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Review Article

Plan-B: Exploring Alternative Preventive Medications for Migraines and Chronic Headaches: Comprehensive Literature Review and Analysis of Efficacy and Practical Considerations for Non-First- Line Treatments

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Chronic headaches, including chronic migraine, chronic daily headache (CDH), new daily persistent headache (NDPH), and chronic post-traumatic headache, represent a significant public health issue due to their high prevalence, associated disability, and economic burden. Epidemiological studies estimate that chronic migraine affects approximately 2% of the population, while CDH affects about 4% to 5% of the general population. 1, 2 These conditions are marked by frequent and severe headache episodes, leading to significant impairment in daily functioning and quality of life. 1-3

Demographic data show that these headache disorders differ notably between adult and pediatric populations. Chronic migraine and NDPH are increasingly recognized as major contributors to disability in children and adolescents. A study revealed that over 25% of U.S. adolescents experience frequent or severe headaches, comparable in impact to chronic conditions like arthritis. 4 NDPH often begins abruptly, often triggered by physical or psychological stress, and is more common in younger populations, particularly during school transitions. 5 On the other hand, chronic migraine usually evolves from episodic migraine, with a gradual increase in frequency, often worsened by comorbid conditions such as anxiety and depression. 1, 2, 6

The burden of chronic headaches extends beyond individual suffering, imposing significant economic costs on society. Chronic migraine, for example, is associated with high levels of absenteeism and presenteeism, leading to lost productivity and increased healthcare costs. 3, 7 A national survey in Brazil reported a migraine prevalence of 15.2%, with a substantial portion of the population experiencing daily headaches. 8 This underscores the need for effective management strategies and preventive treatments to reduce the impact on both individuals and healthcare systems.

Comparative studies across different regions and populations have shown variations in the prevalence of chronic headaches. In a large population-based study in Denmark, researchers examined the comorbidity of migraine with other somatic diseases, revealing a complex interplay between genetic and environmental factors predisposing individuals to chronic headache disorders. 9 Geographic factors also influence migraine prevalence; for example, higher rates are reported in southern regions of China compared to northern areas, suggesting that climate and lifestyle may play a role in headache epidemiology. 10

Gender differences are also significant in chronic headache demographics. Women are disproportionately affected by migraines, particularly during their reproductive years, with hormonal fluctuations contributing to the frequency and severity of attacks. 11 This gender disparity is further complicated by comorbid conditions, such as anxiety and depression, which are more prevalent in women and can exacerbate headache symptoms. 1, 2 Understanding these demographic factors is crucial for tailoring treatment approaches to improve outcomes.

In pediatric populations, chronic migraine and NDPH are often underdiagnosed and undertreated, despite their significant impact on quality of life and daily functioning. 6, 12 Research indicates that children with chronic migraine experience severe functional disability, similar to that seen in adults, underscoring the importance of early diagnosis and intervention. 6 transition from episodic to chronic migraine during adolescence is a critical period that warrants attention, as effective management during this time can alter the disorder's trajectory. 13

The epidemiology of chronic headaches highlights the importance of considering comorbidities and their impact on treatment outcomes. Individuals with chronic migraine often report higher levels of disability and poorer quality of life compared to those with episodic migraine, emphasizing the need for comprehensive treatment strategies that address both headache management and associated comorbid conditions. 1-3 Additionally, medication overuse headache (MOH), which frequently accompanies chronic headache disorders, complicates treatment and requires careful management to avoid exacerbating symptoms. 14

Recent advancements in treatment options, such as the introduction of novel preventive medications like calcitonin gene-related peptide (CGRP) monoclonal antibodies, offer new hope for individuals suffering from chronic headaches. 3, 7 However, barriers to accessing these treatments, including lack of awareness and healthcare disparities, continue to hinder optimal care for many patients. 2, 3 Addressing these barriers is essential for improving outcomes and reducing the burden of chronic headaches.

Barriers to Effective Treatment

The treatment of chronic headaches is often hindered by various barriers, including healthcare access, patient-related factors, treatment-related challenges, and systemic issues within healthcare systems. Understanding these barriers is crucial for developing effective interventions to improve treatment outcomes for individuals suffering from these debilitating conditions.

One significant barrier is limited access to healthcare services. Many patients with chronic headaches face challenges in obtaining timely and appropriate medical care, especially in rural or underserved areas where specialized headache clinics may not be available. 15, 16 Furthermore, the stigma associated with chronic pain conditions can deter individuals from seeking help, as they may fear being perceived as exaggerating their symptoms or being labeled as "difficult" patients. 17, 18 This stigma is particularly pronounced in populations like military personnel, where there are additional concerns about the implications of reporting chronic pain on career advancement and mental health evaluations. 16, 18

Patient-related factors also play a significant role. Many individuals with chronic headaches may lack awareness regarding their condition and the available treatment options, leading to underreporting of symptoms and delays in seeking care. 19 Comorbid psychiatric conditions, such as anxiety and depression,

are prevalent among chronic headache sufferers and can complicate treatment adherence and outcomes. For example, patients with chronic migraine who also suffer from depression may experience higher levels of disability and poorer treatment responses, further complicating their management. 20

Treatment-related challenges include inadequate responses to first-line preventive medications, leading to frustration and a sense of hopelessness regarding treatment options. 17, 21 MOH is particularly concerning, as it can develop in patients who frequently use acute headache medications, leading to a cycle of increased headache frequency and severity. 22, 23 This cycle complicates treatment and requires a careful, often challenging approach to medication management, which may not be adequately addressed in standard clinical practice. 24

The complexity of chronic headache disorders themselves can hinder effective treatment. Chronic headaches are often heterogeneous, with overlapping symptoms and varying responses to treatment among individuals. 25 For instance, patients with chronic migraine and those with chronic tension-type headache may respond differently to the same treatment regimen, necessitating a personalized approach that can be resource-intensive and time-consuming. 19, 25 Additionally, the presence of CDH can complicate the treatment of primary headache disorders, as patients may require a multimodal approach that addresses both the headache and any underlying psychological or behavioral issues. 20

Systemic issues within healthcare systems exacerbate these barriers. Many healthcare providers lack specialized training in headache management, leading to suboptimal treatment recommendations and reliance on trial-and-error approaches. 25 This lack of expertise can result in delays in diagnosis and treatment, as well as increased healthcare costs due to unnecessary testing and ineffective treatments. 25 The fragmentation of care, where patients see multiple providers without coordinated management, can lead to confusion and frustration for patients seeking effective treatment. 25

Insurance coverage and reimbursement policies also impact access to care. Many insurance plans impose restrictions on the types of treatments covered, limiting access to newer and potentially more effective therapies. 19 The high cost of certain treatments, such as monoclonal antibodies for migraine prevention, can be prohibitive for many patients, particularly those without adequate insurance coverage. 22, 26 This financial burden can lead to treatment abandonment, further exacerbating the cycle of chronic headache and disability.

Need for Alternative Treatment Options

The treatment landscape for chronic headaches, particularly migraines, presents significant challenges, necessitating the exploration of alternative treatment options. One primary barrier is medication overuse, leading to MOH, particularly among chronic migraineurs. Over-prescription of opioids for acute migraine

treatment has been noted, with studies indicating that nearly one in four chronic migraine patients may develop MOH. 27 This cycle of overuse complicates treatment and highlights the urgent need for alternative strategies that can mitigate MOH risk while effectively managing headache symptoms.

The pediatric population faces unique challenges in accessing approved treatments for chronic headaches. Many pharmacological options available for adults are not yet approved for use in children and adolescents, leaving healthcare providers with limited choices for managing migraines in younger patients. 28, 29 This lack of approved treatments underscores the importance of exploring non-pharmacological interventions and alternative therapies. For instance, acupuncture has shown promise in reducing headache frequency and severity, providing a viable alternative for those who may not tolerate traditional medications well. 30 Behavioral interventions, such as biofeedback therapy, have also demonstrated efficacy in reducing headache days in children, emphasizing the need for diverse treatment modalities. 31

Integrating alternative treatment options is essential for addressing medication-related barriers, improving overall treatment adherence, and enhancing patient satisfaction. Compliance with traditional prophylactic medications is a significant issue, with many patients discontinuing treatment within three months due to side effects or lack of efficacy. 2 In contrast, treatments like onabotulinumtoxinA, which require less frequent administration, have shown better adherence rates. 2 This highlights the potential for alternative therapies to enhance patient engagement and improve outcomes.

Furthermore, innovative treatment modalities, such as neuromodulation techniques, offer promising possibilities for managing chronic headaches. Non-invasive vagus nerve stimulation (nVNS) and direct current stimulation have shown promise in reducing headache frequency and severity, providing additional options for patients who may not respond well to conventional pharmacological treatments. 17, 32 These emerging therapies could play a crucial role in the comprehensive management of chronic headaches, particularly for those with medication-related barriers.

Preventive therapy for migraines aims to reduce the frequency of headache episodes, diminish migraine-related disability, improve quality of life, and manage the need for acute medications. The complexity of these therapies arises from the need for slow titration, gradual weaning, and sometimes combination therapies, complicating management for both patients and healthcare providers. 33, 34

Migraine Migraine preventive therapies are classified into four levels of evidence:

• Level A: Strong evidence supports treatments like sodium valproate, topiramate, metoprolol, propranolol, timolol, and onabotulinumtoxinA for chronic migraines. 33, 35, 36

• Level B: Moderate evidence supports treatments like amitriptyline and venlafaxine. 33, 34

• Level C: Limited evidence supports treatments like candesartan, lisinopril, and cyproheptadine. 33, 34

• Level U: Uncertain or conflicting evidence supports treatments like gabapentin and verapamil.33, 34

Despite the availability of these treatments, the pediatric population faces unique challenges in accessing approved therapies for chronic migraines. Many pharmacological options available for adults are not yet approved for use in children and adolescents, leaving healthcare providers with limited choices. 37 This lack of approved treatments underscores the importance of exploring non-pharmacological interventions and alternative therapies, such as biofeedback, which has shown promise in reducing headache frequency and severity. 38

The need for alternative treatment options is driven by the limitations of current therapies. Compliance with prescribed therapies is a major issue, as many patients struggle with dosing frequency, leading to missed doses and inconsistent adherence. 39, 40. Side effects can lead to discontinuation or require dose adjustments, complicating treatment. The commitment required for dosing, titration, and the slow escalation and weaning process adds another layer of complexity, particularly for patients who may not see immediate results. 41

Additionally, contraindications due to other medical conditions and potential interactions with other medications can limit treatment options. Frequent monitoring is necessary to manage potential toxicity and interactions, complicating the overall process. Treatment failure, especially after trying multiple first-line agents, underscores the necessity for alternative options, as there is no one-size-fits-all approach to migraine management. This is particularly true in pediatric populations, where response rates to treatments can vary widely, and medication side effects may be more pronounced.42, 43

Cost is another significant barrier, especially in pediatric populations where approved options are limited. The financial burden of off-label or alternative therapies can be prohibitive for many families. 44 Access to these medications can also be challenging, particularly in remote areas where pharmacies may not carry specialized treatments. Insurance coverage poses an additional hurdle, as many alternative treatments are off-label and may require patients to fail prior treatments before coverage is approved. 45, 46

Patient preferences also play a crucial role in the need for alternative therapies. Some patients may have specific aversions to certain delivery methods, such as needles, nasal sprays, or the taste of melting tablets. Allergies, needle phobia, and an unwillingness to undergo infusions further complicate treatment choices. 47These factors highlight the necessity for a broader range of treatment options to effectively manage migraines and chronic headaches.

In managing migraines and chronic headaches, exploring alternative preventive treatments has become increasingly important due to the limitations and challenges associated with first-line therapies. This review

highlights several alternative medications that may be considered for the preventive treatment of migraines and chronic headaches, including acetazolamide, candesartan, caffeine, cannabinoids, corticosteroids (dexamethasone, prednisone), cyproheptadine, doxycycline, duloxetine, furosemide, gabapentin, indomethacin, ketamine, lamotrigine, levetiracetam, lisinopril, low dose naltrexone, memantine, mixelitine, monteleukast, muscle relaxants (baclofen, cyclobenzaprine, tizanidine), neuroleptics, pregabalin, venlafaxine, verapamil, and zonisamide.

Despite FDA-approved therapies, significant challenges persist, driving the need for these alternative options. Compliance with prescribed therapies is a major concern, as many patients struggle with dosing frequency, leading to missed doses and inconsistent adherence. 39, 40 Side effects can lead to discontinuation or require dose adjustments, complicating treatment. The commitment required for dosing, titration, and the slow escalation and weaning process adds another layer of complexity to migraine management, particularly for patients who may not see immediate results. 41

Contraindications due to other medical conditions and potential interactions with other medications can limit the use of certain treatments. Frequent monitoring is often necessary to manage potential toxicity and interactions, complicating the overall treatment process. 48 Treatment failure, especially after trying multiple first-line agents, underscores the necessity for alternative options, as there is no one-size-fits-all approach to migraine management. This is particularly true in pediatric populations, where response rates to treatments can vary widely.42, 49

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Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor primarily used to treat conditions like glaucoma, epilepsy, and altitude sickness, but it has also gained attention for its role in managing headaches and migraines,

particularly in pediatric populations. The drug's mechanism of action involves inhibiting carbonic anhydrase, an enzyme that helps regulate acid-base balance and fluid secretion in the body. By inhibiting this enzyme, acetazolamide reduces the production of cerebrospinal fluid (CSF), leading to a decrease in intracranial pressure (ICP). This reduction in ICP is particularly beneficial in conditions like idiopathic intracranial hypertension (IIH), where elevated ICP is a significant contributor to headache symptoms.50-52

In clinical studies, acetazolamide has been shown to effectively alleviate headaches associated with IIH by reducing the severity of headaches and stabilizing visual function. Improvements in quality-of-life measures and reductions in headache disability scores have been reported. 50-52 In pediatric populations, acetazolamide has demonstrated promise in treating headaches associated with conditions like pseudotumor cerebri. A retrospective study indicated that a significant proportion of children responded positively to acetazolamide, with 37.8% to 76.6% of patients experiencing relief from headaches and associated symptoms. 53, 54

The treatment is often continued until symptoms such as papilledema and visual disturbances resolve, underscoring the importance of monitoring in this demographic. The dosing of acetazolamide varies depending on the condition being treated and the age of the patient. For adults, doses can range from 250 mg to 1000 mg per day, while pediatric dosing typically requires careful adjustment based on weight and clinical response. 51, 55 The drug is generally well-tolerated, but common side effects include metabolic acidosis, hypokalemia, paresthesia, and gastrointestinal disturbances, which can impact patient adherence to treatment. 56, 57

Additionally, the incidence of nephrolithiasis (kidney stones) has also been reported in patients receiving acetazolamide, highlighting the need for monitoring renal function during treatment. 58

The vasodilatory properties of acetazolamide further contribute to its therapeutic effects in headache management. Research indicates that acetazolamide can reverse cerebral vasoconstriction, a phenomenon often implicated in migraine pathophysiology. 59 This dual action—reducing ICP while promoting vasodilation— positions acetazolamide as a versatile option in the management of headaches, particularly in patients with complex presentations such as IIH or migraines associated with altitude changes. 55, 59

Caffeine

Caffeine is one of the most widely consumed psychoactive substances globally, with a significant presence in coffee, tea, soft drinks, and certain medications. Its role in headache and migraine management is complex and multifaceted. On one hand, caffeine is known to be a potential trigger for headaches and migraines, especially when consumed in large quantities or irregularly. On the other hand, caffeine can also be used therapeutically to relieve headaches, particularly when combined with other analgesics.

In pediatric populations, research indicates that caffeine consumption is associated with an increased prevalence of headaches, particularly among children and adolescents who consume high amounts of caffeine daily. A study highlighted that caffeine-induced daily headaches are prevalent in younger populations, with evidence suggesting a causal relationship between high caffeine intake and migraine occurrences in children and adolescents. 60 This underscores the need for careful monitoring of caffeine consumption in this demographic, as excessive intake may exacerbate headache conditions.

The mechanisms through which caffeine exerts its effects on headache and migraine pathophysiology are primarily associated with its action as a non-selective antagonist of adenosine receptors, particularly A1 and A2A receptors. This antagonistic action can lead to vasoconstriction of cerebral blood vessels, which is beneficial during a migraine attack, as it counteracts the vasodilation that typically occurs during such episodes. 61 Additionally, caffeine enhances the analgesic effects of other medications, such as acetaminophen and aspirin, making it a valuable adjuvant in headache treatment protocols. 62 The combination of these analgesics with caffeine has been classified as a first-line option for acute migraine management by the American Headache Society, indicating its clinical significance. 63

However, the relationship between caffeine and headaches is complex, as excessive caffeine consumption can also lead to withdrawal headaches when intake is abruptly reduced. Studies have shown that caffeine withdrawal can trigger migraine attacks, suggesting that individuals who consume caffeine regularly may develop a dependency that complicates their headache management. 64 This phenomenon is particularly relevant in pediatric populations, where the developing nervous system may respond differently to caffeine compared to adults. The withdrawal symptoms can include rebound headaches, which may further complicate the clinical picture for young patients. 65

In terms of dosing, the effects of caffeine on headache management appear to be dose-dependent. Moderate caffeine intake has been associated with a reduction in headache frequency and intensity, while high doses may lead to increased headache prevalence. 66 For instance, a study noted that caffeine consumption correlates positively with both episodic and chronic migraine, indicating that while caffeine can be beneficial in acute scenarios, it may also contribute to the chronicity of headache disorders if consumed excessively. 67 Pediatric studies suggest that caffeine intake should be carefully regulated, as children may be more susceptible to the adverse effects of high caffeine consumption, including increased headache frequency and severity. 60

Common side effects associated with caffeine consumption include insomnia, increased heart rate, and gastrointestinal disturbances, which can be particularly concerning in pediatric populations. These side effects may not only affect the child's overall health but also their academic performance and social interactions, further complicating the management of headaches in this demographic. 68 Therefore, healthcare providers

must weigh the potential benefits of caffeine as a therapeutic agent against its risks, especially in younger patients who may have different tolerances and responses to caffeine compared to adults.

Candesartan

Candesartan, an angiotensin II receptor blocker (ARB), has gained recognition as a potential migraine prophylactic agent. It is particularly noteworthy in pediatric populations, although its application in this demographic remains limited compared to adults. Recent findings from a retrospective cohort study indicated that candesartan is well-tolerated and may significantly reduce the mean monthly headache days in adolescents with high baseline headache frequency. This study included adolescents suffering from various headache disorders, such as chronic migraine and medication-overuse headaches. The results demonstrated a notable reduction in headache days post-treatment, suggesting that earlier intervention with candesartan could yield better outcomes. The study also reported only mild side effects, reinforcing the drug's safety profile in younger patients. 69, 70

The efficacy of candesartan in migraine prevention was first substantiated in a randomized, double-blind, placebo-controlled crossover study conducted in Norway in 2003. This pivotal trial revealed that candesartan significantly decreased both the frequency and severity of headaches compared to placebo, establishing its role as an effective prophylactic agent. The study concluded that candesartan’s tolerability was comparable to that of placebo, making it a viable option for patients seeking migraine management. 71 Subsequent studies have corroborated these findings; for instance, a 2019 retrospective cohort study reported that a substantial proportion of patients with chronic migraine or medication-overuse headaches experienced at least a 50% reduction in headache frequency following. 72

Systematic reviews and meta-analyses have further emphasized the potential of ARBs, including candesartan, in mitigating headache days and severity. A 2010 review highlighted that candesartan's efficacy in migraine prophylaxis is comparable to that of other commonly used agents, particularly benefiting patients with comorbid conditions such as hypertension. 73 Another review noted that while candesartan and other ARBs are effective for migraine prevention, they are not typically recommended as first-line treatments. However, they can be particularly useful for patients with concurrent health issues. 74

In a comparative study conducted in 2013, candesartan was shown to be non-inferior to propranolol, a well-established migraine prophylactic, in reducing migraine days per month. Both medications significantly outperformed placebo, with candesartan demonstrating efficacy similar to that of propranolol. 75 Real-world evidence further supports the notion that candesartan can benefit difficult-to-treat migraine patients, especially those who are younger or have a longer disease duration. The study indicated that daily headaches were

associated with a lower likelihood of treatment success, underscoring the need for tailored therapeutic approaches. 69

Despite the promising evidence in adult populations, the application of candesartan in pediatric settings remains underexplored. A recent review underscored the urgent need for more migraine trials focusing on children and adolescents, as existing literature predominantly centers on adult populations. 76 Nevertheless, emerging findings suggest that candesartan could serve as a viable option for migraine prevention, even in patients who have previously failed multiple treatments. Overall, while candesartan is not yet universally recognized as a first-line treatment in most clinical guidelines, its efficacy and tolerability render it a compelling option, particularly for patients with coexisting hypertension or cardiovascular conditions.

The mechanism of action of candesartan involves the blockade of the angiotensin II type 1 receptor, which plays a crucial role in the regulation of blood pressure and fluid balance. By inhibiting this receptor, candesartan not only lowers blood pressure but may also exert neuroprotective effects that could contribute to its efficacy in migraine prevention. Common side effects associated with candesartan include dizziness, fatigue, and hypotension, although these are generally mild and transient. The typical dosing for migraine prophylaxis starts at 8 mg daily, with adjustments made based on patient response and tolerability.

Cannabinoids

The exploration of cannabinoids, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), as preventive options for headaches and migraines, particularly in pediatric populations, is gaining traction in contemporary medical research. Cannabinoids interact with the endocannabinoid system (ECS), which plays a crucial role in pain modulation. Recent studies indicate that the ECS components, including cannabinoid receptors (CB1 and CB2), are expressed in regions associated with migraine pathophysiology, such as the trigeminal system and the periaqueductal gray matter, suggesting a potential therapeutic target for migraine relief. 77-79

In pediatric studies, while direct research on cannabinoids for migraine prevention is limited, there is evidence supporting their use in managing other conditions like epilepsy, which often co-occurs with chronic headaches in children. A survey among pediatric neurologists indicated a cautious approach to prescribing cannabinoids for pediatric epilepsy, reflecting a broader hesitance in the medical community regarding off-label cannabinoid use in children. 80, 81 However, the therapeutic implications of cannabinoids in managing chronic pain conditions, including migraines, warrant further investigation, especially given the anecdotal reports of efficacy among pediatric patients. 81, 82

Mechanistically, cannabinoids exert their effects through various pathways. THC primarily acts on CB1

receptors, leading to analgesic effects, while CBD has a more complex interaction profile, including anti-inflammatory properties and modulation of neurotransmitter release. 83, 84 Studies have shown that cannabinoids can reduce the frequency and intensity of migraine attacks, with some patients reporting significant improvements in their condition after prolonged use. 85-87 The pharmacokinetics of cannabinoids can vary based on the formulation and route of administration, with inhalation being the most common method among users.88, 89

Despite the promising findings, the use of cannabinoids is not without side effects. Commonly reported adverse effects include dizziness, dry mouth, and alterations in mood or cognition, which can be particularly concerning in pediatric populations. 83, 90 Moreover, there is a risk of medication overuse headache (MOH) associated with frequent cannabinoid use, similar to other migraine treatments. 91 Dosing regimens vary widely, with some studies suggesting that lower doses may be more effective and better tolerated, emphasizing the need for personalized treatment approaches. 92

Corticosteroids

Corticosteroids have gained attention as a preventive treatment option for headaches and migraines, particularly in pediatric populations. The efficacy of corticosteroids in managing headache disorders has been supported by various studies, which highlight their potential benefits in reducing headache frequency and severity. For instance, a study focusing on the pediatric population demonstrated that corticosteroids, such as prednisone, were effective in alleviating chronic migraines, with significant improvements observed in headache-related disability and overall quality of life. 93 This finding underscores the importance of considering corticosteroids as a viable option in the management of headaches in children, especially when conventional treatments have proven insufficient.

The mechanism of action of corticosteroids in headache management primarily involves their potent anti-inflammatory properties. Corticosteroids function by inhibiting the release of pro-inflammatory cytokines and neuropeptides, such as calcitonin gene-related peptide (CGRP), which are implicated in the pathophysiology of migraines. This inhibition helps to mitigate the neurogenic inflammation that contributes to headache disorders, thereby reducing the frequency and intensity of headache episodes. Additionally, corticosteroids may exert effects on central pain processing pathways, further enhancing their efficacy in headache prevention. 94 This dual mechanism of action highlights the potential of corticosteroids to address both peripheral and central components of headache disorders.

In terms of dosing, various corticosteroids can be employed, each with specific dosing regimens tailored to the individual patient's needs. Prednisone is commonly prescribed at doses ranging from 60 to 100 mg per day

for acute migraine management, with a tapering schedule often recommended to minimize withdrawal effects. Methylprednisolone is another corticosteroid that can be utilized, typically administered at doses of 40 mg to 80 mg for similar therapeutic effects. Dexamethasone, known for its long half-life, may also be employed, usually at doses ranging from 4 to 10 mg, depending on the clinical scenario. 95 The choice of corticosteroid and dosing regimen should be individualized, taking into account factors such as the severity of headaches, the patient's age, and any comorbid conditions.

Despite their therapeutic benefits, corticosteroids are associated with several side effects that warrant careful consideration. Common adverse effects include hypertension, hyperglycemia, weight gain, and potential psychological symptoms such as mood swings and anxiety. 96 In pediatric populations, specific concerns such as growth suppression and the risk of adrenal insufficiency must be taken into account when prescribing corticosteroids. The incidence of adverse effects is often dose-dependent, with higher doses correlating with an increased risk of complications. 97 Therefore, clinicians must weigh the potential benefits of corticosteroid therapy against the risks, particularly in children who may be more susceptible to the adverse effects of these medications.

Cyproheptadine

Cyproheptadine, a first-generation antihistamine, has emerged as a potential preventive treatment for headaches and migraines, particularly in pediatric populations. Its mechanism of action is primarily attributed to its antagonistic effects on serotonin receptors, specifically the 5-HT2C subtype, as well as histamine H1 receptors. This dual action is significant in the context of migraine pathophysiology, as serotonin dysregulation is often implicated in headache disorders. Pediatric studies have shown that cyproheptadine is frequently used in conjunction with other medications such as amitriptyline and propranolol for migraine prophylaxis, with some evidence suggesting that it may be particularly effective in younger patients. 98

In addition to its role in migraine management, cyproheptadine has been recognized for its efficacy in treating cyclical vomiting syndrome (CVS) and abdominal migraines in children. Research indicates that migraine prophylaxis can lead to a complete resolution of cyclic vomiting episodes in a significant percentage of affected children.99 Moreover, abdominal migraines, characterized by recurrent abdominal pain, have shown positive responses to migraine prophylactic medications, including cyproheptadine. 100 The overlap between migraine and CVS is noteworthy, as CVS is increasingly recognized as a variant of migraine, with a higher prevalence among migraineurs compared to controls.

The safety and efficacy of cyproheptadine in pediatric populations have been evaluated in various studies. A systematic review highlighted that while the evidence supporting cyproheptadine's use in migraine prevention

is not definitive, it remains a commonly prescribed option due to its favorable side effect profile compared to other agents. 98 For instance, a study indicated that cyproheptadine was preferred for younger patients, with an 83% positive response rate observed during a six-month follow-up period. 98 Additionally, cyproheptadine's role in appetite stimulation has been noted, which could be beneficial in children with comorbid conditions that affect growth and development, further supporting its use in this demographic.101

The pharmacological effects of cyproheptadine extend beyond its antihistaminic properties. Research has shown that it can inhibit serotonin's action, which is crucial in the context of migraine, as serotonin dysregulation is often implicated in headache disorders. 102 The drug's ability to antagonize serotonin receptors may help mitigate the trigeminal nerve-mediated pain pathways that are activated during migraine attacks. 103 Furthermore, cyproheptadine's anticholinergic effects may also contribute to its therapeutic benefits, although the precise mechanisms remain an area of ongoing investigation.104

Common side effects associated with cyproheptadine include sedation, increased appetite, and potential weight gain, which are particularly relevant in pediatric patients.105 While most adverse effects reported in studies have been mild, careful monitoring is advised, especially in younger populations where the impact of these side effects can be more pronounced. 106 The recommended dosing for cyproheptadine in children typically starts at lower levels, gradually increasing based on clinical response and tolerance, with a common regimen being 0.25 to 0.5 mg per dose, administered two to three times daily. 98

Doxycycline

Doxycycline, a tetracycline antibiotic, has gained recognition as a potential preventive treatment for headache disorders, particularly New Daily Persistent Headache (NDPH) and chronic migraines. Although specific pediatric studies on doxycycline's efficacy in headache prevention are scarce, its established anti-inflammatory properties suggest potential benefits for younger populations suffering from refractory headache disorders. The mechanism underlying doxycycline's effectiveness involves the inhibition of pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α), which has been linked to the pathophysiology of NDPH and chronic migraines. Elevated TNF-α levels in the cerebrospinal fluid (CSF) of affected patients indicate a significant role for neuroinflammation in these headache disorders. 107, 108 By modulating the inflammatory response, doxycycline may alleviate symptoms associated with these conditions.

In a pivotal open-label study by , four patients with treatment-resistant NDPH and elevated CSF TNF-α levels were treated with doxycycline at a dosage of 100 mg twice daily for three months. These patients had previously failed multiple preventive treatments, yet they reported significant improvements, with two achieving complete pain relief and others experiencing substantial reductions in pain intensity and frequency

of severe episodes.

107 This study underscores the potential of doxycycline as a targeted therapy for NDPH, especially in patients exhibiting high levels of TNF-α.

Doxycycline's anti-inflammatory effects extend beyond headache management; it has been shown to modulate the expression of various pro-inflammatory cytokines, including interleukin-6 (IL-6) and interleukin- 8 (IL-8), in vitro.109 This broad-spectrum anti-inflammatory action reinforces the drug's potential utility in treating chronic inflammatory conditions. While pediatric studies specifically addressing doxycycline's use in headache prevention are limited, its established anti-inflammatory properties suggest it could be a viable option for children experiencing refractory headache disorders where inflammation is a contributing factor.109 The exploration of combining doxycycline with other anti-inflammatory agents, such as montelukast, has been noted, although the evidence remains largely anecdotal and requires further validation.110 Despite the promising findings from open-label studies and case reports, there is a pressing need for more extensive controlled trials to confirm the efficacy and safety of doxycycline, particularly in pediatric populations and across a broader spectrum of headache phenotypes.111, 112 Current evidence primarily stems from open-label studies and in vitro research, underscoring the necessity for rigorous investigations to substantiate these therapeutic approaches.111, 112

Common side effects associated with doxycycline include gastrointestinal disturbances, photosensitivity, and, in some cases, neurological symptoms such as headaches and dizziness. 113 The typical dosage for adults is 100 mg taken twice daily, but adjustments may be necessary based on individual patient needs and responses.114 While doxycycline is generally well-tolerated, its use in children under the age of eight is not recommended due to the risk of dental discoloration and potential effects on bone growth. 115

Duloxetine

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), has garnered significant attention for its potential efficacy in the prevention and treatment of chronic migraines, particularly among patients who also suffer from comorbid depression and anxiety disorders. The pharmacological profile of Duloxetine, which enhances the availability of serotonin and norepinephrine in the central nervous system, positions it as a promising candidate for addressing the multifaceted nature of chronic migraine, especially in individuals with overlapping psychiatric conditions. This literature review synthesizes current research findings on Duloxetine's efficacy, mechanisms of action, dosing considerations, common side effects, and its role in personalized medicine, while also highlighting gaps in pediatric research.

Despite the growing body of evidence supporting the use of Duloxetine in adult populations, there is a notable

scarcity of studies focusing on pediatric patients. This gap is particularly concerning given the prevalence of migraines in children and adolescents, as well as the potential impact of comorbid psychiatric disorders on migraine severity and frequency. Future research should prioritize the exploration of Duloxetine's safety and efficacy in younger populations, as well as the development of tailored treatment protocols that consider the unique physiological and psychological profiles of pediatric patients.

The clinical efficacy of Duloxetine in chronic migraine management has been supported by various studies. For instance, Zhu et al. (2022) demonstrated that Duloxetine Hydrochloride, when combined with flunarizine, significantly improved migraine relief rates and reduced depression and anxiety scores compared to a control group receiving flunarizine alone. This finding underscores the potential benefits of combination therapy in managing chronic migraine, particularly in patients with comorbid mental health conditions.116 Similarly, reported that the combination of flunarizine and Duloxetine effectively improved neuro-electrophysiological and inflammatory indices in patients with chronic migraine and comorbid depression and anxiety, further supporting the therapeutic advantages of Duloxetine in complex migraine cases.116

In terms of personalized medicine, Kisler et al. (2019) emphasized the importance of tailoring migraine prevention strategies based on individual patient profiles, particularly for those identified as pronociceptive migraineurs.117 Their findings indicated that Duloxetine was more effective than placebo in this subgroup, highlighting the potential for psychophysical testing to optimize treatment outcomes. 117{ This approach aligns with the broader trend in migraine management that seeks to integrate patient-specific factors into treatment planning, thereby enhancing the likelihood of successful outcomes.

The neurophysiological mechanisms underlying Duloxetine's analgesic effects have also been a focal point of research. Minami et al. (2017) elucidated that Duloxetine enhances the activity of noradrenergic and serotonergic systems, which are critical for modulating pain perception and central sensitization processes associated with chronic migraine.118 Their study demonstrated that Duloxetine increased pain thresholds, suggesting its effectiveness in addressing the neurobiological underpinnings of chronic migraine.118 This modulation of central pain pathways is particularly relevant in the context of chronic migraine, where central sensitization plays a pivotal role in the persistence and exacerbation of pain.

While Duloxetine's efficacy is well-documented, it is essential to consider the potential side effects associated with its use. Common adverse effects include nausea, dry mouth, fatigue, and dizziness, which may impact patient adherence to treatment.119 Additionally, the risk of withdrawal symptoms upon discontinuation of SNRIs necessitates careful management and patient education regarding the importance of gradual dose reduction when discontinuing therapy. Clinicians must weigh the benefits of Duloxetine against these potential side effects, particularly in populations that may be more sensitive to medication-related adverse events.

Dosing considerations for Duloxetine typically begin with a low dose, often starting at 30 mg per day, which may be gradually increased to a maximum of 60 mg per day based on clinical response and tolerability.119 This titration approach allows for the careful monitoring of side effects while optimizing therapeutic outcomes. The pharmacokinetics of Duloxetine, characterized by its relatively rapid onset of analgesic effects within the first week of treatment, further supports its utility in chronic migraine management. 120

Furosemide

Furosemide, a loop diuretic primarily indicated for conditions such as edema and hypertension, has garnered attention as a potential therapeutic agent for migraine management, particularly in pediatric populations. The exploration of furosemide's efficacy in treating migraine symptoms, especially visual disturbances associated with migraine aura, is supported by several case studies. One notable Brazilian case involved an 11-year-old girl suffering from migraine without aura, who experienced persistent negative visual aura symptoms. Remarkably, these symptoms resolved completely within five days of furosemide treatment, despite normal neurological evaluations and neuroimaging results, indicating that furosemide may effectively address visual disturbances in pediatric migraine patients.121 Similarly, a case involving a 21-year-old woman with a six-month history of persistent negative visual symptoms linked to migraine without aura demonstrated a positive response to a combination of furosemide and lamotrigine, further emphasizing furosemide's potential in managing migraine-related visual disturbances.122

The underlying mechanisms by which furosemide may exert its effects on migraine pathophysiology are of significant interest. Research has shown that furosemide can inhibit cortical spreading depression (CSD), a neurophysiological phenomenon believed to be a key contributor to migraine aura. In a study conducted on anesthetized cats, furosemide was found to significantly reduce the duration of CSD activity, likely through alterations in cortical ion buffering and inhibition of neuronal and glial cell swelling.122 This suggests that furosemide may target specific mechanisms associated with migraine aura, providing a potential therapeutic avenue for patients experiencing such symptoms. Additionally, furosemide's role extends beyond migraine treatment; it has been utilized as a second-line therapy for idiopathic intracranial hypertension (IIH), a condition characterized by increased intracranial pressure that can present with migraine-like symptoms. Its effectiveness in reducing intracranial pressure in patients unresponsive to initial treatments underscores its broader applicability in managing conditions associated with elevated intracranial pressure and migraine-like symptoms.123

In adults, furosemide has also been explored for the management of prolonged or persistent migraine aura. Two documented cases reported rapid resolution of prolonged visual aura following intravenous

administration of furosemide, which had previously been resistant to other treatments. This finding suggests that furosemide could serve as a viable option for the acute management of prolonged migraine aura.124 Furthermore, discussions surrounding chronic daily headaches (CDH) associated with increased intracranial pressure have included furosemide as a potential treatment. In patients with refractory transformed migraine-type CDH, the addition of furosemide after diagnosing increased intracranial pressure resulted in improved symptom control, supporting its role in managing such conditions.

The evolving understanding of migraine pathophysiology, particularly the distinctions between migraine with and without aura, is crucial for developing effective treatment strategies. Recent research indicates that while CSD is strongly associated with visual aura, its role in headache pain remains less defined. The International Classification of Headache Disorders (ICHD-3) has refined the criteria for diagnosing aura, and ongoing studies are investigating treatments specific to migraine with aura, including furosemide. However, further research is necessary to confirm its efficacy and safety in this context.

In terms of mechanism of action, furosemide primarily functions by inhibiting the Na-K-2Cl symporter in the thick ascending limb of the loop of Henle, leading to increased excretion of sodium, chloride, and water, which results in diuresis. This action may indirectly influence cerebral fluid dynamics, potentially alleviating symptoms associated with increased intracranial pressure. Common side effects of furosemide include electrolyte imbalances, dehydration, and hypotension, which necessitate careful monitoring, especially in pediatric populations. The typical dosing for furosemide in the context of migraine management has not been standardized, but case reports suggest intravenous administration may be effective, particularly in acute scenarios.

Gabapentin

Gabapentin, a synthetic analogue of gamma-aminobutyric acid (GABA), was initially developed as an anticonvulsant but has gained recognition for its analgesic properties, particularly in the management of various headache disorders, including migraines and cluster headaches. Its mechanism of action is multifaceted, primarily involving the enhancement of GABA-mediated inhibition, inhibition of GABA metabolism, and modulation of voltage-dependent calcium channels by binding to the α2δ subunit. This action may contribute to its efficacy in reducing headache frequency and severity by altering neurotransmitter release and neuronal excitability.125, 126

In pediatric populations, the use of gabapentin for headache prophylaxis is less extensively studied compared to adults. However, some evidence suggests its effectiveness in treating neuropathic pain in children, which may correlate with its potential utility in headache management. For instance, gabapentin has been reported

to be effective in children suffering from neuropathic pain following thoracotomy and complex regional pain syndrome. 127 Despite the limited number of studies focusing specifically on gabapentin for migraine prevention in children, it is noteworthy that the drug has shown promise in managing other pain conditions in this demographic, indicating a potential avenue for further research.128

In adults, gabapentin has been evaluated for its prophylactic effects on migraines, with studies indicating a dosage range of 600 to 2400 mg per day being effective in reducing migraine frequency by at least 50%. 34The drug has been particularly noted for its efficacy in patients with comorbid conditions such as mood and anxiety disorders, which are often associated with chronic migraine. Additionally, gabapentin has been utilized in cases of drug-resistant headaches, such as hemicrania continua and cluster headaches, demonstrating its versatility in headache management.129

Common side effects associated with gabapentin include dizziness, fatigue, and somnolence, which may limit its use in some patients. However, these side effects are generally mild and manageable.125, 130 The safety profile of gabapentin is an important consideration, especially in pediatric populations where medication adherence and tolerance can be significant concerns.131 The lack of FDA-approved medications specifically for migraine prophylaxis in children further emphasizes the need for careful evaluation of gabapentin's use in this age group. 132

The pharmacokinetics of gabapentin suggest that it is well-absorbed orally, with peak plasma concentrations occurring within a few hours of administration. This rapid absorption may contribute to its effectiveness in acute headache management, although its primary role remains in prophylaxis.133 The dosing regimen can be tailored to individual patient needs, and studies have indicated that higher doses may be necessary for optimal efficacy in chronic headache conditions.34, 134

Indomethacin

Indomethacin, a non-steroidal anti-inflammatory drug (NSAID), has been recognized for its unique efficacy in treating various headache disorders, particularly in cases of hemicrania continua (HC) and chronic paroxysmal hemicrania (CPH). Its role as a preventive treatment for headaches and migraines has been explored extensively, with a notable focus on its mechanisms of action, dosing regimens, and potential side effects. This literature review synthesizes findings from various studies, prioritizing pediatric research where applicable, to provide a comprehensive overview of indomethacin's therapeutic profile in headache management.

In pediatric populations, indomethacin has been investigated for its effectiveness in treating migraines and other headache disorders. Although specific studies focusing solely on children are limited, existing research

indicates that indomethacin can be beneficial in managing headaches in younger patients. For instance, the unique pharmacological properties of indomethacin, including its ability to modulate cerebral vasoconstriction, have been highlighted in studies involving pediatric cases of migraine and tension-type headaches. 135, 136 The drug's efficacy in these populations suggests that it may serve as a viable option for children suffering from severe headache disorders, although careful consideration of dosing and potential side effects is essential.

The mechanism of action of indomethacin in headache treatment is multifaceted. Unlike other NSAIDs, indomethacin has been shown to exert a rapid and reversible vasoconstrictive effect on cerebral blood vessels, which is particularly relevant in the context of migraine pathophysiology.137, 138 This vasoconstriction is believed to counteract the vasodilation associated with migraine attacks, thereby alleviating headache symptoms. Additionally, indomethacin has been found to inhibit nitric oxide (NO) signaling pathways, which are implicated in headache mechanisms, thus providing another layer of therapeutic action.137

Dosing regimens for indomethacin vary based on the specific headache disorder being treated. For chronic paroxysmal hemicrania and hemicrania continua, a typical effective dose ranges from 150 to 225 mg per day, administered in divided doses.139 In pediatric cases, dosing must be carefully adjusted to account for body weight and individual tolerance, with lower doses often being effective in younger patients.136 It is crucial to monitor patients closely for any signs of side effects, as indomethacin can lead to gastrointestinal disturbances, renal impairment, and central nervous system effects, including dizziness and headache exacerbation in some cases.140, 141

Common side effects associated with indomethacin use include gastrointestinal discomfort, such as nausea and dyspepsia, as well as potential renal complications, particularly in patients with pre-existing conditions. 140, 141 The prevalence of side effects can vary significantly, with reports indicating that between 20% and 75% of patients may experience adverse reactions.140 In pediatric populations, the risk of side effects necessitates a cautious approach, with careful monitoring and potential dose adjustments to minimize adverse outcomes.

Ketamine

Ketamine has garnered attention as a potential preventive treatment for headaches and migraines, particularly in pediatric populations. This literature review aims to provide a comprehensive overview of the current understanding of ketamine's efficacy, mechanisms of action, dosing regens, and side effects, with an emphasis on pediatric studies.

In pediatric settings, ketamine has been investigated for its analgesic properties in various acute and chronic

pain scenarios. A notable study by demonstrated the efficacy of intranasal ketamine in children presenting with acute pain in emergency departments, reporting a rapid onset of action within 5 to 10 minutes. 142 This rapid effect is crucial in managing acute headache episodes. Additionally, the combination of ketamine with other analgesics has been shown to enhance pain relief while reducing opioid requirements, as evidenced by research indicating that low-dose ketamine can effectively minimize the need for opioids in children undergoing painful procedures. 143, 144

The mechanism by which ketamine exerts its effects in headache management is primarily through its action as an N-methyl-D-aspartate (NMDA) receptor antagonist. By inhibiting NMDA receptors, ketamine reduces the excitatory neurotransmitter glutamate's activity, which is implicated in the pathophysiology of migraines and headaches.145, 146 This blockade may prevent central sensitization, a process that contributes to chronic pain conditions, including migraines. Furthermore, ketamine's ability to modulate the "wind-up" phenomenon— where repeated painful stimuli lead to increased pain sensitivity—supports its potential utility in treating refractory headache disorders.146

Dosing of ketamine varies across studies and clinical settings. In pediatric populations, intranasal ketamine has been administered at doses around 0.5 mg/kg, while intravenous infusions have utilized lower doses, typically ranging from 0.1 to 0.5 mg/kg per hour.147 For instance, a study involving intranasal administration reported effective outcomes with doses of 15 mg every 6 minutes, up to a maximum of five doses.148 The variability in dosing underscores the necessity for individualized treatment plans based on patient response and specific headache characteristics. In adult populations, ketamine has been studied extensively for chronic migraines and cluster headaches, with intravenous infusions often administered at doses of 0.5 mg/kg over a period of 40 minutes to 1 hour.149

Common side effects associated with ketamine administration, particularly in pediatric populations, include transient dissociative symptoms, nausea, and dizziness.150 However, the incidence of severe adverse effects appears to be low, with many studies reporting that the benefits of ketamine in pain management outweigh the risks when used judiciously.142, 150 Clinicians must monitor patients closely during and after administration to manage any potential side effects effectively.

In adult populations, ketamine has been studied extensively for its efficacy in treating chronic migraines and cluster headaches. A systematic review by found that ketamine infusions provided significant relief for patients with chronic refractory migraines, suggesting that it could be a viable option when traditional therapies fail.151 Additionally, documented successful outcomes in patients receiving intravenous ketamine for refractory chronic migraines, reinforcing the drug's potential as a treatment modality.145

The literature also highlights the importance of considering ketamine as part of a multimodal approach to

headache management. Combining ketamine with other analgesics, such as lidocaine, has shown to enhance analgesic efficacy while minimizing side effects.152, 153 This synergistic effect can be particularly beneficial in pediatric patients, where minimizing exposure to opioids is a priority due to the risk of developing tolerance and dependence.

Lamotrigine

Lamotrigine, an anticonvulsant medication primarily used for epilepsy and bipolar disorder, has garnered attention for its potential role in migraine prophylaxis, particularly in patients experiencing migraine with aura (MA). The mechanism of action of lamotrigine involves the inhibition of voltage-gated sodium channels, which stabilizes neuronal membranes and reduces the release of excitatory neurotransmitters, primarily glutamate.154, 155 This action is crucial in mitigating the hyperexcitability associated with both seizures and migraine aura.156, 157

In pediatric populations, the evidence supporting lamotrigine's efficacy in migraine prevention is limited, with only a few studies available. Notably, Smeralda et al. (2020) conducted a significant study that demonstrated lamotrigine's effectiveness in reducing migraine frequency and associated vertigo in children, suggesting its potential as a treatment option in this demographic.158 However, the overall body of research on pediatric migraine treatment with lamotrigine remains sparse, indicating a need for further investigation to establish its safety and efficacy in younger patients.

For adults, several studies have compared lamotrigine with other prophylactic treatments. Smeralda et al. (2020) reported that lamotrigine was more effective than topiramate in reducing the frequency and duration of aura symptoms, with fewer side effects, thus highlighting its potential as a preferable option for patients who do not respond well to traditional migraine prophylactics.158 Similarly, Malik et al. (2006) found significant reductions in both the frequency and intensity of migraine attacks in patients treated with lamotrigine, further supporting its use in MA.157. However, other studies, including those by Pini and Lupo (2001) and Silberstein et al. (2012), noted that while lamotrigine may be beneficial for MA, its overall efficacy in general migraine prevention is less pronounced, with systematic reviews indicating limited effectiveness across broader migraine populations.159, 160

Lamotrigine has also been explored in specific migraine-related conditions, such as persistent aura without infarction and hemiplegic migraine. Scoppola et al. (2021) documented successful outcomes in treating persistent brainstem aura with lamotrigine, while Bisdorff (2004) noted its effectiveness in managing migraine- related vertigo.161-163. These findings, although promising, are primarily based on observational studies or small- scale trials, which limits the generalizability of the results.

Common side effects associated with lamotrigine include skin rashes, dizziness, and gastrointestinal disturbances, with a slow titration required to minimize the risk of serious skin reactions.164 The typical dosing regimen for lamotrigine in migraine prophylaxis starts at a low dose, gradually increasing based on patient tolerance and response, which is crucial for maintaining safety and efficacy.155, 157

Levetiracetam

Levetiracetam, an antiepileptic drug primarily indicated for seizure management, has garnered attention for its potential role in migraine prophylaxis, particularly within pediatric populations. Its mechanism of action is not entirely elucidated; however, it is known to interact with synaptic vesicle protein 2A (SV2A), which modulates synaptic transmission and may reduce neuronal excitability, thereby potentially alleviating migraine symptoms. 165, 166The exploration of levetiracetam's efficacy in pediatric migraine treatment has yielded promising results, albeit with variability across studies.

In a randomized, double-blind, placebo-controlled trial, Montazerlotfelahi et al. (2019) demonstrated that levetiracetam significantly reduced both the frequency and intensity of migraines in pediatric patients compared to a placebo.167 Similarly, Miller (2004) highlighted the potential of levetiracetam in decreasing migraine frequency and severity among children, reinforcing its applicability in this demographic.168 A systematic review by Watkins et al. (2018) further supported these findings, reporting a significant decrease in headache frequency with levetiracetam treatment, although they noted inconsistencies in the evidence regarding its efficacy for chronic migraine prophylaxis.166, 169 also found that levetiracetam was generally well- tolerated in a cohort of pediatric patients, with notable reductions in headache frequency and severity.169 However, Cuvellier (2009) and cautioned that while levetiracetam appears promising, further controlled trials are essential to establish its efficacy definitively.170, 171

Comparative studies have provided additional insights into levetiracetam's effectiveness relative to other prophylactic agents. Kashipazha et al. (2017) found that while levetiracetam was effective in reducing headache frequency and severity, it was less potent than sodium valproate.172 This finding was echoed by Tsaousi et al., 2019, who reported that although levetiracetam improved headache parameters, it was not as effective as sodium valproate in chronic migraine prophylaxis. Sadeghian C Motiei-Langroudi, 2015 noted comparable efficacy between levetiracetam and sodium valproate, both significantly outperforming placebo.171 A Cochrane review by Linde et al. (2013) indicated that levetiracetam could be a viable option for migraine prophylaxis, yet emphasized the necessity for larger, more rigorous clinical trials to confirm its role definitively.173

Lisinopril

Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, has garnered attention for its potential role in migraine prophylaxis, particularly among patients with comorbid hypertension. Initial investigations into lisinopril's efficacy for migraine prevention were highlighted in a randomized, double-blind crossover study, which demonstrated a reduction in headache frequency and severity after 12 weeks of treatment. This study indicated that lisinopril decreased the number of headache hours and days, thereby significantly impacting the overall migraine burden.174 The drug has shown effectiveness in both episodic and chronic migraine cases, making it a viable option for patients managing hypertension concurrently. 174, 175

Subsequent research has reinforced these findings. A systematic review indicated that while lisinopril is not considered a first-line treatment for migraines, it effectively reduced headache days and improved patients' quality of life, particularly when first-line therapies were ineffective or contraindicated.175 Another clinical trial reported that low doses of lisinopril (5 mg daily) led to a decrease in migraine frequency and the necessity for acute medications, although some patients discontinued treatment due to side effects, primarily cough, which is a common adverse effect associated with ACE inhibitors. The mechanism by which lisinopril exerts its effects on migraines remains partially understood; however, it is suggested that ACE inhibitors may influence the endogenous opioid system and modulate neurogenic inflammation, which are both implicated in migraine pathophysiology.73, 174

Despite the promising results associated with lisinopril, the outcomes of studies involving other ACE inhibitors, such as enalapril, have been inconsistent. Some studies have shown no significant difference between enalapril and placebo, while lisinopril consistently demonstrated superior outcomes in reducing migraine frequency. A systematic review of ACE inhibitors and angiotensin receptor blockers (ARBs) indicated that lisinopril was among the more effective agents for decreasing migraine frequency, with substantial reductions in migraine days reported across multiple trials.33Furthermore, a comparative analysis of antihypertensive agents for migraine prevention placed lisinopril among effective options, although it was not recommended as a first-line treatment due to limited trial data. Nevertheless, its dual role in managing hypertension and reducing migraine frequency makes it particularly appealing for patients with both conditions.176

Long-term studies suggest that lisinopril can effectively reduce migraine frequency, although it is often reserved for patients who do not respond to more commonly used preventive medications. Common side effects, such as a persistent cough, have led to treatment discontinuation in several trials.177, 178 Additionally, while lisinopril has been shown to reduce migraine days, its comparative efficacy against other preventive options, such as ARBs like candesartan, remains an area for further investigation.73. Despite these challenges,

lisinopril's ability to significantly reduce both migraine days and pain severity, particularly in hypertensive patients, positions it as a viable option for long-term management.179, 180

Low-dose Naltrexone

Low-dose naltrexone (LDN) has emerged as a potential preventive treatment for headaches and migraines, particularly in patients with chronic pain conditions such as multiple sclerosis and fibromyalgia. Traditionally, naltrexone is utilized at higher doses for opioid and alcohol dependence; however, at lower doses ranging from 0.1 to 4.5 mg per day, it exhibits unique anti-inflammatory properties that are independent of its opioid receptor antagonism.181, 182 These properties are primarily attributed to LDN's ability to modulate neuroinflammation, particularly through the inhibition of microglial activation and the reduction of pro-inflammatory cytokine release within the central nervous system. 181-183Despite the promising theoretical framework, the specific application of LDN for managing headaches and migraines remains underexplored, with existing evidence largely derived from individual case studies and broader chronic pain research.

For instance, a notable case study involving a 62-year-old female patient with multiple sclerosis demonstrated that titrating LDN to 4.5 mg nightly, in conjunction with dietary modifications as part of the Wahls Protocol, led to significant reductions in the severity, duration, and frequency of her chronic migraine headaches, thereby enhancing her overall quality of life.181 However, the literature reveals a significant gap in robust clinical trials specifically investigating LDN's efficacy in treating headaches and migraines, particularly in pediatric populations where such conditions can severely impact quality of life.184 An ongoing open-label study is currently assessing the use of LDN in treating pediatric new daily persistent headache (NDPH), highlighting the need for further research in this demographic.

The mechanisms underlying LDN's action suggest that it functions as an anti-inflammatory agent through microglial inhibition, which distinguishes its low-dose utility from higher-dose applications for addiction treatment.183 Additionally, variability in effective dosing and the necessity for personalized medicine approaches complicate the establishment of standardized treatment protocols. While LDN has been explored for its potential in treating other chronic pain conditions, such as Crohn's disease and complex regional pain syndrome, its use remains largely experimental, characterized by small sample sizes and limited replication in published trials. This experimental status is reflected in the broader literature, where a lack of studies specifically addressing headaches or migraines underscores the need for targeted investigations into LDN's efficacy for these conditions.

Memantine

Memantine, a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, has garnered attention as a potential preventive treatment for migraines due to its ability to modulate neuronal excitability and reduce pain perception. While the majority of research has focused on adult populations, the exploration of memantine's efficacy in pediatric patients remains limited, highlighting a significant gap in the literature. A retrospective study by Charles et al. (2007) involving 60 adult patients demonstrated that memantine treatment led to a notable decrease in headache frequency and improved overall functionality, with only mild and infrequent side effects reported.185 This study suggests that memantine may be beneficial for adults suffering from frequent migraines. Similarly, Shanmugam et al. (2019) confirmed the safety and tolerability of memantine at a dosage of 10 mg daily in adult migraine patients, although pediatric data were not included in their findings.186, 187 further supported the notion that memantine could serve as a viable treatment option for primary headache disorders, especially in refractory cases where patients have not responded to standard prophylactic therapies.187

The mechanism of action of memantine is primarily attributed to its role as an NMDA receptor antagonist, which helps prevent excessive calcium influx into neurons, thereby inhibiting hyperexcitability in pain pathways.188 This action is particularly relevant in the context of migraines, as elevated glutamate levels have been implicated in the pathophysiology of migraine attacks.189 Additionally, memantine's ability to modulate cortical spreading depression (CSD) may contribute to its effectiveness in reducing migraine frequency. 190 Preliminary evidence from Noruzzadeh et al. (2015) suggests that memantine may be particularly useful in treating refractory migraines, although the authors emphasized the need for more rigorous double-blind studies to validate these findings. 189

Systematic reviews and meta-analyses have further corroborated the potential benefits of memantine for migraine prevention. Spengos et al. (2008) conducted a meta-analysis of randomized controlled trials, concluding that memantine significantly reduced both the frequency of migraine attacks and the number of migraine days experienced by patients.191 Mokhtari et al., 2017 also found that memantine was effective and well-tolerated as a prophylactic treatment for episodic migraines, with no significant adverse events reported compared to placebo.192 A recent clinical trial by Vazquez-Guevara et al. (2023) compared memantine to sodium valproate, a first-line migraine prophylactic, and found that both medications significantly decreased migraine attacks over a three-month period, suggesting that memantine could be a viable alternative for patients. 193

Despite these promising findings, Mistry et al. (2021) highlighted that memantine has not yet gained widespread acceptance as a preventive therapy for migraines, primarily due to the lack of high-quality

evidence from large-scale clinical trials. 189, 194 The underutilization of memantine may also stem from insufficient industry promotion and the challenges associated with conducting independent trials for off-label uses. Zhou et al. (2022) confirmed that while memantine effectively reduced headache days, it did not significantly alter the need for acute pain medications or the incidence of adverse events such as nausea or vomiting, underscoring the necessity for more comprehensive studies to establish its definitive role in migraine prevention.188

Mexiletine

Mexiletine, a Class 1B antiarrhythmic drug, has been investigated for its potential as a preventive treatment for headaches and migraines, particularly in populations that have not responded to conventional therapies. While there is a notable absence of pediatric studies specifically addressing the use of mexiletine for headache prevention, some case reports suggest its efficacy in treating pain conditions in children. For instance, a case study documented the successful use of oral mexiletine in a child suffering from primary erythromelalgia, indicating its potential in managing pain syndromes in younger patients.195 However, the lack of systematic research in pediatric populations underscores the need for further investigation to establish safety and efficacy in this demographic.

In adult populations, preliminary studies have shown promising results for mexiletine in chronic daily headache management. A report involving nine patients indicated that seven found mexiletine significantly more effective than previous treatments, while two reported it as more effective.196 Despite these positive outcomes, side effects were common, with gastrointestinal issues being the most frequently reported, affecting seven patients overall.196 The mechanism of action of mexiletine involves blocking voltage-gated sodium channels, which may disrupt pain pathways similar to lidocaine, potentially leading to its analgesic effects in headache disorders.196

In the context of diabetic neuropathic pain, mexiletine has demonstrated effectiveness, particularly in patients experiencing stabbing or burning sensations. A moderate daily dose of 450 mg has been reported to yield positive results with minimal side effects, even lower than those associated with placebo.197 However, higher doses, such as 675 mg per day, have been associated with rapid pain reduction but also increased side effects, leading to recommendations that mexiletine be reserved for patients who are unresponsive or intolerant to standard therapies.198, 199 A systematic review indicated that adverse events were reported in 26.1% of patients treated with mexiletine, with gastrointestinal complaints being the most common.197

In addition to its use in headache and neuropathic pain, mexiletine has been evaluated for its efficacy in thalamic pain syndrome, where it was found to be generally well-tolerated and effective in a small cohort of

patients.200 However, a randomized placebo-controlled crossover study focusing on neuropathic pain with prominent allodynia revealed that while mexiletine reduced stroking-induced pain, its overall effects on pain and allodynia were minimal, suggesting that higher doses might be limited by side effects.201

Montelukast

Montelukast, a leukotriene receptor antagonist primarily indicated for asthma management, has been investigated for its potential role in migraine prophylaxis, particularly in pediatric populations. The mechanism of action of montelukast involves the inhibition of cysteinyl leukotrienes (Cys-LTs), which are inflammatory mediators implicated in the pathogenesis of migraines. By blocking the Cys-LT(1) receptor, montelukast may reduce neurogenic inflammation and modulate the activity of trigeminal sensory neurons, which are central to headache pathophysiology.202 In pediatric studies, montelukast has shown promise; for instance, one study indicated that it is generally well tolerated in children, with mild and transient side effects, and some parents reported it as an effective preventive measure for headaches.203 However, concerns regarding neuropsychiatric side effects, such as sleep disturbances and anxiety, have been raised, necessitating careful monitoring.203

The efficacy of montelukast in migraine prevention has yielded mixed results. A randomized controlled trial involving adults found no significant difference in migraine frequency between montelukast and placebo, suggesting limited effectiveness in this population.204, 205 Conversely, some open-label studies and case reports have indicated potential benefits, particularly when montelukast is combined with other medications, although specific references to such studies were not found in the provided candidates. This highlights the need for further investigation into combination therapies that may enhance the efficacy of montelukast for migraine prevention.

Common side effects associated with montelukast include gastrointestinal disturbances, upper respiratory infections, headaches, and fatigue, which are generally mild.204, 206 The standard dosage for adults is 10 mg once daily, while pediatric dosages vary based on age and weight, typically ranging from 4 mg to 10 mg daily.203, 205 Despite the potential for adverse effects, the overall safety profile of montelukast appears favorable, particularly when compared to other treatments for asthma and allergic conditions.203 206

Nadolol

Nadolol, a non-selective beta-adrenergic antagonist, has garnered attention as a preventive treatment for headaches and migraines, particularly in pediatric populations. Its mechanism of action primarily involves the blockade of β-adrenergic receptors, which is believed to modulate central nervous system pathways associated

with headache pathophysiology. This blockade may lead to a reduction in the frequency and severity of migraine attacks by influencing neurotransmitter release and vascular tone, although the precise mechanisms remain somewhat elusive. 207, 208 Pediatric studies specifically highlight the efficacy of nadolol in managing migraine prophylaxis, demonstrating significant reductions in headache frequency among children and adolescents.207

Common side effects associated with nadolol include fatigue, dizziness, and gastrointestinal disturbances, which are typical of beta-blockers.209 The dosing regimen for nadolol varies, with pediatric doses typically ranging from 20 to 240 mg daily, depending on the severity of the condition and patient response.210 In adults, the dosing can be similar, but adjustments may be necessary based on individual tolerance and therapeutic response.210, 211

Neuroleptics

The exploration of neuroleptics as a preventive option for headaches and migraines, particularly in pediatric populations, reveals a complex interplay of pharmacological mechanisms, clinical efficacy, and safety profiles. Neuroleptics, also known as antipsychotic medications, have been traditionally employed in the management of psychiatric disorders. However, their utility in headache management, especially migraines, has garnered attention due to their potential to modulate neurotransmitter systems involved in pain pathways. The mechanisms of action for neuroleptics in headache prevention primarily involve the antagonism of dopamine D2 receptors, which is thought to play a role in the modulation of pain perception and headache frequency.212-214

In pediatric populations, the use of neuroleptics for headache management is less extensively documented compared to adults. However, studies indicate that atypical neuroleptics, such as quetiapine and olanzapine, may offer therapeutic benefits for children suffering from migraines. These agents are associated with a lower incidence of extrapyramidal side effects compared to first-generation neuroleptics, making them more suitable for pediatric use.213, 214 The consideration of neuroleptics in pediatric headache management is particularly relevant given the unique presentation and underlying pathophysiology of headaches in children, which often differ from adults.

Common side effects associated with neuroleptics include sedation, weight gain, metabolic syndrome, and, in some cases, neuroleptic malignant syndrome, a rare but serious condition.215 216 The dosing of neuroleptics for headache prevention varies based on the specific agent used, the severity of headaches, and individual patient factors. For instance, quetiapine may be initiated at lower doses, gradually titrated based on clinical response and tolerability. 217 In adults, studies have shown that prochlorperazine, a typical neuroleptic, can

be effective in treating acute migraine attacks, with doses typically ranging from 5 to 10 mg administered intravenously.218

The literature indicates that neuroleptics can be beneficial in both acute and preventive settings for migraine management. For instance, the combination of prochlorperazine with other agents like indomethacin and caffeine has been shown to enhance therapeutic efficacy in acute migraine treatment.212, 214 Furthermore, the role of neuroleptics in managing medication-overuse headache (MOH) has been explored, with findings suggesting that they can help alleviate symptoms in patients with chronic headache patterns.219, 220 The use of neuroleptics in this context underscores the importance of a comprehensive approach to headache management, particularly in patients with complex clinical presentations.

Pregabalin

Pregabalin, an antiepileptic drug primarily used to manage epilepsy and neuropathic pain, has garnered attention for its potential as a prophylactic treatment for migraines, particularly in pediatric populations. The mechanism by which pregabalin exerts its effects involves binding to the α2δ subunit of voltage-gated calcium channels, leading to a decrease in calcium influx and a subsequent reduction in the release of excitatory neurotransmitters such as glutamate and norepinephrine.221 222 This action is particularly relevant in the context of migraine pathophysiology, where central sensitization plays a critical role in the development and maintenance of headache disorders.222, 223

In pediatric studies, pregabalin has demonstrated promising results. A randomized clinical trial by Jafari et al. compared pregabalin with sodium valproate in children suffering from migraines, revealing that both medications effectively reduced the intensity and duration of migraine attacks; however, pregabalin was notably more effective in decreasing the frequency of attacks and the reliance on analgesics.221 Similarly, Bakhshandeh Bali et al. found that pregabalin significantly outperformed propranolol in reducing headache frequency and duration in children, suggesting its potential as a more effective treatment option for this demographic.224, 225 These findings underscore the need for further investigation into the safety and efficacy of pregabalin in pediatric migraine patients.

In adult populations, the efficacy of pregabalin has also been explored. Hesami et al. conducted a randomized double-blinded study comparing pregabalin and sodium valproate, concluding that both medications had comparable effects on migraine frequency, intensity, and duration.226, 227 Additionally, Calandre et al. reported significant reductions in headache frequency and severity in chronic migraine patients treated with pregabalin, although the open-label design of the study limits the robustness of these findings.228, 229 A systematic review by highlighted the lack of controlled trials specifically for pregabalin in episodic migraines,

indicating a gap in the literature that necessitates further research. 230

Pregabalin's ability to alleviate central sensitization was further supported by who demonstrated its effectiveness in relieving cutaneous allodynia, a common symptom in migraine patients.223 Moreover, et al. provided evidence that pregabalin inhibits cortical spreading depression, a phenomenon associated with migraine aura, thereby reinforcing its potential role in migraine management.229 The combination of pregabalin with vitamin D supplementation has also shown improved efficacy in treating chronic migraines, as reported by Siniscalchi et al.231 232

Despite the promising results, the use of pregabalin is not without its challenges. Common side effects include dizziness, somnolence, and peripheral edema, which can lead to discontinuation in some patients. 227 Finocchi et al., noted that while pregabalin significantly reduced migraine frequency over a three-month period, some patients discontinued treatment due to adverse effects.233 This highlights the importance of monitoring and managing side effects to enhance treatment adherence.

Skeletal Muscle Relaxants- Cyclobenzaprine, Tizanidine, Baclofen SA

The exploration of skeletal muscle relaxants such as cyclobenzaprine, tizanidine, and baclofen as potential preventive treatments for headaches and migraines has gained traction in recent years. Cyclobenzaprine, primarily indicated for muscle spasms, is a tricyclic antidepressant that has been investigated for its off-label use in headache management. Its structural similarity to amitriptyline suggests a comparable side effect profile, which includes drowsiness, dizziness, and dry mouth, making it less suitable for elderly patients as highlighted by the Beers Criteria.234, 235 While some studies have indicated cyclobenzaprine's efficacy in reducing headache frequency and severity, particularly in myofascial pain syndromes, the evidence remains inconclusive due to small sample sizes and non-significant outcomes in various trials, necessitating further rigorous research to clarify its role in headache prophylaxis.236, 237

Tizanidine, another centrally acting muscle relaxant, is an alpha-2 adrenergic agonist approved for spasticity management but has also been utilized off-label for chronic headaches and migraines. Research indicates that tizanidine can significantly diminish headache frequency, intensity, and duration, especially in patients suffering from chronic daily headaches, including chronic tension-type headaches and migraines. However, the effectiveness of tizanidine is not uniformly supported across all studies; some have found it to be no more effective than placebo in treating chronic tension-type headaches, while others report improvements in headache indices and overall quality of life.238-240 Notably, tizanidine has demonstrated a favorable safety profile in pediatric populations, although it presents a distinct adverse event profile compared to adults, with psychiatric disorders being more prevalent in younger patients, underscoring the need for careful monitoring

in this demographic.241-243 Furthermore, tizanidine has been effectively combined with long-acting NSAIDs for managing analgesic rebound headaches, showcasing its broader applicability in headache management.244,
245 The drug has also been integrated into dynamic optimization strategies for chronic migraine treatment, suggesting its potential role in comprehensive headache management plans.246-248 Non-pharmacologic interventions, including behavioral therapies, may complement the use of tizanidine, potentially enhancing overall treatment outcomes.249

Baclofen, a GABA(B) receptor agonist, is primarily recognized for its role in managing spasticity but has also been investigated for its potential in headache management, particularly in migraines and cluster headaches. Although the data supporting baclofen's efficacy in headache prevention is limited, some small-scale studies have shown promising results, indicating significant reductions in migraine frequency among participants. Baclofen's mechanism of action involves modulation of GABA receptors within the central nervous system, contributing to its antinociceptive properties. Despite these encouraging findings, the need for well-controlled trials remains critical to confirm baclofen's role in headache prevention. Its application in cluster headaches has shown efficacy in small cohorts, suggesting that baclofen could be a viable option for patients who do not respond to conventional treatments.234, 235

Venlafaxine

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has garnered attention for its potential role in the prophylaxis of headaches and migraines, particularly in pediatric populations. The pharmacological action of venlafaxine involves the inhibition of the reuptake of serotonin and norepinephrine, which are neurotransmitters implicated in mood regulation and pain perception. This dual action is believed to contribute to its efficacy in reducing the frequency and severity of migraine attacks. A systematic review by highlights the effectiveness of SNRIs, including venlafaxine, in managing migraine disorders, indicating that doses ranging from 37.5 mg to 150 mg per day are commonly utilized in clinical settings.250

In pediatric studies, the application of venlafaxine has been explored, albeit with caution due to the potential for adverse effects. A retrospective analysis indicated that while venlafaxine is sometimes used off-label for treating depression in children and adolescents, its efficacy in headache prevention remains under-researched.251 However, a systematic review by suggests that venlafaxine may be effective in treating attention deficit hyperactivity disorder (ADHD) in younger populations, which could indirectly suggest its utility in managing comorbid conditions such as migraines.252 Moreover, the findings of reinforce the notion that venlafaxine may have a role in treating ADHD in children, although more robust studies are necessary to

establish its safety and efficacy in this demographic. 253

The mechanism of action of venlafaxine is particularly relevant in the context of migraine prophylaxis. By enhancing the levels of serotonin and norepinephrine in the synaptic cleft, venlafaxine may help modulate pain pathways that are often dysregulated in migraine sufferers. noted that a higher dose of venlafaxine (150 mg) was required to achieve significant headache reduction, emphasizing the importance of dosage in therapeutic outcomes.254 This aligns with findings from Hedayat et al., who reported comparable efficacy between venlafaxine and amitriptyline in migraine prophylaxis, although venlafaxine exhibited a more favorable side effect profile. 255, 256

Common side effects associated with venlafaxine include nausea, dizziness, insomnia, and increased blood pressure, which necessitates careful monitoring, especially in pediatric patients.257 The potential for elevated blood pressure is particularly concerning, as it may limit the use of venlafaxine in certain populations.257 Furthermore, the side effects reported in studies involving venlafaxine are generally milder compared to those associated with tricyclic antidepressants, making it a more tolerable option for some patients. 256

In terms of dosing, clinical studies have indicated that venlafaxine is typically administered in extended-release formulations, with effective doses ranging from 75 mg to 225 mg per day for migraine prophylaxis.258 The study by suggests that venlafaxine can be effective in preventing migraines even in the absence of mood disorders, indicating its potential utility as a first-line treatment option for migraine prophylaxis.259

Verapamil

Verapamil, a calcium channel blocker, has garnered attention as a potential prophylactic treatment for migraines due to its vasodilatory properties and its interactions with serotonergic systems, which are implicated in migraine pathophysiology.177, 260 In pediatric populations, the use of verapamil has been explored off-label, as it is not typically a first-line treatment. Merison C Jacobs (2016) noted that while medications such as amitriptyline and topiramate are more commonly prescribed for pediatric migraine prophylaxis, verapamil's favorable side-effect profile makes it a viable option for certain children, especially when other treatments are contraindicated or poorly tolerated.261 This is particularly relevant given the unique physiological responses and developmental considerations in children that can affect treatment efficacy and tolerability.261

The mechanisms by which verapamil exerts its effects in migraine prevention are multifaceted. It primarily acts as an L-type calcium channel blocker, which may help stabilize neuronal excitability and reduce vasospasm associated with migraine attacks.177, 262 Additionally, verapamil has been shown to inhibit protein kinase C (PKC) activity, further suggesting its role in modulating nociceptive pathways involved in

migraine. 262 Clinical studies have demonstrated varying degrees of efficacy for verapamil in reducing migraine frequency and severity. For instance, Solomon et al. (1983) conducted a double-blind, placebo-controlled trial that revealed a reduction in migraine frequency from 6.7 to 3.8 per month, alongside decreased headache severity. 261, 263A follow-up study by Solomon (1989) indicated that higher doses of verapamil (320 mg/day) were more effective than lower doses (240 mg/day), emphasizing the importance of dose optimization.264, 265

However, the enthusiasm for verapamil's efficacy has been tempered by more recent analyses. Jackson et al. (2015) performed a meta-analysis comparing calcium channel blockers, including verapamil, with other migraine prophylactic agents and found no significant difference in efficacy compared to placebo.177 This suggests that while verapamil may be beneficial for some patients, its overall effectiveness as a first-line treatment remains uncertain. Furthermore, Hsu et al. (2008) reported that intravenous verapamil did not significantly improve acute migraine symptoms compared to placebo, highlighting variability in patient responses.266 This variability may be influenced by pharmacogenomic factors, as identified by Chen et al., (2024), who found specific genetic variations associated with responsiveness to verapamil, underscoring the need for personalized treatment strategies in migraine management. 267

In specialized forms of migraine, such as hemiplegic migraine, verapamil has shown promise. Thomsen C Olesen (2004) indicated that verapamil could be beneficial in sporadic hemiplegic migraine, particularly when genetic factors are considered.268 Yu and Horowitz (2003) similarly reported effective treatment outcomes in cases of sporadic hemiplegic migraine with verapamil, administered either orally or intravenously.260 Despite these positive findings, the Canadian Headache Society's guidelines classify verapamil as a weak recommendation for migraine prophylaxis, reflecting the overall variability and limited evidence base supporting its use.269 Ha and Gonzalez (2019) echoed this cautious stance, noting that while verapamil has demonstrated some effectiveness, it is not considered a first-line treatment due to the availability of more effective alternatives.270, 271

Zonisamide

Zonisamide, an anticonvulsant medication, has emerged as a potential preventive treatment for migraines and headaches, particularly in pediatric populations. Its mechanism of action involves the inhibition of voltage-sensitive sodium and calcium channels, as well as the modulation of dopaminergic and serotonergic pathways, which are crucial in the pathophysiology of migraines. By stabilizing neuronal membranes, reducing cortical spreading depression, and modulating neurotransmitter release, zonisamide addresses key factors involved in the initiation and propagation of migraine attacks.272-274

In pediatric studies, conducted a retrospective chart review in a multidisciplinary headache clinic, revealing that out of 12 pediatric patients treated with zonisamide for headache prophylaxis, eight experienced more than a 50% reduction in headache frequency, with the medication being well-tolerated and only minor side effects reported.275 This suggests that zonisamide may be a viable option for children suffering from refractory headaches. However, further prospective studies are warranted to solidify these findings and establish more definitive guidelines for its use in pediatric populations.275

In adult populations, investigated the effects of zonisamide on refractory migraines, noting a reduction in headache days, although the change was not statistically significant. Adverse effects were reported by nearly half of the patients, with fatigue being the most common side effect.272 Comparative studies have further explored zonisamide's effectiveness against other anticonvulsants. conducted a double-blind, randomized controlled trial comparing zonisamide and sodium valproate, finding both drugs equally effective in reducing migraine attacks, albeit with distinct side effect profiles.276, 277 Mohammadianinejad et al., (2011) similarly compared zonisamide and topiramate, concluding that zonisamide was more effective in reducing headache severity and was better tolerated than topiramate.277

Zonisamide's potential is particularly notable in patients who are refractory to topiramate. observed significant improvements in migraine frequency and severity in patients who had to discontinue topiramate due to side effects, reinforcing zonisamide's role as an alternative treatment.274 Villani et al., (2011) also reported that zonisamide significantly reduced headache days in patients intolerant to topiramate, further supporting its use in this population.277, 278

Additionally, zonisamide has shown promise in treating persistent migraine aura without infarction. documented a case of a 16-year-old female patient who responded positively to zonisamide after failing seven other preventative treatments, with no significant side effects observed.279 A broader review by affirmed zonisamide’s efficacy and safety across various neurological conditions, highlighting its action on sodium and calcium channels and its broad-spectrum antiseizure activity.280 Gidal et al., (2024) supported its effectiveness in patients who did not respond to topiramate, suggesting zonisamide’s role as a second-line or adjunctive therapy.280, 281 Furthermore, conducted an open-label study that found statistically significant improvements in headache severity and frequency after one month of zonisamide treatment, indicating its potential as a safe and effective adjunctive agent for migraine prevention. 273

Conclusion

In conclusion, the need for alternative treatment options for headaches and migraines is underscored by factors such as variable response rates, side effects, and the complexities of dosing, titration, and patient commitment,

which can lead to treatment failure. Additionally, the need for ongoing monitoring, contraindications, and the absence of clear guidelines in pediatric cases highlight the importance of individualized approaches. Access, cost, insurance coverage, and patient preferences further complicate treatment decisions, emphasizing the necessity for a broad spectrum of therapeutic options. The diverse array of medications—acetazolamide, caffeine, cannabinoids, candesartan, corticosteroids, cyproheptadine, doxycycline, duloxetine, furosemide, gabapentin, indomethacin, ketamine, lamotrigine, levetiracetam, lisinopril, low-dose naltrexone, memantine, mexiletine, montelukast, neuroleptics, nadolol, pregabalin, muscle relaxants (cyclobenzaprine, tizanidine, baclofen), venlafaxine, verapamil, and zonisamide—offers a range of therapeutic options for headache and migraine management, with some of these being explored in pediatric studies. Each drug brings distinct mechanisms of action to the table, such as acetazolamide's ability to reduce cerebrospinal fluid production, caffeine's analgesic properties, and the anti-inflammatory effects of corticosteroids and neuroleptics. While some, like cannabinoids and low-dose naltrexone, show potential in pain modulation and anti-inflammatory action, they require further study to confirm their efficacy and safety. Medications like candesartan and lisinopril are particularly beneficial for patients with comorbid hypertension, while serotonin-norepinephrine reuptake inhibitors such as duloxetine and venlafaxine are valuable for those with psychiatric conditions. Drugs like furosemide, indomethacin, and gabapentin offer unique benefits for specific headache disorders, although their use, like that of muscle relaxants and newer agents such as memantine and zonisamide, would benefit from more targeted research to refine dosing strategies and confirm long-term safety. Overall, these medications represent a robust toolkit for clinicians, though further research is necessary to optimize their use and ensure they are tailored effectively to individual patient needs, especially in pediatric populations.

	Medication	Mechanism of Action	Suggested Dose	Side Effects	Special Considerations
1	Acetazolamide	Carbonic anhydrase inhibitor that reduces cerebrospinal fluid production, useful in conditions like idiopathic intracranial hypertension (IIH).	500-1000 mg/day	Paresthesias, fatigue, kidney stones, metabolic acidosis, hypokalemia.	Monitor electrolytes; contraindicated in severe renal or hepatic impairment.
2	Candesartan	Angiotensin II receptor blocker (ARB) that may reduce migraine frequency through modulation of vascular tone.	8-32 mg/day	Dizziness, hyperkalemia, hypotension.	Caution in patients with renal impairment; avoid in pregnancy.
3	Caffeine	Adenosine receptor antagonist that can relieve headache by causing cerebral vasoconstriction.	100-200 mg as needed	Insomnia, jitteriness, palpitations, potential for rebound headaches.	Avoid in patients with anxiety disorders or cardiovascular conditions.
4	Cannabinoids	Modulate neurotransmitter release through endocannabinoid receptors, potential anti-inflammatory effects.	Variable depending on the formulation; used off-label.	Cognitive impairment, dizziness, dependency, psychiatric effects.	Legal status varies; caution in patients with a history of substance abuse or psychiatric conditions.
5	Corticosteroids (Dexamethasone, Prednisone)	Anti-inflammatory effects that reduce neurogenic inflammation and edema.	Dexamethasone 10-24 mg IV/PO as an adjunct in status migrainosus; Prednisone 40-60 mg/day for short-term use.	Weight gain, hyperglycemia, hypertension, adrenal suppression.	Avoid long-term use; taper to avoid adrenal insufficiency.
6	Cyproheptadine	Antihistamine with serotonin antagonism, used for pediatric migraine prophylaxis.	4-16 mg/day	Sedation, weight gain, dry mouth.	Caution in patients with glaucoma or urinary retention.
7	Doxycycline	Antibiotic with anti-inflammatory properties; sometimes used in conditions like idiopathic intracranial hypertension.	100 mg twice daily	Photosensitivity, gastrointestinal upset, esophageal irritation.	Avoid in children under 8 and in pregnancy; avoid lying down immediately after taking.
8	Duloxetine	Serotonin-norepinephrine reuptake inhibitor (SNRI) that modulates pain pathways.	30-60 mg/day	Nausea, dry mouth, dizziness, sexual dysfunction.	Avoid abrupt discontinuation; caution in patients with bipolar disorder.
9	Furosemide	Loop diuretic, reduces fluid retention and intracranial pressure.	20-40 mg/day	Hypokalemia, dehydration, ototoxicity.	Monitor electrolytes; contraindicated in anuria.
10	Gabapentin	Modulates GABAergic neurotransmission, useful in chronic pain and headache.	300-3600 mg/day	Dizziness, somnolence, peripheral edema.	Taper slowly to avoid withdrawal; caution in patients with renal impairment.
11	Indomethacin	Nonsteroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthesis, effective in indomethacin-responsive headaches.	25-150 mg/day	Gastrointestinal bleeding, renal impairment, headache.	Consider gastroprotection; avoid in patients with peptic ulcer disease.
12	Ketamine	NMDA receptor antagonist with potent analgesic properties, used in refractory headaches.	Variable, often used in a monitored setting.	Hallucinations, dissociation, hypertension.	Requires careful monitoring; used off-label.
13	Lamotrigine	Stabilizes neuronal membranes by inhibiting voltage-gated sodium channels, used in migraine with aura.	50-400 mg/day	Rash, dizziness, ataxia.	Slow titration to avoid rash; caution in patients with a history of Steven-Johnson Syndrome.
14	Levetiracetam	Modulates neurotransmitter release via binding to synaptic vesicle protein SV2A, used off-label for headache prophylaxis.	500-3000 mg/day	Fatigue, irritability, dizziness.	Caution in patients with a history of mood disorders.
15	Lisinopril	ACE inhibitor that may reduce migraine frequency by modulating blood pressure and vascular tone.	10-20 mg/day	Cough, hyperkalemia, hypotension.	Contraindicated in pregnancy; caution in renal impairment.

16	Low-Dose Naltrexone	Opioid receptor antagonist at low doses, modulates immune function and reduces neuroinflammation.	1.5-4.5 mg/day	Sleep disturbances, vivid dreams, gastrointestinal upset.	Used off-label; avoid in opioid-dependent patients.
17	Memantine	NMDA receptor antagonist that modulates glutamatergic transmission, used in migraine prophylaxis.	10-20 mg/day	Dizziness, headache, confusion.	Titrate slowly; used off-label.
18	Mexiletine	Sodium channel blocker, similar to lidocaine, used for neuropathic pain and headache.	200-800 mg/day	Nausea, dizziness, tremor.	Monitor ECG; avoid in patients with cardiac conduction abnormalities.
19	Montelukast	Leukotriene receptor antagonist, anti-inflammatory effects, used off-label for migraines.	10 mg/day	Neuropsychiatric events, including agitation, depression, and suicidal thoughts.	Monitor for mood changes; avoid in patients with a history of neuropsychiatric disorders.
20	Muscle Relaxants (Baclofen, Cyclobenzaprine, Tizanidine)	Act on central nervous system to reduce muscle spasm and related tension-type headaches.	Baclofen 5-20 mg three times daily; Cyclobenzaprine 10-30 mg/day; Tizanidine 2-8 mg three times daily.	Sedation, dizziness, dry mouth, muscle weakness.	Taper to avoid withdrawal; caution in patients with renal impairment.
21	Neuroleptics (Various)	Dopamine receptor antagonism, used in acute headache management and refractory migraine.	Variable depending on the drug (e.g., chlorpromazine 25-50 mg IV/IM).	Sedation, extrapyramidal symptoms, tardive dyskinesia.	Monitor for neuroleptic malignant syndrome; use with caution in patients with a history of movement disorders.
22	Pregabalin	Binds to the alpha-2-delta subunit of voltage-gated calcium channels, reducing neurotransmitter release.	150-600 mg/day	Dizziness, weight gain, peripheral edema.	Taper slowly to avoid withdrawal; adjust dose in renal impairment.
23	Venlafaxine	SNRI, modulates serotonin and norepinephrine levels, useful in chronic headache.	75-225 mg/day	Hypertension, nausea, sexual dysfunction.	Avoid abrupt discontinuation; caution in patients with cardiovascular disease.
24	Verapamil	Calcium channel blocker, reduces headache frequency by stabilizing vascular tone.	120-240 mg/day	Constipation, bradycardia, hypotension.	Monitor ECG; avoid in patients with heart block or severe heart failure.
25	Zonisamide	Sulfonamide anticonvulsant that stabilizes neuronal membranes, used off-label for headaches.	100-400 mg/day	Cognitive impairment, kidney stones, metabolic acidosis.	Monitor renal function and bicarbonate levels; avoid in patients with sulfa allergy.

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