

Editorial

NSAID hypersensitivity—the unwitting accomplice in the growing opiate epidemic

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Penicillin allergy is recognized as an important public health concern, and justifiably so. In most cases, the penicillin allergy label is no longer relevant, yet is associated with higher hospital costs and increase morbidity—a significant problem when extrapolated to a global population. Thus, this issue has garnered national attention in the Allergy/Immunology community, the primary care community, and even the lay public. Antibiotic allergies might be the most common listed allergy, but nonsteroidal anti-inflammatory drug (NSAID) allergy ranks *second* in probability of presence in the medical record.¹

In this issue of the *Journal of Allergy and Clinical Immunology*, Li et al² demonstrate that the NSAID allergy label also has potentially serious complications by creating a situation necessitating the use of opiates for pain relief.² The Centers for Disease Control and Prevention estimates that approximately 1000 emergency room visits a day in the United States are related to the misuse of opiates,³ with approximately 91 daily deaths from opiate overdose.⁴ In the United States, this issue has stirred the national conscience in the form of lawsuits directed at pharmaceutical companies who encouraged overuse of opiates. Strict oversight of any narcotic prescription is now commonplace, and required training for any physician who prescribes narcotics highlights the dangers of inappropriate opiate prescribing practices.

Although opiate addiction may disproportionately affect Americans when compared with other countries, this is an epidemic highlighted by the World Health Organization as well. Worldwide, 35.6 million people were estimated to suffer from a drug use disorder in 2018. Although most opiate use disorders stem from illicit sources, the contribution from prescription sources is rising. This highlights the dilemma for physicians who are tasked to ease suffering but do no harm—a challenge when opiate abuse can follow from the overuse of a legitimate medical prescription. Unfortunately, in patients who are opiate naive, up to 6% might become new chronic users.⁵ Even tramadol, long considered unlikely to cause opiate use disorder, has also been shown to be associated with addictive potential.⁶

Few physicians outside of the allergy specialty are familiar with the multiple ways in which an NSAID could lead to hypersensitivity. Most reactions can be categorized into either a specific NSAID hypersensitivity (likely structural and IgE mediated) or a pharmacologic reaction (cyclooxygenase [COX]-1 mediated), which is more frequently seen. Although some patients with a recognized need for an NSAID or aspirin are referred to an allergist for evaluation, in the vast majority, the presence of an NSAID allergy label is not identified as a “medical problem.” Even in a population of 142 patients with documented coronary disease and an aspirin allergy, only 4 were referred to an allergist for evaluation.⁷ Thus, referring physicians are likely unaware of the role of the allergist in this scenario and should be educated regarding our important role in this setting.

The inattention to NSAID allergy is probably compounded by a few issues. First, most physicians recognize that NSAIDs frequently cause bleeding and gastrointestinal upset as side effects—an adverse reaction that may warrant being listed on the “allergy” profile but would not warrant an evaluation by an allergist. Second, there are no *in vitro* or skin tests available to risk stratify an NSAID-hypersensitive patient. Third, there is no standardized approach similar to penicillin allergy where patients can be quickly delabeled. These factors probably lead to ambivalence in the medical community to directly address NSAID allergy.

Perhaps the finding that higher opiate use disorder is occurring in patients labeled with NSAID hypersensitivity should change this perspective! What if all patients with an NSAID allergy label and for whom a narcotic was necessary for pain relief were referred to an allergist to verify whether this was warranted? It would not be surprising that this might have an effect on the larger opiate epidemic.

Although an algorithm to work up every patient with NSAID hypersensitivity does not yet exist, some simple approaches can be considered (suggested in Fig 1). All patients should be offered a COX-2 inhibitor challenge (celecoxib in the United States, etoricoxib and celecoxib in Europe) as a first step. This immediately allows the option for a nonnarcotic for pain relief and is expected to be tolerated in nearly all NSAID-hypersensitive patients. It is unfortunate that in the United States, many times this prescription will be denied by insurance, requiring the allergist/immunologist to spend additional effort justifying medical necessity.

In the second phase, a more refined diagnostic procedure aiming at possibly widening the spectrum of tolerated NSAIDs, including COX-1 inhibitors, could be scheduled.^{8,9} Initially, a different approach should be adopted in patients with aspirin-exacerbated respiratory disease (NSAID-exacerbated respiratory disease) or cutaneous disorders. In fact, if an asthmatic patient experiences an NSAID-induced exacerbation, it is nearly certain that they are a multiple NSAID reactor, and all COX-1 inhibitors will be expected to induce respiratory reactions to some extent. These patients will have to take acetaminophen (paracetamol), other selective COX-2 inhibitors, or an opioid when indicated,

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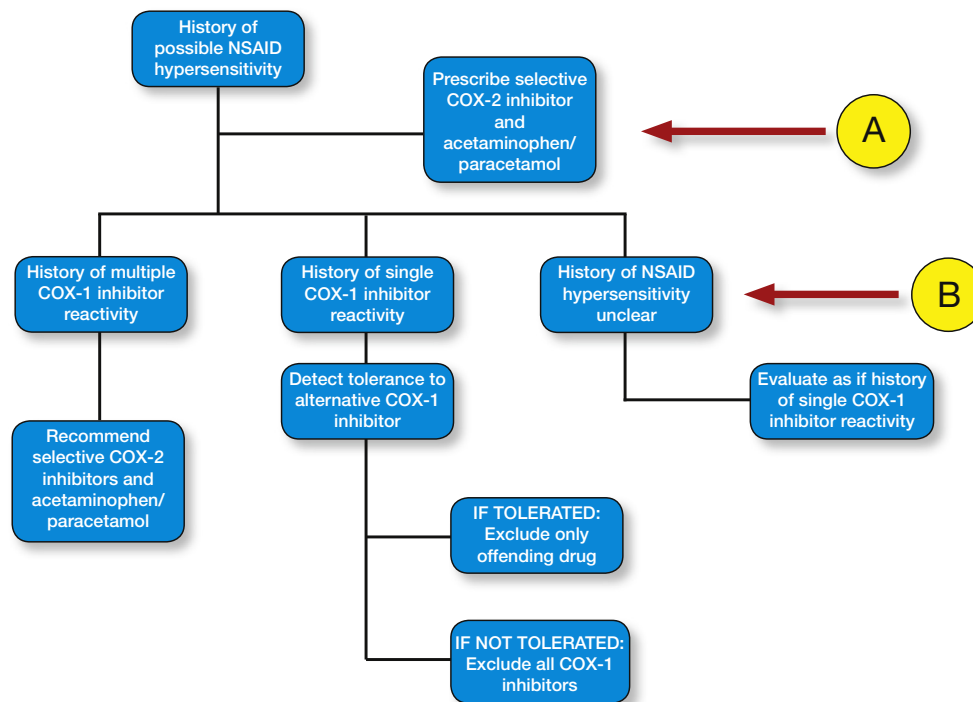


FIG 1. A simplified algorithm to manage patients with a history of possible NSAID hypersensitivity. **A**, Initial management used by any physician. **B**, Subsequent evaluation to be performed by the Allergist/Immunologist.

maybe following a proper allergy workup including oral challenges/tolerance tests. In contrast, the otherwise normal patient presenting with a history of urticaria following the ingestion of a single NSAID should undergo a more complex workup including challenges with alternative COX-1 inhibitors first and, if positive, alternative drugs (ie, selective COX-2 inhibitors) subsequently. In many situations, the patient has completely avoided all NSAIDs. Many times, the reaction is years or decades prior and details have become muddled. In this situation, it is not unusual to see a completely negative challenge. Resolution over time has been reported and is yet another reason to pursue direct challenges, although would not be expected in aspirin-exacerbated respiratory disease or potential IgE-mediated reactions that are unlikely to resolve.¹⁰

The findings by Li et al point out that 39% of those reporting NSAID-induced adverse drug reactions actually had reactions consistent with hypersensitivity reactions and only 38% had ever consulted with an allergist for any reason. It is likely that on many of these visits the NSAID allergy was not addressed. This impression seems to be confirmed by the fact that the “NSAID-allergic” patients did not show an increased rate of COX-2 inhibitor prescriptions compared with controls, which would be expected if they had undergone a proper allergy assessment including challenges with alternative drugs. Offering this simple intervention should not be considered trivial. The allergist should address the likely pattern of reactivity, and if a diagnostic challenge is not performed at the initial consultation, a plan should be clearly outlined in the consultation so that if a more acute need presents itself, referring physicians will understand the potential of using an NSAID in the future.

Given the findings of this study, we suggest an urgency in the Allergy/Immunology community needs to exist when a patient with an NSAID allergy label is seen in the clinic. This should be identified as a high-priority item even if the patient is referred for allergic rhinitis. Allergists should consistently message to their peers that NSAID allergy is a *medical problem* that should be routinely referred to the allergist.

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