

Original Article

Opioid Hypersensitivity: Predictors of Allergy and Role of Drug Provocation Testing

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What is already known about this topic? IgE-mediated opioid hypersensitivity is rare; many reactions are due to direct mast cell degranulation. Opioid skin testing and sIgE are of limited use. Drug provocation testing (DPT) is an underutilized “gold standard” for diagnosis.

What does this article add to our knowledge? Opioid allergy is overdiagnosed. DPT confirms allergy only in a small minority. Angioedema or hypotension as an index reaction increases the likelihood of true opioid allergy. Most codeine/morphine allergic patients tolerate fentanyl, a synthetic opioid.

How does this study impact current management guidelines? Opioid DPT help avoid incorrect diagnosis/over-diagnosis. Angioedema or hypotension as an index reaction might predict the likelihood of true allergy. DPT are safe when performed by experienced clinicians after risk stratification and using individualized protocols.

BACKGROUND: True IgE-mediated hypersensitivity to opioids is rare and many reactions are due to direct mast cell degranulation. Opioid drug provocation testing (DPT) is the gold standard for diagnosis but is underutilized.

OBJECTIVE: The objective of this study was to evaluate the clinical characteristics and predictors of opioid hypersensitivity, as well as outcomes of opioid DPT.

METHODS: Patients referred for opioid DPT over the past 9 years were studied. Patient characteristics, indications for opioid use, symptoms of index reaction, and outcomes of DPT were analyzed. Association analysis was performed to study variables associated with a diagnosis of opioid hypersensitivity.

RESULTS: Of the total of 98 patients referred with suspected opioid hypersensitivity, 15 (15%) were diagnosed with opioid allergy. Angioedema (odds ratio [OR]: 5.66; 95% confidence interval [CI]: 1.49-21.47; $P = .011$) and hypotension (OR: 5.00;

95% CI: 1.15-21.70; $P = .032$) were significantly more frequent in opioid allergic patients than those with a negative DPT.

Patients who received opioids during anesthesia were significantly more likely to be opioid allergic (OR: 6.74; 95% CI: 2.05-22.13; $P = .001$). In contrast, a negative association was identified with patients who received opioids for analgesia (OR: 0.27; 95% CI: 0.08-0.86; $P = .008$).

CONCLUSIONS: Only 15% of our cohort were diagnosed with opioid allergy, emphasizing the importance of DPT in preventing erroneous overdiagnosis. Patients with a history of angioedema or hypotension as their index reaction were significantly more likely to be opioid allergic. DPT are safe when performed by experienced clinicians after risk stratification and using individualized protocols. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

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The term “opioids” refers to all natural, semisynthetic, and synthetic morphine-like drugs. Naturally occurring alkaloids or opiates, such as morphine and codeine, are found in the resin of the opium poppy (*Papaver somniferum*). Semisynthetic opioids, such as oxycodone and pholcodine, are derived from chemical modifications of natural opiates. Fully synthetic opioids, such as fentanyl and pethidine, are artificially synthesized from chemicals that are not derived from natural opiates.¹ Opioids are the most potent and commonly prescribed analgesics. The consumption of opioids has more than tripled over the past 20 years, and the demand for morphine-based opiates rose to 416 tons in morphine equivalent in 2014.¹ Despite this, true IgE-mediated immediate hypersensitivity reactions are rare. Some studies implicate opioids in around 2% of cases of perioperative

Abbreviations used

DPT- Drug provocation testing

sIgE- Specific IgE

SPT- Skin prick testing

ST- Skin test

anaphylaxis, but this is likely to be an overestimate due to the lack of validated testing methods.^{2,3} Most reactions to opioids are non-IgE-mediated due to direct mast cell degranulation and histamine release at clinically used doses.^{4,5} Worryingly many patients are mislabeled with opioid allergy even in the absence of diagnostic evidence or relevant allergy testing. This can not only lead to unnecessary drug avoidance, but other culprits of drug hypersensitivity reactions can be missed. The use of skin tests (ST) in diagnosis is questionable, and because of the histamine releasing properties of most opioids, ST results are not significantly different between opioid allergic patients and tolerant controls.⁶ Some opioids, for example, fentanyl and tramadol, do not provoke direct mast cell degranulation.^{5,7-9} Similarly, the value of specific IgE (sIgE) testing has been questioned mainly because positive results to morphine and pholcodine have been found in 5% of blood donors and 10% of patients with other allergies but no history of opioid allergy.^{10,11} Both skin prick testing (SPT) and sIgE may provide additional information provided their inadequacies are taken into consideration and never interpreted in isolation. Additional steps such as higher dilutions of tested opioids for SPT and appropriate inhibition studies for sIgE may also be considered. In most cases, the diagnosis of a true immediate hypersensitivity ultimately depends on drug provocation testing (DPT) with the index opioid.^{4,12} However, it is often difficult to differentiate pharmacological from allergic symptoms. There is little published data available to a practicing allergists/immunologists faced with such diagnostic dilemma. Although not indicated in every case, DPT with opioids appear underutilized because of the lack of validated protocols, limited clinic capacity, and sometimes physicians' inexperience and apprehension.

In our practice, patients suspected to be allergic to opioids are referred for DPT only after careful risk stratification. It relies on a clinical and drug history review, assessment of serial serum tryptase levels, exclusion of other possible agents, and appropriate allergy testing. In this pragmatic retrospective study, we evaluated the clinical characteristics and predictors of opioid allergy as well as outcomes of patients referred for opioid DPT.

METHODS

We reviewed all available records of patients referred for opioid DPT at Guy's and St Thomas' NHS Foundation Trust (London, UK) and Cambridge University Hospitals NHS Foundation Trust (Cambridge, UK) between 2008 and 2016. This included patients who underwent DPT and those who, in view of their undisputed history, were diagnosed clinically without the need for DPT. Data extracted included gender and age, suspected index opioid (ie, the opioid implicated in the allergic reaction), indication for its use and symptoms of index reaction, other concomitantly administered agents, history of spontaneous urticaria, opioid ST and sIgE results, baseline serum tryptase levels, symptoms, and outcomes of DPT. ST were performed only in patients with suspected fentanyl and tramadol allergy (opioids devoid of direct histamine releasing

TABLE 1. Patient characteristics, indications for opioid use, symptoms of index reaction, and outcomes of provocation testing

	Total (n = 98)	Allergic (n = 15)	Nonallergic (n = 83)
Demographics			
Age (median, range)	43 (12-76)	44 (12-66)	43 (13-76)
Male	26 (27%)	2 (13%)	24 (29%)
History of spontaneous urticaria	12 (12%)	1 (7%)	11 (13%)
Concomitant and suspected agents	46 (47%)	10 (67%)	36 (43%)
Clinical setting of opioid use			
For analgesia	59 (60%)	5 (33%)	54 (65%)
During anesthesia	29 (30%)	10 (67%)	19 (23%)
As antitussive	4 (4%)	0	4 (5%)
Other indications for referral*	5 (5%)	0	5 (6%)
Index reactions			
Skin (urticaria, pruritus, flushing, rash)	56 (57%)	8 (53%)	48 (58%)
Angioedema	37 (38%)	10 (67%)	27 (33%)
Respiratory (dyspnoea, wheeze, stridor, hypoxemia)	20 (20%)	7 (47%)	13 (16%)
Gastrointestinal (nausea, vomiting, abdominal pain)	12 (12%)	2 (13%)	10 (12%)
Hypotension	16 (16%)	6 (40%)	10 (12%)
Other*	9 (9%)	0	9 (11%)
Opioids			
Codeine	34 (35%)	5 (33%)	29 (35%)
Fentanyl	3 (3%)	1	2 (2%)
Meptazinol	1	0	1
Morphine	55 (56%)	8 (53%)	47 (57%)
Oxycodone	1	1	0
Papaveretum	1	0	1
Pethidine	1	0	1
Tramadol	2 (2%)	0	2 (2%)

*See the text for description.

properties). Tramadol hydrochloride 50 and 5 mg/mL (Meda Pharmaceuticals, Bishop's Stortford, UK) and fentanyl citrate 0.05 and 0.005 mg/mL (Janssen Cilag Ltd, Bucks, UK) were used for skin prick and intradermal testing, respectively. Measurements of pholcodine and morphine sIgE were performed using ImmunoCAP (Thermo Fisher Scientific, Göteborg, Sweden). Tested opioids included codeine, fentanyl, meptazinol, morphine, oxycodone, pethidine, tramadol, and papaveretum (a mixture of morphine, codeine, and papaverine). Patients were grouped depending on the clinical setting where opioids had been used: during anesthesia or for analgesia, antitussive, or "other" action in an outpatient or inpatient setting. Symptoms of index reactions were categorized based on the definition criteria for anaphylaxis into skin (urticaria, pruritus, flushing, rash), angioedema, respiratory (dyspnoea, wheeze/bronchospasm, stridor, hypoxemia), gastrointestinal (nausea, vomiting, abdominal pain), hypotension, and "others"/unclassified.^{13,14} DPT protocols were tailored to individual patients. All patients underwent DPT with the same opioid implicated in the index reaction. Index drugs were administered in a graded fashion at 30- to 60-minute intervals, for example, oral morphine sulfate (Oramorph, 10 mg/5 mL; Boehringer Ingelheim Ltd, Bracknell, UK): 5, 10, and 20 mg; codeine phosphate (25 mg/5 mL; Thornton & Ross Ltd, Linthwaite,

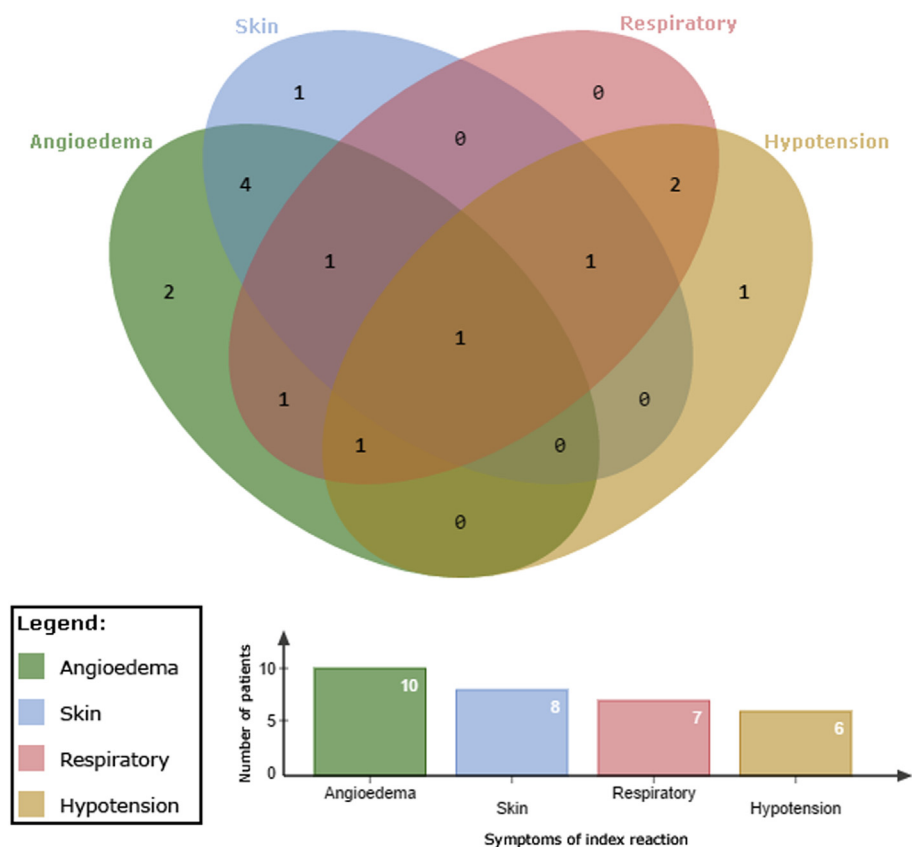


FIGURE 1. Frequency of symptoms during index reactions in 15 patients with opioid allergy. Venn diagram depicting the frequency and overlap of common symptoms during index reactions in 15 patients with opioid allergy. Green = angioedema, blue = skin manifestations (urticaria, pruritus, flushing, rash), red = respiratory manifestations (dyspnoea, wheeze, stridor, hypoxemia), yellow = hypotension.

UK): 7.5, 15, and 30 mg—the protocols were adjusted depending on the individual patient's risk stratification. DPT was positive if objective signs suggestive of an IgE-mediated response developed (acute rash/urticaria, angioedema, and wheeze; significant drop in peak expiratory flow rate, oxygen saturation, or blood pressure). The study was a retrospective review and all patients received the usual standard of care.

Association analysis was performed to study variables associated with a diagnosis of opioid allergy. Categorical variables were expressed as a number (percentage) and continuous variables as median (range) when appropriate. Fisher's exact test and independent samples *t*-test were used to compare categorical and continuous variables between groups in univariate analysis, respectively. Variables with a *P* value $\leq .10$ from univariate analysis were included in multivariate logistic analysis to determine which variables were independent predictors of opioid allergy. A *P* value $< .05$ was considered statistically significant. SPSS Statistics version 20 (IBM) was used for all analyses. The Venn diagram was created using jvenn.¹⁵

RESULTS

Clinical characteristics and DPT outcomes

A total of 98 patients (45 from London and 53 from Cambridge) were referred with suspected opioid hypersensitivity. All of them had been avoiding all opioids since their index reaction. Ninety-four patients underwent DPT. Four patients were

diagnosed with opioid allergy in view of their undisputed and convincing history of severe anaphylaxis, with all other possible agents excluded by appropriate testing. In these 4 patients opioid allergy was diagnosed clinically; DPT was considered unnecessary and unsafe. The demographics, indications for opioid use, symptoms of index reactions, and breakdown of index opioids are summarized in Table I. "Other" indications for referral included previous reactions to illicit opioids and an unclear/"forgotten" reaction but with a label of opioid allergy. "Other" symptoms of index reactions included anxiety, bradycardia, dysphagia, headache, palpitations, tremor, and facial irritation/pain.

Overall, 5 of 59 (8%) patients who received opioids for analgesia and 10 of 29 (34%) during anesthesia were diagnosed with opioid allergy. Detailed information about these patients and the outcomes of their DPT are shown in Figure 1 and Table II.

Seven patients diagnosed with opioid allergy (7 of 15, 47%) agreed to further testing with alternative opioids: 5 patients with either codeine or morphine allergy tolerated synthetic opioids (4 of 5 fentanyl, 1 of 5 pethidine); 2 patients had negative ST to fentanyl but DPT was not performed.

Other allergy investigations: sIgE and serum tryptase

ST, sIgE to morphine, and baseline serum tryptase results were not available for all patients. ST were performed only in

TABLE II. Clinical characteristics of 15 patients with confirmed opioid allergy

No.	Opioid	Indication	Sex/Age	Initial reaction	Threshold cumulative dose (mg)	DPT reaction	Comments
1	Codeine	Analgesia	F/30	Generalized pruritus, angioedema, wheeze	6	Pruritus, rash, conjunctivitis	Negative fentanyl DPT
2	Codeine	Analgesia	F/42	Urticaria, angioedema, dyspnoea	30	Wheeze	Negative pethidine DPT
3	Codeine	Analgesia	M/44	Angioedema, nausea and vomiting, dizziness	9	Urticaria	
4	Codeine	Analgesia	F/45	Generalized pruritus, rash, angioedema	30	Angioedema	
5	Codeine	Analgesia	F/66	Angioedema	52.5	Urticaria	Negative fentanyl DPT
6	Morphine	Anesthesia	F/12	Rash, angioedema	1.8	Urticaria	
7	Morphine	Anesthesia	F/25	Angioedema, bronchospasm	35	Urticaria, angioedema	
8	Morphine	Anesthesia	F/27	Urticaria, angioedema, nausea	5	Urticaria	
9	Morphine	Anesthesia	F/40	Urticaria, angioedema	35	Urticaria	Negative ST to fentanyl, DPT not performed
10	Morphine	Anesthesia	F/66	Urticaria	10	Urticaria	Negative fentanyl DPT
11	Morphine	Anesthesia	F/66	Uncertain history of perioperative reaction	35	Urticaria	
12	Fentanyl	Anesthesia	F/40	Bronchospasm, hypotension	NP	NP	Positive ST, reproducible symptoms on 3 occasions
13	Morphine	Anesthesia	F/48	Urticaria, wheeze, hypotension	NP	NP	Witnessed symptoms immediately after IV morphine and before any other agents
14	Morphine	Anesthesia	F/49	Angioedema, bronchospasm, hypotension	NP	NP	Witnessed symptoms immediately after IV morphine and before any other agents; negative fentanyl DPT
15	Papaveretum	Anesthesia	F/50	Bronchospasm, hypotension, cardiac arrest	NP	NP	Positive sIgE; role of other perioperative agents excluded Negative ST to fentanyl, DPT not performed

DPT, Drug provocation testing; NP, not performed; sIgE, specific IgE; ST, skin tests.

patients with suspected fentanyl and tramadol allergy (opioids devoid of direct histamine releasing properties). The morphine sIgE level was known in 15 patients (27%) with suspected allergy to morphine. In 4 patients with a detectable morphine sIgE, there were 2 congruent positive (true positive) and 1 negative DPT (false positive); 1 patient was diagnosed with opioid allergy without a DPT (see above). In the remaining 11 patients with a negative sIgE result, there were 9 true negative and 2 false negative results confirmed by DPT. In this small cohort, the sensitivity and specificity for morphine sIgE were therefore 50% and 82%, respectively. The baseline serum tryptase level (≥ 24 hours after index allergic reaction) was available for 19 patients (19%): only 1 was raised at 16.1 mcg/L but with a subsequent negative DPT.

Predictors of opioid allergy

Overall, 15 of 98 (15%) patients were diagnosed with opioid allergy. In a univariate analysis, the frequency of angioedema, respiratory reactions, and hypotension was significantly higher in opioid allergic patients than those with negative DPT. However, only angioedema and hypotension remained statistically significant in a multivariate analysis (Table III). Other studied variables including other index reactions, age, gender, presence of other suspected agents, and history of spontaneous urticaria were not

TABLE III. Significant variables associated with opioid allergy

Variable	Odds ratio	95% CI	P value
Index reactions			
Angioedema	5.66	1.49-21.47	.011
Hypotension	5.00	1.15-21.70	.032
Clinical setting			
For analgesia	0.27	0.08-0.86	.008
During anesthesia	6.74	2.05-22.13	.001

CI, Confidence interval.

Nonsignificant variables included age, gender, use of other suspected agents, history of spontaneous urticaria, and other symptoms of index reaction (skin, respiratory, gastrointestinal, others).

significantly associated with opioid allergy (data not shown). Patients who reacted to an opioid during anesthesia were significantly more likely to be opioid allergic. In contrast, a negative association was identified in patients receiving opioids for analgesia (Table III).

DISCUSSION

This is the largest published cohort of patients with suspected opioid allergy investigated with DPT. Most previous

publications on immediate hypersensitivity reactions to opioids relied on very limited evidence of IgE pathomechanism; some were based on clinical history alone without any allergy workup or DPT.¹⁶ Indeed, since 2000, only a few cases of opioid allergy confirmed with DPT have been reported.^{6,17-21} Alternatively, DPT was performed in patients with no history of reaction to opioids.²²⁻²⁴ Therefore, our study uniquely reflects real everyday practice and provides clinical evidence for practicing allergists and immunologists.

Although our cohort was predominantly female (male:female ratio 1:2.8) with a median age of 43 years, neither age nor gender was associated with opioid allergy. The vast majority of cases were referred because of suspected allergy to morphine or codeine. Codeine is a prodrug that is converted into morphine (its active metabolite) via the hepatic cytochrome P-450 2D6 (CYP2D6) pathway.²⁵ Therefore, both drugs could share similar rates of allergy. Our study confirmed a reasonable specificity but low sensitivity of morphine sIgE. This reduces its utility in diagnosis and increases the risk of overdiagnosis of opioid hypersensitivity. Elevated baseline tryptase levels may be indicative of an underlying mast cell disorder that predisposes to severe reactions including anaphylaxis on exposure to opioids.²⁶ However, the only patient with a raised baseline tryptase in our cohort had a negative DPT. Overall, allergy to opioids was confirmed in only 15% of patients, demonstrating a high risk of overdiagnosis/incorrect diagnosis if DPT is not performed. This has significant clinical implications as a patient with confirmed IgE-mediated hypersensitivity may require non-opioid-based analgesia or further testing (including DPT) with alternative opioids. Alternatively, if reactions are thought to be due to direct histamine release, pretreatment with H1/H2 antihistamines may be sufficient.²⁷⁻²⁹ Interestingly, although only 7 of 15 opioid allergic patients underwent tests with an alternative opioid, all those with allergy to natural opioids (codeine or morphine) subsequently tolerated synthetic opioids (fentanyl or pethidine). This might suggest no cross-reactivity between natural and synthetic opioids, although isolated cases have been reported.^{4,12}

We analyzed the association between the symptoms of index reaction and opioid allergy. The most common manifestations of true opioid allergy were angioedema, together with other skin and respiratory manifestations (Figure 1). However, only angioedema and hypotension remained significantly associated with allergy in a multivariate analysis. This may reflect the objectivity and higher specificity of these reactions for true IgE-mediated responses in comparison with other manifestations, for example, subjective dyspnoea related to anxiety or nonspecific pruritus due to direct mast cell degranulation and histamine release. Mechanistically, this can be explained by heterogeneous opioid responsiveness of mast cells from different anatomical sites. Human lung mast cells, unlike cutaneous mast cells, lack surface CD88 (complement component 5a receptor), and do not respond to the anaphylatoxins C3a or C5a, potent inducers of histamine release.²³⁻³² Cutaneous mast cells are more sensitive to direct degranulation and therefore more likely to be involved in non-IgE-mediated reactions.^{8,33} In contrast, severe bronchospasm and cardiorespiratory involvement is usually IgE-mediated and rarely reported in non-IgE-mediated reactions.^{34,35} Opioids predominantly mediate their analgesic effects by acting on μ , κ , and δ opioid receptors on nociceptors. However, IgE-mediated as well as non-IgE/anaphylactoid mast cell activation is not dependent on opioid receptors.³⁶

Interestingly, patients who received opioids for analgesia were significantly less likely to have opioid allergy; the opposite was the case in patients receiving opioids during anesthesia. Although the overall majority of patients were prescribed opioids for analgesia, only 8% patients of them versus 34% in the anesthesia group were diagnosed with opioid allergy. This resonates with our clinical observation that the majority of true opioid allergic patients are usually identified after a perioperative reaction/anaphylaxis. This difference is likely due to the availability of objective measurements, such as monitoring of vital signs, ventilator readings, and acute tryptase levels. We therefore caution against relying solely on a subjective description provided by patients and highlight the importance of reviewing all medical charts and circumstantial evidence.

Lastly, our study confirms that DPT are safe when performed after careful risk stratification by a clinician experienced in the diagnosis and management of drug allergy. In our centers, all opioid DPT were performed by an experienced allergy team in a dedicated allergy day unit. Dose increments and intervals were tailored to each individual based on the comorbidities, severity of the index reaction, and pretest probability of a positive challenge. To minimize false positive results, DPT continued, as far as safe, until objective features were identified. Acute and baseline tryptase levels were also obtained if appropriate. However, patients with a convincing history of a severe reaction (anaphylaxis) to opioids with good supporting circumstantial evidence, and therefore high pretest probability, were not challenged (Table II). Of all positive DPT, 8 (72%) patients developed urticaria, 2 (18%) angioedema, 2 (18%) erythematous rash with conjunctivitis, and 1 (9%) wheeze during DPT. With our individualized and graded approach, all reactions were mild, even in patients with a history of severe anaphylaxis, and treated promptly and appropriately with oral antihistamines and steroids. Administration of adrenaline or naloxone was never required.

The main limitations of this retrospective study stem from the limitation of the medical records review. It was not always possible to ascertain a more precise description of the index reaction. Certain investigations such as sIgE and baseline tryptase levels were not available for every patient. This highlights the necessity of future prospective and multicenter studies. Furthermore, true IgE-mediated reactions are rare and very little is known about the underlying mechanism or allergenic epitopes of opioids (reviewed by Baldo and Pham⁴). Moreover, no test can differentiate between usually clinically indistinguishable IgE-mediated and non-IgE-mediated reactions with 100% certainty. We cannot exclude that a percentage of patients diagnosed with opioid allergy based on DPT were instead idiosyncratically sensitive to direct mast cell degranulation. Nonetheless, this would not alter the subsequent clinical management of these patients. Four patients with convincing and compatible clinical histories of severe anaphylaxis were diagnosed with opioid allergy without DPT. Although there is an inherent small risk of false positivity in this small group of patients, their characteristics provide invaluable data especially on the predictors of severe reactions. Exclusion of all patients in whom DPT was deemed unnecessary/unsafe would hinder the identification of those predictors of allergy in this subset of strongly and convincingly allergic individuals. This would defeat the purpose of this pragmatic study.

Finally, it would be of great interest to further study the role of pharmacogenomics such as CYP2D6 polymorphism in codeine

metabolism and the utility of newer laboratory techniques such as the basophil activation test in opioid allergy.^{18,25,37}

In conclusion, we report the clinical characteristics and DPT outcomes in the largest cohort of patients with suspected opioid allergy described thus far and identify predictors of opioid allergy. The key to accurate diagnosis lies in the constellation of the severity of index reaction (particular respiratory reactions and angioedema), other circumstantial evidence (eg, acute serum tryptase, sIgE), and provocation testing. Overall, only 15% of our cohort were diagnosed with opioid allergy, emphasizing the importance of DPT in preventing erroneous overdiagnosis and its sequelae. DPT were safe and no serious reactions occurred because of meticulous risk stratification, individualized DPT protocols, and expert supervision. Patients who experienced angioedema and/or hypotension with their index reaction were significantly more likely to be opioid allergic. Large prospective studies are needed to further our understanding of this under-researched and clinically extremely relevant area of drug allergy.

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PHL, KLU, AW, and KR collected the data. PHL, KLU, AW, RR, and KR analyzed and interpreted the data. All authors contributed in the writing and revision of the article.

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