

Rapid policy statement

# Acute use of non-steroidal anti-inflammatory drugs (NSAIDs) in people with or at risk of COVID-19 (RPS2001)

14 April 2020, Version 1

## Summary

In response to the public health emergency posed by COVID-19, NHS England has established a rapid policy development process to aid clinicians in offering best care and advice to patients with or at risk of COVID-19. This document sets out the clinical policy for the acute use of non-steroidal anti-inflammatory drugs (NSAIDs) in people with or at risk of COVID-19. The chronic use of NSAIDs is outside of the scope of this policy with a separate review to take place.

## Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Plain language summary

COVID-19 is a disease caused by a coronavirus (named SARS-CoV-2) causing many different symptoms, the most common being fever, fatigue and cough. It has spread rapidly

throughout the world, with countries imposing a range of restrictions on daily life to help reduce the spread of the disease.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications typically used to treat pain, fever and inflammation. There are a number of different NSAIDs: some are prescription-only, and others are available over-the-counter to the public (such as ibuprofen). There have been some reports of possible adverse effects of the use of NSAIDs in acute respiratory tract infections more generally, which has led to suggestions to use paracetamol preferentially for fever/pain in such situations. There is currently no evidence that the acute use of NSAIDs causes an increased risk of developing COVID-19 or of developing a more severe COVID-19 disease.

When patients, carers or healthcare professionals are starting treatment for fever and/or pain in patients (adults or children) with confirmed or suspected COVID-19, all treatment options should be considered and selected based on the greatest benefit compared to potential harms using each medicine's product information. If used, the lowest effective dose of NSAID should be used for the shortest period required to control symptoms. This is in line with the European Medicines Agency (EMA) statement on the 18 March 2020 (European Medicines Agency, 2020).

The long-term use of NSAIDs is outside of the scope of this policy, with the intention to undertake a separate review. The current advice for patients taking long-term NSAIDs for chronic conditions from the EMA and CAS alert is to continue this treatment, which may require re-assessment of medication should COVID-19 infection arise.

## **Overview**

### **The condition**

As of 24 March 2020, over 300,000 people globally and 8,077 in the United Kingdom have developed COVID-19 (World Health Organization (WHO), 2020a), a disease caused by a novel coronavirus (SARS-CoV-2) which emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) as well as the common cold. It has caused a fast-moving public health crisis globally, as countries impose a range of restrictions on daily life to contain the spread of disease. COVID-19 manifests as a respiratory illness, of widely varying clinical severity. The most common symptoms are fever and cough. At the most severe end of the spectrum it results in severe pneumonia with the need for mechanical ventilation and can result in death. Patients are offered best supportive care, with no known effective anti-viral medication currently identified (WHO, 2020b).

## Intervention

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications which act as inhibitors of COX-1 and COX-2 enzymes and so lead to a reduction in production of prostaglandins. Prostaglandins are key mediators in pain, fever, inflammation and swelling whilst also playing a key role in gastric protection and haemostasis. Some are non-selective COX inhibitors (ibuprofen, naproxen, indometacin) whilst others are selective COX-2 inhibitors (etoricoxib, celecoxib), which more specifically target prostaglandins which mediate pain and inflammation.

Ibuprofen is available over the counter and is commonly used for pain and fever in acute illness in both adults and children. It is also used in chronic inflammatory conditions such as rheumatoid arthritis and juvenile idiopathic arthritis. Other NSAIDs are prescription-only medications which are used for acute and chronic pain.

The major adverse effects of non-selective COX inhibitors such as ibuprofen include increased risk of gastric and oesophageal ulceration, while chronic use can lead to an increased risk of thrombotic events such as myocardial infarction and stroke. A link has been noted between ibuprofen use and increased severity of skin disease in varicella infections, including chickenpox and shingles, therefore NICE Clinical Knowledge Summaries CKS advise against the use of ibuprofen in these patients (Gould 2013). NSAIDs may also exacerbate or precipitate bronchospasm in patients with asthma and are contraindicated in this group of patients.

## Clinical problem

This is a rapidly evolving pandemic globally, with countries facing different stages of the spread of disease, and therefore there is limited published information about the disease course, vulnerable populations and mortality rate. Data available, particularly from China, suggest that people over the age of 70 and those with comorbidities are most at risk of critical care admission and death (Chen et al. 2020). Children and young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions in this age group (Lu *et al.* 2020).

On the 14<sup>th</sup> March 2020 the French Health Ministry issued guidance (Ministère des Affaires Sociales et de la Santé, 2020, 2020-REC-12) to avoid the use of anti-inflammatory medications including ibuprofen for treatment of the symptoms of coronavirus, due to an apparent observed worsening in the severity of disease in patients taking anti-inflammatories. Due to these concerns the Medicines and Healthcare products Regulatory Agency (MHRA) issued a central alerting system (CAS) on 17<sup>th</sup> March 2020 (MHRA, 2020, CEM/CMO/2020/010) alert to advise against the use of ibuprofen in patients with confirmed or suspected COVID-19, whilst acknowledging we have limited evidence of the safety of

ibuprofen in these patients. On the 18th March 2020, the WHO posted on social media that it does not recommend against the use of ibuprofen.

## **Evidence summary**

This evidence review aimed to assess the best available evidence to determine whether there is any increased risk of developing COVID-19 in people using NSAIDs acutely, and whether using NSAIDs acutely can lead to an increased risk of developing more severe symptoms of COVID-19..

A literature search identified 156 references, which were screened using their titles and abstracts. Thirteen references were obtained and assessed for relevance; however, none were suitable for inclusion. This means that no evidence from published scientific studies was found to determine whether acute use of NSAIDs is related to increased risk of developing COVID-19 or increased risk of a more severe illness.

At this time, policy decisions on whether NSAIDs should be used for treating symptoms of COVID-19 will need to take into account data extrapolated from studies involving the use of NSAIDs for other acute respiratory tract infections, together with pharmaco-epidemiological studies.

Concerns over using NSAIDs for COVID-19 were raised by the French Health Ministry after 4 people with COVID-19 and no underlying health problems reportedly developed serious symptoms after using these medicines ([Day 2020](#)). On 14 March 2020, the French Health Minister issued advice to avoid using NSAIDs for COVID-19 based on a [2019 evaluation by the French National Agency for Medicines and Health Products Safety](#), which suggested that infection due to chickenpox (varicella) and some bacterial infections could be made worse by ibuprofen and ketoprofen.

On 18 March 2020, the EMA issued a [press release](#) stating there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19. The EMA is monitoring the situation closely and will review any new information that becomes available on this issue in the context of the pandemic.

A CEBM review on [NSAIDs in acute respiratory infection](#) (not including COVID-19) concluded that NSAIDs do not significantly reduce total symptoms or duration of respiratory infections. Also, there are long-standing and well-recognised gastrointestinal and renal safety concerns with all NSAIDs, and evidence confirming an increased risk of cardiovascular events with many NSAIDs, including COX-2 inhibitors and some traditional NSAIDs such as diclofenac and high-dose ibuprofen (2,400 mg daily or more).

The CEBM advises that there is a need for caution when using NSAIDs for acute respiratory infections. Pre-existing medications and conditions need to be considered when deciding whether to use NSAIDs for symptomatic acute respiratory infections. Clinicians should follow advice in the [BNF](#) and the [NICE Clinical Knowledge Summary on issues around prescribing NSAIDs](#). When considering an NSAID, individual risk factors for adverse effects should be taken into account, including any contraindications, drug interactions, medical history, and any monitoring requirements. The lowest effective dose of an NSAID should be used for the shortest period required to control symptoms and the need for long-term treatment should be reviewed periodically. The [MHRA advises](#) that naproxen and low-dose ibuprofen (up to 1,200 mg per day) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.

The [EMA advises](#) that, when starting treatment for fever or pain in COVID-19, patients and healthcare professionals should consider all available treatment options, including paracetamol and NSAIDs. Each medicine has its own benefits and risks which are reflected in its product information, and which should be considered along with EU national treatment guidelines, most of which recommend paracetamol as a first treatment option for fever or pain. In line with EU national treatment guidelines, patients and healthcare professionals can continue using NSAIDs (like ibuprofen) as per the approved product information. Current advice includes that these medicines are used at the lowest effective dose for the shortest possible period. Patients who have any questions should speak to their doctor or pharmacist. There is currently no reason for patients taking ibuprofen to interrupt their treatment. This is particularly important for patients taking ibuprofen or other NSAIDs for chronic diseases.

In summary, the available evidence suggests that, although the anti-inflammatory effects of NSAIDs reduce acute symptoms (such as fever), they may either have no effect on, or worsen, long-term outcomes, possibly by masking symptoms of worsening acute respiratory tract infection. Further evidence is needed to confirm this, and to determine whether these results also apply to infections such as COVID-19.

## **Recommendations and implications for clinical practice**

There have been some reports of possible adverse effects of the use of NSAIDs in acute respiratory tract infections more generally, which has led to suggestions to use paracetamol preferentially for fever/pain in such situations. There is currently no evidence that the acute use of NSAIDs causes an increased risk of developing COVID-19 or of developing a more severe COVID-19 disease.

When patients, carers or healthcare professionals are starting treatment for fever and/or pain in patients (adults or children) with confirmed or suspected COVID-19, all treatment options should be considered and selected based on the greatest benefit compared to potential

harms using each medicine’s product information. If used, the lowest effective dose of NSAID should be used for the shortest period required to control symptoms. This is in line with the European Medicines Agency (EMA) statement on the 18<sup>th</sup> March 2020 (European Medicines Agency, 2020).

The long-term use of NSAIDs is outside of the scope of this policy, with the intention to undertake a separate review. The current advice for patients taking long-term NSAIDs for chronic conditions from the EMA and CAS alert is to continue this treatment, which may require re-assessment of medication should COVID-19 infection arise.

## **Governance**

### **Effective from**

This policy will be in effect from the date of publication.

### **Policy review date**

This is a rapid policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken.

This document will be reviewed when information is received which indicates that the policy requires revision.

## **Definitions**

<b>COVID-19</b>	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus.
<b>Mechanical ventilation</b>	A life support treatment which helps people breathe when they are not able to breathe enough on their own.

## **References**

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