

## Should ibuprofen be used for COVID-19?

*This clinical evidence summary outlines existing evidence on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen, to manage symptoms of COVID-19. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.*

### Background

A news article titled “COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists” was published in BMJ on 17 March 2020.<sup>1</sup> It claims that anti-inflammatory drugs (e.g. ibuprofen and cortisone) could exacerbate symptoms of COVID-19 infection, and paracetamol should be used instead; however different views were expressed.

### Clinical evidence

No clinical trials were identified assessing the safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in managing symptoms of COVID-19. However, there are some studies on the potential mechanisms of inflammatory responses available which propose that systemic anti-inflammatory drugs or corticosteroids may be used together with other agents to prevent severe lung injury.<sup>2,3</sup>

The National Agency for the Safety of Medicines and Health Products (ANSM) of France issued a warning in April 2019 on the use of NSAIDs for patients with infectious diseases, based on an analysis of 20 years of real-world safety data of ibuprofen (n=337) and ketoprofen (n=49). ANSM was concerned that existing infections might be worsened by the use of NSAIDs.<sup>4</sup>

A few recent reviews reporting on the safety of NSAIDs or ibuprofen in other acute viral respiratory infections have been published and are summarised below:

- A rapid systematic review published by the World Health Organization (WHO) on 19 April 2020 assessed the effects of prior and current use of NSAIDs in patients with acute viral respiratory infections. The review included 73 studies but none specifically addressed COVID-19, SARS, or MERS. It concluded that currently there is no evidence of severe adverse events, acute health care utilisation, long-term survival, or improved quality of life in patients with COVID-19, as a result of the use of NSAIDs.<sup>5</sup>
- Two evidence reviews conducted by NICE (UK) found no evidence to determine if there is an increased risk of developing COVID-19 infection, or of developing more severe symptoms of COVID-19 due to acute or long-term use (≥2 weeks) of NSAIDs.
  - For acute use, although the anti-inflammatory effects of NSAIDs reduce acute symptoms (such as fever), the review concluded that NSAIDs 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.<sup>6</sup>
  - For long-term use, currently there is no evidence to suggest that people taking NSAIDs for a chronic condition should be advised to stop treatment. Although NSAIDs may not be first choice for managing symptoms of COVID-19 in people with some chronic diseases, an association between NSAIDs and the disease may merely reflect reverse causality (e.g. the infection makes the person more susceptible to adverse effects of NSAIDs).<sup>7</sup>
- A review by the Centre for Evidence-Based Medicine (CEBM) on NSAIDs in acute respiratory infection assessed a range of adverse outcomes of NSAID use. It concluded that NSAIDs do not significantly reduce total symptoms or duration of respiratory infections. Gastrointestinal and renal safety concerns with all NSAIDs are well-recognised. Further, evidence confirmed an increased risk of cardiovascular events with many NSAIDs, including high-dose ibuprofen

(2,400 mg daily or more). Authors emphasised there is a need for caution when using NSAIDs in the context of acute respiratory infections, and parenteral use of NSAIDs during an acute respiratory infection should be avoided;<sup>8</sup>

- A systematic review found no published evidence to promote or discourage the use of NSAIDs in COVID-19 patients. This review concluded that the existing literature does not currently provide conclusive evidence for or against the use of NSAIDs in the treatment of COVID-19 patients, and caution should be exercised until further evidence emerges;<sup>9</sup>
- A narrative review focused on the safety of ibuprofen and concluded that it has a favorable safety profile compared with other NSAIDs. Gastrointestinal and cardiovascular adverse events are most commonly reported, but their incidence is relatively infrequent. The association of ibuprofen with infections is more complex:
  - Despite some non-controlled evidence showing a higher incidence of streptococcal toxic shock syndrome in patients using NSAIDs, overall, ibuprofen and paracetamol have similar safety profiles when used to treat symptoms of colds and flu;
  - The role of ibuprofen in alleviating symptoms from a variety of infections is currently being studied. It appears to confer benefits in some infections but may be detrimental in other cases. However, the role of ibuprofen as a contributory factor to making patients more susceptible to infections has not been demonstrated;<sup>10</sup>
- A literature review on use of antipyretic drugs in patients with fever and infection reported conflicting results, with some reporting improved patient outcomes and others reporting an increased mortality risk. It concluded that current evidence does not support routine antipyretic administration. Considering patients' comorbidities and symptoms of their underlying illness will promote safe and appropriate administration of antipyretics.<sup>11</sup>

## Recommendations from professional bodies

A number of international professional bodies, acknowledging the lack of scientific evidence, have provided advice on the use of NSAIDs/ibuprofen for patients with COVID-19:

- WHO initially recommended to avoid ibuprofen as self-medication, unless it was prescribed by healthcare professionals. However, it has since retracted the initial recommendation, and issued the following statement: "WHO does not recommend against the use of ibuprofen". The recent systematic review did not result in any change in its recommendation.<sup>5</sup>
- Based on the recent NICE evidence review<sup>6</sup>, NHS England recommends that, when 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 an NSAID is needed, the lowest effective dose should be used for the shortest period required to control symptoms.
- National Institutes of Health (NIH, US) "COVID-19 Treatment Guidelines" recommend that:
  - There is no difference in the strategy of antipyretic use (e.g., with acetaminophen or NSAIDs) for patients with or without COVID-19;
  - Patients with COVID-19 who are taking NSAIDs for a co-morbid condition should continue therapy as previously directed by their physician. Stopping or switching NSAID treatment could have a negative impact on some people.<sup>7,12</sup>
- US FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms. The agency is investigating this issue further and will communicate publicly when more information is available.<sup>13</sup>
- Australian TGA states that, upon investigating the safety concerns, there is currently no published peer-reviewed scientific evidence to support a direct link between use of ibuprofen and more severe infection with COVID-19. TGA is monitoring the situation.<sup>14</sup>
- Health Canada stated that there is no scientific evidence that establishes a link between ibuprofen and the worsening of COVID-19 symptoms and recommended that, when choosing

a fever or pain relief medication for COVID-19, patients and healthcare professionals should consider all available treatment options, including acetaminophen and other NSAIDs.<sup>15</sup>

- Health Service Executive (Ireland) issued an advice about anti-inflammatory medication and COVID-19, suggesting patients should continue taking any existing medication, including NSAIDs such as ibuprofen, naproxen or diclofenac, unless advised not to by their healthcare professionals.<sup>16</sup>

## Conclusion

There is a lack of evidence evaluating the safety of ibuprofen when used for short-term management of symptoms of COVID-19 or long-term use for a co-morbid condition in people with confirmed or suspected COVID-19. Furthermore, evidence on the safety of ibuprofen in other acute viral respiratory infections is inconclusive. There is no evidence suggesting additional harms with ibuprofen compared to paracetamol when used to manage symptoms of upper respiratory infections.

## References

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