

REVIEW

Allergy to illicit drugs and narcotics

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Clinical
&
Experimental
Allergy

Summary

Despite their frequent use, allergy to illicit drugs and narcotics is rarely reported in literature. We present a review of the different classes of drugs of abuse that might be involved in allergies: central nervous system (CNS) depressants (such as cannabis, opioids and kava), CNS stimulants (cocaine, amphetamines, khat and ephedra) and hallucinogens such as ketamine and nutmeg. Diagnosis of drug and narcotic allergy generally relies upon careful history taking, complemented with skin testing eventually along with quantification of sIgE. However, for various reasons, correct diagnosis of most of these drug allergies is not straightforward. For example, the native plant material applied for skin testing and sIgE antibody tests might harbour irrelevant IgE-binding structures that hamper correct diagnosis. Diagnosis might also be hampered due to uncertainties associated with the non-specific histamine releasing characteristics of some compounds and absence of validated sIgE tests. Whether the introduction of standardized allergen components and more functional tests, that is, basophil activation and degranulation assays, might be helpful to an improved diagnosis needs to be established. It is anticipated that due to the rare character of these allergies further validation is although necessary.

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Introduction

Cases of allergy to illicit drugs and narcotics are rare. This might be partly due to an underestimation because of the illegal nature of these substances. Nevertheless, occasional case reports and some small series demonstrate a proneness to allergies of the different classes of psychoactive substances. In this review, we will discuss the evidence of IgE-mediated allergy to central nervous system (CNS) depressants, such as cannabis, natural and (semi)synthetic opioids and kava, CNS stimulants (cocaine, amphetamines, khat and ephedra) and hallucinogens such as ketamine and nutmeg.

CNS depressants (cannabis, opioids and kava)

Cannabis sativa

Cannabis is a generic term for preparations [marijuana (or weed), hashish, hashish oil] derived from *Cannabis sativa* (order: Rosales, family: *Cannabaceae*) that contain high levels of cannabinoids, particularly delta9-tetrahydrocannabinol (THC): several of them are psychoactive substances. Although cannabis use is illegal in most countries, it is ubiquitously used for its relaxing or

euphoric effects, especially by adolescents and young adults. When used, preparations of dried flowers and subtending leaves mostly from the female cannabis plant (marijuana) and preparations derived from resinous extract (hashish) are consumed by smoking, vaporizing, chewing or oral ingestion. The global number of illicit cannabis users was estimated at 125–203 million people (2.8–4.5% of global population aged 15–64 years in 2009) [1, 2].

Although there have been several studies on occupational respiratory and cutaneous allergy to plants of the *Cannabaceae* family including *Cannabis* (hemp) and *Humulus* (hops) [3–5], descriptions of immunoglobulin E antibody (IgE)-mediated *Cannabis sativa* allergy (CSA) in illicit drug abusers remain rare. The first report dates from 1971 and describes a patient who, after smoking a marijuana cigarette, suffered from an allergic reaction [6]. Some cases of CSA after exposure through inhalation, cutaneous contact, ingestion and intravenous use of the drug have been published [7–15]. Actually, cannabis allergen can become airborne (e.g. in fumes or vapours), triggering rhinitis, conjunctivitis and/or asthma and occasionally urticaria or angioedema. It should also be kept in mind that *Cannabis sativa* is an anemophilous plant that produces wind-born pollen.

Cannabis sativa pollen can be transported even over extreme distances, and therefore in some regions these pollen constitute an important outdoor aeroallergen [16–21]. For example, in Nebraska, where hemp is cultivated, the plant pollinates between July and September, and accounts for 36% of the total pollen count during peak pollination mid- to late-August [17]. Quite similar observations were done in Southern European countries such as Italy [18] and Spain [19]. Alternatively, cutaneous contact, chewing or ingestion or intravenous injection generally induces generalized urticaria, angioedema or anaphylaxis.

The allergenic components of *Cannabis sativa* have not been studied thoroughly. However, a non-specific lipid transfer protein (ns-LTP) has been purified from *Cannabis sativa* and designated as Can s 3 [11]. It has been speculated Can s 3 to constitute a major allergen of *Cannabis sativa* and to be a potential source of sensitization towards ns-LTP that might explain particular plant food allergies, such as tomato and peach [11, 13, 22]. In an own series, sensitization towards different ns-LTP including Pru p 3 from peach (*Prunus persica*) was demonstrable in almost all patients with CSA that attended our clinic because of a variety of plant-food allergies [23]. Sensitization towards ns-LTP in these patients might also explain allergic cross-reactions to various alcoholic beverages such as beer and wine [24, 25], tobacco [26] and *Hevea latex* [27, 28].

At present, diagnosis of CSA generally rests upon skin testing using extracts prepared from macerated buds, leaves or flowers [6, 9, 11–13, 15, 23, 29]. *In vitro* tests that have been applied to document CSA are

measurement of sIgE antibodies [5, 12, 13, 23, 29], histamine release tests [5, 29] and flow-assisted basophil activation tests [23] (Table 1). Note that these tests have not been robustly validated and that results are not always absolutely predictive for the clinical outcome [5, 23]. Actually, in skin testing and quantification of sIgE, heterogeneous native allergen extracts are used that might harbour irrelevant IgE-binding structures that hamper correct diagnosis. For example, false-positive test results can result from sensitization to cross-reactive structures such as profilins, ns-LTP and cross-reactive carbohydrate determinants that are ubiquitously present in plant allergens [23, 30]. This phenomenon seems particularly relevant for sIgE antibody assays. Although one could assume serological diagnosis of allergy to plant-derived drugs might benefit from the availability of better standardized and characterized allergen components, to our knowledge, no such allergens have already been cloned. It is anticipated that the validation of novel diagnostics will need to take into account that sensitization might exhibit distinct age-related and geographical patterns (e.g. sensitization to profilins and ns-LTP to be more prevalent in Mediterranean countries [31]. Better knowledge of these allergen sensitization profiles and the potential cross-reactivity with allergens from taxonomically close and more distant related species is mandatory to design an optimized testing strategy for drug allergy.

Finally, and most importantly, positive tests might merely reflect sensitization to cannabis pollen, without there being any clinical manifestations of a genuine CSA [16, 17].

Table 1. Evidence table for IgE-mediated allergy to illicit drugs and narcotics

	Cannabis	Opiates	Semi-synthetic opioids	Synthetic opioids	Cocaine	XTC	Khat	Ketamine	Ephedra	Nutmeg
Source	<i>Cannabis sativa</i>	<i>Papaver somniferum</i>			<i>Erythroxylum coca</i> <i>E. novogranatense</i>		<i>Catha edulis</i>		<i>Ephedra sinica</i>	<i>Myristica fragrans</i>
sIgE*	Hemp	Morphine <i>Papaver somniferum</i>	Pholcodine	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	+
Skin tests†	+	+	+	+	+			+		+
HRT	+	+	+	+	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
BAT/ HistaFlow	+	+	+	+						
PT	N.I.	+	N.I.	+						

*sIgE: In most cases, the demonstration of sIgE antibodies against morphine and pholcodine is not associated with genuine allergy to these opioids. At present, sIgE towards morphine (and a lesser extent also pholcodine) is generally applied to depict sensitization towards tertiary and quaternary ammonium groups, as is frequently observed in patients allergic to curarizing myorelaxants such as suxamethonium and rocuronium.

†Skin testing with opiates is unlikely to be of use in documenting allergy to these drugs. However, for morphine a prick test concentration of maximum 3×10^{-3} M and intradermal test dilution of 3×10^{-7} – 10^{-5} have been reported to be beyond the non-specific histamine releasing concentration [32].

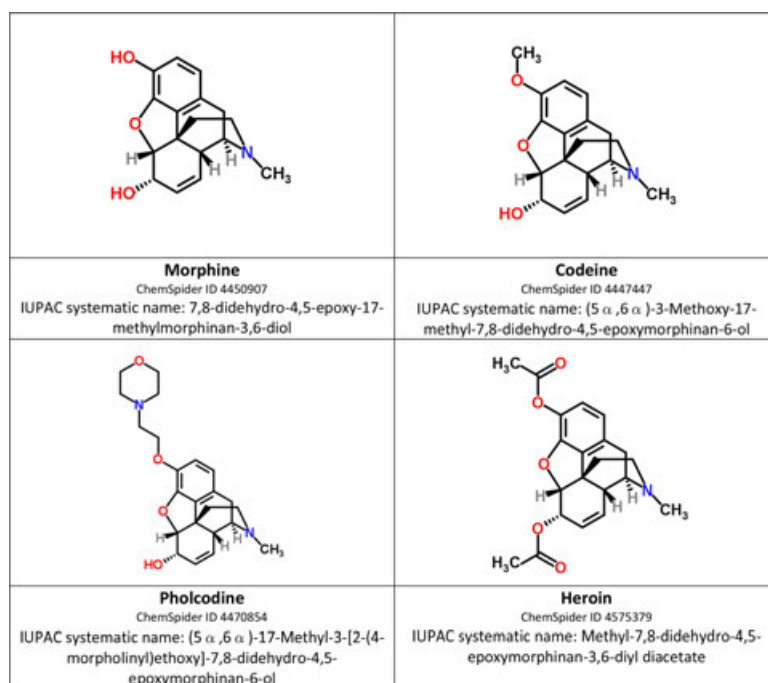
HRT, histamine release tests; BAT/HistaFlow, basophil activation and degranulation assessed by flow cytometry.

NA, not available; N.I., no information. Note that provocation tests (PT) with illegal compounds might not only be hindered by ethically issues but pose a legal problem.

Opioids

Opioids include (a) the natural occurring opiate alkaloids derived from opium (the latex released by scratched immature seed-pods of the opium poppy, *Papaver somniferum*) such as morphine and codeine, (b) semisynthetic opioids such as pholcodine, hydrocodone, hydromorphone and heroin and finally (c) synthetic compounds that are chemically not related to opiates such as methadone, pethidine, fentanyl and tramadol. Figure 1 displays the structure of morphine and some relevant opiates and (semi)synthetic opioids that are

discussed in this review. Opioids are commonly used as analgesics, but are also abused for their strong euphoric effect. Many natural and (semi)synthetic opioids are potent non-specific liberators of histamine, a property to account for (mostly cutaneous) anaphylactic-like reactions that are much more prevalent than IgE-mediated hypersensitivity to these drugs (for review: [32]). Moreover, data suggest many patients labelled with opioid allergy, do not have a genuine opioid allergy [33–36]. Actually, due to uncertainties associated with traditional skin tests with these potent non-specific histamine releasers and unavailability of validated sIgE



IUPAC: International Union for Pure and Applied Chemistry

Drug	Substituent at position				Bond(s) positions 7-8
	3	6	14	17	
Morphine ¹	-OH (hydroxyl)	-OH	-H	-CH ₃	Double
Codeine ¹	-OCH ₃ (methoxy)	-OH	-H	-CH ₃	Double
Pholcodine ¹	-OCH ₂ CH ₂ N<O 2-morpholinylethyl	-OH	-H	-CH ₃	Double
Heroin	-OCOCH ₃	-OCOCH ₃	-H	-CH ₃	Double
Hydrocodone	-OCH ₃	=O	-H	-CH ₃	Single
Hydromorphone	-OH	=O	-H	-CH ₃	Single

¹ note the structural relationship between morphine, codeine and pholcodine. All 3 drugs have a freely accessible tertiary N methyl group and are structural identical except at position 3 where there is a hydroxyl for morphine, a methoxy for codeine and a 2-morpholinoethyl group for pholcodine. A comparable substituted ammonium group is found in curarizing myorelaxants.

Fig. 1. Structural formula of morphine and chemically related natural opiates and (semi)-synthetic opioids. Note that morphine, codeine and pholcodine are structurally almost identical, except the substituent in position 3 (adapted from [32] and ChemSpider: <http://cssp.chemspider.com>).

assays, correct diagnosis of IgE-mediated allergy to most of these agents is not straightforward and the prevalence of opiate allergy might be overestimated. This is probably the case in the 9th French epidemiological survey (2005–2007) on perioperative anaphylaxis. In this series, applying skin tests and measurement of sIgE antibodies, 13 patients were believed to suffer from an IgE-mediated morphine allergy [37]. However, extreme prudence should be called upon the interpretation of positive skin test and serum sIgE antibody result for opiates and opioids (see below).

a. Opiate alkaloids derived from Papaver somniferum. Opium poppy (*Papaver somniferum*, order: Ranunculales, family: *Papaveraceae*) is the plant from which opium and poppy seeds are derived. Opium contains up to 15% morphine, an alkaloid that is frequently processed chemically to produce diacetylmorphine better known as heroin. The latex also contains codeine and various non-narcotic alkaloids such as papaverine, thebaine and noscapine. Despite the common use of morphine and the structurally closely related codeine (3-methylmorphine), as extensively reviewed by Baldo et al. [32], IgE-mediated reactions to these two naturally occurring opioids have only been very rarely reported and appropriately documented. There has been only one case published in whom an IgE-mediated allergy to papaveretum-hyoscine (a drug that contained about 50% morphine and 2.5 to 5% codeine in the late 1980s) was adequately documented [38]. In other publications on morphine allergy [39–41] and codeine allergy [42–46], proof for an IgE-mediated pathomechanism is largely equivocal or simply lacking. Moreover, some authors have recommended drug provocation tests to correctly diagnose an IgE-mediated opiate allergy [45, 46].

Diagnosis of an IgE-mediated opiate allergy, as with other allergies, starts with a thorough history and confirmatory testing by skin tests and measurement of sIgE antibodies (Table 1). However, the correct diagnosis of an IgE-mediated opiate allergy is fraught by major difficulties. First, as for other drugs and addictions, patients might be highly reluctant to openly admit their abuse and/or misconceive/interpret their symptoms. Second, there is considerable risk to over-diagnose opiate allergy. As already exemplified in the introductory paragraph, prudence should be called upon the interpretation of skin test responses to opiates, as these compounds are well-known potent non-specific histamine releasers from cutaneous mast cells (for review: [32]). Moreover, it has repeatedly been demonstrated skin testing to be of limited value in the diagnosis of opiate allergy [45–48]. One should also exert caution when interpreting positive sIgE results to opiates. In Norway, Florvaag et al. [49] found positive sIgE results

to morphine and pholcodine in about 5% of blood donors and 10% of patients presenting with common allergies, respectively. In an own series, sIgE antibodies to morphine and pholcodine were found in about 0.5 to 1% of the general population [50]. Finally, unlike Armentia et al. [51], we do not endorse the use of sIgE antibodies to poppy seed as a marker to document genuine opiate allergy. First, the currently available poppy seed assay uses an aqueous extract that is prepared from native allergens and contains highly cross-reactive components and epitopes, such as CCD and ubiquitous pan allergens such as profilins and ns-LTP that might severely hamper correct diagnosis of opiate allergy [30]. For example, we observed a positive sIgE to poppy seed in 5 of 10 patients with an established allergy to *Cannabis sativa*, tolerant for poppy seed but sensitized to ns-LTP [23]. Alternatively, we found no poppy seed sIgE in 3 patients with a documented allergy to pholcodine [48]. Finally, we have observed several ns-LTP sensitized patients demonstrating a positive sIgE result for poppy seed tolerating both morphine and codeine challenges (unpublished data). Additional collaborative studies are needed to further elucidate on this issue.

On the other hand, opioids do not elicit non-specific histamine liberation from human basophils [52–54]. Moreover, we recently demonstrated that flow-assisted basophil activation tests, but not skin tests, enabled to document pholcodine allergy in patients tolerant for codeine [48]. For the time being, we believe that combined employment of measurement of sIgE (if available) and drug-specific basophil activation assays is the most efficient and reliable strategy to correctly diagnose IgE-mediated opiate allergy.

b. Semisynthetic drugs such as pholcodine, hydrocodone, hydromorphone and heroin. Semisynthetic opioids do not occur naturally and are created from natural opiates and share similar chemical structure. Drugs like pholcodine, hydrocodone, oxycodone, oxymorphone, hydromorphone and diacetylmorphine (heroin) are semisynthetic opioids derived from natural opiates. Pholcodine (3-(2-morpholinyl-ethyl) morphine) is an opioid antitussive indicated in the symptomatic treatment of unproductive coughs. Pholcodine-containing medicines are available as syrups, lozenges, suppositories and oral capsules and can currently be purchased either by prescription or as over-the-counter medicines in different EU member states. In 2005, Codreanu et al. [55] reported on a patient presenting a facial angioedema 8 h after intake of a pholcodine-containing syrup. Diagnosis of pholcodine allergy was based upon skin tests and an open oral challenge with a laryngeal angioedema 9 h after a cumulative dose of 20 mg, but basophil activation test and leukotriene release test were negative. Florvaag et al. [56, 57], describe three

individuals with late-onset (4–7 days) reactions that were related to the intake of pholcodine. In these patients, diagnosis was based only upon a rise of sIgE to pholcodine. Alternatively, the same authors have claimed pholcodine to exert an ‘immunological boosting’ effect and to selectively sensitize to curarising myorelaxants [56, 57] that carry substituted ammonium groups as a main allergenic determinant [58] (Fig. 2). Because the structure of pholcodine is almost identical to the structures of morphine and codeine, except at position 3 where it has a 2-morpholinoethyl group instead of a hydroxyl (morphine) or a methoxy (codeine), the conclusion seems inescapable viz., if these effects are real, only the 2-morpholinoethyl group can

account for the differences. Recently, for the very first time, we described three patients with immediate anaphylactic reactions to pholcodine, in whom diagnosis was documented by quantification of sIgE and flow-assisted basophil activation tests (Fig. 3) [48]. Moreover, in two of these three cases, we confirmed the capacity of the antitussive to boost levels of sIgE antibodies to other substances containing a substituted ammonium (e.g. morphine, curares such as suxamethonium and rocuronium) but apparently not to atracurium [57]. However, the clinical relevance of these positive sIgE findings remains elusive, as these patients demonstrated an entirely negative functional analysis by skin tests and/or basophil activation tests for structurally almost

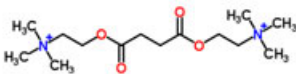
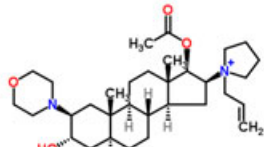
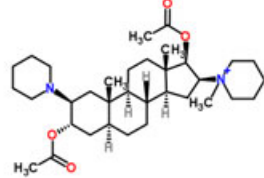
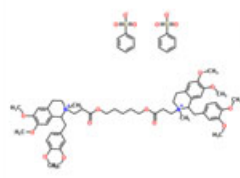
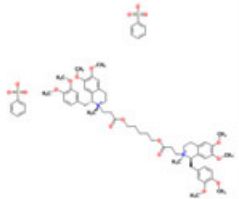
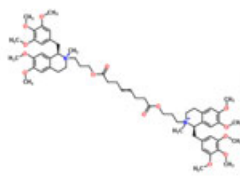
Suxamethonium Suxamethonium ChemSpider ID: 5123 2,2'-[1,4-Dioxo-1,4-butanediyl]bis(oxy)]bis(N,N,N-trimethylethanaminium)			
Aminosteroid-derived curarizing myorelaxants			
			
Rocuronium ChemSpider ID 390053 (2 β, 3 α, 5 α, 16 β, 17 β)-17-Acetoxy-16-(1-allyl-1-pyrrolidiniumyl)-3-hydroxy-2-(4-morpholinyl)androstane		Vecuronium ChemSpider ID 36358 (2 β, 3 α, 5 α, 16 β, 17 β)-3,17-Diacetoxy-16-(1-methyl-1-piperidiniumyl)-2-(1-piperidinyl)androstane	
Benzylisoquinoline-derived curarising myorelaxants			
			
Atracurium besylate ChemSpider ID 43068 2,2'-[1,5-Pentanediy]bis[oxy(3-oxo-3,1-propanediyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium] bisbenzenesulfonate		(1R-cis,1'R-cis)-Atracurium besylate ChemSpider ID 56614 (1R,2R,1'R,2'R)-2,2'-[1,5-Pentanediy]bis[oxy(3-oxo-3,1-propanediyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium] bisbenzenesulfonate	
Mivacurium ChemSpider ID 16744285 (1R,1'R)-2,2'-[1,8-Dioxo-4-octene-1,8-diyl]bis[oxy(3,1-propanediyl)]bis[6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium]			

Fig. 2. Structural formula of curarizing myorelaxants. Note the presence of tertiary or quaternary ammonium groups as main antigenic determinant.

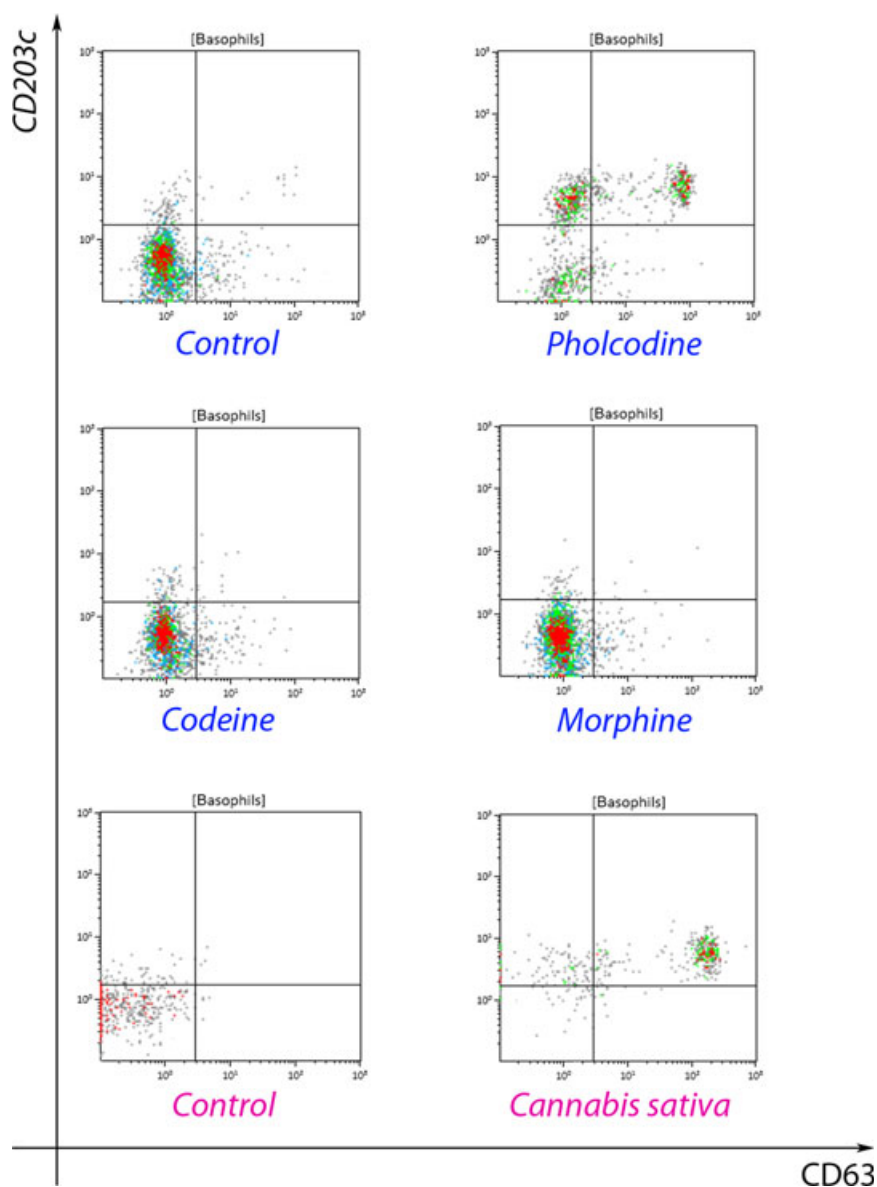


Fig. 3. Representative basophil activation plots of a patient with allergy to the opiate pholcodine (3-morpholinoethyl morphine) tolerant to the structurally related opiates morphine and codeine (3-methyl morphine) [top] and a patient allergic to *Cannabis sativa* [bottom].

identical opiates (i.e. morphine, codeine) and curarizing myorelaxants and had a negative oral provocation test with codeine [48]. To our knowledge, no IgE-mediated allergies to hydrocodone and hydromorphone have been documented so far, and there appears to be one case report on an 'anaphylactoid' reaction to hydromorphone [59].

Heroin (diacetylmorphine or morphine diacetate), also known as diamorphine, was synthesized for the first time by C.R. Alder Wright in 1874 by adding two acetyl groups to the molecule morphine. Heroin, as morphine, is a potent non-specific histamine liberator [54, 60] and frequently causes pruritus after intravenous injection. This pruritus can last 10 min up to 24 h [61, 62]. In up to 4% of the cases, heroin can trigger urticaria that starts about

30 min after injection and can persist over several days [61]. Injection or inhalation of heroin can also elicit more generalized anaphylactic-like reactions with urticaria, severe angioedema and (life-threatening) bronchospasm that might appear to be immediate reactions [45, 63–68]. But, again, firm evidence for an IgE-mediated pathomechanism is lacking. Edston et al. [69] measured tryptase in post-mortem blood of 22 heroin addicts dying suddenly after injection of the drug without other apparent cause. Seven sera (32%) contained elevated tryptase concentrations. Although no drug sIgE quantifications were performed, in the absence of increased total IgE concentrations, the authors speculated that (some of) these heroin fatalities could be attributable to a non-specific mediator release from mast cells.

c. Synthetic compounds that are chemically not related to opiates such as methadone, pethidine, fentanyl and tramadol. The fully synthetic opioids are artificially manufactured and are not related to opiates. Some of the drugs that are fully synthetic are methadone, fentanyl, pethidine and tramadol. Although these synthetic opioids are widely applied, again, documented IgE-mediated allergic reactions to these agents are rare and seem mostly to involve pethidine and fentanyl.

Pethidine (meperidine) was the first synthetic opioid synthesized in 1932 as a potential anti-spasmodic agent by the chemist Otto Eislib and is currently mostly used to treat post-operative pain. Pethidine is a highly potent releaser of histamine [70–72]. In 1951, Butler [73], reported an 'obstetric anaphylaxis' with cyanosis, urticaria and profound hypotension after administration of 100 mg pethidine intramuscularly. Diagnosis of pethidine anaphylaxis was suspected because of a positive pethidine provocation test, but no firm proof of an IgE-mediated mechanism was provided. Actually, the first authors to document an IgE-reaction to pethidine were Levy and Rockoff [74], as they detected pethidine sIgE antibodies (by RAST) in a child presenting life-threatening anaphylaxis within 2 min after intravenous administration of the drug. However, no control subjects were studied. More recently, Anibarro et al. [47] reported on a case of pethidine-related urticaria, facial angioedema, dysphagia and dysphonia documented by skin testing in the patient and 10 control individuals.

Fentanyl citrate is a synthetic narcotic 1000 times more potent than pethidine. Unlike several drugs applied during general anaesthesia, fentanyl does not readily provoke histamine release from cutaneous mast cells [75]. A first case of fentanyl-induced maculae and weals was described in 1974 [76]. However, the first documented case of fentanyl-related anaphylactic shock during general anaesthesia appears to be by Pevny and Danhauser [77], where diagnosis was supported by skin testing. However, some reports of fentanyl-induced pruritus, urticaria and anaphylaxis have been published [78–83]. In the French epidemiological surveys on anaesthesia-related anaphylaxis, 10 of 3769 patients (0.003%) have currently been identified as fentanyl allergic [37, 84]. However, in most of these cases diagnosis might not be unequivocal and fentanyl-specific IgE antibodies have only been reported in one case [85]. Fentanyl contains a tertiary nitrogen group and therefore might cross-react with NMBA [85]. However, in our own series, we observed no positive skin tests for fentanyl in 120 NMBA allergic patients and re-exposure to fentanyl in patients with NMBA allergy was always uneventful (manuscript in preparation).

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. The chemistry and pharmacology of

tramadol are summarized elsewhere [86, 87]. Tramadol seems not to induce histamine release [88]. Some cases of tramadol-induced mild urticaria [89, 90] and angioedema [91, 92] have been published. However, again, firm evidence for an IgE-mediated reaction is generally absent. Moreover, as patients predominantly presented isolated angioedema without pruritus, urticaria or other anaphylactic signs, alternative pathophysiological mechanisms cannot be ruled out. In this context, the fact that several patients with tramadol-induced angioedema had concomitant intake of angiotensin converting enzyme (ACE)-inhibitors [91] or had a history of angioedema to ACE-inhibitors [92] points to bradykinine as a potential mediator of tramadol-induced vasodilatation. Finally, one report states that tramadol cannot *per se* be considered a safe alternative in patients with intolerance to NSAID, and its safety should be assessed through drug provocation tests [90]. Alternatively, three patients with 'allergic reactions' to codeine tolerated a tramadol provocation test [46].

Euhlinger & Conrad [93] reported on five patients participating in an injectable methadone research programme, developing slightly raised round red skin lesions with an annular border that did not reappear after each injection. The lesions were associated with pain along the relevant vein and disappeared within 10 min to 2 h after injection. This single report provides no supporting evidence for an IgE-mediated methadone allergy.

Kava

Kava ('Awa) is a relaxant beverage prepared from the roots and stem of the pepper plant (*Piper methysticum*, family of Piperaceae) [94]. Kava is consumed throughout the Pacific Ocean cultures of Polynesia, including Hawaii, Vanuatu, Melanesia and some parts of Micronesia primarily because of its relaxing properties. Aqueous Kava extracts (but not isolated kavalactones) cause mast cell degranulation [95]. The adverse effects of this herbal drug include an ichthyotic dermatitis and delayed type hypersensitivity reactions [96–98]. Two cases of Kava-induced delayed urticaria have been described [99]. Jappe et al. [100] also reported on two patients who developed erythematous plaques after 3 weeks on systemic therapy with Kava extracts, used to treat anxiety.

CNS stimulants (cocaine, amphetamines, khat and ephedra)

Cocaine

Natural cocaine (benzoylecgonine) is a crystalline tropane alkaloid that is obtained from the leaves of

the coca plant (*Erythroxylum coca* and *E. novogranatense*, family Erythroxylaceae), indigenous to the Andes region of South America [101]. Cocaine is extracted from the harvested leaves by maceration with various solvents (including kerosene) or (sulfuric) acids, until a pasty substance (called 'coca paste') is obtained. This 'paste', containing up to 80% cocaine, is then purified to 'coca base' and finally submitted to reaction with hydrochloric acid, forming cocaine hydrochloride or 'cocaine powder' upon removal of the solvents or acids [102]. Cocaine can also be synthesized from specific precursor chemicals. However, this method is rarely applied as it requires a significantly high level of synthetic expertise and well-equipped laboratory facilities.

Cocaine powder can be used by oral, sublingual, nasal ('snorting'), intravenous, intramuscular, subcutaneous or intra-vaginal routes, in its pure form, or adulterated or 'cut' with various powdery fillers, or even mixed with morphine or heroin ('speedball') or other xenobiotics. Cocaine hydrochloride converted/precipitated as 'free-base cocaine' or 'crack (rock)' can be smoked. The street name 'crack' refers to the crackling sound generated during smoking of free-base cocaine pellets. As recently reviewed by Dinis-Oliveira et al. [103], cocaine abuse can be very detrimental and result in the midline destructive lesion, dental health problems, pseudosclerodermatous triad and crack hands, necrosis and gangrene of extremities and several other skin manifestations, reticular purpura, intracerebral and peripheral haemorrhages, urticaria and angioedema [104], rhabdomyolysis and crack lung. However, to our knowledge, no cases of IgE-mediated cocaine allergy have been reported. The pathomechanisms of the uvular angioedema that has been described in intranasal abuse of cocaine remains elusive [105–108].

Amphetamines

MDMA (3,4-methylenedioxy-*N*-methylamphetamine, widely known as 'ecstasy' or 'XTC'), is an entactogenic drug of the phenethylamine and amphetamine classes of drugs with well-established adverse events and toxic effects [109–111]. However, allergy to MDMA appears exceedingly rare. In 2008, Sauvageau [112] reported on a 13-year-old girl that presented a severe reaction with nausea, vomiting and apnoea and finally loss of consciousness after about 4 h of intake of one and a half tablet of XTC. On arrival at the emergency department she was comatose, hypothermic, hypotensive and tachycardic. Despite treatment she finally died 30 h after intake of the drug. Toxicological analysis revealed presence of MDMA in the blood at concentrations too low to be lethal and excluded other intoxications. Autopsy revealed massive brain oedema, congested lungs and a laryngeal oedema. These findings, together with a prior episode of

lip swelling were considered highly suggestive for an anaphylactic reaction to MDMA. More recently, a papular urticarial facial eruption was described in a patient snorting ecstasy [113]. In both cases, again, no evidence for an IgE-mediated reaction was provided.

Khat

Khat (*Catha edulis*, family: Celastraceae) is a flowering plant indigenous to East Africa and the Arabian Peninsula. The leaves are chewed for their stimulating effect. Cathinone is the principal alkaloid in khat, with sympathomimetic properties similar to amphetamine [114]. Marker and Kroghdahl [115] described a case of plasma cell gingivitis apparently related to the use of khat. The patient presented with reddening and swelling of the gingiva after the prolonged use of khat leaves. Histological examination showed an intense non-specific inflammatory infiltration, compatible with a contact allergic reaction. The lesions disappeared within 2 weeks of the use of khat chewing being discontinued. But, again, the allergic hypersensitivity was not confirmed by IgE- or skin-tests.

Ephedra

Ephedra (*Ephedra sinica*), also known as Ma Huang, is an important herb used in traditional Chinese medicine for the treatment of allergic rhinitis, asthma and common cold [116]. The active compound ephedrine has stimulating and thermogenic effects, and is therefore also used in dietary supplements to stimulate weight loss and enhance athletic performance, and as a party drug due to the increased energy. However, ephedra has some serious side-effects, including heart attacks, seizures, stroke and death [117]. Zaacks et al. [118] reported a case of hypersensitivity myocarditis which appeared to be attributable to ephedra use, but Kurt [119] argued that there is no causal relationship between the myocardial cell sensitization and the ingestion of ephedra.

Hallucinogens such as ketamine and nutmeg

Ketamine

Ketamine is used to induce anaesthesia, sedation, analgesia and amnesia, and for the treatment of bronchospasm [120]. Ketamine is also used as a recreational drug. True allergic reactions to ketamine appear extremely rare. Literature reports a case of a 19-year-old female, presenting with an anaphylaxis-like reaction during anaesthesia [121]. Generalized rash and laryngospasm developed after the use of ketamine. Intradermal tests revealed an allergic reaction to ketamine. Boynes et al. [122] reported an urticarial response in a 6-year-old girl following the

intramuscular administration of ketamine and midazolam. Further skin testing confirmed a positive reaction to ketamine. Maximum non-reactive concentration of ketamine for prick and intradermal skin testing in non-allergic healthy were 10 mg/mL and 0.25 mg/mL respectively [123].

Nutmeg

Nutmeg is the dried ripe seed of *Myristica fragrans*, that is a spice commonly used in cooking, but it is also used at higher doses by drug abusers for its hallucinogenic and euphoric properties [124]. The psychoactive effects are attributed to myristicin (or methoxysafrole), the principal aromatic constituent of the volatile oil of nutmeg. Nutmeg intoxication can lead to psychosis, feelings of doom, nausea, dizziness, tachycardia, and even hypotension and shock [125]. Occasionally, an IgE-mediated hypersensitivity to nutmeg has been described, but remains rare [126]. In other cases nutmeg sensitization and allergy might result from a cross-reactivity with pollen, particularly mugwort (*Artemisia vulgaris*) [127]. To our knowledge, cases of allergic reactions to nutmeg abuse in high doses have not been reported.

Conclusion

At present, little is known about IgE-mediated allergy to illicit drugs and narcotics. Hypersensitivity reactions to these substances are rarely reported in literature, probably partly due to their illegal nature. Cannabis sativa seems the most important substance responsible for allergic hypersensitivity, with Can s 3 as its major allergen. Skin tests, sIgE assays, histamine release tests and basophil activation tests are available for the diagnosis of Cannabis sativa allergy.

Regarding opioids, cocaine, kava, amphetamines, khat, ketamine, ephedra and nutmeg, more research is necessary concerning the presence of allergic compounds, and the tests available for diagnosis.

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Conflict of interest

The authors declare no conflict of interest.

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