MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Adulterations within illicit drugs: Forensic Prospection

Hala M. Heneedak [a*], Mohamed Saleh Elgawish [b], Samia M. Mostafa [b], Khaled M. Darwish [b]

[a] *Forensic chemistry Department, Forensic Medicine Authority, Ministry of Justice, Cairo 11617, Egypt.*

[b] *Medicinal Chemistry Department, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt.*

Received on: 27. 06. 2024

Revised on:

Accepted on:

* Correspondence Author:

Tel: +2 (010)61791706

E-mail address:

hala.hesham@icloud.com

Abstract

Addiction is a complex and global problem. Its profound impacts don't include the addicts only, but also family, and whole society such as homelessness, unemployment, relational conflicts, and psychiatric comorbidity. Physical addictions can be classified into three groups: illicit (illegal) drugs, alcohol, and prescription drugs. The availability of a wide range of illicit drugs, often mixed with unknown substances, poses a significant seriousness on drug users. Many users lack awareness of both content and quality of the compounds they consume. Drug addiction can be a serious hazard, causing acute and chronic effects on health, compounded by the presence of potentially harmful drug adulterants.

Keywords: Addiction, Illicit drugs, Prescription drugs, Adulteration.

1. Introduction

Addiction is a complex and global problem. Its profound impacts don't include the addicts only, but also family, and whole society such as homelessness, unemployment, relational conflicts, and psychiatric comorbidity (Lancet 2012). It affects health both physically and mentally, resulting in financial strain, unstable relationships, and ethical and legal issues. The non-medically used and abused pharmaceutical drugs, gain long-standing domestic and international concerns (Robert K. Brooner * 1998, Lander, Howsare et al. 2013). Generally, physical addictions are the most well-known. These addictions include ingested substances or otherwise those can be put into a human's body. In general, Physical addictions can classified into three groups: illicit (illegal) drugs, alcohol, and prescription drugs (AddictionCenter 2024). Illegal substances (illicit drugs) are forbidden because, when they are used, short-term brain disruptions occur, and reality perception is altered. These drugs alter the brain mainly, and other organs for long-term. Thus, severe addiction resulted. Alcohol addiction is possibly one of the most prevalent types of addiction. It presents itself through alcohol dependence, excessive binge drinking, or frequent heavy consumption. Typically, addiction to alcohol begins with social drinking but gradually escalates until the individual is confronted with an insurmountable addiction. In the addiction of prescription drugs, approved medicines are misused in a manner that doctors haven't prescribed. This type of addiction is becoming problematic in the whole world today (AddictionCenter 2024).

1.1. Illicit Drugs

Illicit drugs encompass strongly addictive and unlawful substances, including heroin, amphetamines, marijuana, and synthetic cannabinoids (SCs). Although the initial choice to try these drugs is often voluntary, the unforeseen development of addiction can greatly complicate the decision to quit later (Max M. Houck PhD 2015). Different categories of illicit drugs and prescription drug addiction can be classified as follows: Cocaine, is derived from the coca plant, cocaine is a highly addictive stimulant commonly found in powder form. Crack cocaine, A purer form of cocaine with higher potency, usually available in crystals or solid blocks (Goulian, Jauffret-Roustide et al. 2022). Ecstasy is Often abused by young adults and those in high schools, as a rave or party drug. Ecstasy causes enhanced sensory perception and reduced inhibitions. Hallucinogens, this category includes drugs like PCP, LSD, Salvia, and Mushrooms fall under this category, causing altered perceptions and mind-altering effects. Heroin is a synthetic opioid derived from the opium poppy plant; it has extreme addictive properties. Inhalants are household items like cleaning supplies, markers and spray paints are used to achieve a high when inhaled through the mouth or nose. Ketamine is originally an anesthetic for veterinary use, ketamine can cause confusion, sedation, and hallucinations when abused. Among the most famous abused illicit drugs is marijuana which its main psychoactive component, THC, induces euphoria temporarily, then drowsiness, reaction time is slowed, and appetite is raised. Methamphetamine is a highly dangerous stimulant that can lead to instant addiction (Radfar and Rawson 2014). Finally, Synthetic Marijuana (synthetic cannabinoids), this category includes artificially produced substances containing chemicals like THC (Antoniou and Juurlink 2014).

1.2. Synthetic marijuana (synthetic cannabinoids)

New psychoactive substances (NPS) possess a field that is evolving at constant rate. Each year new compounds are recorded in the prohibited drug market (UNDOC 2020). The United Nations Office on Drugs and Crime (UNODC) has reported about more than 290 of Synthetic cannabinoids (SCs), they express the largest and most structurally versatile categories of NPS (Banister and Connor 2018, UNDOC 2020). SCs were synthesized to be alternatives for cannabis, to give the same effect of Δ^9-tetrahy-drocannabinol (THC), which is the main psychoactive component (Banister, Arnold et al. 2019).

SCs bind mainly with cannabinoid (CB) receptors, exerting their effects. Cannabinoid receptor type 1 (CB1) spreads in the central nervous system and is in charge of the psychoactive effects (Castaneto, Gorelick et al. 2014). whereas the CB2 subtype occupies immune cells predominantly (Howlett 2002, Shahbazi, Grandi et al. 2020). Potency and efficacy of SCs at CB receptors is greater when compared to THC, which partially activates both subtypes, which may be

the reason for the limited toxicity of cannabis (Banister, Arnold et al. 2019). In opposite, SCs are associated to many health troubles, such as dependence, seizures, psychosis, toxicity of organs, and even death (Anderson, Oprescu et al. 2019, Darke, Duflou et al. 2020).

To control and prevent the synthesis, trafficking, and possession of SCs, applying many of legislative approaches was done at both of national and international levels (Peacock *et al.*, 2019) However, synthesis, designing and selling novel compounds to circumvent current controls of specific SCs motivated (Alam and Keating 2020). Gathering information about pharmacological action of these compounds is very little because they enter the market at a fast paced, despite the human use spreads widely. Recently, SCs are divided based on their heterocyclic core into three groups: Indole SCs, indazole SCs, and 7-aza-indole SCs (Cannaert, Sparkes et al. 2020), (**Fig. 1**)

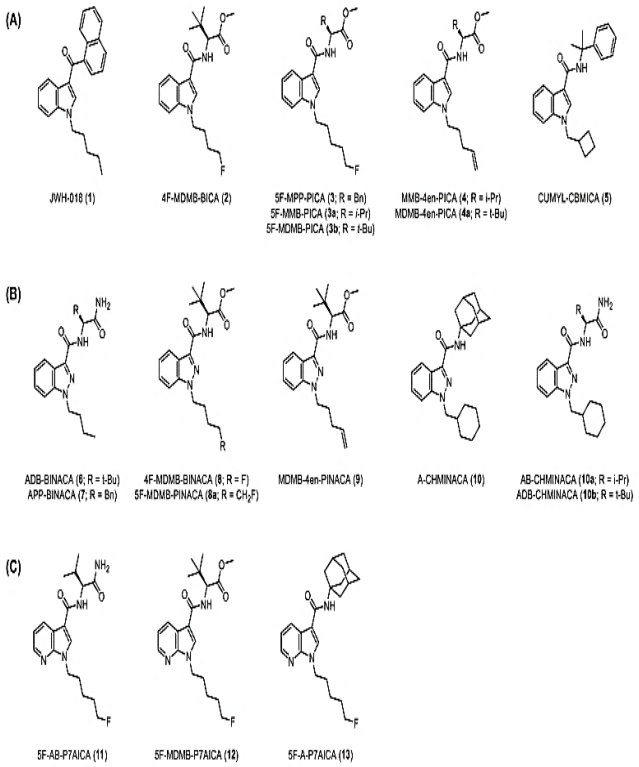

Fig. 1. Chemical structures of SCs, categorized according to their heterocyclic core: (A) SCs with indole core, (B) SCs with indazole core, and (C) 7-aza-indole SCs.

Synthetic cannabinoids (SCs) are illicit substances that are commonly soluble in organic solvents like methanol or acetone to be sprayed onto plant materials such as thyme, mint, or lemon balm. They are marketed and sold in appealing packages under various striking names like Spice or K2, often lacking any quality control, without certain quantity, their distribution occurs frequently over the internet, particularly on the dark web.

Contents of these herbal mixtures may include unidentified substances or other dangerous, illicit compounds with toxic properties like ecstasy, bath salts, or rodenticides, which can furthermore participate in their harmful effects. SCs are typically consumed by smoking using pipes, water pipes, paper, or e-cigarettes, and sometimes they are ingested orally in the form of tablets, herbal infusions, or powders (Cannaert, Sparkes et al. 2020), (**Fig. 2**)

Fig. 2. method of consumption of SCs.

1.2.1. Metabolism of SCs

Regarding their metabolism, while the complete breakdown of many Synthetic cannabinoids is not yet fully understood, available data for some representatives show that they undergo extensive oxidative metabolism. Cytochrome P450 enzymes (CYP) primarily oxidize these substances, producing oxidized metabolites that then undergo a second metabolic phase involving glucuronidation and/or sulfation facilitated by a group of enzymes called UDP-glucuronosyltransferases (UGT), (**Fig. 3**)

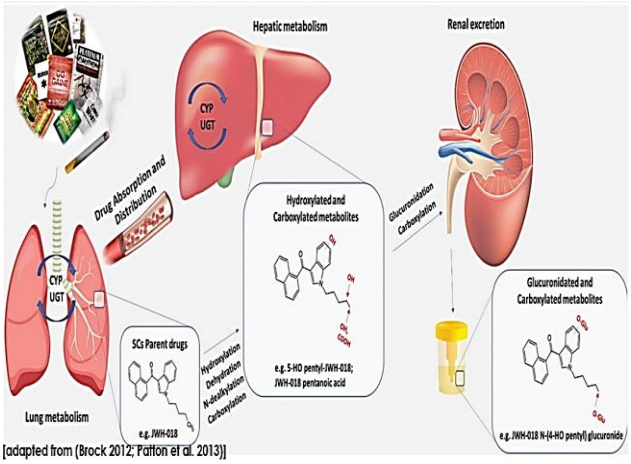

Fig. 3. Diagram illustrates the metabolism of SCs

Eventually, these metabolites are eliminated through renal excretion. Overall, oxidative metabolism predominantly results in the formation of mono-, di-, and tri-hydroxylated, N-dealkylated, and carboxylated compounds (Castaneto, Gorelick et al. 2014).

1.2.2. Toxicity of synthetic cannabinoids

High doses of toxic SCs can have profound and immediate effects on the nervous system. These neurological perturbations can include a range of cognitive impairments and emotional disturbances, flashbacks, short-term Memory Loss and suicidal Ideation**.** (Gurney, Scott et al. 2014, Cohen and Weinstein 2018). Other adverse effects of SCs are cardiovascular effects, musculoskeletal toxicity (muscle breakdown), Liver and Kidney Toxicity and Failure, (Canazza, Ossato et al. 2017, Boland, Reidy et al. 2020) (**Fig. 4**).

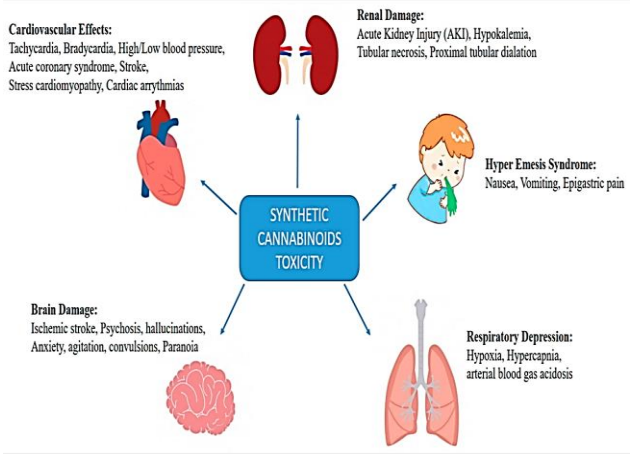

Fig. 4. Diagram illustrating toxicity of SCs.

Given the serious health risks associated with SC use, public health initiatives should focus on education and prevention to reduce the incidence of SC-related health issues (Riederer, Campleman et al. 2016, Kronstrand, Guerrieri et al. 2018).

1.3. Prescription drugs

This category includes opioid analgesics, that are used to manage pain, opioids encompass tramadol, tapentadol, fentanyl, dextromethorphan, methadone, oxycodone, buprenorphine, and codeine (Eikemo, Meier et al. 2023). Stimulants, these medications are used to treat ADHD (attention-deficit/ hyperactivity disorder) and specific sleepiness troubles. Examples include dextroamphetamine-amphetamine (Adderall XR, Mydayis), dextroamphetamine (Dexedrine) and methylphenidate (Ritalin, Concerta, others) (Patel, Chavan et al. 2024). Anti-anxiety medicines, sedatives, hypnotics and antiepileptics, are Prescribed for anxiety and sleepiness disorders, examples include diazepam (Valium), alprazolam (Xanax), Gabapentinoids (pregabalin and gabapentin) are used to treat neuropathic pain and anxiety as well (Cain 1967).

1.3.1. Opioid analgesics

Opioids are a category of medications commonly prescribed for pain management and treatment. They exert their analgesic effects by acting on both presynaptic and postsynaptic sites. On the presynaptic side, opioids block calcium channels located on nociceptive afferent nerves, which hinders the release of neurotransmitters like glutamate and substance P. These neurotransmitters are known to contribute to the sensation of pain. On the postsynaptic side, opioids open potassium channels, leading to hyperpolarization of cell membranes. This hyperpolarization raises the threshold for generating nociceptive transmission, making it more difficult for pain signals to be transmitted (Van Rensburg and Reuter 2019), (**Fig. 5**). The analgesic effects of opioids are mediated by three types of opioid receptors: mu, kappa, and delta receptors, which operate both in the spinal cord and above the spinal cord (supraspinally). These receptors

play a crucial role in modulating pain sensation and providing pain relief (Cohen, Ruth et al. 2024).

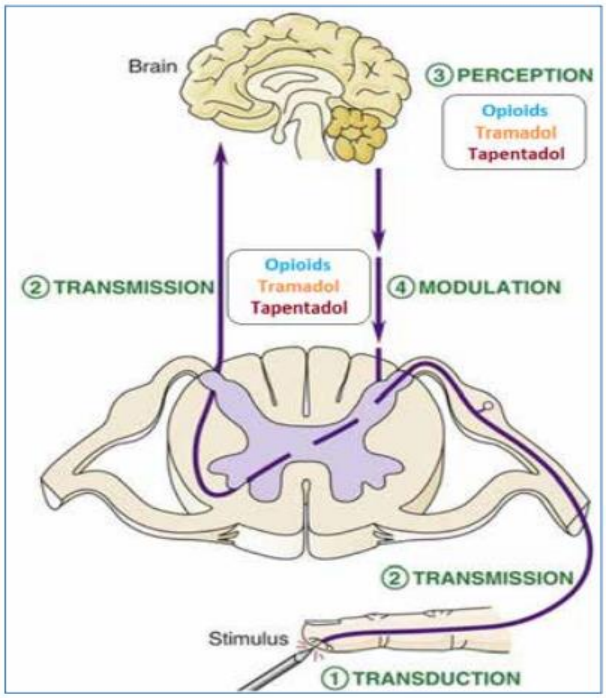

Fig. 5. targets of tramadol, and tapentadol.

Certain opioid medications can have an impact on serotonin levels when used alongside other serotonergic agents. The suggested mechanism for this interaction involves weak inhibition of serotonin reuptake and an increase in intrasynaptic serotonin release, achieved by inhibiting gamma-aminobutyric acidergic presynaptic inhibitory neurons on serotonin neurons.

Opioids that fall into this category include tramadol, tapentadol, methadone, dextromethorphan, meperidine, oxycodone, fentanyl, buprenorphine, and codeine. It's essential to exercise caution when using these opioids in combination with other substances that have serotonergic activity, as they have the potential to cause serotonin syndrome, a serious condition characterized by an excess of serotonin in the body. Careful monitoring and appropriate management are crucial when these medications are used together to minimize the risk of adverse effects.

Indeed, opioids like methadone exhibit activity at a receptor called N-methyl-D-aspartate (NMDA). Methadone could bind to the NMDA receptor and act as an antagonist, which means it opposes the effect of the neurotransmitter glutamate at this receptor site. This mechanism is believed to be one of the reasons why methadone shows effectiveness in treating neuropathic pain, surpassing the pain-relieving properties of other opioids (Cohen, Ruth et al. 2024).

Neuropathic pain is a specific type of chronic pain caused by damage or dysfunction of the nervous system. By antagonizing the NMDA receptor and modulating the glutamate pathways, methadone can provide relief for neuropathic pain that may not be as effectively managed by other traditional opioids. This makes methadone a valuable option for patients suffering from this challenging and often persistent form of pain. However, as with any medication, the use of methadone for pain management requires careful assessment and monitoring by healthcare professionals (Zöllner and Stein 2007).

Due to the presence of opioid receptors both within the nervous system and outside of it, opioid analgesics can lead to a wide range of adverse effects. These effects encompass dysphoria (a state of unease or dissatisfaction), euphoria (a feeling of intense happiness), sedation, respiratory depression (slowed breathing), constipation, suppression of endocrine systems (affecting hormone regulation), cardiovascular issues (e.g., bradycardia, a slow heart rate), convulsions, nausea, pruritus (itching), vomiting, and miosis (constriction of the pupils).

Furthermore, extended use of opioid analgesics can result in tolerance, where higher doses are needed over time to achieve the same pain relief, and in some cases, opioid-induced hyperalgesia (increased sensitivity to pain) and/or allodynia (pain response to non-painful stimuli) may also develop (Aiyer, Mehta et al. 2018).

As previously mentioned, opioids that have serotonergic activity, such as tramadol, and tapentadol, can potentially lead to serotonin syndrome when used in combination with other medications that also have serotonergic activity, such as venlafaxine, an antidepressant with serotonin and noradrenaline reuptake inhibition properties. Therefore, caution should be exercised, or coadministration should be avoided altogether when using opioids with other

serotonergic active medications (Heneedak, Abdelshakour et al. 2024).

Furthermore, opioids can be extremely dangerous and even result in fatal overdose, particularly due to their ability to cause respiratory depression. This risk is significantly heightened when opioids are combined with other central nervous system depressants, such as alcohol and benzodiazepines. The simultaneous use of opioids with sedatives can severely suppress the respiratory system, potentially leading to life-threatening consequences. It is crucial for healthcare providers and patients to be aware of these risks and take necessary precautions to ensure safe medication use and prevent potential adverse outcomes (Smischney, Pollard et al. 2018, Crockett, Greer et al. 2019).

1.3.2. Gabapentinoids

Gabapentin and pregabalin are classified as gabapentinoid drugs, and they are primarily used as antiepileptic medications. They are considered first-line treatments for managing neuropathic pain (NICE 2013).

Additionally, pregabalin has been approved for treating generalized anxiety disorders. Apart from their approved uses, gabapentin and pregabalin are often prescribed off-label for various other conditions. These off-label uses include managing conditions like complex regional pain syndrome, restless legs syndrome, attention deficiency disorder, bipolar disorder, sleepiness disorders, periodic limb movement, alcohol withdrawing syndrome, headaches, fibromyalgia, visceral pain, acute postoperative pain, and chronic back pain (Mack 2003).

The concept of gabapentin originated in the early 1970s when researchers were searching for drugs to treat neurological disorders. At that time, gamma-aminobutyric acid (GABA) was known as a crucial inhibitory neurotransmitter, and inhibiting its action could lead to seizures. To improve the bioavailability of GABA, lipophilic groups were introduced to its carbon backbone, as GABA alone couldn't effectively penetrate the blood-brain barrier (Satzinger 1994). This experimentation resulted in the accidental discovery of gabapentin, which was found to be a potent anticonvulsant. Similarly, the development of pregabalin was also serendipitous. Researchers were analyzing the effects of 3-alkyl-4-aminobutyric acids on glutamic acid decarboxylase (GAD), an enzyme needed for GABA synthesis (Silverman 2008). Among the compounds tested, the S-enantiomer of 3-isobutyl GABA, now known as pregabalin, was found to be an effective anticonvulsant. It's worth noting that even though these drugs share structural similarities with GABA as depicted in **Figure 6**, they do not bind to the GABA receptor (Patel and Dickenson 2016).

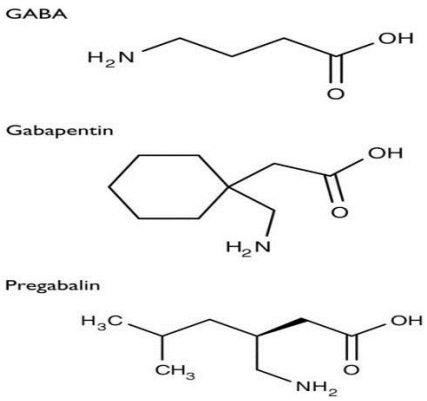

Fig. 6. structure of Gabapentinoids

For example, Pregabalin binds the alpha2-delta subunit of presynaptic voltage-gated calcium channels (VDCCs), located in the central nervous system (Rajappa, Vig et al. 2016, Cross, Viswanath et al. 2024), (**Fig.7**).

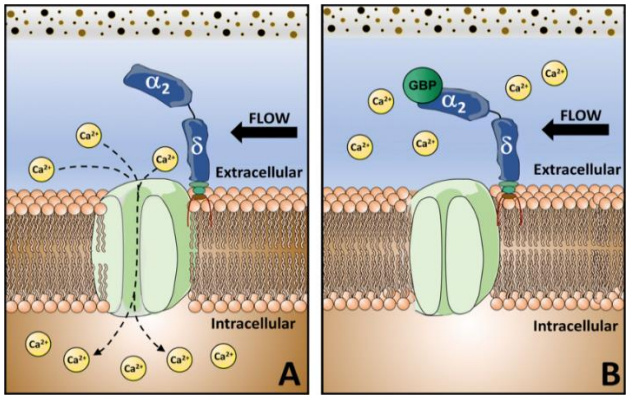

Fig. 7. Effect of Gabapentinoids on Voltage gated Ca channel (Perla C. Reyes Fernandez, 2022)

The modulation of VDCCs is influenced by cannabinoid (CB) ligands, and there are common effects observed between CB agonists and VDCC ligands (Lile, Alcorn et al. 2022).

Initially, gabapentin and pregabalin were marketed as off-label treatments for pain management. However, they eventually received approval from the Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia, a type of nerve pain that occurs following shingles.

1.3.2.1. Misuse of gabapentinoids

There is a growing recognition of the abuse potential associated with gabapentinoids, especially among individuals with opioid abuse history (Evoy, Morrison et al. 2017). Both gabapentin and pregabalin have been reported to induce sensations of sociability, euphoria, calmness, and relaxation, leading to potential misuse. Moreover, these drugs can augment the psychoactive impacts of other substances, making them appealing to some individuals seeking recreational use (Smith, Higgins et al. 2012).

Among the gabapentinoids, pregabalin has a higher abuse potential than gabapentin because of its specific pharmacokinetic properties (Bonnet and Scherbaum 2017). This makes it more susceptible to misuse and diversion.

Notably, the incidence of abuse is more noticed in secure settings, such as prisons and correctional facilities. The prescription rate of gabapentinoids among incarcerated populations is twice that of the general population, with 2.8% of the prison population being prescribed these drugs (Specialist PharmacyServices 2013).

This increasing awareness of abuse potential underscores the importance of careful prescribing and monitoring of gabapentinoids, particularly in individuals with a history of substance abuse or in secure settings, to prevent misuse and promote safe use of these medications for their intended therapeutic purposes.

1.4. Adulteration of illicit drugs

The availability of a wide range of illicit drugs, often mixed with unknown substances, poses a significant seriousness on drug users. Many users lack awareness of both content and quality of the compounds they consume (Darke 2003, Pichini, Busardò et al. 2017). Drug addiction can be a serious hazard, causing acute and chronic effects on health, compounded by the presence of potentially harmful drug adulterants (Chang, Osterloh et al. 2010).

Illicit drug preparations are frequently supplemented with strange and unexpected substances. These additions can be deliberate adulterants included for their pharmacological activity or to increase the quantity of the product being sold, a manner known as cutting. Additionally, some substances may inadvertently contaminate the illicit drugs.

This lack of information and control over the composition of illicit drugs exposes users to significant risks, making it crucial to address the issue from both a public health and law enforcement perspective. Efforts to raise awareness, improve harm reduction strategies, and combat drug trafficking play a vital role in safeguarding the health and well-being of drug users.

There are multiple factors contributing to the presence of additives in illegal drugs (illicit). Other substances are commonly added for dilution, complement, expanding volume, or for amplification the effects of those illegal drugs, creating an illusion of higher quality or disguising a subpar ingredient.

Furthermore, unintended chemical or biological compounds might be present. These elements, such as microorganisms, alkaloids, or other biological agents, can be introduced during the production, manufacture, or storage processes (Cole, Jones et al. 2011). The highly possible risks associated with illicit drugs are widely recognized, but the potential dangers posed by drug adulterants are not as well-established. It's worth noting that these substances used to adulterate drugs are often incorporated in covert laboratories by organized criminal groups, aiming to enlarge drugs'

volume, consequently criminal profit margins are maximized (Broseus, Baechler et al. 2016).

Over time, a thorough understanding of most adulterants commonly present in widely abused drugs, and to a certain extent in all other substances of abuse, has been developed. These adulterants encompass inert fillers like talc and sugars, easily obtainable compounds such as aspirin, caffeine, and paracetamol, as well as additives with pharmacological activity like phenobarbital, lidocaine, levamisole, and quinine. It is important to note that the excessive consumption of these pharmacologically active adulterants can lead to side effects with high severity, and they can threaten human's life (Busardò, Pichini et al. 2016, Pichini, Busardò et al. 2017).

The unpredictable consequences noticed due to adulterated drugs, such as synergistic reactions (synergism), combined with the absence of standardized analyses, pose challenges in comparing adulteration process across different countries and over time. It is crucial to raise awareness about adulterant compounds, especially when they result in severe illness or fatalities (Cole, Jones et al. 2011, Broseus, Gentile et al. 2015, Broseus, Baechler et al. 2016).

Recent literature has not adequately addressed the presence of new psychoactive substances (NPS), also referred to as legal highs or research chemicals, when utilized as adulterants. This alarming trend involves controlled drugs being mixed with NPS, a phenomenon newly documented in Europe. The introduction of these compounds into the black market to replace other substances requires careful regulation (Giné, Espinosa et al. 2014, EMCDDA 2016)

Various countries globally continue to analyze adulterants in samples of illicit drug for forensic purposes, aiming to follow and trace trafficking ways and adulteration processes. Detecting adulterants accurately and assessing drug purity presents an opportunity to uncover potential health risks (Pichini, Busardò et al. 2017). This review seeks to create a comprehensive overview of substances employed for adulteration or cutting agents in those illegally distributed drugs (illicit), particularly focusing on pharmaceuticals or medicines in recent years.

The European drug market continues to present significant challenges due to the high availability and diversity of psychoactive substances. This situation is increasingly complex and risky for individuals who use drugs. Here are some key points: Wide Range of Psychoactive Substances, the market includes a variety of high-potency or high-purity drugs, often in new forms, mixtures, or combinations. This diversity can lead to greater unpredictability in terms of effects and health risks. Consumer Unawareness, drugs are sometimes mis-sold, leading consumers to be unaware of what they are actually taking. This can result in greater health risks, including potentially fatal poisoning. Potent Synthetic Opioids, these substances are sometimes mis-sold or mixed with medicines and other drugs, significantly increasing the risk of overdose and death. MDMA Adulteration, MDMA (ecstasy) is sometimes adulterated with synthetic cathinones, which can enhance its effects but also increase the risk of severe adverse reactions. Cannabis Adulteration, Cannabis products are occasionally adulterated with synthetic cannabinoids, which can be much more potent and dangerous than natural cannabis. New Psychoactive Substances (NPS), By the end of 2023, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring over 950 new psychoactive substances. Among these, 26 new substances were reported in Europe for the first time in 2023 (EMCDDA 2024)

This evolving drug landscape underscores the importance of robust monitoring and public health initiatives aimed at reducing the risks associated with drug use. Awareness campaigns, harm reduction strategies, and stringent regulatory measures are crucial in addressing these challenges and protecting public health.

1.4.1. Medicines as cutting agents

Adulteration applied to controlled drugs is a widespread occurrence. As highlighted by Cole and

colleagues (Cole, Jones et al. 2011), it is commonly observed that illicit drugs often contain additional substances beyond the primary psychoactive component. These added substances can lead to acute health reactions and, in some cases, even fatalities. Various motivations drive the inclusion of adulterants in illicit drugs.

Dealers find it relatively simple to obtain compounds that serve as cutting agents, imitating the desired effects or physical characteristics of the targeted drug. This practice introduces several hazardous substances into the drug, posing risks to unsuspecting consumers. These risks are exacerbated by the secretive manufacturing processes devoid of any quality or safety standards. Importantly, it should be noted that the adulterants themselves might also be adulterated, resulting in fluctuations in the quality of the purchased drug. Consequently, the drug's quality could vary not only from week to week but even from day to day (Behrman 2008).

Numerous medicines or elements with pharmacological activity are utilized as cutting agents in illegally used drugs such as cocaine, heroin, cannabis, and amphetamine-type stimulants, among others. This underscores the diverse range of substances that are incorporated into illicit drugs through adulteration.

1.4.2. Adulteration of opioid analgesics, particularly tramadol and tapentadol

Tramadol (TMD) and tapentadol (TAP) were subjected to adulteration with the intent of augmenting the drug volume, ultimately maximizing the illicit financial gains for criminals. Initial analyses conducted on the confiscated tablets revealed that Paracetamol (PCM), caffeine (CAF), aspirin (ASP), and its degradation product salicylic acid (SAS) emerged as the predominant adulterants frequently encountered in both TMD and TAP tablets. These substances were commonly employed to adulterate and increase the apparent quantity of the drugs, contributing to the profitability of illegal operations (Mohamed A. Abdelshakour 2021).

In the present context, an analysis of seized tablets purportedly containing tramadol (TMD) and tapentadol (TAP) has uncovered the use of venlafaxine (VEN) as an adulterant in TMD and TAP tablets. Illicitly manufactured tablets have been identified to contain all three compounds together or combinations of either TMD or TAP with VEN. This situation presents a grave risk of fatal outcomes due to the development of severe serotonin syndrome, underscoring the potential dangers associated with these adulterated substances [46]. A specific case report highlighted that the combination of tramadol and venlafaxine could potentially induce symptoms of mania [47].

1.4.3. Adulteration applied to synthetic cannabinoids (SCs), particularly (MDMB-4en-Pinaca)

An illustrative case involves more than 70 product samples submitted to the Welsh Emerging Drugs and Identification of Novel Substances Project (Wedinos.org), where the presence of MDMB-4en-PINACA was identified [48]. While most samples contained solely MDMB-4en-PINACA, a subset of samples contained a combination of MDMB-4en-Pinaca with other drugs from different categories, such as pregabalin, other synthetic cathinones, benzodiazepines, opioids, nicotine, or 5F-MDMB-BINACA (ECDD 2020).

Recently, Pregabalin (PGB) is the most frequently detected as an additional component in seized herbal samples suspected to contain synthetic cannabinoids, particularly MDMB-4en-Pinaca. Disturbingly, cases of mixed drug toxicity and fatalities have been reported in various countries due to the co-administration of MDMB-4en-Pinaca and PGB (EMCDDA 2022).

2. Summery and recommendations

It's essential for healthcare providers and patients to be aware of these potential adverse effects and closely monitor the use of illicit drugs to minimize the risks. Adulteration of both illicit and prescription is a matter that should be taken into account, due to unexpected harm effect effects that would be happened.

Conflict of Interest

Authors declare that they have no known competing financial interests or personal relationship that could

3. References

AddictionCenter (2024, May 2024). Illicit Drug Addiction And Abuse. Retrieved June 2024, https://www.addictioncenter.com/drugs/illicit-drugs/.

Aiyer, R., et al. (2018). A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. *Clin J Pain* 34(5): 450-467.

Alam, R. M. and J. J. Keating (2020). Adding more spice to the pot: A review of the chemistry and pharmacology of newly emerging heterocyclic synthetic cannabinoid receptor agonists. *Drug Test Anal* 12(3): 297-315.

Anderson, S. A. R., et al. (2019). Neuropsychiatric Sequelae in Adolescents With Acute Synthetic Cannabinoid Toxicity. *Pediatrics* 144(2): e20182690.

Antoniou, T. and D. N. Juurlink (2014). Synthetic cannabinoids. *CMAJ* 186(3): 210.

Banister, S. D., et al. (2019). Dark Classics in Chemical Neuroscience: Delta(9)-Tetrahydrocannabinol. *ACS Chem Neurosci* 10(5): 2160-2175.

Banister, S. D. and M. Connor (2018). The Chemistry and Pharmacology of Synthetic Cannabinoid Receptor Agonist New Psychoactive Substances: Evolution, Springer International Publishing: 191-226.

Behrman, A. D. (2008). Luck of the draw: common adulterants found in illicit drugs. *J Emerg Nurs* 34(1): 80-82.

Boland, D. M., et al. (2020). Forty-Three Fatalities Involving the Synthetic Cannabinoid, 5-Fluoro ADB: Forensic Pathology and Toxicology Implications. *Journal of Forensic Sciences* 65(1): 170-182.

Bonnet, U. and N. Scherbaum (2017). How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol* 27(12): 1185-1215.

Broseus, J., et al. (2016). Chemical profiling: A tool to decipher the structure and organisation of illicit drug markets: An 8-year study in Western Switzerland. *Forensic Sci Int* 266: 18-28.

Broseus, J., et al. (2015). Qualitative, quantitative and temporal study of cutting agents for cocaine and heroin over 9 years. *Forensic Sci Int* 257: 307-313.

Busardò, F. P., et al. (2016). The Never-Ending Public Health Issue of Adulterants in Abused Drugs. *Journal of Analytical Toxicology* 40(7): 561-562.

Cain, C. K. (1967). Chapter 3. Sedatives, Hypnotics, Anticonvulsants, Muscle Relaxants, *General Anesthetics*: 24 - 32.

Canazza, I., et al. (2017). Pharmaco-toxicological effects of the novel third-generation fluorinate synthetic cannabinoids, 5F-ADBINACA, AB-FUBINACA, and STS-135 in mice. In vitro and in vivo studies. *Human Psychopharmacology: Clinical and Experimental* 32(3): e2601.

Cannaert, A., et al. (2020). Synthesis and in Vitro Cannabinoid Receptor 1 Activity of Recently Detected Synthetic Cannabinoids 4F-MDMB-BICA, 5F-MPP-PICA, MMB-4en-PICA, CUMYL-CBMICA, ADB-BINACA, APP-BINACA, 4F-MDMB-BINACA, MDMB-4en-PINACA, A-CHMINACA, 5F-AB-P7AICA, 5F-MDMB-P7AICA, and 5F-AP7AICA. *ACS Chem Neurosci* 11(24): 4434-4446.

Castaneto, M. S., et al. (2014). Synthetic cannabinoids: Epidemiology, pharmacodynamics, and clinical implications. *Drug and Alcohol Dependence* 144: 12-41.

Chang, A., et al. (2010). Levamisole: A Dangerous New Cocaine Adulterant. *Clinical Pharmacology & Therapeutics* 88(3): 408-411.

Cohen, B., et al. (2024). Opioid Analgesics. StatPearls. Treasure Island (FL).

Cohen, K. and A. M. Weinstein (2018). Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review From Public Health Prospective. Frontiers in Public Health 6.

Cole, C., et al. (2011). Adulterants in illicit drugs: a review of empirical evidence. *Drug Testing and Analysis* 3(2): 89-96.

Crockett, S. D., et al. (2019). American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology* 156(1): 218-226.

Cross, A. L., et al. (2024). Pregabalin. StatPearls. Treasure Island (FL).

Darke, S. (2003). Heroin Overdose: Research and Evidence-Based Intervention. *Journal of Urban Health: Bulletin of the New York Academy of Medicine* 80(2): 189-200.

Darke, S., et al. (2020). Characteristics and circumstances of synthetic cannabinoid-related death. *Clin Toxicol (Phila)* 58(5): 368-37

ECDD, W. (2020). 43rd WHO ECDD Summary assessment and recommendations. WHO Publications, WHO ECDD.

Eikemo, M., et al. (2023). Opioid analgesic effects on subjective well-being in the operating theatre. *Anaesthesia* 78(9): 1102-1111.

EMCDDA (2022). Report on the risk assessment of MDMB-4en-PINACA in accordance with Article 5c of Regulation (EC) No 1920/2006, 2022. Risk Assessments 32. Publications Office of the European Union, 2022, EMCDDA European Monitoring Centre for Drugs and Drug Addiction.

EMCDDA, E. M. C. f. D. a. D. A. (2016). EU Drug Markets Report 2016 Strategic Overview. EMCDDA–Europol Joint publications, Publications Office of the European Union, Luxembourg, European Monitoring Centre for Drugs and Drug Addiction.

EMCDDA, T. E. M. C. f. D. a. D. A. (2024). European drug report 2024: trends and development, The European Monitoring Centre for Drugs and Drug Addiction.

Evoy, K. E., et al. (2017). Abuse and Misuse of Pregabalin and Gabapentin. *Drugs* 77(4): 403-426.

Giné, C. V., et al. (2014). New psychoactive substances as adulterants of controlled drugs. A worrying phenomenon? *Drug Testing and Analysis* 6(7-8): 819-824.

Goulian, A., et al. (2022). A cultural and political difference: comparing the racial and social framing of population crack cocaine use between the United States and France. *Harm Reduction Journal* 19(1).

Gurney, S. M., et al. (2014). Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs. *Forensic Sci Rev* 26(1): 53-78.

Heneedak, H. M., et al. (2024). Green innovation in analytical chemistry: A sustainable densitometric HPTLC approach for the distinctive separation and quantification of structurally related abused drugs - tramadol, tapentadol, and venlafaxine - in seized pharmaceutical dosage forms. *J Pharm Biomed Anal* 243: 116109.

Howlett, A. C. (2002). International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors. *Pharmacological Reviews* 54(2): 161-202.

Kronstrand, R., et al. (2018). Fatal Poisonings Associated with New Psychoactive Substances, Springer International Publishing: 495-541.

Lancet (2012). Addiction—a global problem with no global solution. *The Lancet* 379(9810): 2.

Lander, L., et al. (2013). The Impact of Substance Use Disorders on Families and Children: From Theory to Practice. *Social Work in Public Health* 28(3-4): 194-205.

Lile, J. A., et al. (2022). Influence of pregabalin maintenance on cannabis effects and related behaviors in daily cannabis users. *Exp Clin Psychopharmacol* 30(5): 560-574.

Mack, A. (2003). Examination of the evidence for off-label use of gabapentin. *J Manag Care Pharm* 9(6): 559-568.

Max M. Houck PhD, F., Jay A. Siegel PhD (2015). *Fundamentals of Forensic Science* (Third Edition).

Mohamed A. Abdelshakour, G. M. H., Randa A. Abdel Salam, Dina M. Abo-ElMatty, Eman A. Abdel Hameed, (2021). HPLC and UPLC-MS/MS methods for analyzing TRAMADOL in 70 medicinal illegal products: Application to counterfeit study. *Microchemical Journal* 161.

NICE (2013). Neuropathic pain in adults: pharmacological management in non-specialist settings NICE Clinical Guidelines. National Institute for Health and Care Excellence, National Institute for Health and Care Excellence.

Patel, A., et al. (2024). Changes in real-world dispensing of ADHD stimulants in youth from 2019 to 2021 in California. *Frontiers in Public Health* 12.

Patel, R. and A. H. Dickenson (2016). Mechanisms of the gabapentinoids and calcium channel subunit in neuropathic pain. *Pharmacology Research & Perspectives* 4(2): e00205.

Pichini, S., et al. (2017). Purity and adulterant analysis of some recent drug seizures in Italy. *Drug Testing and Analysis* 9(3): 485-490.

Radfar, S. R. and R. A. Rawson (2014). Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. *Addict Health* 6(3-4): 146-154.

Rajappa, G.C., et al. (2016). Efficacy of Pregabalin as Premedication for Post-Operative Analgesia in Vaginal Hysterectomy. *Anesthesiology and Pain Medicine* 6(3).

Riederer, A. M., et al. (2016). Acute Poisonings from Synthetic Cannabinoids — 50 U.S. Toxicology Investigators Consortium Registry Sites, 2010–2015. MMWR. *Morbidity and Mortality Weekly Report* 65: 692-695.

Robert K. Brooner, M. K., Van L. King, Kenneth Stoller (1998). Preliminary evidence of good treatment response in antisocial drug abusers. *Drug and Alcohol Dependence* 49: 249–260.

Satzinger, G. (1994). Antiepileptics from gamma-aminobutyric acid. *Arzneimittelforschung* 44(3): 261-266.

Shahbazi, F., et al. (2020). Cannabinoids and Cannabinoid Receptors: The Story so Far. *iScience* 23(7): 101301.

Silverman, R. B. (2008). From Basic Science to Blockbuster Drug: The Discovery of Lyrica. *Angewandte Chemie International Edition* 47(19): 3500-3504.

Smischney, N. J., et al. (2018). Serotonin Syndrome in the Perioperative Setting. *American Journal of Case Reports* 19: 833-835.

Smith, B. H., et al. (2012). Substance misuse of gabapentin. *British Journal of General Practice* 62(601): 406-407.

SpecialistPharmacyServices(2013). Gabapentin and pregabalin offender health audit report and audit tool. Retrieved September 2019,https://www.sps.nhs.uk/?s=Gabapentin+and+pregabalin+offender+health+audit+report+and+audit+tool.

UNDOC, U.N.O.D.O.C.(2020). UNODC World Drug Report 2020: Global drug use rising; while COVID-19 has far reaching impact on global drug markets. The World Drug Report UNDOC.

Van Rensburg, R. and H. Reuter (2019). An overview of analgesics: opioids, tramadol, and tapentadol (Part 2). *South African Family Practice* 61(2): 16-23.

Zöllner, C. and C. Stein (2007). Opioids, *Springer Berlin Heidelberg*: 31-63.