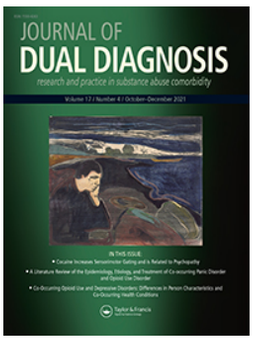

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Catatonic Episodes Related to Substance Use: A Cross-Sectional Study Using Electronic Healthcare Records

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ABSTRACT

Objective: Substance use has increasingly been linked to the onset of catatonic episodes; however, no large observational studies have examined this association. This study aimed to identify catatonic episodes temporally associated with acute intoxication, withdrawal or chronic substance use, investigate which substances were involved, and compare clinical characteristics of substance-related and non-substance-related catatonic episodes. **Methods:** This study retrospectively identified all catatonic episodes recorded in an electronic case register hosted at a large secondary mental health trust in London, UK. Episodes were categorized as substance-related if the clinical record reported either a positive urine drug screen, an ICD-10 diagnosis of a mental or behavioral disorder due to substance use, or documented substance use between two weeks prior to the catatonic episode and the date of the catatonic episode. **Results:** 108 of 2130 catatonic episodes (5.1%) were deemed substance-related. The number of contemporaneously reported substance-related episodes increased between 2007 and 2016 [$r = 0.72$, $p = 0.02$]. Episodes in the context of acute intoxication ($n = 54$) were most frequently related to cannabis ($n = 31$) or cocaine ($n = 5$) use, whilst those in the context of drug withdrawal ($n = 8$) were most commonly related to alcohol, opioids and benzodiazepines. There were 50 episodes of catatonia associated with chronic substance use without intoxication or withdrawal, of which the majority were related to cannabis use ($n = 37$). 21 episodes had overlapping intoxication, withdrawal and chronic use of different substances within an episode. Compared to catatonic episodes not related to substance use, episodes of substance-related catatonia occurred in individuals who were younger (mean age 31.3 years [SD 12.2] vs 35.7 years [SD 16.3], $p = 0.01$) and more likely to be men (74.0% vs 54.3%, $p < 0.001$). The clinical features of catatonia were similar between the two groups. **Conclusions:** A relatively small proportion of catatonic episodes were temporally associated with reported substance use within their electronic records. Substance-related catatonic episodes were mostly related to cannabis use, but other substances including cocaine, alcohol, opioids and benzodiazepines were sometimes implicated. This is likely an underestimate of substance-related catatonia use due to issues with documentation and appropriate investigation.

KEYWORDS
Catatonia; cocaine; alcohol; opioid; intoxication; withdrawal; drug; cannabis; substance misuse; cannabinoid

Catatonia is an important but under-recognized neuropsychiatric disorder characterized by qualitative and quantitative changes in psychomotor activity (Walther et al., 2019). First codified by Karl Kahlbaum, catatonia was considered to be a subtype of schizophrenia for much of the 20th Century (Edward & Fink, 2018). However, it has a diverse range of psychiatric, medical and neurological causes and its etiology is poorly understood (Carroll et al., 1994; Daniels, 2009). Whilst substance intoxication and withdrawal can commonly manifest with diverse neuropsychiatric symptoms including agitation, coma and delirium (Liakoni et al., 2016; Sibanda et al., 2019; Tait et al., 2016; Wojtowicz et al., 2008), they are also increasingly recognized as being temporally associated with catatonic episodes. For example,

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substance-related catatonia has previously been described in a patient with acute amphetamine intoxication (Chern & Tsai, 1993) and in an individual with cannabinoid withdrawal (Caudron et al., 2016). More recently, Palma-Álvarez et al. (2021) conducted a systematic review of catatonia associated with cannabis or synthetic cannabinoid use and identified 11 case series or reports with a total of only 14 patients (Palma-Álvarez et al., 2021). The small number of patients included in this review illustrates the paucity of research in this area.

This study aimed to characterize episodes of catatonia in a large dataset that were temporally associated with acute intoxication, withdrawal or chronic use of illicit or recreational substances, and investigate which substances were most commonly associated with catatonic episodes. We also aimed to compare the clinical and demographic characteristics of these substance-related catatonic episodes with those of non-substance-related catatonic episodes. We anticipated that there might be demographic and clinical differences between these two groups.

Methods

Study design

This study used the Clinical Records Interactive Search database system, a source of anonymized mental healthcare records from approximately 400,000 patients with psychiatric disorders seen in inpatient, emergency department and community settings in South London and Maudsley NHS Foundation Trust NHS Foundation Trust, London, United Kingdom. This system incorporates all healthcare records from 2006 onwards and some from as early as 1999 (Stewart et al., 2009). The Clinical Records Interactive Search has approval from the Oxfordshire C Research Ethics Committee (ref: 18/SC/0372) and this study was approved by its Oversight Committee (ref: 17–102). Episodes of catatonia from August 31, 2002 to December 17, 2018 were identified in a previous study (Rogers et al., 2021) by screening the full text records with a natural language processing app before each possible catatonic episode was validated by a researcher for the presence of two or more items of the Bush-Francis Catatonia Screening Instrument (Bush et al., 1996).

For the present study, we searched among individuals who had already been established to have a diagnosis of catatonia, as validated above, for those with evidence of substance use in the 2-week period prior to the date of onset of the catatonic episode. This timeframe was chosen as it is clinically relevant: urine drug screens can stay positive for some substances for up to 14 days (Moeller et al., 2017) and most drug withdrawal symptoms develop within 2 weeks (Lerner & Klein, 2019).

To establish whether substance use was present, we specified there must be one of (a) a positive urine drug screen result; (b) an International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) diagnosis from the F10–19 diagnostic categories; or (c) a clear reference in the free text to use of recreational drugs. The list of illicit or recreational drugs was derived from the FRANK website's A-Z list and included commonly used colloquial terms (FRANK 2021). Advice was sought from specialist substance misuse clinicians to refine this list and generate a list of the most commonly used words or phrases to describe each recreational or illicit substance (see Supplementary Table 1).

Participants

A search was conducted using the sample of patients identified as having had a catatonic episode, to identify episodes that were deemed substance-related. All these records were then coded by the first author, who judged whether the patient met the criteria for one or more of:

- **Acute *on* chronic use:** acute use of a substance within 2 weeks prior to the onset of catatonia, with evidence of clinical features of acute intoxication on a background of chronic use of the same substance.
- **Acute use *without* chronic use:** acute use of a substance within 2 weeks prior to the onset of catatonia, with evidence of clinical features of acute intoxication but with no reports of chronic use of this substance.
- **Substance withdrawal**: clinically suspected or proven withdrawal of a substance in the 2 weeks prior to the onset of catatonia.
- **Chronic use**: long-term use of a substance without evidence of intoxication or withdrawal during the specified timeframe. Records were only classified as chronic use if they met criteria for a substance-related episode but did not meet criteria for acute intoxication or withdrawal.

Table 1. Demographic and clinical characteristics of substance and non-substance related catatonic episodes.

	Substance-related catatonia	Non-substance-related catatonia	*p*
Number of episodes	108	2,028	–
Number of patients	100	1,388	–
Age at first episode, years (S.D.)	31.3 (12.2)	35.7 (16.3)	0.01
Gender, *n* (%) of patients			<0.001
Men	74 (74.0)	754 (54.3)	
Women	26 (26.0)	634 (45.7)	
Ethnicity, *n* (%) of patients			0.32
White	30 (30.0)	473 (34.1)	
Mixed/Multiple ethnic groups	5 (5.0)	44 (3.2)	
Asian/Asian British	2 (2.0)	92 (6.6)	
Black/African/Caribbean/Black British	56 (56.0)	669 (48.2)	
Other	5 (5.0)	83 (6.0)	
Not stated	2 (2.0)	27 (2.0)	
Bush-Francis Catatonia Screening Instrument score in episode			
Total, median (IQR)	3 (2–5)	3 (2–5)	0.21
Positive features, median (IQR)	0 (0–1)	0 (0–1)	0.26
Negative features, median (IQR)	3 (2–4)	3 (2–4)	0.86
Duration of admission, mean (S.D.) in days[a]	4.2 (1.3)	4.4 (1.3)	0.17
	156	*225*	

[a]Due to positive skew, these results underwent natural logarithm transformation. Log_n results are in normal text with original scores in italics (analyses performed using log_e results).

Reliability

Twenty patient records, which accounted for 1% of the total sample, were examined independently by another investigator (JPR) for drug coding and substantial inter-rater reliability [kappa = 0.63, $p = 0.001$] was demonstrated (McHugh, 2012). Where any cases in the entire sample were unclear, these were discussed with a third, senior investigator (ER) to reach consensus.

Analyses

Demographic variables were compared between catatonic episodes that were related to substance use and those that were not. Continuous variables were compared using unpaired *t*-tests and discrete variables were compared using chi-squared tests. We investigated whether there was a change in the number of substance-related catatonic episodes reported over time by using the Pearson correlation coefficient. Logarithmic transformation was used prior to parametric tests in highly positively skewed variables. In order to compare the nature of catatonic signs between different groups, we used the results of a recent principal component analysis of the Bush-Francis (Cuevas-Esteban et al., 2020) to create categories of positive (excitement, grimacing, stereotypy, verbigeration and negativism) and negative clinical features (immobility, mutism, staring, posturing, rigidity and withdrawal) of catatonia; we then compared the sums of the positive and negative scores between the groups using non-parametric tests.

Results

2,130 episodes of catatonia were identified from the database of electronic healthcare records, which occurred in 1,456 patients. Of these, 108 episodes (from 100 patients) were shown to be temporally associated with substance use (5.1%); 2,022 episodes (from 1,388 patients) were not associated with substance misuse (94.9%). The number of contemporaneously reported substance-related episodes increased between 2007 and 2016 [$r = 0.72$, $p = 0.02$], which was mostly accounted for by an increase in cannabis-related episodes (see Supplementary Table 2). The demographic and clinical characteristics of the two groups are outlined in Table 1. In substance-related episodes, mean age at onset of first episode was 31.3 years (SD 12.2), while in non-substance-related episodes it was significantly older at 35.7 years (SD 16.3), mean difference 4.3 years [95% CI 1.1–7.6, $p = 0.01$]. A significantly higher proportion of the substance-related group were men [74.0% vs. 54.3%; $p < 0.001$]. Bush-Francis Catatonia Screening Instrument scores were similar between the groups (median (IQR) 3 (2–5)) and there was no evidence for differences in numbers of positive or negative features between the groups. There was no evidence for difference in duration of admission between the two groups ($p = 0.17$).

Table 2 gives the full details of substances associated with catatonic episodes. For these episodes, acute substance use both with and without chronic use ($n = 54$) was most commonly associated with cannabis ($n = 31$) and cocaine ($n = 5$), whilst drug withdrawal was associated with far fewer episodes ($n = 8$), and was linked to use of alcohol, benzodiazepines, opioids and cocaine. There were 50 cases of catatonia

Table 2. Substances related to episodes of catatonia.

Drug	Acute intoxication without chronic use	Acute intoxication with chronic use	Withdrawal	Chronic use (without acute intoxication or withdrawal)
Alcohol	2	1	2	0
Amphetamines	0	1	0	0
Benzodiazepines	0	0	2	1
Cannabis	24	7	0	37[a]
Cocaine	2	3[b]	1[c]	2
GBL	0	1	0	0
Khat	0	0	0	3
Opioids	1[d]	1	2	0
Synthetic cannabinoids	2[e]	0	0	0
Mixed	5 Cannabis and cocaine: 2 Cannabis and ketamine: 1 Cocaine and amphetamines: 1 Cocaine, alcohol and opioids: 1	4 Alcohol and synthetic cannabinoids: 1 Cannabis and synthetic cannabinoids: 2 Cannabis and opioids: 1	1 Alcohol and opioids: 1	7 Cannabis and alcohol: 3 Cannabis and cocaine: 1 Cannabis and khat: 1 Cannabis, alcohol, ketamine and psilocybin: 1 Cannabis, cocaine and opioids: 1
Total	36	18	8	50

Overlap with other substance use (number of cases): a—cocaine acute intoxication with chronic use (1), cocaine withdrawal (1), opioid intoxication without chronic use (1), synthetic cannabinoid intoxication without chronic use (1); b—chronic cannabis use (1); c—chronic cannabis use (1); d—chronic cannabis use (1); e—chronic cannabis use (1).

associated with chronic use without evidence of intoxication or withdrawal, and these were predominantly associated with cannabis ($n = 37$). Finally, in 21 episodes there were overlapping presentations of intoxication, withdrawal and chronic use of different substances in the same patient. When cannabis-related and non-cannabis-related episodes were compared, they did not differ in terms of number of catatonic features on the Bush-Francis Catatonia Screening Instrument (median 3, IQR 2–5 in both groups, $p = 0.21$), nor in terms of number of positive or negative features (Table 1).

Discussion

In the largest study of catatonia and substance misuse to date, we demonstrate that a small proportion of catatonic episodes (5.1%) were temporally associated with substance use and a wide variety of illicit and recreational substances were involved. This compares to survey-based figures suggesting that 2.0% of adults in England and Wales aged 16–59 were using drugs at least monthly in 2016–2017. A number of cases in our study involved polysubstance use with an overlapping picture of intoxication and withdrawal from different substances. This highlights the varied nature of substance-related catatonia and expands upon the findings of smaller case reports, which suggest that substance-related catatonia may have a plethora of different triggers. Cannabis was the drug most commonly associated with substance-related catatonic episodes, with a noted high and increasing incidence of cannabis-related episodes. Cannabis is comprised of a large number of organic compounds, and its constitution can vary considerably, but it is generally accepted that its "potency" refers to its tetrahydrocannabinol (THC) content. THC is the psychoactive substance in cannabis and the most studied constituent. It exerts its mechanism of action via partial agonism at the two known cannabis receptors (CB_1 and CB_2) and has been shown to induce transient psychotic symptoms when administered intravenously in healthy subjects without prior psychosis in a dose-dependent manner (D'Souza et al., 2004). Moreover, more potent forms of cannabis have been associated with a five-fold increase in the risk of developing psychosis within this South East London population (di Forti et al., 2015). Cannabidiol, the other compound that attracts the most research interest in cannabis, antagonizes the CB_1 receptor and is a negative allosteric modulator of CB_2 (Levinsohn & Hill, 2020). As such, its actions are markedly different from THC, and there is evidence that it may modulate the actions of THC, and reduce its psychotogenic potential (Leweke et al., 2012). Indeed, users of low-potency forms of cannabis ("hash") were demonstrated to have no greater risk of psychosis than non-users in South East London (di Forti et al., 2015). The relevance of these findings described above for catatonia is yet to be fully explored, but it is possible that a higher potency of cannabis products may account for the increasing number of substance-related catatonic episodes we saw over time in this study.

Additionally, our study found that substance-related catatonic episodes are more common in men and occur in a younger age group compared to non-

substance related catatonic episodes, perhaps reflecting the age, gender and substance misuse profiles of individuals who use illicit drugs in the general population within the United Kingdom (Home Office, 2017). Compared to the catchment population of the mental health service, where 22.8% are from a Black ethnic group, 48.2% of our patients with non-substance-related and 56.0% of those with substance-related catatonia were from a Black ethnic group. It has consistently been demonstrated that ethnic minority populations (particularly those of a Black Caribbean or Black African ethnic group) in south London are at increased risk of psychosis and schizophrenia relative to the white British population (Fearon et al., 2006; Oduola et al., 2021), but there has been little work to date on catatonia diagnoses and ethnic group.

Interestingly, substances linked to catatonia through acute intoxication included the central nervous system (CNS) stimulants (e.g., cocaine, amphetamines), which exert their effects by increasing striatal dopaminergic signaling (both cocaine and amphetamine block the dopamine transporter, but amphetamine additionally facilitates dopamine release) (Jonkman & Kenny, 2013; Fleckenstein et al., 2007). Catatonia in the context of substance withdrawal was more often due to CNS depressants (e.g., alcohol and benzodiazepines), fitting with the hypothesis that hypoactivity at the GABA-A receptor is intrinsically linked to catatonia (Carroll, 2000). This is also in accordance with the fact that benzodiazepines are the mainstay of catatonia treatment, and that premature benzodiazepine withdrawal is linked to relapse of catatonia (Lander et al., 2018).

We identified no differences between substance-related catatonia and non-substance related catatonia in relation to Bush-Francis Catatonia Screening Instrument scores or duration of hospital admission. This could imply that substances were acting as precipitants of catatonia in vulnerable individuals rather than substance-related catatonia representing a distinct clinical syndrome. Moreover, there is an established relationship between some substances and psychosis, and a distinct relationship between psychosis and catatonia, complicating any inferences made from our results (di Forti et al., 2015; Solmi et al., 2018).

There are a number of limitations of this study. Firstly, this was a retrospective study that relied upon documentation of patients' recent substance use, drug and alcohol history, mental state including salient features of catatonia, and urine drug screen (UDS) results, and the formation of a clinical judgment on whether substance use was related to acute intoxication, withdrawal or chronic use. Recording of recent and previous substance misuse and the time between taking an illicit substance and the onset of catatonia was vague and imprecise in many records, which may have led to inaccurate notes and records being incorrectly excluded. There were also surprisingly few entries in which the results of a UDS were recorded, though it is possible in some cases that the UDS was done outside of the time window studied. It should also be noted that the UDS does not test for all illicit substances, and some novel psychoactive substances can go undetected using a conventional UDS. Additionally, information gathered by medical professionals was in turn reliant on the history from patients and their carers, which may have been limited due to the difficulty in obtaining a history from patients with catatonia, who are often mute, patients being reluctant to disclose substance use and carers being unsure of patients' current substance use. Further, it may be that our finding of more substance-related catatonic episodes in younger people and in men reflects a higher index of suspicion in these groups. However, this study is one of the first to look systematically at substance-related catatonia and is valuable in demonstrating on a large scale the involvement of a wide range of illicit substances and the temporal association with catatonic episodes.

This is the largest study to date demonstrating the temporal relationship between acute intoxication, withdrawal and chronic use of illicit substances, and the onset of catatonic episodes. Recommendations arising from this study that are translatable to clinical practice include increasing clinicians' awareness of substance use as a potential trigger of catatonic episodes, alongside more precise documentation of recent and past substance misuse, and for a UDS to be collected as soon as is feasibly possible in patients with catatonia and for those results to be formally documented in the patient record.

In terms of future research, our results would appear to suggest that a focus on catatonic episodes related to cannabis use may represent the most fruitful avenue of exploration. Further studies could also include more nuanced investigation of qualitative differences between substance-related- and non-substance-related catatonic episodes, in addition to any differences in illness duration, treatment response, and prognosis.

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views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Data availability statement

Data are owned by a third party, Maudsley Biomedical Research Center (BRC) Clinical Records Interactive Search (CRIS) tool, which provides access to anonymised data derived from South London and Maudsley NHS Foundation Trust electronic medical records. These data can only be accessed by permitted individuals from within a secure firewall (i.e., the data cannot be sent elsewhere), in the same manner as the authors. For more information please contact: cris.administrator@slam.nhs.uk.

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