Adverse reactions to illicit drugs (marijuana, opioids, cocaine) and alcohol

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ABBREVIATIONS

AERD	Aspirin Exacerbated Respiratory Disease
BAL	bronchial alveolar lavage
BAT	basophil activation test
Bet v	Betula verrucosa
Can s	Cannabis sativa
CBD	cannabidiol
CRS	chronic rhinosinusitis
LA	local anesthetics
LT	leukotrienes
NSAIDs	non-steroidal anti-inflammatory drugs
nsLTP	nonspecific lipid transfer protein
OEEP2	oxygen-evolving enhancer protein 2
SPT	Skin prick tests
sIgE	specific immunoglobulin E
THC	Tetrahydrocannabinol
TLCO	Transfer Factor of the Lung for Carbon Monoxide

ABSTRACT

Drug allergy has been a research topic within the allergy field for decades. However, many drug reactions presumed to be of allergic nature, are not and originate from different mechanisms. Drug-induced reactions can affect numerous organ systems, present with a variety of symptoms, and have more than one mechanism of action. In this rostrum article we want to give an overview of the different allergic and non-allergic reactions that can be expected with the (illicit) use of cannabis, cocaine, opioids and alcohol. In addition, this article focuses on the different methods available to diagnose allergy related to these four drug types and highlight the pitfalls of non-allergic reactions or allergy “mimickers” complicating diagnosis of true drug allergy. Finally, the impact on current medical practices is addressed and future research in support of the allergist in diagnosis and treatment of these medical problems.

INTRODUCTION

The prevalence of drug allergy has been reported as high as 15% in hospitalized populations but to date, the prevalence of hypersensitivity to drugs of abuse is unknown.[1] Some drug reactions are presumed to be of an allergic nature, but closer examination may reveal that they are not. Real drug-induced reactions can affect numerous organ systems, present with a variety of symptoms, and have more than one mechanism of action.[2] The diagnosis of drug allergy relies on the clinical history, physical examination, skin testing, *in vitro/ex vivo* tests and drug provocation tests.[3-6] The problem is that in the case of adverse reactions to illicit drugs, there are no commercialized diagnostic extracts and challenges may be dangerous and can constitute legal and ethical issues.[3 6] This article includes a background on the topic of illicit drug allergy including cannabis, cocaine and opiates/opioids and adverse reactions to alcohol. It focuses on the impact on current medical practices and future research in support of the allergist in diagnosis and treatment of these medical problems.

CANNABIS ALLERGY

Cannabis is an illicit drug derived from the flower tops of the cannabis plant, mostly the *sativa* or *indica* varieties. Its preparations are otherwise known as 'weed', 'hash' or marijuana and are the most widespread (ab)used drugs throughout the world (see figure 1).[7]

The active ingredients are called cannabinoids, of which delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most well-known. THC is (ab)used mainly in a recreational setting for its psychoactive effects. However, there is an increasing trend in decriminalizing and even legalizing THC-rich cannabis use around the world allowing for use in a medical setting as an antispasmodic, analgesic, anxiolytic and anti-emetic drug.[8] On the other hand, CBD has grown in popularity for a variety of benefits, some more evidence-based than others. One of the best documented benefits is found to be its anti-epileptic activity in otherwise therapy resistant Dravet and Lennox-Gastaut syndromes.[9] Although

research has proven that cannabis and its components can be of significant use in medical applications, certain dangers and adverse effects cannot be excluded when its use is uncontrolled, such as is seen when the drug is used recreationally.[10] Cannabis allergy is one of these adverse effects. Although research on the topic is still in its infancy, and the prevalence of such an allergy remains unknown, different research groups around the world have shown that a cannabis allergy can manifest severe and generalized symptoms with detrimental effects on a patient's health and quality of life.[11-14] As such, in this article we aim to describe cannabis allergy and discuss the difficulty discriminating "allergic" symptoms from physiological effects, as well as the challenges associated with diagnosis, and finally debate possible future diagnosis and treatment options.

Physiological effects or allergic symptoms of cannabis?

Although we now know that cannabis allergy exists and can express a variety of symptoms (Figure 2), it can remain challenging to differentiate symptoms mediated by a hypersensitivity reaction from "normal" cannabis effects for several reasons.

First of all, it has been shown that both cannabis smoking and gastrointestinal consumption, can induce a conjunctival injection quite similar to what is seen in allergic rhino-conjunctivitis, even if the subject is not sensitized to cannabis.[15] Multiple pulmonological investigations have discussed cannabis' effects on the bronchi showing that short term effects could induce bronchodilation,[16] whereas chronic use is more often linked to bronchoconstriction which can be hard to clinically differentiate from asthma/allergy.[17 18] Multiple reports stemming from occupational cannabis exposure have suggested that cutaneous cannabis contact and/or contact with the chemical pesticides used in plantations, can induce an irritating reaction[19 20] that can be confused with allergic contact urticaria and/or eczema as seen in cannabis allergic reactions.[11 19-24]

Diagnostic challenges for cannabis allergy

As with most allergies, a diagnosis of cannabis allergy should firstly be based on a detailed history and would ideally include a challenge test. The latter is currently a big hurdle for multiple reasons. For one, in most countries cannabis is still banned thus making challenge tests illegal. Secondly, the physiological effects of cannabis can cloud the interpretation of the challenge as inhaled cannabis can cause (rhino)conjunctivitis and affect the bronchi (constriction/dilatation depending on cited research) [18 25 26]. Finally, the drug induces a mind-altering state complicating the patient's symptom assessment and recollection of experienced symptoms. The lion's share of reports on cannabis allergy make note of an IgE-mediated allergy that has been linked to different allergenic components (see table 1) such as Can s 3 and Can s 4 (OEEP2) and more recently also Can s 2 (Cs-profilin) and Can s 5 (Cs-Bet v 1 homologue).[14 27-29] As some of these allergens belong to a superfamily of panallergens including the nsLTP family (nonspecific lipid-transfer proteins), profilins and Bet v 1 homologues, cannabis allergic patients can experience cross-allergies with multiple plant-foods and *Hevea* latex.[11 12 28 30] This type of cannabis allergy can be diagnosed with different allergy diagnostics, such as skin prick tests (SPTs), specific (s)IgE quantification and basophil activation tests (BATs), using crude extracts or purified/recombinant proteins.[31] As can be expected, test specificity seems to be best using recombinant allergens[11 13 32], whereas sensitivity is found to be superior when using crude cannabis extracts. However, when using the latter, it is important to keep in mind that a significant number of pollen-sensitized individuals can exhibit clinically irrelevant results.[11] Anyhow, as the scientific exploration of cannabis allergy has only just begun, there are no standardized and validated tests on the market as of yet. There is a sIgE hemp (ImmunoCAP) available from Phadia, Thermo Fisher but for research purposes only. So, when there is a clinical suspicion of a cannabis allergy case, as illustrated by the diagnostic algorithm in figure 2, we would pragmatically suggest performing SPT/sIgE with a crude extract (preferably from the patient's own cannabis materials) as false negatives are expected to be few, and further confirmation with component resolved diagnostics can follow, if available.[31]

When it comes to IgE-independent cannabis allergies, to our knowledge only one report has looked into a type 4 hypersensitivity reaction causing contact dermatitis.[33] Finally, in the occupational cannabis setting there is a well-documented body of evidence indicating that cannabis-induced byssinosis can occur; a form of occupational asthma attributed to organic dust exposure, derived in part from naturally occurring microorganisms.[34] Diagnosis of byssinosis starts with a detailed history as symptoms are often solely respiratory, are worst on the first day of exposure, diminish the following days and re-emerge after a period of non-exposure. In addition, spirometry is a helpful tool to objectify cannabis-related bronchoconstriction. A CT-scan (millimetric) can further aid in the diagnosis of byssinosis and other types of pneumonitis as can fluids obtained during bronchoscopy (bronchial alveolar lavage or BAL) and lung diffusion tests such as TLCO.

Prospects for the future

The current evidence has established that IgE-mediated cannabis allergy is a true allergy entity which can manifest severe and generalized symptoms with a variety of cross-reactivities. Nevertheless, prediction of its prevalence remains difficult, in part because of the illegal status of the drug and thus the impact of cannabis allergy on society should still be further explored. In addition, several allergens have been detected with most recently the confirmation of Can s 2 (profilin), Can s 4 (OEEP2) and Can s 5 (a Bet v 1 homologue) as potential cannabis allergens.[27 29] Still, the IgE-reactivity profile seems to be incomplete and remains food for thought. Finally, for the time being there is no available cure for IgE-mediated cannabis allergy nor for the cannabis-related plant-food allergies. Therefore, strict avoidance measures remain of the utmost importance. These measures comprise a complete stop of further cannabis exposure and avoidance of exposures to allergens implicated in the individual cross-reactivity syndrome. Although some case reports claim successful desensitization[35 36], further research is needed to investigate its true potential as cannabis allergy treatment.

COCAINE ALLERGY

Natural cocaine is an alkaloid extracted from the leaves of the coca shrub *Erythroxylum coca* and *E. novogranatense*. The harvested leaves are macerated with various solvents. This process results in a pasty substance ("coca paste") which contains 80% cocaine and is purified to "coca base". Through reaction with hydrochloric acid cocaine powder is formed while the solvents and acids are removed. Cocaine powder can be used via oral, sublingual, intravenous, intramuscular, and subcutaneous routes. The nasal use is called snorting. If cocaine hydrochloride is precipitated it can be smoked as "free-base cocaine" or "crack (rock)".[37] Bronchospasm can occur in patients smoking cocaine[38-40], often in patients with a history of asthma. Research has shown that cocaine use may be responsible for asthma onset, acute asthma exacerbations (which may require intubation and invasive ventilation) and asthma-related death.[41]

Smoking crack cocaine and nasal insufflation of cocaine increases the risk of emergency department visits due to severe angioedema[41]. Studies that investigate the prevalence of potentially harmful adulterants in crack have found that the most prevalent adulterant is lidocaine (92%), followed by phenacetin (69%) and levamisole (31%)[42]. The immunomodulatory adjuvant and antihelminth levamisole is increasingly used as an adulterant in cocaine worldwide. Neutropenia, agranulocytosis, leukoencephalopathy and vasculitis in cases associated with levamisole-adulterated cocaine has been described [43].

In a series of 211 patients with symptoms related to cocaine abuse[37], 41 were diagnosed as cocaine allergic by positive challenge, prick and sIgE to coca leaves.

Some local anesthetics (LA) derived from cocaine (benzocaine, dibucaine, procaine) and cases of anaphylaxis after LA have been described[44 45], but overall IgE -mediated (immediate) allergy to LA is

177 rare.[44] The major source of delayed reactions to LAs is direct contact resulting in allergic contact
178 dermatitis, especially by dibucaine-containing perianal medicaments[46], although benzocaine has been
179 identified as a leading sensitizer.[38 40 41 45]
180 Until now, as for cannabis allergy, there are no efficient commercial diagnostic techniques that
181 demonstrate an IgE-mediated allergy to cocaine. Studies showing that cocaine-dependent patients
182 respond positively to prick and sIgE tests to coca leaf extracts, led to investigate the use of these tests
183 in patients with hypersensitivity to cocaine-derived LA.[37] Component resolved diagnosis (CRD) have also
184 been used to determine its sensitivity and sensibility in detecting sensitivity to the different molecules of
185 complex allergens, such as cocaine, which is often adulterated, or coca leaf extracts. Using a large
186 database [37] , the study focused on patients with anaphylaxis to local anesthesia and patients with drug
187 abuse and symptoms of asthma and anaphylaxis after cocaine use. The diagnostic yield (sensitivity,
188 specificity, and predictive value) of allergy tests using cocaine and coca leaf (figure 1) extracts in
189 determining cocaine allergy was assessed, taking a positive challenge as the gold standard. This
190 research found that SPTs and sIgE to coca leaves (coca tea) had a good sensitivity and specificity for
191 the diagnosis of cocaine allergy and local anesthetic-derived allergy.

192 In summary, cocaine allergy may provoke life-threatening symptoms and should be considered in
193 cocaine-dependent patients with poorly controlled asthma and in candidates for surgery. Cocaine
194 hypersensitivity may be tested with a simple and practical method such as SPTs and sIgE determination
195 to cocaine extracts in the clinical situation. However, more research is necessary to define the exact
196 nature of the allergic compounds and develop standardized and commercially available tests.[47] A
197 correlation of such tests with serum tryptase, plasma histamine and if available, basophil activation test
198 (BAT) would add to the validation of allergic reactions.[47,48]

199 ALLERGY TO OPIATES AND OPIOIDS

Opium is the dried sap that is drained from the seed pod of the opium plant *Papaver somniferum*. Morphine and opioid based drugs are created in refineries. A series of chemical reactions changes morphine to heroin powder (figure 1). Opioids and Opiates constitute an important part of (illicit) drug abuse but on the other hand, they are also potent analgesics of vital importance in a hospitalized setting. An important characteristic of opiates, such as morphine and codeine, is the fact that they can trigger a histamine release from skin mast cells mimicking allergic reactions. Methadone, tramadol, fentanyl and its derivatives do not have this property.[49] This nonspecific histamine release makes the traditional allergy SPT to opiates and (semi-)synthetic opioids difficult to interpret. It is challenging to differentiate IgE-mediated opiate allergy from non-specific reactions.

For several decades, case reports, retrospective studies, and laboratory investigations have demonstrated that heroin inhalation can be associated with increased asthma symptoms (possibly because of non-specific histamine release) and reduced pulmonary function. Smoking or nasal insufflation of heroin increases the risk of emergency department visits and hospitalizations for asthma.[38]

In light of the diagnostic challenges for opiates, researchers debate whether diagnostics based upon opium seed extracts are helpful. Spanish researchers have explored heroin sensitization in a cannabis allergic, multi drug addicted population, to try and prevent hypersensitivity reactions to opioids, during surgery [13 32 50]. To avoid the non-specific histamine release of opiates in SPTs, opium seed extracts (figure 1) were used as a substitute for heroin.[51] Two hundred-and-three patients from said population were selected with hypersensitivity reactions during surgery, and confirmed heroin abuse. Patients sensitized to heroin (defined as a positive challenge) or with severe clinical reactions during surgery, responded to *P. somniferum* seed tests (positive IgE and skin tests). Opium seed SPTs and sIgE, especially the oil body fraction, were more sensitive (64.2%) and specific (98.4%) than morphine, codeine and rocuronium tests for opioid sensitivity. However, a Belgian group also explored sIgE to morphine and opium seed extracts additionally to BAT with morphine/codeine in 22 individuals; they found that positive sIgE results to poppy seed and morphine were not per se predictive for genuine opiate allergy. However, BAT seemed

promising to help discriminate clinical reactivity and sensitization.[52] Genuine IgE-mediated anaphylaxis to opiates and synthetic opioids (methadone, tramadol, fentanyl and its derivatives) is rare.[49] Little or no evidence exists between cross-reactivity of the different opioid subclasses but cross-reactivity between morphine and codeine was reported.[53 54] IgE and skin tests for the oil body fraction of *P. somniferum* had the highest sensitivity for sensitization to opioids. Another concept regards non-specific mediator release, likely because of occupation of the Mas-related G protein-coupled receptor X2, that is mainly expressed by skin mast cells, as much more prevalent.[49 54] At present there is no reliable diagnostic to document such MRGPRX2 reactions that are clinically and biologically indistinguishable from IgE-mediated reactions.[55] A possible diagnostic approach could include ex vivo basophil activation experiments, as these cells barely express this receptor, and do not react non-specifically to MRGPRX2 agonists.[52 56]

A major problem with illicit drugs such as heroin is that their illegal status results in varying drug compositions, ingredients, and possible contaminants. The unknown drug composition can be the cause of "hidden" allergens and may result in serious and sometimes even life-threatening symptoms as exemplified by a case of a heroin addict displaying an endophthalmitis believed to have resulted from fungal contaminants from his heroin as well as an anaphylactic reaction to lemon particles contaminating the drug used.[57]

ADVERSE REACTIONS TO ALCOHOLIC BEVERAGES

There are many causes for adverse reactions to alcohol. These reactions can be non-immunologic (pharmacologic) and immunogenic due to various ingredients of alcoholic beverages. Alcohol consumption, in addition, has an influence on the presentation of certain diseases and reactions to medications. The processing of alcoholic beverages and additives may contribute to the reactions to alcohol.

Hereditary Enzyme Deficiency of the Alcohol Metabolism

One of the most common adverse reactions to alcohol is the so-called “Asian Flush Syndrome” characterized by facial flushing, headache, nausea, dizziness, and cardiac palpitations after consumption of alcoholic beverages. There are two enzymatic steps to metabolize ethanol: The first is the production of acetaldehyde by the enzyme alcohol dehydrogenase (ADH) and the second is the breakdown of acetaldehyde by aldehyde dehydrogenase (ALDH). (figure 3). These enzymes are encoded by different genes, that occur in several variants (alleles). The enzymes encoded by these alleles can differ in the rate at which they metabolize alcohol.[58]

In the Asian Flush Syndrome, there is a mutation of ALDH2*1 to ALDH2*2 as the most common cause.[59-61] This mutation occurs in 560 million people (8%) of the world population. Its highest prevalence (35-45%) is in people of East-Asian descent, hence its name. The situation is even made worse if another mutation in the first ethanol metabolizing enzyme accompanies the problem: a mutated ADH, specifically ADH1B*2.[59] This mutation also occurs more commonly in people of Asian descent. ADH1B*2 metabolizes ethanol fairly fast to acetaldehyde and if ALDH2 does not work the result is an increase in the acetaldehyde level. Acetaldehyde has been implicated in a marked increase in cancer of the upper digestive tract, especially esophageal cancer.[61] Although experiments have been performed to introduce the ALDH2 coding sequence into mice with the help of an adeno-associated virus (AAV) gene transfer to correct the deficiency state, the applications for humans may still take many years.[62]

Immunogenic Reactions to Alcoholic Beverages

In the allergy literature are reports of anaphylactic reactions to ethanol itself. [63 64] The studies mentioned are few, and usually involve the case history of sometimes poorly documented single patients. Skin tests with diluted acetic acid were used which were positive in the majority of patients and negative in controls.

However, almost all patients tolerated vinegar. In addition, provocation tests with ethanol, most of them blinded, were positive in all patients. It is rather difficult to explain the pathogenetic mechanism of these rather rare reactions. Newer research more concentrates on the multitude of components in alcoholic beverages.

One important allergen that occurs in alcoholic beverages is a lipid transfer protein (nsLTP) resistant to heat and acid.[28] Patients sensitized to nsLTP may be asymptomatic, but their reactions seem to be more severe when they are sensitized to the food nsLTP alone.[31] An nsLTP protein is present in grape Vitis vinifera (Vit v 1) and therefore in wine. nsLTP proteins are also present in beer deriving from different cereals that are germinated and heated to obtain malt. They occur in barley, *Hordeum sativa* and *vulgare* (Hor v 7k-nsLTP), wheat, *Triticum aestivum* and in maize *Zea mays* a. o.[65] Another nsLTP protein occurs in hops, *Humulus lupulus,* added for bitterness and flavor. These nsLTPs in sensitized patients, who consume wine or beer can lead to IgE-mediated reactions of different severity that may include anaphylaxis. Such allergic reactions can be amplified by concomitant exercise or use of non-steroidal anti-inflammatory drugs (NSAIDs).[31] Wheat containing beer, especially when consumed with additional wheat products, can lead to wheat-dependent exercise-induced anaphylaxis due to an antibody to wheat-γ-gliadin.[66 67] In wheat beer (Weissbier) barley is mixed with 50 % of wheat malt. Newer proteomic and peptidomic analysis shows that it contains gluten epitopes and is therefore incompatible with a gluten-free diet for celiac patients.[68] In addition, Weissbier, due to the brewing technique, contains more yeast-derived products, mainly from *Saccharomyces spp.*, than other beers. An IgE-mediated yeast allergy is exceptionally rare. One of very few case reports establishes an Ig-E mediated sensitivity to yeast in beer, wine, and cider.[69] Yeast is added in the beer making process and occurs naturally in wine but may also be added to red wine must or to the juice from white wine. ImmunoCAP tests are available for *Saccharomyces* and for barley/malt. An interesting IgE-mediated allergy to red and white wine through oral sensitization to Hymenoptera venom was reported.[70] Hymenoptera venom can contaminate fresh pressed wine as stinging insects are attracted to sugars and alcohol in ripe grape bunches. The allergic

reaction occurred only to fresh pressed wine, and not to wine aged up to one year. In old wines the fermentation decomposes the venom. A rare report of anaphylaxis to gold tequila but not to white tequila was reported in a patient allergic to oak pollen.[71] Gold tequila is aged for months or years in oak barrels whereas clear tequila undergoes little to no aging.

Discussion of the Clinical Implication of the Presence of Histamine in Alcohol

The primary fermentation step produces alcohol and during the secondary fermentation biogenic amines, such as histamine, are formed.[72] The histamine content in beer, white and red wine is 176, 83, and 260 mg/kg, respectively.[73] Scientific research of adverse reactions to ingested histamine, accused of causing symptoms of headache, flushing, diarrhea a.o. due to deficient ability to metabolize histamine,[74] did not reveal an isolated clinical picture.[75] Laboratory tests to study reactions to exogenous histamine are not reliable. Double-blind, placebo-controlled trials with histamine provocation triggered symptoms in healthy subjects.[76] A low histamine diet is of minimal benefit.[77] More scientific evidence is still required to define, diagnose, and treat symptoms of assumed adverse reactions to histamine.[74 75]

Fining Agents in Wine

Fining is a process in winemaking to remove small insoluble and colloidal particles and astringent compounds such as tannins. Fining agents are ovalbumin and lysozyme (extracted from hen's egg), cow's milk, casein, fish gelatin and isinglass (from swim bladders of sturgeon, cod, or hake). The fining process prevents later clouding of the wine, so that it remains stable for storage, transport, and temperature conditions.[72] Only wines with high concentration of fining agents resulted in positive skin prick tests in patients with a food allergy to the fining agent.[78 79] A preliminary study with immunoblotting to detect and quantify ovalbumin and casein in bottled wine showed the samples to be allergen free.[80] Another study reports negligible residual food allergens in wine.[81] Although there is concern regarding

labeling of wines for food-allergic patients in many countries, these studies make a reaction to fining agents in IgE-mediated food allergic patients either rare or highly unlikely. Many wine-producing countries will run more large-scale studies to ensure the safety of handling the removal process of fining agents.

Sulfites in Wine

Small amounts of sulfites occur naturally in all wines. Sulfites are added during the winemaking process to arrest fermentation, to act as preservatives and to prevent spoilage from oxidation and protect from bacteria. Sulfites are at much higher concentration in white than in red wine.[72] Previous studies indicated that wine consumption was associated with worsening of asthma symptoms, but high-and low-sulfite wine challenges did not support a role for sulfites in stable asthmatics.[82] However, asthma patients, mostly with IgE-independent steroid-dependent asthma, in as many as 5% may react with mild wheezing or severe bronchoconstriction to sulfite-containing beverages.[83] The mechanism of sulfite-induced asthma is controversial. An IgE-mechanism has been suspected but not proven. Debated have also been a cholinergic reflex, a partial deficiency of the sulfite-oxidase enzyme, responsible for the final oxidizing of sulfite to inactive sulfate, and a kinin mechanism. Reaction to sulfites seems to be a nonspecific response and specific IgE antibodies to sulfites have not been identified.[84]

Specific alcohol-related Effects on Medical Conditions

Patients with Aspirin Exacerbated Respiratory Disease (AERD) and Chronic Rhinosinusitis (CRS) can experience respiratory reactions with alcohol ingestion.[85] In AERD, the severity of aspirin-induced reactions during aspirin challenge correlated with the severity of the alcohol-induced reaction. As patients

with AERD have a higher excretion of urinary Leukotrienes (LTs) an LT-dependent mechanism may underlie the alcohol-induced respiratory reactions.

Systemic Contact dermatitis Ethanol is used as topical penetration enhancer in transdermal medications as it removes lipids from the skin. Use of such "patches" over a prolonged period of time can lead to ethanol sensitization resulting in a delayed (8 hours) cutaneous reaction.[86] Patients with **Chronic Urticaria** often notice an exacerbation after ingestion of alcohol.[87]

Rosacea flushing, among other factors, is known to be triggered by alcohol, recently thought to be caused by neuronal signaling.[88] In patients with **Hodgkin lymphoma** pain at the site of bone or lymph node involvement may appear minutes after ingestion. This alcohol-related pain is highly specific for the diagnosis and occurs in 1.5 – 5% percent of patients[89], the mechanism is unknown. One of the factors provoking flushing in **Carcinoid Syndrome** is alcohol.[90]

The exacerbation of symptoms of **Mastocytosis** has been thought, amongst other factors, to be influenced by alcohol due to its content of histamine.[91]

Alcohol-Medication Interactions

Many medication reactions involve an interference with the activity of ADH increasing the level of acetaldehyde which causes facial flushing, nausea, vomiting, tachycardia, and hypotension. In this category are medications such as **Disulfiram**, **Cephalosporines** with a methylthiotetrazole side chain and **Chlorpropamide**.[91-93] Another enzyme system that likely plays a role in alcohol-medication interactions is the P450 reductase and the CYP2E1.[94]

However, not all disulfiram-like reactions are yet clarified. One such reaction is a disulfiram-like reaction to metronidazole and other nitroimidazoles in patients consuming alcohol. The interaction between metronidazole and alcohol does not occur in all patients, suggesting an individual susceptibility.[92] Other interesting reactions may occur to the topical calcineurin inhibitors, **Tacrolimus** and **Pimecrolimus**. Five

to ten minutes after a local application not only the treated area can become erythematous but flushing of healthy skin, for example the face, may occur.[92] An unusual reaction in a patient that tolerated topical tacrolimus for years occurred when **Dupilumab** was started. [95] Future research will reveal more information on alcohol-related medication reactions.

CONCLUSIONS

In the field of Allergy, much has already been discovered concerning allergies to pollen, food and plant products. However, the investigations of (illicit) drug allergies seem to be lagging behind. This review highlights what is known about allergies and other adverse reactions to cannabis, cocaine, opiates, opioids and alcohol. In addition, several hurdles, and points of attention specific to this field of research are discussed in the hope to facilitate future qualitative research and help progress our knowledge about (illicit) drug allergy.

Apart from a patient's reticence to discuss their drug use, it is also important to keep in mind that many drugs induce a mind-altering state with different sensations of time and space as well as a varying degree of retrograde amnesia. Thus, the patient might experience symptoms differently impacting for example the accuracy of the reported time between contact and onset of symptoms as well as perceived duration of symptoms; details which are of paramount importance in allergy history taking.

This review shows that cocaine use should be systematically considered in the case of asthma exacerbations. Cannabis, cocaine or heroin use must be considered in cases of acute respiratory symptoms or asthma exacerbation in young people and practitioners must help illicit substance users to stop their consumption.[40 96]

It is necessary to find reliable diagnostic methods based on *in vivo* and *in vitro* tests using extracts of the natural plant source or recombinant proteins in a large series of habitual heroin, cocaine and cannabis

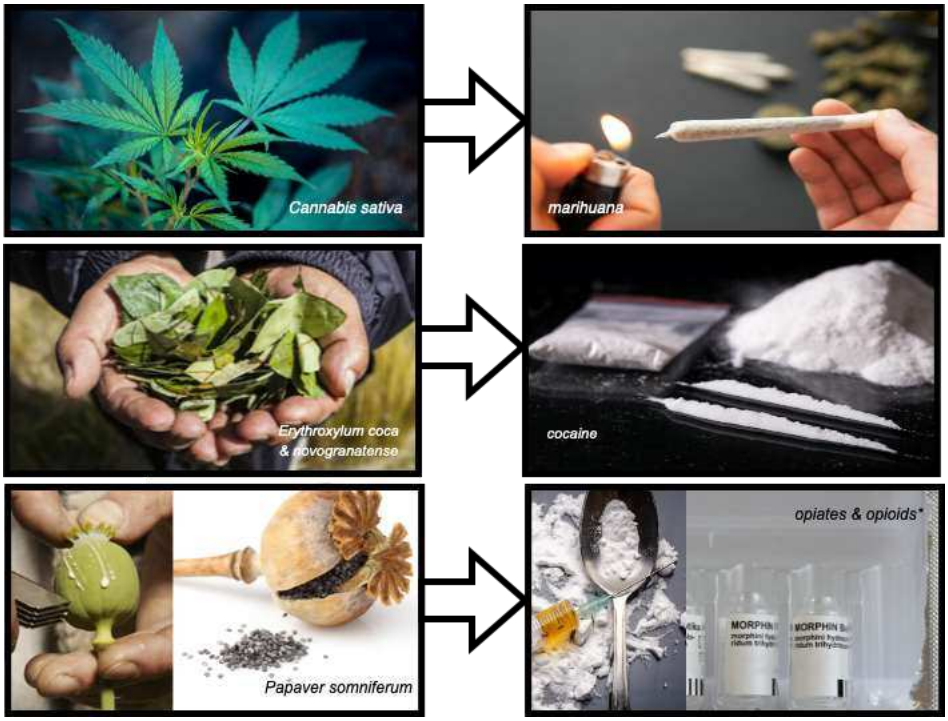
consumers and atopic and non-atopic controls. In patients sensitized to these drugs, antibodies can be measured for many years, which could have legal and forensic implications, and could allow changes in drugs like opium and cocaine-derived anesthetics in patients about to undergo surgery. In closing it is hoped that the outlined factors involved in adverse reactions to alcohol will support a stepwise analysis of situations seen in the clinic.

FIGURES AND TABLES

TABLE 1: Allergens from Cannabis sativa (Can s) indexed in the Allergen list of the IUIS.

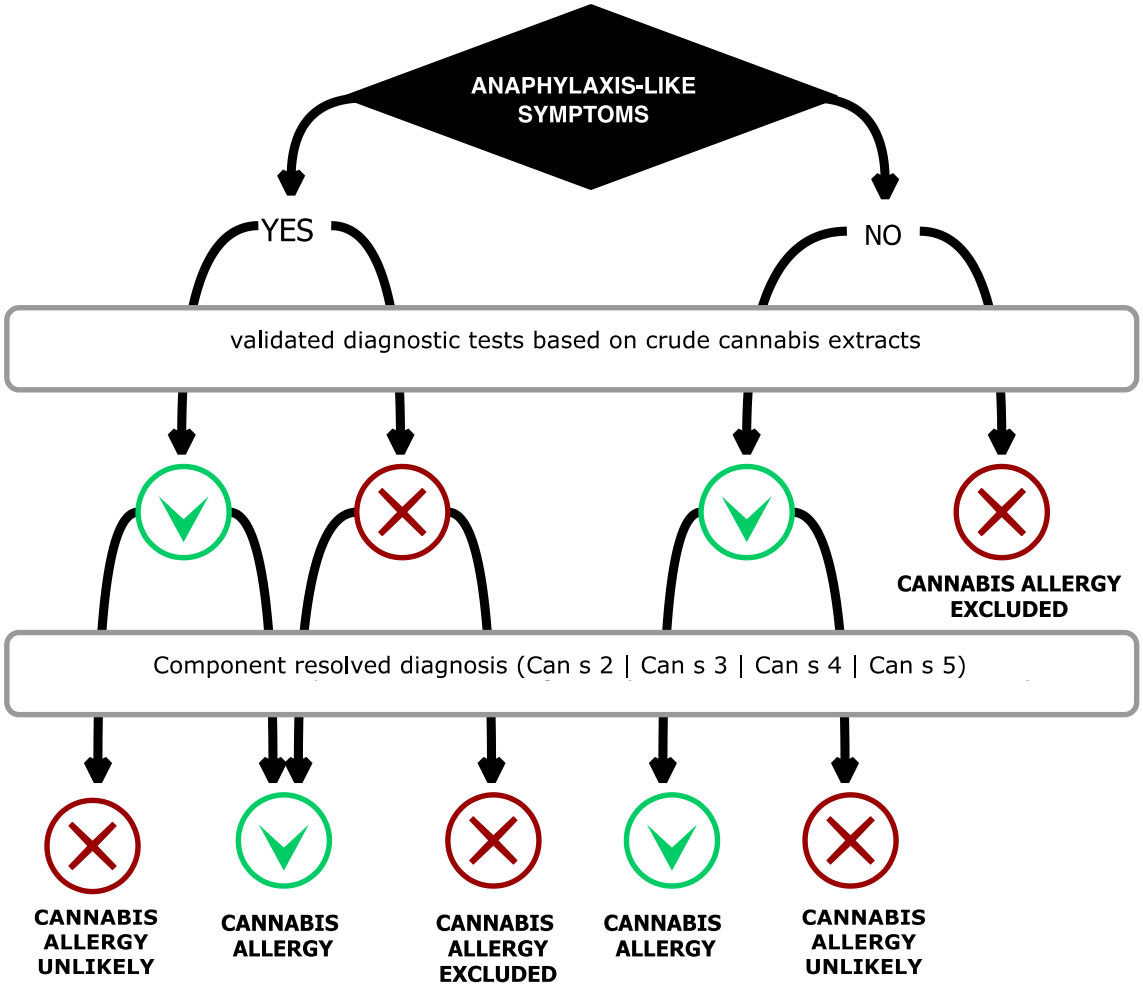
IUIS nomenclature	**Allergen class** Genbank Nucl Genbank Prot	**Molecular weight (kDa)**	**Available from**	**Reference**
Can s 2	**Profilin** XM030636604.1 XP030492464.1	14	H.P. Rihs	[29]
Can s 3	**nsLTP** HE972341 CCK33472	9	H.P. Rihs	[11 28]
Can s 4	**OEEP2** XM030626708.1 XP030482568.1	27.3	H.P. Rihs	[27]
Can s 5	**Bet v 1 homologue** JN6792251.1 AFN42528.1	17.7	H.P. Rihs	[29]

FIGURE 1



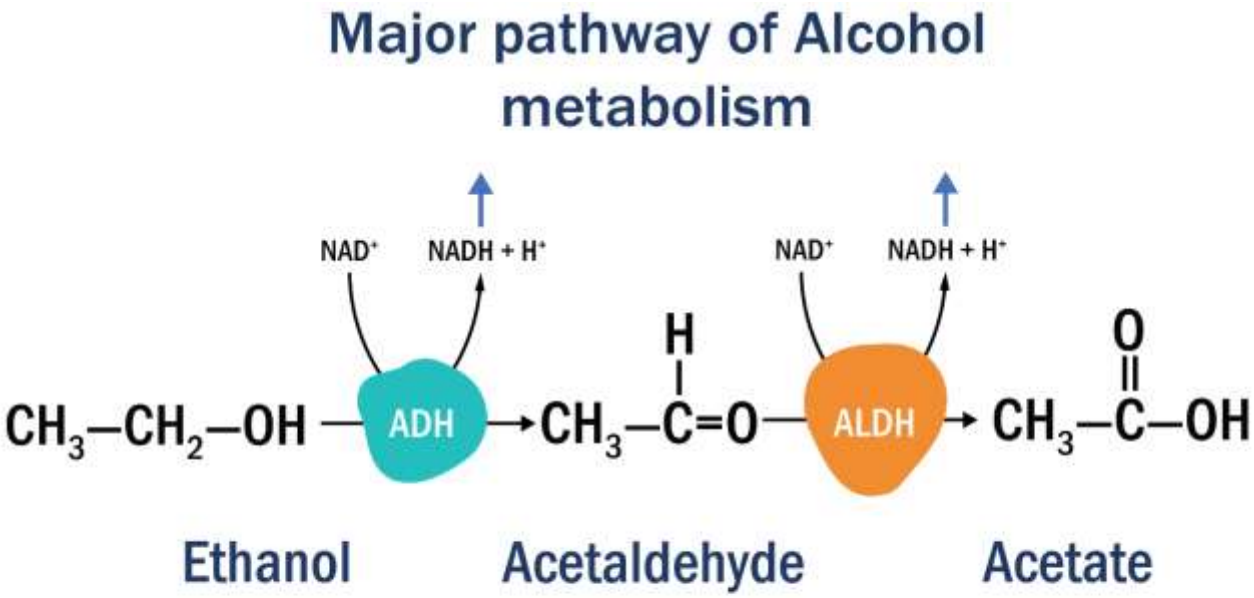
*Legend: *opiates derive from natural whereas opioids from synthetic sources.*

FIGURE 2



Legend: Proposed stepwise diagnostic approach for cannabis allergy. Adapted from Decuyper et al. [31].

FIGURE 3



ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
NAD+	Nicotinamide adenine dinycleotide (oxidized)
NADH	Nicotinamide adenine dinucleotide (reduced)

Namrata Chhabra (2015); 'Alcohol-induced metabolic alterations- a case-based discussion': Our Biochemistry; slide 4(64); https://www2.slideshare.net/namarta28/alcohol-induced-metabolic-alterations-a-case-based-discussion/6

Legend: Column 1 gives an overview of known Cannabis allergens, listed with the name assigned by the International Union of Immunological Societies (IUIS). Column 2 lists the corresponding sequence data of the GenBank for the Nucleotide (Nucl) and the Protein (Prot). The GenBank is a part of the International Nucleotide Sequence Database Collaboration (INSDC).

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