









Review Article

COVID-19 and Headache Medicine: A Narrative Review of Non-Steroidal Anti-Inflammatory Drug (NSAID) and Corticosteroid Use

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Objective.—To summarize the current literature on non-steroidal anti-inflammatory drug and corticosteroid use during the coronavirus disease 2019 (COVID-19) pandemic, recognizing that these are commonly used treatments in the field of headache medicine.

Background.—The use of non-steroidal anti-inflammatory drugs and corticosteroids in patients during the COVID-19 pandemic has been a controversial topic within the medical community and international and national health organizations. Lay press and social media outlets have circulated opinions on this topic despite the fact that the evidence for or against the use of these medications is sparse. In the field of headache medicine, these medications are used commonly and both patients and clinicians may have questions or hesitations pertaining to their use during the COVID-19 pandemic.

Methods.—A detailed search of the scientific and popular literature was performed.

Results.—There is limited literature pertaining to the safety of non-steroidal anti-inflammatory drugs and corticosteroids during the COVID-19 pandemic. To date, there are no clear scientific data that preclude the use of non-steroidal anti-inflammatory drugs in the general population who may acquire COVID-19 or in those acutely infected with the virus. Several health organizations have concluded that treatment with corticosteroids during active infection should be avoided due to concerns of prolonged viral shedding in the respiratory tract and the lack of survival benefit based on the data from past coronaviruses and influenza virus; specific exceptions exist including treatment for underlying asthma or chronic obstructive pulmonary disease, septic shock, and acute respiratory distress syndrome.

Conclusion.—Scientific information regarding the COVID-19 pandemic is constantly evolving, and limited or contradictory information can lead to confusion for both patients and clinicians. It is recommended that prior to prescribing non-steroidal anti-inflammatory drugs and steroids for the treatment of headache, clinicians have open discussions with their patients about the potential risks and benefits of using these medications during the COVID-19 pandemic. This manuscript summarizes the currently available evidence and understanding about these risks and benefits to help clinicians navigate such discussions.

Key words: coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, migraine, headache, non-steroidal anti-inflammatory drugs, steroids

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Abbreviations: ACE2 angiotensin-converting enzyme 2, ARDS acute respiratory distress Syndrome, BMJ British Medical Journal, CDC Center for Disease Control, CoV coronavirus, COVID-19 coronavirus disease 2019, COX cyclooxygenase, CT computed tomography, FDA Food and Drug Administration, IDSA Infectious Diseases Society of America, NIH National Institutes of Health, NSAIDs non-steroidal anti-inflammatory drugs, PG prostaglandin, PPE personal protective equipment, SARS Severe Acute Respiratory Syndrome, WHO World Health Organization

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INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, it is paramount that headache specialists be able to continue to care for patients effectively and safely. Resource prioritization, health policies such as social distancing, and rapidly changing medical information are requiring swift adjustments to clinical practice. Headache neurologists are urging insurance companies to eliminate prior authorizations for migraine therapies and either eliminate or minimize co-payments for migraine-specific medications in order to effectively treat patients with migraine and prevent undue burden on a healthcare system that is in high-demand to care for patients with COVID-19.¹ Furthermore, healthcare workers wearing personal protective equipment (PPE) may be experiencing de novo headache or worsening of underlying primary headache disorders.² Additional demands for headache medicine during the COVID-19 pandemic include a potential increase in patients with a chief complaint of headache, since that can be a symptom of COVID-19.^{3,4} Per a recent meta-analysis of clinical characteristics of patients with COVID-19, 15.4% were reported to have headache.⁴ Another study

found that the median number of days from hospital admission to the onset of headache was one, but ranged from 1 to 14 days.³ Of particular importance to the neurology community, some patients were initially admitted with fever and headache after negative COVID-19 serologic testing and chest CT; however, days later developed other typical respiratory symptoms of COVID-19 and diagnosis was confirmed with nucleic acid testing.⁵

The use of some common medications applied for headache treatment has come under scrutiny in the setting of COVID-19. Non-steroidal anti-inflammatory drug (NSAID) and corticosteroid use in patients during the COVID-19 pandemic has been controversial,^{6,7} with existing evidence indirectly suggesting potential benefits^{7,8} or harms,^{6,9} and international and national health organizations providing inconsistent guidance.⁹⁻¹² Given that all patients are at risk of potentially contracting COVID-19, the headache medicine clinician must consider any risks related to the use of NSAIDs and corticosteroids for headache and weigh them against the potential benefits. We have gathered and summarized the most current literature on the use of NSAIDs and

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corticosteroids in the setting of the COVID-19 pandemic and how this relates to headache medicine.

METHODS

A detailed search of the literature was performed with the assistance of our Health Sciences Librarian. Search terms were selected based upon the terms generated by the principle investigator (JVP) and tested and refined in collaboration with the Health Sciences Librarian. A PubMed search was performed and the following MeSH terms were used: coronavirus, airway management, intratracheal intubation, artificial respiration, respiratory therapy, general anesthesia, headache, neurologic manifestations, non-steroidal anti-inflammatory agents, steroids. Other text/key words included: severe acute respiratory syndrome coronavirus 2, severe-acute-respiratory-syndrome-coronavirus-2, 2019-nCoV, 2019-nCoV, COVID-19, COVID-19, COVID-2019, nCoV-2019, nCoV-2019, HCoV-19, HCoV-2019, HCoV-19, HCoV-2019, SARS-CoV-2, Wuhan, china, Chinese, novel, coronavirus, coronaviruses, corona-virus, corona-viruses, COVID, HCoV, NSAID, steroid. Main topic search terms included truncated keywords NSAID*, steroid*, headache*, migraine*, neurolog*. The following keywords and truncated keywords were limited to the title or abstract of the publication: airway, intubat*, ventilat*, anesthe*, oxygenat*, respiratory. Publications in the English language were queried. No study design or date limits were imposed. MeSH terms and text words were combined using the Boolean operators of "OR" and "AND" which resulted in 224 unique citations over searches conducted on different dates. Each citation was subsequently assessed for applicability to the subject matter of this manuscript. We also evaluated the web pages of regulatory agencies such as the CDC, WHO, and FDA as well as clinicaltrials.gov for relevant information. The clinicaltrials.gov search used the following search terms: headache OR NSAIDs OR steroids OR neurological and COVID. Given the potential delay in formal scientific publication, popular media, news sites, and medical journal websites were also searched for breaking news regarding the topic. Searches were replicated regularly to ensure that the most recent literature was included on the topic (last search date 6/17/2020).

NSAID AND CORTICOSTEROID USE DURING THE COVID-19 PANDEMIC

NSAIDs: Narrative Review.—There is robust evidence that NSAIDs are effective in treating migraine.¹³⁻¹⁶ NSAIDs are widely used for headache management and are accessed by patients over-the-counter or by prescription.

Based on expert opinion and anecdotal evidence publicized through the media, recent concerns were raised that NSAIDs may worsen symptoms of COVID-19 infection.^{6,17} Controversy regarding the use of NSAIDs during the COVID-19 pandemic stemmed from several sources. The concern that NSAIDs, such as ibuprofen, might be causing worse clinical outcomes in those infected with COVID-19 became a topic of international discussion following a tweet from France's health minister, Olivier Véran.¹⁸ This was based on a French physician's observation of 4 young healthy individuals who developed serious symptoms of COVID-19 in the setting of NSAID use. A non-peer-reviewed news article on the British Medical Journal (BMJ) website cautioned clinicians against the use of ibuprofen and sparked many subsequent letters to the editor.⁶ A subsequent non-peer-reviewed editorial from the BMJ cited evidence of the potential harms encountered with NSAID use in the context of underlying respiratory tract infection, but concluded that intermittent use of NSAIDs may be helpful for patients with COVID-19.¹⁹

Several health organizations have made statements regarding the use of NSAIDs during the COVID-19 pandemic. The World Health Organization (WHO) initially advised against the use of ibuprofen in COVID-19, but later concluded that there was insufficient evidence to support this statement.²⁰ The Center for Disease Control (CDC) states that there is no association between the use of NSAIDs and worsening of clinical outcomes in those with COVID-19.⁹ The Food and Drug Administration (FDA) is in agreement with the CDC but cautions individuals that NSAIDs reduce inflammation and may delay or minimize the signs and symptoms of infection.¹¹ Most recently, the NIH stated that there is no difference in using NSAIDs or acetaminophen for their anti-pyretic effects in COVID-19.¹² The pain management community has not made a definitive recommendation on the use of NSAIDs for chronic pain conditions, other than to state that the use of NSAIDs may mask the initial signs of infection.^{21,22}

Theoretical risks of NSAIDs in the setting of severe viral illness include increased risk of pulmonary edema due to reduced renal perfusion resulting in hypervolemia and hyponatremia, masking the first signs of infection, and lowering body temperature which may perpetuate viral replication.^{17,23,24} There is weak evidence showing that the use of NSAIDs before or during viral or bacterial lower respiratory tract infections results in higher rates of complications including complicated pneumonia, pleural effusions, prolonged illness, peritonsillar abscess, dissemination of infection or suppuration, sinusitis, meningitis, and otitis media.^{25,26} NSAIDs inhibit cyclooxygenase-1 (COX-1) and COX-2, thereby reducing the recruitment of neutrophils and inhibiting the synthesis of lipoxins and resolvins, which in turn delays or impairs the resolution of inflammation, as COX-2 plays a pivotal role in the resolution of acute lung injury in animal models.^{19,27} NSAIDs are also thought to increase the expression of angiotensin-converting enzyme 2 (ACE2). A potential concern about NSAIDs during the COVID-19 pandemic is increasing the risk of contracting infection due to the upregulation of ACE2, the cellular entry site for the SARS-CoV2 virus.²⁸ There is speculation that patients with diabetes taking angiotensin II receptor type 1 blockers who concomitantly take ibuprofen may be at increased risk of contracting COVID-19 infection; however, this correlation between ibuprofen and ACE2 was evaluated in diabetic rats and it has not been translated to human studies.^{28,29}

Data from prior coronavirus infections are being used to speculate about what may happen in the current COVID-19 pandemic. The coronavirus responsible for the 2003 severe acute respiratory syndrome (SARS-CoV) outbreak increased prostaglandin (PG) production by binding to the COX-2 promoter.³⁰ Extrapolating from other viral studies, select PGs such as PGE₂ have been shown to have variable effects on the promotion or restriction of viral spread and inflammation.^{31,32} An in-vivo canine study from 2006 evaluating the effect of indomethacin on SARS-CoV found that indomethacin carried potent antiviral activity and was an inhibitor of viral replication.⁸

A case series from France examining patients with COVID-19 in the intensive care unit found that none of 9 patients who died were taking NSAIDs prior to admission, according to their home medication list.³³ There

are certainly many limitations to this type of study, and another similar prospective case-control study based in France is registered but not yet recruiting. Currently, there is one registered clinical trial investigating the efficacy of naproxen in the treatment of critically ill patients with COVID-19 (ENACOVID; NCT04325633)³⁴ and another evaluating the role of ibuprofen in worsening clinical outcomes in patients with COVID-19 (NCT04383899).³⁵ A systematic review of literature pertaining to the use of NSAIDs in both SARS-coronavirus and COVID-19 published on 3/27/20 “did not identify any strong evidence for or against the use of ibuprofen during treatment of COVID-19 specifically.”⁷

Corticosteroids: Narrative Review.—Benefits of steroids in headache medicine include the potential to reduce the recurrence of severe acute migraine following emergency department discharge¹⁵ and as transitional therapy for cluster headache.³⁶⁻³⁸

Based on prior coronavirus (CoV) and influenza infections, the CDC states that the use of steroids is not recommended in COVID-19 due to historical data showing increased mortality and need for mechanical ventilation.⁹ The WHO recommends against the use of corticosteroids in viral pneumonia.¹⁰ The NIH also recommends against the use of steroids in any mechanically ventilated or hospitalized patients with COVID-19 except low-dose corticosteroid use in refractory septic shock¹² which is in agreement with the Surviving Sepsis Campaign.³⁹ Additionally, the WHO advises that steroids could be given for asthma or chronic obstructive pulmonary disease (COPD) exacerbations in COVID-19.¹⁰ The Infectious Diseases Society of America (IDSA) guidelines state that hospitalized patients with COVID-19 pneumonia should not be given corticosteroids.⁴⁰ Experts recommend that people taking cortisone or other steroids for chronic diseases shouldn't stop them, except on advice from their doctor.⁴¹ The pain management community has made recommendations on the use of steroids for chronic pain during the COVID-19 pandemic. One group recommends the use of epidural and other steroid injections at the lowest effective dose during the COVID-19 pandemic, although the risks and benefits should still be weighed for each individual patient.²¹ Another group also suggests discussing treatment options with an infectious disease specialist.²² The pain management community recommends that for

immunosuppressed patients or at high risk for COVID-19 infection, non-steroid injections should be used.²¹

Of note, some studies surrounding the prior SARS-CoV epidemic showed steroids to be associated with positive outcomes in terms of inflammatory response,⁷ and they may be specifically beneficial when used in the acute phase of the infection based on 1 human and 1 animal study which utilized a porcine version of the coronavirus.^{42,43} As time passes, more studies from the current COVID-19 pandemic are coming to light. A non-peer-reviewed retrospective review from Wuhan, China associated the administration of methylprednisolone for 5-7 days in patients with COVID-19 with reduced duration of fever and use of supplemental oxygen as well as improvement in the areas of consolidation on chest computed tomography (CT).⁴⁴ Another larger retrospective review out of Wuhan found that patients with acute respiratory distress syndrome (ARDS) were more likely to be treated with methylprednisolone and among patients with ARDS, those treated with methylprednisolone had a statistically significant reduced risk of death compared with those who did not receive corticosteroids.⁴⁵ In concordance with this, the Surviving Sepsis Campaign suggests the use of steroids in mechanically ventilated patients with ARDS.³⁹ Conversely, a prospective review from Wuhan showed no statistically different outcomes in terms of fever, cough, dyspnea, or duration of illness in those who had received steroids compared to those who did not. However, this study was disproportionate in its comparison with only 9 patients receiving steroids compared to 32 who did not. Those receiving steroids did have a high incidence of ARDS, shock, and acute kidney injury but it is unclear from the data if steroids were given to those already experiencing shock or ARDS. Steroids were administered more frequently to patients in the intensive care unit (ICU).⁴⁶

On 6/16/20, breaking news from the RECOVERY (Randomized Evaluation of COVID-19 thERapY) trial based in the United Kingdom (NCT04381936)⁴⁷ purported that dexamethasone 6 mg daily compared to “usual treatment alone” reduced the risk of death in ventilated patients and in those receiving supplemental oxygen. There was no benefit found in COVID-19 patients not requiring respiratory support.⁴⁸ This data is currently unpublished and has not been peer-reviewed.

Additionally, per the trial’s description on clinicaltrials.gov it appears that if patients had “progressive COVID-19” evidenced by hypoxia and “inflammatory state” that they could undergo second randomization and receive either tocilizumab or no additional treatment.⁴⁷ The preliminary results do not specify if the patients included in the analysis had also received tocilizumab.⁴⁸

Concern surrounding the use of steroids in past viral outbreaks was partly based on the risk of prolonged viral shedding.¹⁰ One retrospective cohort study confirmed that the duration of COVID-19 viral shedding in the stool was extended in patients treated with steroids than those who did not receive steroids.⁴⁹ This is particularly important for consideration in the spread and propagation of coronavirus.

The risks or benefits of steroid use during the COVID-19 pandemic may be dependent on the timing of administration during the disease course. Continued research on this is required to shed additional light on this nuance. Per clinicaltrials.gov, as of 5/27/20, there are at least 12 pending trials, not including RECOVERY, to evaluate the role of steroids in patients with COVID-19 (NCT03852537, NCT04323592, NCT04331470, NCT04355247, NCT04355637, NCT04244591, NCT04331054, NCT04348305, NCT04360876, NCT04278404, NCT04263402, NCT04362474).⁵⁰⁻⁶⁰ Additional trials in China, also investigating the efficacy and safety of steroids in COVID-19, are available through the Chinese Clinical Trial Register.⁶¹

DISCUSSION

The COVID-19 pandemic is a global health crisis in which health care providers, including headache specialists, are adjusting their practices as information evolves. Peer-reviewed scientific literature is the highest quality of information upon which clinicians should base their medical decisions, but the lay press and social media (Ex. Olivier Véran’s tweet on NSAIDs)¹⁸ can often more rapidly and widely spread information that then requires a critical appraisal by the medical community. The goal of this review was to provide a summary of the current literature regarding the use of NSAIDs and steroids during the COVID-19 pandemic, recognizing that these are commonly used medications in the field of headache medicine. Table 1 highlights the

Table 1.—Potential Risks and Benefits of Utilizing NSAIDs or Steroids (Oral or Parenteral) for Migraine or Cluster Headache During the COVID-19 Pandemic

Use of NSAID or Steroid During COVID-19 Pandemic	Potential Risk	Potential Benefit	Summary
Non-steroidal anti-inflammatory drugs	<ul style="list-style-type: none"> • Reduced renal perfusion → hypervolemia, hypernatremia → pulmonary edema • May mask first signs of infection • Lower body temperature which may perpetuate viral replication • Weak evidence that use of NSAIDs before or during viral or bacterial lower respiratory tract infections increases the rate of complications^{25,26} • Parenteral formulations require either emergency department or ambulatory infusion center for administration which may increase the risk of patient exposure to COVID-19 or place strains on health-care resources 	<ul style="list-style-type: none"> • Evidence-based indications for oral and parenteral use in headache medicine, including acute migraine treatment, refractory migraine/status migrainé¹³⁻¹⁶ • No convincing data to date demonstrating that exposure to NSAIDs increases the risk of contracting COVID-19 or worsens clinical course • Oral formulations that can be administered at home reduce exposure to healthcare settings where patients may be exposed to COVID-19 • May prevent emergency department visits and/or hospital admission if parenteral administration in an ambulatory setting 	<ul style="list-style-type: none"> • Recommend a discussion of risks and benefits with all patients prior to prescribing • No evidence to date to limit the use of NSAIDs relative to proven benefit for headache in patients with or suspected of having COVID-19 who are without other contraindications
Steroids	<ul style="list-style-type: none"> • Concern for increased risk of mortality and/or need for mechanical ventilation based on the historical data • Risk of infection with steroid administration is dose-dependent^{60,†} • Parenteral formulations require either emergency department or ambulatory infusion center for administration which may increase the risk of patient exposure to COVID-19 or place strains on health-care resources • Procedural administration (ex. occipital nerve blocks) require in-person visits which may increase the risk of patient exposure to COVID-19 	<ul style="list-style-type: none"> • Evidence-based indications for oral and parenteral use in headache medicine, including reducing migraine recurrence after discharge from the emergency department and transitional therapy in cluster headache^{15,36-38} • Oral formulations that can be administered at home to reduce exposure to healthcare settings where patients may be exposed to COVID-19 • May prevent emergency department visits and/or hospital admission if administered in an ambulatory setting 	<ul style="list-style-type: none"> • Recommend a discussion of risks and benefits with all patients prior to prescribing • Limited evidence suggests avoiding steroids in a patient with COVID-19 or COVID-19 suspect; specific exceptions exist including treatment for underlying asthma or COPD, septic shock, and acute respiratory distress syndrome

†Referring to rheumatology literature; no specific infection being referenced.

potential risks and benefits as it pertains to the use of NSAIDs and corticosteroids for the treatment of migraine, recurrent migraine, and transitional treatment of cluster headache during the COVID-19 pandemic. Given that anyone, including patients with headache, can contract COVID-19, discussing the potential risks and benefits of the use of NSAIDs and steroids is important prior to prescribing them or advising their use. Such discussions align with patient-centered care practices and enhance trust and adherence.

The primary goal of using NSAIDs or steroids in their various forms is pain relief. The early administration of these evidence-based treatments not only helps patients, but may also reduce healthcare utilization if pain is adequately controlled. The safest scenario would be to administer NSAIDs or steroids to a known COVID-19 negative patient; however, in real practice, this cannot always be confirmed since symptom screening may miss asymptomatic patients and testing may be limited. Since we cannot necessarily eliminate risk, we must minimize risk by considering the route of administration (oral vs parenteral) and location of administration (home, outpatient, emergency department, inpatient). Theoretically, limiting exposure to a healthcare setting should reduce the risk of exposure to coronavirus and reduce the risk of contracting COVID-19; however, if an in-person procedural visit can be done safely with appropriate PPE for the provider and the patient, it may limit emergency department visits and hospital admissions, while also freeing hospital beds for patients ill with COVID-19. Overall, the decision on whether to use either NSAIDs or steroids during the pandemic should be individualized to the specific patient.

At this time, there is no specific evidence against the use of NSAIDs, oral or parenteral, in patients with or without COVID-19. Common sense judgment should still be at the forefront in those with co-morbid medical conditions that may limit the use of NSAIDs. Comparing the data regarding steroid use from prior viral outbreaks and the information available from the current pandemic, it remains unclear if steroids offer benefit or harm when administered to patients with COVID-19. Per rheumatology literature, the risk of infection with steroid administration is dose-dependent.⁶²

COVID-19 is being recognized as a multi-system disorder that in addition to affecting the pulmonary system, may affect the cardiovascular, nervous, renal, and hepatobiliary systems.^{4,63} Although concerns have been raised about NSAIDs and steroids, use of other common medications in headache management will require consideration based on the systems affected by COVID-19; for example, the use of vasoactive medications (ex. triptans and ergots), QTc prolonging medications (ex. neuroleptics), and medications that can affect the hepatic system (ex. valproic acid).

Future research involving the use of steroids and NSAIDs in COVID-19 will be critical to determine the most appropriate practice parameters in the headache community during these times. In addition to the previously mentioned ENACOVID³⁴ and NCT04383899³⁵ trials on NSAIDs, at the time of this publication, there are numerous pending trials investigating steroids, parenteral or inhaled, in COVID-19. One study is completed, but results are still pending (NCT04244591)⁵² and the RECOVERY trial⁴⁸ preliminary results are available but not yet formally published. The results of these trials may change various health organizations' stance on the use of these medications during the COVID-19 pandemic and will be of particular importance to extrapolate to the field of headache medicine.

CONCLUSION

Scientific and clinical information regarding the COVID-19 pandemic is constantly evolving, requiring clinicians to be vigilant in searching for the most up to date but also the most vetted information so that they first do no harm. Discussions regarding the risk and benefits of the use of NSAIDs and steroids during the COVID-19 pandemic are important even if the information upon which to base these discussions is limited. The evidence presented for potential risks and benefits in this manuscript is intended to help clinicians navigate this conversation with patients.

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