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Use patterns of classic, novel, and herbal opioids

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ABSTRACT

Background: Data on use patterns and psychological and physical effects of novel synthetic opioids (NSOs) and herbal opioids like kratom *(Mitragyna speciosa)* lags behind that of classic opioids.

Aims: This study aimed to describe use patterns, adverse events, subjective experience and motivation of use with classic, novel and herbal opioids.

Methods: A two-part survey was used. The first part examined the prevalence, use patterns (dosage, administration route, duration of effects), and associated adverse events of classic, novel and herbal opioids. The second part delved into detailed retrospective experiences of survey responders with an opioid of preferred choice, mostly kratom.

Results: Between May 2020 and February 2023, 467 respondents started the survey, of which 310 met the inclusion criteria. Of these, 52 % ($N = 161$) completed the first part, 65.6 % ($N = 105$) started the second part of which 72 completed. Most respondents were male, highly educated, based in North America or Europe, often using multiple opioids. A total of twenty-seven different compounds were reported, of which hydrocodone/dihydrocodeine, kratom, acetylfentanyl, and U-47700 were used the most. A wide range of doses was reported for each compound. Median effect durations ranged between 3 and 4 h for most of the compounds. Administration routes varied, with oral intake being most prevalent. Fentanyl analogues were often administered intravenously. Physical/psychological adverse events were frequently reported by users of oxycodone, kratom, acetylfentanyl, and U-47700. User reports revealed that both kratom and classic opioids were used for recreational and medical purposes, including ameliorating pain, addiction/withdrawal, anxiety, and mood enhancement.

Conclusion: Psychological and physical adverse events were widely present among classic, novel and herbal opioids suggesting a need for risk monitoring worldwide. Similarities between classic opioids and kratom include medical utility as well as addictive potential.

1. Introduction

Classic opioids are natural and synthetic compounds (Platosz et al., 2020; Reisfield et al., 2007; Vearrier and Grundmann, 2021) such as prescription opioids commonly utilized for pain management (e.g., morphine and oxycodone) (Hales et al., 2020; Reuben et al., 2015; Vearrier and Grundmann, 2021; Volkow and McLellan, 2016), and other substances (e.g., heroin, initially marketed as an anti-tussive medication) that are used recreationally (Fattore et al., 2008; Platosz et al., 2020; Reisfield et al., 2007; Vearrier and Grundmann, 2021). Besides heroin abuse (Bauman et al., 2019), it is clear that prescription opioids are also subject to misuse (Dart et al., 2021; Mojtabai et al., 2019; Vearrier and Grundmann, 2021). For example, the 2019 National Survey on Drug Use and Health suggests that misuse of prescriptions opioids affected almost 4.4 % of 89 million individuals from the United States (US) (Mojtabai et al., 2019; Vearrier and Grundmann, 2021). This is a relevant problem for public health (UNODC, 2019) as the medical use of opioids for pain treatment may also facilitate their non-medical use (Cook, 2022; Dart et al., 2021; Jones et al., 2014; McCabe et al., 2013; Mojtabai et al., 2019) and addiction (Bauman et al., 2019; Kelley-Quon

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et al., 2019; Pollini et al., 2011).

Therefore, the over prescription and misuse of opioids on one hand, and the increase in heroin use on the other hand (Bedene et al., 2022; Berge et al., 2012; CDC, 2024; Cook, 2022) have been identified as the driving forces behind the increase in opioids related deaths within the first wave (since 1999) and the second wave (since 2010) of the so-called "opioid epidemic" (Bauman et al., 2019; Bedene et al., 2022; Cook, 2022; Robert et al., 2023). It began especially in Canada and the US (Cook, 2022; Gardner et al., 2022; Manchikanti et al., 2010; Robert et al., 2023), where opioid overdoses significantly decreased life expectancy in the period 2014–2017 (Murphy et al., 2018; UNODC, 2019). From North America, the opioid crisis spread across the world (e.g., Australia, Europe, United Kingdom; Costantino et al., 2022; Kalkman, 2019; Larance et al., 2018; UNODC, 2019, 2020; Winstock et al., 2013). To date, millions of adult individuals misuse prescription opioids in the US (e.g., 7.2 millions over 2021; SAMHSA, 2022) and worldwide (UNODC, 2019, 2020), leading to high healthcare costs and a need for strategies to reduce harm.

A subsequent restriction on the prescription of opioids has urged a need to develop novel pharmacological treatments for pain that can substitute opioids (Bedene et al., 2022). It has also compelled numerous consumers to seek alternative opioid analogues (Lutfy, 2020; Prozialeck et al., 2021; Smith et al., 2023). These include some novel psychoactive substances (NPS), which are typically defined, according to the United Nations Office on Drugs and Crime (UNODC), as *"substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat"* (UNODC, 2016). Among such compounds, there are novel synthetic opioids (NSOs), and plant-based NPS, like the so-called herbal opioids.

NSOs include fentanyl analogues, usually added to or substituted for heroin (e.g., acetylfentanyl, butyrylfentanyl, carfentanyl, etc.), and other compounds, such as O-Desmethyltramadol, AH-7921, U-47700 (Frisoni et al., 2018; Ventura et al., 2018; Zawilska, 2017; Zawilska et al., 2023). Evidence indicates that fentanyl and its analogues have been responsible for many overdose deaths since 2013, defining the so-called "third wave" of the opioid epidemic (Gladden et al., 2016; O'Donnell et al., 2017). For example, according to the CDC report (2021) there has been an increase of 1040 % in death rates in the US due to NSOs in a brief period (2013–2019) (Mattson et al., 2021; Vearrier and Grundmann, 2021). Currently, it is not possible to capture all available NSOs, as the market is continuously and rapidly changing. They appear simultaneously on illicit and online drug markets, rendering detection difficult. Further, limited tools are available to screen and identify these substances in commercial products or biological samples (Arillotta et al., 2020; Armenian et al., 2018; Edinoff et al., 2023; Palmquist et al., 2023).

Herbal opioids include opium, some crude opiate extracts, and products derived from the kratom *(Mitragyna speciosa)* plant that is native of Southeast Asia (e.g., Malaysia, Vietnam, Indonesia, Borneo, New Guinea), among other countries (Cinosi et al., 2015; Green et al., 2024; Grundmann et al., 2023). Historically, kratom has been used in these countries to increase energy when working under the sun and as folk medicine for managing infections, diabetes, pain, among other health problems (Cinosi et al., 2015; Kruegel and Grundmann, 2018; McCurdy et al., 2024; Singh et al., 2017). It has also been used for treating withdrawal from opioids (Singh et al., 2017) and poly-drug use (Singh et al., 2020). In the US, the prevalence of kratom (powder, capsules, etc.) use increased concurrently with the emergence of the opioid epidemic (Prozialeck, 2016; Prozialeck et al., 2021; Smith et al., 2023) as kratom products are used as an alternative treatment for pain and opioid use disorder outside clinical settings (Arenson et al., 2024; Henningfield et al., 2024; Prevete et al., 2022). Accumulating (pre) clinical data also suggests a potential for other medical applications of kratom (McCurdy et al., 2024; Prevete et al., 2023; Vicknasingam et al., 2020). Similarly, anecdotal reports on the use of kratom for self-treatment of pain, withdrawal/dependence from substances, and some psychiatric conditions have increased as well (Grundmann et al., 2022; Henningfield et al., 2024; McCurdy et al., 2024; Smith et al., 2023).

All the previously mentioned opioids are typically characterised by their action on opioid systems that underlies their analgesic action. Opioid receptor binding profiles however do differ between opioids. For example, most of the classic opioids induce analgesia through mu-opioid receptors involving G protein activation (Dahan et al., 2001; Matthes et al., 1996). At the same time, beta-arrestin involvement is believed to underlie some of its major adverse events, such as respiratory depression (Bedene et al., 2022; Bohn et al., 1999; Raehal et al., 2005). On the other hand, the major alkaloid of kratom, *mitragynine*, possesses a complex pharmacology. It acts as partial agonist on mu-opioid receptors, as antagonist on delta and kappa opioid receptors (Kruegel et al., 2016; Váradi et al., 2016), while also binding to receptors outside of the opioid system, such as adenosine, adrenergic, dopaminergic and serotonergic receptors (Annuar et al., 2024; Foss et al., 2020; Henningfield et al., 2024; León et al., 2021). Kratom has generated interest as an alternative to opioids because it may not recruit beta-arrestin (Kruegel et al., 2016; Váradi et al., 2016), and hence might cause less side effects as compared to classic opioids (McCurdy et al., 2024; Obeng et al., 2021; Váradi et al., 2016). Other herbal opioids (e.g., salvia divinorum and salvinorin A/B) act on kappa opioid receptors (Brito-da-Costa et al., 2021; Coffeen and Pellicer, 2019; Hernández-Alvarado et al., 2020), with salvinorin A being mainly used for its hallucinogenic/psychedelic activity (Butelman and Kreek, 2015; Hernández-Alvarado et al., 2020) and analgesic potential (Chakraborty and Majumdar, 2021; Coffeen and Pellicer, 2019). Conversely, the majority of fentanyl analogues and NSOs act primarily on mu-opioid receptors with a higher potency than morphine (Al-Hasani and Bruchas, 2011; Armenian et al., 2018; Frisoni et al., 2018; Zawilska et al., 2023). A summary of the main pharmacological properties of classic, novel opioids and kratom/mitragynine is provided in Table 1.

Several toxic effects, including overdoses and fatalities, have been associated with classic opioids (Bedene et al., 2022; Cook, 2022; Robert et al., 2023), NSOs (Drummer, 2019; Frisoni et al., 2018; Giorgetti et al., 2017; Schiller et al., 2024), and kratom (Alsarraf et al., 2019; Corkery et al., 2019; Wong and Mun, 2020). However, adverse events related to kratom use have mainly been described in the West (Eggleston et al., 2019; Prevete et al., 2023; Striley et al., 2022), with fatalities often involving contaminants and not only mitragynine *per se* (Corkery et al., 2019; Henningfield et al., 2019; Nacca et al., 2020). The high number of deaths linked to opioids worldwide (Cook, 2022; UNODC, 2019) in part is also related to contributing factors such as high dose preparations and high potency of NSOs available on the internet and dark web, as well as their low price (UNODC, 2019).

However, our understanding of NSOs and herbal opioids is not as extensive as it is for classic opioids. For example, a clear knowledge of clinical pharmacokinetics and toxicity for NSOs is not available (Arillotta et al., 2020; Armenian et al., 2018), and long-term effects of these substances on health parameters are unknown. Knowledge on kratom effects comes mainly from drug fora, case reports, and observations in regular users, while randomized controlled trials (RCTs) or large-scale epidemiological studies are lacking. This knowledge gap creates challenges for clinical research and the formulation of drug policies which are necessary to face the increasing prevalence of these substances and their associated health issues. The latter might affect not only users but also communities, healthcare systems and providers in terms of increased healthcare costs, addiction treatment demands, and public safety concerns, underlying the need of more control measures (Cook, 2022; UNODC, 2019, 2020).

Therefore, the question arises if the different opioids or opioid analogues have different risks. Thus, the present study aimed to explore the use patterns and associated side effects of classic, novel and herbal opioids. The second aim was to describe the phenomenology of the subjective experience with these opioids, focussing specifically on

Table 1
Pharmacological properties of classic, novel opioids and kratom. NSOs=novel synthetic opioids.

Opioids	Pharmacodynamics		Reference
Classic Opioids	Mu-, delta-, kappa-opioid receptors (with beta-arrestin recruitment)	Analgesia, anxiety, decrease in gastrointestinal motility, itching, hypothermia, miosis, respiratory depression, sedation, physical dependence, tolerance, antidepressant effects	(Vearrier and Grundmann, 2021)
Kratom/ mitragynine	Mu-, delta-, kappa-opioid receptors (no beta-arrestin recruitment)	Similar to classic opioids (with less respiratory depression and physical dependence), attenuation of opioid and alcohol withdrawal symptoms	(Annuar et al., 2024; Kruegel et al., 2016; León et al., 2021; McCurdy et al., 2024)
	Alpha-2 adrenergic receptors	Analgesia, decrease in opioid withdrawal symptoms, increase in energy, focus, sociability	
	D2-dopaminergic receptors	Antipsychotic and anxiolytic effects	
	Serotonergic receptors	Anxiolytic and mood-enhancing effects	
NSOs	Mu-receptors, with less activity on delta- and kappa-opioid receptors	Effects and adverse events linked to opioid receptors but higher potency in comparison to classic opioids	(Arillotta et al., 2020; Armenian et al., 2018; Zawilska, 2017; Zawilska et al., 2023)

kratom. We hypothesized that users appreciate kratom for its medical benefits while being aware of its addictive potential. Overall, our findings might contribute to the knowledge of healthcare providers and policy makers for defining harm reduction strategies to face safety concerns linked to opioid use. Moreover, with the lack of RCTs on kratom, its phenomenology might add potentially useful data for future clinical research on kratom's therapeutic use as alternative to opioids.

2. Materials and methods

2.1. Participants and procedures

The present study comprised an anonymous, voluntary, and uninCentivized online research survey that investigated the effects and pattern of use of classic, novel and herbal opioids. It was advertised on internet fora, traditional community groups (e.g., facebook groups like shop.kratom, KratomResearchTeam), websites related to opiates or kratom use (kratom.com), and some discussion boards like Reddit. Participants were informed about the study's purpose by means of an information letter, which stated that: *participation in the study was completely voluntary; they were free to decline participation or withdraw from the study at any time without justifying their decision and without any negative consequences; the study data could not be traced back to participants; and that there were no direct benefits or risks in participating in this research*. Inclusion criteria were: (i) age of 18 years or older; (ii) having experience with a classic, a novel, and/or an herbal opioid; (iii) signed informed consent, which was provided after reading the information letter. The study was approved by the Ethical Committee of Psychology and Neuroscience (ERCPN), Maastricht University (ERCPN-222_77_04_2020) and all procedures were performed in compliance with the relevant laws and institutional guidelines, assuring that no personal data other than declaration of consent form was used and stored by Maastricht University for this study.

Created and hosted on the Qualtrics software platform (XM 12) that was chosen for its versatile nature, easy dissemination and administration following the method used in a previous published work (Mallaroni et al., 2022), the survey consisted of two parts. The first part was related to the general use of classic, novel and herbal opioids that was investigated by means of some questions with both open-endend (e.g., *what is the average amount you take?*) and closed-ended answers (e.g., *did you experience negative physical side effects from this substance?*); for more details see also Section 2.2.2. In the second part respondents were asked to provide further details (including the description of the psychological and physical effects of the substance) about their full-dose experience with one particular opioid of their own choice that was consumed in the past 6 months, and not in combination with other drugs by means of both open-ended (e.g., *what dose did you take? If you are not certain, can you give an average?*) and closed-ended answers (e.g., *yes/no* for *do you believe opioids in general are potentially addictive drugs?*). For more details on the second part see also measures described in Section 2.2.3.

Completion of this survey was variable based on (i) the number of substances a respondent chose to provide information on in the first part of the survey; and (ii) the choice to complete the second part. There was also the possibility to pause and continue the survey at another time, resulting in an average completion time of 79 min.

467 responses were collected between May 2020 and February 2023. Among these eligible respondents, the final cohort consisted of 310 respondents (mean age (SD) = 38.34 (14.52); $F = 100$) starting the first part of the survey. They had mainly a secondary ($N = 94$; 30.3 %) or tertiary ($N = 215$; 69.4 %) education level and most of them lived in North America ($N = 249$; 80.3 %) or Europe ($N = 49$; 15.8 %), with only a few respondents from South America ($N = 5$; 1.6 %), Asia ($N = 5$; 1.6 %), Africa and Australia ($N = 2$; 0.6 %). There were dropouts throughout this section that might be linked to the survey length and to methodological nature of surveys *per se*, resulting in different numbers of responders across opioid categories (their demographics are reported in Table 3). Of 161 (52 %) responders who completed the first part, 160 started the second part, with 65.6 % of them providing information on a recent experience with a classic, a novel, or an herbal opioid. Among them, 72 participants (mean age (SD) = 38.43 (14.06); $F = 19$) completed the survey. They mainly had a secondary ($N = 18$; 25 %) and a tertiary ($N = 53$; 73.6 %) education level and most of them resided in North America ($N = 56$; 77,8 %) or Europe ($N = 14$; 19,4 %). The flowchart depicting the number of respondents through the survey is reported in Fig. 1.

2.2. Measures

2.2.1. Demographics

Demographic information collected consisted of age, gender, biological sex, highest level of education, continent of living, and country of origin.

2.2.2. Opioid use

In the first part of the survey participants were asked to provide information (dose, route, average duration of acute effects) on their previous experience with each of the following opioids: classic, novel and herbal opioids. Provided information was based on self-reported data. For each class, examples of representative and previously documented substances (Arillotta et al., 2020; Prevete et al., 2023) were provided. These included a total of 34 compounds, which were: 11 classic opioids, 5 herbal opioids, 18 NSOs (9 fentanyl analogues and 9 other). A

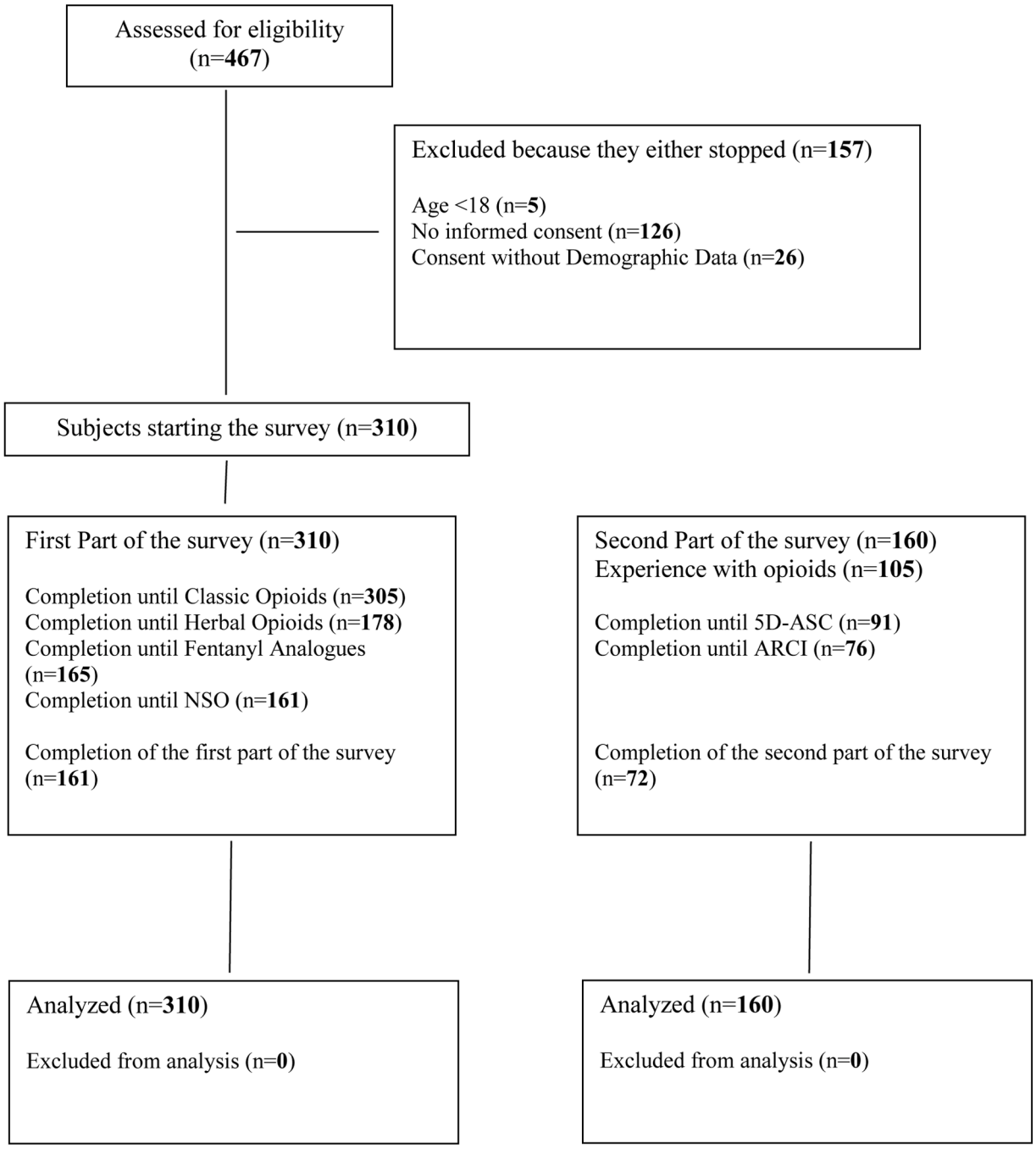

Fig. 1. Schematic representation of the initial sample and the flow of respondents through the study.

complete list of all compounds is reported in Table 2. For each class, there was also the possibility to include an unlisted substance by choosing an 'other' text option.

According to the method used in a previous work (Mallaroni et al., 2022), participants were also asked to report (binary answer yes/no) on the potential occurrence of clinically relevant physical and/or psychological side effects (physical: gastrointestinal, cardiovascular, seizures; psychological: anxiety, paranoia, low mood) and when these occurred (e.g., acutely or long-term).

2.2.3. *Recent opioid experience*

Respondents who completed the first part of the survey could provide details on a particular experience with an opioid of their own choice that they had consumed the last 6 months. The choice was facilitated by providing a fixed list of substances, alongside an "other" category for new entries. Upon selection of a substance, respondents were asked to provide information on the estimated dose and the phenomenology of this experience. Thus, the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale (Studerus et al., 2010) and the Addiction Research Center Inventory (ARCI) (Haertzen et al., 1963; Martin et al., 1971) were used to assess subjective drug effects retrospectively and to define the experiential components underlying the phenomenology of the mentioned experience. These questionnaires are considered valuable, standardised, reliable and valid tools, typically used in clinical trials to evaluate the acute effects of psychoactive drugs (Kuypers et al., 2019; Liechti et al., 2017; Mallaroni et al., 2022; Martin et al., 1971; Mason et al., 2020; Papaseit et al., 2016) on states of consciousness (Dittrich, 1998; Studerus et al., 2010) and subjective experience (Haertzen et al.,

Table 2
List of opioids made available to users to select from and organized according to their structural family.

Classic Opioids	Herbal Opioids	NSOs	
		Fentanyl Analogues	Other NSOs
Codeine	Kratom (*Mitragyna speciosa*)	Acetylfentanyl	AH-7921
Fentanyl	Opium	Alpha methylfentanyl	MT-45
Heroin	Salvinorin A	Butyrylfentanyl	O-Desmethyltramadol
Hydrocodone/dihydrocodeine	Salvinorin B	Carfentanyl	U-47700
Hydromorphone	Salvia divinorum	Furanylfentanyl	U-49900
Meperidine		4-methylfentanyl	U-50488
Methadone		4-fluorofentanyl	U-51754
Morphine		Tetrahydrofuranylfentanyl	W-15
Oxycodone		Valerylfentanyl	W-18
Oxymorphone			
Tramadol			

1963; Martin et al., 1971). More details about these instruments are reported in the Supplementary Materials.

Finally, data on motives of use and the environmental context in which the drug was taken (e.g., party, festival, home, work, ceremonial or spiritual context, or another) were collected. Respondents were asked to indicate motives for their personal use and rank them from 1 (main motivation) to 3 (3rd main motivation) selecting options from a list derived from an extension of the 18-item reasons for drug-use scale (Boys et al., 2001; Kettner et al., 2019). Other motivations, derived from qualitative interviews (Prepeliczay, 2016), included self-exploration, social context, escapism, and the option to enter a motive that was not in the list. A question with binary (yes/no) answer was available to state whether participants had reached their main motivation.

3. Statistical analyses

The IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 28.0 was used for cleaning survey data. Outliers were defined as those with an incorrectly used mass (mg/g/μg) metric, due to possible variance of mean recreational doses caused by lack of exact dose knowledge, intraindividual motives, and tolerance.

Frequencies (N) and proportions (%) are reported for demographic data (gender, biological sex, highest level of education, continent of living, and country of origin), individual drug use, and information related to a recent opiod experience.

The incidence of physical adverse events, psychological adverse events, type of adverse events, and if they were acute or long-term, were investigated using descriptive statistics, including frequencies (N) and proportions (%).

4. Results

4.1. Sample

There was a high dropout rate throughout the first part of the survey. The number of respondents varied across opioids: 305 for classic opioids, 178 for herbal opioids, 165 for fentanyl analogues, and 161 for other NSOs (see also Fig. 1). Most respondents in each category were male, highly educated, primarily located in North America or Europe, and poly-opioid users. All details and socio-demographic data can be found in Table 3.

Table 3
Demographic data of survey participants for classic, novel and herbal opioids.

		Classic Opioids	Herbal Opioids	NSOs	
				Fentanyl Analogues	Other NSOs
Respondents for Each Subpart N		305	178	165	161
Use N (%)	Yes	265 (86.8)	146 (82)	18 (10.9)	16 (9.9)
	No	40 (13.1)	32 (18)	147 (89.1)	145 (90.1)
Age Mean (SD)		38.70 (14.24)	36.6 (13.84)	36.28 (14.09)	27.12 (4.27)
Biological Sex N (%)	Male	172 (64.9)	110 (75.3)	12 (66.7)	14 (87.5)
	Female	93 (35.1)	36 (24.7)	6 (33.3)	2 (12.5)
Gender N (%)	Male	163 (61.5)	107 (73.3)	12 (66.7)	13 (81.3)
	Female	90 (34)	34 (23.3)	6 (33.3)	2 (12.5)
	Non-Binary	1 (0.4)	0 (0)	0 (0)	0 (0)
	Prefer to self-describe	4 (1.5)	2 (1.4)	0 (0)	0 (0)
	Prefer not to say	6 (2.3)	3 (2.1)	0 (0)	1 (6.3)
Continent of Living N (%)	North America	227 (85.7)	109 (74.7)	18 (100)	12 (75)
	South America	3 (1.1)	1 (0.7)	0 (0)	0 (0)
	Europe	31 (11.7)	32 (21.9)	0 (0)	4 (25)
	Asia	2 (0.8)	3 (2.1)	0 (0)	0 (0)
	Africa	1 (0.4)	0 (0)	0 (0)	0 (0)
	Australia	1 (0.4)	1 (0.7)	0 (0)	0 (0)
Highest Level of Education N (%)	Primary/ Elementary	1 (0.4)	1 (0.7)	0 (0)	0 (0)
	Secondary	85 (32.1)	39 (26.7)	6 (33.3)	4 (25)
	Tertiary	179 (67.5)	106 (72.6)	12 (66.7)	12 (75)
Polyuse of Different Opioids N (%)	No	125 (47.2)	0 (0)	0 (0)	0 (0)
	Yes	140 (52.8)	146 (100)	18 (100)	16 (100)

4.2. Frequency of use

A variety (27 of the 34 available choices) of opioids was reported to have been tried by users. Classic opioids ($N = 265$; 86.8 %) and herbal opioids ($N = 146$; 82 %) had the highest prevalence of use, while novel opioids ($N = 34$; 20.8 %) had the lowest. Hydrocodone/dihydrocodeine ($N = 193$; 72.8 %), kratom ($N = 136$; 93.2 %), U-47700 ($N = 7$; 43.8 %), and acetylfentanyl ($N = 5$; 27.8 %) were the most used for each class respectively. Frequencies and raw percentages for prior opioid use can be found in Fig. 2 and Table S1.

Some respondents entered an alternative substance that was not part of the fixed list. These are reported in Table S2.

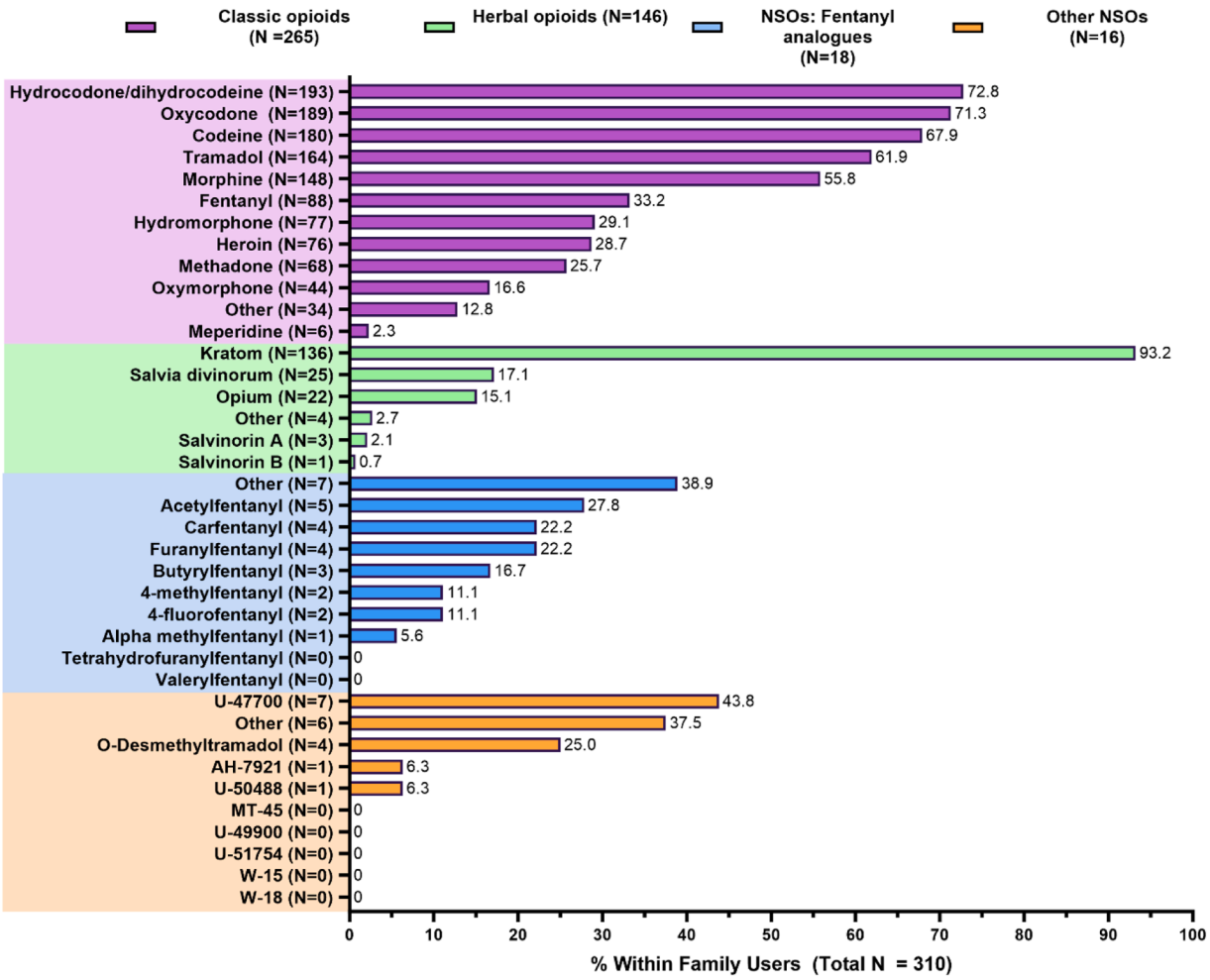

Fig. 2. Percentage of opioids (per structural family) reported to have been previously tried by respondents. Proportions (%) are listed according to each family sample size.

4.3. Pattern of use

4.3.1. Dose

Users reported wide dose ranges for each compound. In regards to the most used compounds, the median reported doses were 15 mg for hydrocodone/dihydrocodeine, which appears in line with the therapeutic dose of 5–60 mg for hydrocodone (Acharya et al., 2023; Nerenberg and Fudin, 2010; Valtier and Bebarta, 2012) and 30–60 mg for dihydrocodeine (Edwards et al., 2000); 5000 mg for kratom, whose typical dose ranges from 1.14 to 10.9 g in the West (Smith et al., 2022, 2024) or more in the traditional countries. Dose ranges were lower for NSOs, with a median reported dose of 0.15 mg for acetylfentanyl, which is in line with its narrow window described in some fatalities (e.g., blood concentration of 270 ng/mL; Takase et al., 2016); and 16 mg for U-47700, whose dose can range from 1 to 50 mg (Nikolaou et al., 2017).

4.3.2. Duration

For each drug, effect durations are presented as median alongside their min-max values. Median effect durations were between 3 and 4 h for most classic, novel and herbal opioids. Among classic opioids, methadone had the longest reported median effect duration of 8 h, while codeine, hydromorphone, fentanyl, and meperidine had the shortest effect duration of around 3 h. Opium and kratom had the longest median effect durations among herbal opioids at 5.5 h and 4 h respectively, while salvia divinorum and salvinorin A/B had the shortest (<30 min). Among NSOs, 4-methylfentanyl and U-50488 had the longest median effect duration of 14 h and 15 h respectively, while the shortest effect durations were reported for alpha-methylfentanyl (3 h) and AH-7921 (1 h).

4.3.3. Patterns of use

Oral intake was the most frequently reported mode of administration across all classic opioids ($N = 516$; 69.3 %), herbal opioids ($N = 139$; 79 %), including kratom ($N = 129$; 99.2 %), and NSOs ($N = 10$; 62.5 %). On the other side, intravenous administration was the most frequently reported mode of administration ($N = 9$; 40.9 %) for fentanyl analogues. Other routes across classic, novel and herbal opioids were reported.

Patterns of classic, novel and herbal opioids use in terms of dose, duration, and route of administration for each compound are reported in Table 4 (and S3). Self-reported comparison for each substance and details regarding the perception of the effects (if they were stronger, weaker, or equivalent to the average dose taken of the classic substance) are reported in Table S4.

4.4. Adverse events

4.4.1. Physical adverse events

For classic opioids, oxycodone users reported the highest number of physical adverse events ($N = 52$; 19.6 %), while meperidine users reported the fewest ($N = 2$; 0.8 %). Among herbal opioids, kratom users reported the most physical adverse events ($N = 49$; 33.6 %), while salvinorin A users reported the fewest ($N = 1$; 0.7 %). Among NSOs, acetylfentanyl ($N = 5$; 27.8 %) and U-47700 ($N = 5$; 31.3 %) users reported the highest number of physical adverse events, while other fentanyl

Table 4
Mean and median dose and effect duration (with its min-max ranges) for each opioid, as reported by survey participants. It should be noted that the accuracy of these reports is limited.

		Substance	Dose (mg)		Duration (hours)		
			Mean	Median	Mean	Median	Min-Max
Classic Opioids (*N* = *265*)		**Codeine**	701.8	50	3.3	3	1–8
		Fentanyl	209	0.1	5.6	3	1–25
		Heroin	505.9	100	4.1	4	1–8
		Hydrocodone/dyhydrocodeine	128	15	3.4	4	1–10
		Hydromorphone	18.5	13	3.2	3	1–8
		Meperidine	45	50	3	3	2–4
		Methadone	37.6	22.5	9.8	8	2–25
		Morphine	78.7	30	4	4	1–12
		Oxycodone	320.2	20	3.9	4	1–12
		Oxymorphone	30.4	17.5	3.9	4	1–6
		Tramadol	187.9	70	4.4	4	1–24
		Other Classic Opioids	745.3	15.5	4.2	4	1–12
Herbal Opioids (*N* = *146*)		**Kratom**	7272.6	5000	4	4	1–10
		Opium	886.6	300	6.4	5.5	1–25
		Salvinorin A	25.10	25.10	0.4	0.4	0.4–0.4
		Salvinorin B	0.1	0.1	0.4	0.4	0.4–0.4
		Salvia divinorum	832.4	100	1.1	0.4	0.4–9
		Other Herbal Opioids	1510	1510	7.3	8	4–10
NSOs	**Fentanyl Analogues (*N* = *18*)**	**Acetylfentanyl**	0.2	0.15	4.2	4	3–6
		Alpha methylfentanyl			3	3	3–3
		Butyrylfentanyl	0.2	0.2	3.5	3.5	3–4
		Carfentanyl	66.7	0.01	9.3	5	5–22
		Furanyl fentanyl	0.1	0.02	4.3	4	4–5
		4-methyl fentanyl	0.5	0.5	14	14	3–25
		4-fluorofentanyl	0.2	0.2	4	4	4–4
		Tetrahydrofuranylfentanyl					
		Valerylfentanyl					
		Other Fentanyl Analogues	850	200	2.5	2.5	1–4
	Other NSOs (*N* = 16)	**AH-7921**			1	1	1–1
		MT-45					
		O-Desmethyltramadol	85	70	4.3	4	3–6
		U-47700	18.9	16	3	3	2–4
		U-49900					
		U-50488			15	15	15–15
		U-51754					
		W-15					
		W-18					
		Others	43.7	27.5			

analogues users reported the fewest (*N* = 1; 5.6 %).

4.4.2. Psychological adverse events

For classic opioids, oxycodone users reported the highest number of psychological adverse events (*N* = 34; 12.8 %), while meperidine users reported the lowest (*N* = 1; 0.4 %). For herbal opioids, kratom users reported the most psychological adverse events (*N* = 25; 17.1 %), while salvinorin A users reported the fewest (*N* = 2; 1.4 %). Among NSOs, acetylfentanyl (*N* = 4; 22.2 %) and U-47700 (*N* = 3; 18.8 %) users reported the highest number of psychological adverse events, while users of other fentanyl analogues reported the lowest (*N* = 1; 5.6 % for each compound).

The incidence rate of physical and psychological adverse events is reported in Fig. 3 and Table S5, while their type and duration are reported in Table S6-S7.

4.5. Retrospective reports of subjective experience with classic, novel and herbal opioids

The complete list of experiences with classic, novel and herbal opioids reported by users can be found in Table S8. Overall, among 72 subjects completing the second part of the survey, kratom was the most chosen option (*N* = 72; 67.9 %), followed by classic opioids (*N* = 27; 25.5 %). Mean (SD) subjective experiences as rated by the 5D-ASC and the ARCI are reported in Fig. 4 and Table S9-S10. Classification of their effects in terms of comparisons with other drugs is reported in Table S11.

4.5.1. Patterns, motivations, and settings of kratom and classic opioids' use

Most users of kratom (*N* = 33; 45.8 %) and classic opioids (*N* = 8; 29.6 %) in our sample reported daily usage and found kratom (*N* = 31; 43.1 %) and classic opioids (*N* = 9; 33.3 %) effective for their intended purposes. The main motivations for use are shown in Fig. 4. A complete overview of motivations and environmental setting of kratom and classic opioids' use is reported in Table S12.

Among other motivations, kratom was used for pain relief in chronic pain and rheumatoid arthritis (*N* = 2; 2.8 %), as well as for irritable bowel syndrome diarrhea-predominant (IBS-D) (*N* = 1; 1.4 %). It was also used to taper off other opioids (*N* = 1; 1.4 %) and as an alternative to other drugs (*N* = 16; 22.2 %), particularly classic opioids (*N* = 11; 15.4 %; e.g., oxycodone, hydrocodone, hydrocodeine, tramadol, and heroin). Classic opioids were also used legally as an alternative to fentanyl (*N* = 1; 3.7 %). In our sample, 33 (45.8 %) and 16 (59.3 %) users viewed respectively kratom and classic opioids as potentially addictive. Of these, 15 (20.8 %) kratom and 9 (33.3 %) classic opioid users did not consider themselves addicted. However, the majority of users (*N* = 49; 68.1 % for kratom; *N* = 16; 59.3 % for classic opioids) considered opioids *in general* potentially addictive. Other information on kratom and classic opioids' use in terms of addictive potential, purpose and frequency of use is reported in Table S13.

Finally, a total of 28 anecdotal reports on kratom use were collected.

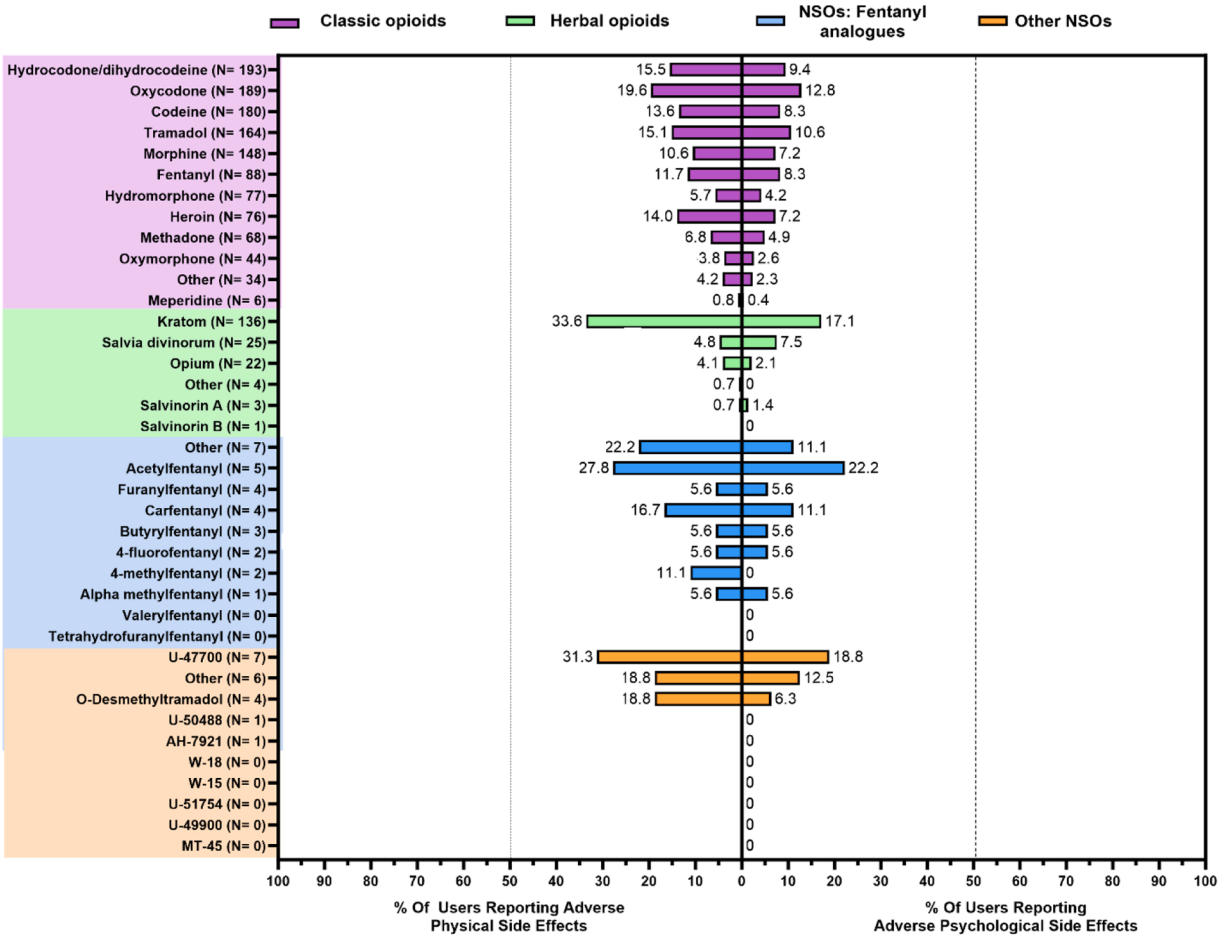

Fig. 3. Incidence rate of adverse physical and psychological side effects for each opioid. Proportions (%) are listed according to each family sample size.

These reports suggested that kratom was used for pain management, addiction treatment, withdrawal relief, anxiety reduction, mood enhancement, energy boost, and socialization (see also Table S14). In the light of current research on alternative and herbal substances for pain management (Chakraborty and Majumdar, 2021; Prozialeck et al., 2021) and opioid use disorder (Arenson et al., 2024), such results confirm previous users' claims and (pre)clinical evidence on kratom's therapeutic potential for acute/chronic pain (Grundmann, 2017; Henningfield et al., 2024; Prevete et al., 2021, 2023) and opioid withdrawal (Boyer et al., 2008, 2007; Coe et al., 2019; Smith et al., 2021), providing some support for further studies on the potential of kratom/mitragynine as alternative to opioids.

5. Discussion

This study aimed to outline the frequency and patterns of use, and side effects of classic, novel, and herbal opioids among adult users; and to describe individual subjective experiences with a single opioid chosen by the respondent. A total of twenty-seven different compounds were used for both medical and recreational purposes by users mainly based in the West. Kratom was most used as an alternative to classic opioids and was particularly appreciated by users for its medical benefits, while its addictive potential was recognised as well, confirming our initial hypothesis. The respondents were predominantly male, well-educated, and multi-opioid users. These demographics are in contrast with data suggesting that misuse of classic opioids is more frequent among women (Cook, 2022; Fattore et al., 2020) or among individuals with a lack of education (Judd et al., 2023). Yet, these findings are consistent with existing epidemiological data on kratom use (Covvey et al., 2020; Palamar 2021; Schimmel et al., 2021) and NPS in general (Assi et al., 2017; Palamar et al., 2015; Soussan and Kjellgren, 2016). This might partially reflect a change in type of NPS users over the last years, which expanded from recreational users to professional use and students (d'Angelo et al., 2017), to manage emotions and anxiety, sleep problems, chronic pain and addictions (Soussan and Kjellgren, 2016).

Hydrocodone/dihydrocodeine, kratom, acetylfentanyl, and U-47700 emerged as the most commonly used substances within their respective classes. Classic and herbal opioids like kratom had the highest number of users. In line with the interest in the analgesic potential of herbal opioids during last years (Chakraborty and Majumdar, 2021; Coffeen and Pellicer, 2019; Prozialeck et al., 2021), our findings suggest a preference for substances claimed to have medical benefits, or for those most easy to get ahold of over those primarily used recreationally. The latter included other herbal opioids (e.g., salvia divinorum, opium, salvinorin A/B), fentanyl analogues (e.g., acetylfentanyl, carfentanyl, furanylfentanyl, butyrylfentanyl, 4-methylfentanyl, 4-fluorofentanyl, and alphamethylfentanyl), and other NSOs (e.g., U-47700, O-Desmethyltramadol, AH-7921, and U-50488, which had the least number of users). Thus, these findings confirm that misuse of classic, novel and herbal opioids continues to affect people worldwide each year (Bedene et al., 2022). They also underscore the importance of monitoring the use of classic, novel, and herbal opioids globally, particularly in the light of the opioid epidemic (Cook, 2022; Kalkman, 2019; Prozialeck et al., 2021; Smith et al., 2023) in the US and Europe, where the majority of the respondents reside.

Users reported a wide range of doses for each compound and variable duration of perceived effects. This variability might be influenced by individual differences in tolerance and physical dependence,

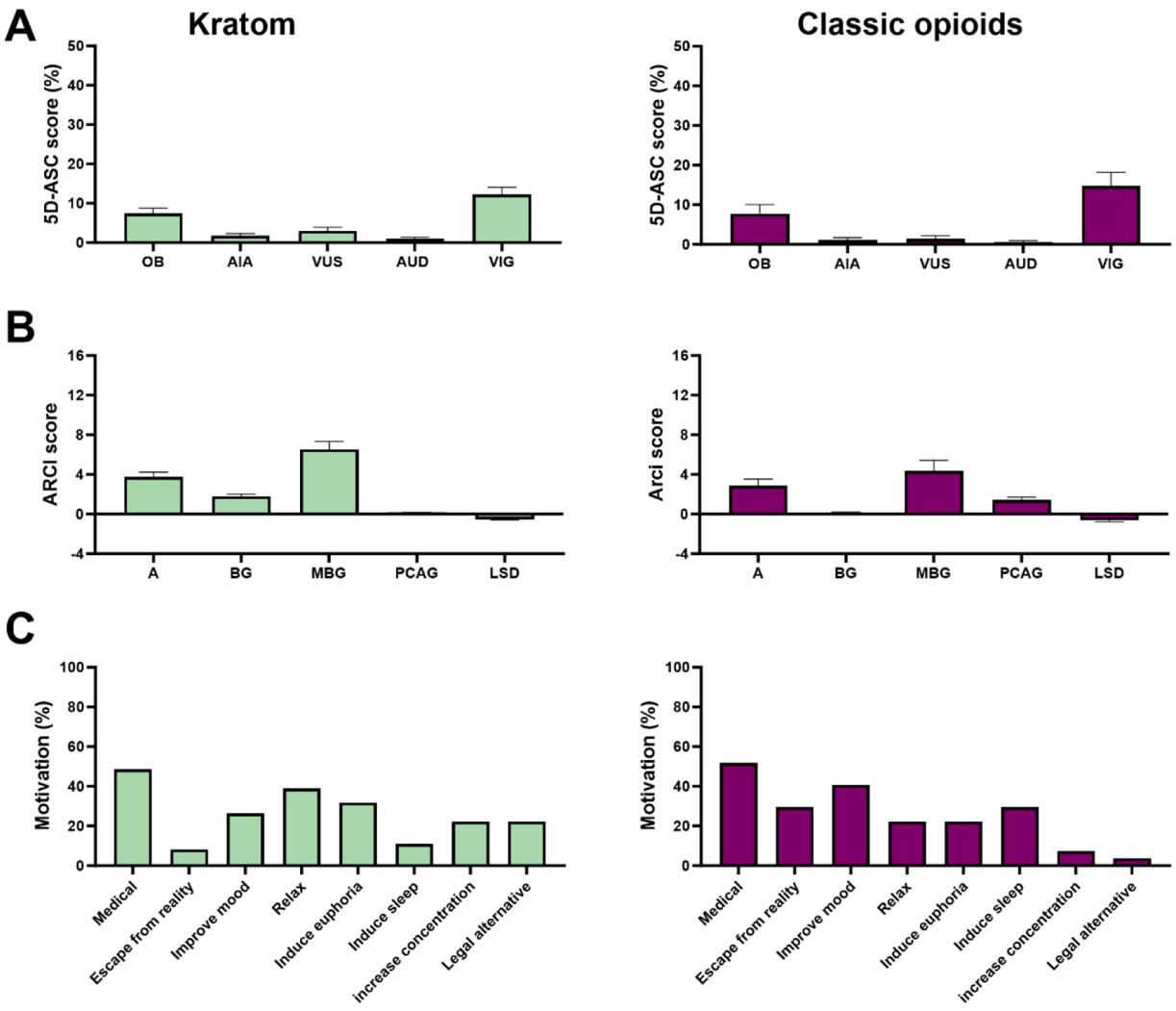

Fig. 4. Subjective experience of kratom ($N = 68$) and classic opioids use ($N = 20$) as rated with (A) the 5-dimension altered state of consciousness scale (5D-ASC) and (B) the addiction research center inventory (ARCI), and (C) the main motivation of use. OB=oceanic boundlessness, AED=anxious ego dissolution, VIS=visionary restructuralization, AUD=auditory alterations, VIG=reduction in vigilance, A=amphetamine, BG=benzedrine group, MBG=morphine benzedrine group, PCAG=pentobarbital-chlorpromazine-alcohol group, LSD=LSD group.

biopsychosocial factors, the specific context of use (Nerenberg and Fudin, 2010), inaccuracy in reporting, the method of administration and the predominance of male respondents in our survey whose pharmacokinetic and pharmacodynamic response may differ from that of females (Fattore et al., 2008, 2020). Kratom users reported having tried different doses with a maximum of 60 g, confirming that kratom dosing can vary (Garcia-Romeu et al., 2020; McCurdy et al., 2024; Smith et al., 2022) and suggesting the need of further research to better define dose-effect relationships. For NSOs, salvia divinorum and salvinorin A/B, users reported perceiving effects at doses in the order of mg or microgram. This confirms a higher potency for the latter compounds as also suggested in the literature (Armenian et al., 2018; Brito-da-Costa et al., 2021; Frisoni et al., 2018; Zawilska et al., 2023). Overall, doses of classic opioids and kratom were comparable to those reported in the literature in the context of safe, therapeutic use (Acharya et al., 2023; Edwards et al., 2000; Nerenberg and Fudin, 2010; Smith et al., 2022, 2024; Valtier and Bebarta, 2012) and less than those for NSOs linked to serious health hazards (Nikolaou et al., 2017; Takase et al., 2016; Zawilska et al., 2023). This underlies the need of harm reduction strategies such as supply control measures (UNODC, 2019), and consumers and healthcare providers education on these risks.

Kratom's median effect duration (4 h) appeared similar to that of most classic opioids, and to previous reports showing a duration for kratom effects between 5 and 7 h (Prozialeck et al., 2012; Smith et al., 2022; Warner et al., 2016). So far, effect duration of kratom has been studied preclinically and only in a few studies in humans (Huestis et al., 2024; Smith et al., 2024; Tanna et al., 2022; Trakulsrichai et al., 2015). Kratom's duration was different to that reported for the other herbal opioids, salvia divinorum and salvinorin A/B, which typically last <30 min. Short effect duration of salvia divinorum and salvinorin A/B might constitute an important motive for use as also suggested in the literature (Brito-da-Costa et al., 2021; Hernández-Alvarado et al., 2020; Singh, 2007). Some NSOs (e.g., alpha-methylfentanyl) showed durations comparable to kratom, while others had longer-lasting effects (e.g., 4-methylfentanyl and U-50488). Such results confirm how NSOs' effect duration can vary, presumably depending on their pharmacokinetics and potency. However, effect durations were based on users' subjective perception of acute drug effects and therefore might be subject to estimation error. Therefore, there is the need for more pharmacokinetic assessments in controlled studies to validate these findings, which might further contribute also to a better understanding of their pharmacodynamics.

Respondents commonly administered classic, novel and herbal opioids orally, with the exception of fentanyl analogues that were primarily administered intravenously. Herbal opioids, particularly those used recreationally, like salvia divinorum and salvinorin A/B, were often

inhaled. Additionally, users reported various routes such as nasal, sublingual, rectal, skin absorption and injection. The latter was more common among classic opioids and other NSOs. Further, most users consumed substances alone. However, some classic opioid users reported to mix substances with other drugs or to purchase pre-mixed products. Our findings showed that classic, novel and herbal opioids are available in several formulations and can be taken through several routes. Such findings confirm previous evidence (Brito-da-Costa et al., 2021; Frisoni et al., 2018; Prozialeck et al., 2012; Zawilska et al., 2023) and highlight that the trends of using mixed products need to be monitored carefully as they have been associated with the development of adverse events (Corkery et al., 2019; Nacca et al., 2020; Schiller et al., 2024). Although more strategies are available today to identify such substances in products and biological samples (Jasim et al., 2023; Palmquist et al., 2023; Platosz et al., 2020; Voelker et al., 2021), further method development will be needed to increase their specificity and sensity.

Oxycodone, kratom, acetylfentanyl, and U-47700 users reported the highest frequency of acute physical and psychological adverse events (see also Fig. 3) presumably linked to their action on opioid receptors. Conversely, meperidine, salvinorin A, and several fentanyl analogues (e.g., alphamethylfentanyl, butyrylfentanyl, furanylfentanyl, and 4-fluorofentanyl) users reported fewer adverse events within their classes. It might be surprising that fentanyl analogues users reported the fewest adverse events, but this might partly be related to their low prevalence among survey responders and might also be influenced by the self-reported nature of the data. In regards to physical adverse events, classic opioids and kratom showed similar profiles in terms of gastrointestinal and cardiovascular adverse events. Reports of fainting and seizures were lower for kratom and NSOs, while more common for classic opioids and salvia divinorum. Regarding psychological adverse events, incidences of anxiety and low mood were higher for some classic opioids (respectively oxycodone and hydrocodone/dihydrocodeine), kratom, acetylfentanyl, and U-47700. Paranoia was mainly reported among classic opioids and salvia divinorum users, while NSOs produced the fewest psychological adverse events. Overall, these findings underscore the medical and psychiatric risks associated with these substances (Abidali et al., 2024; Alsarraf et al., 2019; Arillotta et al., 2020; Schiller et al., 2024; Striley et al., 2022; Zawilska et al., 2023), further emphasizing the necessity to monitor their use and distribution.

Participants predominantly reported on experiences with a classic opioid and kratom in the 2nd part of the survey. These were often used daily for both medical and recreational purposes (e.g., *to feel elated or euphoric or to just get really stoned or intoxicated, to escape from reality and as legal alternative to substitute another drug*). These substances were mainly used at home (alone or with others), but also at work, with most kratom users considering its effects similar to classic opioids. Kratom was primarily used for self-treatment of pain, addiction/withdrawal/dependence, anxiety, head injury, irritable bowel syndrome diarrhea-predominant, or to increase mental well-being and to replace opioid use. Our findings are consistent with previous evidence on its versatile recreational and medical use (Bath et al., 2020; Coe et al., 2019; Grundmann, 2017; Grundmann et al., 2022; Henningfield et al., 2024; McCurdy et al., 2024; Smith et al., 2023). Other reasons for kratom use included boosting energy (e.g., concentrating on work/study/staying awake) and improving mood when feeling down or depressed; sleeping, relaxing, and avoiding worrying about a problem; socialization/feeling more confident or more able to talk to people in a social situation/enjoying the company of friends. Consistently, users reported that kratom has both sedative and stimulatory action as shown in the ARCI questionnaire by the ratings on the PCAG and on the BG subscale, respectively. However, kratom was reported to have lower sedative action compared to classic opioids. Overall, these data would add evidence to kratom's double profile as it is known to exert stimulatory action at low doses and sedative opioid-like effects at high doses, with enhancing effects on socialization and attentional focus (Prevete et al., 2021; Smith et al., 2023; Swogger et al., 2015). Findings related to the subjective experiences reported by kratom users also confirm previous notions that kratom is widely used for its performance enhancement/nootropic effects (Annuar et al., 2024), and for improving health and well-being (Henningfield et al., 2024). This is due to its complex pharmacology (Annuar et al., 2024; Foss et al., 2020; Henningfield et al., 2024; Kruegel et al., 2016; León et al., 2021; Váradi et al., 2016) with fewer hazards respect to classical opioids. However, our findings also suggest that kratom can be used for *broadening consciousness, taking a different perspective on the world,* or *inducing/enhancing a spiritual experience*. Kratom was often utilized as a legal alternative for classic opioids. On the other hand, opioids were more used for mood improvement and inducing sleep if compared to kratom. These findings contribute to the understanding of the patterns and motivations of kratom use beyond traditional contexts, shedding light on the experiences of users in the West. Survey participants were aware of the addiction risk of kratom but also viewed it as having clinical potential. Thus, in the light of the accumulating data on the balance between kratom's potential medical benefits and health problems, it is important to highlight that its addictive potential needs to be better assessed and evaluated.

This research has several limitations that may impact the interpretation of the results. First, from a methodological perspective, participants were reflecting either on general (not specific) use (part 1), or on a specific past experience that they may not have remembered fully (part 2). Second, data on dosing, route, and duration for opioid use were based on self-reported data and therefore might be prone to self-reporting bias. Third, there are some limitations in the sampling methods because, as it commonly happens in surveys, the number of completers was limited and biased towards highly educated males in North America and Europe. This may limit generalisation of the current findings to the general population. Moreover, advertisement targeting kratom consumers may have led to selection bias resulting in a higher representation of kratom users ($N = 146$), among which kratom experiences were explored. However, this is a small sample size compared to larger surveys with kratom users, e.g., (Grundmann, 2017; Grundmann et al., 2022), and the study should be replicated in a broader sample. Finally, authors are aware that the NPS market is constantly evolving and some adverse events (e.g., constipation, dizziness, dry mouth, pruritus, respiratory depression, sedation) typical of opioids were not specifically investigated. Therefore, future surveys should include the evaluation of such adverse events and the extent to which new compounds, such as nitazenes, are influencing the opioid epidemic.

5.1. Conclusions

In conclusion, this study helps to delineate use characteristics for various classic, novel and herbal opioids, revealing different patterns of use and adverse event rates. Findings hint also at similarities between classic opioids and kratom, with users reporting its medical benefits, particularly in pain relief, but also risk of addiction. Therefore, our results highlight the need of monitoring classic, novel and herbal opioids use worldwide, especially in the light of the public health challenge posed internationally by the opioid epidemic. They also highlight the need for a multidisciplinary approach, including healthcare providers with appropriate training, and strategies for monitoring classic, novel and herbal opioids' toxicities. Moreover, enforcement agencies and policymakers should be involved in order to regulate access and sale of opioids (Bedene et al., 2022; Cook, 2022; Robert et al., 2023; UNODC, 2019), and should be continuously updated by information on user trends. Still, despite growing awareness of opioid-related risks, more toxicological data on emerging compounds are needed to fully define safety risks of opioids. Finally, with the growing need of different and appropriate strategies for treating pain and opioid use disorder, kratom's therapeutic potential as an alternative to opioids warrants randomized controlled clinical trials to elucidate user claims.

CRediT authorship contribution statement

Elisabeth Prevete: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Natasha L. Mason:** Writing – review & editing, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kim P. C. Kuypers:** Writing – review & editing, Visualization, Validation, Conceptualization. **Eef L. Theunissen:** Writing – review & editing, Visualization, Validation, Conceptualization. **Pablo Mallaroni:** Writing – review & editing, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation. **Massimo Pasquini:** Writing – review & editing, Visualization, Validation. **Johannes G. Ramaekers:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.etdah.2024.100166.

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