated with severe neuropathic pain nerve injury must be suspected.
- Say SORRY. This is NOT an admission of guilt.
- Additional scanning or radiography is not essential.
- Initiate medical management.
  - High dose oral NSAIDs (600–800 mgs Ibuprofen PO QDS)
  - GMP prescription for Prednisolone 5-day step-down dose 50–40–30–20–10 mg PO (not for patients with contraindications for steroids or NSAIDs)
- Prompt removal of the implant to maximise potential resolution of the nerve injury is advised.
- Review patient and report CQC

22.1.6.2 Late Phase

After 3–7 days nerve injury is likely to be permanent and therapeutic management is indicated. With patients presenting with IAN neuropathy late postoperatively the author no longer removes implant similar to other specialists (Pogrel A, personal communication), as it appears to be of little value in reversing nerve damage and associated symptoms.

Overall management of patients with iatrogenic trigeminal nerve injury

Management options for post-traumatic neuropathy will depend upon the mechanism, duration of injury and the patients' wishes. Management options include;

- Reassurance and review
- Medical management – early intervention for minimising neural inflammation (steroids, NSAIDs, although the protocol is not evidence-based) and pain management or for the management of depression
- Counselling
- Surgery

The clinician must discern exactly what need to be addressed based upon the patients;

- *Disability*
- *Can't cope!*

The planned treatment must address the patients' concerns appropriately and the aims of treatment would ideally provide:

- *Improved function*: Treatment will NOT restore function completely
- *To improve sensation*: Treatment will NEVER restore normal sensation
- *To reduce pain or altered sensation*: The neuropathic pain can be managed using antiepileptic drugs if the pain is neuralgic, tricyclic antidepressants if the pain is constant and burning in nature or external local anaesthetic patches if the lip is very sensitive to touch or change in temperature.

22.1.7 Summary of Possible Management Tools

1. Timing of intervention and mechanism of injury are paramount in decision making in treatment of trigeminal nerve injuries.
2. Counselling is the most useful tool for managing patients with permanent sensory problematic nerve injuries.
3. Medical symptomatic therapy is indicated for patients with pain or discomfort and for patients with anxiety and/or depression in relation to chronic pain. But due to the extensive side effects of chronic pain medication, less than 8 % of patients remain on medication

- Topical agents for pain (Versatis Patches topical Lidocaine 5 % 12 h on and 12 h off) [22]
- Systemic agents for pain [11]
  - Tricyclic antidepressants (Amitriptyline and nortriptyline)
  - Antiepileptics (Pregabalin or Gabapentin) [46]

4. Surgical exploration
   - Immediate repair if nerve section is known
   - Remove implant within 24 h (ideally)
   - Explore IAN injuries is no longer indicated for nerve injuries older than 4 weeks
   - Exploratory surgery for lingual nerve injuries within 3 months post-injury [43, 44]

None of these interventions 'fix' the patient, but the aim is to manage their symptoms as best as possible, often not very satisfactorily. The prospect of lifelong neuropathic pain combined with functional difficulties and the psychological impact of the iatrogenesis is often a significant challenge for any patient and clinician to manage.

22.2 Burning Mouth Syndrome

Burning mouth syndrome is a rare but impactful condition affecting mainly postmenopausal women resulting in constant pain and significant daily difficulty with eating, drinking and daily function. The aetiology of BMS remains an enigma. Recent evidence suggests a likely neuropathic pain, the cause of which remains unknown. There is no cure for this condition and the unfortunate patients remain managed on a variety of neuropathic pain analgesics, salivary substitutes and other non-medical interventions that help the patient 'get through the day'.

Burning sensations in the mouth can result from a variety of causes including oral candidiasis, lichen planus, allergies, oral galvanism, xerostomia, systemic diseases like diabetes, deficiencies in vitamin B12, folic acid or iron, hormonal changes and autoimmune disease. In these cases, the term *secondary* burning mouth syndrome is used [9, 42]. The burning sensations may then subside if the primary cause is managed successfully. Primary Burning Mouth Syndrome (BMS), in which none of these potential etiological factors are present, is considered a neuropathic pain condition.

Up to now, no clear diagnostic criteria have been formulated for BMS, which may explain why the reported prevalence is between 0.7 and 15 %, predominantly in postmenopausal women [5, 9]. Clinically, patients complain of a mild to severe burning sensation and pain of especially the tongue, but also other mucosae in the oral cavity (lips, cheek, palate). Most of them do not have pain during the night, and little in the morning, while pain intensity increases throughout the day. Chewing, drinking of cold water and relaxation may alleviate the pain.

From a pathophysiological point of view, most recent studies point towards a small fibre neuropathy of the tongue and oral mucosae, and elements of central pain

related to hypofunction of the dopaminergic neurons in the basal ganglia (for review see Jääskeläinen [18]). In addition, dysregulation of the HPA-axis, influencing hormones and resulting in steroid alterations [47] and also neurodegenerative processes with hypofunction of the chorda tympani nerve [27] have been proposed.

A recent review article on BMS [41] summarises that recent neurophysiologic, psychophysical, neuropathological, and functional imaging studies may have elucidated multiple neuropathic mechanisms, mostly subclinical, acting at different levels of the neuroaxis and contributing to the pathophysiology of primary BMS. As in neuropathic pain, decreased brain activation to heat stimuli has been demonstrated with fMRI in BMS patients [4]

Some authors conclude that the clinical diagnosis of primary BMS may encompass three distinct, subclinical neuropathic pain states that may overlap in individual patients [13].

- Subgroup 1 (50–65 %) is characterised by peripheral small diameter fibre neuropathy of intraoral mucosa.
- Subgroup 2 (20–25 %) consists of patients with subclinical lingual, mandibular, or trigeminal system pathology that can be dissected with careful neurophysiological examination but is clinically indistinguishable from the other two subgroups.
- Subgroup 3 (20–40 %) fits the concept of central pain that may be related to hypofunction of dopaminergic neurons in the basal ganglia.

The neurogenic factors acting in these subgroups differ, and will require different treatment strategies. In the future, with proper use of diagnostic tests, BMS patients may benefit from interventions specifically targeted at the underlying pathophysiological mechanisms.

Management of BMS is difficult and more randomised clinical trials are warranted. For some approaches, like the use of clonazepam and cognitive behavioural treatment, evidence is available [7]. Several drugs acting as GABA modulators or agonists have been reported successful : sucking and/or swallowing clonazepam 0.5 mg, one to three times daily resulted in significant pain relief. Also diazepam and ketazolam have been tested with success. Gabapentin appeared to have some benefit if combined with alfa lipoic acid, while effect of pregabalin is limited to one case report. Also olanzapine and amilsulpride were reported effective. Some conflicting results were reported for the SSRIs: while duloxetine resulted in significant pain relief, two studies on Milnacipram gave opposite results.

Several natural supplements have been studied and reported effective in reducing the burning sensations, some in controlled trials: catuama, a herbal supplement, resulted in significant symptom reduction, while supplementation of zinc in case of deficiency, decreased the pain scores. Capsaicin rinses in order to desensitise the receptors was tested and found efficacious. Several studies focused on alfa lipoic acid in the management of BMS, with conflicting results: no significant effect if used as such, but clear pain reduction if combined with gabapentin. Several other approaches have been advocated: low level laser therapy was reported effective and

also acupuncture had beneficial results. A single study documented impressive pain reduction after electroconvulsive therapy. Cognitive behavioural approach and psychotherapy have been shown effective in BMS.

Despite such ongoing research, central and peripheral pain mechanisms in BMS are still not understood in their entirety. Questions remain regarding the possibility of a dominating nervous system driving the condition or a more complex network of central, peripheral and psychological aspects impacting on a susceptible patient, with a possible genetic involvement

References

1. Alhassani AA, AlGhamdi AS (2010) Inferior alveolar nerve injury in implant dentistry: diagnosis, causes, prevention, and management. J Oral Implantol 36(5):401–407. doi:10.1563/aaid-joi-d-09-00059
2. Barrowman RA, Grubor D, Chandu A (2010) Dental implant tourism. Aust Dent J 55(4):441–445. doi:10.1111/j.1834-7819.2010.01267.x
3. Bede SY, Ismael WK, Al-Assaf DA, Omer SS (2012) Inferior alveolar nerve injuries associated with mandibular fractures. J Craniofac Surg 23(6):1776–1778. doi:10.1097/SCS.0b013e318266fda3
4. Bergdahl BJ, Anneroth G, Anneroth I (1994) Clinical study of patients with burning mouth. Scand J Dent Res 102(5):299–305
5. Bergdahl M, Bergdahl J (1999) Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med 28(8):350–354
6. Blackburn CW (1990) A method of assessment in cases of lingual nerve injury. Br J Oral Maxillofac Surg 28(4):238–245
7. Charleston L 4th (2013) Burning mouth syndrome: a review of recent literature. Curr Pain Headache Rep 17(6):336
8. Cheung LK, Leung YY, Chow LK, Wong MC, Chan EK, Fok YH (2010) Incidence of neurosensory deficits and recovery after lower third molar surgery: A prospective clinical study of 4338 cases. Int J Oral Maxillofac Surg 39(4):320–326. doi:10.1016/j.ijom.2009.11.010
9. Coculescu E, Tovaru S, Coculescu B (2014) Epidemiological and etiological aspects of burning mouth syndrome. J Med Life 7(3):305–309. Epub 2014 Sep 25. Review
10. Coulthard P, Bailey E, Esposito M, Furness S, Renton TF, Worthington HV (2014) Surgical techniques for the removal of mandibular wisdom teeth. Cochrane Database Syst Rev 29;7:CD004345. doi: 10.1002/14651858. CD004345
11. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD (2010) Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 85(3 Suppl):S3–S14. doi:10.4065/mcp.2009.0649
12. Elian N, Mitsias M, Eskow R, Jalbout ZN, Cho SC, Froum S, Tarnow DP (2005) Unexpected return of sensation following 4.5 years of paresthesia: Case report. Implant Dent 14(4):364–367
13. Forssell H, Jääskeläinen S, List T, Svensson P, Baad-Hansen L (2014) An update on pathophysiological mechanisms related to idiopathic oro-facial pain conditions with implications for management. J Oral Rehabil. doi:10.1111/joor.12256
14. Fukuda K, Ichinohe T, Kaneko Y (2012) Pain management for nerve injury following dental implant surgery at Tokyo dental college hospital. Int J Dent 2012:209474. doi:10.1155/2012/209474

15. Gomes AC, Vasconcelos BC, de Oliveira e Silva ED, da Silva LC (2005) Lingual nerve damage after mandibular third molar surgery: A randomized clinical trial. J Oral Maxillofac Surg 63(10):1443–1446. doi:10.1016/j.joms.2005.06.012
16. Hegedus F, Diecidue RJ (2006) Trigeminal nerve injuries after mandibular implant placement–practical knowledge for clinicians. Int J Oral Maxillofac Implants 21(1):111–116
17. Iannetti G, Fadda TM, Riccardi E, Mitro V, Filiaci F (2013) Our experience in complications of orthognathic surgery: A retrospective study on 3236 patients. Eur Rev Med Pharmacol Sci 17(3):379–384
18. Jääskeläinen SK (2012) Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol 123(1):71–77. doi:10.1016/j.clinph.2011.07.054. Epub 2011 Oct 24
19. Juodzbalys G, Wang HL, Sabalys G, Sidlauskas A, Galindo-Moreno P (2013) Inferior alveolar nerve injury associated with implant surgery. Clin Oral Implants Res 24(2):183–190. doi:10.1111/j.1600-0501.2011.02314.x
20. Kehlet H, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: Risk factors and prevention. Lancet 367(9522):1618–1625. doi:10.1016/s0140-6736(06)68700-x
21. Khawaja N, Renton T (2009) Case studies on implant removal influencing the resolution of inferior alveolar nerve injury. Br Dent J 206(7):365–370. doi:10.1038/sj.bdj.2009.258
22. Khawaja N, Yilmaz Z, Renton T, Khawaja N, Yilmaz Z, Renton T (2013) Case studies illustrating the management of trigeminal neuropathic pain using topical 5% lidocaine plasters. Br J Pain 7(2):107–113. doi:10.1177/2049463713483459
23. Leckel M, Kress B, Schmitter M (2009) Neuropathic pain resulting from implant placement: Case report and diagnostic conclusions. J Oral Rehabil 36(7):543–546. doi:10.1111/j.1365-2842.2009.01950.x
24. Loescher AR, Robinson PP (1998) The effect of surgical medicaments on peripheral nerve function. Br J Oral Maxillofac Surg 36(5):327–332
25. Long H, Zhou Y, Liao L, Pyakurel U, Wang Y, Lai W (2012) Coronectomy vs. Total removal for third molar extraction: A systematic review. J Dent Res 91(7):659–665. doi:10.1177/0022034512449346
26. Mason DA (1988) Lingual nerve damage following lower third molar surgery. Int J Oral Maxillofac Surg 17(5):290–294
27. Nasri-Heir C, Gomes J, Heir GM, Ananthan S, Benoliel R, Teich S, Eliav E (2011) The role of sensory input of the chorda tympani nerve and the number of fungiform papillae in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 112(1):65–72
28. Pichler JW, Beirne OR (2001) Lingual flap retraction and prevention of lingual nerve damage associated with third molar surgery: A systematic review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 91(4):395–401. doi:10.1067/moe.2001.114154
29. Pogrel MA (2009) An update on coronectomy. J Oral Maxillofac Surg 67(8):1782–1783. doi:10.1016/j.joms.2009.03.065
30. Pogrel MA, Schmidt BL, Sambajon V, Jordan RC (2003) Lingual nerve damage due to inferior alveolar nerve blocks: A possible explanation. J Am Dent Assoc 134(2):195–199
31. Renton T (2010). Prevention of iatrogenic inferior alveolar nerve injuries in relation to dental procedures. Dent Update 37(6): 350–352, 354–356, 358–360 passim
32. Renton T (2012) Notes on coronectomy. Br Dent J 212(7):323–326. doi:10.1038/sj.bdj.2012.265
33. Renton T, Adey-Viscuso D, Meechan JG, Yilmaz Z (2010) Trigeminal nerve injuries in relation to the local anaesthesia in mandibular injections. Br Dent J 209(9), E15. doi:10.1038/sj.bdj.2010.978
34. Renton T, Dawood A, Shah A, Searson L, Yilmaz Z (2012) Post-implant neuropathy of the trigeminal nerve. A case series. Br Dent J 212(11):E17. doi:10.1038/sj.bdj.2012.497
35. Renton T, Devine M (2013) Diagnosis and management of inferior alveolar nerve damage associated with dental implant surgery. Forum Implantologicum 9:16–27
36. Renton T, Hankins M, Sproate C, McGurk M (2005) A randomised controlled clinical trial to compare the incidence of injury to the inferior alveolar nerve as a result of coronectomy and removal of mandibular third molars. Br J Oral Maxillofac Surg 43(1):7–12. doi:10.1016/j.bjoms.2004.09.002

37. Renton T, Janjua H, Gallagher JE, Dalgleish M, Yilmaz Z (2013) UK dentists' experience of iatrogenic trigeminal nerve injuries in relation to routine dental procedures: Why, when and how often? Br Dent J 214(12):633–642. doi:10.1038/sj.bdj.2013.583
38. Renton T, Yilmaz Z (2011) Profiling of patients presenting with posttraumatic neuropathy of the trigeminal nerve. J Orofac Pain 25(4):333–344
39. Renton T, Yilmaz Z (2012) Managing iatrogenic trigeminal nerve injury: A case series and review of the literature. Int J Oral Maxillofac Surg 41(5):629–637. doi:10.1016/j.ijom.2011.11.002
40. Rood JP, Shehab BA (1990) The radiological prediction of inferior alveolar nerve injury during third molar surgery. Br J Oral Maxillofac Surg 28(1):20–25
41. Sardella A (2007) An up-to-date view on burning mouth syndrome. Minerva Stomatol 56(6):327–340
42. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA (2003) Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 14(4):275–291
43. Strauss ER, Ziccardi VB, Janal MN (2006) Outcome assessment of inferior alveolar nerve microsurgery: A retrospective review. J Oral Maxillofac Surg 64(12):1767–1770. doi:10.1016/j.joms.2005.11.111
44. Susarla SM, Kaban LB, Donoff RB, Dodson TB (2007) Does early repair of lingual nerve injuries improve functional sensory recovery? J Oral Maxillofac Surg 65(6):1070–1076. doi:10.1016/j.joms.2006.10.010
45. Van Assche N, van Steenberghe D, Guerrero ME, Hirsch E, Schutyser F, Quirynen M, Jacobs R (2007) Accuracy of implant placement based on pre-surgical planning of three-dimensional cone-beam images: A pilot study. J Clin Periodontol 34(9):816–821. doi:10.1111/j.1600-051X.2007.01110.x
46. van Seventer R, Bach FW, Toth CC, Serpell M, Temple J, Murphy TK, Nimour M (2010) Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. Eur J Neurol 17(8):1082–1089. doi:10.1111/j.1468-1331.2010.02979.x. Epub 2010 Mar 4
47. Woda A, Dao T, Gremeau-Richard C (2009) Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 23(3):202–210
48. Ziccardi VB, Assael LA (2001) Mechanisms of trigeminal nerve injuries. Atlas Oral Maxillofac Surg Clin North Am 9(2):1–11