

Opioid Intolerance Decision Algorithm

—For help with dose conversion, please see our Detail-Document #200915, “Equianalgesic Dosing of Opioids for Pain Management.”—

When patients say they’re allergic to an opioid, are all opioid analgesics off limits? The key is getting a detailed description of the reaction. Answer the questions below and follow the instructions to find the best options for your patient.

- Check the symptoms the patient describes, and follow the instructions in the far right column.

Flushing, itching, hives, sweating, and/or mild hypotension only		Go to A
Itching, flushing, or hives at injection or application site only		Go to A
Severe hypotension		Go to B
Skin reaction other than itching, flushing, or hives (e.g., rash)		Go to B
Breathing, speaking, or swallowing difficulties		Go to B
Swelling of face, lips, mouth, tongue, pharynx, or larynx		Go to B

A. These symptoms **may** be due to a *pseudoallergy*. It’s a result of histamine release, a pharmacologic side effect of some opioids. Options for this patient include:

1. A nonopioid analgesic (e.g., acetaminophen, an NSAID)
2. Avoidance of codeine, morphine, and meperidine, the opioids most commonly associated with pseudoallergy
3. Use of a more potent opioid less likely to release histamine. Potency, from lower to higher:

meperidine<codeine<morphine<hydrocodone<oxycodone<hydromorphone<levorphanol<fentanyl

4. If needed, concurrent administration of an antihistamine...an H1 (e.g., diphenhydramine) and perhaps an H2 blocker (e.g., cimetidine)
5. Dose reduction, if tolerated

B. This patient **may** have experienced a true allergy. Options for this patient include:

1. A nonopioid analgesic (e.g., acetaminophen, an NSAID)
2. An opioid in a chemical class *different* from the one to which the patient reacted, with close monitoring:

Phenylpiperidines: meperidine (*Demerol*), fentanyl (*Duragesic, Actiq, Sublimaze*), sufentanil (*Sufenta*), remifentanyl (*Ultiva*)

Diphenylheptanes: methadone (*Dolophine*), propoxyphene (*Darvon*)

Morphine group: morphine, codeine, hydrocodone (*Vicodin, Lorcet*), oxycodone (*Percocet, OxyContin*), oxymorphone (*Numorphan*), hydromorphone (*Dilaudid*), nalbuphine (*Nubain*), butorphanol (*Stadol*), levorphanol (*Levo-Dromoran*), pentazocine (*Talwin*)

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Analgesic Options for Patients with Allergic-Type Opioid Reactions

Background

Opioid allergy is a common patient complaint. But true allergy is rare.¹ Upon questioning, it often becomes clear the “allergy” is only a side effect, such as stomach upset. But when the symptoms are those associated with allergic-type reactions (e.g., hives), there’s a need to determine which, if any, opioid is safe. To choose a safe alternative, a thorough description of the reaction and an understanding of opioid reactions are needed.

Types of Reactions to Narcotics

Most allergic-type reactions to opioids involve codeine, morphine, or meperidine.¹ A common type of reaction to these opioids is pseudoallergy. Symptoms can resemble a true allergy, but are caused by histamine release from cutaneous mast cells, a nonimmunologic effect.² Symptoms of pseudoallergy include itching, flushing, and sweating.³ Hives, increased heart rate, and low blood pressure can be due to pseudoallergy,¹ but are also seen with true allergy.^{4,5}

Unlike true allergy, prior exposure to the opioid or related opioid is not necessary.

In vitro and clinical data suggest risk of pseudoallergy depends on the concentration of the opioid at the mast cell.^{2,4} This is dependent on opioid potency, dose, and route of administration.

True allergy to opioids seems to be IgE-mediated or T-cell mediated.⁵⁻⁷ Allergic skin reactions to opioids include hives, maculopapular rash, erythema multiforme,⁸ and pustular rash.⁹ Bronchospasm is thought to represent true allergy only.¹⁰ Reports suggest angioedema is usually a manifestation of true allergy, but pseudoallergy is also possible.^{7,11,13}

Narcotic Cross-reactivity

There are three main opioid structural classes. One structurally similar group is comprised of morphine, codeine, hydrocodone, oxycodone,

oxymorphone, hydromorphone, nalbuphine, butorphanol, levorphanol, and pentazocine.¹²

Methadone and propoxyphene are in the diphenylheptane class.⁴ And meperidine and fentanyl are phenylpiperidines.

Patients allergic to one opioid are thought to be less likely to react to an opioid in a different structural class.⁴ But because true allergy is rare, there’s not enough information to assess the chance of cross-reactivity.^{10,13}

It’s important to note there is evidence patients can be allergic to more than one narcotic class. For example, IgE antibodies isolated from a patient allergic to morphine were able to bind to fentanyl.¹⁴ Morphine antibodies have also shown some reactivity with methadone and meperidine.

Diagnosis of Opioid Allergy

It’s important to take steps to avoid labeling nonallergic patients allergic.¹ If the nature and cause of the reaction are not clarified, opioids may be withheld unnecessarily. Even if the reaction is found to be opioid-related, information from the history can be used to choose a safer opioid.⁴ For example, history of tolerability of other opioids can be a clue to the mechanism of the reaction, and guide narcotic choice.

Patients should be asked about symptoms, and foods and other medications ingested several hours before the reaction.¹⁵ Also inquire about preceding activities, and the possibility of bites or stings. Medical records pertaining to the reaction, if available, should be reviewed. Alternate diagnoses (e.g., hereditary angioedema, scombroid fish poisoning, carcinoid syndrome) should be considered.

Elevated total IgE levels during the acute reaction suggest true allergy.⁴ But IgE could be elevated for reasons unrelated to drug allergy.¹⁶ Tests for IgE to specific opioids have been developed,¹⁰ but are not readily available.

Skin testing has been suggested before using a structurally unrelated opioid in a patient with a

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serious opioid reaction.⁴ But false-positive results due to pharmacologic histamine release have been documented with codeine, morphine, and meperidine.¹⁷ Patch testing may produce false-negative results.⁷

History is the most important diagnostic tool.¹⁵ Patients requiring a detailed workup should be referred to an allergist or immunologist.

Choosing an Analgesic

When choosing an analgesic for a patient with a history of an allergic-type opioid reaction, the benefits of an opioid must be weighed against the risk of a serious reaction.

If the reaction is **only** flushing, itching, sweating, hives, and/or mild hypotension, the opioid can usually be continued with an antihistamine or dose reduction [Evidence level C; expert opinion].^{3,4,18}

Because pseudoallergic reactions appear to be a function of opioid dose and potency, consider use of a higher potency opioid [Evidence level C; expert opinion]. Start with a low dose [Evidence level C; expert opinion].¹⁸ If possible, avoid parenteral administration, or slow the administration rate [Evidence level C; expert opinion].²

Some patients have a reaction under the fentanyl patch. For these patients, spraying triamcinolone nasal spray (*Nasacort*) to the area before patch application may be helpful [Evidence level C; expert opinion].¹⁹

It's prudent to assume other reactions (e.g., rash, severe hypotension, bronchospasm, angioedema) have an allergic mechanism. If an opioid is necessary, choose one in a different structural class if possible, and monitor the patient closely [Evidence level C; expert opinion].^{1,4}

When choosing an alternative opioid, consider the risks, benefits, and practicality of the drug. For example, the fentanyl patch (*Duragesic*) is best reserved for chronic pain due to its slow onset of action.²⁰ *Duragesic* and the fentanyl lozenge (*Actiq*) are for patients who've been taking, at minimum, morphine 60 mg daily or equivalent for a week.^{21,22} Both methadone (*Dolophine*) and levorphanol (*Levo-Dromoran*) must be dosed cautiously. Their long half-lives can cause drug accumulation and CNS and respiratory depression with repeated dosing. And remember that meperidine should be limited to short-term use because of its neurotoxic side

effects.²⁰ Tramadol (*Ultram*) is not an option for patients allergic to any opioid; it's contraindicated, according to the prescribing information.²³ Propoxyphene and codeine are not recommended due to poor efficacy.²⁴ Pentazocine (*Talwin*) should be avoided due to psychiatric side effects (e.g., dysphoria).^{19,24,25} Patients with mild to moderate pain may be best served by acetaminophen or an NSAID.^{4,24}

Conclusions

Most patients who say they're allergic to an opioid have only experienced a side effect. For patients with a history of allergic-type reaction, options include a nonopioid or a carefully chosen opioid. Potential risks and benefits must be considered.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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