DIAGNOSIS AND TREATMENT OF MIGRAINE ATTACKS

Prof. Dr. F. Cankat Tulunay

"A one-sided headache isn't always a migraine; a migraine isn't always one-sided."

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I thank my daughter, Aslı Canay Tulunay Riordan, for her meticulous efforts in the design and digital adaptation of this book.

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About The Author

Prof. Dr. F. Cankat Tulunay is one of the pioneers of academic studies in the field of headache and migraine in Turkey. With his work beginning in the mid-1980s, he led the way for headache to be accepted as a distinct neurological sub-specialty in Turkey.

In 1990, he established Turkey's first multidisciplinary Headache Center within the Ankara University Faculty of Medicine and directed it until 2011. In the same year, he founded the Turkish Headache Society and served as its president for many years.

Taking on an active role in the international arena as well, Prof. Dr. Tulunay served as a founding member and board member of the European Headache Federation (EHF) and became the first Turkish physician to receive certification in the field of headache in Europe. Through his membership in the International Headache Society and editorial roles in various scientific journals, he continues to contribute to the understanding of migraine not merely as a headache, but as a complex neurological disease.

CHAPTER 1: Preface

My academic and clinical work in the field of headache and migraine in Türkiye began in the mid-1980s. At that time, headaches were not yet considered a distinct neurological subspecialty in our country, and migraine and other primary headache disorders were mostly approached with symptomatic strategies. The scientific gap and clinical need in this field constituted the main motivation for my work.

Türkiye's first international publication in the field of headache was realized in 1987 with our study on the use of dihydroergotamine nasal spray in migraine attacks (Cephalalgia, 1987). This publication became one of the first scientific studies in Türkiye in which migraine was addressed using modern pharmacological approaches.

In 1990, within Ankara University Faculty of Medicine, with the support of the then Dean Prof. Dr. Hayati Ekmen, Head of the Department of Internal Medical Sciences Prof. Dr. Güner Tokgöz, and Head of the Department of Neurology Prof. Dr. Adnan Güvener, I founded the first multidisciplinary Headache Center in Türkiye and directed it until 2011. In this center, thousands of patients—primarily with migraine, tension-type headache, chronic daily headache, and cervicogenic headache—were diagnosed and treated, while educational and research activities were carried out simultaneously. In 1990, I founded the Turkish Headache Society and served as its president until 2011. In the same year, as a founding member of the European Headache Federation (EHF), I served on its Board of Directors between 1990 and 2005 and as Vice President of the EHF between 1996 and 1998. In 2002, together with my colleagues on the Board of Directors of the Turkish Headache Society, we organized the 6th European Headache Congress in Istanbul. With the approval of the EHF administration, the first European Headache School was held in Türkiye, after which we established international headache summer schools in various cities and organized scientific meetings.

By extending my academic work in the field of headache to the international level, I became the first Turkish physician to receive certification in the field of headache in Europe.

During this period, I played an active role not only in clinical research but also in scientific organization and guideline development activities in the field of headache. I undertook responsibilities such as membership in the International Headache Society, participation in the preparation of international headache guidelines, and service on editorial boards of scientific journals.

My academic work encompasses the epidemiology of migraine and tension-type headache; acute and prophylactic treatments; mechanisms of action of analgesics; the role of dipyrone (Novalgin) and NSAIDs in migraine treatment; headache frequency in children, adolescents, and Turkish women; and analyses of pain burden from a health economics perspective. The first comprehensive evaluations of acute and chronic pain prevalence in Türkiye, as well as cost analyses of migraine prophylaxis, are also part of these studies. During this process, I developed the first Turkish headache anamnesis format, enabling its use both in patient care and in social research.

In my professional approach, I have addressed headache not merely as a symptom but as a complex disease with biological, neurological, pharmacological, and societal dimensions. I have advocated a holistic perspective that evaluates clinical practice together with scientific research, pharmacology, and health policies.

Looking back today, I derive great professional satisfaction from having contributed to the development of headache science in Türkiye, from having played a pioneering role in the formation of a school in this field, and from seeing that the physicians trained within this tradition continue their work.

Some of my studies in the field of headache

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CHAPTER 2: Definition, Historical Background, Pathogenesis, and Classification

Definition: Migraine is a disabling neurological disorder characterized by moderate to severe, often unilateral, pulsating headache, accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. Attacks occur episodically, may last up to 72 hours, and frequently progress through prodromal, aura, headache, and postdromal phases [1].

Migraine affects more than one billion people worldwide and represents the leading cause of disability among women aged 15–49 years. The Global Burden of Disease (GBD) studies identify migraine as one of the neurological disorders with the greatest impact on quality of life [2]. The burden of migraine extends beyond clinical symptoms, resulting in reduced productivity, loss of workforce participation, educational impairment, and substantial socioeconomic consequences.

Historical Background: Descriptions of migraine date back to antiquity. Aretaeus of Cappadocia described migraine in the 1st century AD using the term heterocrania, noting features such as unilateral pain, nausea, and sensitivity to light and sound—hallmarks that remain central to migraine diagnosis today. Hippocrates provided detailed descriptions of migraine-like headaches, while Galen introduced the term hemicrania.

Between the 17th and 19th centuries, migraine was largely considered a vascular disorder. In the mid-20th century, Harold Wolff linked migraine pain to cranial vasodilation. From the 1980s onward, the neurovascular theory demonstrated that purely vascular explanations were insufficient. Since the early 2000s, migraine has been recognized primarily as a brain-based disorder involving dysfunction of neural networks [3]. This conceptual evolution has clarified that migraine is not merely a “headache,” but a complex neurological disease.

Migraine Pathogenesis: Current Theories

Migraine pathogenesis reflects a complex interaction between genetic susceptibility, environmental triggers, and neurological mechanisms.

Activation of the Trigeminovascular System: The trigeminovascular system plays a central role in migraine pathophysiology. Activation of trigeminal nerve fibers leads to the release of mediators such as nitric oxide (NO), serotonin (5-HT), histamine, calcitonin gene-related peptide (CGRP), substance P, and neurokinin A [4]. These mediators induce cranial vasodilation, plasma protein extravasation, neurogenic inflammation, and both peripheral and central sensitization, amplifying pain signaling within the nervous system.

Cortical Spreading Depression (CSD): CSD, considered the primary mechanism underlying migraine with aura, is a slowly propagating wave of transient neuronal depolarization across the cortex. CSD explains aura

symptoms, indirectly activates trigeminal afferents, and triggers CGRP release, playing a critical role in the transition to the headache phase [5].

Brainstem and Central Pain Networks: Functional imaging studies have demonstrated abnormal activation in regions such as the dorsal pons, periaqueductal gray (PAG), and hypothalamus during migraine attacks. These findings support the concept that migraine is fundamentally a disorder of central pain modulation rather than a purely peripheral phenomenon [6].

Migraine Classification

According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), migraine is categorized under primary headache disorders and divided into the following major types [1]:

1. Migraine Without Aura (ICHD-3 Code: 1.1)

The most common form of migraine, characterized by:

- Attacks lasting 4–72 hours
- Typically unilateral, pulsating pain
- Worsening with physical activity
- Associated nausea/vomiting and/or photophobia–phonophobia

Sub-features:

- Variable attack frequency
- May be associated with the menstrual cycle

2. Migraine With Aura (ICHD-3 Code: 1.2)

Aura consists of reversible focal neurological symptoms.

2.1. Typical Aura with Headache (1.2.1)

- Visual (≈90%), sensory, or speech disturbances
- Aura lasts 5–60 minutes
- Headache follows or accompanies aura

2.2. Typical Aura without Headache (1.2.2)

- Aura without subsequent headache
- Differential diagnosis is critical, particularly in older patients

2.3. Hemiplegic Migraine (1.2.3)

- Familial or sporadic
- Associated with mutations in CACNA1A, ATP1A2, and SCN1A
- Characterized by motor weakness during aura

Feature:

- Motor weakness during aura
- Rare but clinically dramatic

2.4. Migraine with Brainstem Aura (1.2.4)

- Vertigo, diplopia, dysarthria, tinnitus
- Altered consciousness may occur
- No motor weakness

2.5. Retinal Migraine (1.2.5)

- Transient monocular visual loss
- Rare; vascular causes must be excluded

3. Chronic Migraine (ICHD-3 Code: 1.3)

Defined as:

- For ≥3 months
- Headache on ≥15 days per month
- Headache with migraine features on ≥8 days

Features:

- High disability
- Frequent association with Medication-Overuse Headache (MOH)
- Central sensitization is prominent

4. Migraine Complications (ICHD-3 Code: 1.4)

4.1. Status Migrainosus (1.4.1)

- Severe attack lasting >72 hours

4.2. Persistan Aura (1.4.2)

- Aura lasting >1 week
- Normal imaging

4.3. Migrainous infarction (1.4.3)

- Ischemic stroke during aura
- Rare but important, especially in young women

5. Probable Migraine (ICHD-3 Code: 1.5)

- Missing one migraine criterion
- Frequently encountered in clinical practice

Migraine and Gender Differences: Female/male ratio: ≈3:1. Significant increase in women after puberty. Frequency decreases after menopause. B**iological Bases:** Estrogen fluctuations, hormonal sensitivity in the trigeminal system, sex-specific differences in CGRP release.

In Women: More frequent. Longer attacks. More nausea and photophobia, higher risk of chronification. **In Men:** Rarer. Shorter attacks and fewer associated symptoms.

Predisposing Factors

Genetic: First-degree relatives increase risk 2–3 fold; polygenic inheritance

Hormonal: Menstruation, pregnancy, oral contraceptives, menopausal transition

Environmental: Sleep disturbance, stress, fasting, dehydration, bright light, odors, noise

Dietary/Chemical: Alcohol (especially red wine), nitrates, monosodium glutamate, caffeine withdrawal

Comorbidities: Depression, anxiety, epilepsy, fibromyalgia, irritable bowel syndrome

Conclusion

Migraine is a systemic brain disorder characterized by the interplay of neural networks, neuropeptides, central sensitization, and genetic susceptibility—far beyond simple vascular changes. Treatment must therefore be individualized and type-specific. Not every unilateral headache is migraine, and not every migraine presents with unilateral pain. Comprehensive evaluation is essential, and the first clinical assessment of a patient with migraine should last no less than 30 minutes. Both patient and physician must approach management with patience and precision.

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CHAPTER 3: Analgesics and NSAIDs

Although the fundamental role of trigeminal system activation, neurogenic inflammation, and central pain modulation in migraine pathophysiology has been clearly demonstrated, in the reality of clinical practice the vast majority of migraine attacks are still treated with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). The main reasons for this are the wide accessibility of these drugs, their low cost, rapid onset of action, and decades of accumulated clinical experience (1). Real-world data also show that a significant proportion of patients with migraine use analgesics/NSAIDs as first-line therapy and can often achieve adequate symptom control (2). This demonstrates that analgesics are not a "primitive" option in migraine treatment, but a fundamental and indispensable step.

Paracetamol

Paracetamol is one of the most frequently used analgesics in the acute treatment of migraine. Its mechanism of action is related not to peripheral anti-inflammatory effects but to suppression of central prostaglandin synthesis and modulation of serotonergic pathways (3). Randomized controlled trials have shown that paracetamol is superior to placebo in mild and moderate migraine attacks (4). However, the lack of an anti-inflammatory effect, limited efficacy in severe attacks, and the potential for high rates of attack recurrence (relapse) are important limitations. Therefore, in clinical practice paracetamol is often used in combination with NSAIDs or antiemetics (5).

Aspirin (Acetylsalicylic Acid)

Aspirin (acetylsalicylic acid, ASA) is an effective analgesic that has been used for a long time in acute migraine attacks, yet has often remained in the background of the modern literature. The value of aspirin in a migraine attack derives not only from its analgesic effect but also from suppression of prostaglandin-mediated inflammatory processes. Aspirin irreversibly inhibits cyclooxygenase-1 and cyclooxygenase-2 enzymes, thereby reducing prostaglandin synthesis. Given the peripheral sensitization and neurogenic inflammation that occur with trigeminal system activation during a migraine attack, this mechanism is clinically meaningful (6).

In acute migraine attacks, the decisive factor for aspirin is dose. Clinical trials have mostly demonstrated efficacy with a single dose of 900–1000 mg aspirin; insufficient response at low doses may reinforce the incorrect perception that aspirin is "ineffective" in migraine treatment (7). With the correct dose and early administration, aspirin can provide meaningful analgesia, particularly in mild and moderate migraine attacks (7).

Because gastric stasis is common during migraine attacks, aspirin formulation may be determinant for clinical response. It has been reported that effervescent/soluble aspirin preparations may increase efficacy

by providing faster absorption; and that intravenous aspirin (lysine acetylsalicylate) options used in some countries may be considered an effective alternative in cases where oral intake is not possible (7,8).

The most important limitation of aspirin is gastrointestinal adverse effects. Patients with a history of peptic ulcer or gastrointestinal bleeding, those using anticoagulants, and older age groups are at increased risk with aspirin use. In addition, aspirin should not be used in children and adolescents in the presence of viral infection because of the risk of Reye's syndrome (9).

Metamizole (Dipyrone, Novalgin)

Metamizole (dipyrone) is a potent non-opioid analgesic with analgesic, antipyretic, and spasmolytic properties. Although it has been widely used for many years in migraine treatment in some countries, it has often failed to receive the visibility it deserves in the modern migraine literature. Unlike classical NSAIDs, metamizole has a multi-modal mechanism: in addition to inhibition of prostaglandin synthesis in the central nervous system, it is thought to act on the endocannabinoid system and glutamatergic pathways that modulate descending pain pathways, and to suppress spinal pain transmission (10,11). Its spasmolytic effect on smooth muscle may provide an additional advantage in pain control related to the vascular component of migraine (12).

Clinical studies show that both oral and intravenous (IV) forms of metamizole are statistically significantly superior to placebo in relieving acute migraine pain (12,13). With oral use, a single 1 g dose of metamizole has been associated with marked pain reduction at 2 hours and complete resolution in some patients (13,14). In severe attacks, 1 g IV metamizole has been observed to control symptoms within a short period such as 30–60 minutes (12).

In some studies, the efficacy of metamizole has been found similar to that of acetylsalicylic acid (aspirin), and it has been emphasized as a strong alternative in patients who do not respond to triptans or cannot use them / have contraindications (12–14). Although "traditional" randomized head-to-head trials directly comparing metamizole and triptans are limited, a recent systematic review and network meta-analysis found no statistically significant difference between metamizole and triptans with respect to the "pain freedom" outcome at 2 hours (15). However, in a large-scale real-world analysis based on more than 10 million self-reported attack records, the triptan class overall stood out with the highest probability of "benefit," while the non-opioid analgesics/NSAIDs group (including metamizole) occupied a lower position in an efficacy hierarchy (16). When these two findings are considered together, it is understood that metamizole may be a strong option in many patients, but that treatment response is patient-specific and that choice should be individualized according to attack severity, accompanying nausea-vomiting, contraindications, and history of prior response.

The agranulocytosis risk of metamizole has historically been a subject of debate; however, modern pharmacovigilance data confirm that this risk is extremely rare, at a level such as 1.1 cases per million. This risk has led to restriction or withdrawal of the drug in some countries. Nevertheless, epidemiological

evaluations have shown that agranulocytosis is rare and may vary depending on geographic/genetic factors (17). The information that the risk of metamizole-associated agranulocytosis is around 1.1 per million is based particularly on the large epidemiological study known as "The Latin Study." This study revealed that the risk is not as high as previously thought, and that incidence varies between approximately 0.4 and 1.2 cases per million. (22)

NSAIDs

NSAIDs reduce prostaglandin synthesis by inhibiting cyclooxygenase enzymes. Considering the role of prostaglandins in pain transmission and sensitization during migraine attacks, this mechanism of action is clinically meaningful (6). Naproxen, due to its long half-life (approximately 12–17 hours), not only reduces pain but may also limit attack recurrence. Cochrane reviews show that naproxen is superior to placebo in the acute treatment of migraine and may be effective especially in combination therapies (18). Ibuprofen is frequently preferred in migraine attacks because of its rapid onset of action, and its efficacy in moderate attacks is well documented (19). Diclofenac, particularly in potassium salt formulations, may provide rapid analgesia; however, its cardiovascular risk profile may be more problematic compared with some other NSAIDs and it should be used with caution (20).

Limits of Analgesic and NSAID Use

The most important problem of analgesics and NSAIDs in migraine treatment is overuse. Use on more than 10–15 days per month may lead to medication overuse headache, treatment-resistant chronic migraine, and gastrointestinal and renal complications (21). Therefore, although these drugs are effective, they are not unlimited; early use, correct dosing, and the implementation of prophylaxis strategies when attack frequency increases are essential.

Conclusion

Analgesics and NSAIDs continue to form the backbone of acute migraine treatment despite the development of new migraine drugs. The relegation of "old" but effective drugs such as aspirin and metamizole to the background is often related more to perceptual and regulatory dynamics than to scientific evidence. The fundamental problem in migraine treatment is not the insufficiency of analgesics, but incorrect dosing, incorrect patient selection, and uncontrolled use.

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CHAPTER 4: Triptans

Triptans (5-HT_1B/1D agonists) have been presented as "migraine-specific" drugs since the 1990s and were claimed to represent a paradigm shift in the acute treatment of migraine. However, despite the passage of more than thirty years, the true clinical value of this drug class continues to generate serious debate with respect to the endpoints used, comparison strategies, publication bias, and industry influence. The widespread adoption of triptans has been shaped largely by analgesic anxiety arising from the opioid crisis and by the narrative of "targeted therapy" (1,2).

The development of triptans was based on the role of the serotonergic system in migraine pathophysiology, and particularly on the hypothesis that activation of 5-HT_1B/1D receptors in the trigeminovascular system could suppress neuropeptide release (2). While this biological framework is pharmacologically coherent, the claim that it translated directly and robustly into clinical outcomes was constructed largely on placebo-controlled trials (1). The discourse of "migraine specificity" created the impression that triptans were qualitatively different and superior to other analgesics; however, it is difficult to argue that this superiority was systematically tested against inexpensive and effective analgesic/NSAID options (5–7).

Statistical Manipulation in Clinical Trials?

One of the most critical methodological problems in the triptan literature is the systematic "loosening" of clinical endpoints over time, with clinically weaker measures being transformed into success criteria. While early migraine studies centered on "complete pain freedom," later trials increasingly emphasized outcomes such as "pain relief" or "≥50% pain reduction," which carry lower clinical relevance (3). Although this shift facilitated the achievement of statistical significance, it did not guarantee patient-meaningful benefit. Methodological analyses have shown that "pain relief" endpoints can exaggerate absolute benefit and do not always align with patient expectations (4).

This endpoint engineering resulted in the replacement of the question "Did the patient's pain resolve?" with "Did the score change significantly?" In classical analgesic research, complete pain relief, functional recovery, and return to daily life were clearer patient-centered goals; in contrast, triptan trials increasingly relied on endpoints such as "statistically significant pain score reduction at 2 hours," "downgrading from moderate/severe to mild pain," or "30–50% reduction," all of which can generate "success" while the patient is still in pain (3,4). Thus, the past thirty years of migraine pharmacotherapy should be read not only as the era of new molecules, but also as a period in which the very measurement of pain was rewritten.

The vast majority of triptan trials were designed against placebo, with extremely limited direct comparisons against active agents (NSAIDs, strong analgesics—particularly metamizole) (5–7). Placebo response rates in migraine trials are known to reach 30–40% (7). This reality weakens the clinical meaning of the statistical

superiority demonstrated over placebo, because the real-world comparator is not placebo but already-used effective analgesics.

More importantly, the lack of strong, direct comparisons with inexpensive and widely used analgesics such as naproxen and ibuprofen has prevented an objective assessment of the true therapeutic value of triptans (8–10). The narrative of a "migraine-specific revolution" is therefore largely built upon a "silent victory" over drugs that were never compared head-to-head. The central clinical question remains: what would have happened if triptans had been directly compared with cheap and widely used analgesics and NSAIDs?

In most phase III development programs for triptans, active comparators were deliberately absent. This was not accidental. NSAIDs (naproxen, ibuprofen, diclofenac) and metamizole were already widely used, effective, and inexpensive. Direct comparison would have risked undermining claims of clinical superiority. Thus, placebo was chosen and head-to-head comparisons were systematically avoided.

The critical maneuver at the market entry of triptans was redefining what constitutes "success" in a migraine attack. "Pain resolution" is a difficult target; "pain reduction" is statistically easier to achieve. As a result, trials could be reported as "successful" while the patient was still in pain. Meta-analyses show that absolute 2-hour pain-free rates are low, with only 20–30% of patients achieving complete pain freedom in many studies (5–7). These rates are not dramatically superior to results obtained with some NSAIDs (10).

Although direct head-to-head trials are scarce, indirect comparisons are revealing: NNT values for NSAIDs may be similar to many triptans; naproxen and ibuprofen may be more successful in mild-to-moderate attacks; metamizole may provide rapid and marked analgesia in some studies (10–12). This suggests that while triptans may be pharmacologically "specific," they are not clinically "absolutely superior."

Combination Studies

The existence of triptan + NSAID combination studies indirectly reveals another reality. The finding that sumatriptan + naproxen is more effective than sumatriptan monotherapy (8) demonstrates that the standalone clinical success of triptans may be limited and enhanced by "analgesic contribution." If triptans alone constituted a sufficiently strong and consistent "revolution," the need for such combinations would not appear so clinically meaningful.

Risk–Benefit Balance and Cost

In some studies where triptans and NSAIDs were directly compared in the same patient population using identical endpoints, efficacy differences were minimal, nonexistent, or even favored NSAIDs. In such cases, cost differences—triptans being more expensive—further weaken clinical justification. Moreover, triptans carry class-specific effects such as vasoconstriction, chest tightness, and paresthesia, whereas NSAID risks are generally more predictable and manageable (15,16). Such findings would have made it far more difficult to defend triptans as first-line therapy. Active-comparator trials are costly, carry a high risk of failing to demonstrate superiority, and weaken marketing narratives. Consequently, the clinical story of triptans has been shaped by "marketing comfort" gained over drugs they were never compared against.

Clinical and Ethical Consequences

Had triptans been compared in large, well-designed head-to-head trials with agents such as naproxen or metamizole, the "migraine-specific revolution" narrative would likely have been more restrained; triptans would have been positioned as second- or third-line options, and cost-effectiveness would have faced more rigorous scrutiny. The question that must now be asked is this: do triptans truly treat migraine better, or are they simply better marketed?

The Recurrence Problem

Another major limitation of triptans is the high recurrence rate, defined as headache return within 24 hours after initial response. A substantial proportion of initially responsive patients experience recurrence, suggesting that triptans provide transient symptom suppression rather than fundamentally altering the pathophysiological process (13,14).

Adverse Effects and Cardiovascular Safety

Due to their vasoconstrictive effects, triptans carry cardiovascular risk. Chest tightness, paresthesia, and rarely serious cardiovascular events have been reported (15,16). Their use is therefore limited in individuals with cardiovascular disease or risk factors. When efficacy may be similar to that of inexpensive analgesics, this risk–benefit balance becomes even more critical.

Industry Influence, Publication Bias, and "Migraine Barons"

It is well known that industry-sponsored studies are more likely to report positive outcomes and that publication bias, selective endpoints, and comparison strategies can inflate perceived efficacy (17). The triptan literature is no exception. Broader methodological critiques questioning the reliability of biomedical literature have highlighted more sophisticated biases—obtaining "correct answers by asking the wrong questions" (18). Endpoint selection and comparator strategy in migraine research provide a particularly instructive example.

In recent years, guidelines have begun to position triptans more cautiously. NICE and American Headache Society documents now place triptans at the same step as NSAID + antiemetic combinations, with a noticeably softer tone regarding "migraine-specific superiority" (19,20). This reflects growing skepticism toward the notion of absolute superiority in clinical practice.

The past thirty years of migraine pharmacotherapy represent not only the development of new molecules, but also a rewriting of how pain is defined and how "success" is reported. At the center of this transformation lies the progressive shift of primary and secondary endpoints toward more flexible, statistically advantageous definitions. Among the most frequently cited figures in this academic shift are Jes Olesen and his school. Olesen and colleagues reframed migraine as a trigeminal-vascular syndrome, providing a strong scientific foundation for the clinical development of triptans and later CGRP-targeted therapies. The blurring boundary between scientific contribution and industrial objectives remains the core problem.

In classical analgesic research, the clinical question was simple: “Did the patient become pain-free?” In migraine trials, this question gradually evolved into easier ones: “Did the score decrease at 2 hours?”, “Did pain become mild?”, “Was there statistical significance?” While complete pain freedom is a difficult endpoint, pain “reduction” is statistically easier to achieve. Thus, clinical success can be detached from patient experience, and statistical significance can replace clinical meaning.

This paradigm shift legitimized testing migraine-specific drugs with special endpoints and served as a methodological shield against direct comparison with strong analgesics. In retrospect, many pivotal migraine trials are deeply intertwined with industry funding, consultancy/speaker relationships, and CRO-based statistical analyses. The issue is often not data falsification, but the more sophisticated act of structuring studies to produce favorable outcomes by asking the wrong questions.

Endpoints such as “50% pain reduction” may not fundamentally change a patient’s life, but they can “save” the p-value. As a result, drugs with limited effect are declared successful, while risk–benefit balance and cost discussions are pushed aside. This trend in migraine literature can be read as a shift from patient-centered science to product-centered statistics. The key question today is therefore: have we truly progressed in migraine treatment, or have we merely changed the measurement tools?

Danish migraine research, particularly the work of Jes Olesen, has been pivotal in the transformation of migraine trial endpoints. By centering concepts such as the trigeminal-vascular system and CGRP, this school strengthened the neurobiological framework of migraine, which in turn shaped the clinical development strategies of migraine-specific therapies (1–3). The most important reflection of this approach in clinical research has been the redefinition of primary endpoints: replacing complete pain freedom with 2-hour pain reduction, downgrading to mild pain, and partial improvement of accompanying symptoms (3,4). This methodological preference facilitated the reporting of statistically significant but clinically limited results. The dominance of placebo comparisons and the rarity of direct comparisons with strong analgesics/NSAIDs in triptan programs are particularly notable in this context (5,6).

In the global burden of migraine literature, Tim Steiner is among the most prominent figures. Steiner and colleagues quantified migraine’s individual and societal impact using DALY/YLD metrics and introduced functionality-based indices such as Headache-Attributed Lost Time (HALT) (7–9). While these contributions are valuable for demonstrating societal burden, they may also have indirectly encouraged acceptance of more flexible endpoints such as “functional improvement” and “partial recovery” instead of absolute pain relief. From a critical perspective, this paradigm may contribute to an inflated perception of the clinical value of modestly effective but statistically advantageous treatments. The increasing use of functionality/burden-based outcomes in industry-supported migraine trials therefore warrants careful interpretation (9,10).

Conclusion

Triptans are neither completely ineffective nor as revolutionary as claimed. They demonstrate statistical superiority over placebo, but this superiority has not been adequately tested against active analgesics;

clinically meaningful endpoints have been progressively relaxed; and high cost and class-specific adverse effects have been embedded within a powerful marketing narrative. At the present point, the role of triptans in acute migraine treatment should not be "absolute" but "contextual." Routine and unquestioned use of triptans without simultaneous consideration of patient profile, alternative analgesics, cost, and risk is scientifically indefensible.

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CHAPTER 5: Gepants (CGRP Receptor Antagonists)

Gepants (ubrogepant, rimegepant, atogepant) are small-molecule CGRP receptor antagonists that have been presented as "revolutionary" in the treatment of migraine in the post-2018 period. The narrative constructed around the vasoconstrictive effects of triptans and concerns about cardiovascular safety is as follows: "Triptans were old and risky; gepants are safer, more targeted, and more modern." However, when the historical trajectory of migraine pharmacotherapy is taken into account, the clinical success of gepants—just like that of triptans—is tightly dependent on which questions are asked, which comparisons are not made, and which outcome measures (end-points) are selected (1–3). For this reason, gepants should be critically evaluated not only in terms of pharmacological innovation, but also with respect to methodology, clinical meaning, and industry influence.

The CGRP Hypothesis and the Discovery of Gepants

CGRP (calcitonin gene-related peptide) has been known since the 1980s as a potent vasodilatory neuropeptide released in the trigeminovascular system. Studies by Jes Olesen and colleagues demonstrated that CGRP levels increase during migraine attacks and that this increase can be suppressed by triptans (4,5). Over time, this biological observation was transformed into the following assumption: "The fundamental cause of migraine is CGRP; if we block CGRP, we can treat migraine." While this assumption is pharmacologically appealing, it clearly oversimplifies migraine pathogenesis by reducing it to a single theory and, at the same time, opens a new revenue channel for the pharmaceutical industry. Migraine is a heterogeneous syndrome involving the complex interaction of CGRP, serotonin, glutamate, nitric oxide, cortical spreading depression, and central neural networks (6,7). Indeed, clinical data clearly show that CGRP blockade does not eliminate migraine, but provides only modest reductions in attack severity and frequency (8).

Clinical Efficacy

Nearly all gepant trials share the following common characteristics: they are placebo-controlled, lack active analgesic or NSAID comparators, and the primary end-point is usually "pain-free at 2 hours (pain-free at 2h)."

In phase III trials of ubrogepant and rimegepant, pain-free rates at 2 hours were reported as 19–21% in most studies, compared with 11–14% for placebo. The absolute difference is approximately 7–10%, meaning that there is no major superiority even over placebo (9–11). Even if this difference is statistically significant, can a treatment that provides additional benefit in only 1 out of 10 patients truly be described as "revolutionary"? Number Needed to Treat (NNT) values have been reported to range between 8 and 14 in most studies (12). These values are not superior to those reported for naproxen, ibuprofen, and some triptans.

As in the triptan literature, gepants have not been directly compared with inexpensive and effective analgesics such as naproxen, ibuprofen, diclofenac, or metamizole (13,14). This deficiency is not methodological but strategic. Had such comparisons been conducted, the efficacy difference would have been minimal or absent, the cost difference would have become dramatically apparent, and the illusion of "migraine-specific superiority" would have collapsed.

The end-points used in gepant trials are almost a direct continuation of the triptan literature:

- Measurement at 2 hours instead of complete pain freedom
- Score differences instead of functional recovery
- Recurrence, need for rescue medication, and real-world performance are mostly treated as secondary end-points

This approach has been shaped not by the needs of clinical practice, but by the requirements of regulatory approval dossiers (15,16). The outcome is once again the same: statistically successful, clinically mediocre.

A frequently repeated claim regarding gepants is: "Triptans are vasoconstrictive; gepants are safe." This statement is technically correct, but misleading when taken out of context. Triptans carry a higher risk of serious cardiovascular events (17). On the other hand, CGRP is a physiologically protective neuropeptide, and the long-term effects of its chronic blockade on cardiovascular adaptation, the gastrointestinal system, and neurovascular homeostasis are not yet sufficiently known (18). Such risks cannot be detected in short-term licensing trials.

Gepants are significantly more expensive than triptans and especially NSAIDs. Despite their limited clinical efficacy, they have rapidly entered the market in many countries under the label of "next-generation" therapies. Cost-effectiveness analyses are often addressed only as secondary topics in clinical guidelines (19). This situation evokes portfolio renewal strategies rather than genuine scientific progress.

Conclusion

Gepants are neither a revolution nor the solution to migraine. They are pharmacologically intelligently designed, clinically modestly effective, methodologically inheritors of the triptan legacy, and economically high-cost drugs. The problem is not their existence, but how they are positioned. Real progress in migraine treatment is not achieved by producing new molecules, but by asking the right questions. Gepants may be new, but the questions are still old.

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CHAPTER 6: Ditans (5-HT$_1$F Agonists)

Ditans are the class of 5-HT$_1$F receptor agonists whose first and, to date, only representative to enter clinical practice is lasmiditan. This drug class was developed in response to safety concerns constructed around the vasoconstrictive effects of triptans. The industrial narrative is explicit: "Triptans constrict blood vessels; ditans do not, therefore they are safer." However, when the recent history of migraine pharmacotherapy is examined, the clinical positioning of ditans—just like triptans and gepants—has been shaped by which comparisons were not made, which outcome measures were selected, and which patient experiences were ignored (1,2). For this reason, ditans are viewed not merely as a pharmacological innovation, but largely as a marketing product in terms of clinical meaning, methodology, and regulatory pragmatism.

Lasmiditan is a selective agonist of the serotonin 5-HT$_1$F receptor. This receptor is thought to be located on trigeminal nerve endings and may indirectly suppress CGRP release (3). This mechanism theoretically allows suppression of migraine attacks without vasoconstriction. Indeed, in vitro and animal models have shown that lasmiditan does not exert a significant vasoconstrictive effect on vascular smooth muscle (4). However, the critical question here is the following: Does the absence of vasoconstriction translate into clinical superiority?

The clinical development program of lasmiditan (the SAMURAI and SPARTAN trials) followed the classic pattern of industry-type migraine drug studies (5,6): placebo-controlled, no active comparator (no NSAIDs, triptans, or metamizole), primary end-point: complete freedom from pain at 2 hours. In these studies, pain-free rates at 2 hours were reported as 28–32% with lasmiditan and 15–21% with placebo. The absolute difference was 9–13% (5,6). In other words, the drug is effective in only 9–13% of patients. Even if this difference is statistically significant, the same clinical question arises once again: If only one out of every 8–10 patients experiences additional benefit, can this result be interpreted as "high clinical value"?

Number Needed to Treat (NNT) values range between 7 and 12; these values are similar to those reported for triptans and many NSAIDs (7). Therefore, lasmiditan is not superior to existing treatments in terms of efficacy. As with other agents, no active-controlled trials were conducted in lasmiditan studies. Had active-controlled trials been performed, the efficacy difference would likely have remained minimal, the cost-effectiveness balance would have shifted against lasmiditan, and the illusion of a new effective migraine drug would have collapsed.

The outcome measures used in lasmiditan trials are a direct continuation of the triptan and gepant literature. While this approach facilitates short-term statistical success, it relegates issues that directly matter to patients—such as post-attack sedation, cognitive impairment, and return to daily life—to the background (8).

The most striking aspect of lasmiditan is its central nervous system adverse effects. The following have been reported in clinical trials (5,6,9): dizziness (15–20%), sedation, somnolence, impaired concentration, and paresthesia. These adverse effects are so pronounced that the FDA has mandated the following warning for lasmiditan: patients must not drive or operate heavy machinery for at least 8 hours after taking the drug (10).

This warning is clinically highly problematic for a patient experiencing an acute migraine attack whose daily functioning is already impaired. Pain may be partially reduced, but the patient is functionally disabled.

Conclusion

Ditans are not a revolution in migraine treatment. If lasmiditan had been compared—within the same patient population and using patient-centered end-points—with strong analgesics, NSAIDs, and triptans, it would most likely have been positioned as a second- or even third-line option.

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CHAPTER 7: Ergot Alkaloids

Ergot alkaloids—primarily ergotamine and dihydroergotamine (DHE)—were among the first pharmacological agents developed specifically for the treatment of migraine. Introduced decades before triptans, these drugs were designed to target the vascular component of migraine and, for many years, represented the cornerstone of acute migraine therapy. Today, however, ergot alkaloids have been relegated to the background in most clinical guidelines and are often labeled as "obsolete." This decline is not attributable solely to pharmacological aging; rather, it reflects the complex balance between high efficacy, a narrow therapeutic window, and a significant adverse-effect burden [1].

Pharmacology and Mechanisms of Action

Ergot alkaloids act as non-selective agonists at multiple receptor systems, including 5-HT_1B/1D serotonergic receptors, α-adrenergic receptors, and dopaminergic receptors [2]. This pharmacological non-selectivity results in two parallel clinical consequences: potent suppression of migraine attacks and a substantial risk of adverse effects and toxicity.

Ergotamine and DHE strongly inhibit trigeminovascular system activity, reduce CGRP release, and induce vasoconstriction [3]. Compared with triptans, their receptor binding profile is broader and less selective, which partly explains both their robust efficacy and their unfavorable safety profile.

Clinical Efficacy

Historically, ergot alkaloids demonstrated clear superiority over placebo in the treatment of acute migraine. Early clinical studies reported migraine-aborting efficacy rates comparable to those later observed with triptans [4]. In particular, dihydroergotamine—especially when administered intravenously—has maintained a role in the treatment of status migrainosus and refractory migraine attacks. In specialized settings, IV DHE remains an effective option for patients who fail to respond to other acute therapies.

Unlike many modern migraine drugs, ergot alkaloids were developed and adopted in an era when placebo-controlled trials were not the sole benchmark for therapeutic acceptance. Their clinical reputation was built largely on consistent real-world efficacy rather than on narrowly defined short-term endpoints.

Limitations and Adverse Effects

The principal limitation of ergot alkaloids is their safety profile. Vasoconstrictive effects are not confined to cranial vessels and may involve peripheral and coronary circulation, leading to ischemic complications. Adverse effects include nausea, vomiting, paresthesia, muscle cramps, and, in severe cases, ergotism—characterized by prolonged vasospasm and tissue ischemia.

Drug–drug interactions further complicate ergot use. Concomitant administration with potent CYP3A4 inhibitors (e.g., macrolide antibiotics, azole antifungals, certain antiretrovirals) can markedly increase ergot alkaloid plasma concentrations, substantially raising the risk of toxicity. Repeated or excessive use may also lead to medication-overuse headache and cumulative vascular risk.

Ergot Alkaloids in the Modern Migraine Landscape

The decline of ergot alkaloids in contemporary migraine management reflects a shift in therapeutic priorities rather than a complete loss of clinical relevance. The emergence of triptans, gepants, and ditans—with more selective mechanisms and improved tolerability—has reduced the routine use of ergot derivatives. However, this transition has also been influenced by regulatory standards favoring drugs with cleaner safety profiles and by market dynamics that prioritize newer agents.

Importantly, the marginalization of ergot alkaloids does not imply inferiority in efficacy. Instead, it underscores the growing emphasis on safety, convenience, and risk minimization in modern migraine therapy. In carefully selected patients and controlled clinical settings, particularly for refractory cases, DHE remains a valuable therapeutic tool.

Conclusion

Ergot alkaloids represent a historically important and pharmacologically potent class of migraine therapies. Their reduced role in current practice reflects concerns regarding safety and tolerability rather than a lack of efficacy. When used judiciously and with appropriate patient selection, particularly in refractory or status migrainosus cases, ergot alkaloids—especially dihydroergotamine—continue to occupy a legitimate, if specialized, place in migraine treatment.

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CHAPTER 8: Antiemetics

Antiemetics are often defined in migraine treatment merely as “adjunctive drugs for associated symptoms.” This approach significantly distorts both clinical practice and scientific literature. However, nausea and vomiting in a migraine attack are not secondary and insignificant symptoms; they are fundamental components that directly determine the severity of the attack, the response to treatment, and the efficacy of the administered drugs (1).

Gastric stasis, which frequently occurs during a migraine attack, delays and reduces the absorption of orally administered drugs. This situation severely limits the bioavailability not only of non-specific analgesics but also of agents considered fundamental in migraine treatment, such as triptans, gepants, and NSAIDs (2). Therefore, antiemetics should be evaluated not merely as helper drugs providing symptomatic relief, but as agents forming the pharmacokinetic backbone of migraine treatment.

Among the most frequently used antiemetics in migraine treatment are metoclopramide, domperidone, and prochlorperazine; ondansetron is used more rarely. These drugs suppress nausea and vomiting via different mechanisms and affect the clinical course of the migraine attack either directly or indirectly.

Metoclopramide holds a special position within this group. As a dopamine D2 receptor antagonist, metoclopramide accelerates gastric emptying by increasing gastric motility and exerts a central antiemetic effect. Beyond this, it can also be effective on migraine pain itself by indirectly suppressing trigeminovascular system activity. Indeed, metoclopramide is one of the rare antiemetics shown to be able to reduce migraine pain on its own (3).

In emergency department-based randomized controlled trials, intravenous metoclopramide was found to be clearly superior to placebo, showed similar efficacy to sumatriptan in some studies, and yielded equivalent results to NSAID–antiemetic combinations (4–6). These data clearly reveal that antiemetics can be active therapeutic agents in migraine treatment, not just “supportive” ones.

Domperidone, a peripherally acting dopamine D2 antagonist, is considered safer regarding extrapyramidal side effects due to its limited penetration into the central nervous system. Its low sedative effect provides an advantage, especially in outpatient treatment. However, caution is required in high-dose and long-term use due to the risk of QT interval prolongation (7). Although domperidone’s direct effect on migraine pain is more limited compared to metoclopramide, its clinical value in terms of nausea control and improvement of oral drug absorption is high (8).

Prochlorperazine has demonstrated remarkable results, particularly in emergency department studies. Randomized studies have shown that prochlorperazine is more effective than opioids and some triptans, and that both pain and nausea can be controlled together (9). Despite this, it has been pushed to the background in outpatient clinic use over time due to the risk of extrapyramidal side effects.

The strongest aspect of antiemetics is their ability to respond directly to the real-life conditions of a migraine attack. During a migraine attack, patients frequently vomit, cannot tolerate oral drugs, and are in expectation of rapid relief. In this context, intravenous or intramuscular antiemetics can be a more rational first-line treatment option when compared to many agents theoretically considered "migraine-specific" (10).

The reasons for antiemetics remaining in the background in migraine literature are largely structural, not scientific. The lack of patent value of these drugs, their low cost, and their failure to fit the "new generation" pharmacotherapy narrative, as well as the absence of large industry-supported phase III studies, have limited the academic and clinical visibility of antiemetics. Ultimately, antiemetics have remained the silent but indispensable actors of migraine pharmacotherapy.

When current guidelines are examined, it is seen that NICE, the American Headache Society, and emergency department-based guidelines recommend antiemetics in combination with NSAIDs or as an alternative/adjunct to triptans (11,12). However, these recommendations are mostly presented with secondary language, and the independent clinical value of antiemetics is not sufficiently emphasized.

Conclusion

Antiemetics are agents that are clinically effective, compatible with real-life conditions, low cost, and have a predictable side effect profile. Despite this, they have been systematically undervalued in modern migraine literature. This situation inevitably raises the following fundamental question: Is the most effective treatment really being preferred in migraine therapy, or the best marketed one? Antiemetics constitute one of the most disturbing answers to this question.

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CHAPTER 9: Non-Pharmacological Approaches

When acute migraine treatment is mentioned, pharmacotherapy reflexively comes to mind. However, a migraine attack is not just a biochemical event; it is a complex process with neurophysiological, autonomic, and behavioral components. Therefore, non-pharmacological methods in acute attacks are not "alternative," but are primary treatment elements in some patients and complementary in most.

These methods become clinically significant especially in cases of drug intolerance, inadequate response, pregnancy, polypharmacy, and risk of Medication-Overuse Headache (MOH) (1).

Dark and Quiet Environment (Sensory Deprivation): Photophobia and phonophobia in migraine attacks are associated with the hypersensitivity of trigeminothalamic networks. A dark, quiet, and low-stimulus environment can reduce brainstem and thalamic hyperactivation. Although this approach seems simple, neuroimaging studies have shown that sensory networks are indeed "overloaded" during a migraine attack (2).

Cold Application (Cold Therapy / Cryotherapy): Cold applied to the head and neck region suppresses trigeminal nerve activity, provides vasoconstriction, and modulates pain transmission. Randomized studies have shown that frontal cold gel application, in particular, provides significant relief in some patients (3). The effect of this method is heterogeneous; it is pronounced in some patients and minimal in others.

Sleep and Short-Term Rest: Sleep is one of the rare physiological interventions that can terminate a migraine attack. Sleep acts through REM/non-REM transitions, central pain modulation, and autonomic balance. Many patients use the expression "if I can sleep, it passes"; this clinical observation is also supported physiologically (4).

Neuromodulation Devices: Transcutaneous Supraorbital Nerve Stimulation (tSNS – Cefaly®) modulates trigeminal afferents with low-voltage electrical stimulation. A small but statistically significant effect compared to placebo has been shown in acute attacks (5). Vagus Nerve Stimulation (nVNS – gammaCore®) is non-invasive and increases parasympathetic activation. A decrease in acute pain scores has been reported in some studies; however, the effect size is weak (6). Studies of these devices have been conducted via small clinical trials and are industry-supported. They may be helpful in some patients, especially due to the high placebo effect.

Biofeedback and Relaxation Techniques: In an acute attack, these may be helpful especially in stress-triggered migraines in terms of breathing regulation, muscle relaxation, and restoring autonomic balance. Biofeedback is limited in acute attacks; however, it is effective in shortening attack duration and reducing associated symptoms (7). This method has been widely used, especially in prophylactic treatment, at the Ankara University Medical Faculty Headache Center.

Acupuncture and Acupressure: Although acupuncture has been studied more in prophylaxis, and while it has been used to reduce pain severity in acute attacks in some patients, acute efficacy data are heterogeneous and susceptible to the placebo effect (8).

Hydration and Metabolic Support: Dehydration can both trigger and sustain a migraine attack. In severe acute attacks, oral or IV fluid support and regulation of electrolyte balance provide a significant contribution, especially in the emergency department.

Avoidance of Triggers: In an acute attack: The rapid elimination of triggers such as hunger, caffeine withdrawal, bright light, and strong odors can limit the progression of the attack. This approach is simple but not sufficiently emphasized in most guidelines (9).

Conclusion

Non-pharmacological methods in acute migraine treatment are neither miracles nor meaningless. With the right patient selection, they can reduce the need for medication and lower the side effect burden. Progress in migraine treatment is possible not only with new molecules but by understanding how we interact with the patient's nervous system. Success in migraine treatment depends not only on drugs but on the relationship the doctor establishes with the patient. Treatment success is achieved by the doctor giving the patient enough time to explain their complaints and offering the patient assurance, not a guarantee.

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CHAPTER 10: Clinical Approach to the Migraine Patient and the Role of the Physician

Although migraine is a disease whose neurobiological foundations have been described in detail, its clinical outcomes largely depend on the physician's approach, the patient–physician interaction, and the quality of the evaluation process. The marked variability in treatment response among patients carrying the same diagnosis demonstrates that migraine is a heterogeneous and highly individualized disease that cannot be managed solely through pharmacological interventions. For this reason, migraine treatment requires a holistic clinical approach and a long-term follow-up process rather than standardized prescriptions (1,2).

Although international guidelines provide clear algorithms for migraine diagnosis and treatment, these algorithms constitute only a framework for clinical practice. Migraine patients are highly heterogeneous with respect to attack frequency, pain severity, aura characteristics, triggers, and accompanying psychiatric and systemic diseases. This heterogeneity shifts the physician's role from that of a mere algorithm implementer to one that requires clinical judgment and experience (3).

This perspective was strongly emphasized early on by **J. N. Blau,** who placed the physician's role at the center of migraine clinical management. Blau defined migraine not merely as a headache syndrome but as a subjective experience that disrupts the patient's life, and therefore argued that the physician's attitude in migraine treatment can directly influence the course of the disease (13,14).

Under ideal conditions, the initial evaluation of a patient with migraine should last at least 30 minutes. Migraine diagnosis is clinical and requires a detailed medical history. The presence and type of aura, prodromal and postdromal symptoms, the temporal pattern of attacks, triggers, medication use habits, and previous treatment responses cannot be reliably established in a brief encounter. Short evaluations frequently lead to misdiagnosis, unnecessary investigations, and premature labeling of "treatment resistance" (4).

Blau emphasized that the duration of the consultation is not only a diagnostic but also a **therapeutic tool.** Allowing the patient to describe how they experience their attacks, listening without interruption, and conveying that this narrative is taken seriously constitute the first step of treatment. According to Blau, unless the patient feels that their migraine is accepted as a "real and recognized disease," even the most effective pharmacological treatments may fail (15).

In migraine patients, physical examination is not merely a symbolic procedure but a fundamental component of diagnosis and differential diagnosis. Although neurological examination is prominent in patients presenting with headache, a **full physical examination must be performed** in migraine patients. Systemic infections, inflammatory diseases, hypertension, and endocrine or metabolic disorders may trigger or mimic headache. Excluding these causes renders the assumption that the headache is primary more secure (5).

Neurological examination is normal in the vast majority of migraine patients. However, as Blau also emphasized, a normal examination should not be conveyed passively but **demonstrated actively**. It is not sufficient for the physician to state "your examination is normal"; the reasons why it is normal and what this means must be explained. This approach convinces the patient that there is no serious brain disease and significantly reduces unnecessary demands for imaging (6,16).

Assessment of the neck, shoulder girdle, temporomandibular joint, and pericranial muscles is an integral part of the migraine examination. Cervical muscle spasm, postural disorders, and temporomandibular joint dysfunction may trigger or perpetuate migraine attacks. Neglecting these areas may lead to overlooking tension-type or cervicogenic headache components under the diagnosis of migraine (7).

Magnetic resonance imaging (MRI) is one of the most frequently misused tools in migraine management. In patients with a typical migraine history, long-standing attacks of similar character, and a normal neurological examination, routine MRI often provides no diagnostic contribution. Blau highlighted this issue early on and emphasized that imaging should not become a tool to compensate for physician uncertainty (17). Incidental findings may lead to unnecessary anxiety, additional investigations, and increased medical consumption (8).

In contrast, imaging is not optional but **mandatory** in the presence of sudden-onset severe headache, progressively worsening pain patterns, new-onset headache after the age of 50, focal neurological signs, or systemic disease manifestations (9).

The physician's role in migraine treatment is often trivialized under the concept of the "placebo effect." However, modern neuroimaging studies demonstrate that patient–physician interaction can directly influence pain modulation networks. A clinical encounter based on trust can alter pain perception by increasing activation in pain-regulating centers such as the prefrontal cortex, anterior cingulate cortex, and periaqueductal gray (10,11). These findings confirm Blau's clinical observations at the neurobiological level.

One of Blau's most important contributions was emphasizing the effect of language used with migraine patients on treatment outcomes. Statements such as "this disease does not go away" or "you must learn to live with it" create learned helplessness in patients. In contrast, clearly stating that migraine is a controllable disease increases the patient's active participation in the treatment process. The goal of migraine treatment is not to eliminate pain completely but to provide the patient with a sense of control (12,18).

Conclusion

Migraine treatment is not limited to selecting the correct medication. Successful migraine management is possible through a detailed medical history taken with adequate time, a comprehensive physical and neurological examination, an approach that avoids unnecessary investigations while not delaying necessary ones, and an individualized treatment plan that takes the patient seriously. **The most effective treatment**

for a migraine patient is often not a new drug, but a physician who allocates time, listens carefully, and evaluates accurately.

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CHAPTER 11: What Should the Migraine Patient Do?

Migraine treatment does not depend solely on the physician's knowledge and experience. Equally decisive is the extent to which the patient participates in the process actively, openly, and honestly. Although migraine is a biological neurological disease, it is a multidimensional condition that is profoundly influenced by lifestyle, psychological state, social environment, and individual habits. For this reason, the migraine patient must not be a passive "prescription recipient" in treatment, but rather a conscious co-participant (1).

The multidimensional nature of migraine brings not only clinical consequences but also economic consequences. Migraine has a broad economic impact ranging from loss of workforce productivity to the burden placed on health care systems, and this impact is often not recognized or is underestimated by patients.

The migraine patient must first accept the disease. Migraine is not a simple headache; according to World Health Organization data, it is one of the leading causes of disability, particularly among individuals in their most productive years (2). Failure to acknowledge the seriousness of migraine not only impairs treatment adherence but also leads to an unsustainable pattern of "endurance" in professional and social life. This situation negatively affects both the patient's health and economic productivity.

The information conveyed by the migraine patient to the physician determines the fate of diagnosis and treatment. The mode of pain onset, duration, severity, aura characteristics, accompanying symptoms, and triggers must be described completely. In addition, the impact of migraine on work, family life, and social functioning must be clearly expressed. Inability to attend work due to attacks, reduced productivity while at work, and avoidance of social activities are not merely personal problems; they constitute the core components of the indirect economic costs of migraine (3).

The economic burden of migraine is not limited to health care expenditures alone. Direct costs include physician visits, medications, emergency department visits, and diagnostic investigations, whereas indirect costs are far greater. Loss of workforce participation, reduced productivity (presenteeism), early retirement, and career limitation constitute the principal economic burden of migraine (4). Studies indicate that 70–90% of the total cost of migraine arises from indirect costs (5).

A substantial proportion of migraine patients are unable to go to work during attacks (absenteeism), or, even if present at work, are unable to function productively (presenteeism). Presenteeism results in a much greater economic loss than absenteeism and is often not reflected in official records (6).

Inadequate control of migraine leads to increased direct costs through frequent emergency department visits, unnecessary imaging studies (particularly brain MRI), inappropriate medication use, and the development

of medication-overuse headache (7). At this point, the quality of patient–physician communication and sufficient consultation time become key determinants not only of clinical success but also of cost-effectiveness.

The table below conceptually summarizes the annual economic burden of migraine on a per-patient basis and at the societal level. The figures are representative ranges derived from average values reported in studies conducted in Europe and OECD countries and are suitable for use in a book chapter format (4,5,8).

Table. Annual Cost Components of Migraine from a Health Economics Perspective

Cost Type	Components	Average Annual Cost (per patient)
Direct Medical Costs	Outpatient visits, emergency care, medications (analgesics, triptans, prophylaxis), diagnostic tests (MRI, CT)	300–800 €
Direct Non-Medical Costs	Transportation, caregiver needs, alternative/ complementary treatments	100–300 €
Indirect Costs (Absenteeism)	Work absenteeism, lost workdays	1.000–3.000 €
Indirect Costs (Presenteeism)	Reduced productivity at work	2.000–5.000 €
Total Annual Economic Burden	Direct + indirect costs	**3.500–9.000 €**

When evaluated at the societal level, the annual economic burden of migraine in Europe is measured in tens of billions of euros. The majority of this burden does not originate from health care budgets but from loss of productivity (5,8).

Migraine patients often avoid discussing psychological, social, and sexual problems with their physicians. However, depression, anxiety, sleep disorders, and reduced sexual desire both increase migraine severity and lead to additional losses in occupational and social functioning (6). Concealment of these problems results in inadequate treatment and further increases the economic burden.

It is of vital importance that migraine patients openly report all medications they use, including over-the-counter analgesics and previous treatment attempts. Uncontrolled and frequent use of analgesics leads to medication-overuse headache, thereby chronicizing the disease and exponentially increasing health care costs (7).

Similarly, herbal products, vitamins, supplements, and traditional methods must be reported to the physician. Time and money spent on ineffective or harmful methods constitute part of the hidden economic losses associated with migraine (8).

Keeping a migraine diary is one of the most powerful tools available to the patient from both a clinical and an economic perspective. Regular recording of attack frequency, medications used, and treatment responses reduces unnecessary medication use, facilitates the development of more effective treatment strategies, and lowers indirect costs (9).

Conclusion

Migraine treatment does not merely aim to reduce pain; it seeks to preserve the patient's quality of life, productivity, and economic independence. When migraine patients communicate their experiences openly and physicians evaluate this information holistically, treatment becomes not only more effective but also more sustainable and more economical. The true cost of migraine is often hidden not in drug prices, but in lost time, energy, and life opportunities.

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CHAPTER 12: Diagnostic Form for Primary Headaches

DOWNLOAD: Tulunay Primary Headache Form and Algorithm

TULUNAY PRIMARY HEADACHE DIAGNOSTIC FORM FOR PRIMARY CARE PHYSICIANS.

Tested on over 10,000 patients, ICHD-3 and MIDAS compliant, form to be completed by the patient.

A. PATIENT INFORMATION

Full Name: _____

Age: _____

Sex: ☐ Female ☐ Male

Occupation: _____

Date of Visit: _____

B. DURATION AND FREQUENCY OF HEADACHE

1. How long have you had headaches?

- ☐ <6 months
- ☐ 6 month – 1 year
- ☐ 1–5 years
- ☐ >5 years

2. How many days did you have a headache in the last 1 month?

- ☐ 1–3 days
- ☐ 4–7 days
- ☐ 8–14 days

☐ ≥15 days

C. ATTACK DURATION (ICHD-3)

3. How long does your headache usually last if untreated or unsuccessfully treated?

☐ <1 hour

☐ 1–4 hours

☐ 4–72 hours

☐ >72 hours

D. LOCATION AND ONSET OF HEADACHE

4. Where does your headache usually start?

☐ Temple

☐ Forehead

☐ Eye / behind the eye

☐ Nape / back of head

☐ Whole head

☐ Variable / Moves

5. How does the headache usually start?

☐ Suddenly

☐ Gradually

E. PAIN CHARACTERISTICS

(More than one option may be selected – INCLUDES TURKISH PATIENT-SPECIFIC DEFINITIONS)

The expressions that best describe your pain:

☐ Throbbing, pounding like a heartbeat

☐ **As if my brain is being squeezed**

☐ **As if my head is in a vise / clamp**

☐ **My head feels full, there is pressure**

☐ **As if my brain is leaking out.**

☐ Like a knife stabbing

☐ Very severe, unbearable

F. PHYSICAL ACTIVITY AND BEHAVIOR

6. Does physical activity (walking, climbing stairs) worsen the pain?

☐ Yes ☐ No

7. During pain:

☐ I want a dark and quiet environment

☐ I cannot stay still, I become restless

G. ASSOCIATED SYMPTOMS

Do the following occur during headache?

(Mark all that apply)

☐ Nausea

☐ Vomiting

☐ Sensitivity to light

☐ Sensitivity to sounds

☐ Sensitivity to odors

H. AURA SCREENING

8. Before the headache, do you experience visual or sensory changes that completely resolve?

☐ Yes ☐ No

If yes:

☐ Flashes / zigzag lights in vision

☐ Loss of vision

☐ Numbness in face or arm

☐ Difficulty speaking

I. CLUSTER HEADACHE DIFFERENTIAL DIAGNOSIS BLOCK

9. Is your pain always one-sided?

☐ Yes ☐ No

10. Is the pain usually around the eye / behind the eye / at the temple?

☐ Yes ☐ No

11. During pain, does one of the following occur on the same side?

(Mark all that apply)

☐ Tearing of the eye

☐ Nasal discharge or congestion

☐ Drooping/swelling of eyelid

☐ Facial redness or pallor

☐ Forehead/facial sweating

12. Do you pace around and cannot stay still during pain?

☐ Yes ☐ No

13. The pain usually:

☐ Lasts 15–180 minutes

☐ Repeats 1–3 times per day

☐ Occurs in clusters lasting weeks–months

J. TENSION-TYPE HEADACHE (TTH) DIFFERENTIAL BLOCK

14. The pain is usually:

☐ Bilateral

☐ Associated with nape and shoulders

☐ A pressure sensation lasting all day

15. Does nausea occur during pain?

☐ Yes ☐ No

16. Does light or sound significantly worsen the pain?

☐ Yes ☐ No

K. TRIGGERS

☐ Stress / emotional distress

☐ Insomnia

☐ Hunger

☐ Alcohol

☐ Bright light

☐ Menstrual period

☐ Other: _____

L. FAMILY HISTORY

17. Is there migraine or similar headache in first-degree relatives?

☐ Yes ☐ No

M. MEDICATION USE (MOH SCREENING)

18. In the last 3 months, on how many days per month did you use painkillers?

☐ 0–4 days

☐ 5–9 days

☐ 10–14 days

☐ ≥15 days

N. MIDAS – DISABILITY ASSESSMENT

(Last 3 months)

☐ 19. Number of days you missed work/school: _____

☐ 20. Number of days your productivity at work was reduced by more than 50%: _____

☐ 21. Number of days you could not do household chores: _____

☐ 22. Number of days you cancelled social activities: _____

MIDAS TOTAL SCORE *(to be calculated by the doctor)*: _____

PRIMARY CARE HEADACHE DIAGNOSTIC ALGORITHM

(ICHD-3 compatible, adapted to Turkish real-world practice)

STEP 0 – PRE-SCREENING (mandatory)

Monthly headache days *(B2)*:

☐ <15 days/month

☐ ≥15 days/month

▶ If ≥15 days/month: **Chronic headache spectrum** is considered

▶ If <15 days/month: **Episodic headache spectrum**

STEP 1 – EXCLUDE / IDENTIFY CLUSTER HEADACHE

Are <u>at least 4</u> of the following positive?

☐ 1. Pain is **always unilateral** *(I9 = Yes)*

☐ 2. Pain is **around the eye** / **behind the eye** / **at the temple** *(I10 = Yes)*

☐ 3. Ipsilateral **autonomic symptom** present
(≥1 from I11: tearing, nasal discharge, ptosis, facial redness, etc.)

☐ 4. **Restlessness** / **inability to stay still** during attack *(I12 = Yes)*

☐ 5. Attack duration **15–180 minutes** *(I13 = Yes)*

☐ 6. Attacks occur **1–3 times a day** or **in clusters** *(I13 = Yes)*

✓ **If ≥4 criteria positive:**

● **SUSPECT CLUSTER HEADACHE**

▶ **Refer to Neurology**

▶ DO NOT continue migraine algorithm

STEP 2 – IDENTIFY TENSION-TYPE HEADACHE (TTH)

Are ALL three groups satisfied?

A) PAIN DESCRIPTION *(≥2 from Section E)*

☐ "As if my brain is being squeezed"

☐ "As if my head is in a vise / clamp"

☐ "My head feels full, there is pressure"

☐ "As if my brain is leaking out"

B) ASSOCIATED SYMPTOMS *(must be negative)*

Nausea: ☐ No

Vomiting: ☐ No

C) BEHAVIORAL / FUNCTIONAL

Worsening with physical activity: ☐ No

Light/sound sensitivity: ☐ No or mild

Stress: ☐ Yes

✓ **If A + B + C are met:**

● **PROBABLE TENSION-TYPE HEADACHE (TTH)**

Note: This block is specifically designed **to identify TTH cases frequently misdiagnosed as migraine in Türkiye.**

STEP 3 – PROCEED TO MIGRAINE DIAGNOSIS (after exclusion)

Core migraine conditions:

1. Attack duration:

4–72 hours when untreated *(C3)*

2. Pain characteristics *(D/E)*:

At least 2 of the following:

☐ Throbbing

☐ Moderate or severe

☐ Worsened by physical activity

3. Associated symptoms:

At least 1 of the following:

☐ Nausea or vomiting

☐ Sensitivity to light

☐ Sensitivity to sound

✓ **If all three conditions are met:**

● **PROBABLE MIGRAINE**

STEP 4 – AURA DIFFERENTIATION

Aura question *(H8)*:

☐ Yes → **Migraine with aura**

☐ No → **Migraine without aura**

Aura that **fully resolves** and lasts **5–60 minutes** is supportive.

STEP 5 – CHRONIC MIGRAINE SCREENING

If:

Monthly headache **days ≥15**

AND

There is history of attacks meeting the above migraine criteria

● **PROBABLE CHRONIC MIGRAINE**

▶ Neurology evaluation recommended

STEP 6 – MEDICATION OVERUSE HEADACHE (MOH)

Analgesic days *(M18)*:

≥15 days/month → **High MOH risk**

10–14 days/month → **Moderate MOH risk**

<10 days/month → Low risk

Note: MOH is marked **independently** of diagnosis.

STEP 7 – SEVERITY CLASSIFICATION WITH MIDAS

(Independent of diagnosis, for follow-up and epidemiology)

MIDAS total (N19–22):

0–5 → Minimal

6–10 → Mild

11–20 → Moderate

≥21 → Severe

AUTOMATIC OUTPUT (TO BE MARKED ON FORM)

Probable Diagnosis:

☐ Migraine (without aura)

☐ Migraine (with aura)

☐ Chronic migraine (screening)

☐ Tension-type headache

☐ Cluster headache – referal

☐ MOH risk present

MIDAS Derecesi: ☐ Minimal ☐ Mild ☐ Moderate ☐ Severe

The Importance of Accurate Diagnosis in Primary Care: "Headache is a Condition Every Physician Must Know"

Effective treatment of migraine attacks begins with accurate and timely diagnosis. However, it is known that in clinical practice, especially at the primary care level, migraine is frequently misdiagnosed, while cluster headache and tension-type headache are significantly overlooked. It is observed that a significant portion of patients diagnosed with migraine in Turkey actually suffer from tension-type headache or other primary headache syndromes, while cluster headache is diagnosed late or not at all due to low awareness. One of the fundamental reasons for this problem is that international diagnostic criteria do not exactly match patient

expressions. Turkish patients often describe their headaches not with classic terms like “throbbing,” but with phrases such as “they are squeezing my brain,” “it’s like my head is in a vice,” “my head is full,” or “it feels like my brain is leaking out.” These expressions are descriptions that have no direct equivalent in standard English scales but strongly suggest tension-type headache clinically. Similarly, the restlessness, agitation, and autonomic symptoms that are distinctive in cluster headache are often confused with migraine when not sufficiently questioned.

The primary care headache diagnostic algorithm added to the end of this section has been developed based on ICHD-3 diagnostic criteria to strengthen the distinction between migraine, tension-type headache, and cluster headache. The algorithm offers a holistic approach that evaluates not only pain characteristics but also patient behavior, accompanying autonomic symptoms, language patterns specific to the Turkish patient, and functional impairment (MIDAS) together. The purpose of this algorithm is not to make a definitive diagnosis, but to guide the primary care physician to the correct diagnosis, prevent unnecessary migraine treatments, and ensure the early recognition of presentations requiring specific approaches, such as cluster headache. At the same time, the data obtained thanks to the structure of the form and algorithm are of a quality that can be directly used in epidemiological studies. Success in the treatment of migraine attacks is possible not only by selecting effective drugs but by making the correct diagnosis for the right patient. Therefore, this algorithm should be evaluated not as an “adjunctive tool” complementing migraine treatment, but as an integral part of the treatment.

Headache is a common subject not only of neurology but of all disciplines of medicine. Primary care physicians, emergency department physicians, internal medicine specialists, and family physicians constitute the group of doctors who encounter patients with headaches most frequently. Therefore, the accurate evaluation of headache and the differentiation of primary headaches should be within the basic clinical competency area of every physician, not just neurologists. Accurate recognition of headache in primary care ensures the prevention of unnecessary tests, inappropriate drug use, and incorrect migraine diagnoses. It also allows for the early detection of presentations requiring specific and targeted treatment, such as cluster headache. Instead of viewing headache as a complaint that must absolutely be referred, evaluating it within the framework of a specific algorithm increases patient safety and reduces the burden on the healthcare system. For this reason, the diagnosis-guiding form and algorithm presented in this book have been prepared not only for neurology practice but also to support the daily clinical decisions of primary care physicians.

When Should a Patient Be Referred to Neurology?

One of the most critical decisions in headache management for the primary care physician is determining which patient can be safely monitored in primary care and which requires referral for further evaluation. The primary care physician should be able to diagnose primary headaches (migraine, cluster, and tension-type). They must also be able to decide when to refer secondary headaches and subgroups of primary headaches to a specialist. While a structured anamnesis and diagnosis-guiding algorithms greatly facilitate this distinction, referral to a neurologist or other relevant specialty fields should not be delayed in certain clinical situations.

In patients presenting with unilateral, very severe, short-duration pain accompanied by autonomic symptoms, and showing marked restlessness and agitation during pain, the possibility of **cluster headache** should be considered, and a neurology referral should be made in the early period regardless of the diagnosis. Standard migraine treatments are generally ineffective in this patient group, and specific treatment approaches are required.

In patients experiencing headaches on **fifteen days or more per month,** those for whom sufficient clinical response is not obtained despite appropriate acute treatments, or whose attack frequency and severity increase over time, further evaluation is required regarding the **chronic headache spectrum.** It would be appropriate to refer these patients for diagnostic clarification and the creation of long-term treatment plans.

In patients using analgesics, triptans, or combined painkillers on more than **ten to fifteen days per month,** the risk of **Medication-Overuse Headache (MOH)** should be taken into consideration. In these cases, neurology support is important for the reorganization of treatment, limitation of drug use, and, if necessary, the planning of a structured detoxification process.

If the duration, character, or accompanying symptoms of the headache are not compatible with primary headaches; if the clinical presentation shows **atypical features** or if the diagnosis is uncertain, the referral decision should not be delayed. Similarly, a distinct change in the character of the headache over time also requires further evaluation.

In headaches that are new-onset, progressively worsening, accompanied by neurological deficits, or presenting with fever, involuntary weight loss, or signs of systemic disease, the possibility of **secondary headache** must absolutely be excluded, and an **emergency referral** must be made for further investigation.

Accurate diagnosis of headache is not just about answering the question “Is it migraine or not?” Accurate diagnosis ensures the right treatment, referral at the right time, and avoidance of unnecessary interventions. Structured forms and diagnostic algorithms used in primary care exist not to replace the physician's clinical intuition, but to support and standardize it. Effective treatment of migraine attacks gains meaning only within this holistic approach. ■

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