As most popular choice of drugs for

As mentioned previously, NSAIDs are currently the most popular choice of drugs for the management of acute as well as chronic pain and inflammation.

Considering the high incidence of NSAID use, both by prescription and over-the-counter, it is crucial to ensure their safety for patients. Prolonged COX inhibition resulting from chronic NSAID use has been shown to cause adverse gastrointestinal effects. Further, they have also led to serious cardiovascular concerns, not only in patients with pre-disposing pathological conditions but even in healthy people. This cardiovascular risk has been associated mainly with thromboembolic effects such as myocardial infarction and stroke (Joshi et al.,...). Efforts to explore the molecular mechanisms underlying these adverse effects have brought to light several off-target actions of NSAIDs.

They have been shown to modulate the activity of numerous targets other than COX. Noteworthy are the effects of NSAIDs on various ion channels. Normal functioning of ion channels is crucial for a plethora of activities in the body, from the generation of nerve impulses to maintenance of homeostasis in various organ systems. In the cardiovascular system, ion channels are particularly important for the generation of action potential. The effects of different non-selective and selective NSAIDs on ion channels discussed above, shed light on the possibility of these drugs to have both beneficial and toxic implications that may not necessarily be related to standard NSAIDs properties. For instance, the inhibition of L-type calcium channels is instrumental in causing peripheral analgesia.

However, blocking the calcium influx in cells can potentially lead to cell death. Further, chronic suppression of sodium and calcium channels has been associated with cardiac arrhythmogenesis or neurological channelopathies. Different NSAIDs modulate the ion channel activities via various mechanisms. In some cases, these mechanisms may coincide with COX inhibition.

For example, ion channels such as Kv1. 3, ASICs, and calcium channels are modulated by PGE2, but, they are also sensitive to blockade by direct binding of the drugs. Most of these effects are independent of COX inhibition and may include direct drug binding to block the channels, gating modifications or allosteric modulations. Some effects may be indirect via generation of second messengers. The effects of these drugs on cardiac ion channels shed light on the potential of arrhythmias as an underlying cause of the several sudden cardiac deaths associated with these drugs.

While most of the studies evaluating the effects on ion channels are on other animal and cell models, any speculation that these results may be extrapolated to humans would be premature. However, these do provide a good impetus to explore these drugs in humans from the point of view of arrhythmogenesis. As more and more information on the underlying mechanisms of these drugs becomes available, it will facilitate further progress in exploring other potential targets for these drugs.

Moreover, on a separate yet relevant note, The FDA has blocked the use of any drugs from coming into the market that inhibit the hERG channel due to the correlation between the hERG channels and arrhythmias. However, the

effects of some of the NSAIDs on the hERG channel and their arrhythmogenic potential suggest that that drugs that block the hERG channel may not always lead to cardiac arrhythmias. Evidently, drugs that do cause arrhythmias may not necessarily have any effect on the hERG channels.

These observations raise the question- “ Are the FDA regulations concerning hERG channels preventing some potentially beneficial drug molecules from being introduced for the benefit of patients?” It is essential to revisit some of the guidelines stated by FDA since these may be hindering the introduction of some potentially useful drugs from coming into the market owing to their effects on the hERG channels. Thus, knowledge of the effects of NSAIDs on ion channels is crucial in guiding future efforts for development of analgesics and anti-inflammatories. More research is essential to elucidate the exact underlying mechanisms in humans/ the extrapolation of these effects in other model systems to humans and discovering other molecular targets for analgesic medications.