

# Patterns of ketamine use among people with substance use disorder in France: Multisource analysis of the data from the French Addictovigilance Network

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## Abstract

**Background:** Due to its psychoactive effects, ketamine has become a drug used for non-medical purpose.

**Objectives:** To assess the latest trends in ketamine use among people with substance use disorder and to characterize its clinical complications using complementary health data sources of the French Addictovigilance Network.

**Methods:** First, we extracted all reports involving ketamine from 2012 to 2021 from the database of the OPPIDUM program (i.e., a multicentric program conducted in collaboration with hundreds of substance abuse treatment facilities that collects data on drugs used by subjects with substance use disorders). We described the reports globally and the changes from 2012 to 2021. Second, we extracted all cases involving ketamine from July 2020 to December 2022 from the French National Pharmacovigilance Database (BNPV). We identified the cases related to ketamine use among people with substance use disorder and described them.

**Results:** There was a 2.5-fold increase in the number of ketamine users with substance use disorder in the OPPIDUM program, from 35 (0.7%) subjects in 2012 to 89 (1.7%) subjects in 2021. There was an increase in the proportion of subjects who were daily users, had distress upon discontinuation, and presented addiction. There were 238 cases related to ketamine use among people with substance use disorder in the French National Pharmacovigilance Database from July 2020 to December 2022. Among them, 94 (39.5%) cases involved ketamine use disorder, 20 (8.4%) cases involved urinary tract and kidney symptoms, and 13 (5.5%) cases involved hepatobiliary symptoms.

**Abbreviation:** BNPV, French National Pharmacovigilance Database.

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**Conclusion:** The trend observed over 10 years reflects the growth in ketamine use among people with substance use disorder, although it does not allow to estimate the rates of non-medical use of ketamine in the general population. Ketamine-induced uropathy and cholangiopathy are reported in ketamine users with substance use disorder, especially in case of repeated and/or prolonged use of high doses.

**KEYWORDS**

addictovigilance, drug abuse, ketamine, substance use disorder

## 1 | INTRODUCTION

Ketamine is a pleiotropic drug. It mainly is a non-competitive antagonist of the N-methyl-D-aspartic acid receptors, one of the glutamate receptors [1]. Ketamine is authorized in many countries, including in France, in induction and maintenance of anesthesia, and is also used in depression and pain management [2]. Due to its pharmacological properties, the main clinical complications of ketamine use are psychiatric adverse reactions (e.g., hallucinations, dissociations, and anxiety) [2]. Cardiovascular adverse reactions (e.g., tachycardia and hypertension) are also frequently reported [2].

Due to its psychoactive effects and the reinforcing and rewarding properties induced by dopamine release [3], ketamine has become a drug used for non-medical purpose. Ketamine is often initiated in a context of raves, clubs, and chemsex, as a part of polydrug use [4, 5]. The prevalence and geographic spread of ketamine use among people with substance use disorder has grown steadily worldwide in the past a few decades [6]. Though its precise prevalence is unknown, small single-country studies estimated use rates of ketamine between 0.1% and 4% of those surveyed [7]. Ketamine use among people with substance use disorder appears to be most common in East and South-East Asia [8]. Hong Kong reported ketamine as the second-most popular drug after heroin from 2007 to 2010 [7]. It is often stated that illicitly available ketamine is derived by diversion of legitimate veterinary and medical supplies. However, illicit manufacturing laboratories have also been reported, particularly in China and South-East Asia [9].

In France, ketamine use among people with substance use disorder is closely monitored by the French Addictovigilance Network, in coordination with the French Drug Agency [10]. The first cases in France date back to the 90s within the medical field. More recently, a disproportionality analysis found a signal of ketamine abuse [11]. However, the last published study focusing on patterns of ketamine use among people with substance use disorder dates back to 2003 [12]. In this context, this study aims to assess the latest trends in ketamine use among people with substance use

disorder and to characterize its clinical complications using complementary health data sources of the French Addictovigilance Network.

## 2 | MATERIALS AND METHODS

### 2.1 | Data source

This study is a multisource analysis of complementary data sources.

First, we used the database of the OPPIDUM program [13, 14]. OPPIDUM is an annual, nationwide surveillance program conducted since 1995 by the French Addictovigilance Network. It is a multicentric program conducted in collaboration with hundreds of substance abuse treatment facilities distributed throughout France. It collects data on drugs used by subjects with substance use disorders in the week prior to the survey. Data collected include sociodemographic characteristics and patterns of drug use.

Second, we used the French National Pharmacovigilance Database (BNPV). The BNPV centralizes adverse reactions reported by healthcare professionals and patients in France. Since April 2021, the BNPV is the first database at the international level to also record addictovigilance cases (i.e., cases related to abuse and/or addiction) in addition to classical pharmacovigilance cases [15]. All cases are documented and analyzed by clinical pharmacologists from the 31 French Pharmacovigilance Centers and the 13 French Addictovigilance Centers. As a result, the cases are thoroughly documented with clinical and pharmacological information.

### 2.2 | Data selection and analyses

In order to assess the latest trends in ketamine use among people with substance use disorder, we extracted all reports involving ketamine from 2012 to 2021 from the database of the OPPIDUM program. We described the following data globally and their change from 2012 to 2021: sociodemographic characteristics (e.g., age and sex), patterns of ketamine use

(e.g., route of administration, frequency, and polydrug use), indicators of ketamine use disorder (i.e., daily use, distress upon discontinuation, and addiction), and indicators of social integration (i.e., stable housing, regular income, and employment).

In order to characterize the clinical complications of ketamine use among people with substance use disorder, we extracted all cases involving ketamine from July 2020 to December 2022 from the BNPV (i.e., cases recorded after the last addictovigilance report [10]). Three authors (i.e., PG, TS, and JM) reviewed and analyzed all cases to identify cases related to ketamine use among people with substance use disorder. According to previous communication from the French Drug Agency regarding new, unexpected clinical complications of ketamine use [16], the analyses focused on cases of ketamine use disorder, urinary tract and kidney symptoms, and hepatobiliary symptoms. The following data were retrieved from the cases and described: sociodemographic characteristics (e.g., age and sex), patterns of ketamine use (e.g., frequency, context of use, route of administration, and other drugs used), and clinical profile (e.g., clinical complications of ketamine use, seriousness, and care).

The study protocol was not recorded a priori.

### 3 | RESULTS

#### 3.1 | Trends in ketamine use according to the OPPIDUM program

There were 438 ketamine users with substance use disorder in the OPPIDUM program from 2012 to 2021 (Table 1). The median age was 30 years and 11 (2.5%) subjects were less than 18 years old; 336 (76.7%) subjects were men; 242 (55.3%) subjects were under opioid maintenance treatment, 167 (38.1%) had alcohol dependence, and 407 (92.9%) were tobacco users. Regarding indicators of ketamine use disorder, 36 (8.2%) subjects were daily users, 57 (13.8%) had distress upon discontinuation, and 47 (10.7%) presented addiction. The most frequent routes of administration were nasal route ( $n = 331$ , 75.6%) and intravenous route ( $n = 97$ , 22.1%). Regarding indicators of social integration, 251 (57.3%) subjects had stable housing, 152 (34.7%) had regular income, and 127 (29.0%) were employed.

When focusing on trends in the OPPIDUM program from 2012 to 2021, there was a 2.5-fold increase in the number of ketamine users with substance use disorder, from 35 subjects in 2012 to 89 subjects in 2021, while the number of subjects included remained stable around 5000 subjects each year (Figure 1 and Table 1). This corresponded to an increase from 0.7% to 1.7% in the prevalence of ketamine use among all subjects included in the OPPIDUM program. Regarding

indicators of ketamine use disorder, there was an increase in the proportion of subjects who were daily users (from 5.7% to 10.1%), had distress upon discontinuation (from 8.6% to 14.6%), and presented addiction (from 8.6% to 15.7%). Regarding indicators of social integration, there was an increase in the proportion of subjects who had stable housing (from 54.3% to 59.6%), regular income (from 22.9% to 39.3%), and employment (from 22.9% to 27.0%).

#### 3.2 | Clinical characterization of ketamine users with substance use disorder from the BNPV

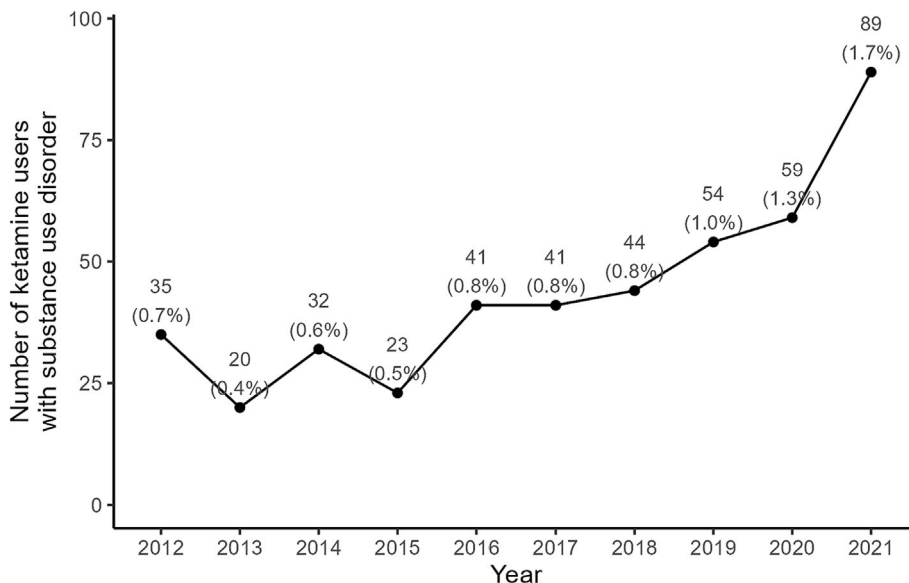
Among the 630 cases involving ketamine recorded in the BNPV from July 2020 to December 2022, there were 238 cases related to ketamine use among people with substance use disorder (Table 2). The median age was 23 years, and 26 (10.9%) subjects were less than 18 years old. One hundred fifty-three (64.3%) subjects were men. There was one case of death in a woman due to a cardiac arrest in a context of polydrug use, including ketamine, cannabis, and her usual treatment (i.e., diazepam, duloxetine, cyamemazine, and alimemazine). A coma occurred in 20 (8.4%) cases. Care involved emergency visit in 99 (41.6%) cases, hospitalization in 51 (21.4%) cases, and admission in intensive care unit in 15 (6.3%) cases. There were 197 (82.8%) polydrug users, and 41 (17.2%) subjects used only ketamine. Ketamine use occurred in a recreational context in 60 (25.2%) cases and in a chemsex context in 10 (4.2%) cases. Two (0.8%) cases involved health-care professionals (i.e., an anesthetist and a nurse) who obtained ketamine at work. One case involved a subject who diverted ketamine prescribed for his pet by a veterinarian. Ninety-eight (41.2%) subjects used the nasal route, 17 (7.1%) the intravenous route, and 12 (5.0%) the oral route. One subject switched to intramuscular route when intravenous route was impossible. There were 36 (15.1%) daily users and 62 (26.1%) regular users of ketamine.

Ninety-four (39.5%) cases involved ketamine use disorder. Forty-nine (52.1%) of them also involved other psychiatric symptoms. The median age was 23 years, and there were 56 (59.6%) men. Twenty-two (23.4%) subjects used only ketamine, and the others mainly used cannabis, cocaine, MDMA, and benzodiazepines. Fifty (53.2%) subjects used nasal route, 8 (8.5%) used the intravenous route, and 3 (3.2%) used the oral route. There were 32 (34.0%) daily users and 40 (42.6%) regular users of ketamine. There were cases involving repetitive use of very high doses (i.e., up to 10 g/day). There were hospitalizations for ketamine withdrawal in 28 (29.8%) cases. Among them, most subjects presented craving, agitation, and/or motivational decrease. In some cases, hospitalization for withdrawal followed a

**TABLE 1** Sociodemographic characteristics of ketamine users with substance use disorder in the OPPIDUM program from 2012 to 2021.

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total from 2012 to 2021
Number of cases, <i>n</i>	35	20	32	23	41	41	44	54	59	89	438
Age, years, median [Q1, Q3]	26.0 [23.0, 30.5]	27.0 [23.8, 33.2]	30.0 [24.8, 33.2]	31.0 [26.0, 36.0]	33.0 [25.0, 38.0]	28.0 [22.0, 32.0]	29.0 [23.0, 36.0]	29.5 [22.0, 35.0]	29.5 [23.0, 36.8]	32.0 [25.8, 39.0]	30.0 [23.5, 36.0]
Sex, <i>n</i> (%)											
Men	24 (68.6)	16 (80.0)	28 (87.5)	18 (78.3)	30 (73.2)	33 (80.5)	34 (77.3)	38 (70.4)	46 (78.0)	69 (77.5)	336 (76.7)
Women	11 (31.4)	4 (20.0)	4 (12.5)	4 (17.4)	11 (26.8)	8 (19.5)	9 (20.5)	16 (29.6)	12 (20.3)	20 (22.5)	99 (22.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.7)	0 (0.0)	3 (0.7)
Polydrug users, <i>n</i> (%)	34 (97.1)	20 (100.0)	32 (100.0)	23 (100.0)	40 (97.6)	40 (97.6)	43 (97.7)	52 (96.3)	56 (94.9)	86 (96.6)	426 (97.3)
Opioid maintenance treatment, <i>n</i> (%)	25 (71.4)	15 (75.0)	24 (75.0)	11 (47.8)	27 (65.9)	19 (46.3)	21 (47.7)	20 (37.0)	30 (50.8)	50 (56.2)	242 (55.3)
Alcohol dependence, <i>n</i> (%)	13 (37.7)	10 (50.0)	12 (37.5)	13 (56.5)	11 (26.8)	14 (34.1)	19 (43.2)	17 (31.5)	18 (30.5)	40 (44.9)	167 (38.1)
Tobacco users, <i>n</i> (%)	32 (91.4)	19 (95.0)	30 (93.8)	23 (100.0)	38 (92.7)	36 (87.8)	41 (93.2)	47 (87.0)	57 (96.6)	84 (94.4)	407 (92.9)
Indicators of ketamine use disorder, <i>n</i> (%)											
Daily use	2 (5.7)	1 (5.0)	2 (6.2)	2 (8.7)	1 (2.4)	2 (4.9)	4 (9.1)	5 (9.3)	8 (13.6)	9 (10.1)	36 (8.2)
Distress upon discontinuation	3 (8.6)	3 (15.0)	3 (9.4)	6 (26.1)	6 (14.6)	4 (9.8)	6 (13.6)	6 (11.1)	7 (11.9)	13 (14.6)	57 (13.8)
Addiction	3 (8.6)	1 (5.0)	0 (0.0)	4 (17.4)	3 (7.3)	3 (7.3)	1 (2.3)	7 (13.0)	11 (18.6)	14 (15.7)	47 (10.7)
Route of administration, <i>n</i> (%)											
Nasal	25 (71.4)	13 (65.0)	19 (59.4)	17 (73.9)	29 (70.7)	37 (90.2)	33 (75.0)	46 (85.2)	44 (74.6)	68 (76.4)	331 (75.6)
Intravenous	9 (25.7)	4 (20.0)	9 (28.1)	2 (8.7)	12 (29.3)	6 (14.6)	12 (27.3)	8 (14.8)	11 (18.6)	24 (27.0)	97 (22.1)
Oral	4 (11.4)	1 (5.0)	6 (18.8)	4 (17.4)	1 (2.4)	0 (0.0)	5 (11.4)	2 (3.7)	6 (10.2)	7 (7.9)	36 (8.2)
Indicators of social integration, <i>n</i> (%)											
Stable housing	19 (54.3)	12 (60.0)	20 (62.5)	10 (43.5)	20 (48.8)	28 (68.3)	24 (54.5)	30 (55.6)	35 (59.3)	53 (59.6)	251 (57.3)
Regular income	8 (22.9)	6 (30.0)	5 (15.6)	7 (30.4)	13 (31.7)	17 (41.5)	16 (36.4)	21 (38.9)	24 (40.7)	35 (39.3)	152 (34.7)
Employment	8 (22.9)	6 (30.0)	8 (25.0)	7 (30.4)	10 (24.4)	18 (43.9)	15 (34.1)	15 (27.8)	16 (27.1)	24 (27.0)	127 (29.0)

**FIGURE 1** Number and prevalence of ketamine users with substance use disorder in the OPPIDUM program from 2012 to 2021.



hospitalization for somatic issues, such as urinary tract and kidney symptoms or suicidal behavior/ideations. In the other cases, withdrawal was the primary cause for hospitalization.

Twenty (8.4%) cases involved urinary tract and kidney symptoms. Notable cases involved repeated and/or prolonged use of very high doses, and severe clinical complications that lead to cystectomy and bladder replacement in some cases (Table 3). In some cases, severe urinary tract damages resulted in kidney damages. Several cases involved both urinary tract and kidney symptoms and hepatobiliary symptoms. Other cases involved bladder thickening, inflammations, cystitis, frequent urination, ulcerated areas, hematuria, and burning sensation during urination. Urinary tract symptoms were systematically associated with negative cytobacteriological examination of urine. Thirteen (65.0%) subjects used the nasal route. There were 9 (45.0%) daily users and 10 (50.0%) regular users of ketamine.

Thirteen (5.5%) cases involved hepatobiliary symptoms, in particular hepatitis, cholestasis, and cholangitis. Notable cases involved use of very high doses of ketamine, young men, including a 15-year-old subject, and severe clinical complications requiring admission in intensive care unit in one case (Table 4). Several cases involved both hepatobiliary symptoms and urinary tract and kidney symptoms. There were 5 (38.5%) daily users and 5 (38.5%) regular users of ketamine.

Beside ketamine use disorder, urinary tract and kidney symptoms, and hepatobiliary symptoms, the most frequent symptoms were psychiatric symptoms ( $n = 117$ , 49.2%) (e.g., suicide attempts using ketamine, hallucinations, dissociation, depressed mood following repeated use, anxiety, psychotic decompensation, and acute delirious episode), other central nervous system symptoms ( $n = 75$ , 31.5%)

(e.g., drowsiness, dizziness, loss of consciousness, coma, confusion, headaches, and loss of coordination of movements), cardiovascular symptoms ( $n = 38$ , 16.0%) (e.g., tachycardia and hypertension), and gastrointestinal symptoms ( $n = 24$ , 10.1%) (e.g., vomiting and abdominal pain). The other cases involved respiratory symptoms ( $n = 15$ , 6.3%) (e.g., dyspnea), general non-severe symptoms ( $n = 12$ , 5.0%) (e.g., falling, oral burn, wounds excluding self-inflicted wounds, erythema, itching, allergic reactions, and skin rash), infections ( $n = 3$ , 1.3%) (e.g., infections in a context of use of the intravenous route), and pregnancy-related troubles ( $n = 3$ , 1.3%) (e.g., intrauterine ketamine exposure, and neonatal abstinence syndrome).

## 4 | DISCUSSION

To the best of our knowledge, this is the first national study aimed at assessing the latest trends in ketamine use among people with substance use disorder and characterizing its clinical complications. This was made possible by analyzing complementary data from the French Addictovigilance Network (i.e., data from the OPPIDUM program and addictovigilance cases).

There was a 2.5-fold increase in the number of ketamine users with substance use disorder, from 35 subjects in 2012 to 89 subjects in 2021, in the hundreds of substance abuse treatment facilities included in the OPPIDUM program from 2012 to 2021. Marked increases were already observed for other drugs monitored by the French Addictovigilance Network, such as cocaine (i.e., from 11% in 2006 to 16% in 2016) [17], tramadol (i.e., a 2.2-fold increase from 2013 to 2018) [18], and pregabalin (i.e., from 5 subjects in 2008 to 60 subjects in 2022) [19]. The profile of ketamine users with substance use disorder also changed,



**TABLE 2** Sociodemographic and clinical characteristics of ketamine users with substance use disorder in the BNPV from July 2020 to December 2022.

Number of cases, <i>n</i>	238
Age, years, median [Q1, Q3]	23.0 [20.0, 29.0]
Sex, <i>n</i> (%)	
Men	153 (64.3)
Women	85 (35.7)
Serious, <i>n</i> (%)	
Yes	146 (61.3)
No	92 (38.7)
Death, <i>n</i> (%)	1 (0.4)
Coma, <i>n</i> (%)	20 (8.4)
Ketamine frequency, <i>n</i> (%)	
Daily use	36 (15.1)
Regular use	62 (26.1)
Occasional use	4 (1.7)
Experimentation	4 (1.7)
Unknown	132 (55.5)
Context of ketamine use, <i>n</i> (%)	
Recreational	60 (25.2)
Chemsex	10 (4.2)
Unknown	170 (71.4)
Use by healthcare professionals, <i>n</i> (%)	2 (0.8)
Route of ketamine administration, <i>n</i> (%)	
Nasal	98 (41.2)
Intravenous	17 (7.1)
Oral	12 (5.0)
Unknown	113 (47.5)
Polydrug users, <i>n</i> (%)	197 (82.8)
Alcohol and other drug use, <i>n</i> (%)	
Alcohol	103 (43.3)
Cannabis	93 (39.1)
Cocaine	91 (38.2)
Care, <i>n</i> (%)	
Emergency visit	99 (41.6)
Hospitalization	51 (21.4)
Admission in intensive care unit	15 (6.3)
Hospitalization for ketamine withdrawal	28 (11.8)
Addictology consultation	56 (23.5)
Clinical complication, <i>n</i> (%)	
Ketamine use disorder	94 (39.5)
Urinary tract and kidney symptoms	20 (8.4)
Hepatobiliary symptoms	13 (5.5)
Other psychiatric symptoms	117 (49.2)
Other central nervous system symptoms	75 (31.5)
Cardiovascular symptoms	38 (16.0)
Gastrointestinal symptoms	24 (10.1)
Respiratory symptoms	15 (6.3)
General non-severe symptoms	12 (5.0)
Infections	3 (1.3)
Pregnancy-related troubles	3 (1.3)

**TABLE 3** Notable cases of urinary and renal complication in ketamine users with substance use disorder in the BNPV from July 2020 to December 2022.

Age	Sex	Ketamine use	Clinical complication and care
From 22 to 24 years old	1 man, 3 women	For more than a year, at least once a week in rave parties, via nasal route	Cluster of friends being ketamine users with substance use disorder All presented severe bladder affections: interstitial cystitis, parietal calcifications, bladder bleeding, reduced bladder capacity up to 50 mL, polyuria Care included endoscopic resection of the calcifications No certainty of reversibility of the intravesical lesions; risk of cystectomy
38 years old	Woman	For the past 10 years, 5 g/day, every 30 min, via nasal route	Significant painful bladder activity; indication for cystectomy and urostomy (i.e., Bricker procedure) Disruption in liver function tests Restrictive anorexia with reduced hunger sensation and nausea during food intake
24 years old	Woman	Unknown	Interstitial cystitis; pollakiuria every 30 min to 1 h, especially at night; painful bladder activity Intravesical instillation of dimethyl sulfoxide associated with ketamine withdrawal has led to a clear improvement
30 years old	Man	2 g twice a week, via nasal route	Urological complication for 2 years Interstitial cystitis 1 year ago with polyuria every 30 min that leads to a bilateral pyelocalic dilatation

with an increase in daily users, distress upon discontinuation, and addiction. Finally, ketamine was by far mainly used along with other substances in polydrug users.

Our results among people with substance use disorder, carried out over 10 years, confirm the signal of ketamine abuse in France, as highlighted in previous work using disproportionality analysis [11]. Ketamine use for recreational purpose is particularly reported in South-East Asia [8] and to a lesser extent in Sweden, the United Kingdom, and Australia [20]. In France, the last published study focusing on patterns of ketamine use among people with substance use disorder dates back to 2003 [12]. The last European Drug Report, from 2023, highlights that the quantity of ketamine seized and reported to the EU Early Warning System on new psychoactive substances has varied over time but has remained at relatively high levels in recent years [21]. This suggests that ketamine is likely to be consistently available in some national drug markets and may have become an established drug of choice in some settings. Although not on the scale of the situation in South-East Asia, the growing number of ketamine users being treated in substance abuse treatment facilities in France is particularly striking. While the use of ketamine was marginal and confined to certain subcultures until just a few years ago, it has recently become more mainstream, being increasingly used for both festive and chemsex purposes.

Another important result is the pattern of harms associated with ketamine use among people with substance use disorder as illustrated by the recent Addictovigilance cases. The analysis of the cases found the expected, well-known clinical profiles (e.g., psychiatric and cardiovascular adverse reactions). The analysis also found serious cases of ketamine-induced uropathy and cholangiopathy, especially in case of repeated and/or prolonged use of high doses. The most concerning is ketamine-induced cystitis, which appears more common in those using the drug on a regular, often daily basis. Ketamine-induced cystitis may require surgical management [22], as illustrated by a cluster of four cases in our results. It is therefore important that young subjects presenting with urinary tract symptoms are asked about drug use, especially as ketamine use is no longer marginal. Since ketamine withdrawal is the cornerstone of treating ketamine-induced cystitis, accurate and early diagnosis is crucial. Physicians should consider ketamine-induced cystitis as a differential diagnosis in lower urinary tract symptoms [2]. The abuse liability of ketamine is widely recognized based on preclinical and clinical studies [23]. Our results confirm ketamine abuse liability, also showing that many regular users presented addiction, failed to stop ketamine, and needed hospitalization for withdrawal.

Finally, the repeated and/or prolonged use of ketamine outside the approved medical conditions (i.e., anesthesia) has led to modify its safety profile.

**TABLE 4** Notable cases of hepatic complication in ketamine users with substance use disorder in the BNPV from July 2020 to December 2022.

Age	Sex	Ketamine use	Clinical complication and care
15 years old	Man	Ketamine at a rave party, with LSD, methadone, and MDMA	Helicopter transport to emergency Main clinical complications included hepatic cytolysis, renal insufficiency with rhabdomyolysis, and deep sedation improved with naloxone
22 years old	Man	10 g/day for 6 months, via nasal route	Mild disruption of liver function with a cytolytic pattern that worsened within 1 week Sterile cystitis with functional voiding symptom; previous urological assessment 4 months prior was normal
23 years old	Man	1 to 5 g/day over several years, via nasal route	Anicteric cholestasis and ALAT-predominant cytolysis; second hospitalization for the same reason; diagnosis of cholestasis secondary to several years of high-dose ketamine use; mention of damage of the sphincter of Oddi Altered general condition Functional urinary symptoms with bilateral pyeloreteritis and right ureterohydronephrosis; probable chronic cystitis in relation to intranasal ketamine use
Unknown	Man	Increase of ketamine use over the past month for pain relief	Epigastric abdominal pain for several months Cytolysis and cholestasis with dilation of the bile ducts on abdominal CT and MRI leading to a diagnosis of cholangitis
21 years old	Unknown	Ketamine and MDMA	Intubated due to neurological failure and admission in intensive care unit Positive urine toxicology tests for midazolam, amphetamines, and MDMA Multi-organ failure and fulminant hepatitis due to drug use Transfer to a neurology department for rehabilitation
19 years old	Man	Increase of ketamine use for pain relief, started 6 months ago, via nasal route	Digestive bleeding of biliary origin; anemia requiring blood transfusion Dilation of gall bladder leading to cholecystectomy Acute hepatitis

Recently, intranasal esketamine (i.e., the S-enantiomer of racemic ketamine) has been approved in treatment-resistant depression [24]. Legitimate concerns have been raised with respect to safety of long-term intranasal esketamine. As mentioned in the Summary of Product Characteristics, there were no cases of interstitial cystitis in clinical studies with esketamine [24]. However, a higher rate of lower urinary tract symptoms was observed (e.g., pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine-treated patients compared with placebo-treated patients. [25] A recent review that assessed the quality of reporting of adverse events in clinical trials studying esketamine suggests that an assessment of the benefits/risks balance of esketamine based on the results reported in trial publications is flawed due to the poor accuracy and completeness of harm data [26].

## 4.1 | Strengths and limitations

Our results are based on the triangulation of complementary real-world data from distinct sources and with independent biases. This approach is extensively used by the French Addictovigilance Network [17, 18], because it enables to minimize the limitation of each source taken individually. However, the study protocol was not recorded a priori.

The main limitations of the study are that the OPPI-DUM program does not allow to estimate the rates of non-medical use of ketamine in the general population, because it only includes people seen in substance abuse treatment facilities. Similarly, the BNPV does not allow to estimate the rates of clinical complications of ketamine use in the general population, because of underreporting.



## 5 | CONCLUSION

Overall, the trend observed over 10 years reflects the growth in ketamine use among people with substance use disorder, which is no longer marginal. Two complementary health data sources of the French Addictovigilance Network showed in particular an increase of repeated and/or prolonged ketamine use. Ketamine use among people with substance use disorder is an important public health issue, leading to serious neuropsychiatric and cardiovascular complications, some of which require medical care (e.g., emergency visits, hospitalization, and admission in intensive care unit). As observed in South-East Asia, ketamine-induced uropathy and cholangiopathy are also reported among ketamine users with substance use disorder in France. Recently, the French Drug Agency launched a communication on ketamine based on previous unpublished addictovigilance and pharmacovigilance analysis [10]. This updated analysis strengthens the warning toward ketamine use among people with substance use disorder and its clinical complications and should lead to the dissemination of a strong harm reduction message.

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### CONFLICT OF INTEREST STATEMENT

None.

### DATA AVAILABILITY STATEMENT

The data from the BNPV are available on request from the French Drug Agency. The data from OPPIDUM are available on request from the corresponding author upon reasonable request.

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