Opioid Allergy

Opioid allergy is a common patient complaint. But less than 2% of opioid reactions are true allergies.[1,2] Upon questioning, it often becomes clear the "allergy" is only a side effect, such as stomach upset. But when patients have symptoms that are associated with allergic-type reactions (e.g., hives), it may be more difficult to distinguish between a true allergy and a side effect, which is necessary to determine which, if any, opioid is safe for the patient to take.[3] 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).[4] Options for this patient include:

1. A non-opioid analgesic (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]).[5]
2. Avoidance of codeine, morphine, and meperidine (the opioids most commonly associated with pseudoallergy).[6]
3. Use of a more potent opioid less likely to release histamine.[7] Potency, from lower to higher:[8] 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.)[5]
4. Consider tramadol, which does not appear to cause histamine release.[7]
5. If needed, concurrent administration of an antihistamine (H1-blocker [e.g., cetirizine] and/or an H2-blocker [e.g., famotidine]).[1,5,7,9]
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, NSAIDs).[5]
2. An opioid in a chemical class **different** (see chart below) from the one to which the patient reacted, with close monitoring.[10,11]

--Continue to the next section for an FAQ about Opioid Allergies--

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**.[6] o Common culprits are codeine, morphine, and meperidine.[6] Itching due to spinally administered fentanyl and sufentanil is also a pseudoallergy, but it is thought not to be histamine related.[5] o **Symptoms of pseudoallergy include** itching, flushing, and sweating.[5] Hives, increased heart rate, and low blood pressure can be due to pseudoallergy,[2] but are also seen with true allergy.[13] o In vitro and clinical data suggest risk of pseudoallergy depends on the concentration of the opioid at the mast cell.[6] This is dependent on opioid potency, dose, and route of administration (e.g., higher risk with a rapid intravenous administration).[5,7] o Prior exposure to the specific opioid or a related opioid is not necessary for a patient to experience a pseudoallergic response.
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].[5,13,14] • 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].[14] If possible, avoid parenteral administration, or slow the administration rate (e.g., administer intravenous morphine over four or five minutes[15]) [Evidence level C].[16] Tramadol is another option; it does not appear to cause histamine release.[7] • Some patients have a reaction on the skin under the fentanyl patch. For these patients, spraying triamcinolone nasal spray (*Nasacort*) to the area before patch application may be helpful [Evidence level C].[17] • Treat life-threatening reactions as you would any anaphylactoid reaction (e.g., epinephrine, corticosteroids).[4]
What symptoms suggest true opioid allergy?	• **True allergy** to opioids seems to be IgE-mediated or T-cell mediated.[18,19] Allergic skin reactions to opioids include hives, maculopapular rash, erythema multiforme, and pustular rash.[20,21] Bronchospasm is thought to represent true allergy only.[22] Angioedema and/or hypotension are significantly more likely to suggest a true allergy, but pseudoallergy is also possible.[2,19,23,24] • 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].[12,13]
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.[12] If the nature and cause of the reaction are not clarified, opioids may be withheld unnecessarily. • **Patient history** is the most important diagnostic tool.[25] Information from the history can be used to choose a safer opioid.[13] Ask about (and record) tolerability of other opioids, specific symptoms, and symptom severity. This information can provide clues to the mechanism of the reaction and guide analgesic choice.

Clinical Question	Pertinent Information
Points to consider when evaluating potential opioid allergy, continued	• Patients should be asked about symptoms, and foods and other medications ingested several hours before the reaction.[25] Also inquire about preceding activities, and the possibility of bites or stings.[25] Medical records pertaining to the reaction, if available, should be reviewed.[25] Alternate diagnoses (e.g., hereditary angioedema, scombroid fish poisoning, carcinoid syndrome) should be considered.[25] • Elevated total IgE levels during the acute reaction suggest true allergy.[13] But IgE could be elevated for reasons unrelated to drug allergy.[26] Some opioid-specific IgE tests (e.g., morphine) have been developed; however, they are not always readily available.[2,7] • Skin testing has been suggested before using a structurally unrelated opioid in a patient with a serious opioid reaction.[13] However, results are questionable (i.e., false positives) because most opioids release histamine.[2,7] Specific IgE testing and skin prick testing may add information for diagnosis of an allergy but are not conclusive on their own.[2] • Patients requiring a detailed workup for diagnosis of opioid allergy should be referred to an allergist or immunologist.[25] Workup may include a drug provocation test with the index opioid, which should be performed and interpreted by an experienced clinician.[2]
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).[13] But because true allergy is rare, there's not enough information to assess the chance of cross-reactivity.[22,24] • 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.[27] Morphine antibodies have also shown some reactivity with methadone and meperidine.[27] • **When choosing an alternative opioid**, consider the risks, benefits, and practicality of the drug. For example: o The **fentanyl** patch is only for chronic, stable pain in opioid-tolerant patients.[28] o All non-injectable **fentanyl** products should be used only in opioid-tolerant patients (i.e., taking ≥60 MME/day for at least a week).[28,29] o Both **methadone** and **levorphanol** (US) must be dosed cautiously.[30,31] Their long half-lives can cause drug accumulation and CNS and respiratory depression with repeated dosing.[30,31] o **Meperidine** is NOT routinely recommended for pain management because of its neurotoxic metabolite.[28] o **Codeine** is usually avoided due to its unpredictable efficacy and toxicity due to interindividual differences in metabolism.[32] o The analgesic efficacy of **pentazocine**, **nalbuphine**, **butorphanol**, and **buprenorphine** is limited by a dose ceiling.[33] They can also cause dysphoria, psychomimetic effects, and feedback inhibition of the endorphin system, leading to dysesthesia.[33,34] These drugs may cause withdrawal in opioid-tolerant patients.[7] o **Buprenorphine** also has a limited role in pain management. o Note that for several opioids, product labeling contraindicates their use in patients hypersensitive to any opioid.[15]

Clinical Question	Pertinent Information
Which opioids are in which classes?	• **Morphine group (phenanthrenes)**:[35] buprenorphine, butorphanol, codeine, hydrocodone, hydromorphone, levorphanol (US), morphine, oxycodone, oxymorphone (US), nalbuphine, pentazocine. • **Phenylpiperidines**:[35] alfentanil, fentanyl, meperidine, remifentanil, sufentanil. • **Phenylpropyl amines**:[35] tapentadol, tramadol. • **Diphenylheptanes**:[35] methadone.

Abbreviations: CNS = central nervous system, MME = morphine milligram equivalent.

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 randomized controlled trial (RCT) 2. Systematic review (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).

[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.
https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

References

1. Wang K, Raouf M. Opioid allergy, pseudo-allergy, or adverse effect? March 6, 2018. https://www.pharmacytimes.com/contributor/jeffrey-fudin/2018/03/opioid-allergy-pseudo-allergy-or-adverse-effect. (Accessed November 19, 2022).
2. Li PH, Ue KL, Wagner A, et al. Opioid Hypersensitivity: Predictors of Allergy and Role of Drug Provocation Testing. J Allergy Clin Immunol Pract. 2017 Nov-Dec;5(6):1601-1606.
3. Powell MZ, Mueller SW, Reynolds PM. Assessment of Opioid Cross-reactivity and Provider Perceptions in Hospitalized Patients With Reported Opioid Allergies. Ann Pharmacother. 2019 Nov;53(11):1117-1123.
4. Miller B, Vahle R, Ferguson MC. What is a true opioid allergy? Pract Pain Manag. 2021;21(1).
5. Shepherd G, Guyton J. Drug hypersensitivity reactions. In: Zeind CS, Carvalho MG, editors. Applied Therapeutics: the Clinical Use of Drugs. 11th ed. Philadelphia, PA: Wolters Kluwer Health, 2018: pp. 679-99.
6. Zhang B, Li Q, Shi C, Zhang X. Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms. Pharmacology. 2018;101(1-2):104-110.
7. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. Anaesth Intensive Care. 2012 Mar;40(2):216-35.
8. Utah Medicaid. Opioid oral morphine milligram equivalent (MME) conversion factors. https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf. (Accessed November 22, 2022).
9. American Academy of Allergy, Asthma & Immunology. Recommendations for pain control in a patient with history of severe opiate intolerance. November 28, 2018. https://www.aaaai.org/allergist-resources/ask-the-expert/answers/old-ask-the-experts/pain. (Accessed November 22, 2022).
10. Kalangara J, Potru S, Kuruvilla M. Clinical Manifestations and Diagnostic Evaluation of Opioid Allergy Labels - A Review. J Pain Palliat Care Pharmacother. 2019 Sep-Dec;33(3-4):131-140.
11. Our Lady's Hospice & Care Services. Question: a patient presents with an allergy to an opioid, can an alternative be prescribed? February 2017. https://olh.ie/wp-content/uploads/2019/01/A-patient-presents-with-an-allergy-to-an-opioid-can-an-alternative-opioid-be-prescribed-1.pdf. (Accessed November 22, 2022).
12. Gilbar PJ, Ridge AM. Inappropriate labeling of patients as opioid allergic. J Oncol Pharm Practice. 2004;10:177-82.
13. Crabe Erush S. Narcotic allergy. P&T. 1996;21:250-2, 292.
14. Nutescu E, Hunt C, Teeters J. Multidisciplinary approach to improving allergy documentation. Am J Health Syst Pharm. 1998 Feb 15;55(4):364-8.
15. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2022. http://www.clinicalkey.com. (Accessed November 19, 2022).
16. VanArsdel PP. Pseudoallergic drug reactions. Introduction and general review. Immunol Allergy Clin North Am. 1991;11:635-44.
17. Otis JA, Fudin J. Use of long-acting opioids for the management of chronic pain. U.S. Pharmacist. 2005;30(3 Suppl):1-14.
18. Estrada JL, Puebla MJ, de Urbina JJ, et al. Generalized eczema due to codeine. Contact Dermatitis. 2001 Mar;44(3):185.
19. Möhrenschlager M, Glöckner A, Jessberger B, et al. Codeine caused pruritic scarlatiniform exanthemata: patch test negative but positive to oral provocation test. Br J Dermatol. 2000 Sep;143(3):663-4.
20. Machet L, Martin L, Machet MC, et al. Acute generalized exanthematous pustulosis induced by dextropropoxyphene and confirmed by patch testing. Acta Derm Venereol. 2000 May;80(3):224-5.
21. Cooper SM, Shaw S. Dihydrocodeine: a drug allergy diagnosed by patch testing. Contact Dermatitis. 2000 May;42(5):307-8.
22. Fisher MM, Harle DG, Baldo BA. Anaphylactoid reactions to narcotic analgesics. Clin Rev Allergy. 1991 Fall-Winter;9(3-4):309-18.

23. Vidal C, Pérez-Leiros P, Bugarín R, Armisén M. Fever and urticaria to codeine. Allergy. 2000 Apr;55(4):416-7.
24. Anibarro B, Vila C, Seoane FJ. Urticaria induced by meperidine allergy. Allergy. 2000 Mar;55(3):305-6.
25. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis--a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015 Nov;115(5):341-84.
26. Emanuel IA. In vitro testing for allergy diagnosis. Otolaryngol Clin North Am. 2003 Oct;36(5):879-93.
27. Baldo BA, Pham NH, Zhao Z. Chemistry of drug allergenicity. Curr Opin Allergy Clin Immunol. 2001 Aug;1(4):327-35.
28. Kral LA, Ghafoor VL. Pain and its management. In: Zeind CS, Carvalho MG, editors. Applied Therapeutics: the Clinical Use of Drugs. 11th ed. Philadelphia, PA: Wolters Kluwer Health, 2018: pp. 1170-1204.
29. CDC. Calculating total daily dose of opioids for safer dosage. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf. (Accessed November 22, 2022).
30. Product information for levorphanol. Sentynl Therapeutics. Solana Beach, CA 92075. January 2021.
31. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014 Apr;15(4):321-37.
32. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014 Apr;95(4):376-82.
33. Helm S, Trescot AM, Colson J, et al. Opioid antagonists, partial agonists, and agonists/antagonists: the role of office-based detoxification. Pain Physician. 2008 Mar-Apr;11(2):225-35.
34. Terrie YC. An overview of opioids. Pharmacy Times. June 13, 2011. http://www.pharmacytimes.com/publications/issue/2011/june2011/an-overview-of-opioids. (Accessed November 19, 2022).
35. Schumacher M, Fukuda. Opioids. In: Gropper MA, ed. Miller's Anesthesiology, 9th ed. Elsevier. Philadelphia, PA. 2020.

Cite this document as follows: **Clinical Resource,** ***Opioid Allergy. Pharmacist's Letter/Prescriber's Letter.*** **December 2022. [3812xx]**