



# Navigating migraine care through the COVID-19 pandemic: an update

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## Abstract

The worldwide treatment gap for migraine before COVID-19 inevitably widens as attention focuses on an international emergency. Migraine hits people particularly in their early and middle years, potentially reduces quality of life and productivity, and remains a common emergency presentation. This article examines the impact of COVID-19 on migraine, and changing aspects of migraine care during and after the pandemic. Many risk factors for severe COVID-19—older age, male gender, cardiac and respiratory diseases, diabetes, obesity, and immunosuppression—are less frequent in migraineurs. Telemedicine is effective for migraine follow-up, and needs ongoing evaluation. Most migraine treatments can start or continue in acute COVID-19, with care to avoid drug interactions. Close contact procedures (botulinum toxin, acupuncture and steroid injections) are avoided in lockdown or in the vulnerable. Secondary effects of COVID-19, including long COVID and its economic impact, are probably equal or greater in people with migraine. Migraine and other long-term conditions need adequate resourcing to prevent personal, social and economic suffering. Treating migraine, a sequel of COVID, potentially reduces the impact of long COVID.

**Keywords** COVID-19 · Migraine · Headache · Telemedicine · Long COVID · CGRP antagonists

## Introduction

Migraine has an annual cost of €95 billion in Europe (93% due to lowered productivity) [1], causing 9.5% of years lived with disability in 15–49-year-olds [2]. Most management occurs outside of secondary care—only 100,000 (4%) of 2.5 million primary care headache consultations in the United Kingdom (UK) are referred to specialists [3], but headache is the fourth most common emergency department

presentation, 90% of which are migraine [3]. The COVID-19 (coronavirus, severe acute respiratory syndrome coronavirus 2, SARS-COV-2) pandemic creates unprecedented challenges and new working patterns for clinicians. Challenges for health practitioners and physicians and neurologists include protection of vulnerable patients, and tackling neurological complications of COVID-19. Pro-active management of long-term conditions, such as migraine and epilepsy [4], is essential to prevent suffering, secondary morbidity, particularly mental health problems, and avoidable emergency attendances [1, 2, 4, 5]. A World Health Organization (WHO) survey of 155 countries found that almost half of patients with chronic diseases missed their regular medical care and medications since COVID-19 pandemic began [6].

## COVID-19 risks in people with migraine

There are little specific data on migraine as a risk factor for COVID [7]. Extrapolation suggests people with migraine are at average, or lower risk, of severe acute COVID-19. COVID-19 mortality associates with cardiac and pulmonary diseases, diabetes, older age, male gender, obesity, Asian and black ethnicities and deprivation [8, 9]. Prevalence of

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migraine in younger women militates against two of these risk factors. A UK study found migraine was most common in white women, without correlations with education or income [10] and a global review found headache disorders did not follow sociodemographic indices [2]. A meta-analysis found that migraine is more common in those with low, or very high, BMI (but not high BMI), suggesting this may be epiphenomenal rather than causal [11]. Many population studies conclude that migraineurs have a higher burden of vascular disease, which would place migraineurs at higher risk of poor COVID outcomes. Problematically, the iceberg effect in these studies identified patients with documented migraine, but much migraine is unrecorded. Prevalence rates of migraine in these female cohorts (15%) [12] is lower than population prevalence (15 vs. 18–22%) at comparable peak migraine age [13]. In a London primary care practice of 8477 patients, migraine was also underreported. Only 494 (6%) have documented migraine. 11/121 (9%) with suspected COVID had recorded migraine and 1/16 (6%) with confirmed COVID had migraine, 0/6 COVID deaths were in migraine sufferers, from March–July 2020 (KB, unpublished).

## The effects of COVID-19 on migraine

Fever, sleep disturbance and dehydration with acute COVID-19 may trigger a migraine episode [14, 15]. There is little to differentiate worsening of pre-existing migraine from headaches described with COVID-19 reported in 13% of a hospitalized Wuhan cohort [16] or later studies [17, 18]. A meta-analysis found reports of headaches in 3.5–34% of studies with a pooled prevalence of 11% and high heterogeneity [18]. Most reports with large sample size are broad-brush, lacking the granularity to differentiate whether these are migraine exacerbations, new migraine, non-specific headache associated with fever [8,

16, 17, 19], or permutations of all three. Studies of the phenotype in COVID-9 suggest variability in semiology [20]. A Turkish web-based survey found headache in those with COVID-19 were associated with anosmia, ageusia and gastrointestinal complaints, as expected for the COVID-19 disease phenotype, but not necessarily indicative of a causal or specific relationship. Headaches were significantly more likely to be bilateral, lasting longer than 72 h, resistant to analgesia and more common in males. They were variably described as pulsating, pressing, or stabbing in quality [21]. One study of headache in acute COVID found one-third had pre-existing migraine [22] but others report no link [21]. Headaches with COVID-19 in migraineurs were different from their usual headache in 92% of 25 studied, usually holocranial and pressing [23]. Phenotypic variations in migraine and other primary headaches are well described clinically including in individual patients [15, 24], and genetically [25].

Even before COVID-19, most migraineurs lacked professional advice, relying on over-the-counter medications [2]. A survey suggests a 60% increase in analgesia use by migraine sufferers during the pandemic [22], aligning with WHO findings of reduced medical care for people with chronic illnesses during the pandemic [6] and echoed in a Hawaiian survey [26]. Migraineurs may be particularly vulnerable to the chronic and indirect effects of the pandemic, including low mood [26], post-viral fatigue and disrupted education and childcare, increased domestic violence, and reduced income particularly affecting self-employed, part-time zero-hour contract workers [27, 28]. 60% of 1000 Kuwaitis surveyed reported worsening of their headaches, and 80% reported anxiety and depression [22]. Other studies found that working from home during lockdown was associated with reduced stress for some migraineurs [29], and an Italian survey found quarantine had negative effects in northern Italy, but not in the south [30].

**Table 1** Example of useful free resources for migraine during COVID and long COVID

Organisation	Website	Contents
International Headache Society	<a href="https://ihs-headache.org/en/">https://ihs-headache.org/en/</a>	Guidelines, classification, training for professionals
Migraine Trust	<a href="https://www.migrainetrust.org">https://www.migrainetrust.org</a>	Resources and information for patients and professionals
American Headache Society	<a href="https://americanheadachesociety.org/">https://americanheadachesociety.org/</a>	Resources and information for patients and professionals, including video tutorials on telemedicine
British Association for the Study of Headache	<a href="https://www.bash.org.uk/">https://www.bash.org.uk/</a>	Resources and information for professionals, including educational webinars
National Institute for Health and Care Excellence (NICE)	<a href="https://cks.nice.org.uk/topics/migraine/management/">https://cks.nice.org.uk/topics/migraine/management/</a>	Migraine management guidelines
Drug interactions and COVID-19	<a href="https://www.covid19-druginteractions.org/">https://www.covid19-druginteractions.org/</a>	Drug interaction charts, regularly updated

## Remote consultations in current migraine care

Phone, video, online, and “e-consults” reduce direct COVID-19 risk to migraine patients and professionals [31]. Clinicians have rapidly upskilled to use these, usually without formal training. In many parts of the world, remote consultations are by phone. There are pockets of pre-existing high levels of telemedicine adoption and expertise [31] and freely available resources for clinicians and patients (see Table 1) [32]. Research on the long-term effectiveness of telemedicine and training in these new skills is lacking. Remote medicine is here to stay, encouraged by governments, as it is cost saving, and effective when used well. Benefits beyond COVID include patient convenience; and saved travel, time, financial and environmental costs. Problems include inability to fully examine, “digital exclusion” of vulnerable patients, and reduced non-verbal communication, particularly reduced ability to gauge mood [32]. An underexplored problem is maintaining enthusiasm, with less of the usual warmth of patient and colleague contact, flagged by a recent qualitative survey of neurologists [33].

## Missing the diagnosis of secondary headache

This is a fear for both patients and healthcare workers, but the risk of missed brain tumours or other sinister causes of headache in remote consultations is low with a previous diagnosis of migraine and no change in headache features [34]. Variations on migraine not conforming to consensus definitions are sometimes tricky, such as migraine aura without headache presenting with tingling, dizziness or visual symptoms [14], all of which have a wide differential diagnosis. Clear guidance on “red flag” features must trigger urgent face-to-face assessment and investigation [35]. Most can be picked up remotely through systematic questioning (for example sudden onset, worsening or visual symptoms, scalp and temporal tenderness, jaw claudication) and patient access to thermometers and home sphygmomanometers aid assessment. In people with headache, elevated BMI and visual symptoms, urgent ophthalmological assessment is needed, looking for idiopathic intracranial hypertension as headache features may overlap with migraine [36]. Ophthalmologists and opticians have adapted safe modes of eye examination suitable for the pandemic [37]. Timely specialist advice for atypical or new-onset headaches and the need for imaging, is critical, noting the yield of headache imaging is only about 9% in

unselected series [38]. Telephone and email advice, “hot-lines” and urgent clinic slots allow avoidance of inappropriate emergency department attendances, and mitigates incorrect diagnoses [31].

## Acute migraine treatments and COVID-19 (Table 2)

There is no evidence that triptans, paracetamol or aspirin increase the risk of COVID-19. Reports of four French COVID-19 patients taking ibuprofen with poor outcomes (Level 4 evidence) [39] triggered authorities to advise paracetamol instead of NSAIDs or aspirin for COVID-19-related fever. The National Institute for Health and Care Excellence (NICE) found no relevant evidence in a rapid review of 156 potential sources [40]. Ibuprofen increases angiotensin-converting enzyme-2 (ACE-2) bioavailability, a binding site for COVID-19, and could potentially enhance initial infectivity, based on extrapolations from animal studies in cardiac muscle using sevenfold the weight-adjusted doses for humans [41]. However, NSAIDs also attenuate inflammation through reduced inflammatory cytokine activation [42]. Another proposed mechanism of harm of NSAIDs is the reduction of fever and host defence [40] implying that paracetamol and aspirin are also unsafe [40]. Informed patients can decide on ibuprofen and aspirin for their acute migraine, given the lack of definitive data.

Opioids are not indicated for migraine as they have no proven efficacy, adverse effects, are addictive and may cause analgesia overuse headache [43]. In older people, opioids increased respiratory mortality by 40–75% and some (codeine, morphine, fentanyl and methadone) are immunosuppressive [44].

## Preventive treatment (migraine prophylaxis)-(Table 2)

Beta-blockers, low-dose aspirin (75 mg daily), pizotifen, and self-injected calcitonin gene-related peptide (CGRP) antagonists can be safely used during the pandemic, with no evidence that they increase COVID-19 risk or mortality. CGRP antagonist availability is limited by cost and bureaucracy in many countries.

Anti-epileptic drugs, also used on- and off-label for migraine and mood disorders, have no known impact on COVID-19 risks, but there are some cautions in migraineurs developing acute COVID while taking them.

**Table 2** Acute and preventive migraine treatments and COVID-19

Treatment	Risk of COVID-19	Impaired recovery from COVID-19	Recommendations: use in COVID 19 patients	Level of evidence
Acute				
Paracetamol	Nil	Nil	USE	*
NSAIDs, eg Ibuprofen	Indirect, possible	Possible	USE paracetamol in preference	Indirect: level 4
Aspirin-high dose	Nil	Possible	USE paracetamol in preference	Indirect: level 4
Triptans	Nil		USE	*
Opioids	Nil	Nil direct; Indirect -may cause sedation or confusion	AVOID	Indirect: level 1
Preventive				
Beta-blockers, e.g. propranolol	Nil	Nil	USE: reduce dose if hypotensive	*
Tricyclic antidepressants, e.g. amitriptyline	Nil	Nil direct; indirect: may cause sedation, confusion, prolongs QT interval	STOP: if giving hydroxychloroquine or azithromycin (all prolong QT interval), Caution: monitor sodium—may need to reduce or stop	Indirect: level 1/2
Pizotifen	Nil	Nil	USE—reduce dose if over-sedated	*
Candesartan, losartan, and ARBs	Possible	Possible	USE	Indirect: level 3; treatment trials for covid-19
Valproate	Nil	Nil	USE	Treatment trials for covid-19
Topiramate	Nil	Nil direct; indirect—increased risk of AKI and rhabdomyolysis	CAUTION : monitor hydration and renal function—may need to reduce or stop	Indirect: level 1
Carbamazepine	Nil	Nil direct	CAUTION: monitor sodium—may need to reduce or stop	Indirect: level 1
Pregabalin, gabapentin	Nil	Nil direct; indirect—may cause sedation or confusion	CAUTION: monitor sedation, mental state—may need to reduce dose	Indirect: level 1
Botulinum toxin	Yes: through close contact	Nil	AVOID during shielding and lockdown	Level 2; treatment trials for covid-19
Steroid injection (nerve blocks)	Yes: through close contact	Yes: reduced immunity	AVOID during shielding and lockdown	Level 2
CGRP antagonists (monoclonal antibodies), e.g. erenumab	Nil	Nil	USE	*
Non-invasive self-administered devices, e.g. e-TNS	Nil	Nil	USE	*
Invasive devices, e.g. neurostimulators	Yes: through close contact	Nil	AVOID during shielding	Level 2

Levels of evidence graded according to Oxford Centre for Evidence-Based Medicine [39]

AKI acute kidney injury, NSAIDs non-steroidal anti-inflammatory drugs, ARBs angiotensin receptor blockers, CGRP calcitonin gene-related peptide receptor, e-TNS external trigeminal nerve stimulation devices

\*no evidence of harm

Carbonic anhydrase inhibitors such as topiramate may trigger acute kidney injury or rhabdomyolysis in dehydrated patients [45]. There are no data that valproate worsens COVID-19 outcomes, but it must be avoided if pregnancy is possible. Gabapentin and pregabalin do not increase the risks of acute COVID-19, but may cause over-sedation [46]. In older people, a study found a 1.6-fold increased risk of pneumonia on anticholinergic medication including amitriptyline or nortriptyline [47]. Whether this applies to migraineurs with acute COVID-19 is unknown. Animal studies raised theoretical concerns that ACE inhibitors and angiotensin receptor blockers (ARBs) may worsen infection, by up-regulation of ACE receptors promoting COVID-19 attachment to host membranes [48]. There are no sound human data to recommend avoiding these agents as a preventive treatment for migraine, and stopping them in those with co-morbid hypertension may cause harm. A recent population-based study in 1.4 million people found no increased mortality in COVID-19 patients taking ARBs and ACE inhibitors [49].

Procedures and invasive treatments including botulinum toxin, acupuncture, implantable neurostimulators [50] and steroid injections are avoided under lockdown conditions and in vulnerable people, because of the risks of hospital and close contact. Steroids have the additional unquantified risk of immunosuppression [51]. External Trigeminal Nerve Stimulation devices (e-TNS), such as supraorbital nerve stimulation are self-administered, safe but expensive and of disputed effectiveness [50].

### Treating migraine in pregnancy during COVID-19

Only 8% of migraineurs worsen during pregnancy [52]. Greater occipital nerve block and acupuncture are usually recommended, but, during a pandemic, carry the risks of close contact. Propranolol, tricyclic antidepressants and low-dose aspirin (75–83 mg) remain suitable [53].

### Potential treatments of COVID-19 relevant to migraine: interactions and repurposing

Hydroxychloroquine, chloroquine and azithromycin have been investigated as preventives or treatments for COVID-19. Despite little evidence, some governments recommend their use, and there is widespread self-medication. All prolong QT intervals, as do tricyclic antidepressants, commonly used for migraine, and this combination should be avoided.

Several migraine preventive therapies have been postulated from first principles and bioinformatics [54] as

treatments for COVID-19. Valproic acid could potentially be repurposed for its anti-viral and anti-inflammatory actions. It inhibits viral replication by reducing RNA-dependent virus RNA polymerase [55, 56] and cell surface binding [56]. Valproate also has systemic and pulmonary anti-inflammatory effects [55, 57]. Injection of SARS-CoV spike protein into mice worsens acute lung failure in vivo that can be attenuated by blocking the renin-angiotensin pathway, suggesting that ARBs and ACE-I are a potential therapy to prevent the cytokine storm and acute respiratory distress syndrome associated with severe COVID-19 [58, 59]. This remains of unproven efficacy against COVID-19 in humans as is use of ARBs [60]. Low-dose botulinum toxin may also attenuate the COVID-19 hyper-inflammatory response, attenuate cough and acute respiratory failure, but this is speculative at the current time [61]. Potential acute anti-viral treatments and vaccination may trigger acute migraine, but there is no evidence they exacerbate migraine long-term [62, 63].

### Strategies for migraine during acute and long COVID

We face the medical and social consequences of COVID and its aftermath for people with migraine. The development of COVID-19 vaccines highlights that rapid changes are possible. For many people with migraine, education and self-help will control their condition, with emphasis on avoiding excess analgesics. There is no need to re-invent the wheel with new migraine guidelines, there are plenty (see Table 1). Analgesia overuse is a specific problem in migraine, contributing to up to 50% of chronic migraine [64]. It has increased during the pandemic [22, 26], and needs recognition, education and preventive treatment. Many people with migraine have increased depression and anxiety during COVID and treatment of this is critical to avoid a vicious spiral of worsening mental health and migraine [22]. There is a backlog of missed appointments for those most severely affected migraine patients requiring botulinum toxin and other procedures [65]. Extra specialist clinics are needed. CGRP antagonists are approved in many countries, but subject in the UK and elsewhere to a tug-of-war about who will pay for them. This is a waste of time for clinicians and disheartening for patients, and could be resolved by a standardised system with minimalistic bureaucracy [66]. Long COVID must be unpicked and there are no shortcuts to a careful analysis of the cause and best treatment of its symptoms in individuals. Systematic reviews found headache in 38–44% of patients with long COVID [67, 68], and migraine and other headaches are frequent postdromes of viral illness



[69] and part of chronic fatigue syndromes in 84% [70]. Treating associated migraine will potentially reduce the burden of long COVID.

## Conclusions

Remote consultations can be tailored for migraine, but need attention to maintain the therapeutic relationship. Telemedicine allows screening of most secondary headache features and onward urgent referral. Current acute migraine treatments with paracetamol and triptans; and preventive treatments with pizotifen, beta-blockers, CGRP antagonists and e-TNS, can be safely started or continued during COVID. They are a key to preventing avoidable emergency consultations. There is little evidence for the concerns about use of anti-inflammatories, aspirin, ACE-inhibitors and ARBs during the pandemic. Care is needed with antiepileptic and tricyclic drugs used for migraine, which may cause sedation, renal and fluid imbalance in acute COVID-19. Addition of medications also causing QT prolongation (such as hydroxychloroquine) to tricyclics is a potential hazard. Procedures involving close contact, such as steroid injections, botulinum toxin and acupuncture, are avoided during lockdowns and in vulnerable people; leaving a backlog of patients needing treatment. The minority of people with severe migraine unresponsive to standard treatments should be offered CGRP antagonists rapidly and without bureaucratic fuss. Migraine is a treatable component of long COVID, warranting rapid research and resources. Migraine is an invisible and undertreated disability. Flexibility and action are essential to ensure sufferers have the resources and care to maximise their quality of life and their contribution to society.

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