A Markov approach to characterizing the PK-PD relationship of anti-migraine drugs

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General introduction: analysis of the treatment response of anti-migraine drugs in clinical trials

1.1 Summary and outline

Migraine is a disabling disease that affects roughly 12% of the population. New pharmacological treatments are under development that potentially abort or prevent migraine attacks. However, the evaluation of the efficacy of new anti-migraine drugs is complicated by the episodic, dynamic nature of the disease, high variability in placebo response and the lack of sensitive biomarkers. In this thesis, a novel pharmacokinetic-pharmacodynamic (PK-PD) approach is proposed that is based on Markov models. This approach aims at improving the assessment of drug efficacy within the current clinical setting. Specifically, this method allows:

1. time-independent comparison of the effects of different drugs;
2. prediction of the influence of pharmacokinetic properties (*e.g.* absorption rate) on the onset of the effect;
3. evaluation of the relevance of covariates (*e.g.* age) on treatment effect;
4. characterisation of the time course of secondary clinical endpoints such as headache recurrence.

This introduction first defines migraine in terms of its symptoms, pathophysiology and its burden on society. Next, the pharmacological approaches to migraine treatment are reviewed and current directions in drug development are considered. Thirdly, the assessment of migraine headache in clinical trials is discussed. The analgesic effect of a drug on migraine headache is usually quantified using randomised, double-blind, placebo controlled, parallel group design, in which standard statistical analysis are performed for estimating the contrast between active and placebo treatment arms at pre-defined time points after dosing rather than based on modelling of the concentration-effect relationships. A few examples in which modelling techniques that have been proposed are briefly reviewed. Lastly, it is argued that anti-migraine effects can be suitably quantified by applying the PK-PD concept to Markov models, by which the individual time course of headache is delineated as a transition between different (disease) states. The notion of state transition to describe drug action and quantify treatment response under non-stationary conditions has not been explored previously in migraine or other episodic disease conditions.

1.2 The burden of migraine

1.2.1 Patient viewpoint

Clinical symptomatology

Though the migraine attack has been subdivided in various stages, most subdivisions include premonitory, headache and postdrome phases. The most characteristic feature of an attack is the headache, which is generally unilateral and of a throbbing nature. It is aggravated by physical activity. Untreated or unsuccessfully treated, the headache lasts between 4 and 72 hours. It is accompanied by nausea, vomiting and/or sensitivity to light and sound [1]. Between attacks, the neurological examination of migraine patients is normal. On a sub-clinical level, electrophysiological features have been found that suggest cortical hyperexcitability and seem to be characteristic of the migrainous brain. However, large intra- and interindividual variability preclude the use of these methods as diagnostic tools [2]. In rare cases cerebral lesions can be detected that are the result of prolonged neurological symptoms during a previous migraine attack.

Before the onset of headache, subtle symptoms occur in 55% to 65% of patients [3]. These so-called premonitory symptoms develop between several hours and three days before an attack. Non-headache symptoms may persist into the headache phase and may last up till two days after resolution of pain, at which time they are termed postdromal.

In a diary card study of non-headache symptoms the three most prevalent symptoms during the premonitory phase, the headache phase and postdrome were respectively, fatigue (72.5%, 84.3%, 88.2%), difficulty with concentration (51.1%, 72.6%, 55.5%) and stiff neck (49.7%, 62.8%, 41.9%). However, in this study not all self-reported premonitory symptoms led to headache within 72 hours. Alternatively, some headaches developed without patients reporting these symptoms. The three most consistent predictors of headache were difficulty with speech, difficulty with reading and writing, and yawning.

Respectively, these symptoms resulted in an attack 4.90, 3.49 and 2.07 times more often than not [4].

Fifteen to twenty percent of migraine patients experience aura just before or at the onset of headache. Aura is a focal cerebral dysfunction consisting of visual, sensory or speech problems, or a combination of those. The visual disturbance is most common and presents in the form a bright zigzag figure that may gradually spread and curve outward in one direction while flashing on the edge and leaving variable degrees of vision loss in its track. A sensory aura is a tingling sensation slowly spreading up or down one side of the body, leaving numbness in its track. Less common are impairments of speech and verbal comprehension. Aura develops over 5 minutes or longer and usually last between 15 and 30 minutes [1, 3].

Following its onset, headache intensity usually increases and reaches a moderate or severe level in 30 minutes to 3 hours [5]. However, some patients only develop mild headache. Attacks of "familial hemiplegic migraine" can even be completely void of headache. The symptomatic course of migraine is illustrated in Figure 1.1.

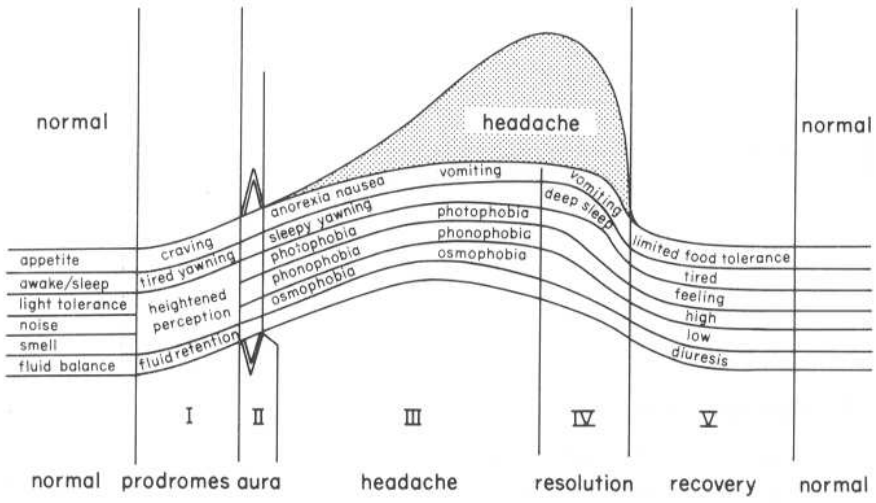

Figure 1.1: *Phases of a migraine attack and associated clinical symptomatology, from [6].*

Migraine heterogeneity

Migraine is a heterogeneous disorder. In a patient population, the symptoms experienced during an attack can vary widely in intensity, frequency and duration. A complete picture of the migraine attack can be obtained by characterising the statistical distributions of the various symptoms. Reliable descriptors for these distributions are commonly obtained by summarising the findings of a number of representative studies and surveys in a meta-analysis. Unfortunately, pain intensity, duration and frequency of attacks have

Table 1.1: *Diagnostic drift over a 12-month period. At the start of the study, the distribution of patients over the states* migraine, migrainous disorder *and* other episodic headache *was [0.32, 0.32, 0.36], respectively. Adapted from [12].*

		second diagnosis		
		migraine	migrainous	other
first diagnosis	migraine	0.62	0.29	0.09
	migrainous	0.23	0.50	0.27
	other	0.07	0.23	0.70

been assessed using a variety of scales and categories. This lack of conformity prevents a straightforward summary of symptom characteristics. Yet, in one review of clinical studies the proportion of patients reporting headache intensity that is severe or worse ranges between 24% and 84%. The frequency varies between 0.4 and 1.5 attacks per month and the median duration ranges from 9 h to 24 h [7].

In a cross-section of migraineurs, the heterogeneity of symptoms may be due to the presence of different subtypes of migraine and different stages of progression of the illness. For example, the headache of a migraine that typically occurs at menses (menstrual migraine) on average is more intense than other types of migraine [3]. Over the course of years the frequency and intensity of attacks gradually declines in some patients [8]. On the other hand, a history of medication overuse may cause migraine to develop into a chronic and more painful form of migraine [9]. The expression of symptoms is also dependent on or limited by patient characteristics such as stress, co-morbidity and use of contraceptives [10, 11]. Furthermore, some reports suggest that overuse of analgesics and other anti-migraine treatments can negatively impact the severity, duration and frequency of migraine episodes. Heterogeneity is not only observed in a cross-section of patients. Disease progression, medication use and lifestyle changes also introduce heterogeneity in the course of an individual patient's migraine. Even in short longitudinal studies of migraine, symptoms can vary to the extent that a patient is diagnosed differently on subsequent occasions. Indeed, although two-thirds of sufferers retain their migraine diagnosis one to two years after initial examination, the symptomatic profiles of the remaining third no longer meet the requirements for strict migraine [12, 13]. Nachit-Ouinekh *et al.* [12] presented the one-year alterations as a transition matrix (Table 1.1).

The precipitation and course of single migraine episodes have been shown to be influenced by external factors. Many patients identify strong sensory stimuli as capable of eliciting attacks. During an attack, physical exercise and smell are known to aggravate illness [14]. The patient's ability to avoid these external factors strongly influences the manifestation of symptoms. The varying degree of reproducibility found for various migraine symptoms may be an indication of the patient's effort to avoid aggravating factors: in a two-year interval, vomiting was found less reproducible than headache [12, 13].

Migraine resembles other visceral headaches in that all involve autonomic mechanisms that cause nausea, photophobia and tiredness [5]. Based on their variable chronic-

ity, a range of headache types, including migraine, has been proposed to constitute a continuum. Patients can progress on this continuum from the episodic end to the chronic end and vice versa [15]. Owing to these dynamics, migraine's close association with other diseases and its susceptibility to external factors, the impact of migraine will be different from one patient to the other.

Pathophysiology

The pathophysiological mechanisms behind most of the symptoms of migraine have been elucidated. However, the primary cause of migraine remains to be uncovered.

The pain in migraine and other primary headache types, such as cluster headache, arises from stimulation of the first division of the trigeminal nerve. This stimulation may be caused by dilatation of blood vessels supplying the meninges. The nociceptive trigeminal fibres converge in the trigeminal nucleus of the brain stem and the upper divisions of the cervical spinal cord. Here, the pain signal is relayed to central neurons that carry it to higher cortical centres, which register pain, photophobia and phonophobia. The activated trigeminal nucleus also connects with adjacent brain stem centres. Among these is the *nucleus tractus solitarius*, which upon activation mediates nausea and vomiting [16]. Activation of trigeminal pain fibres also triggers the release of inflammatory mediators from their nerve endings. The resulting neurogenic inflammation maintains the stimulation of the trigeminal nerve which causes the headache to persist [17].

The central neurons receive input not only from trigeminal fibres but also from cervical afferents innervating head and neck areas. Continued stimulation of trigeminal fibers leads to constitutively activated central neurons. As a consequence of this sensitisation process pain is perceived in all receptive fields that provide input to the central neurons, including the head, neck and arms [18]. In parallel, the stimulation of nociceptive structures in the meninges is thought to be initiated by a phenomenon termed cortical spreading depression. It involves a wave of neuronal excitation followed by neuronal depression that migrates along the cortex at approximately 3 mm/min. Concomitantly, blood flow first increases and then decreases and extracellular levels of ions and neurotransmitters rise. These mediators can initiate trigeminal activity and thus precipitate a migraine episode [19]. Cortical spreading depression is also implicated in migrainous aura. Indeed, the similarities in timing and dynamics between these phenomena are striking [20].

What is it that causes the vulnerability to cortical spreading depression in migraine patients? Rather than a transitory phenomenon due to an organic dysfunction, genes seem to underlie the aetiology of cortical spreading depression. Especially in migraine with aura a strong genetic influence has been detected. The gene coding for the brain-specific P/Q type calcium channel α-1 subunit has been found causative of familial hemiplegic migraine [21]. Inherited mutations in ion channels affect membrane excitability. The ensuing brain dysfunctions are at the basis of a number of diseases that are collectively termed channelopathies. Between migraine attacks, patients showed increased excitability of the visual and auditory cortex. At the same time, a lack of habituation to sensory stimuli was demonstrated. During an attack, habituation normalises: cortical ac-

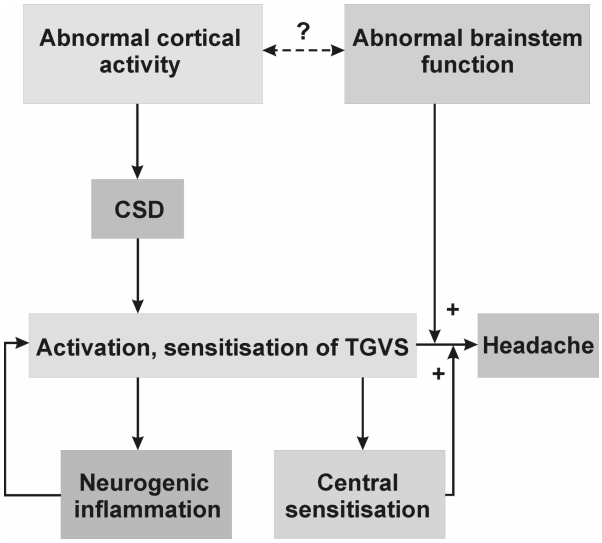

Figure 1.2: *Proposed pathophysiology of migraine. Abnormal brain activity allows environmental and internal trigger factors to provoke a cortical spreading depression (CSD). CSD stimulates the nociceptive trigeminal nerve and its vasculature (TGVS) which causes headache. The release of inflammatory mediators from nerve terminals renders the TGVS auto-stimulating. Prolonged activation causes sensitisation of higher-order neurons, adding to the nociceptive response and widening its scope. Lastly, a diminished descending inhibition by the brainstem permits worsening of the headache. Reproduced from [17].*

tivity does not increase anymore with increasing frequency of the stimulus. Is has been hypothesised that the simultaneous occurrence of a period of hyperexcitability and an appropriately intense stimulus can elicit an attack [17].

The proposed pathophysiology of migraine is schematically depicted in Figure 1.2.

1.2.2 Epidemiological viewpoint

The impact of a disease on a patient population and the relevance of the development of medications for the disease are often substantiated by epidemiological data. Lately, the epidemiology of migraine and other headache types has received much attention, which has resulted in a better appreciation of the healthcare needs of migraine patients.

Incidence, prevalence and mortality are the epidemiological starting points upon which all studies assessing the burden of a disease are based. In migraine, incidence and prevalence are dependent on the patient's sex, age, type of migraine, geography and socio-economical status [22]. The age-specific number of new cases per risk unit (incidence) is summarised in Figure 3. The age-specific percentage of migraine patients in the population (prevalence) is given by Figure 4. It is thought that the high incidence in adolescent women is associated with the hormonal changes occurring during puberty [23].

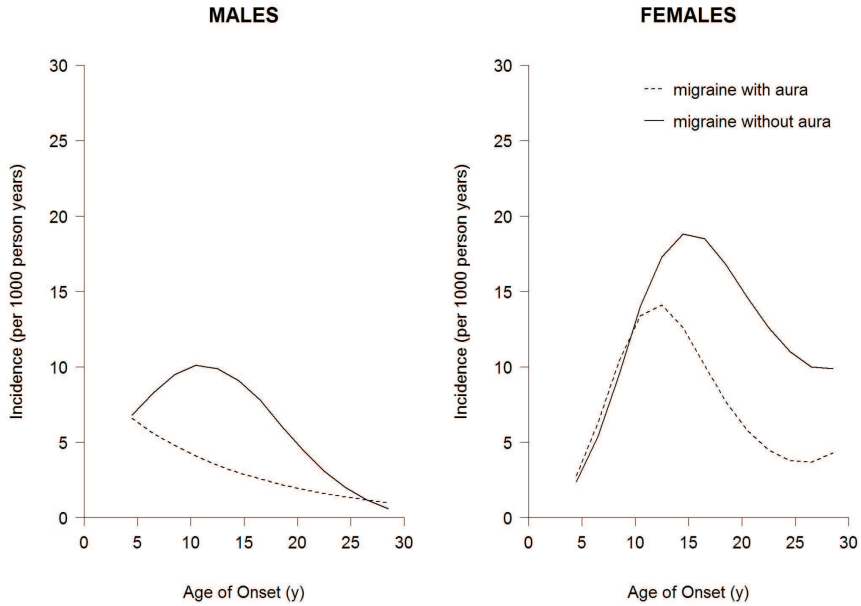

Figure 1.3: *Sex- and age-specific incidence of migraine headache with and without aura among 10,131 respondents 12-29 years of age: Washington county, Maryland, US, 1987. Reproduced from [23].*

Hormonal factors are also believed to be the reason for the higher overall prevalence in women (18% vs 6% in men [24]).

Migraine is not a cause of mortality, although it has been contended that it is a risk factor for stroke [25]. In particular, migraine accompanied by visual disturbances (aura) and migraine with high frequency of attacks add to this risk. In contrast, consensus exists about migraine morbidity. The damaging effect of migraine attacks on the brain has been demonstrated in a clinical study which showed evidence of lesions that were attributed to migraine attacks [26]. In addition, migraine is co-morbid with epilepsy. It is present 2.4 times more often in epileptics than in their non-epileptic relatives [27]. A direct causal relation between these diseases has been ruled out based on epidemiological considerations. However, a state of hyperexcitability common to both has been suggested as a mechanism of co-morbidity [28].

In order to enable thorough characterisation of the burden of migraine, other epidemiological measures have been defined that take into account disability and chronicity. “Years lived with disability” (YLD) combines the incidence within a certain period, the age at onset, the duration of the disease-related disability and the weight of the disability [29]. The weight takes into account both frequency and severity. In their year 2000 Global Burden of Disease study, the World Health Organisation (WHO) estimated the

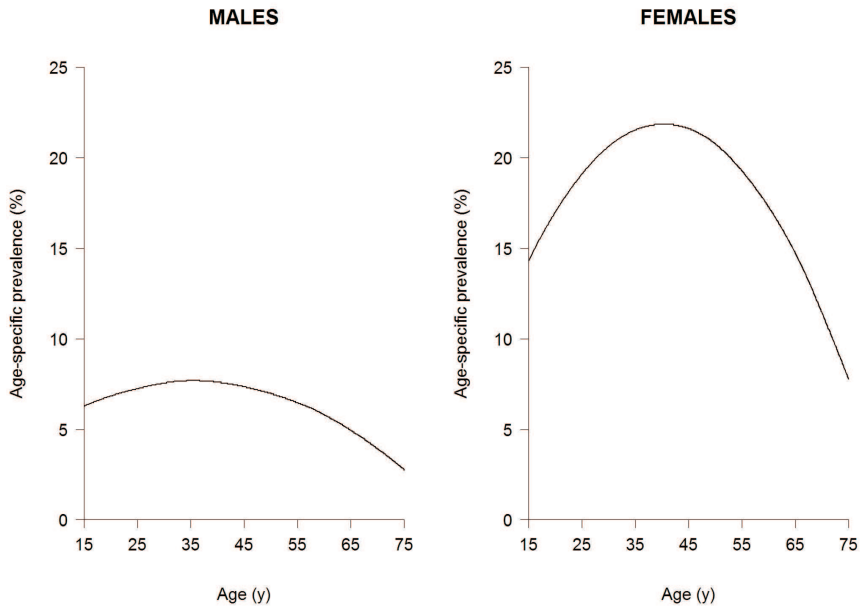

Figure 1.4: *Sex- and age-specific prevalence of migraine, from a meta-analysis of studies using International Headache Society (IHS) criteria. Reproduced from [22].*

worldwide YLD for migraine at 2044 and 7536 life years lived with disability (0.8% and 1.4% of all causes of YLD), in men and women, respectively [30]. The disability weight of migraine was estimated at 0.029 on a scale between 0 and 1 [31]. For reference, epilepsy disability was estimated at 0.113. In the 2002 WHO survey, based on the YLD endpoint, migraine was the 10th cause of disability among women [31].

Cost-of-illness analyses have been performed that further underline the impact of migraine. These analyses require not only prevalence data, but also estimates of direct and indirect costs. Direct costs mainly include medication and outpatient care, whereas indirect costs are associated with absenteeism and reduced work productivity. In a review of 11 European studies, the annual total cost per patient was estimated at 461, the largest part of which was taken up by the indirect costs [32].

With the introduction of the relatively expensive triptan drugs the question of cost-effectiveness became an important issue. The cost-effectiveness of triptans has been determined in a number of phase IV studies [33]. These studies compared the net costs associated with sumatriptan therapy with those associated with conventional therapy. Alternatively, decision-analytical models have been developed incorporating prevalence, direct and indirect costs and measures of drug efficacy [33]. Efficacy estimates can be directly derived from clinical data or from meta-analyses of clinical data. They are expressed as the probability of pain relief occurring within a certain time given a standard

dose of the drug. From these studies, it appears that triptans are cost-effective. Little consensus exists about the representation of the benefit and uncertainty levels are usually not given. For example, using a model-based approach and data from a multi-national study, annual cost savings of US$352 and US$410 per patient have been reported, for oral doses of 50mg and 100mg sumatriptan, respectively [34].

Epidemiological studies quantifying the burden of migraine have increased awareness of the impact of this disease. As a result, more resources are spent on migraine care and research. To a large extent the research focuses on unravelling the mechanisms of migraine pathogenesis [35]. At the same time, clinical research and drug development exploit mechanistic findings to better understand the course of migraine in patients and improve existing therapies.

1.3 Anti-migraine therapy

1.3.1 Acute therapy

Increased insight into the pathophysiology of migraine has greatly improved options for treatment. In particular, the development of serotonin 1B and 1D (5-HT$_{1B/1D}$) receptor agonists, collectively termed triptans, was driven by advances in the understanding of the role of serotonin in migraine.

The observation that serotonin can abort migraine attacks led researchers to synthesise serotonin agonists with the same anti-migraine efficacy but without the corresponding side effects [36]. The first publication mentioning the effects of such a compound appeared in 1988 [37]. Later named sumatriptan, it was the first drug in this class to be developed and marketed. Though sumatriptan is most often administered orally in doses of 50 mg or 100 mg, it is the only triptan for which also intranasal (20 mg) and subcutaneous (6 mg) formulations are available. The intranasal form (10 mg) has been approved for use in children. Attempts to improve the poor bioavailability of oral sumatriptan (14%) resulted in the development of the second-generation triptan naratriptan. About 60% of this drug is absorbed after administration of an oral dose of 2.5 mg [38]. Furthermore, its half-life (5h to 5.5h) is considerably longer than that of sumatriptan (2h). At efficacious concentrations, a prolonged exposure may reduce the risk of migraine pain reoccurring after initial relief from treatment [39].

Initially, the efficacy of triptans was considered to be due to a peripheral action on meningeal blood vessels. Activation of 5-HT$_{1B}$ receptors is known to constrict the middle meningeal artery in many species. However, studies of triptans in animal models of trigeminal pain have shifted this view toward a greater involvement of neuronal 5-HT$_{1B/1D}$ receptors [40, 41]. Due to the widespread occurrence of these receptors throughout the trigeminal system, multiple mechanisms of action have been proposed. In a review of naratriptan all of the following neuronal mechanisms were considered likely [42]:

1. Naratriptan can prevent neurogenic inflammation at trigeminal sensory nerve endings by blocking the release of neuropeptides. This inhibitory action is mediated

by 5-HT$_{1B/1D}$ and 5-HT$_{1F}$ receptors.

2. Activation of 5-HT$_{1B/1D}$ receptors at the trigeminal ganglion hyperpolarises neurons decreasing signal transmission to central neurons.

3. Inhibition of trigeminal sensory neurons at the central end attenuates 5-HT$_{1D}$-mediated signal transmission to central neurons.

4. Naratriptan may inhibit second-order neurons upon binding to post-synaptic 5-HT$_{1B/1D}$ and 5-HT$_{1A}$ receptors.

5. By activating central neurons in the peri-aqueductal grey naratriptan stimulates a descending pain-inhibiting pathway that may be dysfunctional in migraine patients.

6. Finally, naratriptan supposedly inhibits structures in the thalamus that are associated with pain-perception through 5-HT$_{1B/1D}$ receptors.

Naturally, any central action of triptans is dependent on the compound's capacity to cross the blood-brain barrier. Brain penetration studies have only been performed with sumatriptan. In these pre-clinical studies, only 0.006% to 0.05% of a dose was distributed to brain tissue [43, 44]. This would make a central action of sumatriptan unlikely. Yet, experiments in an animal model of trigeminal pain suggested sumatriptan's primary action is at centrally located pre-synaptic receptors of the trigeminal sensory nerve [45].

In humans, a central action is possible if during migraine attacks the blood-brain-barrier becomes permeable to sumatriptan [46]. Since the improved absorption profile of second-generation triptans is mainly due to their increased lipophilicity, one could deduce that naratriptan is more brain-penetrable than sumatriptan. Despite considerable differences in the octanol-water partition coefficients for naratriptan and sumatriptan at pH 7.4 (*i.e.* -0.2 *vs* -1.3, respectively), no significant correlation has been found between a triptan's lipophilicity and its anti-migraine efficacy [42]. Therefore, the relative contribution of central effects to clinical efficacy remains unclear.

In the recovery phase of a migraine attack, nausea and headache often subside simultaneously. Trigeminal sensory neurons have been shown to project directly to the *nucleus tractus solitarius* and indirectly through the *trigeminal nucleus* [42]. The effect of triptans on nausea may be achieved by binding to serotonin receptors located on nerve cells of either of these nuclei.

The specific action of triptans at 5-HT$_{1B/1D}$ receptors is an advantage over alternative medications such as analgesics and ergot alkaloids. Side-effects can be neurological and vascular in nature and are usually mild or moderate and short-lasting ($\leq$ 3h). Their occurrence also strongly depends on the route of administration. Adverse events are more frequent following subcutaneous injection than after oral administration. Neurological symptoms include numbness, tingling, warm sensations and flushing. Chest pain is an infrequently reported adverse event that is possibly linked to contraction of myocardial vasculature. Although in vitro experiments indicate that triptans can cause constriction

of human coronary arteries, clinical tests have found no proof of this mechanism. Yet, triptans are not prescribed for patients with signs of ischemic disease [47].

Before the emergence of triptan therapy ergotamine was the most-widely used and most effective acute anti-migraine treatment. Less selective than triptans, ergotamine binds to various serotonin receptor sub-types and to α -adrenoceptors. Such a lack of selectivity has precluded investigations into the mechanism of action. Moreover, in the ergotamine era the vascular theory was the leading pathophysiological theory of migraine. This means that all proposed mechanisms were based on the vasoactive properties of the compound. Perhaps more notable than its anti-migraine action are ergotamine's adverse event profile and its erratic absorption kinetics [6]. Due to a narrow therapeutic window, ergotamine is easily overdosed. In addition, with a terminal half-life of 20h, the drug is prone to accumulation. Side effects can be very similar to the symptoms of a migraine attack. This has often led to patients being wrongly diagnosed with *status migrainosus*, a chronic form of migraine. Rarer are the occurrences of gangrene, convulsions, dementia, coma and cardiac arrest.

Despite the availability of triptans, analgesic drugs have remained popular for the treatment of migraine. This is partly so because many migraine patients are never diagnosed and these drugs are available over-the-counter. Typical analgesics used in migraine are aspirin, paracetamol and non-steroidal anti-inflammatory drugs such as naproxen. Apart from paracetamol, these drugs likely act by suppressing the prostanoid component of the neurogenic inflammation. However, as aspirin binding studies have showed high affinity to dorsal horn and brain stem nuclei, central effects cannot be dismissed. Indeed, many analgesics do not only inhibit pain, but also decrease nausea and photophobia, indicating central mechanisms. From a safety aspect, gastric discomfort is the most common adverse event that occurs after the administration of aspirin. It is caused by inhibition of the enzyme cyclooxygenase isotype 1 (COX-1), whilst inhibition of the isotype 2 (COX-2) is associated with the desired anti-inflammatory effect [48].

Analgesic drugs are non-specific and are less efficacious against severe migraine pain. Nevertheless, combination tablets of sumatriptan and naproxen have shown more efficacy than either of the drugs alone [49]. In fact, a polytherapeutic approach has been advocated especially in refractory patients and in those with headache recurrence after initial therapy with triptan [50].

With the abundance of triptans that are currently available, little improvement can be expected from new varieties of 5-$HT_{1B/1D}$ receptor agonists. Among new targets being investigated are selective 5-HT_{1F} agonists and antagonists of the calcitonin gene-related peptide. This peptide is the main mediator of neurogenic inflammation and is also a neurotransmitter of the trigeminal system [51]. Yet, most of ongoing clinical research on potential targets for abortive therapy is symptomatic in nature, lacking a mechanistic rationale aimed at triggering mechanisms. Anti-emetics by suppository or injection may be needed in cases where vomiting dominates the symptoms. These drugs are most efficacious when they are taken in the early phase of the attack.

1.3.2 Prophylaxis

About 5% percent of migraine patients use pharmacological treatment outside attacks to reduce their frequency, duration or intensity [52]. Secondary benefits include a better response to acute medication, a reduced disability and possibly a smaller risk of progressing to a more chronic or severe form of migraine [53]. Preventive therapy is most commonly prescribed to patients with recurring and disabling migraines and to patients that cannot take acute medication due to lack of efficacy, contraindication, overuse or adverse events [54].

The discovery of preventive drugs is often an empirical process and the use of migraine prophylactics is limited due to their rather poor efficacy. Few drugs are more than 50% effective at reaching a 50% reduction in attack frequency. One reason for this low success rate is the lack of understanding of the initiation of a migraine attack, which complicates the search for drug targets. Any clinical efficacy may further be obscured by a poor patient compliance and a powerful placebo effect. Placebo-mediated reductions of up to 70% of the migraine frequency have been observed within 3 months [55, 56, 57].

The currently available migraine prophylactics are thought to act through either one or both of the following mechanisms: They may increase the threshold for neuronal excitability in the same way anticonvulsants do in epilepsy. Alternatively, they may modulate the nociceptive system in a way that is similar to that of acute anti-migraine drugs [58].

The β-adrenoceptor antagonists propranolol and metoprolol are the most prescribed migraine prophylactics. They are thought to reduce hyperexcitability by decreasing the central adrenergic function and by interfering with the central serotonergic system. Through these actions they appear to normalise the lack of habituation that migraine patients show in response to sensory stimuli (see section 1.2.1) [59]. As these drugs are brain-penetrable, they may cause central nervous system (CNS) side-effects such as fatigue, depression, nausea, dizziness and insomnia.

The preventive effect of a therapeutic dose of the calcium channel antagonist flunarizine is comparable with that of the β blockers. By blocking calcium release, flunarizine may both interfere with the cortical spreading depression at the initiation of an attack and inhibit the formation of pain-inducing prostaglandins [21, 60].

The anticonvulsants valproic acid, topiramate and gabapentin are more recent additions to the arsenal of migraine prophylactics. Most studies have focused on valproic acid, a two-chain fatty acid that exhibits many actions on neurotransmission. The assumed mechanisms by which it prevents hyperexcitability include increased GABA-ergic transmission, reduction of membrane excitability and inhibition of the excitatory neurotransmitter aspartate. It has also demonstrated central and peripheral anti-nociceptive effects.

Analgesics (aspirin, naproxen) prevent migraine episodes much in the same way as they abort them, through modulating pain transmission at various levels of the nervous system [60].

Since no prophylactic drug can completely prevent the occurrence of attacks, patients using preventive therapy also require acute medication.

1.4 Clinical trials of acute anti-migraine drugs

The efficacy of an acute anti-migraine drug is assessed in a randomised clinical trial [61]. In most trials, the patient response to drug is compared with the response to placebo treatment. The difference between these responses at a specific time point is then taken as a measure of drug efficacy. This endpoint has been widely used by clinical researchers and is currently accepted by regulatory agencies as a primary measure of efficacy.

The assessment of efficacy at a fixed time point after dosing requires, however, a number of assumptions about variability in disease processes as well as pharmacokinetic and pharmacodynamic properties, particularly when comparing treatments and their effectiveness. Based on the aforementioned, it is evident that different factors may affect the extent of the difference in the response between drug and placebo. This section explores the roles of the clinical endpoint, the placebo effect, the timing of treatment and patient demographics in the observed efficacy. We will show that these factors can be controlled within certain limits by the clinician when designing a trial. The challenge is to adjust them so that the expected efficacy is maximal. In the subsequent chapters of this thesis, we will introduce how a modelling approach based on Markov properties can be used for evaluating treatment response.

1.4.1 Clinical endpoints

Ideally, the response to anti-migraine therapy should be captured by a physiological marker that closely reflects the underlying disease process(es). The availability of such a biomarker would allow efficient dose selection and treatment monitoring mainly because symptomatic changes are preceded by changes in the biomarker and because they are less prone to external input (noise) than clinical symptoms [62]. Investigations have shown that biomarkers of trigeminal activation correlate with response to triptans. The levels of specific neuropeptides differ significantly between responders and non-responders, both at baseline and over the course of an attack. However, the sensitivity of these biomarkers is not high enough to be used in clinical drug development [63].

The assessment of pain and treatment response therefore relies completely on clinical observations, the main one being headache intensity. This subjective measure is quantified in terms of rating scales. Clinical trial guidelines allow the use of a four-point verbal/numerical scale or, alternatively, a visual analogue pain severity scale [61]. The first scale identifies four intensities: no headache (0), mild headache (1), moderate headache (2) and severe headache (3). The visual analogue scale is continuous and ranges between "no pain" and "worst pain ever". About 20 different levels of pain can be differentiated by patients using this scale [64]. Because of this distinctive power, it is mainly used in trials where patients with mild or moderate headache are treated. It should be noted that neither of these scales is anchored, *i.e.* the extremes do not refer to "real" painful experiences. This is thought to negatively influence the interpretation of between-patient variability [7].

Based on the four-point scale, various clinical endpoints have been defined. A clinical endpoint is a measure that indicates whether or not the trial provides evidence at an

acceptable statistical level (p value) that a treatment is efficacious [65]. Usually, such evidence is based on a single pre-specified endpoint, the primary endpoint. In migraine trials, the choice of this endpoint has been motivated by patient preference because no adequate biomarkers are available. Interview studies have confirmed that complete and fast resolution of pain is a property that most patients desire from their acute anti-migraine drugs [66, 67]. Thus, the International Headache Society (IHS) advised that the primary endpoint should be the proportion of patients free of pain at 2 hours post-dose [61]. This measure is in short referred to as "pain free". In terms of the four-point scale, "pain free" is expressed as the proportion of patients that experience a headache severity of score 2 or 3 at the time of dose administration and a severity of score 0 two hours later. If a drug has a rapid onset of action, time points earlier than 2 hours may be selected.

The role of secondary endpoints in clinical decision-making is more limited. Sometimes these endpoints are not used at all for confirmatory analysis based on the fact that analysis of multiple endpoints induces the risk of finding false positive results. In other instances, evidence for drug efficacy is gathered from all endpoints [68]. In migraine trials, the percentage of patients with a decrease in headache from moderate or severe to none or mild at 2 h after dosing is commonly used as a secondary endpoint and is referred to as "pain relief". Though pain relief is more readily achieved than pain free status, patients often do not consider their treatment satisfactory until they are pain free. Before new guidelines for trials were established, pain relief was often the primary endpoint. To allow for comparison with results from previous trials, pain relief is routinely recorded in current migraine trials.

As well as being fast and complete, patients like their pain relief to be sustained. The return of pain after initial relief is therefore usually measured. The recommended measure is "relapse", which is defined as a return of pain of any severity within 48 h post-dose after initially reaching pain-free status at 2 h. "Recurrence" is a similar measure that represents the return of moderate or severe pain after initial pain relief. As the definition of relapse is closely associated with the primary endpoint "pain free", the use of relapse is preferred over recurrence [61]. In practice, recurrence is still used frequently because of historical reasons. Low "pain free" percentages may also be a reason for investigators to measure recurrence instead of relapse. As relapse is conditional on being pain free at 2 h, the number of patients that may experience relapse during a trial can be very small. For this reason, alternative definitions of relapse or recurrence are sometimes used that measure the return of pain after initial relief at 4 h post-dose.

Instead of using endpoints that consider a pain score at a fixed time point, the time until an event (score) may be chosen as a measure of response. Using time intervals the onset of action of a drug can be more accurately characterised. Furthermore, time-to-event measures may give more statistical power because they use information from a range of time points [69]. The analysis of time-to-event data is discussed in Survival analysis.

1.4.2 Timing of treatment

All aforementioned measures assume that treatment is started when pain is of moderate or severe intensity. This helps to assure that the treated headache is indeed a migraine headache. Moreover, the sensitivity of migraine as a pain model is thought better at high baseline pain levels [61]. However, it has been found that drug administration shortly after the onset of an attack, when pain is still mild, tends to result in higher response rates and less recurrence [70, 71]. Though these findings were mostly obtained by retrospective analysis, they are mechanistically supported by migraine pathophysiology. Firstly, many patients develop allodynia over the course of an attack, which means that pain sensation expands to receptive fields other than the primary site of pain. As allodynia is maintained by central neurons, peripherally-acting triptans are less efficacious once it has established.

Another mechanism that would argue for early intervention is the development gastric stasis soon after the onset of an attack. When this occurs, drug absorption is delayed. The administration route is therefore an important factor when considering the timing of treatment.

Though early intervention may be advantageous in the case of oral administration, subcutaneous sumatriptan has shown a consistent efficacy at any time during the migraine attack [72]. This was mainly attributed to its avoidance of gastric stasis. It is, however, also conceivable that the majority of patients in that particular study did not developed allodynia.

There is evidence that the cumulative effect of migraine attacks over the years can increase the risk of allodynia [40]. As a result, migraine attacks in these patients can become more frequent and the attack duration may increase. Treatment of these patients is more difficult, in particular when they have grown accustomed to treating their attacks only after pain has become moderate or severe. In the early stages of disease when allodynia is absent, delaying medication may still be advantageous. However, as migraine progresses, this strategy may become ineffective due to increased sensitisation. These patients may mistakenly assume that triptans no longer work for them. Thus, they should realise that they need to adapt the timing of treatment to the changed dynamics of the disease, and start taking triptans at the onset of an attack.

1.4.3 Patient demographics

Several demographic factors have been found to account for some of the heterogeneity that is observed in migraine symptomatology. In particular, the age and sex of the patient appear to predictive of certain migraine features and responsiveness to medication.

As has been discussed, migraine progresses over the course of a patient's life. Therefore, naturally, "patient age" is an important determinant of the characteristics of the migraine attack: the clinical features of migraine seem to differ with age [73]. Migraine attacks in children are of shorter duration than those in adults. Childhood migraine may also be more difficult to distinguish from other forms of headache as the pain is not always unilateral. The intensity of the headache can be quite severe. In young children,

attacks are often resolved during sleep. Due to ethical considerations, knowledge on the action of triptans in the young has long been limited. Recent studies though seem to confirm that sumatriptan nasal spray is an effective and safe treatment option in both children and adolescents [74].

Fluctuations in estrogen levels are thought to be the main trigger of menstrual migraines. This form of migraine usually presents without aura in the period around menstruation. Menstrual migraine is believed to be more refractive to treatment than other types of migraine. Yet, triptans are effective in the treatment of menstrual migraine, in particular when taken early during the attack [75]. In case of severe menstrual migraine, hormonal therapy may be indicated.

Timing of treatment is particularly important in menstrual migraine. The onset of an attack can be predicted using diaries. Writing down the response to treatment in subsequent attacks helps in deciding which is the best timing strategy.

In conclusion, a more adequate assessment of headache intensity and duration, better timing of treatment and special attention for patient demographics can increase the percentage of responders and the consistency of response, which for triptans are 25-35% and $< 67\%$, respectively [63].

1.4.4 Placebo response

In order to assure that results of clinical trials are consistent, adopting adequate methodology for their planning and execution is essential. Factors such as route of administration, geographical location, study population and information given to the patient can influence the results of a study and are determinants of trial quality. However, keeping these factors as constant as possible cannot prevent unknown factors from affecting the outcomes of clinical trials. Therefore, the use of a placebo group is desirable to minimise potential biases.

However, the response to placebo is not uniform and may depend on several factors. Due to the subjective nature of pain measurement, analgesic studies are commonly characterised by high placebo responses. This is certainly the case with migraine. After placebo treatment, headache responses have been observed varying between 7% and 50% of patients after 2 h. The mean response is 30%. The pain-free response at two hours after treatment with placebo is 9% (range 7–17%) [76].

Some trends can be detected in the placebo responses in different types of studies. Placebo responses after administration of subcutaneous sumatriptan are on average 7% higher than those after oral administration [77]. Furthermore, placebo rates in children are higher than those in adults [78] (this may however be due to the intrinsically shorter duration of attacks in children). Interestingly, phenomena such as recurrence and relapse also occur after placebo administration.

It is evident that the design of a clinical study and the patient population may influence the placebo response. A high placebo response is undesirable as it prevents the detection of an effect of the active treatment.

Based on the aforementioned, it is also clear that in order to assess net improvement one must estimate the difference between active treatment and placebo. Such a difference

is defined as therapeutic gain and is currently used as a secondary endpoint in clinical trials.

1.5 Analysis of data from trials of acute anti-migraine drugs

The assessment of efficacy, safety and, since recently the effectiveness of a treatment, is a key objective of clinical development and statistically sound evidence should be presented that demonstrate these properties for regulatory submission and drug approval. However, compound differentiation has become another important aspect in the overall evaluation of a compound in clinical development as well as at the post-launch phase, during which focus is given to the so-called product line extensions, including secondary indications, new formulations and route of administration. Therefore, the ability to explore differentiating features in the pharmacological and therapeutic properties of drug ought to be considered from various perspectives. From a pharmacostatistical standpoint, it is not only study design factors, including population size and statistical power that matters for the estimation of efficacy, but also the nature of the clinical endpoint and the parameterisation or measure of drug effect. In fact, the sensitivity of an endpoint to varying drug levels plays a major role in one's ability to detect drug effect and separate it from placebo or confounder. In addition to sensitivity, two disease-related factors ought to be considered in the estimation of treatment effect size, namely, nonlinearity and non-stationarity. Both factors will influence how model parameterisation quantifies varying pharmacokinetic and pharmacodynamic properties. In the subsequent sections, we will introduce the use of different approaches to estimating treatment effect in migraine, which attempt to account for the nonlinear nature of disease and for nonstationarity during a migraine attack.

1.5.1 Change from baseline

In parallel-group designs, comparisons between groups can be made directly by comparing the outcomes of treatment periods or indirectly comparing the changes relative to baseline. In addition, the use of the baseline value as a covariate is a frequently used technique. However, a justification for this separation of baselines is often not given.

Whatever method is used, confidence intervals for differences are recommended. "A statement that two drugs are comparable without giving confidence intervals is unacceptable" [61].

In spite of trial guidelines, differences in the execution among trials are unavoidable. As mentioned before, subtracting the placebo response from the active response is a good way of controlling for at least part of the differences. The endpoint derived after subtraction is called placebo-subtracted proportion or therapeutic gain. This use of therapeutic gain assumes that drug and placebo effect are additive. [79].

The analysis should consider the efficacy data obtained directly from the patient. Assessments made by physicians are usually retrospective and more global and should

therefore not be used. Normally, one time point (2 hours) is chosen as the time for evaluation of the primary endpoint. The responses at other times may also be analysed. However, it should be noted that by performing multiple comparisons, the probability of finding a false-positive result at the 5% level is larger than 5%.

Performing multiple comparisons is an inefficient way of analysing repeated measures. Instead, the methods described in the following sections try to take into account sequences of headache observations.

1.5.2 Time-to-event analysis

If two treatments need to be compared, it is intuitively attractive to consider all observations from the time of dosing up to a certain time point, rather than considering just that last point [69]. Time-to-event analysis is a method that takes sequences of observations into account. More specifically, it takes into account all time points leading up to an event (*e.g.* headache relief).

In most migraine studies, observations are made at discrete time points. As a result, the precise time at which the event takes place, is unknown. The time-to-event data that are obtained using this method are interval-censored. In contrast, some of the more recent migraine studies allow headache to be assessed on a continuous time-scale [80].

By including more observations in the analysis, the analysis can gain statistical power. However, this is only true if hazards are proportional. This means that, in a time-to-event analysis of an anti-migraine drug, the drug treatment should have an effect on the "risk" of feeling pain relief that is proportional over time.

Using the hazard concept, the relative effects of two drugs can be expressed in terms of their hazard ratio. The hazard ratio represents the ratio of the hazard functions of the two treatments. This hazard function is defined as the instantaneous risk of an event, given that no event has taken place yet.

In migraine studies, the proportional hazards assumption is valid at least up to 2 h after dosing. At later times, the process cannot be regarded as monotonic any longer, since headache recurrence will become an important factor influencing the response.

1.5.3 Proportional odds models

Proportional odds models are used when the modelling variable consists of more than two categories (which is the case with the headache intensity score). Using the natural order in the categories (*e.g.* scores 0, 1, 2, 3), the categories are collapsed into cumulative probabilities as follows: $Pr(score \leq 0)$, $Pr(score \leq 1)$, $Pr(score \leq 2)$. These probabilities are then transformed to cumulative logits by means of the transformation in equation 1.1.

$$logit(Pr(score \leq k)) = log\left(\frac{Pr(score \leq k)}{1 - Pr(score \leq k)}\right) \tag{1.1}$$

This cumulative logit is then described in terms of a set of equations. For k different categories, there are $k-1$ equations, each representing a set of cumulative probabilities.

In their prediction of naratriptan responses, Nestorov *et al.* [81] initially build a log-odds model, but as they are only interested in predicting the probability of headache relief, the model structure is simplified and the resulting model is a binary logistic one.

The model structure consists of a cut-off probability, a component that describes the placebo response as a logarithm of time, and a drug effect which takes the shape of an $Emax$ model. Furthermore, random effects can be added to the model structure to allow for interindividual variability to be estimated. In addition, other covariates can be added, such as an interaction term between drug concentration and time.

Though log-odds and logistic modelling can take all headache assessments in a sequence into account and good fits can be obtained with it, the concept is empirical: The choice for the logit transformation is mainly based on it convenient properties. Also, the choice for the component that describes the placebo response as a logarithm of time is rather based on convenience than on any mechanistic considerations.

1.5.4 Multistate Models

The nonlinear and non-stationary nature of migraine

Nonlinearity and non-stationarity conditions in migraine can be explained by the underlying pathophysiological processes and corresponding overt symptomatology. An important pharmacostatistical notion that can be derived from such conditions includes the concept of disease state(s) and of transition rate. The possibility of identifying disease state(s) and probabilities or rates of transition enables different parameterisation of disease and drug properties in the presence of time-varying processes and statistical time series. Moreover, it allows comparison of the pharmacological properties of two or more compounds without the confounding effect of disease.

More than one neuroanatomical substrate can be identified that support the notion of varying disease states in migraine. In particular, one should consider the existence of a “migraine generator” and the inconstant liability of patients to migraine attacks, including the known heterogeneity in the overt features of the disease.

The characterisation of system states and corresponding transition rates or probabilities describing the shift of a subject from one state to another is described by Markov methods.

Markov methods

Multi-state models are common models for describing the development of process in time [82]. A multi-state model is a model for a stochastic process which at any time occupies one of a set of discrete states. In medicine, for example, the states can describe conditions like healthy, diseased, diseased with complication and dead. A change of state is called a transition. This corresponds to outbreak of disease, occurrence of complication, or death. It is important to recognise the difference between a transition (like death)

and a state (like dead).

The state structure defines the states and which transitions from state to state are possible. It is possible to make a figure of the state structure. The full statistical model specifies the state structure and the form of the function that gives the instantaneous transition rate (or hazard or intensity function) for each possible transition. The state structure is not unique. Choosing the most appropriate structure can render the model assumptions more transparent. It is a clear advantage if the model is a Markov model, because this allows for an intuitive graphical understanding of the model.

Applying this concept to the migraine field, Hassani and Ebbutt [83] developed a Markov model to describe data on headache relief, nausea and photophobia/phonophobia in a clinical migraine study. These endpoints were treated as binary variables (*e.g.* headache *vs* no headache). Analysing a sequence of points up to 240 minutes after treatment administration, they argued that this type of stochastic modelling is more appropriate for the analysis of repeated binary assessments than analysis at each time point separately since each patient's assessments are modelled simultaneously.

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