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Predictors of controlled prescription drug nonmedical and lifetime use among patients accessing public mental health services in Uganda: a cross-sectional study

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Abstract

Objectives: We determined the prevalence of controlled prescription drug (CPD) nonmedical and lifetime use and their predictors among patients at three public mental clinics in Uganda to identify missed practice opportunities, enhanced screening priorities, and drug control needs.

Methods: A cross-sectional survey of 1275 patients was performed from November to December, 2018. Interviewer-administered semi-structured questionnaire, desk review guide, and urine drug assays were employed. Questionnaire recorded nonmedical CPD and illicit drug use history from patients' files, CPDs lifetime use, and risk factors. Desk review guide recorded recently prescribed drugs in patients' files to corroborate with urine assays. Predictors were analyzed by multivariate logistic regression.

Results: From desk review, 145 (11.4%) patients had history of CPD nonmedical use and 36 (2.8%) had used illicit drugs. Of 988 patients who provided urine, 166 (16.8%) self-medicated CPDs, particularly benzodiazepines while 12 (1.2%) used illicit drugs. Of those with drug-positive urine, 123 (69.1%) had no documented history of nonmedical controlled drug use. Type of patient (OR = 10.90, $p < 0.001$) was independently associated with CPD nonmedical use. Additionally, type of patient (OR = 8.29, $p < 0.001$) and tobacco consumption (OR = 1.85, $p = 0.041$) were associated with all substance use (CPDs and illicit drugs combined). Among participants, 119 (9.3%) reported CPD lifetime use, and this was independently associated with education level (OR = 2.71, $p < 0.001$) and history of treatment for substance abuse (OR = 2.08, $p = 0.018$).

Conclusions: CPD nonmedical use is common among Uganda's psychiatric patients, and more prevalent than illicit drug use. Rapid diagnostic assays may be needed in psychiatric care in

resource limited settings. It is necessary to assess how CPD nonmedical use impacts mental care outcomes and patient safety. High risk groups like inpatients and tobacco consumers should be prioritized in psychiatric screening.

Strengths and limitations of this study

- A major strength of this study is the large sample size (high power), fair representation of different psychiatric disorders and patient categories (inpatients versus outpatients) in the sample, and wide geographical coverage of Uganda.
- It also derives strength from the combined use of patient records and urine drug assays to detect nonmedical use.
- It is the first study of controlled prescription drug nonmedical use and its predictors in any population group in Uganda and most of sub-Saharan Africa.
- One limitation is that we used a convenience sample of only psychiatric patients attending public clinics which excluded those who are not in care and those who attend private clinics.
- We did not investigate if the nonmedical CPD use was a drug use disorder or not, which limits our insights on the impact of the observed behavior on mental health outcomes.

Background

Drugs that moderate the function of the central nervous system such as opioids, stimulants, sedatives, hypnotics and anaesthetics are the backbone of modern operative surgery, mental health and neurology. However, these drugs induce such strong reward feelings that they are prone to nonmedical use in which they are consumed without prescriber authorization, in unapproved doses and routes of administration, and for nontherapeutic causes. [1-3] Consequently, these drugs are judiciously controlled to prevent nonmedical use, hence the synonym controlled prescription drugs (CPDs). [4-6] As seen in the prescription opioid and methamphetamine nonmedical use escalations in high income countries, [7-12] deterrence of CPD nonmedical use can be difficult. Less economically endowed countries have not been spared too. Among Nigeria's 98 million of 15 – 64 year olds, a recent household survey found that 4.7% had engaged in unauthorized use of prescription opioids in the past year, accounting for 32% of all nonmedical drug use in the country. [13] There are also escalations in nonmedical use of methamphetamine in South Africa [14] and tramadol in West and North Africa. [15]

Nonmedical CPD use produces devastating health outcomes like neurological impairment and severe mental disorders. [12, 16] Opioid nonmedical use exacerbates the prevalence of suicides and common mental disorders while amphetamines cause drug-induced psychosis, anxiety, and depression. [11, 12, 16] Independent association has been reported between drug dependence and psychiatric disorders in HIV-infected patients. [17] In another study, the incidence of psychosis in patients with attention deficit-hyperactivity disorder on amphetamine treatment was at least twice that on methylphenidate. [11]

Meanwhile, mental disorders exacerbate the propensity for controlled drug nonmedical use. [18-20] A strong association between severe mental distress and benzodiazepine use disorders has been reported among club dwellers in Florida. [21] Problem drug use, depressive and other psychiatric disorders, and post-traumatic stress disorder increase likelihood of opioid nonmedical use. [18-20, 22] There is also association between mental disorders and lifetime prescription opioid use. A longitudinal U.S study found association between common mental disorders and prescription opioid use, and between problem drug use and prescription opioid use. [23] In HIV patients, independent associations between psychiatric disorders and drug dependence [17] and between depression and repeat opioid prescriptions [22] have been recorded. Association of depression, anxiety disorders, panic attacks and posttraumatic stress disorder with prescribed opioid nonmedical use has also been reported among patients on chronic opioid therapy and injection drug users. [24-27] Elsewhere, a study of 194 outpatients with schizophrenia in Australia found high levels of substance and drug nonmedical use with prevalence of 26.8% and 59.8% in the last 6 months and lifetime, respectively. [28]

Thus, mental disorders and CPD nonmedical use feed on each other. If not mitigated, CPD nonmedical use among psychiatric patients may compromise treatment outcomes, medication adherence and quality of life. Critically, nonmedical use of one drug typically increases likelihood of other drug use disorders. [16, 29, 30] Thus, the burden and predictors of CPD nonmedical use in high risk populations ought to be understood. Unfortunately, data on CPD nonmedical use in low income countries is limited, [16] particularly in sub-Saharan Africa. [31] Therefore, we determined the prevalence of CPD nonmedical and lifetime use among Uganda's mental health patients and associated factors. Factors known to favor CPD nonmedical and illicit drug use in literature informed our conceptual design. These include socio-demographics like

age, sex, marital status, religion, employment status, years of schooling; tobacco consumption; alcohol consumption; chronic pain; illicit drug use history; and occupation. [7, 16, 17, 19, 20, 28, 30, 32-36]

Methods

Study design

A cross-sectional survey of CPD nonmedical and lifetime use and associated factors was conducted in a convenience sample of 1275 psychiatric patients at the mental health clinics of three referral hospitals in Uganda in November and December 2018.

Study setting

Study was conducted at Mulago Hospital, Butabika Hospital and Mbale Hospital. Located in Uganda's capital Kampala in Central Uganda, Mulago and Butabika hospitals are the country's two national referral hospitals where the highest level of specialist care is provided. Mbale Hospital is located in the Eastern regional business district of Mbale. All three hospitals provide psychiatric care, though Butabika is the major provider and the national referral mental hospital. Annual psychiatric patient attendances are Butabika (6200 inpatients, 56000 outpatients); Mulago (400 inpatients, 800 outpatients); and Mbale (400 inpatients, 2500 outpatients). [37, 38]

Participants

Sample size was computed from a study population of patients that attend mental health services of the three hospitals weekly, namely 135 inpatient admissions and 1140 outpatients [37, 38] in two steps. Firstly, the sample size for a homogenous population was computed using the Cochran formula for categorical data [39] at 5% margin of error, 95% confidence level, and effect prevalence of 40% [19], followed by a Cochran correction. [39] This yielded a sample size of 285 which was finally adjusted to 1277 with a design effect of 4.48 to cater for variation in living environment and severity of mental illness between inpatients and outpatients. Multistage,

proportionate stratified sampling was used to distribute the 1277 sample into135 inpatients and 1142 outpatients, and into the three hospitals. Overall, 1275 participants (1196 Butabika, 56 Mbale, 23 Mulago) were enrolled into the study by convenience consecutive sampling based on availability and willingness to participate in the study. All clinician (psychiatrist or psychiatric clinical officer) diagnosed patients attending the mental health clinics during data collection were sampled. Pediatric patients below adolescence (less than 10 years), severely ill and non-speakers of the two widely spoken Ugandan languages in which the questionnaire was written (English and Luganda) were excluded.

Data collection

The prevalence of CPD nonmedical use was assessed using a combination of interviewer-administered semi-structured questionnaire, prescribed drug history desk review guide, and urine drug immunoassays. Questionnaire and review guide were designed by the study team. The guide recorded all medications in the patient's last prescription and date of last dose. Urine drug immunoassays employed the 10-drug vaxpert™ rapid test cups (Vaxpert Onc, Miami, Fl) that detect barbiturates, benzodiazepines, morphine, methadone, amphetamine, methamphetamine, tricyclic antidepressants, methylenedioxymethamphetamine, cocaine and marijuana. The assay uses monoclonal antibodies to detect elevated levels of these drugs and their metabolites. Urine specimen were collected in labeled 120 ml plastic urine bottles, stored in cool boxes and analyzed at the Department of Pharmacy, Makerere University. Test results were read within 5 minutes of adding urine to the vaxpert™ cup.

The questionnaire also inquired into socio-demographic and other participant attributes that have been associated with nonmedical controlled drug use in previous studies. These include age, sex,

marital status, religion, employment status, years of schooling, tobacco consumption, alcohol consumption, chronic pain, illicit drug use history, and occupation.

Study outcomes

There were three study outcomes: 1) Prevalence of CPD nonmedical use. 2) Prevalence of all controlled drug nonmedical use. 3) Prevalence of CPD lifetime use. Nonmedical use was when a participant with no documented history of prescribed drug use in the hospital file posted a positive urine assay or when one had a documented diagnosis of a drug use disorder in their hospital files. Lifetime use was when a patient reported having ever used at least one of 22 commonly prescribed CPDs.

Data analyses

Questions on the questionnaire were coded after which data was entered into EpiData 3.1. The desk review guide was examined by the first author and the prescribed drug history coded as CPD, illicit drug or neither, along with the class of the CPD (opioids, benzodiazepines, barbiturates, amphetamines, anaesthetics). This data was then merged with questionnaire data in EpiData, after which the dataset was cleaned and transcribed into SPSS 13. Final data cleaning, descriptive analysis and bivariate analysis of predictors of CPD nonmedical use and lifetime use was done in SPSS. We then transcribed SPSS data into STATA 12 after which multivariate logistic regression was done. Regression analysis was guided by a conceptual framework informed by literature. Multivariate regression employed backward elimination in which factors with statistically significant associations from bivariate analysis were fixed while sequentially removing those with weak associations from the multivariate model until only those with p-values less than 0.5 remained.

Patient and public involvement

The public was involved in the design of study as the institutional review Board and Uganda National Council of Science and Technology guided improvements in the protocol before approval. Authorities from the study sites also recommended further refinements in the study protocol before issuing administrative clearance. Patients were involved in assessing the risks of the study during consenting.

Results

Responses were received from 1275 participants of which 988 (77.5%) volunteered urine samples for CPD screening. Among these, 1196 were from Butabika, 23 were from Mulago, and 56 were from Mbale hospitals.

Characteristics of participants

As shown in **Table 1**, most participants were outpatients of Christian faith, single marital status, peasants, informal sector workers, and greater than 25 years of age. There was fair distribution of participants by sex and employment status.

Table 1. Characteristics of study participants

Characteristic	Category	Sample size, N	Frequency n (%)
Sex of patient	Male	1275	681 (53.4%)
	Female	1275	594 (46.6%)
Age of patient	≤ 25	1275	290 (22.7%)
	>25	1275	985 (77.3%)
Type of patient	Inpatient	1275	257 (20.2%)
	Outpatient	1275	1018 (79.8%)
Religious background of patient	Christian	1275	1071 (84.0%)
	Muslim	1275	198 (15.5%)
	Other	1275	6 (0.5%)
Marital status of patient	Single	1275	916 (71.8%)
	Married	1275	359 (28.2%)
Highest education level	Secondary school and below	1275	979 (76.8%)
	Beyond secondary school	1275	296 (23.2%)
Employment status	Employed	1272	554 (43.6%)
	Unemployed	1272	718 (56.4%)
Most represented occupations	Peasant, informal sector	1275	654 (51.3%)
	Student	1275	80 (6.3%)
	Teacher	1275	57 (4.5%)
	Driver	1275	23 (1.8%)
	Security/armed forces	1275	21 (1.6%)
	Administrator	1275	20 (1.6%)
	Medical worker	1275	20 (1.6%)
Urine specimen provided	Yes	1275	988 (77.5%)
	No	1275	287 (22.5%)

Prevalence of nonmedical use of CPDs among patients accessing mental health services

Hospital files for 1267 of the 1275 participants enrolled into the study were examined for history of CPD nonmedical and illicit drug use. Files for eight participants were not accessible. We found that 181 (14.3%) of the participants had history of controlled drug use disorders of which 145 (11.4%) were CPD nonmedical use and 36 (2.8%) were illicit drug use, particularly cannabis. Among the CPDs, highest nonmedical consumption was with benzodiazepines, alone or in combination with opioids and illicit drugs (**Table 2**).

Table 2. Prevalence of documented nonmedical CPD and illicit drug use by drug class

Drug class	Sample size, N	Frequency n (%)
Opioids[1]	1267	1 (0.1%)
Benzodiazepines[2]	1267	142 (11.2%)
Opioids plus Benzodiazepines[3]	1267	1 (0.1%)
Benzodiazepines plus illicit drugs[4]	1267	1 (0.1%)
Illicit drugs[5]	1267	36 (2.8%)

[1]Three were documented for same patients, namely, pethidine, morphine and tramadol. [2]Only diazepam was documented. [3]This was a case of dual use of diazepam and codeine. [4]This was a case of dual use of diazepam and khat. [5]Illicit drugs are narcotic and psychotropic drugs that prohibited from medical use by international law due to higher risk of dependence than benefits.[16] Of the 36 cases, 24 (66.7%) are cannabis, 7 (19.4%) are cannabis and khat, 3 (8.3%) are khat, 1 (2.8%) is heroine, and 1 (2.8%) is unspecified illicit substance.

Among the 988who provided urine, 166 (16.8%) who had not been prescribed any CPDs in their hospital records tested positive for these drugs. Another 12 (1.2%) participants tested positive for illicit drugs, mainly Δ9-tetrahydrocannabinol, a constituent of illicit cannabis. The overall burden of all controlled drug nonmedical use was 178 (18.0%) of the 988 participants. When categorized by mental disorder diagnosis documented in patients' files, the prevalence of controlled drug nonmedical use was similar but slightly higher among patients with psychotic disorders than those with mood and other non-drug induced disorders (**Supplementary Table 1**).

Among the CPDs, the highest nonmedical consumption detected in urine was for benzodiazepines, alone and occasionally in combination with barbiturates and illicit drugs (**Table 3**). Out of the 178 patients with nonmedical CPD and illicit drug use by urine assay, 22

(12.4%) had multiple controlled drugs, particularly benzodiazepines and cannabis. On further analysis, 123 (69.1%) of the drug positive urine was from patients with no documented history of controlled drug nonmedical use.

Table 3. Prevalence of urine detected nonmedical CPD and illicit drug use by drug class

Drug class	Sample size, N	Frequency n (%)
Opioids	988	1 (0.1%)
Amphetamines	988	3 (0.3%)
Amphetamines plus illicit drugs[1,2]	988	1 (0.1%)
Benzodiazepines	988	138 (14.0%)
Barbiturates	988	2 (0.2%)
Benzodiazepines plus barbiturates[3]	988	1 (0.1%)
Benzodiazepines plus illicit drugs[1,2,3]	988	20 (2.0%)
Illicit drugs[1,4]	988	12 (1.2%)

[1]Assay tested for Δ9-tetrahydrocannabinol (THC), cocaine and methylenedioxymethamphetamine (MDMA). [2]THC was the illicit drug in both. Among the 166 who tested positive for CPD nonmedical use, the prevalence is 159 (95.8%) benzodiazepines, 4 (2.4%) amphetamines, 3 (1.8%) barbiturates and 1 (0.6%) opioids. [3]A total of 21 (13.2%) of the 159 participants with benzodiazepines tested positive for other controlled drugs. [4]Of these, 10 and 2 participants tested positive for THC and MDMA, respectively.

Predictors of CPD nonmedical use among patients accessing mental health services

After controlling for sex and current alcohol consumption, the type of patient was independently associated with CPD nonmedical and illicit drug use (**Table 4**). The odds of CPD nonmedical use were significantly higher among inpatients than outpatients.

Table 4. Predictors of nonmedical CPD use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		Nonmedical CPD use	No nonmedical CPD use					
Type of patient	Inpatient	109	120	202.25	11.19 (7.69 – 16.27)	< 0.001	10.90 (7.25 – 16.38)	< 0.001
	Outpatient	57	702					
Employment status	Employed	82	368	1.14	1.20 (0.86 – 1.67)	0.286	1.30 (0.87 – 1.94)	0.195
	Unemployed	84	452					
History of treatment at substance abuse facility	Yes	29	58	18.71	2.79 (1.73 – 4.52)	< 0.001	0.72 (0.41 – 1.28)	0.265
	No	136	760					
History of traumatic injury	Yes	42	159	3.03	1.41 (0.96 – 2.09)	0.082	0.79 (0.50 – 1.25)	0.308
	No	124	663					
History of chronic back pain	Yes	36	164	0.26	1.11 (0.74 – 1.67)	0.612	0.81 (0.50 – 1.30)	0.375
	No	130	658					
Currently consumes tobacco	Yes	36	60	23.43	2.99 (1.89 – 4.73)	< 0.001	1.68 (0.91 – 3.09)	0.096
	No	142	749					

Predictors of all controlled drug use among patients accessing mental health services

After controlling for sex and current alcohol consumption, the type of patient and current tobacco consumption were independently associated with all controlled drug use (**Table 5**). The odds of controlled drug use were significantly higher among inpatients and those with current tobacco consumption than their corresponding counterparts.

Table 5. Predictors of all controlled drug use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		Nonmedical CPD use	No nonmedical CPD use					
Age in years	≤ 25	54	174	6.45	1.59 (1.11 – 2.28)	0.012	1.44 (0.95 – 2.19)	0.089
	> 25	124	636					
Type of patient	Inpatient	110	119	181.86	9.39 (6.56 – 13.46)	< 0.001	8.29 (5.62 – 12.22)	< 0.001
	Outpatient	68	691					
Employment status	Employed	88	362	1.26	1.20 (0.87 – 1.67)	0.261	1.21 (0.82 – 1.78)	0.340
	Unemployed	90	446					
History of treatment at substance abuse facility	Yes	31	56	20.09	2.84 (1.77 – 4.56)	< 0.001	0.69 (0.39 – 1.21)	0.197
	No	146	750					
History of severe traumatic injury	Yes	45	156	3.27	1.42 (0.97 – 2.08)	0.071	0.77 (0.50 – 1.20)	0.248
	No	133	654					
Currently consumes tobacco	Yes	36	60	27.26	3.16 (2.02 – 4.97)	< 0.001	1.85 (1.02 – 3.32)	0.041
	No	142	749					

Prevalence of lifetime CPD use among patients accessing mental health services

Of the 1275 participants, 119 (9.3 %) reported having ever used CPDs in their lifetime. Most exposure was to diazepam, tramadol capsules, codeine, oral morphine, tramadol injection and amphetamine in descending order (**Supplementary Table 2**). Among 25% of the participants who reported lifetime CPD use, index exposure was nonmedical either through self-prescription or friends' influence (**Supplementary Table 3**). Lastly, we found that index CPD exposure was occasioned by treatment for mental illness and restlessness, operative pain and lack of sleep, and pressure from friends (**Supplementary Table 4**).

Predictors of CPD lifetime use among patients accessing mental health services

After controlling for age, sex, employment status, history of traumatic injury and current tobacco consumption, education level and history of treatment at a substance abuse facility were associated with CPD lifetime use (**Table 6**). The odds of exposure to CPDs were significantly higher among patients educated beyond secondary school and those with history of treatment at a substance abuse facility.

Table 6. Predictors of CPD lifetime use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		Exposed to CPDs	Not exposed to CPDs					
Type of patient	Outpatient	88	930	2.83	0.69 (0.45 – 1.07)	0.094	0.82 (0.51 – 1.33)	0.422
	Inpatient	31	226					
Marital status	Married	28	331	1.39	0.77 (0.49 – 1.19)	0.240	0.71 (0.44 – 1.13)	0.145
	Single	91	825					
Education level	Beyond secondary school	52	244	30.89	2.90 (1.97 – 4.28)	< 0.001	2.71 (1.81 – 4.08)	< 0.001
	Secondary school and below	67	912					
Ever been treated at a	Yes	19	85	10.74	2.40 (1.40 – 4.11)	0.018	2.08 (1.14 – 3.80)	0.018
substance abuse facility	No	99	1063					
History of chronic back pain	Yes	16	213	1.83	0.69 (0.40 – 1.19)	0.179	0.77 (0.43 – 1.36)	0.366
	No	103	942					
Has sickle cell disease	Yes	1	2	2.04	4.89 (0.44 – 54.28)	0.197	6.17 (0.47 – 76.72)	0.157
	No	118	1153					

Discussion

Understanding the interplay between mental disorders and CPD nonmedical use can enable improvements in mental health treatment outcomes. We found a high prevalence of CPD nonmedical use among patients with mental disorders using both document review (11.4%) and urine assays (17%). This prevalence is two-to-three fold the 5.5% global prevalence of nonmedical controlled drug use in the general population. [40] Similar findings have been reported elsewhere. In Australia, 11.3% of schizophrenia outpatients had lifetime history of prescription drug use disorder and 27.8% tested positive to recent controlled drug use. [28] A recent meta-analysis of stimulant use disorders in hospital patients with psychosis generated a pooled prevalence of 13.9%. [41] These and our data suggest that having a mental illness provides similar risk for controlled drug abuse in different socio-economic and geographical settings.

Controlled drug nonmedical use exacerbates HIV transmission and mental disorders. [14, 16] Thus, controlled drug nonmedical use among Uganda's mental health patients needs mitigation. Multipronged strategies could achieve this, including deployment of rapid drug assays for enhanced detection of nonmedical controlled drug use and strengthening CPD regulation. Uganda's specialist mental health clinics lack assay kits for controlled drugs and rely on clinical screening/assessment to identify nonmedical controlled drug use [42] yet assays are important because patients commonly conceal drug use in fear of legal, social and cultural repercussions. [13, 16, 43] We found that clinical screening had missed about 70% of patients taking CPDs and illicit drugs. In Australia, urine assay detected drugs in one third of patients who had reported zero recent drug use. [28] Therefore, clinical screening alone precludes many patients with drug use disorders from receiving care. Besides, there is need to understand how mental patients obtain

CPDs for nonmedical use considering that Uganda's laws restrict supply to doctor authorized prescriptions. [44, 45]

Nonmedical use of controlled drugs among patients accessing mental health services in Uganda involved mostly benzodiazepines and illicit cannabis. Benzodiazepines were particularly popular, with a total prevalence of 16.1%, five times that of cannabis at 3.3%. Our cannabis use findings are lower than the 17% reported previously among mental health patients by Vudriko and coworkers. [42] Comparison of our prevalence for recent and historical controlled drug use showed a similar pattern. Benzodiazepines still dominated the historical prevalence at 11.4% followed by cannabis at a distant 2.9%. For both current and historical nonmedical use, opioids were far less involved than in high income settings. [28, 46]

Although benzodiazepines nonmedical use is elevated in psychiatric patients globally, [47] there is high variation in dominant drug classes by country. Among inpatient psychiatric patients in Germany, benzodiazepines had the highest prevalence among those with drug use disorders followed by barbiturates, psychostimulants and opioids. [46] In contrast, an Australian study of psychosis outpatients had cannabis leading lifetime nonmedical use ahead of amphetamines, benzodiazepines and opioids. [28] Cannabis still led in recent use prevalence in that study followed by benzodiazepines, opioids and amphetamines. [28] The prevalence of amphetamine nonmedical use in Uganda's psychiatric patients falls short of the global prevalence of stimulant use disorders in this population which is 8.9% with highs of 30%. [41] Similarly, the 0.1% prevalence of prescription opioid nonmedical use among Uganda's mental patients contrasts with the prevalence of chronic opioid use of 8.6 to 11% in the U.S. [19] Lastly, the drug class use pattern among Uganda's mental patients differs from global profiles for the general population. Globally, cannabis leads in controlled drug nonmedical use followed by amphetamines. [34] In the

U.S, opioids top tranquilizers and stimulants. [7, 48] In Europe, sedatives edge opioids and stimulants. [3] In Nigeria, cannabis leads followed by prescription opioids; sedatives and amphetamines score low. [13]

The high burden of benzodiazepine nonmedical use transcends 60 countries. [10] As central nervous system depressants, benzodiazepines cause fatal interactions with other CNS suppressants like opioids, other sedatives, hypnotics, neuroleptics and alcohol. They are involved in 30% of prescription drug related deaths, trailing only opioids at 75%. [43] Benzodiazepines have also been implicated in 80% of accidental opioid-related overdose deaths in some settings. [43] Therefore, the high burden of benzodiazepine nonmedical use in Uganda's psychiatric patients raises concerns on medication safety.

We found that being inpatients favored CPD nonmedical use, and that being inpatients and tobacco consumption favored overall controlled drug use. Typically, it is severely ill patients who are admitted into inpatient care. Therefore, there could be a role of CPD nonmedical use in severe mental illnesses in Uganda. Tobacco consumption is a known gateway to nonmedical controlled drug use. [35] Elevated odds of nonmedical CPD and illicit drug use among tobacco consumers have been reported in several studies. [19, 28, 29, 32, 36] Routine clinical screening and urine assays of these high risk categories of patients for CPD nonmedical use are necessary. In chronic pain patients, random drug testing significantly reduced the prevalence of illicit drug use. [49] Combination of baseline and random periodic drug testing is another option. [43]

Lifetime use of CPDs was also disproportionately high for benzodiazepines among patients with mental disorders in Uganda. Problematic CPD use is typically ignited by index exposure through medical prescription or unauthorized channels like recreation and social

networks. [1, 19, 50, 51] History of CPD lifetime use strongly predicts nonmedical use. [33, 50] The U.S opioid crisis is attributed to the exponential rise in opioid prescriptions for chronic pain. [7, 20, 51, 52] Therefore, high exposure to benzodiazepines among Uganda's psychiatric patients ought to be mitigated. Vigilant screening of patients for drug use disorder risk, education of clinicians on judicious prescribing and dispensers on appropriate dispensing, tight control of CPD access, and prescription drug monitoring programmes are necessary. [9, 52-56]

High formative education and previous treatment at a substance abuse facility favored lifetime use. Highly educated people are possibly more exposed to stressful situations, are more aware of the effects and availability of CPDs, or have higher access to these drugs than other people. However, previous studies have reported inconsistent relationships between education level and CPD nonmedical use. One study of patients on prescribed chronic opioid therapy found that low education level independently favored opioid use disorders [24] while studies of benzodiazepine use disorders found no association. [21, 57] Meanwhile, nonmedical use of one controlled drug or substance typically culminates into use of other drugs and/or poly-drug use. [21, 29, 30, 32, 50, 58] Therefore, high level vigilance in clinical screening is needed to ensure CPD nonmedical use is not missed in mentally ill patients previously treated for substance abuse.

The high burden of CPD nonmedical use among patients with mental disorders suggests that vigilance and professionalism in their prescription and control needs improvement. It would also be useful to investigate how the sole use of clinical screening/assessment impacts mental health treatment outcomes in Uganda. There is also need for enhanced vigilance in clinical and laboratory screening of high risk patient categories identified here.

This study derives strengths in the high power of the sample, fair representation of different psychiatric disorders and patient categories (inpatients, outpatients), and wide geographical coverage of Uganda. Further strength derives from the combined use of patient records and urine assays to detect nonmedical use. We used a convenience sample of only those patients attending public mental clinics which excluded those outside care and those attending private mental health clinics. Affluent patients and those with institutional health insurance have broad choice of care providers and could be underrepresented at public clinics, yet they are the ones most likely to afford CPDs. A study of CPD nonmedical use among patients at private mental clinics is necessary. Our study sites were also in large urban centres where access to CPDs is easy. It is possible that a different pattern of nonmedical CPD and illicit drug use could be observed among patients from rural settings where CPD supply is limited. Furthermore, not all the 1275 study participants provided urine, although the 988 who did so was still large. Lastly, we did not investigate if the CPD nonmedical use was problematic or not.

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Supplementary Table 1. Distribution of urine detected CPD nonmedical and substance use by mental disorder

Mental disorder[1]	Sample size, N	Frequency n (%)
Psychotic disorders	323	21.4%
Mood disorders	378	19.3%
Other disorders	86	18.6%
Substance use disorders	23	87.0%

[1]Psychotic disorders included diagnoses of schizophrenia, psychosis, substance or drug-induced psychosis, alcohol-induced psychosis, HIV-related psychosis, brief psychosis, psychotic depression, delusional disorders, paranoid psychosis, and schizoaffective disorder. Mood disorders included depression, hypomania, bipolar affective disorder, bipolar disorder. Other disorders included epilepsy/seizures (predominantly), dementia, and mental retardation.

Supplementary Table 2. Self-reported lifetime CPD use among patients accessing mental health services in Uganda

Controlled prescription drug[1]	Sample size, N	Frequency n (%)
Morphine injection	1274	6 (0.5%)
Oral morphine	1274	7 (0.6%)
Codeine tablets	1273	9 (0.7%)
Oxycodone	1274	2 (0.2%)
Hydrocodone	1272	1 (0.1%)
Pethidine injection	1274	4 (0.3%)
Tramadol injection	1273	6 (0.5%)
Oral tramadol (tablets or capsules)	1272	16 (1.3%)
Amphetamine	1274	6 (0.5%)
Ketamine	1273	1 (0.1%)
Propofol	1272	1 (0.1%)
Oxycontin	1273	1 (0.1%)
Phenobarbitone	1274	3 (0.2%)
Diazepam	1273	95 (7.5%)
Alprazolam	1273	1 (0.1%)
Bromazepam	1274	4 (0.3%)

[1]Exposure to methamphetamine, fentanil, alfentanil, sufentanil, amorbabital and secobarbital was also assessed but yielded zero prevalence.

Supplementary Table 3. Distribution of psychiatric patients with lifetime CPD use by channel of index exposure

Channel of index exposure	Sample size, N	Frequency n (%)
Doctor prescribed the drug	110	81 (73.6%)
Friends' influence[1]	110	17 (15.5%)
Self-prescription[1]	110	12 (10.9%)

[1]A total of 26.4% of the patients had been introduced to CPDs without doctor's authorization.

Supplementary Table 4. Distribution of indications for index exposure to CPDs by psychiatric patients

Indication	Sample size, N	Frequency n (%)
Was stressed by work	111	3 (2.7%)
Was stressed by family problems	111	5 (4.5%)
Was in pain, was operated	111	19 (17.1%)
Had mental illness, was restless	111	53 (47.7%)
Was influenced by pressure from friends	111	11 (9.9%)
Lacked sleep	111	19 (17.1%)
Had flu	111	1 (0.9%)

COMPLIANCE WITH STROBE CHECKLIST

Our manuscript satisfies the requirements of the STROBE checklist for cross-sectional studies as shown below.

Manuscript section		Requirement	Has the requirement been satisfied?
Title and abstract	1	a) Indicate the study's design with a commonly used term in the title or the abstract b) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes Yes
Introduction			
	2	**Background/rationale**: Explain the scientific background and rationale for the investigation being reported	Yes
	3	**Objectives**: State specific objectives, including any prespecified hypotheses	Yes
Methods			
	4	**Study design**: Present key elements of study design early in the paper	Yes, this was done.
	5	**Setting**: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, this was done.
	6	**Participants**: (*a*) Give the eligibility criteria, and the sources and methods of selection of Participants	Yes, this was done.
	7	**Variables**: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, outcome and predictor variables were defined.
	8	**Data sources/measurement**: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, this was done.
	9	**Bias**: Describe any efforts to address potential sources of bias	Yes. Used multiple methods to answer the same question.
	10	**Study size**: Explain how the study size was arrived at	Yes. Sample size calculation was described.
	11	**Quantitative variables**: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, this was done.
	12	**Statistical methods**: a) Describe all statistical methods, including those used to control for confounding	Yes, this was done.
		b) Describe any methods used to examine subgroups and interactions	Not applicable.
		c) Explain how missing data were addressed	Yes, this was done. Individual analyses excluded missing data.
		d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable.
		e) Describe any sensitivity analyses	Not applicable. Interaction between predictor variables controlled by inclusion of all

			those with significant association with outcomes from bivariate analysis into the multivariate model.
Results			
	13	**Participants**: a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes. This was done.
		b) Give reasons for non-participation at each stage	Yes. This has been done.
		c) Consider use of a flow diagram	
	14	**Descriptive data** a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes. This was done.
		b) Indicate number of participants with missing data for each variable of interest	Yes. This was done for each variable.
	15	**Outcome data**: Report numbers of outcome events or summary measures	Yes. This was done.
	16	**Main results** a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes. This was done.
		b) Report category boundaries when continuous variables were categorized	Yes. This was done.
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.
	17	**Other analyses**: Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable.
Discussion			
	18	**Key results**: Summarise key results with reference to study objectives	Yes. This was done for each result.
	19	**Limitations**: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes. This was done.
	20	**Interpretation**: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes. This was done.
	21	**Generalizability**: Discuss the generalisability (external validity) of the study results	Yes. This was done.
Other information			
	22	**Funding**: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes. This was done.

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Predictors of controlled prescription drug nonmedical and lifetime use among patients accessing public mental health services in Uganda: a cross-sectional study

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Predictors of controlled prescription drug nonmedical and lifetime use among patients accessing public mental health services in Uganda: a cross-sectional study

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Abstract

Objectives: We determined the prevalence of controlled prescription drug (CPD) nonmedical and lifetime use and their predictors among patients at three public mental clinics in Uganda to identify missed care opportunities, enhanced screening priorities, and drug control needs.

Methods: A cross-sectional survey of 1275 patients was performed from November to December, 2018. Interviewer-administered semi-structured questionnaires, desk review guide, and urine drug assays were employed. Questionnaire recorded CPD nonmedical and illicit drug use history from patients' files, CPD lifetime use, and risk factors. Desk review guide recorded recently prescribed drugs in patients' files to corroborate with urine assays. Predictors were analyzed by multivariate logistic regression.

Results: From desk review, 145 (11.4%) patients had history of CPD nonmedical use and 36 (2.8%) had used illicit drugs. Of 988 patients who provided urine, 166 (16.8%) self-medicated CPDs, particularly benzodiazepines while 12 (1.2%) used illicit drugs. Of those with drug-positive urine, 123 (69.1%) had no documented history of CPD nonmedical and illicit drug use. Being an inpatient (OR = 10.90, $p < 0.001$) was independently associated with CPD nonmedical use. Additionally, being an inpatient (OR = 8.29, $p < 0.001$) and tobacco consumption (OR = 1.85, $p = 0.041$) were associated with CPD nonmedical and illicit drug use combined. Among participants, 119 (9.3%) reported CPD lifetime use, and this was independently associated with education level (OR = 2.71, $p < 0.001$) and history of treatment for substance abuse (OR = 2.08, $p = 0.018$).

Conclusions: CPD nonmedical use is common among Uganda's psychiatric patients, and more prevalent than illicit drug use. Rapid diagnostic assays may be needed in psychiatric care in

resource limited settings. It is necessary to assess how CPD nonmedical use impacts mental care outcomes and patient safety. High risk groups like inpatients and tobacco consumers should be prioritized in psychiatric screening.

Strengths and limitations of this study

- A major strength of this study is the large sample size (high power), fair representation of different psychiatric disorders and patient categories (inpatients versus outpatients) in the sample, and wide geographical coverage of Uganda.
- It also derives strength from the combined use of patient records and urine drug assays to detect nonmedical use.
- It is the first study of controlled prescription drug nonmedical use and its predictors in any population group in Uganda and most of sub-Saharan Africa.
- One limitation is that we used a convenience sample of only psychiatric patients attending public clinics which excluded those who are not in care and those who attend private clinics.
- We did not investigate if the CPD nonmedical use was a drug use disorder or not, which limits our insights on the impact of the observed behavior on mental health outcomes.

Background

Drugs that moderate the function of the central nervous system such as opioids, stimulants, sedatives, hypnotics and anaesthetics are the backbone of modern operative surgery, mental health and neurology. However, these drugs induce such strong reward feelings that they are prone to nonmedical use in which they are consumed without prescriber authorization, in unapproved doses and routes of administration, and for nontherapeutic causes. [1-3] Consequently, these drugs are judiciously controlled to prevent nonmedical use, hence the synonym controlled prescription drugs (CPDs). [4-6]As seen in the prescription opioid and amphetamine-group (amphetamine and methamphetamine) drugs nonmedical use escalations in high income countries, [7-12] deterrence of CPD nonmedical use can be difficult. Less economically endowed countries have not been spared too. Among Nigeria's 98 million of 15 – 64 year olds, a recent household survey found that 4.7% had engaged in prescription opioid nonmedical use in the past year, accounting for 32% of all nonmedical drug use in the country. [13] There are also escalations in nonmedical use of methamphetamine in South Africa [12, 14] and tramadol in West and North Africa. [15] Globally, at least 60 countries have a high burden of benzodiazepine nonmedical use. [11]

Nonmedical CPD use produces devastating health outcomes like neurological impairment and severe mental disorders. [8, 16] Opioid nonmedical use exacerbates the prevalence of suicides and common mental disorders while amphetamines cause drug-induced psychosis, anxiety, and depression. [8, 16]Independent association has been reported between drug dependence and psychiatric disorders in HIV-infected patients. [17] A higher risk of incident psychosis has also been reported among patients with attention deficit-hyperactivity disorder on medically prescribed amphetamine treatment compared to methylphenidate. [18] Meanwhile, benzodiazepines

fatally interact with other CNS suppressants and are involved in 30% of prescription drug related deaths, trailing only opioids at 75%. [19] In some settings, benzodiazepines play a part in 80% of accidental opioid-related overdose deaths. [19]

Intriguingly, mental disorders exacerbate the propensity for CPD nonmedical and illicit drug use. [20-22] A strong association between severe mental distress and benzodiazepine use disorders has been reported among club dwellers in Florida. [23] Problem drug use, depressive and other psychiatric disorders, and post-traumatic stress disorder increase likelihood of opioid nonmedical use. [20-22, 24] There is also association between mental disorders and lifetime prescription opioid use. A longitudinal U.S study found association between common mental disorders and prescription opioid use, and between problem drug use and prescription opioid use. [25] In HIV patients, independent associations between psychiatric disorders and drug dependence [17] and between depression and repeat opioid prescriptions [24] have been recorded. Association of depression, anxiety disorders, panic attacks and posttraumatic stress disorder with prescription opioid nonmedical use has also been reported among patients on chronic opioid therapy and injection drug users. [26-29] Elsewhere, a study of 194 outpatients with schizophrenia in Australia found high levels of substance and drug nonmedical use with prevalence of 26.8% and 59.8% in the last 6 months and lifetime, respectively. [30]

Thus, mental disorders and CPD nonmedical use feed on each other. If not mitigated, CPD nonmedical use among psychiatric patients may compromise treatment outcomes, medication adherence and quality of life. Critically, nonmedical use of one drug typically increases likelihood of other drug use disorders. [16, 31, 32] Thus, the burden and predictors of CPD nonmedical use in high risk populations ought to be understood. Unfortunately, data on CPD nonmedical use in low income countries is limited, [16] particularly in sub-Saharan Africa. [33]

Therefore, we determined the prevalence of CPD nonmedical and lifetime use among Uganda's mental health patients and associated factors. Factors known to favor CPD nonmedical and illicit drug use in literature informed our conceptual design. These include socio-demographics like age, sex, marital status, religion, employment status, years of schooling; tobacco consumption; alcohol consumption; chronic pain; illicit drug use history; and occupation. [7, 16, 17, 21, 22, 30, 32, 34-38]

Methods

Study design

A cross-sectional survey of CPD nonmedical and lifetime use and associated factors was conducted in a convenience sample of 1275 psychiatric patients at the mental health clinics of three referral hospitals in Uganda in November and December 2018.

Study setting

Study was conducted at Mulago Hospital, Butabika Hospital and Mbale Hospital. Located in Uganda's capital Kampala in Central Uganda, Mulago and Butabika hospitals are the country's two national referral hospitals where the highest level of specialist care is provided. Mbale Hospital is located in the Eastern regional business district of Mbale. All three hospitals provide psychiatric care, though Butabika is the major provider and the national referral mental hospital. Reported annual psychiatric patient attendances are Butabika (6200 inpatients, 56000 outpatients); Mulago (400 inpatients, 800 outpatients); and Mbale (400 inpatients, 2500 outpatients). [39, 40]

Participants

Sample size was computed from a reported study population of patients that attend mental health services of the three hospitals weekly, namely 135 inpatient admissions and 1140 outpatients [39, 40] in two steps. Firstly, the sample size for a homogenous population was

computed using the Cochran formula for categorical data [41] at 5% margin of error, 95% confidence level, and effect prevalence of 40% [21], followed by a Cochran correction. [41] This yielded a sample size of 285 which was finally adjusted to 1277 with a design effect of 4.48 to cater for variation in living environment and severity of mental illness between inpatients and outpatients. Multistage, proportionate stratified sampling was used to distribute the 1277 sample into inpatients and outpatients, and into the three hospitals. The sample was first distributed into 135 inpatients and 1142 outpatients based on literature [39, 40], after which it was adjusted to 257 inpatients and 1020 outpatients to match the prevailing weekly load of each type of patient in the hospitals based on guidance obtained during pre-data collection site visits. Overall, 1275 participants (1196 Butabika, 56 Mbale, 23 Mulago) were enrolled into the study by convenience consecutive sampling based on availability and willingness to participate in the study. All clinician (psychiatrist or psychiatric clinical officer) diagnosed patients attending the mental health clinics during data collection were sampled. Pediatric patients below adolescence (less than 10 years), severely ill and non-speakers of the two widely spoken Ugandan languages in which the questionnaire was written (English and Luganda) were excluded.

Data collection

The prevalence of CPD nonmedical use was assessed using a combination of interviewer-administered semi-structured questionnaire, desk review guide for drugs prescribed for patients in their hospital files, and urine drug immunoassays. The questionnaire inquired into the presence of documented diagnosis of CPD nonmedical and illicit drug use, as well as whether a urine sample was provided by the patient for drug analysis. The questionnaire also inquired into the history of lifetime use of individual CPDs and how these drugs were introduced to the participants the first time they used them. The guide recorded all medications in the patient's last

prescription and date of last dose. Questionnaire and review guide were designed by the study team. Urine drug immunoassays employed the 10-drug vaxpert™ rapid test cups (Vaxpert Onc, Miami, Fl) that detect barbiturates, benzodiazepines, morphine, methadone, amphetamine, methamphetamine, tricyclic antidepressants, methylenedioxymethamphetamine, cocaine and marijuana. The assay uses monoclonal antibodies to detect elevated levels of these drugs and their metabolites. Urine specimen were collected in labeled 120 ml plastic urine bottles, stored in cool boxes and analyzed at the Department of Pharmacy, Makerere University. Test results were read within 5 minutes of adding urine to the vaxpert™ cup.

The questionnaire also inquired into socio-demographic and other participant attributes that have been associated with controlled drug nonmedical use in previous studies. These include age, sex, marital status, religion, employment status, years of schooling, tobacco consumption, alcohol consumption, chronic pain, illicit drug use history, and occupation. Numerical variables such as age were collected as individual values after which binary categories for bivariate and multivariate logistic regression were created using the median as cut-off.

Study outcomes

There were three study outcomes: 1) Prevalence of CPD nonmedical use. 2) Prevalence of CPD nonmedical and illicit drug use combined. 3) Prevalence of self-reported CPD lifetime use. Nonmedical use was when a participant with no documented history of having been prescribed a CPD in the hospital file posted a positive urine assay or when one had a documented diagnosis of a drug use disorder in their hospital files. Self-reported lifetime use was measured using a checklist of 22 commonly prescribed CPD products, comprising 12 opioids, two amphetamine-group products, two intravenous anaesthetics, three barbiturates and three benzodiazepines. A

patient had self-reported CPD lifetime use if they responded affirmatively as having ever used at least one of the 22 CPD products.

Data analyses

Questionnaire was coded by adding a letter for the questionnaire section before each question number to distinguish questions from different sections of the tool sharing the same number numeral. A data entry template for the coded questionnaire was then created in EpiData 3.1, followed by data entry. The desk review guide for drugs prescribed in the patients' files was examined by the first author and the drugs documented therein were coded as CPD or not, along with the class of the CPD (opioids, benzodiazepines, barbiturates, amphetamines, anaesthetics). This data was then merged with questionnaire data in EpiData, after which the dataset was cleaned and transcribed into SPSS 13. Final data cleaning, descriptive analysis and bivariate analysis of predictors of CPD nonmedical use and lifetime use was done in SPSS. We then transcribed SPSS data into STATA 12 after which multivariate logistic regression was done. Regression analysis was guided by a conceptual framework informed by literature. Multivariate regression employed backward elimination in which factors with statistically significant associations from bivariate analysis were fixed while sequentially removing those with weak associations from the multivariate model until only those with p-values less than 0.5 remained. In all analyses, missing data was excluded.

Patient and public involvement

The public was involved in the design of study as the institutional review Board and Uganda National Council of Science and Technology guided improvements in the protocol before

approval. Authorities from the study sites also recommended further refinements in the study protocol before issuing administrative clearance. Patients were involved in assessing the risks of the study during consenting.

Results

Responses were received from 1275 participants of which 988 (77.5%) volunteered urine samples for CPD screening. Among these, 1196 were from Butabika, 23 were from Mulago, and 56 were from Mbale hospitals.

Characteristics of participants

As shown in **Table 1**, most participants were outpatients of Christian faith, single marital status, peasants, informal sector workers, and greater than 25 years of age. There was fair distribution of participants by sex and employment status.

Table 1. Characteristics of study participants

Characteristic	Category	Sample size, N	Frequency n (%)
Sex of patient	Male	1275	681 (53.4%)
	Female	1275	594 (46.6%)
Age of patient	≤ 25	1275	290 (22.7%)
	>25	1275	985 (77.3%)
Type of patient	Inpatient	1275	257 (20.2%)
	Outpatient	1275	1018 (79.8%)
Religious background of patient	Christian	1275	1071 (84.0%)
	Muslim	1275	198 (15.5%)
	Other	1275	6 (0.5%)
Marital status of patient	Single	1275	916 (71.8%)
	Married	1275	359 (28.2%)
Highest education level	Secondary school and below	1275	979 (76.8%)
	Beyond secondary school	1275	296 (23.2%)
Employment status	Employed	1272	554 (43.6%)
	Unemployed	1272	718 (56.4%)
Most represented occupations	Peasant, informal sector	1275	654 (51.3%)
	Student	1275	80 (6.3%)
	Teacher	1275	57 (4.5%)
	Driver	1275	23 (1.8%)
	Security/armed forces	1275	21 (1.6%)
	Administrator	1275	20 (1.6%)
	Medical worker	1275	20 (1.6%)
Urine specimen provided	Yes	1275	988 (77.5%)
	No	1275	287 (22.5%)

Prevalence of CPD nonmedical use among patients accessing mental health services

Hospital files for 1267 of the 1275 participants enrolled into the study were examined for history of CPD nonmedical and illicit drug use. Files for eight participants were not accessible. We found that 181 (14.3%) of the participants had history of CPD nonmedical and illicit drug use disorders of which 144 (11.4%) had CPD nonmedical use only, 1 (0.08%) had both CPD nonmedical and illicit drug use and 36 (2.8%) had illicit drug use only, particularly cannabis. Among the CPDs, highest nonmedical consumption was with benzodiazepines, alone or in combination with opioids and illicit drugs (**Table 2**).

Table 2. Prevalence of documented CPD nonmedical and illicit drug use by drug class

Drug class	Sample size, N	Frequency n (%)
Opioids[1]	1267	1 (0.1%)
Benzodiazepines[2]	1267	142 (11.2%)
Opioids plus Benzodiazepines[3]	1267	1 (0.1%)
Benzodiazepines plus illicit drugs[4]	1267	1 (0.1%)
Illicit drugs[5]	1267	36 (2.8%)

[1]Three were documented for same patient, namely, pethidine, morphine and tramadol. [2]Only diazepam was documented. [3]This was a case of dual use of diazepam and codeine. [4]This was a case of dual use of diazepam and khat. [5]Illicit drugs are narcotic and psychotropic drugs that are prohibited from medical use by international law due to higher risk of dependence than benefits.[16] Of the 36 cases, 24 (66.7%) are cannabis, 7 (19.4%) are cannabis and khat, 3 (8.3%) are khat, 1 (2.8%) is heroine, and 1 (2.8%) is unspecified illicit substance.

Among the 988who provided urine, 166 (16.8%) who had not been prescribed any CPDs in their hospital records tested positive for these drugs. Another 12 (1.2%) participants tested positive for illicit drugs, mainly Δ9-tetrahydrocannabinol, a constituent of illicit cannabis. The overall burden of CPD nonmedical and illicit drug use combined was 178 (18.0%) of the 988 participants. When categorized by mental disorder diagnosis documented in patients' files, the prevalence of CPD nonmedical and illicit drug use combined was similar but slightly higher among patients with psychotic disorders than those with mood and other non-drug induced disorders (**Supplementary Table 1**).

Among the CPDs, the highest nonmedical consumption detected in urine was for benzodiazepines, alone and occasionally in combination with barbiturates and illicit drugs

(**Table 3**). Out of the 178 patients with CPD nonmedical and illicit drug use by urine assay, 22 (12.4%) had multiple controlled drugs, particularly benzodiazepines and cannabis. On further analysis, 123 (69.1%) of the drug positive urine was from patients with no documented history of CPD nonmedical and illicit drug use (**Supplementary Table 2**).

Table 3. Prevalence of urine detected CPD nonmedical and illicit drug use by drug class

Drug class	Sample size, N	Frequency n (%)
Opioids	988	1 (0.1%)
Amphetamines	988	3 (0.3%)
Amphetamines plus illicit drugs[1,2]	988	1 (0.1%)
Benzodiazepines	988	138 (14.0%)
Barbiturates	988	2 (0.2%)
Benzodiazepines plus barbiturates[3]	988	1 (0.1%)
Benzodiazepines plus illicit drugs[1,2,3]	988	20 (2.0%)
Illicit drugs[1,4]	988	12 (1.2%)

[1]Assay tested for Δ9-tetrahydrocannabinol (THC), cocaine and methylenedioxymethamphetamine (MDMA). [2]THC was the illicit drug in both. Among the 166 who tested positive for CPD nonmedical use, the prevalence is 159 (95.8%) benzodiazepines, 4 (2.4%) amphetamines, 3 (1.8%) barbiturates and 1 (0.6%) opioids. [3]A total of 21 (13.2%) of the 159 participants with benzodiazepines tested positive for other controlled drugs. [4]Of these, 10 and 2 participants tested positive for THC and MDMA, respectively.

Predictors of urine-positive CPD nonmedical use among patients accessing mental health services

After controlling for sex and current alcohol consumption, the type of patient was independently associated with urine-positive CPD nonmedical use (**Table 4**). The odds of CPD nonmedical use were significantly higher among inpatients than outpatients.

Table 4. Predictors of urine-positive CPD nonmedical use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		CPD nonmedical use	No CPD nonmedical use					
Type of patient	Inpatient	109	120	202.25	11.19 (7.69 – 16.27)	< 0.001	10.90 (7.25 – 16.38)	< 0.001
	Outpatient	57	702					
Employment status	Employed	82	368	1.14	1.20 (0.86 – 1.67)	0.286	1.30 (0.87 – 1.94)	0.195
	Unemployed	84	452					
History of treatment at substance abuse facility	Yes	29	58	18.71	2.79 (1.73 – 4.52)	< 0.001	0.72 (0.41 – 1.28)	0.265
	No	136	760					
History of traumatic injury	Yes	42	159	3.03	1.41 (0.96 – 2.09)	0.082	0.79 (0.50 – 1.25)	0.308
	No	124	663					
History of chronic back pain	Yes	36	164	0.26	1.11 (0.74 – 1.67)	0.612	0.81 (0.50 – 1.30)	0.375
	No	130	658					
Currently consumes tobacco	Yes	36	60	23.43	2.99 (1.89 – 4.73)	< 0.001	1.68 (0.91 – 3.09)	0.096
	No	142	749					

Predictors of urine-positive CPD nonmedical and illicit drug use combined among patients accessing mental health services

After controlling for sex and current alcohol consumption, the type of patient and current tobacco consumption were independently associated with urine-positive CPD nonmedical and illicit drug use combined (**Table 5**). The odds of CPD nonmedical and illicit drug use combined were significantly higher among inpatients and those with current tobacco consumption than their corresponding counterparts.

Table 5. Predictors of CPD nonmedical and illicit drug use combined among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		CPD nonmedical & illicit drug use	No CPD nonmedical & illicit drug use					
Age in years	≤ 25	54	174	6.45	1.59 (1.11 – 2.28)	0.012	1.44 (0.95 – 2.19)	0.089
	> 25	124	636					
Type of patient	Inpatient	110	119	181.86	9.39 (6.56 – 13.46)	< 0.001	8.29 (5.62 – 12.22)	< 0.001
	Outpatient	68	691					
Employment status	Employed	88	362	1.26	1.20 (0.87 – 1.67)	0.261	1.21 (0.82 – 1.78)	0.340
	Unemployed	90	446					
History of treatment at substance abuse facility	Yes	31	56	20.09	2.84 (1.77 – 4.56)	< 0.001	0.69 (0.39 – 1.21)	0.197
	No	146	750					
History of severe traumatic injury	Yes	45	156	3.27	1.42 (0.97 – 2.08)	0.071	0.77 (0.50 – 1.20)	0.248
	No	133	654					
Currently consumes tobacco	Yes	36	60	27.26	3.16 (2.02 – 4.97)	< 0.001	1.85 (1.02 – 3.32)	0.041
	No	142	749					

Prevalence of self-reported CPD lifetime use among patients accessing mental health services

Of the 1275 participants, 119 (9.3 %) reported having ever used CPDs in their lifetime. Most exposure was to diazepam, tramadol capsules, codeine, oral morphine, tramadol injection and amphetamine in descending order (**Supplementary Table 3**). Among those who reported CPD lifetime use, about 25% first used the drug without medical authorization either through self-prescription or friends' influence (**Supplementary Table 4**). Lastly, we found that first time CPD use was occasioned by treatment for mental illness and restlessness, operative pain and lack of sleep, and pressure from friends (**Supplementary Table 5**).

Predictors of self-reported CPD lifetime use among patients accessing mental health services

After controlling for age, sex, employment status, history of traumatic injury and current tobacco consumption, education level and history of treatment at a substance abuse facility were associated with self-reported CPD lifetime use (**Table 6**). The odds of CPD lifetime use were significantly higher among patients educated beyond secondary school and those with history of treatment at a substance abuse facility.

Table 6. Predictors of self-reported CPD lifetime use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		Self-reported CPD use	No self-reported CPD use					
Type of patient	Outpatient	88	930	2.83	0.69 (0.45 – 1.07)	0.094	0.82 (0.51 – 1.33)	0.422
	Inpatient	31	226					
Marital status	Married	28	331	1.39	0.77 (0.49 – 1.19)	0.240	0.71 (0.44 – 1.13)	0.145
	Single	91	825					
Education level	Beyond secondary school	52	244	30.89	2.90 (1.97 – 4.28)	< 0.001	2.71 (1.81 – 4.08)	< 0.001
	Secondary school and below	67	912					
Ever been treated at a substance abuse facility	Yes	19	85	10.74	2.40 (1.40 – 4.11)	0.018	2.08 (1.14 – 3.80)	0.018
	No	99	1063					
History of chronic back pain	Yes	16	213	1.83	0.69 (0.40 – 1.19)	0.179	0.77 (0.43 – 1.36)	0.366
	No	103	942					
Has sickle cell disease	Yes	1	2	2.04	4.89 (0.44 – 54.28)	0.197	6.17 (0.47 – 76.72)	0.157
	No	118	1153					

Discussion

Understanding the interplay between mental disorders and CPD nonmedical use can enable improvements in mental health treatment outcomes. We found a high prevalence of CPD nonmedical use among patients with mental disorders using both document review (11.4%) and urine assays (17%). This prevalence is two-to-three fold the 5.5% global prevalence of controlled drug nonmedical use in the general population. [42] Similar findings have been reported elsewhere. In Australia, 11.3% of schizophrenia outpatients had lifetime history of prescription drug use disorder and 27.8% tested positive to recent controlled drug use. [30] A recent meta-analysis of stimulant use disorders in hospital patients with psychosis generated a pooled prevalence of 13.9%. [43] These and our data suggest that having a mental illness provides similar risk for controlled drug abuse in different socio-economic and geographical settings.

Controlled drug nonmedical use exacerbates HIV transmission and mental disorders. [12, 16] Thus, controlled drug nonmedical use among Uganda's mental health patients needs mitigation. Multipronged strategies could achieve this, including deployment of rapid drug assays for enhanced detection of controlled drug nonmedical use and strengthening CPD regulation. Uganda's specialist mental health clinics lack assay kits for controlled drugs and rely on clinical screening/assessment to identify controlled drug nonmedical use [44] yet assays are important because patients commonly conceal drug use in fear of legal, social and cultural repercussions. [13, 16, 19] We found that clinical screening had missed about 70% of patients taking CPDs and illicit drugs. In Australia, urine assay detected drugs in one third of patients who had reported zero recent drug use. [30] Therefore, clinical screening alone precludes many patients with drug use disorders from receiving care. Besides, there is need to understand how mental patients obtain

CPDs for nonmedical use considering that Uganda's laws restrict supply to doctor authorized prescriptions. [45, 46]

Nonmedical use of controlled drugs among patients accessing mental health services in Uganda involved mostly benzodiazepines and illicit cannabis. Benzodiazepines were particularly popular, with a total prevalence of 16.1%, five times that of cannabis at 3.3%. Our cannabis use findings are lower than the 17% reported previously among mental health patients by Vudriko and coworkers. [44] Comparison of our prevalence for recent and historical controlled drug use showed a similar pattern. Benzodiazepines still dominated the historical prevalence at 11.4% followed by cannabis at a distant 2.9%. For both current and historical nonmedical use, opioids were far less involved than in high income settings. [30, 47]

Although benzodiazepines nonmedical use is elevated in psychiatric patients globally, [48] there is high variation in dominant drug classes by country. Among inpatient psychiatric patients in Germany, benzodiazepines had the highest prevalence among those with drug use disorders followed by barbiturates, psychostimulants and opioids. [47] In contrast, an Australian study of psychosis outpatients had cannabis leading lifetime nonmedical use ahead of amphetamines, benzodiazepines and opioids. [30] Cannabis still led in recent use prevalence in that study followed by benzodiazepines, opioids and amphetamines. [30] The prevalence of amphetamine nonmedical use in Uganda's psychiatric patients falls short of the global prevalence of stimulant use disorders in this population which is 8.9% with highs of 30%. [43] Similarly, the 0.1% prevalence of prescription opioid nonmedical use among Uganda's mental patients contrasts with the prevalence of chronic opioid use of 8.6 to 11% in the U.S. [21] Lastly, the drug class use pattern among Uganda's mental patients differs from global profiles for the general population. Globally, cannabis leads in controlled drug nonmedical use followed by amphetamines. [36] In the

U.S, opioids top tranquilizers and stimulants. [7, 49] In Europe, sedatives edge opioids and stimulants. [3] In Nigeria, cannabis leads followed by prescription opioids; sedatives and amphetamines score low. [13]

The high burden of benzodiazepine nonmedical use transcends 60 countries. [11] As central nervous system depressants, benzodiazepines cause fatal interactions with other CNS suppressants like opioids, other sedatives, hypnotics, neuroleptics and alcohol. They are involved in 30% of prescription drug related deaths, trailing only opioids at 75%. [19] Benzodiazepines have also been implicated in 80% of accidental opioid-related overdose deaths in some settings. [19] Therefore, the high burden of benzodiazepine nonmedical use in Uganda's psychiatric patients raises concerns on medication safety.

We found that being inpatients favored CPD nonmedical use, and that being inpatients and tobacco consumption favored CPD nonmedical and illicit drug use combined. Typically, it is severely ill patients who are admitted into inpatient care. Therefore, there could be a role of CPD nonmedical use in severe mental illnesses in Uganda. Tobacco consumption is a known gateway to nonmedical controlled drug use. [37] Elevated odds of CPD nonmedical and illicit drug use among tobacco consumers have been reported in several studies. [21, 30, 31, 34, 38] Routine clinical screening and urine assays of these high risk categories of patients for CPD nonmedical use are necessary. In chronic pain patients, random drug testing significantly reduced the prevalence of illicit drug use. [50] Combination of baseline and random periodic drug testing is another option. [19]

Lifetime use of CPDs was also disproportionately high for benzodiazepines among patients with mental disorders in Uganda. Problematic CPD use is typically ignited by index exposure through medical prescription or unauthorized channels like recreation and social

networks. [1, 21, 51, 52] History of CPD lifetime use strongly predicts nonmedical use. [35, 51] The U.S opioid crisis is attributed to the exponential rise in opioid prescriptions for chronic pain. [7, 22, 52, 53] Therefore, high exposure to benzodiazepines among Uganda's psychiatric patients ought to be mitigated. Vigilant screening of patients for drug use disorder risk, education of clinicians on judicious prescribing and dispensers on appropriate dispensing, tight control of CPD access, and prescription drug monitoring programmes are necessary. [10, 53-57]

High formative education and previous treatment at a substance abuse facility favored lifetime use. Highly educated people are possibly more exposed to stressful situations, are more aware of the effects and availability of CPDs, or have higher access to these drugs than other people. However, previous studies have reported inconsistent relationships between education level and CPD nonmedical use. One study of patients on prescribed chronic opioid therapy found that low education level independently favored opioid use disorders [26] while studies of benzodiazepine use disorders found no association. [23, 58] Meanwhile, nonmedical use of one controlled drug or substance typically culminates into use of other drugs and/or poly-drug use. [23, 31, 32, 34, 51, 59] Therefore, high level vigilance in clinical screening is needed to ensure CPD nonmedical use is not missed in mentally ill patients previously treated for substance abuse.

The high burden of CPD nonmedical use among patients with mental disorders suggests that vigilance and professionalism in their prescription and control needs improvement. It would also be useful to investigate how the sole use of clinical screening/assessment impacts mental health treatment outcomes in Uganda. There is also need for enhanced vigilance in clinical and laboratory screening of high risk patient categories identified here.

This study derives strengths in the high power of the sample, fair representation of different psychiatric disorders and patient categories (inpatients, outpatients), and wide geographical coverage of Uganda. Further strength derives from the combined use of patient records and urine assays to detect nonmedical use. We used a convenience sample of only those patients attending public mental clinics which excluded those outside care and those attending private mental health clinics. Affluent patients and those with institutional health insurance have broad choice of care providers and could be underrepresented at public clinics, yet they are the ones most likely to afford CPDs. A study of CPD nonmedical use among patients at private mental clinics is necessary. Our study sites were also in large urban centres where access to CPDs is easy. It is possible that a different pattern of CPD nonmedical and illicit drug use could be observed among patients from rural settings where CPD supply is limited. Furthermore, not all the 1275 study participants provided urine, although the 988 who did so was still large. Lastly, we did not investigate if the CPD nonmedical use was problematic or not.

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Supplementary data: Supplementary Table 1, Supplementary Table 2, Supplementary Table 3, Supplementary Table 4, Supplementary Table 5.

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participant's next-of kin or caring nurse and assent from the participant were obtained prior to administration of the study tools.

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Supplementary Table 1. Distribution of urine detected CPD nonmedical and substance use by mental disorder

Mental disorder[1]	Sample size, N	Frequency n (%)
Psychotic disorders	323	21.4%
Mood disorders	378	19.3%
Other disorders	86	18.6%
Substance use disorders	23	87.0%

[1]Psychotic disorders included diagnoses of schizophrenia, psychosis, substance or drug-induced psychosis, alcohol-induced psychosis, HIV-related psychosis, brief psychosis, psychotic depression, delusional disorders, paranoid psychosis, and schizoaffective disorder. Mood disorders included depression, hypomania, bipolar affective disorder, bipolar disorder. Other disorders included epilepsy/seizures (predominantly), dementia, and mental retardation.

Supplementary Table 2. Overlap of patients who self-reported CPD lifetime use, those with documented CPD nonmedical and illicit drug use, and those with positive CPD and illicit drug urine assay

Data description	Sample size, N	Frequency (%)
Proportion of patients with CPD nonmedical and illicit drug use combined by urine assay who had documented history of CPD nonmedical and illicit drug use	178	55 (30.9%)
Proportion of patients with CPD nonmedical use only by urine assay who had documented history of CPD nonmedical use	166	50 (30.1%)
Proportion of patients with CPD nonmedical use by urine assay who self-reported CPD lifetime use	166	16 (9.6%)
Proportion of all patients with positive CPD urine drug assay who self-reported CPD lifetime use	300	34 (11.3%)
Proportion of patients with documented CPD nonmedical and illicit drug use who self-reported CPD lifetime use	181	41 (22.7%)

Supplementary Table 3. Self-reported lifetime CPD use among patients accessing mental health services in Uganda

Controlled prescription drug[1]	Sample size, N	Frequency n (%)
Morphine injection	1274	6 (0.5%)
Oral morphine	1274	7 (0.6%)
Codeine tablets	1273	9 (0.7%)
Oxycodone	1274	2 (0.2%)
Hydrocodone	1272	1 (0.1%)
Pethidine injection	1274	4 (0.3%)
Tramadol injection	1273	6 (0.5%)
Oral tramadol (tablets or capsules)	1272	16 (1.3%)
Amphetamine	1274	6 (0.5%)
Ketamine	1273	1 (0.1%)
Propofol	1272	1 (0.1%)
Oxycontin	1273	1 (0.1%)
Phenobarbitone	1274	3 (0.2%)
Diazepam	1273	95 (7.5%)
Alprazolam	1273	1 (0.1%)
Bromazepam	1274	4 (0.3%)

[1]Exposure to methamphetamine, fentanil, alfentanil, sufentanil, amorbabital and secobarbital was also assessed but yielded zero prevalence.

Supplementary Table 4. Distribution of psychiatric patients with lifetime CPD use by channel of index exposure

Channel of index exposure	Sample size, N	Frequency n (%)
Doctor prescribed the drug	110	81 (73.6%)
Friends' influence[1]	110	17 (15.5%)
Self-prescription[1]	110	12 (10.9%)

[1]A total of 26.4% of the patients had been introduced to CPDs without doctor's authorization.

Supplementary Table 5. Distribution of indications for index exposure to CPDs by psychiatric patients

Indication	Sample size, N	Frequency n (%)
Was stressed by work	111	3 (2.7%)
Was stressed by family problems	111	5 (4.5%)
Was in pain, was operated	111	19 (17.1%)
Had mental illness, was restless	111	53 (47.7%)
Was influenced by pressure from friends	111	11 (9.9%)
Lacked sleep	111	19 (17.1%)
Had flu	111	1 (0.9%)

COMPLIANCE WITH STROBE CHECKLIST

Our manuscript satisfies the requirements of the STROBE checklist for cross-sectional studies as shown below.

Manuscript section		Requirement	Has the requirement been satisfied?
Title and abstract	1	a) Indicate the study's design with a commonly used term in the title or the abstract b) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes; page 1 Yes; page 2-3
Introduction			
	2	**Background/rationale**: Explain the scientific background and rationale for the investigation being reported	Yes; page 4-6
	3	**Objectives**: State specific objectives, including any prespecified hypotheses	Yes; page 5-6
Methods			
	4	**Study design**: Present key elements of study design early in the paper	Yes, this was done; page 6
	5	**Setting**: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, this was done; page 6
	6	**Participants**: (*a*) Give the eligibility criteria, and the sources and methods of selection of Participants	Yes, this was done; page 7
	7	**Variables**: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, outcome and predictor variables were defined; page 8
	8	**Data sources/measurement**: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, this was done; page 7-8
	9	**Bias**: Describe any efforts to address potential sources of bias	Yes. Used multiple methods to answer the same question; page 7-8
	10	**Study size**: Explain how the study size was arrived at	Yes. Sample size calculation was described; page 6-7
	11	**Quantitative variables**: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, this was done; page 8
	12	**Statistical methods**: a) Describe all statistical methods, including those used to control for confounding	Yes, this was done; page 9
		b) Describe any methods used to examine subgroups and interactions	Not applicable.
		c) Explain how missing data were addressed	Yes, this was done. Individual analyses excluded missing data; page 9
		d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable.
		e) Describe any sensitivity analyses	Not applicable. Interaction

			between predictor variables controlled by inclusion of all those with significant association with outcomes from bivariate analysis into the multivariate model; page 9
Results			
	13	**Participants**: a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes. This was done; page 11
		b) Give reasons for non-participation at each stage	Yes. This has been done; page 11
		c) Consider use of a flow diagram	
	14	**Descriptive data** a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes. This was done; page 11
		b) Indicate number of participants with missing data for each variable of interest	Yes. This was done for each variable; page 11-18
	15	**Outcome data**: Report numbers of outcome events or summary measures	Yes. This was done; 11-18
	16	**Main results** a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes. This was done; page 14, 16, 18
		b) Report category boundaries when continuous variables were categorized	Yes. This was done; page 11, 16
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.
	17	**Other analyses**: Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable.
Discussion			
	18	**Key results**: Summarise key results with reference to study objectives	Yes. This was done for each result; page 19-23
	19	**Limitations**: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes. This was done; page 23
	20	**Interpretation**: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes. This was done; page 19-23
	21	**Generalizability**: Discuss the generalisability (external validity) of the study results	Yes. This was done; page 23
Other information			
	22	**Funding**: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes. This was done; page 24

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Predictors of controlled prescription drug nonmedical and lifetime use among patients accessing public mental health services in Uganda: a cross-sectional study

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Abstract

Objectives: We determined the prevalence of controlled prescription drug (CPD) nonmedical and lifetime use and their predictors among patients at three public mental clinics in Uganda to identify missed care opportunities, enhanced screening priorities, and drug control needs.

Methods: A cross-sectional survey of 1275 patients was performed from November to December, 2018. Interviewer-administered semi-structured questionnaires, desk review guide, and urine drug assays were employed. Questionnaire recorded CPD nonmedical and illicit drug use history from patients' files, CPD lifetime use, and risk factors. Desk review guide recorded recently prescribed drugs in patients' files to corroborate with urine assays. Predictors were analyzed by multivariate logistic regression.

Results: From desk review, 145 (11.4%) patients had history of CPD nonmedical use and 36 (2.8%) had used illicit drugs. Of 988 patients who provided urine, 166 (16.8%) self-medicated CPDs, particularly benzodiazepines while 12 (1.2%) used illicit drugs. Of those with drug-positive urine, 123 (69.1%) had no documented history of CPD nonmedical and illicit drug use. Being an inpatient (OR = 10.90, $p < 0.001$) was independently associated with CPD nonmedical use. Additionally, being an inpatient (OR = 8.29, $p < 0.001$) and tobacco consumption (OR = 1.85, $p = 0.041$) were associated with CPD nonmedical and illicit drug use combined. Among participants, 119 (9.3%) reported CPD lifetime use, and this was independently associated with education level (OR = 2.71, $p < 0.001$) and history of treatment for substance abuse (OR = 2.08, $p = 0.018$).

Conclusions: CPD nonmedical use is common among Uganda's psychiatric patients, and more prevalent than illicit drug use. Rapid diagnostic assays may be needed in psychiatric care in

resource limited settings. It is necessary to assess how CPD nonmedical use impacts mental care outcomes and patient safety. High risk groups like inpatients and tobacco consumers should be prioritized in psychiatric screening.

Strengths and limitations of this study

- A major strength of this study is the large sample size (high power), fair representation of different psychiatric disorders and patient categories (inpatients versus outpatients) in the sample, and wide geographical coverage of Uganda.
- It also derives strength from the combined use of patient records and urine drug assays to detect nonmedical use.
- It is the first study of controlled prescription drug nonmedical use and its predictors in any population group in Uganda and most of sub-Saharan Africa.
- One limitation is that we used a convenience sample of only psychiatric patients attending public clinics which excluded those who are not in care and those who attend private clinics.
- We did not investigate if the CPD nonmedical use was a drug use disorder or not, which limits our insights on the impact of the observed behavior on mental health outcomes.

Background

Drugs that moderate the function of the central nervous system such as opioids, stimulants, sedatives, hypnotics and anaesthetics are the backbone of modern operative surgery, mental health and neurology. However, these drugs induce such strong reward feelings that they are prone to nonmedical use in which they are consumed without prescriber authorization, in unapproved doses and routes of administration, and for nontherapeutic causes. [1-3] Consequently, these drugs are judiciously controlled to prevent nonmedical use, hence the synonym controlled prescription drugs (CPDs). [4-6]As seen in the prescription opioid and amphetamine-group (amphetamine and methamphetamine) drugs nonmedical use escalations in high income countries, [7-12] deterrence of CPD nonmedical use can be difficult. Less economically endowed countries have not been spared too. Among Nigeria's 98 million of 15 – 64 year olds, a recent household survey found that 4.7% had engaged in prescription opioid nonmedical use in the past year, accounting for 32% of all nonmedical drug use in the country. [13] There are also escalations in nonmedical use of methamphetamine in South Africa [12, 14] and tramadol in West and North Africa. [15] Globally, at least 60 countries have a high burden of benzodiazepine nonmedical use. [11]

Nonmedical CPD use produces devastating health outcomes like neurological impairment and severe mental disorders. [8, 16] Opioid nonmedical use exacerbates the prevalence of suicides and common mental disorders while amphetamines cause drug-induced psychosis, anxiety, and depression. [8, 16]Independent association has been reported between drug dependence and psychiatric disorders in HIV-infected patients. [17] A higher risk of incident psychosis has also been reported among patients with attention deficit-hyperactivity disorder on medically prescribed amphetamine treatment compared to methylphenidate. [18] Meanwhile, benzodiazepines

fatally interact with other CNS suppressants and are involved in 30% of prescription drug related deaths, trailing only opioids at 75%. [19] In some settings, benzodiazepines play a part in 80% of accidental opioid-related overdose deaths. [19]

Intriguingly, mental disorders exacerbate the propensity for CPD nonmedical and illicit drug use. [20-22] A strong association between severe mental distress and benzodiazepine use disorders has been reported among club dwellers in Florida. [23] Problem drug use, depressive and other psychiatric disorders, and post-traumatic stress disorder increase likelihood of opioid nonmedical use. [20-22, 24] There is also association between mental disorders and lifetime prescription opioid use. A longitudinal U.S study found association between common mental disorders and prescription opioid use, and between problem drug use and prescription opioid use. [25] In HIV patients, independent associations between psychiatric disorders and drug dependence [17] and between depression and repeat opioid prescriptions [24] have been recorded. Association of depression, anxiety disorders, panic attacks and posttraumatic stress disorder with prescription opioid nonmedical use has also been reported among patients on chronic opioid therapy and injection drug users. [26-29] Elsewhere, a study of 194 outpatients with schizophrenia in Australia found high levels of substance and drug nonmedical use with prevalence of 26.8% and 59.8% in the last 6 months and lifetime, respectively. [30]

Thus, mental disorders and CPD nonmedical use feed on each other. If not mitigated, CPD nonmedical use among psychiatric patients may compromise treatment outcomes, medication adherence and quality of life. Critically, nonmedical use of one drug typically increases likelihood of other drug use disorders. [16, 31, 32] Thus, the burden and predictors of CPD nonmedical use in high risk populations ought to be understood. Unfortunately, data on CPD nonmedical use in low income countries is limited, [16] particularly in sub-Saharan Africa. [33]

Therefore, we determined the prevalence of CPD nonmedical and lifetime use among Uganda's mental health patients and associated factors. Factors known to favor CPD nonmedical and illicit drug use in literature informed our conceptual design. These include socio-demographics like age, sex, marital status, religion, employment status, years of schooling; tobacco consumption; alcohol consumption; chronic pain; illicit drug use history; and occupation. [7, 16, 17, 21, 22, 30, 32, 34-38]

Methods

Study design

A cross-sectional survey of CPD nonmedical and lifetime use and associated factors was conducted in a convenience sample of 1275 psychiatric patients at the mental health clinics of three referral hospitals in Uganda in November and December 2018.

Study setting

Study was conducted at Mulago Hospital, Butabika Hospital and Mbale Hospital. Located in Uganda's capital Kampala in Central Uganda, Mulago and Butabika hospitals are the country's two national referral hospitals where the highest level of specialist care is provided. Mbale Hospital is located in the Eastern regional business district of Mbale. All three hospitals provide psychiatric care, though Butabika is the major provider and the national referral mental hospital. Reported annual psychiatric patient attendances are Butabika (6200 inpatients, 56000 outpatients); Mulago (400 inpatients, 800 outpatients); and Mbale (400 inpatients, 2500 outpatients). [39, 40]

Participants

Sample size was computed from a reported study population of patients that attend mental health services of the three hospitals weekly, namely 135 inpatient admissions and 1140 outpatients [39, 40] in two steps. Firstly, the sample size for a homogenous population was

computed using the Cochran formula for categorical data [41] at 5% margin of error, 95% confidence level, and effect prevalence of 40% [21], followed by a Cochran correction. [41] This yielded a sample size of 285 which was finally adjusted to 1277 with a design effect of 4.48 to cater for variation in living environment and severity of mental illness between inpatients and outpatients. Multistage, proportionate stratified sampling was used to distribute the 1277 sample into inpatients and outpatients, and into the three hospitals. The sample was first distributed into 135 inpatients and 1142 outpatients based on literature [39, 40], after which it was adjusted to 257 inpatients and 1020 outpatients to match the prevailing weekly load of each type of patient in the hospitals based on guidance obtained during pre-data collection site visits. Overall, 1275 participants (1196 Butabika, 56 Mbale, 23 Mulago) were enrolled into the study by convenience consecutive sampling based on availability and willingness to participate in the study. All clinician (psychiatrist or psychiatric clinical officer) diagnosed patients attending the mental health clinics during data collection were sampled. Pediatric patients below adolescence (less than 10 years), severely ill and non-speakers of the two widely spoken Ugandan languages in which the questionnaire was written (English and Luganda) were excluded.

Data collection

Data on both CPD nonmedical use and illicit drug use was collected. Illicit drugs are those narcotic and psychotropic drugs that are prohibited from medical use by international law due to higher risk of dependence than benefits.[16]

A combination of interviewer-administered semi-structured questionnaire, urine drug immunoassays, and desk review guide for drugs prescribed for patients in their hospital files was used. The questionnaire inquired into the presence of documented clinician's diagnosis of CPD

nonmedical and illicit drug use in a patient's lifetime in their hospital files, as well as whether a urine sample was provided by the patient for drug analysis. The questionnaire also recorded self-reported history of lifetime use of individual CPDs and how these drugs were introduced to the participants the first time they used them. Drug immunoassays assessed for presence of both CPDs and illicit drugs in a participant's urine. These assays employed the 10-drug vaxpert™ rapid test cups (Vaxpert Onc, Miami, Fl) that detect barbiturates, benzodiazepines, morphine, methadone, amphetamine, methamphetamine, tricyclic antidepressants, methylenedioxymethamphetamine, cocaine and marijuana. The assay uses monoclonal antibodies to detect elevated levels of these drugs and their metabolites. Urine specimen were collected in labeled 120 ml plastic urine bottles, stored in cool boxes and analyzed at the Department of Pharmacy, Makerere University. Test results were read within 5 minutes of adding urine to the vaxpert™ cup. The desk review guide assessed only recent CPD use by recording all medications in the patient's last prescription (from hospital patients' files) and date of last dose. Data from this guide was used to determine if a positive CPD urine assay was due to recent medical use or not. A positive CPD urine result was deemed nonmedical use if desk review guide data had no CPD among drugs in a participant's recent prescription. The questionnaire and review guide were designed by the study team.

The questionnaire also inquired into socio-demographic and other participant attributes that have been associated with controlled drug nonmedical use in previous studies. These include age, sex, marital status, religion, employment status, years of schooling, tobacco consumption, alcohol consumption, chronic pain, illicit drug use history, and occupation. Numerical variables such as

age were collected as individual values after which binary categories for bivariate and multivariate logistic regression were created using the median as cut-off.

Study outcomes

There were three study outcomes: 1) Prevalence of CPD nonmedical use. 2) Prevalence of CPD nonmedical and illicit drug use combined. 3) Prevalence of self-reported CPD lifetime use. We defined CPD nonmedical use in two ways; a) if patient posted a positive urine assay for given CPDs but desk review guide found no medical use of such CPDs in their last prescription; b) if questionnaire found a documented clinician's diagnosis of CPD drug use disorder in a patient's lifetime in their hospital files. Illicit drug use was also defined in two ways; a) all patients with positive urine assays for any illicit drug; b) if questionnaire found a documented clinician's diagnosis of illicit drug use disorder in a patient's lifetime in their hospital files.

Self-reported lifetime use was measured using a checklist of 22 commonly prescribed CPD products, comprising 12 opioids, two amphetamine-group products, two intravenous anaesthetics, three barbiturates and three benzodiazepines. A patient had self-reported CPD lifetime use if they responded affirmatively as having ever used at least one of the 22 CPD products.

Data analyses

A single data entry template merging the questionnaire and desk review guide was created in EpiData 3.1, followed by data entry. Before entry, desk review guide data on drugs recently prescribed in the patients' files was examined by the first author and the drugs documented

therein were categorized as CPD or not, along with the class of the CPD (opioids, benzodiazepines, barbiturates, amphetamines, anaesthetics). After data entry, the dataset was cleaned and transcribed into SPSS 13. Final data cleaning, descriptive analysis and bivariate analysis of predictors of CPD nonmedical use and lifetime use was done in SPSS. We then transcribed SPSS data into STATA 12 after which multivariate logistic regression was done. Regression analysis was guided by a conceptual framework informed by literature. Multivariate regression employed backward elimination in which factors with statistically significant associations from bivariate analysis were fixed while sequentially removing those with weak associations from the multivariate model until only those with p-values less than 0.5 remained. All cases with missing data on a given variable were excluded from analyses involving that variable.

Patient and public involvement

The public was involved in the design of study as the institutional review Board and Uganda National Council of Science and Technology guided improvements in the protocol before approval. Authorities from the study sites also recommended further refinements in the study protocol before issuing administrative clearance. Patients were involved in assessing the risks of the study during consenting.

Results

Responses were received from 1275 participants of which 988 (77.5%) volunteered urine samples for CPD screening. Among these, 1196 were from Butabika, 23 were from Mulago, and 56 were from Mbale hospitals.

Characteristics of participants

As shown in **Table 1**, most participants were outpatients of Christian faith, single marital status, peasants, informal sector workers, and greater than 25 years of age. There was fair distribution of participants by sex and employment status.

Table 1. Characteristics of study participants

Characteristic	Category	Sample size, N	Frequency n (%)
Sex of patient	Male	1275	681 (53.4%)
	Female	1275	594 (46.6%)
Age of patient	≤ 25	1275	290 (22.7%)
	>25	1275	985 (77.3%)
Type of patient	Inpatient	1275	257 (20.2%)
	Outpatient	1275	1018 (79.8%)
Religious background of patient	Christian	1275	1071 (84.0%)
	Muslim	1275	198 (15.5%)
	Other	1275	6 (0.5%)
Marital status of patient	Single	1275	916 (71.8%)
	Married	1275	359 (28.2%)
Highest education level	Secondary school and below	1275	979 (76.8%)
	Beyond secondary school	1275	296 (23.2%)
Employment status	Employed	1272	554 (43.6%)
	Unemployed	1272	718 (56.4%)
Most represented occupations	Peasant, informal sector	1275	654 (51.3%)
	Student	1275	80 (6.3%)
	Teacher	1275	57 (4.5%)
	Driver	1275	23 (1.8%)
	Security/armed forces	1275	21 (1.6%)
	Administrator	1275	20 (1.6%)
	Medical worker	1275	20 (1.6%)
Urine specimen provided	Yes	1275	988 (77.5%)
	No	1275	287 (22.5%)

Prevalence of CPD nonmedical use among patients accessing mental health services

Hospital files for 1267 of the 1275 participants enrolled into the study were examined for history of clinician's diagnosis of CPD nonmedical and/or illicit drug use in patient's lifetime. Files for

eight participants were not accessible. We found that 181 (14.3%) of the participants had history of clinician's diagnosed CPD nonmedical and illicit drug use disorders of which 144 (11.4%) had CPD nonmedical use only, 1 (0.08%) had both CPD nonmedical and illicit drug use and 36 (2.8%) had illicit drug use only, particularly cannabis. Among the CPDs, highest nonmedical consumption was with benzodiazepines, alone or in combination with opioids and illicit drugs (**Table 2**).

Table 2. Prevalence of documented CPD nonmedical and illicit drug use by drug class

Drug class	Sample size, N	Frequency n (%)
Opioids[1]	1267	1 (0.1%)
Benzodiazepines[2]	1267	142 (11.2%)
Opioids plus Benzodiazepines[3]	1267	1 (0.1%)
Benzodiazepines plus illicit drugs[4]	1267	1 (0.1%)
Illicit drugs[5]	1267	36 (2.8%)

[1]Three were documented for same patient, namely, pethidine, morphine and tramadol. [2]Only diazepam was documented. [3]This was a case of dual use of diazepam and codeine. [4]This was a case of dual use of diazepam and khat. [5]Of the 36 cases, 24 (66.7%) are cannabis, 7 (19.4%) are cannabis and khat, 3 (8.3%) are khat, 1 (2.8%) is heroine, and 1 (2.8%) is unspecified illicit substance.

Among the 988who provided urine, 166 (16.8%) who had not been recently prescribed any CPDs in their hospital records tested positive for these drugs. Another 12 (1.2%) participants tested positive for illicit drugs, mainly Δ9-tetrahydrocannabinol, a constituent of illicit cannabis. The overall burden of CPD nonmedical and illicit drug use combined was 178 (18.0%) of the 988 participants. When categorized by mental disorder diagnosis documented in patients' files,

the prevalence of CPD nonmedical and illicit drug use combined was similar but slightly higher among patients with psychotic disorders than those with mood and other non-drug induced disorders (**Supplementary Table 1**).

Among the CPDs, the highest nonmedical consumption detected in urine was for benzodiazepines, alone and occasionally in combination with barbiturates and illicit drugs (**Table 3**). Out of the 178 patients with CPD nonmedical and illicit drug use by urine assay, 22 (12.4%) had multiple controlled drugs, particularly benzodiazepines and cannabis. On further analysis, 123 (69.1%) of the drug positive urine was from patients with no documented history of clinician's diagnosed CPD nonmedical and illicit drug use in their lifetime (**Supplementary Table 2**).

Table 3. Prevalence of urine detected CPD nonmedical and illicit drug use by drug class

Drug class	Sample size, N	Frequency n (%)
Opioids	988	1 (0.1%)
Amphetamines	988	3 (0.3%)
Amphetamines plus illicit drugs[1,2]	988	1 (0.1%)
Benzodiazepines	988	138 (14.0%)
Barbiturates	988	2 (0.2%)
Benzodiazepines plus barbiturates[3]	988	1 (0.1%)
Benzodiazepines plus illicit drugs[1,2,3]	988	20 (2.0%)
Illicit drugs[1,4]	988	12 (1.2%)

[1]Assay tested for Δ9-tetrahydrocannabinol (THC), cocaine and methylenedioxymethamphetamine (MDMA). [2]THC was the illicit drug in both. Among the 166 who tested positive for CPD nonmedical use, the prevalence is 159 (95.8%) benzodiazepines, 4 (2.4%) amphetamines, 3 (1.8%) barbiturates and 1 (0.6%) opioids. [3]A total of 21 (13.2%) of the 159 participants with benzodiazepines tested positive for other controlled drugs. [4]Of these, 10 and 2 participants tested positive for THC and MDMA, respectively.

Predictors of urine-positive CPD nonmedical use among patients accessing mental health services

After controlling for sex and current alcohol consumption, the type of patient was independently associated with urine-positive CPD nonmedical use (**Table 4**). The odds of urine-positive CPD nonmedical use were significantly higher among inpatients than outpatients.

Table 4. Predictors of urine-positive CPD nonmedical use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		CPD nonmedical use	No CPD nonmedical use					
Type of patient	Inpatient	109	120	202.25	11.19 (7.69 – 16.27)	< 0.001	10.90 (7.25 – 16.38)	< 0.001
	Outpatient	57	702					
Employment status	Employed	82	368	1.14	1.20 (0.86 – 1.67)	0.286	1.30 (0.87 – 1.94)	0.195
	Unemployed	84	452					
History of treatment at substance abuse facility	Yes	29	58	18.71	2.79 (1.73 – 4.52)	< 0.001	0.72 (0.41 – 1.28)	0.265
	No	136	760					
History of traumatic injury	Yes	42	159	3.03	1.41 (0.96 – 2.09)	0.082	0.79 (0.50 – 1.25)	0.308
	No	124	663					
History of chronic back pain	Yes	36	164	0.26	1.11 (0.74 – 1.67)	0.612	0.81 (0.50 – 1.30)	0.375
	No	130	658					
Currently consumes tobacco	Yes	36	60	23.43	2.99 (1.89 – 4.73)	< 0.001	1.68 (0.91 – 3.09)	0.096
	No	142	749					

Predictors of urine-positive CPD nonmedical and illicit drug use combined among patients accessing mental health services

After controlling for sex and current alcohol consumption, the type of patient and current tobacco consumption were independently associated with urine-positive CPD nonmedical and illicit drug use combined (**Table 5**). The odds of urine-positive CPD nonmedical and illicit drug use combined were significantly higher among inpatients and those with current tobacco consumption than their corresponding counterparts.

Table 5. Predictors of CPD nonmedical and illicit drug use combined among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		CPD nonmedical & illicit drug use	No CPD nonmedical & illicit drug use					
Age in years	≤ 25	54	174	6.45	1.59 (1.11 – 2.28)	0.012	1.44 (0.95 – 2.19)	0.089
	> 25	124	636					
Type of patient	Inpatient	110	119	181.86	9.39 (6.56 – 13.46)	< 0.001	8.29 (5.62 – 12.22)	< 0.001
	Outpatient	68	691					
Employment status	Employed	88	362	1.26	1.20 (0.87 – 1.67)	0.261	1.21 (0.82 – 1.78)	0.340
	Unemployed	90	446					
History of treatment at substance abuse facility	Yes	31	56	20.09	2.84 (1.77 – 4.56)	< 0.001	0.69 (0.39 – 1.21)	0.197
	No	146	750					
History of severe traumatic injury	Yes	45	156	3.27	1.42 (0.97 – 2.08)	0.071	0.77 (0.50 – 1.20)	0.248
	No	133	654					
Currently consumes tobacco	Yes	36	60	27.26	3.16 (2.02 – 4.97)	< 0.001	1.85 (1.02 – 3.32)	0.041
	No	142	749					

Prevalence of self-reported CPD lifetime use among patients accessing mental health services

Of the 1275 participants, 119 (9.3 %) reported having ever used CPDs in their lifetime. Most exposure was to diazepam, tramadol capsules, codeine, oral morphine, tramadol injection and amphetamine in descending order (**Supplementary Table 3**). Among those who reported CPD lifetime use, about 25% first used the drug without medical authorization either through self-prescription or friends' influence (**Supplementary Table 4**). Lastly, we found that first time CPD use was occasioned by treatment for mental illness and restlessness, operative pain and lack of sleep, and pressure from friends (**Supplementary Table 5**).

Predictors of self-reported CPD lifetime use among patients accessing mental health services

After controlling for age, sex, employment status, history of traumatic injury and current tobacco consumption, education level and history of treatment at a substance abuse facility were associated with self-reported CPD lifetime use (**Table 6**). The odds of CPD lifetime use were significantly higher among patients educated beyond secondary school and those with history of treatment at a substance abuse facility.

Table 6. Predictors of self-reported CPD lifetime use among patients accessing mental health services in Uganda

Factor	Category	Frequency (n)		χ^2	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
		Self-reported CPD use	No self-reported CPD use					
Type of patient	Outpatient	88	930	2.83	0.69 (0.45 – 1.07)	0.094	0.82 (0.51 – 1.33)	0.422
	Inpatient	31	226					
Marital status	Married	28	331	1.39	0.77 (0.49 – 1.19)	0.240	0.71 (0.44 – 1.13)	0.145
	Single	91	825					
Education level	Beyond secondary school	52	244	30.89	2.90 (1.97 – 4.28)	< 0.001	2.71 (1.81 – 4.08)	< 0.001
	Secondary school and below	67	912					
Ever been treated at a substance abuse facility	Yes	19	85	10.74	2.40 (1.40 – 4.11)	0.018	2.08 (1.14 – 3.80)	0.018
	No	99	1063					
History of chronic back pain	Yes	16	213	1.83	0.69 (0.40 – 1.19)	0.179	0.77 (0.43 – 1.36)	0.366
	No	103	942					
Has sickle cell disease	Yes	1	2	2.04	4.89 (0.44 – 54.28)	0.197	6.17 (0.47 – 76.72)	0.157
	No	118	1153					

Discussion

Understanding the interplay between mental disorders and CPD nonmedical use can enable improvements in mental health treatment outcomes. We found a high prevalence of CPD nonmedical use among patients with mental disorders using both document review (11.4%) and urine assays (17%). This prevalence is two-to-three fold the 5.5% global prevalence of controlled drug nonmedical use in the general population. [42] Similar findings have been reported elsewhere. In Australia, 11.3% of schizophrenia outpatients had lifetime history of prescription drug use disorder and 27.8% tested positive to recent controlled drug use. [30] A recent meta-analysis of stimulant use disorders in hospital patients with psychosis generated a pooled prevalence of 13.9%. [43] These and our data suggest that having a mental illness provides similar risk for controlled drug abuse in different socio-economic and geographical settings.

Controlled drug nonmedical use exacerbates HIV transmission and mental disorders. [12, 16] Thus, controlled drug nonmedical use among Uganda's mental health patients needs mitigation. Multipronged strategies could achieve this, including deployment of rapid drug assays for enhanced detection of controlled drug nonmedical use and strengthening CPD regulation. Uganda's specialist mental health clinics lack assay kits for controlled drugs and rely on clinical screening/assessment to identify controlled drug nonmedical use [44] yet assays are important because patients commonly conceal drug use in fear of legal, social and cultural repercussions. [13, 16, 19] We found that clinical screening had missed about 70% of patients taking CPDs and illicit drugs. In Australia, urine assay detected drugs in one third of patients who had reported zero recent drug use. [30] Therefore, clinical screening alone precludes many patients with drug use disorders from receiving care. Besides, there is need to understand how mental patients obtain

CPDs for nonmedical use considering that Uganda's laws restrict supply to doctor authorized prescriptions. [45, 46]

Nonmedical use of controlled drugs among patients accessing mental health services in Uganda involved mostly benzodiazepines and illicit cannabis. Benzodiazepines were particularly popular, with a total prevalence of 16.1%, five times that of cannabis at 3.3%. Our cannabis use findings are lower than the 17% reported previously among mental health patients by Vudriko and coworkers. [44] Comparison of our prevalence for recent and historical controlled drug use showed a similar pattern. Benzodiazepines still dominated the historical prevalence at 11.4% followed by cannabis at a distant 2.9%. For both current and historical nonmedical use, opioids were far less involved than in high income settings. [30, 47]

Although benzodiazepines nonmedical use is elevated in psychiatric patients globally, [48] there is high variation in dominant drug classes by country. Among inpatient psychiatric patients in Germany, benzodiazepines had the highest prevalence among those with drug use disorders followed by barbiturates, psychostimulants and opioids. [47] In contrast, an Australian study of psychosis outpatients had cannabis leading lifetime nonmedical use ahead of amphetamines, benzodiazepines and opioids. [30] Cannabis still led in recent use prevalence in that study followed by benzodiazepines, opioids and amphetamines. [30] The prevalence of amphetamine nonmedical use in Uganda's psychiatric patients falls short of the global prevalence of stimulant use disorders in this population which is 8.9% with highs of 30%. [43] Similarly, the 0.1% prevalence of prescription opioid nonmedical use among Uganda's mental patients contrasts with the prevalence of chronic opioid use of 8.6 to 11% in the U.S. [21] Lastly, the drug class use pattern among Uganda's mental patients differs from global profiles for the general population. Globally, cannabis leads in controlled drug nonmedical use followed by amphetamines. [36] In the

U.S, opioids top tranquilizers and stimulants. [7, 49] In Europe, sedatives edge opioids and stimulants. [3] In Nigeria, cannabis leads followed by prescription opioids; sedatives and amphetamines score low. [13]

The high burden of benzodiazepine nonmedical use transcends 60 countries. [11] As central nervous system depressants, benzodiazepines cause fatal interactions with other CNS suppressants like opioids, other sedatives, hypnotics, neuroleptics and alcohol. They are involved in 30% of prescription drug related deaths, trailing only opioids at 75%. [19] Benzodiazepines have also been implicated in 80% of accidental opioid-related overdose deaths in some settings. [19] Therefore, the high burden of benzodiazepine nonmedical use in Uganda's psychiatric patients raises concerns on medication safety.

We found that being inpatients favored CPD nonmedical use, and that being inpatients and tobacco consumption favored CPD nonmedical and illicit drug use combined. Typically, it is severely ill patients who are admitted into inpatient care. Therefore, there could be a role of CPD nonmedical use in severe mental illnesses in Uganda. Tobacco consumption is a known gateway to nonmedical controlled drug use. [37] Elevated odds of CPD nonmedical and illicit drug use among tobacco consumers have been reported in several studies. [21, 30, 31, 34, 38] Routine clinical screening and urine assays of these high risk categories of patients for CPD nonmedical use are necessary. In chronic pain patients, random drug testing significantly reduced the prevalence of illicit drug use. [50] Combination of baseline and random periodic drug testing is another option. [19]

Lifetime use of CPDs was also disproportionately high for benzodiazepines among patients with mental disorders in Uganda. Problematic CPD use is typically ignited by index exposure through medical prescription or unauthorized channels like recreation and social

networks. [1, 21, 51, 52] History of CPD lifetime use strongly predicts nonmedical use. [35, 51] The U.S opioid crisis is attributed to the exponential rise in opioid prescriptions for chronic pain. [7, 22, 52, 53] Therefore, high exposure to benzodiazepines among Uganda's psychiatric patients ought to be mitigated. Vigilant screening of patients for drug use disorder risk, education of clinicians on judicious prescribing and dispensers on appropriate dispensing, tight control of CPD access, and prescription drug monitoring programmes are necessary. [10, 53-57]

High formative education and previous treatment at a substance abuse facility favored lifetime use. Highly educated people are possibly more exposed to stressful situations, are more aware of the effects and availability of CPDs, or have higher access to these drugs than other people. However, previous studies have reported inconsistent relationships between education level and CPD nonmedical use. One study of patients on prescribed chronic opioid therapy found that low education level independently favored opioid use disorders [26] while studies of benzodiazepine use disorders found no association. [23, 58] Meanwhile, nonmedical use of one controlled drug or substance typically culminates into use of other drugs and/or poly-drug use. [23, 31, 32, 34, 51, 59] Therefore, high level vigilance in clinical screening is needed to ensure CPD nonmedical use is not missed in mentally ill patients previously treated for substance abuse.

The high burden of CPD nonmedical use among patients with mental disorders suggests that vigilance and professionalism in their prescription and control needs improvement. It would also be useful to investigate how the sole use of clinical screening/assessment impacts mental health treatment outcomes in Uganda. There is also need for enhanced vigilance in clinical and laboratory screening of high risk patient categories identified here.

This study derives strengths in the high power of the sample, fair representation of different psychiatric disorders and patient categories (inpatients, outpatients), and wide geographical coverage of Uganda. Further strength derives from the combined use of patient records and urine assays to detect nonmedical use. We used a convenience sample of only those patients attending public mental clinics which excluded those outside care and those attending private mental health clinics. Affluent patients and those with institutional health insurance have broad choice of care providers and could be underrepresented at public clinics, yet they are the ones most likely to afford CPDs. A study of CPD nonmedical use among patients at private mental clinics is necessary. Our study sites were also in large urban centres where access to CPDs is easy. It is possible that a different pattern of CPD nonmedical and illicit drug use could be observed among patients from rural settings where CPD supply is limited. Furthermore, not all the 1275 study participants provided urine, although the 988 who did so was still large. Lastly, we did not investigate if the CPD nonmedical use was problematic or not.

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Patient consent: Obtained.

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Supplementary data: Supplementary Table 1, Supplementary Table 2, Supplementary Table 3, Supplementary Table 4, Supplementary Table 5.

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participant's next-of kin or caring nurse and assent from the participant were obtained prior to administration of the study tools.

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Supplementary Table 1. Distribution of urine detected CPD nonmedical and substance use by mental disorder

Mental disorder[1]	Sample size, N	Frequency n (%)
Psychotic disorders	323	21.4%
Mood disorders	378	19.3%
Other disorders	86	18.6%
Substance use disorders	23	87.0%

[1]Psychotic disorders included diagnoses of schizophrenia, psychosis, substance or drug-induced psychosis, alcohol-induced psychosis, HIV-related psychosis, brief psychosis, psychotic depression, delusional disorders, paranoid psychosis, and schizoaffective disorder. Mood disorders included depression, hypomania, bipolar affective disorder, bipolar disorder. Other disorders included epilepsy/seizures (predominantly), dementia, and mental retardation.

Supplementary Table 2. Overlap of patients who self-reported CPD lifetime use, those with documented CPD nonmedical and illicit drug use, and those with positive CPD and illicit drug urine assay

Data description	Sample size, N	Frequency (%)
Proportion of patients with CPD nonmedical and illicit drug use combined by urine assay who had documented history of CPD nonmedical and illicit drug use	178	55 (30.9%)
Proportion of patients with CPD nonmedical use only by urine assay who had documented history of CPD nonmedical use	166	50 (30.1%)
Proportion of patients with CPD nonmedical use by urine assay who self-reported CPD lifetime use	166	16 (9.6%)
Proportion of all patients with positive CPD urine drug assay who self-reported CPD lifetime use	300	34 (11.3%)
Proportion of patients with documented CPD nonmedical and illicit drug use who self-reported CPD lifetime use	181	41 (22.7%)

Supplementary Table 3. Self-reported lifetime CPD use among patients accessing mental health services in Uganda

Controlled prescription drug[1]	Sample size, N	Frequency n (%)
Morphine injection	1274	6 (0.5%)
Oral morphine	1274	7 (0.6%)
Codeine tablets	1273	9 (0.7%)
Oxycodone	1274	2 (0.2%)
Hydrocodone	1272	1 (0.1%)
Pethidine injection	1274	4 (0.3%)
Tramadol injection	1273	6 (0.5%)
Oral tramadol (tablets or capsules)	1272	16 (1.3%)
Amphetamine	1274	6 (0.5%)
Ketamine	1273	1 (0.1%)
Propofol	1272	1 (0.1%)
Oxycontin	1273	1 (0.1%)
Phenobarbitone	1274	3 (0.2%)
Diazepam	1273	95 (7.5%)
Alprazolam	1273	1 (0.1%)
Bromazepam	1274	4 (0.3%)

[1]Exposure to methamphetamine, fentanil, alfentanil, sufentanil, amorbabital and secobarbital was also assessed but yielded zero prevalence.

Supplementary Table 4. Distribution of psychiatric patients with lifetime CPD use by channel of index exposure

Channel of index exposure	Sample size, N	Frequency n (%)
Doctor prescribed the drug	110	81 (73.6%)
Friends' influence[1]	110	17 (15.5%)
Self-prescription[1]	110	12 (10.9%)

[1]A total of 26.4% of the patients had been introduced to CPDs without doctor's authorization.

Supplementary Table 5. Distribution of indications for index exposure to CPDs by psychiatric patients

Indication	Sample size, N	Frequency n (%)
Was stressed by work	111	3 (2.7%)
Was stressed by family problems	111	5 (4.5%)
Was in pain, was operated	111	19 (17.1%)
Had mental illness, was restless	111	53 (47.7%)
Was influenced by pressure from friends	111	11 (9.9%)
Lacked sleep	111	19 (17.1%)
Had flu	111	1 (0.9%)

COMPLIANCE WITH STROBE CHECKLIST

Our manuscript satisfies the requirements of the STROBE checklist for cross-sectional studies as shown below.

Manuscript section		Requirement	Has the requirement been satisfied?
Title and abstract	1	a) Indicate the study's design with a commonly used term in the title or the abstract b) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes; page 1 Yes; page 2-3
Introduction			
	2	**Background/rationale**: Explain the scientific background and rationale for the investigation being reported	Yes; page 4-6
	3	**Objectives**: State specific objectives, including any prespecified hypotheses	Yes; page 5-6
Methods			
	4	**Study design**: Present key elements of study design early in the paper	Yes, this was done; page 6
	5	**Setting**: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, this was done; page 6
	6	**Participants**: (*a*) Give the eligibility criteria, and the sources and methods of selection of Participants	Yes, this was done; page 7
	7	**Variables**: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, outcome and predictor variables were defined; page 8
	8	**Data sources/measurement**: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, this was done; page 7-8
	9	**Bias**: Describe any efforts to address potential sources of bias	Yes. Used multiple methods to answer the same question; page 7-8
	10	**Study size**: Explain how the study size was arrived at	Yes. Sample size calculation was described; page 6-7
	11	**Quantitative variables**: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, this was done; page 8
	12	**Statistical methods**: a) Describe all statistical methods, including those used to control for confounding	Yes, this was done; page 9
		b) Describe any methods used to examine subgroups and interactions	Not applicable.
		c) Explain how missing data were addressed	Yes, this was done. Individual analyses excluded missing data; page 9
		d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable.
		e) Describe any sensitivity analyses	Not applicable. Interaction

			between predictor variables controlled by inclusion of all those with significant association with outcomes from bivariate analysis into the multivariate model; page 9
Results			
	13	**Participants**: a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes. This was done; page 11
		b) Give reasons for non-participation at each stage	Yes. This has been done; page 11
		c) Consider use of a flow diagram	
	14	**Descriptive data** a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes. This was done; page 11
		b) Indicate number of participants with missing data for each variable of interest	Yes. This was done for each variable; page 11-18
	15	**Outcome data**: Report numbers of outcome events or summary measures	Yes. This was done; 11-18
	16	**Main results** a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes. This was done; page 14, 16, 18
		b) Report category boundaries when continuous variables were categorized	Yes. This was done; page 11, 16
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.
	17	**Other analyses**: Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable.
Discussion			
	18	**Key results**: Summarise key results with reference to study objectives	Yes. This was done for each result; page 19-23
	19	**Limitations**: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes. This was done; page 23
	20	**Interpretation**: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes. This was done; page 19-23
	21	**Generalizability**: Discuss the generalisability (external validity) of the study results	Yes. This was done; page 23
Other information			
	22	**Funding**: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes. This was done; page 24