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REVIEW

The Role of the Combination Paracetamol/Caffeine in Treatment of Acute Migraine Pain: A Narrative Review

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ABSTRACT

Introduction: Thirty years ago, the first migraine-specific drugs (triptans) appeared. Today two new categories (gepants and ditans) are marketed for acute migraine treatment. That said, is there still a role for conventional therapy? The aim of the present narrative review is to provide an expert overview examining the possible role of the combination paracetamol/caffeine in treatment of acute migraine pain.

Methods: To understand possible settings for more appropriate use of paracetamol/caffeine (1000 mg/130 mg) in treatment of acute migraine, a structured literature search was performed using the PubMed database by a panel of experts from major Italian headache centers; articles not referring to migraine pain were excluded from this review; review articles were prioritized.

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Results: Overall response, even to newer specific and selective trigeminal targeted drugs (TTTs), is not over 60%; thus, there is still room for conventional therapies in acute migraine treatment. The panel identified settings in which the use of paracetamol/caffeine combination to treat acute migraine attacks might offer benefit considering the consolidated use through years, despite the lack of studies directly addressing the efficacy of paracetamol/caffeine in the identified populations: subjects > 65 years of age; presence of cardiovascular (CV) comorbidities; TTTs non-responders; pregnancy and breastfeeding; subjects < 18 years of age; paracetamol/caffeine as add-on therapy.
Conclusions: Paracetamol is included in the World Health Organization (WHO) essential drug list and has a high level of popularity among patients. Caffeine enhances the analgesic effect of other drugs including paracetamol. In early treatment of acute migraine pain, prescribing physicians might consider using the paracetamol/caffeine combination among other options.

Keywords: Migraine; Paracetamol; Caffeine; Combination therapy; Elderly; Comorbidities; Pregnancy; Adolescents

Key Summary Points

Migraine has an average prevalence of about 52% (44.4% in male individuals, 57.8% in female individuals) and it is one of the most expensive neurologic disorders in Europe.

Earlier use of effective treatments to prevent chronification lowers direct costs and the use of healthcare resources.

Recommendations for treatment of acute migraine pain from major guidelines include the use of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and acetylsalicylic acid (ASA).

Considering migraine, efficacy is the primary need for patients. Acute therapies, including the most recent options (specific and selective trigeminal targeted therapies, TTTs), do not offer pain relief over 60%.

Given its tolerability (and despite the lack of direct evidence of efficacy and safety in these scenarios), paracetamol/caffeine combination can be proposed as first-line treatment of acute migraine pain in specific settings, including subjects > 65 years of age, presence of cardiovascular (CV) comorbidities, TTTs non-responders, pregnancy and breastfeeding, and subjects < 18 years of age.

INTRODUCTION

Headache is a widespread neurological disorder. Stovner et al.'s review [1] of literature data from all prevalence studies up to 2020 investigating the past-year prevalence of active headache disorders in the general adult population (i.e., how many people report suffering from headaches during the year preceding the survey) reported an overall average prevalence of about 52% (44.4% in male individuals, 57.8% in female individuals). The World Health Organization (WHO) identifies important key points on headache: (a) Headache is among the most common disorders of the nervous system. (b) It has been estimated that almost one half of the adult population has had a headache at least once within the past year. (c) Recurrent headaches are associated with personal and social burdens of pain, disability, damaged quality of life, and financial cost. Nowadays, still a minority of people with headache are diagnosed appropriately by a healthcare provider; therefore, headache disorders are underestimated, underrecognized, and undertreated throughout the world [2].

Headaches can be classified as primary or secondary. Tension-type headache (TTH), migraine, and cluster headaches are the most common primary headaches. Migraine can be episodic, if it occurs up to 14 days during the month, or chronic if it is present 15 days/month or more. Primary headaches are defined by using clinical criteria of the International Classification of Headache Disorders, third edition (ICHD-3) [3].

Migraine

Stovner et al. indicate an overall average past-year prevalence of migraine of 14% (8.6% in male individuals, 17.0% in female individuals) [1].

While in adults migraine pain is usually located in the unilateral frontotemporal region, in children and adolescents it is more often bilateral. Migraine in women often has a menstrual relationship.

Migraine can occur with or without aura. Migraine without aura definition (ICHD-3) includes headache attacks lasting 4–72 h (untreated or unsuccessfully treated) and shows at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravated by or causing avoidance of routine physical activity (e.g., walking, climbing stairs), nausea and/or vomiting or photophobia and phonophobia. Cutaneous allodynia and unilateral cranial autonomic symptoms may also occur during the attack. In patients with migraine with aura, visual, sensory, or language alteration symptoms may precede headache, and the description of aura symptoms may be difficult. Not rarely, migraine aura may occur without headache [3].

Costs of Migraine

As a result of the high prevalence and years of life lived with disability, migraine is one of the most expensive neurologic disorders in Europe. In the EU, the total annual cost of headache amongst adults aged 18–65 years was calculated, according to the Eurolight study prevalence estimates, at €173 billion, of which €111 billion (64%) was due to migraine [4].

An Italian study [5] investigated the healthcare resource utilization, analyzing data from 420 subjects attending a tertiary level headache center who had had at least four monthly migraine days and at least two preventive treatment failures. Investigators found that in the previous 6 months 58% of the patients had visited general practitioners, 32% had visited neurologists, and 26% had visited headache specialists. In the previous 12 months, 32% of patients had had at least one emergency room visit (mean number of visits [MNV] 2.8) and 15% had at least one hospitalization (MNV 2.9) because of migraine.

In the first report from the Italian Migraine Registry (I-GRAINE), a multicenter, prospective, observational study aimed at providing data on migraine to ensure proper clinical disease management, reported that most patients (N = 231 enrolled by December 2021) underwent at least one specialist visit (66.9%) or diagnostic investigation (77.4%) over the past 3 years. Visits were classified as inappropriate in 64.9% and 25% of the cases, respectively, and were mostly subsidized by the Italian national health system [6].

The direct costs were further evaluated in a retrospective analysis of electronic medical records of patients with episodic migraine (EM) and chronic migraine (CM) undergoing continuous treatment for 2 years, finding that (1) costs were 4.8 times higher for patients with CM than for patients with EM, (2) they were significantly higher for women than for men, and (3) they increased with patients' age [7].

Earlier use of effective treatments to prevent chronification lowers direct costs and the use of healthcare resources, compared with costs of stable or worsened migraine [8].

The risk of developing chronic migraine over 1 year is three times higher for patients with "very poor response efficacy" than for patients who experience "maximum treatment efficacy" [9].

Correct symptomatic treatment in episodic primary headaches can help to contain the costs and avoid chronification. Symptomatic treatment of migraine attack should be aimed at

reducing intensity and duration of pain and associated symptoms.

Therefore, choosing the best acute treatment strategy represents the challenge for an effective, safe, tolerable, and cost-saving treatment of episodic migraine. Today, we have a large spectrum of drug targets and classes; this is important for tailoring therapy to the individual patient. Currently available drug classes with different mechanism of action, efficacy, and safety profile span from simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) to antiemetics, opioid analgesics, ergot alkaloids, selective serotonin 5-$HT_{1B/1D}$ receptor agonists (triptans), calcitonin gene-related peptide (CGRP) receptor antagonists (gepants), and the 5-HT_{1F} receptor agonists (ditans).

Several triptans have been introduced onto the market since 1990, such as sumatriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, naratriptan. Between 2018 and 2020 gepants and ditans were approved, following recent advances in understanding the role of CGRP and 5-HT_{1F} receptors in migraine pathophysiology. Major approvals include rimegepant, lasmiditan, and several similarly acting products [10].

Owing to the availability of modern and traditional drugs, it is of great importance to highlight how migraine attacks should be treated, considering what the best treatment is for the patient. This is of utmost importance for the treatment of acute attacks, which lack any pharmacological option with an efficacy over 60% even considering the new medications [11], as opposed to migraine preventive therapy when the introduction of the new anti-CGRP monoclonal antibodies generated consensus on the most effective options to consider.

In this context, the use of combinations of different therapeutic substances may be considered an opportunity, as combination drugs provide an advantage in terms of efficacy, if they are sufficiently safe [12].

The aim of the present narrative review is to provide an expert overview evaluating the possible role of the combination paracetamol/caffeine in the treatment of acute migraine pain, being a condition in which unmet needs for effective treatment are still present. The possibility of using such combinations of drugs is based on the consideration that guidelines still consider paracetamol and NSAIDs as first-line treatment options for pain related to acute migraine attacks and that caffeine is a proven efficacy enhancer for analgesic drugs. Specific groups of patients who could benefit from the combination paracetamol/caffeine have been examined.

METHODS

A group of experts belonging to six major third-level Italian headache centers met for the first time to (a) share and discuss the unmet needs in the treatment of acute headache attacks with a main focus on migraine, (b) review major guideline recommendations for treatment of acute migraine, (c) understand principal needs of patients suffering from acute episodes of migraine, (d) agree upon the possible settings for use of the fixed-dose combination of paracetamol/caffeine (1000 mg/130 mg) in treatment of acute migraine attacks, with the aim to see if newer but more costly options could be spared for non-responders to simple analgesics.

During the meeting, evidence from the literature was presented and discussed, starting from data related to paracetamol and caffeine as pain relievers, evaluating mechanisms of action and studies on efficacy and safety in migraine. Then, agreement was reached on the settings in which to explore the effectiveness of paracetamol/caffeine combination, and the rationale for use in clinical practice, based on findings from published literature. A structured literature search was performed in July 2023 using the PubMed database; decision was made to set the lower time limit of the search to 1990 when trigeminal targeted therapies (TTTs) were first introduced into practice, and to prioritize review articles versus single studies. Publications written in a language other than English or Italian were excluded. Articles not referring to migraine pain, though showing results on pain relief with the use of paracetamol/caffeine combination, were excluded from the review. Further articles deemed relevant for discussing a

topic were also selected in addition to originally identified ones. The content was targeted towards a broad readership of primary care practitioners and headache specialists.

Finally, main topics to be evaluated and find consensus upon were identified, considering guideline suggestions for the acute treatment of migraine, unmet needs, patient's preference, evidence from literature, and the potentially target populations who are likely to respond to and benefit from the combination therapy with paracetamol/caffeine. Agreed topics that will be addressed in the manuscript are (1) subjects > 65 years of age, (2) presence of comorbidities, (3) TTTs non-responders, (4) pregnancy and breastfeeding, (5) subjects < 18 years of age, (6) paracetamol/caffeine as add-on therapy, and (7) tolerability of paracetamol/caffeine combination.

Each expert had at least one topic to work on individually. Some topics were partially overlapping and treated cross-sectionally. Experts convened to review topics previously drafted and to reach agreement on conclusions in a second meeting. In continuous email correspondence, all authors reviewed the initial draft article and contributed to all subsequent reviews. The views of each author were taken fully into consideration and revisions were made until unanimous consensus was reached.

The present manuscript was then elaborated and finalized, to provide an expert overview to assist clinicians in their daily practice in treatment of acute migraine attacks, meeting patient needs, and possibly avoiding overtreatment.

The present manuscript is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

With the aim to improve the quality of patient care and the level of assistance, many countries have published national clinical practice guidelines for migraine/headache treatment. Medical institutions and societies continuously update clinical practice guidelines to ensure the best treatment for patients.

Table 1 summarizes the recommendations of principal European, Italian, and North American guidelines published as a single article or review. The choice of guidelines was agreed upon by the experts on the basis of representativeness of European and North American clinical practice. The use of review articles to extrapolate recommendations helped to avoid excluding important guidelines. Of note, other guidelines not reported in Table 1 were examined and deemed not to provide any additional or different recommendation to those already reported.

In addition to guidelines reported in Table 1, in a recent update, the UK National Institute for Health and Care Excellence (NICE) has published guidance recommending oral administration of rimegepant as a cost-effective option for acute treatment of migraine in adults [13].

HOW IMPORTANT IS IT TO MEET PATIENTS' PREFERENCE IN CHOOSING THE MOST EFFECTIVE TREATMENT?

Several unmet needs of patients arose from different studies. Inadequate migraine relief was reported by up to 56% of 8233 eligible respondents in the American Migraine Prevalence and Prevention Study [14]. Adverse events were experienced by 43% of 37,250 patients evaluated in a Cochrane review on oral triptans [15]. Recurrence of migraine occurs after initial relief within 24 h in between 17% and 40% of patients depending on the triptan used [16]. Medication overuse headache (MOH) is a common consequence of overuse of many prescription and over-the-counter acute therapies for migraine [17].

Fourteen studies related to patient preferences and values for acute symptomatic treatment of migraine were analyzed in a systematic review by Xu et al. [18]. Efficacy was the primary need for patients with migraine: patients expected prompt analgesia, with rapid and complete pain relief, then return to normal activities, no recurrence, and no adverse events. First-line medications used by patients for acute

Table 1 Recommendations for acute treatment of headache from guidelines

Title and authors	Journal	Treatment approach	Recommendations*	Comments and recommendations from authors*
Headaches in over 12s: diagnosis and management	Clinical guideline Last updated: 17 December 2021 First publication: 19 September 2012 http://www.nice.org.uk/guidance/cg150	Improve the recognition and management of headaches, with more targeted treatment to improve the quality of life for people with headaches, and to reduce unnecessary investigations	Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, considering the person's preference, comorbidities and risk of adverse events. For people who prefer to take only one drug, monotherapy with an oral triptan, NSAID, high-dose aspirin or paracetamol should be considered. Anti-emetics should be considered in addition to other acute migraine treatment even in the absence of nausea and vomiting	This guideline covers advice on the diagnosis and management of tension-type headache, migraine (including migraine with aura and menstrual-related migraine), cluster headache and medication overuse headache in young people (aged 12 years and older) and adults
Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology Diener et al.	Clin Transl Neurosci January–June 2019: 1–40 https://doi.org/10.1177/2514183X18823377 journals.sagepub.com/home/ctn	Stratified	Acute medication for migraine attack treatment (limit intake to < 10/15 days/month) ASA 1000 mg (ASA 900 mg + MCP 10 mg) Ibuprofen 200 mg/400 mg/600 mg Metamizole 1000 mg Diclofenac potassium 50 mg/100 mg Combination analgesics: 2 tablets ASA 250 mg/265 mg + paracetamol/acetaminophen 200 mg/265 mg + caffeine 50 mg/65 mg For moderate and severe migraine attacks and (known) lack of response to analgesics use triptan therapy If monotherapy is insufficient: triptan + NSAIDs (naproxen 1000 mg)	In case of contraindications against NSAIDs: paracetamol/acetaminophen 1000 mg oral or metamizole 1000 mg oral The combination of ASA, paracetamol, and caffeine was more effective than 50 mg sumatriptan Triptans are more effective if taken early in the migraine attack or when the headache is still mild

Table 1 continued

Title and authors	Journal	Treatment approach	Recommendations*	Comments and recommendations from authors*
Italian guidelines for primary headaches: 2012 revised version Sarchielli et al.	J Headache Pain. 2012 May; 13(Suppl 2): 31–70 Published online 2012 May 12. https://doi.org/10.1007/s10194-012-0437-6	Stratified	Drugs for migraine attacks include triptans, analgesics (NSAIDs), ergot derivatives and antiemetics Combination analgesics Indications. They have the same indications of simple analgesics and NSAIDs. Few studies have been performed on these combination drugs. Efficacy has been demonstrated only for the association with acetylsalicylic acid, paracetamol, and caffeine. Recent trials have demonstrated a significant efficacy on migraine attacks of moderate intensity and moderate disability. This association has been demonstrated to be effective in migraine attacks related to the menstrual cycle	A stratified approach, consisting in a different choice of initial treatment based on the severity of the attack (migraine-specific drugs, i.e., triptans, for moderate/severe attacks and non-specific drugs like analgesics and NSAIDs for mild/moderate attacks) is recommended The most appropriate drug should be taken at the lowest useful dosage as early as possible after the attack begins As a rule, preparations with only one active principle should be preferred It is convenient to provide some alternatives for attacks of different severity Rescue drugs should be provided in case of first-choice medication failure
A review of current European treatment guidelines for migraine Antonaci et al.	J Headache Pain (2010) 11:13–19 https://doi.org/10.1007/s10194-009-0179-2	The question of which approach is the best is still unresolved. The common approach to treating a migraine attack is based on early intervention when the pain is still mild, which can result in shortening the time to achieve a pain-free response	Acute therapies are generally divided into two categories: non-specific treatments, such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs, including aspirin), opioids and combinations of analgesics, these are usually the first choice for the treatment of mild or moderate migraine attacks; and specific anti-migraine treatments, including ergotamine and the triptans, including almotriptan, naratriptan, sumatriptan, zolmitriptan, etc., which are usually first-line drugs for the treatment of severe migraine attacks	Some guidelines recommend a stepwise approach to the treatment of migraine [European Headache Federation (EHF), UK and Scotland]: initially acute attacks are treated with the safest, least expensive therapies and migraine-specific medication is only used if the initial treatment fails. Other guidelines recommend a stratified approach (EFNS, Italy), which is based on severity of illness and matches the patient's needs to the characteristics of the migraine (severity, frequency, disability, symptoms, time to peak); this approach recommends migraine-specific drugs for severe attacks

Table 1 continued

Title and authors	Journal	Treatment approach	Recommendations*	Comments and recommendations from authors*
EFNS guideline on the drug treatment of migraine revised report of an EFNS task force Evers et al.	Eur J Neurol. 2009 Sep;16(9):968–81 https://doi.org/10.1111/j.1468-1331.2009.02748.x	Stratified	For the acute treatment of migraine attacks, oral NSAID and triptans are recommended The administration should follow the concept of stratified treatment. Before intake of NSAID and triptans, oral metoclopramide or domperidone is recommended. In very severe attacks, intravenous ASA or subcutaneous sumatriptan are drugs of first choice. Status migrainosus can be treated by cortoicosteroids, although this is not universally held to be helpful, or dihydroergotamine	Analgesics and NSAIDs are effective in the treatment of acute migraine attacks The effectiveness has been best demonstrated for ASA and ibuprofen The threshold for the development of medication-overuse headache according to ICHD-3 is 10 days of intake/month for combination analgesics and 15 intake days/month for mono analgesics Opioid analgesics should not be used in the therapy of acute migraine attacks
Outpatient Primary Care Management of Headaches: Guidelines from the US Department of Veterans Affairs and US Department of Defense (VA/DoD)	Am Fam Physician. 2021;104(2):316–320	Stratified	Ibuprofen and high-dose acetaminophen improve acute tension-type headaches Triptans, ibuprofen, naproxen, aspirin, and high-dose acetaminophen are effective treatments for acute migraine. Intravenous magnesium and greater occipital nerve blocks are also effective	Headache disorders affect two-thirds of people in their lifetime, and a large number of potential treatments exist. The US Department of Veterans Affairs and US Department of Defense (VA/DoD) published updated guidelines for the treatment of headache disorders based on a systematic review. Tension-type, migraine, and cluster headaches are the most common primary headaches

Table 1 continued

Title and authors	Journal	Treatment approach	Recommendations*	Comments and recommendations from authors*
Guideline for primary care management of headache in adults. Clinical review Becker et al.	Canadian Family Physician • Le Médecin de famille canadien Vol 61: August 2015	Stepwise	First-line ibuprofen 400 mg, ASA 1000 mg, naproxen sodium 500–550 mg, acetaminophen 1000 mg Second-line triptans: oral sumatriptan 100 mg, rizatriptan 10 mg, almotriptan 12.5 mg, zolmitriptan 2.5 mg, eletriptan 40 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg Antiemetics: domperidone 10 mg or metoclopramide 10 mg for nausea Third-line naproxen sodium 500–550 mg in combination with a triptan Fourth-line fixed-dose combination analgesics (with codeine if necessary; not recommended for routine use)	There was debate among the Guideline Development Group members about incorporating newly emerging headache treatments that were not identified in the seed guidelines A conservative approach was adopted whereby a recommendation for an emerging intervention was created only if it had been assessed in a systematic review None of the seed guidelines included formal economic evaluations or cost analyses, nor did they discuss the economic implications of their recommendations
The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies Marmura et al.	Headache. 2015 Jan;55(1):3–20. https://doi.org/10.1111/head.12499	Level of evidence Level A evidence requires at least 2 class I studies, and level B evidence requires 1 class I or 2 class II studies	The specific medications—triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) and dihydroergotamine (nasal spray, inhaler) are effective (level A) Effective nonspecific medications include acetaminophen, NSAIDs (aspirin, diclofenac, ibuprofen, and naproxen), opioids (butorphanol nasal spray), sumatriptan/naproxen, and the combination of acetaminophen/aspirin/caffeine (level A)	There are many acute migraine treatments for which evidence supports efficacy. Clinicians must consider medication efficacy, potential side effects, and potential medication-related adverse events when prescribing acute medications for migraine. Although opioids, such as butorphanol, codeine/acetaminophen, and tramadol/acetaminophen, are probably effective, they are not recommended for regular use

NSAIDs non-steroidal anti-inflammatory drugs, *ASA* acetylsalicylic acid, *MCP* metoclopramide, *ICHD-3* Third International Classification of Headache Disorders

*Text as it appears in the publication has been reported in the columns "Recommendations" and "Comments and recommendations from authors"

symptomatic treatment of mild to moderate migraine attacks were paracetamol and NSAIDs, whereas triptans were used for moderate to severe migraines. Though triptans have shown good effectiveness in treatment of mild and moderate attacks they were sometimes less preferred because of cost concerns; dihydroergotamine, opioids, and antiemetics were reserved as second-line drugs because of adverse effects, abuse potential, route of administration, or cost.

One Italian study (DRONE) [19] investigated the illness experience with migraine using the Narrative Medicine (NM) method to understand daily life, needs, and personal resources of patients, their caregivers (parents and partners), and clinicians. The NM method allows one to better understand patient needs and preferences. In the collected narratives, 67% of patients reported that migraine negatively impacted their quality of life in terms of time and energy loss. Physical discomfort and pain were reported as interfering with patients' relationships and work activities, with average numbers of days lost per year for activity/work and social relationships being 60 and 64, respectively. Forty-eight percent of patients reported the attitude to self-treat and 35% declared to have overused medications for migraine management; 15% of patients reported that current therapies have no efficacy. Conversely, only 9% of clinicians reported treatment inefficacy in their patients.

According to the above and considering the populations identified as the target for primary use of paracetamol/caffeine, we raised some questions to address.

WHICH TREATMENT SHOULD BE USED IN THE ELDERLY?

Migraine is a common disorder in all age groups. Prevalence is highest during the first three decades of life, with a slight peak at puberty and a decline after the age of 40 years; however, it is not unusual to find migraine in the elderly population [20]. Prevalence decreases after the age of 60; however, migraine still affects 7% of women and 3% of men over 65. Despite elderly patients being underrepresented in clinical trials with a lack of information on appropriate adaptations of drug prescription, they deserve to be treated with pain relievers [21].

The association between migraine and concomitant presence of cardiovascular (CV) and cerebrovascular diseases is well documented in several studies in patients with migraine, but not as extensively in the elderly suffering from migraine. It could be argued that CV safety of migraine treatments should not differ much in the younger versus older population; however, migraine treatment still represents a challenge in elderly patients. This topic has been discussed in several studies, all highlighting peculiar aspects of migraine in the elderly population where advancing age is generally associated with increased susceptibility to a great number of diseases. Moreover, several physiological and pathological changes typical of aging can alter the effects of drugs and increase the occurrence of adverse effects as a result of not only altered pharmacokinetics but also decrease in body weight, hydration, muscle/fat ratio, albumin levels, and presence of comorbidities and polypharmacy. Authors also underline that as advancing age changes the risk–benefit ratio of many drugs, adverse drug reactions occurring in older people are more likely to be severe and life-threatening [21–23].

New drugs with good tolerability in the elderly are today available for treatment of migraine-related pain [24], but nonetheless the drug class selection should be primarily dictated by patients' comorbidities. Among symptomatic treatments, triptans are not indicated in elderly patients with CV risk factors, while lasmiditan showed a favorable cardiac tolerability profile in phase 3 clinical trials. However, dizziness reported in about 20% of patients (lasmiditan SmPC [25]) could represent an obstacle to prescription in elderly patients with ambulation problems.

In general, simple analgesics, particularly paracetamol, are still recommended as first-choice treatment of acute migraine in the elderly [26].

Paracetamol should be preferred to NSAIDs in patients with other risk factors such as renal

and hepatic diseases, myocardial infarction, arthritis [22], and in the presence of concomitant conditions including osteoarthritis, gastrointestinal conditions, bleeding disorders, CV disease, and renal disease [27]. Paracetamol is still considered the safest drug for symptomatic treatment of migraine in the elderly. Use of triptans is not recommended, even in the absence of CV or cerebrovascular risk, and NSAID use should be limited because of potential gastrointestinal adverse effects [22].

One point to take into consideration when dosing paracetamol in geriatric patients, namely over 80s, is the different pharmacokinetics (PK). In a population PK analysis, van der Heijden et al. [28] found an unexpected variability with a relevant proportion of patients that remained either above or below the target effective analgesic concentration of 10 mg/L. On average, patients achieved target mean steady state concentration when paracetamol was dosed 1000 mg q6h, while dosing q8h resulted in underexposure for the majority of them, raising questions about the efficacy and safety of paracetamol in the geriatric population.

Caffeine has been used in combination with mild analgesics for many decades, with utility deriving from its adjuvant properties. Ward et al. [29] observed that 65 mg and 130 mg of caffeine were superior to placebo in alleviating headaches. In a review of 2007, Haan et al. [22] found that the addition of caffeine to simple analgesics does not lead to an increased risk of adverse events in the elderly. Suggestion of cautious use of caffeine as an adjuvant to pain relievers was given by Sarchielli et al. [23] in their practical consideration for treatment of migraine in the elderly, because caffeine could increase anxiety and insomnia.

In conclusion it seems reasonable to consider the careful use of the combination paracetamol/caffeine effective and safe in elderly patients. Attention should be paid to conditions that can seriously alter the PK of paracetamol or caffeine causing less efficacy, side effects, or unwanted interactions with other drugs taken by patients.

SHOULD CARDIOVASCULAR SAFETY BE A CONCERN IN THE TREATMENT OF ACUTE MIGRAINE PAIN?

The American College of Cardiology published the "Migraine and Cardiovascular Disease: Key Points" in August 2023 [30]. Several questions were addressed with the aim to give to cardiologists a rapid overview of what to know about migraine and cardiovascular diseases (CVD). As they reported, there is ample evidence supporting the association of migraine and increased risk for CVD including stroke (especially with migraine with aura), atherosclerotic diseases, atrial fibrillation, and CV mortality. Higher rates of CV risk factors, including hypertension and dyslipidemia, are observed among patients with migraine, especially with aura, compared to those without migraine. Other studies have observed higher prevalence of metabolic syndrome and smoking among patients with migraine. Two female-specific risk factors for CVD—gestational hypertension and pre-eclampsia—occur more often in women with migraine [31–34].

The 2021 European Society of Cardiology (ESC) guidelines on CVD prevention recommend that migraine with aura should be considered in CVD risk assessment [35].

CV contraindications are present for acute migraine medications with vasoconstrictive properties; it has been estimated that this impacts approximately 2.6 million people with episodic migraine in the USA [36]; however, medication for acute and prophylactic treatments of migraine is frequently prescribed in patients with CVD. Antiemetics, pain relievers, such as paracetamol and NSAIDs, and combination products that include caffeine are commonly used as first-choice therapeutic medications [37]. Chronic use/overuse of NSAIDs raises concern due to a higher risk of venous thromboembolism and atrial fibrillation and can increase conversion from episodic to chronic migraine. Triptans are among the most prescribed acute antimigraine drugs in the general population. These drugs, however, cause vasoconstriction, and should be avoided

in patients with atherosclerotic disease. CGRP receptor antagonists have been proved to be an effective treatment option in patients with migraine, but caution is needed for use of these medications in patients with CV or cerebrovascular ischemic events because the possibility of blocking the vasodilatory effect of CGRP during (silent or transient) ongoing cerebral and cardiac ischemia could possibly lead to larger infarcts [38].

The risk–benefit of paracetamol combined with caffeine in the short-term management of acute pain condition such as migraine has been evaluated in several clinical studies assessing the efficacy of the combination. Studies have not reported any clinically significant adverse events. In particular, no CV adverse event was reported and, though considering possible hepatotoxicity of paracetamol, addition of caffeine did not increase adverse drug reactions [39]. In addition, in patients with coronary artery disease, caffeine at a dose of 250 mg was evaluated in exercise stress tests, showing to have no effect on exercise duration, time to onset of angina, and time to onset of ST-segment depression, although peak blood pressure increased by 7 mmHg [40].

In conclusion, paracetamol is widely used as first-line therapy in acute treatment of migraine, and it can be considered safe with no associated CV risk reported so far. The adjunct of caffeine does not alter the CV safety and tolerability profile.

WHICH TREATMENT SHOULD BE USED DURING PREGNANCY AND BREASTFEEDING?

Pregnancy

Migraine occurrence may be reduced during pregnancy likely owing to stable elevated estrogen levels. Paracetamol is indicated as first-choice drug for migraine attacks during pregnancy [41] and is the only drug included by the US Food and Drug Administration (FDA) in risk category B. It should be used for acute treatment, whereas preventive treatment should be avoided if possible [42]. NSAIDs are not advised during pregnancy and their use on 15 days or more a month should be avoided because of the risk of side effects and migraine chronification [41].

A recently published consensus statement by Bauer et al. [43] warns about the use of paracetamol during pregnancy since human observational studies suggest that prenatal paracetamol exposure might be associated with both reproductive and neurobehavioral abnormalities in both sexes. Authors showed that paracetamol is widely used by at least 50% of pregnant women in the world as a result of limited alternatives but they pointed out that most pregnant women might use paracetamol without strong indications or with limited efficacy in some conditions, including migraine. Reducing the use of analgesics is likely to be more effective in decreasing days of migraine.

Another cohort study assessing the association between paracetamol use in 760 pregnant women and risk of preterm birth, low birth weight, and small for gestational age concluded that there is not an increased associated risk, but paracetamol should be used carefully [44].

When considering the combination treatment of paracetamol and caffeine, it is noteworthy to remember that although paracetamol is rated as a category B pregnancy medicine by the FDA, even with the limitations highlighted above, caffeine use cannot be clearly recommended during pregnancy. There is not full agreement about its use in pregnancy and lactation, though a certain level of alignment emerges to consider safe a daily dose below 200 mg. According to a document released by the Italian Ministry of Health [45], "Other nutrients and other substances with nutritional or physiological effects (Revised October 2022)" caffeine is "Not recommended for children, in pregnancy and during breastfeeding". On the other hand, its use is not prohibited provided that the daily dose does not exceed 200 mg.

Noteworthy, the maximal dose of 200 mg, recommended also by the WHO and European Food Safety Authority, may be too high for certain individuals. In fact, at the molecular level, the mechanisms of caffeine-induced

disease susceptibility and heritability remain unclear [46].

A review article by Chen et al. [47] showed that higher maternal caffeine intake was associated with a higher risk of pregnancy loss.

Other publications agree in suggesting that moderate caffeine consumption (less than 200 mg per day) does not appear to be a major contributing factor in miscarriage or preterm birth. According to the American College of Obstetricians and Gynecologists (ACOG 2022) [48], the acute treatment of migraine headaches in pregnant patients should be initiated with paracetamol. When paracetamol monotherapy is ineffective, the combination with caffeine may be considered. Total recommended daily dose of paracetamol or caffeine should not be exceeded; therefore, caffeine intake from all sources should be limited to no more than 200 mg/day during pregnancy.

Published evidence suggests that triptans may be equally or more safe than paracetamol during pregnancy [49]; however, they are rated category C by the FDA and are strongly suggested only as second-line therapy if patients do not respond well to other treatments.

Breastfeeding

Many of the drugs used in the treatment of migraine do not have sufficient safety data to warrant lactation use. Paracetamol, NSAIDs, and triptans are mainly used for treatment of migraine during breastfeeding [50].

In particular, according to the data in the review by Amundsen et al. [50], paracetamol and sumatriptan can be considered safe, while other triptans are deemed probably compatible with breastfeeding; NSAIDs (ibuprofen, diclofenac, and naproxen) can be considered generally compatible with breastfeeding, with preference for ibuprofen; ASA should be avoided.

In conclusion, there is no evidence of complete safety of paracetamol during pregnancy and breastfeeding, although paracetamol remains the most used drug in these contexts, with a large number of treated patients and with acceptable risk–benefit profile as suggested by FDA risk-category rating. Evidence supporting the addition of caffeine, to enhance the analgesic action of paracetamol when used in migraine pain, remains debatable though suggestive, as already reported in the 2011 Italian AGENAS (Italian Agency for Regional Health Services) reference guidelines for prevention and treatment of headache in adults [41]. International guidelines reported that paracetamol has been the drug of choice in the first-line treatment of pain in pregnancy for more than 40 years, and its extensive use at therapeutic doses has never been related to any particular harm; therefore, it can be argued that fetal exposure in the first trimester of gestation does not increase the risk of the onset of major or minor abnormalities. Paracetamol represents so far, at least for attacks of mild or medium severity, the analgesic of first choice in the first, second, and third trimesters. The association with caffeine can enhance its efficacy in pregnancy as well, if taken in limited doses. Triptans should remain second-line choice because of possible adverse effects, with the possible exception of sumatriptan whose use during breastfeeding can be considered a safe option.

WHICH MEDICATION SHOULD BE USED IN CHILDREN AND ADOLESCENTS?

Special considerations should be made when treating migraine pain in children and adolescents: (a) headaches are a common symptom in childhood; (b) prevalence increases with age and it is lower in very young children; (c) primary headaches (migraine and TTH) are the more prevalent forms; (d) especially after puberty migraine attacks in girls can be triggered by the menstrual cycle, causing great impact on quality of life, (e) presentation can differ from migraine in adults, (f) parents have an important role in the management of young children, (g) in younger children bed rest alone may represent a sufficient treatment, (h) ibuprofen or paracetamol can be used for acute treatment [42, 51].

Management of migraine in pediatric age requires an individually tailored strategy. It is often based both on behavioral and/or non-

pharmacological measures (i.e., lifestyle modification and avoidance of trigger factors), and pharmacological approaches.

Pharmacological therapy should be prescribed considering both pharmacokinetic and pharmacodynamic characteristics of different drugs over the course of developmental age and especially the limited number of therapeutic options available for young patients, since most licensed drugs used in adults are not indicated in children. Only paracetamol and ibuprofen do not have age limitations. Ibuprofen and paracetamol have been shown to be more effective than placebo. However, in children some migraine attacks may be refractory to these drugs. In this contest, triptans should be considered as a useful therapeutic option in adolescents. The use of triptans is quite limited in pediatric age since most of them are not indicated below 18 years of age (in Europe only sumatriptan nasal spray 10 mg and zolmitriptan nasal spray can be administered in adolescents over 12 years), even if they have shown a good safety profile in younger populations [52].

In recent years, significant advancements have been made in the acute treatment of migraine. The development of small molecules (gepants) and monoclonal antibodies against CGRP and serotonin receptor 5-HT_{1F} agonists (ditans) has profoundly changed migraine patient care. However, randomized clinical trials (RCTs) on these new drugs in the pediatric population are ongoing, meaning that evidence-based guidance for these patients is still unavailable and it will be for some years [53].

The American Academy of Neurology and the American Headache Society recommend the use of non-prescription medicines in children and adolescents as effective options: "Migraine treatment should aim to achieve fast, complete pain relief, with minimum side effects. Improved efficacy with early treatment is likely to be seen in children and adolescents as well. Many children and adolescents use and benefit from nonprescription oral analgesics like acetaminophen, ibuprofen, and naproxen. Triptans are less commonly prescribed in children than in adults" [54].

Clinical guideline from NICE recommends to "offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities, and risk of adverse events. For young people aged 12 to 17 years consider a nasal triptan in preference to an oral triptan" [55].

The use of the combination paracetamol/caffeine is not approved in Italy below 15 years of age, though in small clinical studies it has been considered safe [39]. It is worth highlighting that wide use of caffeine among adolescents increased exponentially in recent decades as a result of consumption of energy drinks and other supplemented beverages and food. However, there is weak evidence so far of physiological, psychological, or behavioral effects of habitual caffeine use in this young population [56].

According to a recent review by Soos et al. [57], caffeine and energy drink consumption is not recommended at all for children and adolescents at any dosage. For young adults, low ($\geq$ 3 mg/kg) or moderate (3–6 mg/kg) caffeine dosages are acceptable or recommended. Though moderate intake of energy drinks and other caffeinated drinks and food is considered harmless in adolescents [58], about 30% of energy drink consumers with no sex differences exceed the safe intake of caffeine through their consumption of energy drinks alone [59].

Current available data suggest being cautious in prescribing pain relievers containing caffeine to adolescents because of the risk of overdose if combined with widely consumed energy drinks and supplemented food. However, considering that triptans are mostly not indicated below 18 years, careful prescription of the combination paracetamol/caffeine accompanied by clear education on the effects of caffeine overconsumption and recommendation to avoid caffeinated beverages and food can offer an effective relief from acute pain in adolescents aged 15 years and older.

TRIGEMINAL TARGETED THERAPIES (TTTS) NON-RESPONDERS: IS THERE ROOM FOR ADDING SIMPLE ANALGESICS?

TTTs are proven to have around 60% efficacy as pain relievers in acute headache attacks; moreover, considering the pain freedom, efficacy decreases to 20–30%. This is one of the most important factors to be taken into account when prescribing drugs for acute treatment of migraine [11].

In the acute therapy setting, there appears to be a lot of room to find effective therapies. In fact, during an acute attack a patient does not like a therapy that works 60%; indeed, they require the headache to disappear completely and possibly quickly [18]. Thus, it is of great importance to point out how the acute headache attack should be treated, not only considering the latest drugs introduced but evaluating what is best for the patient.

A systematic review by Leroux et al. in 2020 [60] highlighted how the use of triptans for acute treatment of migraine is associated with insufficient efficacy and/or tolerability in approximately 30–40% of people, generating large unmet needs. Authors found that factors associated with negative outcome with triptans include severe baseline headache, photophobia, phonophobia, nausea, and depression. Evidence suggests that a proportion of patients with insufficient efficacy and/or tolerability to one triptan may benefit from switching to a different triptan. For the outcome of pain freedom and pain relief at 2 h, 6–42% and 25–70% of patients, respectively, responded to a different triptan. Other studies analyzed in the systematic review demonstrated that there was benefit with a higher dose or different formulation of the same triptan. Some identified benefit may occur by adding an NSAID. The combination of a triptan with an NSAID is recognized as a strategy for insufficient triptan efficacy in German, French, UK, Canadian, and European Headache Federation (EHF) treatment guidelines [61–66]. Two different studies showed that effectiveness of sumatriptan is associated with regular coffee consumption [67, 68]. In another study, combinations of caffeine with analgesic drugs, including paracetamol, acetylsalicylic acid, and ibuprofen, were more effective in the treatment of patients with migraine, compared with analgesic medication alone [69].

NICE recommendations for acute treatment of migraine include offering combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, taking into account the person's preference, comorbidities, and risk of adverse events [55].

In conclusion evidence exists that increasing the dose or changing triptan is effective in TTTs non-responders, though in some cases with modest increase of benefit. Addition of analgesics to triptans can also be suggested. There is no strong supported evidence that addition of paracetamol/caffeine combination to triptans can enhance response to treatment, though a systematic review and network meta-analysis by Cameron et al. [70] found that for 2-h headache relief, standard dose triptan achieved better outcomes (42–76% response) than ergots (38%); equal or better outcomes than NSAIDs, ASA, and acetaminophen (46–52%); and equal or slightly worse outcomes than combination therapy (62–80%), concluding that use of triptans in combination with ASA or acetaminophen may be associated with slightly better outcomes than standard dose triptan tablets. All the above may suggest that paracetamol with caffeine—given the mechanism of action, good tolerability, and low cost—could help to improve the effectiveness of triptans, such as sumatriptan, making the prescription of this combination reasonable. Addition of paracetamol or caffeine to other drugs is considered effective by EHF guidelines for treatment of episodic migraine [66].

IS COMBINATION THERAPY MORE EFFECTIVE THAN MONOTHERAPY?

The combination therapy is extensively used to treat many diseases (e.g., hypertension and other CVD, diabetes, oncological conditions, infectious disease, asthma, and several other conditions) since it is well documented that

striking different targets with drugs involving complementary mechanisms of action generates a synergistic effect rather than a simple additive effect. Regarding pain, it is a very complex phenomenon since it has several dimensions: in addition to sensory perception, there are emotional and affective aspects that increase its complexity. A network of brain areas is involved in pain perception and pain control. Seen in this light, the simultaneous use of different substances, active against different components of pain experience, might be more helpful than targeting a single dimension of pain.

A review by Straube et al. in 2011 [71] details the scientific evidence for the superior efficacy of fixed-dose combinations and their role in the pharmacotherapy of pain and particularly of headaches. Findings from the review can be summarized as substantial clinical evidence that combination therapy is more effective than single therapy alone, and there is no evidence that drug combinations generally bear a higher risk for adverse effects. A brief summary of the outcomes of some combination analyzed in the review is reported in Table 2.

The analgesic-enhancing effect of caffeine was also investigated in an old review by Migliardi et al. [72] examining six RCTs in which the efficacy of two caffeine-containing analgesic combinations, paracetamol and acetylsalicylic acid, were compared with a 1000 mg paracetamol and with placebo, respectively. Authors concluded that the caffeine-containing analgesics were significantly superior to both placebo and 1000 mg of paracetamol, and paracetamol was significantly superior to placebo. The significant adjuvant analgesic effect of caffeine was independent of habitual caffeine use.

A more recent review by Lipton et al. [73] analyzed seven RCTs with similar protocols (two considering migraine; two TTH; three mixed) comparing different analgesics alone and in combination (ASA, ibuprofen; paracetamol). Combinations were more effective. No serious adverse events emerged. Efficacy of combinations with caffeine was demonstrated in a subgroup of patients aged less than 15 years old as well.

A multicenter randomized double-blind, double-dummy, crossover controlled trial compared the efficacy and tolerability of the combination of paracetamol 1000 mg + caffeine 130 mg with sumatriptan 50 mg in migraine attacks. The efficacy was assessed by the sum of pain intensity differences, the curve of mean pain intensity, the number of patients pain free at 2 h, and the total pain relief. The two regimens afforded completely overlapping results in terms of pain relief and patients' evaluation, confirming the efficacy and safety of paracetamol/caffeine combination versus sumatriptan in the treatment of migraine attacks and suggesting its use in patients that cannot use triptans [74].

A 2012 Cochrane review by Derry et al. assessed the relative efficacy in acute pain (including headache) of a single dose of any analgesic plus caffeine against the same dose of analgesic alone. They identified 19 studies with a total of 7238 participants, most using paracetamol or ibuprofen, with 100–130 mg caffeine, finding that most comparisons individually demonstrated numerical superiority of caffeine combinations, but not statistical superiority, and concluding that the addition of caffeine to a standard dose of commonly used analgesics provides a small but important increase in the proportion of participants who experience a good level of pain relief [75].

A 2017 review by Lipton et al. considered the role of caffeine in the over-the-counter treatment of headache. Combinations of caffeine with analgesic medications compared with analgesic medication alone—including acetaminophen, acetylsalicylic acid, and ibuprofen—showed significantly improved efficacy in the treatment of headache, with favorable tolerability in the vast majority of patients, and providing evidence for the role of caffeine as an analgesic adjuvant in the acute treatment of primary headache with over-the-counter drugs. Caffeine doses of at least 100 mg enhance benefits in migraine [76].

The Italian AGENAS Guidelines include analgesic combinations among the drugs most commonly used to control migraine attacks: "acetyl salicylic acid often associated with phenacetin, barbiturate, caffeine, and anti-emetics

Table 2 Combination therapy

Drug combination	Setting	Outcome of studies	Number of studies examined in the review article per combination	Reference studies in the review article [71]
Indomethacin + prochlorperazine + caffeine	Acute treatment of migraine and TTH	1. No difference with sumatriptan 50 mg 2. Superior to nimesulide 100 mg	2 studies Primary endpoint: 2-h pain relief response[1,2]	1. Galeotti N et al. Pharmacol Res 2002, 46:245–50 2. Cerbo R et al. Eur J Neurol 2005, 12:759–767
Triptans + NSAIDs or other drugs	Migraine	Multitarget combination therapy with a triptan plus an NSAID is more effective in acute migraine treatment than monotherapy with either drug alone; equal to superior pain relief (2-h pain response)	11 studies, multiple triptans evaluated in different combinations with NSAIDs: sumatriptan, rizatriptan, almotriptan; multiple NSAIDs evaluated: tolfenamic acid, naproxen sodium, rofecoxib, trimebutine, paracetamol, aceclofenac Primary endpoint: recurrence rate of migraine attacks[1,2,6,7]; 24-h pain relief response[3]; 2-h pain relief[4,8,9,11]; pain-free response at 2 h and 24-h sustained pain-free response (co-primary endpoints)[5,10]	1. Krymchantowski AV, et al. Cephalalgia 1999, 19 2. Krymchantowski AV. Arq Neuropsiquiatr 2000, 58:428–430 3. Smith TR et al. Headache 2005, 45:983–991 4. Brandes JL, et al. JAMA 2007 297:1443–1454 5. Lipton RB et al. Cephalalgia 2009, 29:826–836 6. Krymchantowski AV. Cephalalgia 2002, 22:309–312 7. Krymchantowski AV. BMC Neurol 2004, 4:10 8. Krymchantowski AV et al. Cephalalgia 2006, 26:871–874 9. Freitag F et al. Headache 2008, 48 10. Schoenen J et al., the Belgian Headache Society. Cephalalgia 2008, 28:1095–1105 11. Brandes et al. JAMA 2007,297:1443–1454

Table 2 continued

Drug combination	Setting	Outcome of studies	Number of studies examined in the review article per combination	Reference studies in the review article [71]
Caffeine in multitarget pain therapeutics	Migraine/headache	1. Superior to placebo in alleviating non-migrainous headaches 2. Superior efficacy of the combination of ibuprofen (400 mg) and caffeine (200 mg) shown in a study in patients with TTH 3. Small pilot study in 12 children with headaches with ibuprofen (100–400 mg, dosage was selected depending on body weight) and caffeine (50–100 mg) combination showed trend toward superior efficacy 4. Diclofenac sodium (100 mg) and caffeine (100 mg) is more effective than diclofenac sodium (100 mg) alone in the acute treatment of migraine 5. Combination of paracetamol (1000 mg) and caffeine (130 mg) was significantly more effective than paracetamol alone in the treatment of TTH 6. In the treatment of TTH, the combination of paracetamol (1000 mg) with caffeine (130 mg) was significantly superior to placebo	6 studies in headache + other pain models Primary endpoint of studies: Average pain change over time[1]: time to first perceptible relief and time to meaningful relief over 6 h[2]; cumulative response scores from five-faces severity scale, measure of clinical disability, and scale of pain severity[3]; percentage of subjects with headache relief at 60 min[4]; pain and its relief hourly for 4 h[5]: sum of pain intensity differences (SPID) and the total pain relief (TOTPAR)[6]	1. Ward N et al. Pain 1991, 44:151–155 2. Diamond S et al. Clin Pharmacol Ther 2000, 68:312–319 3. Dooley JM et al. Pediatr Neurol 2007, 37:42–46 4. Peroutka S et al. Headache 2004, 44 5. Migliardi JR et al. Clin Pharmacol Ther 1994, 56:576–586 6. Pini LA et al. J Headache Pain 2008, 9:367–373

Table 2 continued

Drug combination	Setting	Outcome of studies	Number of studies examined in the review article per combination	Reference studies in the review article [71]
ASA + paracetamol + caffeine for the treatment of headache. In six randomized, controlled, double-blind studies	Migraine/headache	Combination was superior both to placebo[1,2] and to the control therapies sumatriptan (50 mg),[3] ibuprofen (400 mg), ASA[4] + paracetamol, ASA, paracetamol, and caffeine in patients with migraine and/or TTH in terms of their analgesic effectiveness	4 studies in migraine (primary endpoints of studies: 2-h pain relief,[1] time to 50% pain relief,[2] sum of pain intensity differences from baseline at 4 h postdose—SPID4,,[3] 2-h pain relief[4]	1. Lipton RB et al. Arch Neurol 1998, 55:210–217 2. Diener HC et al. Cephalalgia 2005, 25:776–787 3. Goldstein J et al. Headache 2005, 45:973–982 4. Goldstein J et al. Headache 2006, 46:444–453

Data are adapted from efficacy outcomes reported in studies with different combinations of analgesics in the review by Straube et al. [71]
Superscript numbers in the table refer to the references in the final column
TTH tension-type headache, *NSAIDs* non-steroidal anti-inflammatory drugs, *ASA* acetylsalicylic acid

or paracetamol derivatives or indomethacin are useful in migraine attacks" [41].

Efficacy and rapid onset of action of paracetamol/caffeine combination can be explained by the pharmacokinetic and pharmacodynamic characteristics of the two drugs when combined, as illustrated in Table 3. Following a single oral dose of the combination paracetamol/caffeine, paracetamol reaches the maximum plasma concentration 30 min after administration (paracetamol/caffeine SmPC [77]). Orally administered paracetamol alone has peak plasma concentrations occurring within 30–60 min after ingestion (paracetamol SmPC [78]).

Caffeine has a peak plasma dose at about 30 min after administration (paracetamol/caffeine SmPC [77]). Caffeine increases the efficacy of paracetamol by improving its absorption, thereby prolonging analgesic action. Consistent with results from other acute pain states, caffeine acts as an analgesic adjuvant and enhances the analgesic action of paracetamol (see Sect. "Pharmacological Features of Caffeine").

One point to consider when drug combinations are used in migraine treatment is the possibility to develop medication overuse headache (MOH). MOH is described in ICHD-3 [3] as an interaction between a therapeutic agent used excessively and a susceptible patient with pre-existing primary headache. Approximately half of people with headache on 15 or more days per month for more than 3 months have MOH, and the majority of patients improve after discontinuation of the overused medication. Prevention by accurately explaining causes and consequences of MOH is also mentioned as especially important in patients prone to frequent headache.

The inappropriate use of paracetamol and caffeine may lead not only to MOH (when taken on at least 10 days/month for more than 3 months) but also to caffeine-withdrawal headache as a headache developing within 24 h after regular consumption of caffeine in excess of 200 mg/day for more than 2 weeks, which has been interrupted. It resolves spontaneously within 7 days in the absence of further consumption.

It is worth remembering that possible safety issues other than MOH can arise if the total amount of daily caffeine consumption exceeds the advisable dosage. In general consuming about 400 mg of caffeine per day is considered

Table 3 Variation in pharmacokinetic properties of paracetamol in the presence or absence of caffeine

	PK of paracetamol 1000 mg/caffeine 130 mg combination (paracetamol/caffeine ratio 7.69:1)		PK of paracetamol alone
	Paracetamol	Caffeine	
C_{max}	23 μg/ml	4.3 μg/ml	20 μg/ml
t_{max}	30 min	30 min	30–60 min
AUC_{0-t}	68 μg/ml	28 μg/ml	60 μg/ml
$t_{1/2}$	4 h	5 h	2 h
Distribution volume	0.9 L/kg	0.5–0.7 L/kg	0.9 L/kg
Metabolism	Hepatic	Hepatic	Hepatic
Excretion	Urinary	Urinary	Urinary
	2–5% of unchanged dose	1–5% of unchanged dose	< 5% of unchanged dose

safe by the US Department of Agriculture (USDA) and the European Food Safety Authority (EFSA) [79].

Myat et al. [80], in their 2019 study addressing pharmacological interaction of coffee with paracetamol, concluded that coffee may enhance the production of the optimal therapeutic effect of and prolong the duration of acetaminophen action. So, acetaminophen taken together with coffee containing 65 mg and 195 mg of caffeine (one to three cups of coffee) may produce a better therapeutic outcome.

A 2020 review by Belayneh et al. [81] evidenced that coffee consumption at varying levels has a significant influence on the absorption, distribution, and elimination of some drugs. Though the review is not aimed specifically at evaluating the effects of caffeine consumption over drugs already containing caffeine, the authors note that these effects of coffee on the pharmacokinetics of drugs could cause an enhanced therapeutic response, therapeutic failure, and/or may cause toxic reactions in patients receiving those drugs. The authors also suggest that clinicians should be aware of the potential risks of pharmacokinetic interaction between dietary coffee intake and medications, and that consumption of coffee and other caffeine-containing food and beverages should be restricted as appropriate.

PHARMACOLOGICAL FEATURES OF PARACETAMOL

Paracetamol (international name in Europe) and acetaminophen (international name in the USA) are the two names of the chemical compound *N*-acetyl-*para*-aminophenol.

Paracetamol has a long history in the WHO analgesic scale: it was included in the first step of the original (1986) three-step WHO ladder and is still there in the modified four-step ladder for treatment of all intensity grades of pain. It is recommended at the first step in various types of moderate pain, alone or with co-analgesics. In case the pain persists or increases, it is indicated in combination with weak (e.g., codeine, tramadol) or strong (e.g., morphine, fentanyl) opioids on the second and third grades of the analgesic ladder, respectively. Paracetamol/acetaminophen is one of the most popular and most used analgesic and antipyretic drugs around the world, available without a prescription, both in mono- and multicomponent preparations. It is the drug of choice in patients that cannot be treated with NSAIDs. It is recommended as a first-line treatment of pain

associated with several conditions including headache.

The mechanism of analgesic action of paracetamol is complex and not completely described though it was marketed decades ago and despite its widespread use. The analgesic effect of paracetamol can be traced to a direct action at the level of the central nervous system (CNS). The mechanism of action includes effects on both the peripheral (COX inhibition) and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway, cannabinoid system) antinociception processes and redox mechanism. Paracetamol antinociception is through interference with serotonergic descending pain pathways, probably mediated by the opioid and serotonergic systems, as well as an action of inhibiting prostaglandin synthesis at the central level [82, 83].

The clinical pharmacological profile of paracetamol includes analgesic and antipyretic effects and little anti-inflammatory activity as well as minor gastrointestinal, renal, and vascular side effects. Speed of onset of antipyretic and analgesic effects of paracetamol depends on the formulation (tablets, suppositories, and oral and injectable solutions), route of administration, and compartment distribution that can be affected by individual physiological features such as age, body size, BMI, presence of comorbidities, and conditions that can alter pharmacokinetics. In recent years several reviews trying to better explain the mechanism of action, the safety, and the analgesic and antipyretic activity of paracetamol have been published [28, 83, 85–87].

Interestingly, both efficacy and safety were questioned in several publications. In the Cochrane review published in 2016 [88] assessing the efficacy and safety of acute treatment of episodic TTH in adults, authors concluded that paracetamol 1000 mg provided a small benefit in terms of being pain free at 2 h for people with frequent episodic TTH who have an acute headache of moderate or severe intensity. As regards safety, no difference was found with respect to placebo, most side effects being mild or moderate in intensity without no serious side effect.

Despite these results and the continuous scrutiny of its efficacy and safety, paracetamol is recommended across guidelines for the treatment in diverse acute and chronic pain. The safety and tolerability advantages of paracetamol over other classes NSAIDs and opioid analgesics are among the reasons for its maintenance or inclusion in pain treatment guidelines by expert panels [87].

PHARMACOLOGICAL FEATURES OF CAFFEINE

Caffeine is a methylxanthine, structurally related to theophylline, endowed with various pharmacological actions at the level of the central and peripheral nervous system. At doses of low as those contained in common drinks, caffeine has a weak analgesic effect (Fig. 1) and acts as a competitive adenosine antagonist on peripheral A2A and A1 receptors, whose activation is responsible for pain perception [89]. In the CNS, caffeine activates noradrenergic neurons by stimulating their antinociceptive action and appears to induce dopamine release. Another possible mechanism of caffeine's pain-relieving action is the activation of inhibitory glycinergic transmission on nociceptive stimuli [90].

Caffeine is a frequent adjuvant of paracetamol and other analgesic drugs whose action it potentiates by a facilitating mechanism that is not entirely clear. It has been postulated (a) that the competitive binding of caffeine to adenosine receptors induces changes in the pharmacokinetics of paracetamol, increasing its maximum concentration (C_{max}) and AUC, and decreasing its clearance, resulting in increased analgesic action [91]; (b) that caffeine increases gastric circulatory flow, promoting greater and more rapid absorption of paracetamol, which thus reaches the CNS in a shorter time than observed with monotherapy [92].

LIMITATIONS

Although the present narrative review has been conducted through careful review of published

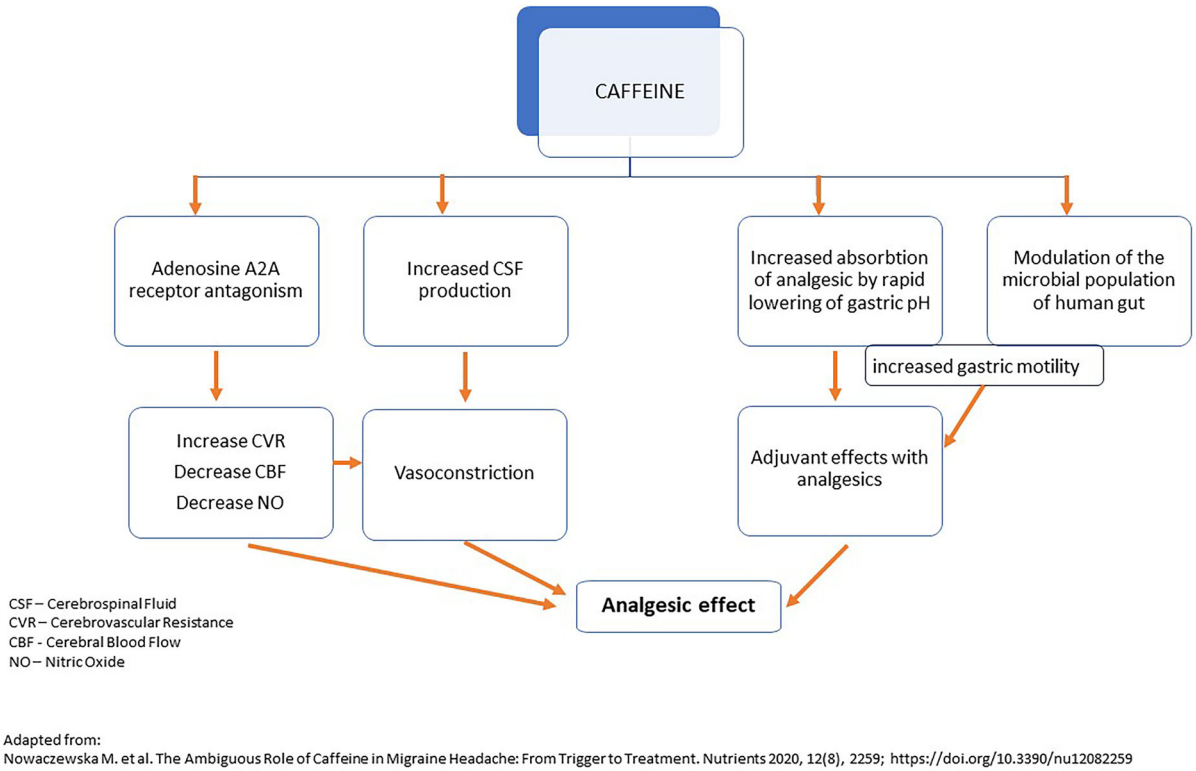

Fig. 1 Mechanism of caffeine analgesic effect

literature and several rounds of discussion among panelists, we recognize the limitation of it not being a systematic review. From literature review it emerged that both paracetamol and caffeine have been widely used to relieve pain, including migraine acute pain, for decades with acceptable efficacy and tolerability, despite lack of data from well-designed randomized studies supporting efficacy in comparison with more recently marketed drugs. This certainly represents a weakness in supporting evidence for use in the populations considered in the present article; however, lots of data have been generated through the years on paracetamol efficacy and safety and on caffeine as an adjuvant in a variety of populations, without showing severe safety issues. Comparative studies in specific populations with the combination paracetamol/caffeine are limited and most of the evidence is indirect; nevertheless, paracetamol is still included in guidelines for treatment of acute migraine. Addition of caffeine enhances efficacy of co-administered drugs without evidence of increasing adverse events.

Despite limitations, we deem the information given in the present article to be of interest to primary-care practitioners and headache specialists to consider when they evaluate the possibility of prescribing paracetamol and its combination with caffeine, as first-line therapy in acute migraine episodes, in their daily practice.

CONCLUSIONS FROM PANELISTS

The studies analyzed in the present narrative review underline the need to produce further data, in different contexts, on the use of paracetamol, alone or in combination with caffeine. Authors generally point out how, despite paracetamol being currently used by billions of people, including pregnant women, very young children, and other week populations, as pain reliever or antipyretic with a favorable efficacy–tolerability ratio, its mechanism of action

is still not completely known. Contradictory results in terms of efficacy arise, and safety signals (especially hepatotoxicity) sporadically emerge. RCTs and meta-analyses generally reported fewer adverse events with paracetamol than with NSAIDs and comparable to those of placebo. Long-term observational data reported increased CV, gastrointestinal, and renal adverse events during therapy with paracetamol, especially in the high dose range; acute liver failure has been reported in some cases after overdose of paracetamol. Acute liver failure appears infrequent with an approximate incidence for all causes of 1 per million per year [87]. It is rather unlikely that further well-designed and controlled studies will be performed with such an old drug, but in consideration of the widespread use of paracetamol, data from daily practice will continue to be generated. Guidelines generally value newer drugs in their recommendations owing to evidence data from RCTs, but older drugs can count on consolidated clinical experience for their use. Today, paracetamol is included in the WHO essential drug list and has a high level of popularity among patients.

Prescribing physicians might consider the option to use paracetamol, especially combined with caffeine to enhance its efficacy, in early treatment of acute migraine pain among other more costly or less safe options. The use of the combination paracetamol/caffeine as first-line treatment does not limit in any way further therapeutic options. In prescribing the combination paracetamol/caffeine, attention should be paid to educate patients not to take medication without prior consultation with a physician and to alert them about a possible overdosage of caffeine, depending on their alimentary use of this substance.

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Declarations

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