

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

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Keywords

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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 un-

conscious 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 fentanyls 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 μ -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 opi-

oids [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

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)	-	0.444
Methadone	116 (75.32)	87 (77.67)	28 (68.29)	1 (100)	
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: 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
Benzodiazepines**	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.

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.

Sample Collection and Biological Analysis

At recruitment, a clinical assessment was performed and a urine sample obtained. Urine samples were analysed by two different set-ups and validated methodologies: ultra-high-performance liquid chromatography-high-resolution mass spectrometry for extensive screening for NSOs and general NPS and high-sensitivity gas chromatography-mass spectrometry for confirmation of identified compounds [25].

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 χ^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

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

	Total $N = 32$	Men $N = 24$ (21.04%)	Women $N = 8$ (19.51%)	p value
Opioids (except heroin), n (%)				
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 (%)				
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	–

* Carfentanyl. ** Scale scores (0–4): 0 = not true at all, 1 = rather not true, 2 = partly true, 3 = rather true, 4 = completely true.

(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

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

	Detected in biological sample ($N = 114$), N (%)	Non-prescribed, N (%)
Substitution opioids	93	7
Methadone	90 (79)	7 (6.1)
Morphine	4 (3.5)	–
Buprenorphine	1 (0.9)	–
Fentanyl and derivatives	7	5
Fentanyl/norfentanyl	4 (3.5)	2 (1.8)
Beta-hydroxyfentanyl	1 (0.9)	1 (0.9)
Fluorofentanyl	2 (1.8)	2 (1.8)
Fluoro acetyl fentanyl	1 (0.9)	1 (0.9)
Fluoro valeril fentanyl	1 (0.9)	1 (0.9)
Norfentanyl	1 (0.9)	1 (0.9)
Heroin and other opioids	36	34
Heroin	14 (12.3)	14 (12.3)
Anileridine	3 (2.6)	3 (2.6)
Codeine	2 (1.8)	2 (1.8)
Dextromethorphan	20 (17.5)	20 (17.6)
Difenoxin	1 (0.9)	1 (0.9)
Hydromorphone	3 (2.6)	3 (2.6)
Hydrocodone	1 (0.9)	1 (0.9)
Levorphanol/Dextrorphan	5 (4.4)	5 (4.4)
N-Desmethyltramadol	1 (0.9)	1 (0.9)
Norpropoxifene	5 (4.4)	5 (4.4)
Tapentadol	1 (0.9)	–
Tramadol	3 (2.6)	2 (1.8)

found for age, current opioids agonist treatment, methadone 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 opioids in total). In addition, information provided by the participants regarding the prescription or not of any opioid 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 subjects, 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 morphine slow sustained-release preparation (mean 390 mg/day; SD = 128.1).

In case of fentanyl and derivatives/analogues, fentanyl itself was detected in 7 participants (6.1%), but the presence 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 remaining 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-fentanyl derivatives), among the 36 subjects, 19 (52.8%) participants 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-fentanyl 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 Addiction (EMCDDA) in which the proportion of non-fentanyl 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 European 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 population. 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 analgesic 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 substance. These two reasons are also among those most highly rated in the study by Kapitány-Fövény et al. [23].

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 fentanyls, 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 treat-

ment 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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Author Contributions

Conception and design of the work: Marta Torrens, Simona Pichini, Roberta Pacifici, and Magí Farré. Validation and investigation: Marta Torrens, Maria Alías-Ferri, Emilia Marchei, Roberta Pacifici, Simona Pichini, Manuela Pellegrini, Clara Pérez-Mañá, Esther Papaseit, Roberto Muga, Francina Fonseca, and Magí Farré. Analysis and interpretation of the data: Marta Torrens, Maria Alías-Ferri, Emilia Marchei, Simona Pichini, Manuela Pellegrini, and Magí Farré. Draft preparation: Maria Alías-Ferri, Simona Pichini, Francina Fonseca, Marta Torrens, and Magí Farré. Critical review: Marta Torrens, Maria Alías-Ferri, Roberta Pacifici, Simona Pichini, and Magí Farré. All the authors: Marta Torrens, Maria Alías-Ferri, Emilia Marchei, Roberta Pacifici, Simona Pichini, Manuela Pellegrini, Clara Pérez-Mañá, Esther Papaseit, Roberto Muga, Francina Fonseca, and Magí Farré approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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.

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