New Synthetic Opioids Use among Patients in Treatment for an Opioid Use Disorder in Barcelona

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Keywords
New drugs · Opiate addiction · Psychoactive substances · New synthetic opioids

Abstract

Introduction: New synthetic opioids (NSO), a class of new psychoactive substances (NPS), have recently emerged and pose an upcoming global public health challenge. The effects produced by NSO are similar to those from morphine, but they present greater pharmacological potency and abuse potential. Due to the increasing number of fatal overdoses and seizures in which NSO have been detected as heroin substitutes or adulterants, individuals with Opioid Use Disorder (OUD) represent a vulnerable population. The aim of our study was to describe and characterize from a gender perspective a Spanish cohort of potential conscious or unconscious NSO users. Methods: A cross-sectional study was conducted in a cohort of OUD participants under treatment in addiction care services in Barcelona and Badalona, Spain. Clinical evaluation was performed through an ad hoc survey, a scale to evaluate reasons to use an opioid without prescription (range 0–4) and the Wellbeing Index (WHO-5) (range 0–100). Objective consumption of NSO was assessed by urinalysis carried out by two validated methods: high-sensitivity gas chromatography-mass spectrometry (MS) and ultra-high-performance liquid chromatography-high-resolution MS. Results: A total of 154 participants with OUD were enrolled. They were mainly men (72.7%), mean age 47.8 years. Methadone was the predominant medication for opioid agonist treatment (mean dose 61.25 mg/day). A total of 32 (20.8%) participants reported having consumed some opioid to become “high” in the previous 3 months. The principal reasons for consuming illicit opioids were Replacing other...
drugs (mean 2.03) and Availability (mean 1.62), although Low price, was more highly valued by men (p = 0.045) and Shorter effect duration, most highly rated by women (p = <0.001). In the WHO-5, the mean score was 55 (SD = 30.1) without differences by gender. Fentanyl and derivatives or/ and metabolites were detected in 7 (6.1%) participants, but illicit/non-prescribed NSOs were found in 5 out of 114 patients (4.4%), and other non-fentanyl opioids in 36 participants (26 men and 10 women). Conclusion: A non-negligible consumption of NSO-fentanyl’s (positive detection in 6.1% of biological samples) was detected. The reasons for using these substances and also the well-being differed between the genders. There is therefore both voluntary and involuntary NSO consumption in our country which highlights the importance of approaching this potential public health problem.

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Introduction

The most recent emerging class of New Psychoactive Substances (NPS) has been the one of new synthetic opioids (NSO) [1, 2]. For two decades, the USA has faced a worsening opioid crisis, resulting from the misuse prescription opioids and the abuse of illegal opioids, which represents one of the greatest health and political challenges for the country [3, 4]. Different waves in this epidemic can be differentiated according to the predominant opioid and it is since 2013 approximately that synthetic opioids are the predominant ones [5], with an increase in the detection of fentanyl and derivatives [6]. This opioid crisis extended to other Commonwealth Countries (e.g., Australia and New Zealand) finally reaching Europe with case data are fragmented and quite different between countries [7].

In fact, since 2009, 67 NSO have been detected on the European drug market, 10 of which were reported for the first time in 2020 [1]. NSO selectively bind to the μ-, δ-, and/or κ-opioid receptors in the endogenous opioid system [8–10]. In a similar manner to morphine and other mu-agonist active compounds, NSO effects include analgesia, sedation, anxiolysis, euphoria, somnolence, and feelings of relaxation [11]. NSO potency, ranging from 100- to 1,000-fold that of morphine/heroin, results in an elevated risk of overdose [12–14] especially when administered as a heroin substitute, heroin adulterants, or counterfeit products.

NSO can be classified into three groups: fentanyl, fentanyl analogues, and nonfentanyl-derived synthetic opioid and it is since 2013 approximately that synthetic opioids are the predominant ones [5], with an increase in the detection of fentanyl and derivatives [6]. This opioid crisis extended to other Commonwealth Countries (e.g., Australia and New Zealand) finally reaching Europe with case data are fragmented and quite different between countries [7].

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NSO can be classified into three groups: fentanyl, fentanyl analogues, and nonfentanyl-derived synthetic opioids [11, 15, 16]. Of these, fentanyl analogues have been the compounds most involved in non-fatal and fatal intoxications particularly in the USA and in recent years in some European countries, [1, 17, 18]. It is believed that the real extent of NSO toxicity is probably underestimated. This is probably due to the fact that NSO overdoses are underdisclosed; in the majority of cases, they lack specific investigations and objective evidence of the intoxicating agent (parent drugs and/or metabolites) in the biological fluids of the affected individuals [12, 19].

Actual figures for the fentanyl epidemic are unknown given that NSO are used in place of heroin, as a cheaper alternative, or as an adulterant [12, 20]. There is therefore a greater likelihood of substitution, adulteration, and miss-selling of these substances which could lead to a higher number of intoxications [21].

To date, there is scarce information regarding NSO use by individuals with heroin or other opioid addictions who represent a predominantly male population (around 80% men). Moreover, specific data on some European regions and Mediterranean areas are missing. The aim of the study was to establish the prevalence of NSO consumption in individuals with Opioid Use Disorder (OUD) attending two different addiction care facilities in the greater Barcelona area (Barcelona city and Badalona) and to characterize the feature of their use and related motivation.

Materials and Methods

Participants

This is a cross-sectional study with one group of treatment seeking patients with an OUD. The study sample was made up of patients with an OUD diagnosis according to DSM-5 criteria [22] in treatment at the addiction care services from Hospital del Mar, Barcelona, Spain and Hospital Universitari Germans Trias i Pujol, Badalona, Spain. Recruitment was carried out from February 2019 to March 2020 and from July to October 2020.

Inclusion criteria were subjects with an OUD (DSM-5), older than 18 years, attending any of the two addiction care facilities and speaking/understanding Spanish. The exclusion criteria included linguistic and cognitive barriers that impaired the subject’s correct evaluation. All participants gave their written consent, and the study was approved by the Ethics Committee in Clinical Research Parc de Salut MAR (CEIC-PSMAR, number 2018/8138/I) and Hospital Universitari Germans Trias i Pujol (CEIC-HUGTIP number (PI-18-126).

Clinical Assessments

Clinical assessment was performed through a structured face-to-face interview of approximately 20–30 min. Instruments used in the interview were: (a) An “ad-hoc questionnaire” including: sociodemographic data, history of opioid use (lifetime history of overdoses, age of first treatment, current treatment), any substance
consumed in the previous 3 months, and being “high” without prescription; (b) in the case participants reported the use of any without prescription opioid resulting a sensation of being “high,” they were asked to evaluate 14 potential reasons why they chose it on a five-point Likert scale (0 = not true at all; 1 = rather not true; 2 = partly true; 3 = rather true; 4 = “completely true”) [23]; and (c) The Wellbeing Index (WHO-5, 1998) was used to assess the subject’s subjective and psychological well-being [24]. This self-administered index consists of five questions that refer to the patient’s physical-emotional state over the previous two weeks. The total score obtained ranges from 0 to 100 points; the higher the score, the greater the well-being.

Table 1. Sociodemographic and clinical characteristics of the 154 study participants

|                        | Total N = 154 | Men N = 112 (72.72%) | Women N = 41 (26.62%) | Transgender N = 1 (0.66%) | p value |
|------------------------|---------------|-----------------------|------------------------|---------------------------|---------|
| Age (mean SD)          | 47.80 (8.72)  | 48.20 (8.49)          | 46.76 (9.46)           | 46 (–)                    | 0.653   |
| Birthplace, N (%)      |               |                       |                        |                           |         |
| Spain                  | 121 (78.57)   | 90 (80.35)            | 30 (73.17)             | 1 (100)                   | 0.550   |
| Other                  | 33 (21.43)    | 22 (19.65)            | 11 (26.83)             | –                         |         |
| Current opioid agonist treatment, N (%) |               |                       |                        |                           |         |
| Total                  | 142 (92.20)   | 102 (91.07)           | 39 (95.12)             | 1 (100)                   | 0.768   |
| Buprenorphine          | 20 (12.99)    | 12 (10.71)            | 8 (19.51)              | –                         |         |
| Methadone              | 116 (75.32)   | 87 (77.67)            | 28 (68.29)             | 1 (100)                   | 0.444   |
| Morphine slow release  | 5 (3.25)      | 2 (1.79)              | 3 (7.32)               | –                         |         |
| Other*                 | 1 (0.65)      | 1 (0.89)              | –                      | –                         |         |
| Methadone doses, mg/day (mean SD) | 61.25 (44.92) | 61.03 (42.00) | 62.15 (54.32) | 55 (–) | 0.137 |
| Min: 2                 |               | Min: 5                | Min: 2                 | Max: 220                  |         |
| Max: 235               |               | Max: 235              | Max: 220               |                           |         |
| Age of first drug treatment (mean SD) | 28.53 (13.82) | 29.42 (14.76) | 26.07 (10.82) | 30 (–) | 0.415 |
| Lifetime overdose, N (%)|               |                       |                        |                           |         |
| Heroin                 | 59 (38.31)    | 41 (36.60)            | 18 (43.90)             | –                         | 0.522   |
| Other opioid           | 2 (1.30)      | 0 (–)                 | 2 (4.88)               | –                         | 0.684   |
| Other substances       | 25 (16.23)    | 7 (6.25)              | 17 (11.04)             | 1 (100)                   | 0.072   |
| Substances used in the last 3 months, N (%) |               |                       |                        |                           |         |
| Heroin                 | 52 (33.77)    | 43 (38.39)            | 9 (21.95)              | –                         | 0.126   |
| Speedball              | 16 (10.39)    | 13 (11.60)            | 3 (7.32)               | –                         | 0.701   |
| Cocaine                | 59 (38.31)    | 45 (40.18)            | 14 (34.15)             | –                         | 0.581   |
| Amphetamine**          | 11 (7.14)     | 9 (8.04)              | 2 (4.88)               | –                         | 0.768   |
| Cannabis               | 63 (40.91)    | 48 (42.86)            | 14 (34.15)             | –                         | 0.302   |
| Alcohol                | 24 (15.58)    | 21 (18.75)            | 3 (7.32)               | –                         | 0.205   |
| Gabapentin**           | 1 (0.65)      | 1 (0.89)              | –                      | –                         | 0.828   |
| Benzoacepines**        | 18 (11.69)    | 13 (11.61)            | 5 (12.19)              | –                         | 0.931   |
| Ketamine               | 2 (1.30)      | –                     | 2 (4.88)               | –                         |         |
| MDMA                   | 1 (0.65)      | 1 (0.89)              | –                      | –                         |         |

* Fentanyl. ** Without prescription.

Data Analysis

The statistical analysis was carried out with the SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive analyses were used to characterize the samples. The estimations of the rates for each categorical variable were described in frequencies and percentages, and for the continuous ones in mean and standard deviations. Comparisons of sociodemographic and clinical data, reasons for NSO use, and the WHO-5 score according to gender were performed using Student’s t test for continuous variables and the $\chi^2$ test for categorical ones. Statistical significance level was set at $p < 0.05$.

Results

Sociodemographic and Clinical Assessment

A total of 154 participants were enrolled in the study. Men ($N = 112; 72.7\%$) outnumbered women ($N = 41; 26.6\%$) and there was one transgender individual (0.7%). The mean age for all participants was 47.80 years and 121
(78.6%) were Spanish, without differences between genders. Main clinical characteristics are described in Table 1.

Of the 154 participants, 142 (92.2%) were included in a current opioid agonists treatment program, and 12 (7.8%) were not in an opioid agonist treatment (first day of contact to the addiction facility). Among opioid agonist treatment, methadone was the most frequent prescribed medication ($N = 116, 75.3\%$), with a mean dose of 61.25 mg/day, although near half of the participants ($N = 59, 51\%$) received a dose below 60 mg/day (mean = 31.8; SD = 13.6). The mean age for the first treatment for OUD was 28.53 years, and heroin was the main drug consumed ($N = 123, 79.9\%$). Interestingly, 59 (38.3\%) participants reported at least one lifetime overdose episode with heroin. In relation to the use of other substances in the previous 3 months, the most commonly consumed ones were cannabis ($N = 63; 40.9\%$), cocaine ($N = 59; 38.3\%$), and benzodiazepines without prescription ($N = 18; 11.7\%$).

A total of 32 (20.8\%) participants, 24 (21.4\%) men and 8 (19.5\%) women, reported the use of non-prescribed opioids other than heroin to get “high” in the previous 3 months. The mean number of non-prescribed reported opioids was 1.28 (SD = 0.57). Methadone without prescription was the most commonly reported (16 participants), followed by tramadol (11) and fentanyl (7). The reasons for use were principally Replacing other drugs (mean 2.03, SD = 1.84) and Availability (mean 1.62, SD = 1.69). Differences between gender were found in two reasons: Low price, which was more highly valued by men than women ($p = 0.045$), and Shorter effect duration, most highly rated by women ($p < 0.001$) (Table 2).

The mean score for all the participants in the WHO-5 questionnaire was 55 (SD = 30.1) without significant gender differences [men: mean = 57.1 (SD = 29.7) versus women mean = 49.9 (SD = 30.8), $p = 0.860$]. In addition, no differences between male and female participants were

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### Table 2. Participants who reported use of any opioid (except heroin) in the previous 3 months to get “high” and reasons for selecting them ($N = 32$)

| Opioids (except heroin), n (%) | Total $N = 32$ | Men $N = 24$ (21.04\%) | Women $N = 8$ (19.51\%) | $p$ value |
|-------------------------------|---------------|--------------------------|---------------------------|-----------|
| Oxycodone                     | 1 (0.65)      | 1 (0.89)                 | -                         | 0.828     |
| Fentanyl                      | 7 (4.55)      | 3 (2.68)                 | 4 (9.76)                  | 0.173     |
| Other fentanyl derivatives*   | 1 (0.65)      | -                        | 1 (2.44)                  | 0.250     |
| Tramadol                      | 11 (7.14)     | 8 (7.14)                 | 3 (7.32)                  | 0.961     |
| Morphine                      | 4 (2.60)      | 3 (2.68)                 | 1 (2.44)                  | 0.983     |
| Tapentadol                    | 1 (0.65)      | 1 (0.89)                 | -                         | 0.828     |
| Methadone                     | 16 (10.39)    | 14 (12.50)               | 2 (4.88)                  | 0.370     |
| Buprenorphine                 | 1 (0.65)      | 1 (0.89)                 | -                         | 0.828     |
| Codeine                       | 2 (1.30)      | 1 (0.89)                 | 1 (2.44)                  | 0.918     |
| Hydrocodone                   | 1 (0.65)      | 1 (0.89)                 | -                         | 0.828     |

| Reasons for consuming opioids (mean scale score [0–4**]), n (%) | Total $N = 32$ | Men $N = 24$ (21.04\%) | Women $N = 8$ (19.51\%) | $p$ value |
|---------------------------------------------------------------|---------------|--------------------------|---------------------------|-----------|
| Curiosity                                                     | 1.09 (1.67)   | 1.17 (1.76)              | 0.88 (1.46)               | 0.161     |
| Replacing other drugs                                        | 2.03 (1.84)   | 1.88 (1.90)              | 2.5 (1.69)                | 0.094     |
| Availability                                                  | 1.62 (1.69)   | 1.63 (1.69)              | 1.63 (1.85)               | 0.742     |
| My friends also used it                                       | 0.91 (1.44)   | 0.88 (1.33)              | 1 (1.85)                  | 0.241     |
| More intense subjective effects                               | 1.06 (1.66)   | 0.92 (1.67)              | 1.5 (1.69)                | 0.713     |
| I did not know why I used                                     | 0.53 (1.19)   | 0.46 (1.10)              | 0.75 (1.49)               | 0.279     |
| Low price                                                     | 1.56 (1.70)   | 1.92 (1.67)              | 0.5 (1.41)                | 0.045     |
| Legality                                                      | 0.56 (1.24)   | 0.58 (1.21)              | 0.5 (1.41)                | 0.888     |
| Shorter effect duration                                       | 0.31 (0.93)   | 0.13 (0.45)              | 0.88 (1.64)               | <0.001    |
| It cannot be detected in biological samples                   | -             | -                        | -                         | -         |
| Exotic brand name                                             | -             | -                        | -                         | -         |
| I thought it was safer                                        | 0.13 (0.55)   | 0.17                     | -                         | 0.134     |
| Attractive packaging                                          | 0.09 (0.53)   | 0.13                     | -                         | 0.242     |
| I thought it was more natural                                 | 0.03 (0.17)   | -                        | 0.13                      | -         |

* Carfentyn. ** Scale scores (0–4): 0 = not true at all, 1 = rather not true, 2 = partly true, 3 = rather true, 4 = completely true.
found for age, current opioids agonist treatment, metha- 
done dose, age of first drug treatment, lifetime overdose, 
and substances used in last 3 months (Table 1).

Sample Collection and Biological Sample Analysis

Of the 154 participants in the study, we obtained single 
samples from 114 of the subjects (74.0%). All the types 
of opioids detected in the samples are shown in Table 3. In 
some of them more than one opioid was found (164 opi- 
oids in total). In addition, information provided by the 
participants regarding the prescription or not of any opi- 
id is depicted in the same table.

Opioids other than those prescribed were detected in the 
urine samples of 41 subjects (35.9%). Of these 41 sub- 
jects, 27 were on methadone treatment (mean mg/day 
74.3; SD = 52.3), five on buprenorphine treatment (mean 
buprenorphine mg/day 6.8; SD = 5.6) and four on mor- 
phine slow sustained-release preparation (mean 390 mg/ 
day; SD = 128.1).

In case of fentanyl and derivatives/analogues, fentanyl 
alone was detected in 7 participants (6.1%), but the pres- 
ence of illicit/non-prescribed NSOs was found in only 5 
out of 114 patients (4.4%). Other opioids (non-fentanyl 
derivatives) were found in 36 (31.6%) participants, and in 
only 2 (1.8%) cases, those were under prescription, one 
case for tapentadol and one case for tramadol. The re- 
maining 34 (29.8%) cases were illegal/non-prescribed 
opioids. Dextromethorphan, without prescription, was 
The most frequent opioid detected in the urine samples (N 
= 20; 17.5%), followed by heroin (N = 14; 12.3%), and 
methadone without prescription (N = 7; 6.1%).

Regarding awareness of having taken NSO, none of the 
5 participants in which illegal fentanyl/derivatives was 
detected, reported having used it in the previous 3 months 
to “get high.” With respect to other opioids (non-fentan- 
yl derivatives), among the 36 subjects, 19 (52.8%) partici- 
pants reported their use in the previous 3 months to “get 
high.”

Discussion

The results show that synthetic opioids are consumed 
within our social context. Only 30% of the participants in 
the identified cases reported using an opioid to “get high.” 
When distinguishing in between nonprescribed non-fen- 
tanyl opioids and fentanyls and analogues, we observed 
that the prevalence of detection in urine for the former 
was higher (25.4%) than that of the latter (4.4%). Such 
findings are consistent with recent data provided by the 
European Monitoring Centre for Drugs and Drug Addic- 
tion (EMCDDA) in which the proportion of non-fentan- 
yl opioids reported in seizures was higher than that of 
fentanyl’s and analogues [21, 26]. It is also important to 
mention that in case non-prescribed fentanyls, this 4.4% 
is a very limited figure that is significantly smaller than 
similar numbers in the USA, Canada, and some other Eu- 
ropean countries [7, 27]. Considering opioids detected, 
most frequent was dextromethorphan, it is a weak opioid 
that is present as an ingredient in coughing syrup and 
probably available as a licit over the counter opioid, and 
this may explain its relatively frequent use in this popula-
tion. It is also important to mention that oxycodone was 
not detected (and hydrocodone only once) in this group 
of patients although oxycodone/naloxone a relative used 
algesic in our country (13% opioid prescriptions) [27, 
28].

When participants were asked why they consumed 
opioids other than heroin, the two principal responses 
were Replacing other drugs and Availability of the sub-
stance. These two reasons are also among those most 
highly rated in the study by Kapitány-Fővény et al. [23].

Table 3. Opioids and metabolites detected in biological samples 
(N = 114)

| Detected in biological sample (N = 114), N (%) | Non-prescribed, N (%) |
|----------------------------------------------|-----------------------|
| **Substitution opioids**                       |                       |
| Methadone                                     | 90 (79)               |
| Morphine                                      | 4 (3.5)               |
| Buprenorphine                                 | 1 (0.9)               |
| **Fentanyl and derivatives**                  |                       |
| Fentanyl/norfentanyl                          | 4 (3.5)               |
| Beta-hydroxyfentanyl                          | 1 (0.9)               |
| Fluorofentanyl                                | 2 (1.8)               |
| Fluoro acetyl fentanyl                        | 1 (0.9)               |
| Fluoro valeril fentanyl                       | 1 (0.9)               |
| Norfentanyl                                   | 1 (0.9)               |
| **Heroin and other opioids**                  |                       |
| Heroin                                        | 14 (12.3)             |
| Anileridine                                   | 3 (2.6)               |
| Codeine                                       | 2 (1.8)               |
| Dextromethorphan                              | 20 (17.5)             |
| Difenoxin                                     | 1 (0.9)               |
| Hydromorphone                                 | 3 (2.6)               |
| Hydrocodone                                   | 1 (0.9)               |
| Levorphanol/Dextrophan                        | 5 (4.4)               |
| N-Desmethyltramadol                           | 1 (0.9)               |
| Norpropoxifene                                | 5 (4.4)               |
| Tapentadol                                    | 1 (0.9)               |
| Tramadol                                      | 3 (2.6)               |

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Other authors have indicated pleasure/enjoyment and coping with some kind of problem such as pain, anxiety, and insomnia as the main causes for NSO consumption [29]. Relatively low dose of methadone might suggest that higher doses in this population may be having resulted in lower levels of illicit opioid use. Understanding the reasons behind NSO use is crucial in order to design better harm reduction and treatment strategies, as increase the doses of the opioid agonist treatment, provide information of different NSO in addiction facilities (including self-injection rooms), easy availability of naloxone kits.

A key issue in the World Health Organization health definition is well-being. In this respect, our participants obtained a WHO-5 score lower than the average reported for the general Spanish population (65.4 points) [30]. When classifying the scores for the general Spanish population by gender, it can be observed that the women’s was lower (mean = 64.9) than the men’s (mean = 70.5) [31]. Several studies have pointed to the usefulness of the WHO-5 as an instrument to detect depression, reaching a consensus that a score equal to or less than 50 indicates that there is a risk of depressive disorder [32]. In the particular case of OUD women, their mean score was lower than 50 points for the WHO-5 so a comprehensive examination would be recommended in order to determine whether or not a depressive disorder exists. In our results, among 154 participants included in this study, 19 (46.3%) women and 45 (40.2%) men, showed a score <50 for the WHO-5 scale, suggesting the presence of comorbid depression that emphasizes the need of study the presence of other psychiatric disorders in patients with substance use disorder, mainly in women [33].

According to the EMCDDA 2020 [26], opioids, often together with other substances, have been detected in the majority of fatal overdoses, and the age at which this occurs is increasing year by year. Several acute intoxications and fatal overdoses involving fentanyl, fentanyl analogues, and non-fentanyl opioids have been reported in recent years [34–37]. In addition, the number of NSO poisonings has been rising [38] and these substances are being sold as heroin or added as adulterants [39]. Taking into account such circumstances, individuals with an OUD are a population particularly at risk. Among our participants, approximately 5 of 7 (70%) of those with urinalysis positive for fentanyl and/or metabolites/analogues and synthetic opioids were unaware they were taking that type of substance. Although the small sample size in our study, such a finding highlights the need to develop effective strategies for the detection in biological samples of these compounds in order to provide effective treatment response and prevent NSO overdose [40, 41]. In addition, as a high percentage of NSOs are adulterants or counterfeit substances, consumers need to be informed about the products contained in the substances they intend to use.

In a similar manner to other studies, a tendency for patients in opiate agonist treatment to use other illicit drugs, particularly cocaine, was observed [42, 43]. Regarding the detection of classical illicit drugs, we confirmed that cocaine was the most frequent substance. Some studies have suggested that cocaine consumption may have a negative impact on treatment retention for opioid substitution [43], facilitating the use of opioids, including NSO.

Among the limitations of the study is the relatively small sample size. The mean methadone dose was relatively low, which may be a risk factor for illicit opioid use in patients receiving opioid agonist treatment. A higher maintenance dose or greater control of the treatment could be effective in reducing the consumption of illicit opioids.

Nevertheless, NSO represent a minor percentage of NPS, the consumption prevalence of which in Spain is 1.7% among individuals aged 15–64 years [44]. In addition, gender differences require further research due to the limited number of women in our sample. With respect to design, our study was transversal, a sole one-point sample was collected from each participant, and thus the possibility of substance detection depended on the time of consumption, dose, and elimination half-life in urine. Although further research is warranted for a comprehensive understanding of the situation, our study provides an overview of NSO use and highlights the importance of remaining vigilant to this potential public health problem.

Conclusion

This study provides a preliminary description of the situation regarding NSO consumption among opiate users in the greater Barcelona area. We can conclude there is no an opioid crisis in our area as reported by the USA and some European countries. Despite this, a starting phenomenon has been observed which, according to the experience of the countries mentioned above, requires attention even in a limited number of individuals. Our preliminary results demonstrate that in individuals with OUD there is both voluntary and involuntary NSO consumption with the risks such behaviour entails, particu-
larly when such substances are used unknowingly. Such findings emphasize the importance of appropriately adapting the public health system so as to reduce any consequences arising from NSO consumption in individuals with OUD.

Statement of Ethics

The study was conducted in accordance to the national and international guidelines (Declaration of Helsinki) and the legislation regarding the treatment, communication, and transfer of personal data (protection data regulation of the EU 2016/679 of the European Parliament and of the Council April 27th 2016, Protection data [RGPD]). The study was approved by the Ethics Committee in Clinical Research Parc de Salut MAR (CEIC-PSMAR, number 2018/8138/I) and Hospital Universitari Germans Trias i Pujol (CEIC-HUGTIP number (PI-18-126). Written informed consent was obtained from each participant after a complete description of the study and any question/issue being fully answered.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European drug report 2021: trends and developments. 2021.
2 United Nations Office on Drugs and Crime (UNODC). SMART update: the growing complexity of the opioid crisis. 2020.
3 van Amsterdam J, Pierce M, van den Brink W. Is Europe facing an emerging opioid crisis comparable to the U.S. Ther Drug Monit. 2021 Feb;43(1):42–51.
4 Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: a comprehensive overview. Curr Pain Headache Rep. 2018 Mar;22(3):16.
5 Centre for Disease Control and Prevention (CDC). Understanding the epidemic. 2017 [cited 2021 Sep 28]. Available from: https://www.cdc.gov/opioids/basics/epidemic.html.
6 Drug Enforcement Administration (DEA). 2019 national drug threat assessment (NDTA). 2019.
7 Pierce M, van Amsterdam J, Kalkman GA, Scheltekens A, van den Brink W. Is Europe facing an opioid crisis like the United States? An analysis of opioid use and related adverse effects in 19 European countries between 2010 and 2018. Eur Psychiatry. 2021;64(1):e47.
8 Frisoni P, Bacchio E, Bilel S, Talarico A, Maria Gaudio R, Barbieri M, et al. Novel synthetic opioids: the pathologist’s point of view. Brain Sci. 2018;8(9):170.
9 Baumann MH, Majumdar S, Le Rouzic V, Hunkele A, Upreti R, Huang XP, et al. Pharmacological characterization of novel synthetic opioids (NSO) found in the recreational drug marketplace. Neuropharmacology. 2018;134:101–7.
10 Pérez-Mañá C, Papaseit E, Fonseca F, Farré A, Torrens M, Farré M. Drug interactions with new synthetic opioids. Front Pharmacol. 2018 Oct;9:1145.
11 Suzuki J, El-Haddad S A. A review: fentanyl and non-pharmaceutical fentanyl. Drug Alcohol Depend. 2017 Feb;171:107–16.
12 Pichini S, Pacifici R, Marinelli E, Busarò FP. European drug users at risk from illicit fentanyl mix. Front Pharmacol. 2017;8:785.
13 Prekupec MP, Mansky PA, Baumann MH. Misuse of novel synthetic opioids: a deadly new trend. J Addict Med. 2017;11(4):256–65.
14 Salle S, Bodeau S, Dherin A, Ferdonnet M, Goncalves R, Lenski M, et al. Novel synthetic opioids: a review of the literature. Toxicol Anal Clin. 2019 Dec;31(4):298–316.
15 Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. Neuropharmacology. 2018;134:121–32.
16 Tabarria I, Soares S, Rosado T, Gonçalves J, Luis Á, Malaca S, et al. Novel synthetic opioids: toxicological aspects and analysis. Forensic Sci Res. 2019 Apr;4(1):111–40.
17 Jones CM, Einstein EB, Compton WM. Changes in synthetic opioid involvement in drug overdose deaths in the United States, 2010–2016. JAMA. 2018;319(17):1819–21.
