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Scoping Review: The Effects of Interrupted Onabotulinumtoxin A Treatment for Chronic Migraine Prevention During the COVID-19 Pandemic

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Objective: To systematically examine the literature on the clinical consequences of inadvertent delays in scheduled onabotulinumtoxin A (OTA) therapy for chronic migraine during the COVID-19 pandemic and assess recommendations when access to OTA is limited.

Background: The coronavirus (COVID-19) pandemic was unprecedented in its impact on the global medical community. Most healthcare institutions in the United States (US) and the world had begun significantly limiting elective procedures, undermining management of many debilitating chronic conditions. OTA injections, were similarly involuntarily postponed, leading to significant setbacks in symptom control.

Methods: A comprehensive literature search was conducted on databases of Medline and Embase with search timeframe defined as the point of database inception to March 1st, 2024, and the search was performed on March 2nd, 2024. The search strategy was independently formulated by two authors (QR and CR) and was reviewed and approved by all authors of the article after appropriate amendments.

Results: A total of nine articles met the defined inclusion criteria. They collectively demonstrated marked delays in OTA treatment with decline in migraine symptom control measured in the form of migraine intensity, frequency, as well as patient satisfaction in disease management. Quality of care in the form of follow-ups also appeared compromised. Alternative strategies of telemedicine and the administration of calcitonin gene-related peptide monoclonal antibodies (CGRP mAb) were adopted in place of conventional treatment.

Conclusion: The COVID-19 pandemic had caused marked clinical deterioration in the migraine patient populations across US, Europe, and the Middle East. Strategies employed to circumvent this limitation included the adoption of remote consultation via telemedicine as well as the use of pharmacological agents such as CGRP antagonists. In the event of a reoccurrence of a worldwide pandemic, strategies should be implemented to prevent the cessation of needed treatment for those suffering from chronic migraine.

Keywords: COVID-19, chronic migraine, onabotulinumtoxin A, scoping review

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Introduction

The coronavirus (COVID-19) pandemic was unprecedented in its impact on the medical community throughout the world. By March 2020, the majority of medical centers and healthcare institutions in the United States (US) had begun significantly limiting elective procedures and restricting the use of medical resources only to emergent life-saving surgeries.[1] Similar measures were implemented to various degrees across the globe, severely undermining the appropriate management of many debilitating chronic conditions. A World Health Organization (WHO) survey of over 150 countries revealed that approximately 50% of patients with chronic illnesses missed their scheduled appointments for care and interventions, with chronic migraine being one of these conditions.[2]

As reported in 2019, the global incidence of migraine had increased to 87.6 million (97% UI: 76.6, 98.7), which is 40.1% higher compared to 1990. Four countries consisting of the US, China, India, and Indonesia accounted for 43.6% of global incidence.[3] Overall, this condition affects over a billion people worldwide.[4] The economic cost of migraine in the US has been estimated to exceed $56 billion annually,[5–8] and in 2014, this figure sits at $78 billion in data presented by the National Health and Nutrition Examination Survey.[9] In Europe, this figure increased to 95 billion EUR annually, as reported by the Council for Advocacy on Migraine in 2019.[10] In the United Kingdom (UK), headache is the fourth most common presenting complaint in the emergency department, of which 90% is deemed to be migraine.[11] Patients with migraine had been a challenging group to manage even before the onset of the pandemic, and this trend was only amplified over the course of the pandemic due to the presence of multiple stressors.[12,13]

By the International Classifications of Headache Disorders, 3rd edition (ICHD-3) definition, migraine is characterized by a headache, often unilateral, pulsating/throbbing quality, moderate to severe in pain intensity, aggravated by/avoidance of physical activity and is associated with photophobia, phonophobia and/or nausea, and/or vomiting, usually lasting between 4–72 hours when untreated or unsuccessfully treated.[14] Furthermore, it is divided into the presence or absence of aura and the number of monthly headache/migraine days. Secondary causes of headache, such as a space-occupying lesion, must be excluded.[4] Chronic migraine is defined as 15 or more headache days per month for over three months, with at least eight days of migraine-typical characteristics. Prevention is naturally indicated when the intensity and/ or frequency of migraine attacks significantly interfere with daily activities, or where adverse events from acute treatments cannot be tolerated.[15] Individuals with such severe manifestations of migraine benefit from prophylactic measures, which come in the form of effective management and control of triggers, which could be physiological, environmental, dietary, or behavioral in nature.[16] Beta-blockers, antidepressants, antiepileptic agents and, more recently, calcitonin gene-related peptide (CGRP) targeting therapies are employed as pharmacological measures in migraine prevention.[15,16] The use of onabotulinumtoxin A (OTA) as both a pharmacological and interventional modality for preventive treatment of chronic migraine is also well-established.

OTA has been shown to inhibit a whole host of nociceptive receptors, including but not limited to TRPV1, TRPM8, TRPA1, P2X3, and GABA-A.[17–27] Moreover, it also appears to exhibit agonistic effects on μ-opioid receptors.[18,28,29] Since the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) proteins are not specific in the release of vesicle types, a myriad of neurotransmitters could potentially be inhibited by the neurotoxin.[30] It has been suggested that the release of CGRP,[31–35] substance,[33,36–39] GABA,[40] dopamine,[41] and glycine[42] could all be effectively inhibited by OTA. The ability of OTA to display both retrograde and antegrade transport along the axon also indicates a regional or even central mechanism of influence on the cellular level.[43–48] A transsynaptic pattern of transport which allows for OTA to traverse adjacent neurons and glial cells has also been proposed, further enhancing the action of OTA.[44,46,49–53] Collectively, OTA appears to impede SNARE-mediated exocytosis of pro-inflammatory neurotransmitters and signaling molecules and inhibits implantation of pain-sensitive membrane receptors as well as ion channels.[54,55] Its delivery likely targets the complex networks of trigeminal and cervical nerves, thereby dampening the pain signals traveling through the spinal trigeminal nucleus, downregulating excitatory transmissions in the spinal, brainstem, thalamic, and cortical neurons.[54,55] This effect of the toxin reverses over time in response to neuronal sprouting, thereafter forming transient novel synapses and the recovery of original neurotransmitter functions.[56,57]

Approved for chronic migraine prevention by the United States Food and Drug Administration (FDA) since 2010, it has been demonstrated that OTA treatment reduces headache frequency, severity and improves overall quality of life for

chronic migraine patients, especially in individuals afflicted with more severe and frequent symptoms.[58,59] Most providers and institutions adopted the migraine injection protocol first stipulated in the PREEMPT I trial, which recommended 1 set of injections every 12 weeks.[59] With the shuttering of non-emergent interventions in the outpatient setting at the inception of COVID-19, a significant proportion of these scheduled OTA injections had been involuntarily postponed, leading to major setbacks in the group most refractory to conventional migraine treatment.[60,61]

The objective of the scoping review is to systematically examine the literature on the clinical consequences of inadvertent delays in routinely scheduled OTA therapy for chronic migraine during the COVID-19 pandemic and assess available recommendations in place of this clinically proven practice when access to OTA intervention is limited.

Methods

This scoping review adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (PICO strategy presented in Figure 1).[62] A comprehensive literature search was conducted on databases of Medline and Embase with a search timeframe defined as the point of database inception to March 1st, 2024, and with the search being performed on March 2nd, 2024.

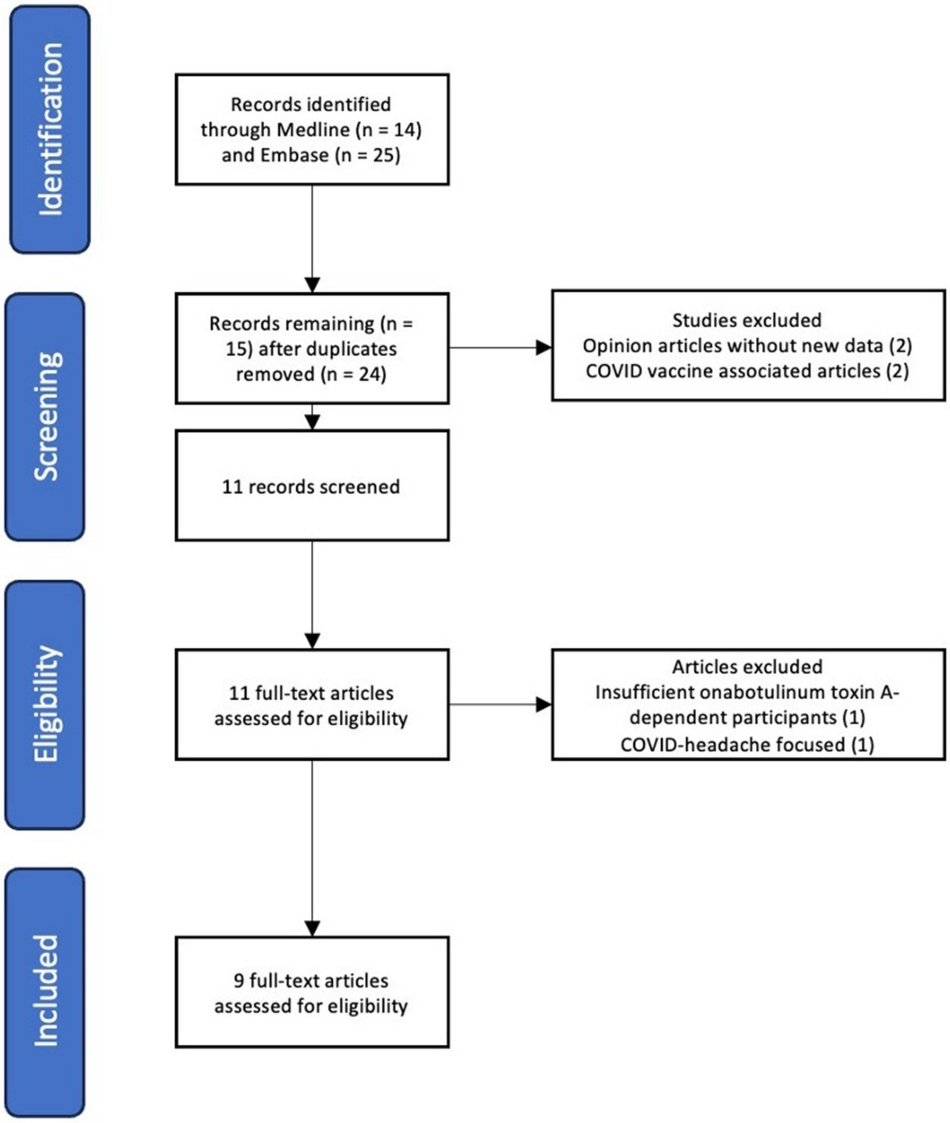

Figure 1 Flowchart overview of the scoping review analysis.

The search strategy was independently formulated by two authors (QR and CR) and was reviewed and approved by all authors of the article after appropriate amendments. The initial data extraction was completed by two authors (QR and CR). In the event of discrepancy, a third author (DP) was consulted for final approval. This scoping review paper conforms with the guidelines of PRISMA Extension for Scoping Reviews (PRISMA-ScR) and opts to exclude in-depth appraisals of source evidence.[62] The query was completed on Medline in March 2024 using the search strategy ("COVID-19" OR "coronavirus") AND ("botulinum toxin" OR "Botox") AND ("headache" OR "migraine"), and for Embase, the following search strategy was used ("covid-19" OR 'coronavirus') AND ("botulinum toxin" OR "botox") AND ("headache" OR "migraine").

Inclusion Criteria

Inclusion criteria for selection of eligible studies were the following: 1. Title, article and abstract must be published in the English language. 2. Literature must be published in a peer-reviewed academic journal. 3. Studies must consist of human subjects only. 4. Subjects must be over 18 years of age as the efficacy and safety of OTA has yet to be officially recognized by the FDA in pediatric and adolescent populations.[63] 5. Published since 2019 as initial literature on COVID-19 was first written in 2020. 6. Eligible literature included case series ($N \geq 10$), cross-sectional surveys, retrospective reviews, and case-control studies delineating the extent of OTA treatment delay and alternatives to migraine management during COVID-19 (Table 1).

Exclusion Criteria

Exclusion criteria were the following: 1. Literature not written in the English language. 2. Studies on non-human subjects. 3. Studies with subjects at and below the age of 18. 4. Literature published before 2019. 6. Articles in the form of reviews, editorials or expert opinions, as well as literature describing generic medical treatment delay during the pandemic without principal focus on OTA-dependent chronic migraine subjects. The rationale for exclusion of literature with composite diagnoses is that it makes the OTA-chronic migraine association challenging to establish.

Results

A total of nine articles met the defined inclusion criteria (Figure 1). The studies were collectively published between 2020 and 2023, largely under authors based in Europe (6 of 9) and the United States (2 of 9) (Table 1). Cross-sectional retrospective chart reviews were the most common modality of investigation (4 of 9).[64,69] The study involving the highest number of subjects (n = 1172) was performed as a cross-sectional survey study,[1] while one case series had the least (n = 20).[66]

Severity of OTA Injection Delay

Delays in acquiring OTA injections during the COVID-19 pandemic at the recommended frequency were consistently demonstrated across health systems, and the lengths of delay were specifically defined in three out of the nine studies selected.[64,67,69] In Italy, delayed interval in days in accessing OTA for migraine was shown to be 73.61 ± 26.54 days.[64] A separate study conducted in Italy further corroborated the severity of treatment delay and reported 52.14 ± 26.27 days as the mean duration.[67] Similarly, in Portugal, the mean first follow-up interval during the pandemic in patients deemed to have experienced treatment delay was 5.5 (range 4.1–5.8) months.[69] Although the exact length of delay was not discussed, in Norway and Denmark, only 35% and 38% of patients, respectively, who were regularly receiving preventative OTA injections continued to do so at the recommended 12-week intervals through the pandemic, with the rest of the population experiencing varying lengths of delay.[65]

Clinical Consequences of OTA Delay

Studies have revealed a decline in migraine symptom control due to the delays in performing preventative OTA injections in patients who previously received scheduled injections prior to the pandemic. In Spain, migraine frequency increased steadily from 9.5 ± 5.11 to 17.95 ± 8.94 days/month, with 75% of patients expressing dissatisfaction with their headache management.[66] In Italy, an increase in mean headache days per month was also noted (14.78 ± 7.71 vs 17.35 ± 8.8, p = 0.0313).[67] Of note, the

Table 1 Study Demographics and Results Summary

Year	Author	Country	Study Type	n	Age	Female: Male	Length of OTA Delay	Results	Conclusions
2020	Al-Hashel et al[61]	Kuwait	Cross-sectional survey/ Observational study	1018	20–40 (72%), 40–60 (23.1%)	858:160	Unreported	Migraine frequency increased in 59.6% of patients from 5.7 to 8 per month and 10.3% reported transition to chronic migraine; 64.1% reported increased migraine intensity; 66.1% reported negative effects from OTA cancellation; migraine frequency associated with non-compliance with migraine treatment ($p< 0.001$) and difficulty getting medication ($p< 0.001$)	Promotion of telemedicine use and administration of self-injectable monoclonal antibodies, neuromodulation devices and corticosteroids as potential alternatives in times of crises
2020	Erro et al[64]	Italy	Case control study	137	Case age 56.94 ± 17.04; control age 61.72 ± 13.95	72:65	73.61 ±26.54 days	Cases experienced mean OTA treatment delay of 73.61 ±26.54 days, displaying significantly higher VAS of 5.16 ± 3.09 vs 1.83 ± 3.34 of controls ($p< 0.001$); no change in QoL measures of ED-VAS ($p>0.05$) and EQ-5D ($p>0.05$)	Study suggested significant worsening clinical picture due to OTA service cutback during the pandemic, which is not reflected in QoL measures; will require further research to determine optimal schedule for OTA use
2020	Gonzalez-Martinez et al[60]	Italy	Cross-sectional review/ Observational study	67	44.5 ± 12.1	65:2	Unreported	Significant increase in mean headache days per month ($p=0.0313$), analgesia use ($p=0.0394$), pain score ($p=0.0069$) and 6-item headache impact test score ($p=0.0372$) after OTA use suspension	OTA should continue to be safely administered in patients with chronic and high-frequency migraine even during events of lockdown

(*Continued*)

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Table 1 (Continued).

Year	Author	Country	Study Type	n	Age	Female: Male	Length of OTA Delay	Results	Conclusions
2020	Kristoffersen et al[65]	Norway	Cross-sectional survey/ Observational study	29	Unreported	Unreported	Unreported	Reduced inpatient management of acute headache (60%) and migraine (68%); Reduction of OTA treatment from 86% to 36% of hospitals with 28% of facilities completely stopping OTA administration; 54% hospitals admit lower standard of headache care provided during pandemic	Telemedicine and use of alternative therapies such as GCRP antibodies can be used as potential alternatives to OTA
2020	Porta-Etessam et al[66]	Spain	Case series	20	48.7 ± 8.12	Unreported	Unreported	Mean headache frequency per month increased from 9.5 to 17.95 during the pandemic without access to OTA and 15/20 (75%) patients were dissatisfied with management	OTA protocol should be adjusted to accommodate patients with chronic treatment-refractory migraine during times of crises; GCRP antibodies should be considered in situations where OTA is not accessible
2021	Baraldi et al[67]	Italy	Retrospective review/ Observational study	80	50.41 ± 12.06	60:20	52.14 ± 26.27 days	After OTA suspension, there was significant increase in NDH 14.78 ± 7.71 vs 17.35 ±8.8 (p= 0.0313), analgesia consumption (p= 0.0421), headache intensity (p= 0.0069) and HIT6 (p= 0.0372)	Delaying OTA is detrimental to migraine patients especially those concurrently afflicted by medication overuse headache
2021	Chiang et al[1]	United States	Cross-sectional survey/ Observational study	1172	Mean 49.5	1017:138	Unreported	62.1% and 20.7% of responders rated telemedicine experience as 'very good' and 'good'; 89.8% would continue using telemedicine for future care	Telemedicine is a feasible modality to implement for headache care

2023	Moskatel et al[68]	United States	Retrospective review/ Observational study	2385	Unreported	Unreported	Unreported	OTA use decreased from 37.7% pre-pandemic to 17.9% during pandemic ($p<0.001$) and subsequently picked up to 30.7%; CGRP antibody prescription increased from 8.1% to 19.9% and dropped to 11.5% over same period	OTA continues to be preferred prescription among physicians when clinically appropriate to administer when compared to CGRP antibodies
2023	Nascimento et al[69]	Portugal	Case control study	36	Case age 47.0 ± 14.5; control age 57.7 ± 13.2	33:3	>2 weeks	Prolonged OTA treatment interval worsened migraine control with more headache days ($p=0.003$), increased rescue triptan per month use ($p=0.027$), worsened pain intensity ($p=0.012$)	It is crucial to maintain regular OTA schedule, and use CGRP antibodies and other therapies if in-person consultations deemed inappropriate

Abbreviations: CGRP, Calcitonin Gene-Related Peptide; EQ-5D, EuroQoL 5D; HIT6, Six-Item Headache Impact Test; NDH, Number of Headaches per Month; NRS, Numerical Rating Scale; OTA, Onabotulinumtoxin A; QoL, Quality of Life; VAS, Visual Analogue Scale.

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greater magnitude of deterioration in headache frequency, defined as >30% worsening in mean headache days per month, was associated with patient groups with a longer migraine history (p = 0.001) and more complex headache symptoms related to medication overuse headache (MOH) (p = 0.0017).[67]

Data from the Middle East had a similar finding, where the mean number of migraine flare-ups per month increased from 5.7 ± 5.5 before the pandemic to 8.0 ± 7.1 after the onset of the pandemic.[61] About 64.1% (653/1018) of respondents indicated a worsening of migraine severity, of which 22.7% (n = 231) rated the degree of worsening as "significant."[61] This trend was further mirrored in Italy when quantifying pain numerically using the visual analogue scale (VAS).[64] The VAS score was significantly higher in the group that experienced OTA delay of 73.61 ± 26.54 days versus regular OTA injections (5.16 ± 3.09 vs 1.83 ± 3.34, p < 0.001).[64] This was once again demonstrated in the measurement of the numeric rating scale (NRS), where there was a significant increase in pain score following a delay of 51.24 ± 26.27 days in OTA administration (6.1 ± 1.92 vs 6.87 ± 1.92, p = 0.0069).[67] This deterioration was also seen in Portugal, where patients meeting criteria for chronic migraine exhibited a VAS increase from a median of 7.0 (5.8–10.0) to 9.0 (7.0–10.0) during the pandemic (p = 0.012).[69]

When assessing the quality of care that was delivered for chronic migraine patients in Norway and Denmark, regardless of the modality of consultation that was utilized, only 38% of the patients received the same number of follow-up appointments, with 54% of the hospitals admitting that the overall standard of care had decreased over the same period.[65]

Alternative Strategies to OTA Injections During the Pandemic

In lieu of scheduled OTA injections, alternatives in the form of remote consultations and alternative pharmacotherapeutics were offered. CGRP monoclonal antibodies (CGRP mAbs) were consistently prescribed, with literature suggesting that its barriers to use ought to be lowered during the pandemic due to its efficacy and ease of self-application.[66] Use of CGRP mAbs, however, is often limited by cost and regulations of the region. At Stanford healthcare facilities in California, prescriptions for CGRP mAbs doubled to 19.9% from 8.1% (p < 0.001) at the beginning of the pandemic from January to May 2020.[68] This was mirrored by hospitals in Norway, where 29% (5/17) of the facilities reported funneling more patients to CGRP mAbs therapy from OTA injections.[65] On the contrary, hospitals in Denmark demonstrated reluctance to embrace alternative management, and none of the surveyed facilities (0/15) shifted to CGRP mAbs use.[65] Furthermore, for newly diagnosed chronic migraine, Norwegian clinics were more than twice as likely to adopt CGRP mAbs as the first prophylactic agent (41%) compared to similar facilities in Denmark (17%).[65]

The adoption of alternative preventive management was often reinforced through telemedicine to be inclusive in the holistic management of the patient and forge camaraderie during this challenging period. Despite the clinical limitations posed by remote consultations, patients were generally satisfied, with the majority rating these clinical encounters as "very good" or "good" (62.1% and 20.7%, respectively).[1] About 44.8% of patients agreed to continue to use telemedicine for future headache consultations, and a further 45.0% indicated that they would, but not for all visits.[1]

Discussion

The COVID-19 pandemic has drastically altered the provision of medical care and distribution of healthcare resources. This is seen in the management of chronic conditions such as migraine that has a significant socioeconomic burden. Moreover, justification for migraine interventions during times of resource constraints becomes challenging as active treatments could be deemed both essential and elective depending on the context. Collectively, the articles analysed revealed a real, considerable delay in scheduled OTA preventative treatment, which consequently resulted in a perceivable deterioration in migraine symptom control. The loss of access to preventive therapy could be related a study examining the healthcare cost borne by patients who experienced varying numbers of preventive treatment failures during migraine management.[70] The population with the highest number of treatment failures were subjected to exponentially higher healthcare costs and consumed significantly more healthcare resources in the form of unplanned emergency room visits.[70] Notably, this cohort could be considered a medically vulnerable group that utilizes regular OTA injections for prevention.

COVID-19 headache and Migraine

Migraine triggers are commonly associated with inciting factors such as infection, sleep deprivation, and dehydration among others.[71,72] These are, however, also frequent byproducts of ailments from a great variety of non-specific sources, thereby complicating relations of cause and effect. In the context of the COVID-19 pandemic, there have been suggestions of migraine exacerbations being brought on specifically by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus infection.[73,74] The characteristics of the headache attributed to COVID-19 infection remained challenging to distinguish from a migraine attack, with overall headache prevalence varying widely, ranging from 11% to 72%.[73–75] Proposed mechanisms of pain generation include explosive cytokine release driven by interleukin-6, pathological stimulation of the trigeminal system, as well as angiotensin-converting enzyme 2 mediated viral infiltration of both peripheral and central nervous systems.[75] Attempts were made to better define the nature of COVID-19-induced headaches.[76] One study done in Turkey reported headache associations with anosmia, ageusia, and gastrointestinal symptoms with a higher likelihood of a bilateral cranial distribution of pain, longer-lasting symptoms (>72 hours), and pain being more resistant to analgesics.[77] Patients with migraine diagnoses also appeared more susceptible to developing virus-associated headaches and subsequently long COVID headaches.[78] To further complicate headache etiology, the active adoption of COVID-19 vaccines had also been shown to drive a headache that closely mimicked migraine features, being shown to occur in 22% (95% CI: 18–27%) and 29% (95% CI: 23%–35%) of individuals after the first and second inoculations, respectively.[79] Collectively, the relationship between COVID-19 and migraine is exceptionally sophisticated, calling for prudent use of effective migraine treatment modalities following exposure to the SARS-COV2 virus.[73,74]

COVID-19 Quarantine and Migraine Chronicity

It is uncommon to uncover articles linking positive outcomes of migraine management to the health crisis of the COVID-19 pandemic. It was, however, suggested that the quarantine imposed by governments in many regions of the world in curbing the spread of the virus had a somewhat positive effect on the clinical well-being of migraine patients.[80] In Italy, 47.1% of those surveyed meeting the definition of episodic or chronic migraine with or without aura by ICHD-3 criteria in a single institutional observational study registered an improvement in the frequency and intensity of their attacks.[80] This was attributed to the changes in the pattern of work and psychological well-being that were promoted by being in a stable relationship and being gainfully employed, as identified through multivariate logistic regression. Having the diagnosis of "chronic migraine" was interestingly favorable for symptom improvement during the pandemic (p=0.003).[80] However, OTA preventative treatment, which was taken by close to a quarter of the population surveyed (n = 42, 24.7%), resulted equally in patients' migraine symptoms improving and worsening over the same period (p = 0.4).[80]

CGRP Monoclonal Antibodies (CGRP mAb) and Migraine

CGRP levels are elevated during acute migraine flares and are thought to play a significant role in the pathophysiology of migraine.[79,80] CGRP has been shown to trigger migraine attacks both with and without aura following intravenous infusions.[81] CGRP mAbs were developed to target either the CGRP ligand or receptors and were adopted as a migraine prophylactic agent.[82–84] In treatment-refractory migraine patients, CGRP mAbs were shown to be highly efficacious in reducing mean monthly migraine days and exhibited excellent safety profiles.[85,86] Collectively as demonstrated in a network meta-analysis, CGRP mAbs may be marginally better in migraine prevention compared to botulinum toxins, although the latter proved to be superior in reducing monthly headache days when CGRP mAbs (fremanezumab) were administered quarterly.[86] This finding is in line with a recent statement released by the American Headache Society (AHS), which concluded that CGRP targeting therapies ought to be a first-line therapy in migraine prevention without the need to exhaust other modalities of migraine prophylaxis.[87]

Healthcare Resource Distribution and Equity

The debate on healthcare equity was magnified during the COVID-19 pandemic on multiple levels, and the use of CGRP mAbs was specifically identified as a point of contention.[88] Given the proven efficacy of CGRP mAbs during the pandemic, there had not been a perceivable conversion of treatment to replace OTA.[76] The incremental cost-effectiveness ratio (ICER) for OTA use in migraine management in Europe ranged from £15,028 to £16,598, while CGRP mAbs such as erenumab, fremanezumab, and galcanezumab ranged from £59,712 to £182,128, with the CGRP mAbs ICER being above the willingness-to-pay thresholds.[89] This suggested that cost considerations superseded wider clinical benefits in adoption of health policies. Furthermore, even in the face of evidence showing combination therapy of mAbs and OTA achieving better control of symptoms in treatment-resistant and refractory migraine,[90] European guidelines continue to recommend monotherapy as the standard of care.[15,91] It is worthwhile to note that as of April 2024, the American Headache Society (AHS) published in its position statement that CGRP mAbs be considered a first-line agent to be used in migraine prophylaxis.[92] This is unfortunately a moot point in economically less-developed countries where both options of novel therapeutic agents and epidemiological data itself are lacking.[93]

Limitations

The review incorporated all published peer-reviewed articles amenable to our search strategy. Patient samples were derived mostly from the clinic setting and therefore the ideal representation of the general population. There were a number of observational studies in the form of surveys, which would have been classified as lower evidence, non-experimental literature due to their inherent selection, information, and confounding biases. Overall, the exact duration of OTA administration delay was rarely defined. Specifically, only three out of the nine articles explicitly stated the durations of OTA therapy delay,[64,67,69] making it difficult to make correlations between the length of treatment suspension and severity of clinical deterioration. It was also challenging to suggest a relationship stronger than mere association for observations like the concurrent worsening of migraine and medication-overuse headache during the pandemic, as the quantity and type of medication used in place of OTA was not revealed.[67]

Conclusion

The COVID-19 pandemic significantly limited the use of prophylactic OTA due to the feasibility of in-person medical consultations, which in turn resulted in marked clinical detriments to patient populations across the US, Europe and the Middle East. Strategies employed to circumvent the limitations imposed during the time of crisis included adoption of remote consultation via telemedicine as well as the use of pharmacological agents such as CGRP mAbs, which are patient administered. Healthcare systems could formally incorporate these alternative modalities into their treatment plans in the event of future large-scale disruptions to routine provisions of needed care to migraine patients.

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