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Opioid Allergy

Opioid allergy is a common patient complaint. But less than 2% of opioid reactions are true allergies.[21] 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 safer alternative, a thorough description of the reaction and an understanding of opioid reactions are needed. Answer the questions below and follow the instructions to find the best options for your patient. For more details about opioid intolerance, see the FAQ chart below. For information on switching opioids, see our chart, *Equianalgesic Dosing of Opioids for Pain Management*.

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* (a result of direct histamine release caused by some opioids; not immune mediated; **see chart**, below for more information). Options for this patient include:

1. A non-opioid analgesic (e.g., acetaminophen, an NSAID).[3]
2. Avoidance of codeine, morphine, and meperidine, the opioids most commonly associated with pseudoallergy.[1]
3. Use of a more potent opioid less likely to release histamine.[28] Potency, from lower to higher:[29-31]

meperidine<codeine<morphine<hydrocodone<oxycodone<oxymorphone<hydromorphone<levorphanol<fentanyl (note that fentanyl and related opioids commonly cause itching with spinal administration, which can be managed with antihistamines plus low-dose naloxone or nalbuphine[3]).

4. Consider tramadol, which does not appear to cause histamine release.[28]
5. If needed, concurrent administration of an antihistamine (H1-blocker and an H2-blocker [e.g., cimetidine]).[3,21,28]
6. Dose reduction, if tolerated. Reduce infusion rate, if applicable.

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

1. A non-opioid analgesic (e.g., acetaminophen, an NSAID).[3]
2. An opioid in a chemical class **different** (see chart below) from the one to which the patient reacted, with close monitoring.[4]

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Clinical Question	Pertinent Information
What is a pseudoallergy?	• Pseudoallergy is a side effect of opioids that can resemble a true allergy, but it is usually caused by histamine release from cutaneous mast cells, **a nonimmunologic effect**.[2] Common culprits are codeine, morphine, and meperidine.[1] Itching due to spinally administered fentanyl and sufentanil is also a pseudoallergy, but it is thought not to be histamine-related.[3] **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] *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 (e.g., rapid intravenous administration).[3,28]
How do you handle pseudoallergy?	• 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].[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]. Start with a low dose [Evidence level C].[18] If possible, avoid parenteral administration, or slow the administration rate (e.g., administer intravenous morphine over four or five minutes[25])[Evidence level C].[2] Tramadol is another option; it does not appear to cause histamine release.[28] • 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].[19] • Treat life-threatening reactions as you would for any anaphylactoid reaction (e.g., epinephrine, corticosteroids, antihistamines).[3]
What symptoms suggest true opioid allergy?	• **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] • It's prudent to assume reactions such as rash, severe hypotension, bronchospasm, or 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].[1,4]
What are some points to consider when evaluating potential opioid allergy? *Continued…*	• It is important to take steps to avoid labeling nonallergic patients as allergic.[1] If the nature and cause of the reaction are not clarified, opioids may be withheld unnecessarily. • **Patient history** is the most important diagnostic tool.[15] Information from the history can be used to choose a safer opioid.[4] Ask about tolerability of other opioids, specific symptoms, and symptom severity. This information can provide clues to the mechanism of the reaction and guide analgesic 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.[15] Medical records pertaining to the

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Clinical Question	Pertinent Information
Points to consider when evaluating potential opioid allergy, continued	reaction, if available, should be reviewed.[15] Alternate diagnoses (e.g., hereditary angioedema, scombroid fish poisoning, carcinoid syndrome) should be considered.[15] • 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.[28] • Skin testing has been suggested before using a structurally unrelated opioid in a patient with a serious opioid reaction.[4] But false-positive results due to pharmacologic histamine release have been documented with codeine, morphine, and meperidine.[17,28] Patch testing may produce false-negative results.[7] • Patients requiring a detailed workup for diagnosis of opioid allergy should be referred to an allergist or immunologist.[15]
How do you choose an opioid in a patient suspected of true opioid allergy?	• Patients allergic to one opioid are thought to be less likely to react to an opioid in a different structural class (see below).[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.[14] • **When choosing an alternative opioid**, consider the risks, benefits, and practicality of the drug. For example, the **fentanyl** patch is only for chronic, stable pain in opioid-tolerant patients.[20] In fact, product labeling for all non-injectable fentanyl products specifies their use for opioid-tolerant patients only (i.e., taking 60 mg or more oral morphine [or its equivalent] daily for at least a week). Both **methadone** and **levorphanol** (U.S.) must be dosed cautiously.[22,23] Their long half-lives can cause drug accumulation and CNS and respiratory depression with repeated dosing.[22,23] And **meperidine** is not routinely recommended because of its neurotoxic metabolite.[20] **Codeine** is also a poor choice due to unpredictable efficacy and toxicity due to interindividual differences in metabolism.[24] The analgesic efficacy of **pentazocine**, **nalbuphine**, **butorphanol**, and **buprenorphine** is limited by a dose ceiling.[26] They can also cause dysphoria, psychomimetic effects, and feedback inhibition of the endorphin system, leading to dysesthesia.[26,27] These drugs may cause withdrawal in opioid-tolerant patients.[28] **Buprenorphine** also has a limited role in pain management. • Note that for several opioids, product labeling contraindicates their use in patients hypersensitive to any opioid.
Which opioids are in which classes?	**Morphine group**: morphine, codeine, hydrocodone, oxycodone (e.g., *OxyContin*), oxymorphone (U.S.), hydromorphone (e.g., *Dilaudid*), nalbuphine (*Nubain* [Canada]), butorphanol, levorphanol (U.S.), pentazocine (*Talwin*),[12] buprenorphine[21] **Phenylpiperidines**: meperidine (*Demerol*), fentanyl, sufentanil, remifentanil[4,21] **Phenylpropyl amines**: tramadol, tapentadol[21] **Diphenylheptanes**: methadone[4]

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Users of this resource 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 our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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