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Illicit substances detected through high-resolution MS analysis in urine samples are associated with greater symptom burden in patients with psychosis

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ABSTRACT

Background: The prevalence of new psychoactive substances (NPS) in acute psychotic patients has not been investigated systematically. We applied a highly sensitive and specific mass spectrometry method for detection of NPS as well as traditional drugs of abuse (including illicit or prescription substances) in order to assess their prevalence and associations with symptom severity. Identification of these substances is useful in both the diagnostic process and evaluation of treatment effects.

Methods: Demographic data, results from the Positive and Negative Syndrome Score (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) and urine samples from admission were collected from 53 patients recruited into a clinical study of psychosis during 2014-2017. Urine samples were analysed with liquid chromatography high resolution mass spectrometry (LC-QTOF-MS), through both highly specific detection of 191 substances using internal standards and untargeted screening by means of pre-defined libraries. PANSS and CDSS scores in patients with or without drugs of abuse were compared.

Results: Potential drugs of abuse, i.e. drugs that could be used in a controlled therapeutic or a non-prescribed manner, were detected in samples from 20 of the 53 patients. Seven samples contained illicit drugs, but no NPS were detected. In this small patient subgroup, PANSS total score and CDSS score were significantly higher than in patients with negative urine sample results.

Conclusion: Drug screening could play an important role in the differential diagnostic evaluation of patients admitted with psychotic symptoms. Although no NPS were detected in the study population, we found other substances that were associated with psychotic and depressive symptoms.

1. Introduction

The use of illicit substances represents several challenges in patients suffering from psychotic disorders. Illicit substances can elicit acute psychotic symptoms, but substance abuse is also associated with a subsequent diagnosis of schizophrenia, particularly in vulnerable individuals (Marconi, Di Forti et al. 2016, Kendler, Ohlsson et al. 2019, Murrie, Lappin et al. 2020). In addition, psychoactive drugs may interact with psychotropic medication, altering both the effects and tolerability of treatment (Beckett, Martin et al. 2020). Increased attention towards drugs of abuse as a risk factor, both in context of clinical care and research, has been called for (Murrie, Lappin et al. 2020).

Previous studies in Norwegian psychiatric wards have shown a prevalence of drug abuse in 47%-64% of patients (Mordal, Bramness et al. 2008, Flovig, Vaaler et al. 2009, Mordal, Holm et al. 2010, Mordal, Holm et al. 2011, Mordal, Medhus et al. 2013). This corresponds with reported prevalence from other countries (Fioritti, Ferri et al. 1997, Lambert, Conus et al. 2005, Addington and Addington 2007, Archie, Rush et al. 2007). Although interviews and clinical observation can identify the majority of patients with substance use and/or recent intake of illicit substances, information of potential clinical value

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can be overlooked when relying solely on these sources of information (Helseth, Lykke-Enger et al. 2005, Mordal, Holm et al. 2010).

Biological samples can be analysed by means of on-site screening methods, which provide rapid answers, or with more advanced methods, commonly in a laboratory setting. On-site screening methods using urine samples have been shown to significantly underestimate the prevalence of illicit substance use in acute psychiatric settings (Bagoien, Morken et al. 2009, Reidy, Junquera et al. 2014). External lab methods can be divided into non-specific methods (immunoassays) and specific methods (chromatography with mass spectrometry). Immunoassays have often been favoured as they are inexpensive and rapid to perform, and do not require the same degree of training and competence among laboratory staff as chromatographic methods. However, immunoassays may be hampered both by lack of sensitivity and selectivity for specific drugs, leading to both false positive and false negative results (Saleh, Stephanson et al. 2012).

During the last decade, numerous new psychoactive substances (NPS) have entered the illegal substance market (Peacock, Bruno et al. 2019). This chemically heterogenous group of substances includes (but is not limited to) synthetic cannabinoids, opioids, psychedelics, and benzodiazepines, the common feature being similar or even more potent psychoactive effects than traditional recreational drugs. NPS are synthesized to circumvent drug legislation, and marketed online as “legal highs”, “bath salts”, or “research chemicals” (Peacock, Bruno et al. 2019, Schifano, Napoletano et al. 2021). Many of the NPS have pharmacological properties that can trigger a wide range of somatic and psychiatric adverse effects, including psychotic symptoms (Bersani and Prevete 2017, Schifano, Napoletano et al. 2021). While NPS have been detected in clinical samples in Norway, they are often not suspected by clinicians as a cause of psychotic symptoms (Mounteney, Griffiths et al. 2016, Vallersnes, Persett et al. 2017). NPS will not necessarily be detected by on-site screening methods, although studies have shown that some NPS cross-react with immunoassays (Petrie, Lynch et al. 2013, Kronstrand, Brinkhagen et al. 2014, Regester, Chmiel et al. 2015, Pettersson Bergstrand, Helander et al. 2017). For instance, most designer benzodiazepines seem to cross-react with benzodiazepine (BZD) immunoassays (Pettersson Bergstrand, Helander et al. 2017). For others, like stimulants and psychedelic NPS, the degree of cross-reactivity is highly dependent on the type of immunoassay (Regester, Chmiel et al. 2015). Because of the shifting drug market, with more than 50 NPS being discovered every year, the demand for rapid evolvement of specific chromatography and mass spectrometry methods is high (European Monitoring Centre for Drugs and Drug Addiction 2020). Most NPS are highly potent substances, meaning that concentrations in biological samples are low. Thus, the detection of NPS requires highly sensitive analytical methods, as well as the possibility to screen for unknown substances.

Liquid chromatography quadrupole time of flight mass spectrometry (LC-QTOF-MS) satisfies requirements of both specificity and flexibility, making it the method of choice to keep up with the rapidly changing drug market. LC-QTOF-MS allows for the use of several parameters to identify substances at different levels of confidence (Schymanski, Jeon et al. 2014). This includes screening against a huge number of substances contained in predefined libraries (Schymanski, Jeon et al. 2014, Pasin, Cawley et al. 2017). A library can include numerous substances, e.g. prescription drugs used for psychiatric and somatic disorders, recreational substances, and illicit substances. Moreover, the collection of high-resolution mass data allows for retrospective re-analysis of data for drugs which were unidentified at the original time of analysis.

In this study, urine samples from patients diagnosed with psychosis were collected at the time of inclusion in the Bergen Psychosis 2/Bergen-Stavanger-Innsbruck-Trondheim (BP2/BeSt Intro study). This study comprised both an observational cohort and a pragmatic, rater-blind semi-randomized clinical trial comparing the clinical efficacy of three different antipsychotics (Johnsen, Kroken et al. 2020). All included patients were diagnosed with psychotic disorders, and underwent symptom scoring using the Positive and Negative Syndrome Score (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) (Kay, Fiszbein et al. 1987, Addington, Addington et al. 1990).

The aims of the study were to apply LC-QTOF-MS analysis to samples from patients suffering from psychosis in order to get a complete picture of substances, including illicit substances and NPS, and to examine whether the presence of such substances was correlated with symptom severity.

2. Materials and methods

2.1. Patients and study design

The BP2/BeSt InTro study involved a two-step design, with initial inclusion of an observational cohort with diverse psychotic disorders (ICD-10 diagnoses F13 (n=1), F20 (n=31), F22 (n=9), F23 (n=6), F25 (n=1), F29 (n=3), F31 (n=2) (Johnsen, Kroken et al. 2020). Drug abuse was not an exclusion criterium. From the cohort, eligible patients with ICD-10 diagnoses F20-29 and symptoms of ongoing psychosis were selected for a semi-randomized trial comparing the clinical effect of the antipsychotics amisulpride, aripiprazole and olanzapine. Inclusion ran from late 2011 through 2016. Medication for concomitant medical or psychiatric conditions was permitted. The present study included 16 patients from the original cohort, and 37 patients who had been recruited into the RCT arm of the study. All urine samples analysed in the present study, and all clinical data, were collected at baseline, as detailed below.

2.2. History and symptom screening

A thorough, interview-based drug screening was undertaken upon inclusion in the BP2/BeSt InTro study. The presence and severity of psychotic symptoms were evaluated by means of PANSS, as assessed by trained and certified interviewers using the Structured Clinical Interview for the PANSS (Johnsen, Kroken et al. 2020). Symptoms of depression were evaluated using the Calgary Depression Scale for Schizophrenia CDSS (Addington, Addington et al. 1990). The PANSS is widely used in order to quantify presence of positive and negative symptoms of psychosis, while the CDSS has been validated to distinguish between negative symptoms and symptoms of depression, which has been shown to be quite frequent in patients with psychosis (Lako, Bruggeman et al. 2012, Kjelby, Gjestad et al. 2018). Information was also collected with regard to lifetime history of drug use, age at first use, and drug intake during the last 14 days. Prescription drugs, i.e. prescribed drugs taken on a regular (daily) basis at the point of inclusion were registered, while drugs administered as acute doses e.g. during recent hospitalisation were not. Alcohol consumption was evaluated using the Clinic Alcohol Use Scale (CAUS) (Mueser KT 1995). Here, potential alcohol-related problems are rated by the clinician according to the following scale: 1=abstinent, 2=use without impairment, 3=abuse, 4=dependence, 5=dependence with institutionalization.

2.3. Urine samples

While the BP2/BeSt InTro was a multicentre study, all urine samples for this study were collected from patients included at the study centre in Bergen, Norway. Urine sampling started in 2014 and ran through 2017. Urine samples were stored at -80°C, and thawed at 4°C on the day of analysis.

2.4. LC-QTOF-MS analysis of urine samples

Urine specimens (20 μL) were diluted with 114 μL BIS-TRIS propane buffer (56 mM, pH 7.0), 10 μL Kura BGTurboGF beta-glucuronidase (Kura Biotec, Puerto Varas, Chile) and 6 μL stable isotope labeled internal standards in methanol (suppliers listed in Supplementary Methods). Conjugated substances were deconjugated with enzyme treatment

through incubation at 55˚C for 2 hours. Urine samples were analyzed using a SCIEX X500R QTOF system with an ExionLC AD UHPLC (SCIEX; Concord, ON, Canada). The QTOF was operated with electrospray ionization in positive (ESI+) mode with SWATH® acquisition (Data Independent Acquisition) and scheduled product ion scans. 4 µL was injected onto a Phenomenex Kinetex biphenyl column (50 × 2.1 mm, 2.6 µm) at 50˚C using Milli-Q water and LC-MS grade methanol, both containing 0.01 % formic acid and 5 mM ammonium formate as mobile phases. As detailed in "Supplementary Methods", a 12-minute gradient elution at 0.5 mL/min was used. Mass correction was performed with ESI positive tuning solution (SCIEX) every eight samples throughout the run. Substances were identified on two levels, as outlined by Schymansky et al. (Schymanski, Jeon et al. 2014). First, 191 substances/metabolites listed in Supplementary Table 1 (Level 1, confirmed structure) were identified according to the European Guidelines for workplace drug testing in urine (Society 2015). Validation according to ISO 15189:2012 was performed for 117 of these substances. To be reported as detected, drugs had to meet the following criteria; a mass accuracy of less than 5 ppm of its theoretical charged mass, elution within a ± 1 % retention window, isotope ratio comparability better than 80 %, signal to noise > 3:1 and a fit value of > 70 % for MS/MS spectra matching. These criteria were used for the validation of the limit of identification (LOI), whereas the limit of detection (LOD) was taken as the smallest peak with an accurate mass and correct isotope ratio at the defined retention time. Fragments were chosen for quantification if there were interferences in TOF-MS or to reduce the signal intensity in order to achieve better linearity for quantification. Then, referring to Level 2a (probable structure) described by Schymansky et al., additional substances were identified using non-targeted data analysis. To be reported as detected, drugs had to meet the following criteria; a mass accuracy of less than 5 ppm of its theoretical charged mass, isotope ratio comparability better than 70 %, signal to noise > 3:1, one fragment with mass accuracy within ± 10 ppm and a fit value of > 50 % for MS/MS spectra matching against the Forensics HR-MS/MS Spectral Library 2.0 (SCIEX, 1667 compounds) and NIST Standard Reference Database 1A v17 (13808 compounds) (National Institute of Standards and Technology 2017). An example of the detection of mefloquine is included in the supplementary material (Supplementary Figure 1). Cannabis (THC-COOH) was analyzed in a separate method using a SCIEX QTRAP 6500 + with an ExionLC AD UHPLC (SCIEX; Concord, ON, Canada), using base hydrolysis for deconjugation of THC-COOH-glucuronide in the samples.

2.5. Statistical analysis

Statistical analyses were performed using R (R Core Team 2020). A Welch's two-sample t-test was used to examine whether the mean PANSS or CDSS values at baseline were different between patients whose samples contained illicit drugs and patients whose samples did not. Equal variance in the groups was not assumed. Normality of the data, and hence the group averages, was examined visually in a qq-plot. When normality was not present, the Wilcoxon-Mann-Whitney test was applied.

2.6. Ethical considerations

The study was approved by the Regional Committees for Medical and Health Research Ethics (2010/3387), and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients provided written informed consent before inclusion.

3. Results

A total of 53 urine samples were available for analysis. Patient characteristics are detailed in Table 1.

Table 1
Demographic variables for the 53 patients. Numbers in [brackets] indicate number of missing observations.

Age (average ± SD)	31.2 ± 12.7
Sex (men/total subjects)	37/53 (70%)
Smoker (non-smokers/ total subjects)	28/53 (55%) [2]
Ethnicity (Caucasian/ total subjects)	40/53 (78%) [2]
# patients in RCT/cohort	37/16 (70%/30%)
AP naïve (naïve/total subjects)	15/53 (28%)
Reported illicit drug use (lifetime)	28/53 (55%) [2]
Reported illicit drug use (last 14 days)	3/53(6%)

Table 2
Detected substances, and number of urine samples where the substance was detected. Substances are sorted according to number of findings (descending). * findings were made in samples from the same patient.

Substance	Detected in # of samples
Oxazepam	14 (25%)
Temazepam	7 (13%)
Nordiazepam	7 (13%)
Norzopiclone	6 (11%)
THC-COOH	6 (11%)
Pregabalin	2 (4%)
7-Aminoclonazepam	2 (4%)
Morphine	1 (2%)
Ethyl morphine	1 (2%)
Amphetamine	1 (2%)*
Methamphetamine	1 (2%)*
Zolpidem Phenyl-4-carboxylic acid	1 (2%)

As shown in Table 2, a total of 12 substances with potential for abuse were found, but no substances classified as NPS were among them. Nordiazepam and temazepam were only detected in samples also containing oxazepam. The presence of the three substances most likely represents intake of diazepam, while detection of oxazepam alone could represent intake of diazepam or oxazepam (Smith-Kielland, Skuterud et al. 2001, Temte, Kjeldstadli et al. 2019). Amphetamine and methamphetamine were detected in the same sample, and could represent intake of methamphetamine or both substances (Kim, Oyler et al. 2004).

Illicit substances, i.e. THC and/or amphetamine/methamphetamine, were detected in samples from 7 patients, i.e. 13% of the 53 samples (Table 3a).

Patients whose samples contained illicit substances were all male smokers. At the point of inclusion, four of the seven patients had provided information confirming illicit substance intake during the 14 days prior to baseline, while all seven had drug use in their lifetime history (mean age when first trying THC, average ± SD: 17.7 ± 2.6). Alcohol consumption affecting functional level, defined here as a CAUS score of 3 or above, had been noted in a very low number of patients both in the subpopulation with detected illicit substance and in subjects without such substances. Interestingly, among patients with detected illicit substances, PANSS total was significantly higher (average ± SD: 91.7 ± 8.3) than in patients with no illicit substances detected (average ± SD:75.0 ± 20.9) (difference: 16.7; P=0.002). There were no significant differences in PANSS positive or negative sub-scores (data not shown). With regard to CDSS, a higher score in the group with detected drugs was observed (average ± SD: 13.3 ± 7.0) compared to the score in the group with no detected drugs (7.1 ± 5.9). As CDSS scores were far from normally distributed a Wilcoxon-Mann-Whitney test was applied, yielding a P-value of 0.039. One PANSS observation was missing in the group with detected drugs, while one CDSS observation was missing in each group.

When patients with detected BZD, which could represent prescribed or illicit drug use, were included, twenty samples were positive for illicit substances and/or BZD (Table 3b). In samples from 10 of 13 patients, two or more substances were detected. Personal data protection issues

Table 3a
Illicit substance detected in urine, with patient characteristics in each group. Numbers in [brackets] indicate number of missing observations.

	Illicit drug detected (n=7)	No illicit drug detected (n=46)
Age (average ± SD)	26.9 ± 5.1	31.8 ± 13.4
Sex (male)	7 (100%)	30 (65%)
Non-smoker	0 (0%)	21 (47%) [2]
Ethnicity (Caucasian)	5 (71%)	35 (80%) [2]
AP naïve	0 (0%)	15 (33%)
Reported illicit drug use (lifetime)	7 (100%)	20 (45%) [3]
Reported illicit drug use (last 14 days)	4 (57%)	1 (2%)
CAUS ≥3	1 (14%)	2 (5%) [1]

Table 3b
Illicit substance and/or BZD detected in urine, with patient characteristics in each group. Numbers in [brackets] indicate number of missing observations.

	Illicit drug/BZD detected (n=20)	No illicit drug/BZD detected (n=33)
Age (average ± SD)	27.9 ± 7.9	33.1 ± 14.6
Sex (male)	14 (70%)	23 (70%)
Non-smoker	5 (25%)	18 (58%) [2]
Ethnicity (Caucasian)	15 (75%)	25 (81%) [2]
AP naïve	2 (10%)	13 (39%)
Reported illicit drug use (lifetime)	15 (79%) [1]	12 (39%) [2]
Reported illicit drug use (last 14 days)	4 (20%)	2 (6%)
CAUS ≥3	1 (5%)	2 (6%) [1]

prevented further presentation of substances detected in each individual. The presence of a harmful alcohol intake, as rated using the CAUS, was low in both groups.

In the corresponding 20 patients, the PANSS total score ± SD was 83.4 ± 24.6, while in patients with negative urine samples, PANSS total was not significantly lower at 73.1 ± 17.1 (difference: 10.3; P=0.118). There were no significant differences in PANSS positive or negative subscores (data not shown). With regard to CDSS, a higher score was observed in the group with detected drugs (average ± SD: 10.3 ± 6.7) compared to the score in the group with no detected drugs (6.4 ± 5.6). As CDSS scores were far from normally distributed a Wilcoxon-Mann-Whitney test was applied, yielding a significant P-value of 0.044. One PANSS observation was missing in the group with detected drugs, while one CDSS observation was missing in each group.

We also examined whether PANSS scores differed between patients remaining in the observational cohort (16 patients) and patients recruited into the RCT arm of the study (37 patients). PANSS total score and PANSS negative subscore did not differ between the groups (data not shown). The PANSS positive score was 16.8 ± 6.5 in the cohort compared to a significantly higher score of 21.4 ± 6.1 in the RCT (difference: 4.6; P=0.029). No differences were detected in the CDSS score (data not shown).

Lastly, the use of LC-QTOF-MS revealed the presence of prescription drugs used relatively rarely in Norway, but not usually associated with misuse; hyoscyamin, mefloquine, and quinine, all found in samples from different patients.

4. Discussion

We applied LC-QTOF-MS analysis to 53 urine samples from a thoroughly screened population of patients diagnosed with psychosis. The LC-QTOF-MS method has several advantages. First, the method allows for screening for a very extensive number of substances. Second, high resolution mass spectrometry enables highly specific detection of substances. Third, the method is flexible in the sense that new substances and metabolites can quickly be identified and included in an NPS repertoire (Allen and McWhinney 2019).

Illicit substances were detected in samples from 13 % of the patients. In agreement with other studies indicating low prevalence, NPS were not detected in any of the samples, indicating a limited use of these substances in this population in the catchment area (Western Norway) during 2014-2017, in accordance with studies in comparable populations (Gundersen, Spigset et al. 2019, Peacock, Bruno et al. 2019). In an Italian study from 2013-2015, the reported use of NPS was more prevalent in patients with bipolar disorder than patients with schizophrenia, but only 2% of the patients reported consuming NPS during the previous 3 months (Acciavatti, Lupi et al. 2017).

The analyses did result in findings illustrating the potential of high-resolution MS to detect other drugs of interest. The anticholinergic drugs atropine, and hyoscyamine which has pharmacological properties similar to atropine, are therapeutic drugs that have been associated with hallucinations and even psychosis (Eriksson 1969, Lakstygal, Kolesnikova et al. 2019). Mefloquine is an antimalarial medication with recognized psychiatric side effects. Psychiatric conditions like schizophrenia and depression are considered contraindications for treatment with mefloquine, and the drug could represent a contributing factor to psychotic symptoms (Bjorkman 1989, Ritchie, Block et al. 2013).

The PANSS score of patients with detected illicit substances was significantly higher than that of patients with no detected illicit substances in their urine samples. In a study of individuals with psychosis and primary stimulant addiction, PANSS positive score was associated with duration of drug abuse (Lichlyter, Purdon et al. 2011). Acute intake of THC was associated with significant increases in positive, negative, general, and total symptoms with large effect sizes in adults with no history of psychotic or other major psychiatric disorder (Hindley, Beck et al. 2020). Effect sizes were greater for positive symptoms than for negative symptoms, indicating that THC is associated with positive symptoms to a greater extent than negative symptoms. However, in a Canadian study, no association was found between substance use disorder (SUD) and PANSS score (Potvin, Pampoulova et al. 2008). In the same study, patients with schizophrenia and SUD had a higher CDSS compared to schizophrenia patients without SUD. In the present study, CDSS score was differentially distributed among the two groups, and findings indicated a higher burden of depressive symptoms in patients with detected illicit substances. Our results, while supporting that illicit substances could have the potential of increasing the severity of psychosis and related depression, point towards the need for follow-up studies in larger patient cohorts.

When patients with detected BZD, which could represent drugs of abuse or be prescribed, were included, the difference in PANSS total score compared to patients with no detected substances was no longer

significant. Differences in CDSS remained significant, but were less pronounced when evaluating absolute scores. BZD are frequently prescribed in a therapeutic setting in patients with mental health symptoms. Although affected by the properties of the specific drug, by dose, and by the number of intakes, in general the detection window for BZD in urine is relatively long (days to weeks) (Temte, Kjeldstadli et al. 2019). Unfortunately, drugs prescribed as acute treatment in the corresponding period prior to inclusion in the BP2/BestIntro study were not recorded, and a major limitation of the study is therefore the inability to distinguish between prescribed and non-prescribed BZD. Conclusions based on the presence of BZD, i.e. whether they were present in samples from particularly ill patients having received symptomatic treatment or whether they can be viewed as markers of drug abuse, cannot be drawn based on the material available for analysis.

The study has several additional limitations, the most prominent being the limited number of samples. However, as cohorts consisting of thoroughly examined patients suffering from psychosis are rarely very large, we still found analysis of the material worthwhile. Repeated sampling, particularly in the acute stages of psychosis, would significantly increase the impact of results, but particular care is necessary in order to ensure compliance with a more intensive sampling scheme.

High-resolution MS is highly sensitive and specific. While there is a theoretical possibility of false negative samples due to a selected number of NPS included in the repertoire, aspects related to sample collection and storage might be more relevant in terms of sources of error. Time from the last intake of illicit substances to the time of urine sampling was not recorded. This could affect the percentage of samples positive for illicit substances with a short biological half-life, such as cocaine (Cone, Sampson-Cone et al. 2003). Furthermore, because most NPS are potent drugs with low concentrations in blood and urine, time from drug intake to sampling is of essence. Thus, data can only be interpreted in a strictly cross-sectional manner, and we cannot rule out that some of patients with negative urine samples had a history of illicit substance/NPS use before admission.

In addition to the limitations represented by lack of recorded drug prescription and short detection windows in urine, an issue of concern is the stability of drugs when frozen urine samples are stored for an extended period of time. Some of the drugs in question, such as zopiclone, some BZD/BZD metabolites, and cocaine have been shown to degrade over months to years at -20° C (Moody, Monti et al. 1999, Mata 2016). For other drugs of interest the stability seems to be adequate, although there is lack of data for most of the NPS (Gonzales, Ng et al. 2013). Although we attempted to counteract degradation through storage at -80° C, degradation affecting substances to different degrees could still have occurred, and performing the analyses at the time of sample collection could have led to a more accurate overview of the drug panorama in the samples.

In conclusion, despite the abovementioned issues, LC-QTOF-MS distinguished a subgroup of patients with samples containing illicit substances and more pronounced symptoms of psychosis and depression. Although false negative samples cannot be ruled out, NPS were not detected in the small cohort of patients with psychosis in Western Norway during the relevant period of time. On the other hand, other drugs discovered with LC-QTOF-MS could have both diagnostic and therapeutic relevance. Broad and sensitive screening provides reliable detection of substances and, importantly, an opportunity to rapidly detect a changing drug panorama, with subsequent inclusion of new substances into analytical libraries (Pope, Choy et al. 2019). Requiring no preformed hypothesis of causal agent in suspected drug-induced psychosis, LC-QTOF-MS may also provide valuable results in diagnostically challenging situations.

Author contributions

Silje Skrede: Conceptualization, Investigation, Writing - Original Draft, Writing - Review & Editing, Project administration. **Jon Andsnes Berg:** Conceptualization, Investigation, Writing - Original Draft, Writing - Review & Editing. **Kjell Ove Fossan:** Methodology, Formal analysis, Investigation, Writing - Review & Editing. **Christoffer Bartz-Johannessen:** Conceptualization, Formal analysis, Writing - Review & Editing. **Else-Marie Løberg:** Conceptualization, Methodology, Writing - Review & Editing, Funding acquisition. **Rune Andreas Kroken:** Conceptualization, Methodology, Writing - Review & Editing, Funding acquisition. **Erik Johnsen:** Conceptualization, Methodology, Resources, Writing - Review & Editing, Project administration, Funding acquisition.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Role of funding source

The funder of the study had no influence on study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.etdah.2021.100024.

References

Acciavatti, T., Lupi, M., Santacroce, R., Aguglia, A., Attademo, L., Bandini, L., Ciambrone, P., Lisi, G., Migliarese, G., Pinna, F., Quattrone, D., Ribolsi, M., Signorelli, M.S., Calo, S., Schifano, F., di Giannantonio, M., Martinotti, G., 2017. Novel psychoactive substance consumption is more represented in bipolar disorder than in psychotic disorders: A multicenter-observational study. Hum. Psychopharmacol. 32 (3).

Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. Schizophr. Res. 3 (4), 247–251.

Addington, J., Addington, D., 2007. Patterns, predictors and impact of substance use in early psychosis: a longitudinal study. Acta Psychiatr. Scand. 115 (4), 304–309.

Allen, D.R., McWhinney, B.C., 2019. Quadrupole Time-of-Flight Mass Spectrometry: A Paradigm Shift in Toxicology Screening Applications. Clin. Biochem. Rev. 40 (3), 135–146.

Archie, S., Rush, B.R., Akhtar-Danesh, N., Norman, R., Malla, A., Roy, P., Zipursky, R.B., 2007. Substance use and abuse in first-episode psychosis: prevalence before and after early intervention. Schizophr. Bull. 33 (6), 1354–1363.

Bagoien, G., Morken, G., Zahlsen, K., Aamo, T., Spigset, O., 2009. Evaluation of a urine on-site drugs of abuse screening test in patients admitted to a psychiatric emergency unit. J. Clin. Psychopharmacol. 29 (3), 248–254.

Beckett, R.D., Martin, J.R., Stump, C.D., Dyer, M.A., 2020. Evaluation of drug information resources for interactions between therapeutic drugs and drugs of abuse. J. Med. Libr. Assoc. 108 (4), 584–590.

Bersani, G., Prevete, E., 2017. Novel psychoactive substances (NPS) use in severe mental illness (SMI) patients: Potential changes in the phenomenology of psychiatric diseases. Hum. Psychopharmacol. 32 (3).

Bjorkman, A., 1989. Acute psychosis following mefloquine prophylaxis. Lancet 2 (8667), 865.

Cone, E.J., Sampson-Cone, A.H., Darwin, W.D., Huestis, M.A., Oyler, J.M., 2003. Urine testing for cocaine abuse: metabolic and excretion patterns following different routes of administration and methods for detection of false-negative results. J. Anal. Toxicol. 27 (7), 386–401.

Erikssen, J., 1969. Atropine psychosis. Lancet 1 (7584), 53–54.

Fioritti, A., Ferri, S., Galassi, L., Warner, R., 1997. Substance use among the mentally ill: a comparison of Italian and American samples. Community Ment. Health J. 33 (5), 429–442.

Flovig, J.C., Vaaler, A.E., Morken, G., 2009. Substance use at admission to an acute psychiatric department. Nord. J. Psychiatry 63 (2), 113–119.

Gonzales, E., Ng, G., Pesce, A., West, C., West, R., Mikel, C., Latyshev, S., Almazan, P., 2013. Stability of pain-related medications, metabolites, and illicit substances in urine. Clin. Chim. Acta 416, 80–85.
Gundersen, P.O.M., Spigset, O., Josefsson, M., 2019. Screening, quantification, and confirmation of synthetic cannabinoid metabolites in urine by UHPLC-QTOF-MS. Drug Test. Anal. 11 (1), 51–67.
Helseth, V., Lykke-Enger, T., Aamo, T.O., Johnsen, J., 2005. [Drug screening among patients aged 17-40 admitted with psychosis]. Tidsskr. Nor. Laegeforen. 125 (9), 1178–1180.
Hindley, G., Beck, K., Borgan, F., Ginestet, C.E., McCutcheon, R., Kleinloog, D., Ganesh, S., Radhakrishnan, R., D'Souza, D.C., Howes, O.D., 2020. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. Lancet Psychiatry 7 (4), 344–353.
Johnsen, E., Kroken, R.A., Loberg, E.M., Rettenbacher, M., Joa, I., Larsen, T.K., Reitan, S.K., Walla, B., Alisauskiene, R., Anda, L.G., Bartz-Johannessen, C., Berle, J.O., Bjarke, J., Fathian, F., Hugdahl, K., Kjelby, E., Sinkeviciute, I., Skrede, S., Stabell, L., Steen, V.M., Fleischhacker, W.W., 2020. Amisulpride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeSt InTro): a pragmatic, rater-blind, semi-randomised trial. Lancet Psychiatry 7 (11), 945–954.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Kendler, K.S., Ohlsson, H., Sundquist, J., Sundquist, K., 2019. Prediction of Onset of Substance-Induced Psychotic Disorder and Its Progression to Schizophrenia in a Swedish National Sample. Am. J. Psychiatry 176 (9), 711–719.
Kim, I., Oyler, J.M., Moolchan, E.T., Cone, E.J., Huestis, M.A., 2004. Urinary pharmacokinetics of methamphetamine and its metabolite, amphetamine following controlled oral administration to humans. Ther. Drug Monit. 26 (6), 664–672.
Kjelby, E., Gjestad, R., Sinkeviciute, I., Kroken, R.A., Loberg, E.M., Jorgensen, H.A., Johnsen, E., 2018. Trajectories of depressive symptoms in the acute phase of psychosis: Implications for treatment. J. Psychiatr. Res. 103, 219–228.
Kronstrand, R., Brinkhagen, L., Birath-Karlsson, C., Roman, M., Josefsson, M., 2014. LC-QTOF-MS as a superior strategy to immunoassay for the comprehensive analysis of synthetic cannabinoids in urine. Anal. Bioanal. Chem. 406 (15), 3599–3609.
Lako, I.M., Bruggeman, R., Knegtering, H., Wiersma, D., Schoevers, R.A., Slooff, C.J., Taxis, K., 2012. A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. J. Affect. Disord. 140 (1), 38–47.
Lakstygal, A.M., Kolesnikova, T.O., Khatsko, S.L., Zabegalov, K.N., Volgin, A.D., Demin, K.A., Shevyrin, V.A., Wappler-Guzzetta, E.A., Kalueff, A.V., 2019. DARK Classics in Chemical Neuroscience: Atropine, Scopolamine, and Other Anticholinergic Deliriant Hallucinogens. ACS Chem. Neurosci. 10 (5), 2144–2159.
Lambert, M., Conus, P., Lubman, D.I., Wade, D., Yuen, H., Moritz, S., Naber, D., McGorry, P.D., Schimmelmann, B.G., 2005. The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. Acta Psychiatr. Scand. 112 (2), 141–148.
Lichlyter, B., Purdon, S., Tibbo, P., 2011. Predictors of psychosis severity in individuals with primary stimulant addictions. Addict. Behav. 36 (1-2), 137–139.
Marconi, A., Di Forti, M., Lewis, C.M., Murray, R.M., Vassos, E., 2016. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr. Bull. 42 (5), 1262–1269.
Mata, D.C., 2016. Stability of 26 Sedative Hypnotics in Six Toxicological Matrices at Different Storage Conditions. J. Anal. Toxicol. 40 (8), 663–668.
Moody, D.E., Monti, K.M., Spanbauer, A.C., 1999. Long-term stability of abused drugs and antiabuse chemotherapeutical agents stored at -20 degrees C. J. Anal. Toxicol. 23 (6), 535–540.
Mordal, J., Bramness, J.G., Holm, B., Morland, J., 2008. Drugs of abuse among acute psychiatric and medical admissions: laboratory based identification of prevalence and drug influence. Gen. Hosp. Psychiatry 30 (1), 55–60.
Mordal, J., Holm, B., Gossop, M., Romoren, M., Morland, J., Bramness, J., 2011. Psychoactive substance use among patients admitted to an acute psychiatric ward: laboratory findings and associations with clinical characteristics. Nord. J. Psychiatry 65 (3), 208–215.
Mordal, J., Holm, B., Morland, J., Bramness, J.G., 2010. Recent substance intake among patients admitted to acute psychiatric wards: physician's assessment and on-site urine testing compared with comprehensive laboratory analyses. J. Clin. Psychopharmacol. 30 (4), 455–459.
Mordal, J., Medhus, S., Holm, B., Morland, J., Bramness, J.G., 2013. Influence of drugs of abuse and alcohol upon patients admitted to acute psychiatric wards: physician's assessment compared to blood drug concentrations. J. Clin. Psychopharmacol. 33 (3), 415–419.
Mounteney, J., Griffiths, P., Sedefov, R., Noor, A., Vicente, J., Simon, R., 2016. The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. Addiction 111 (1), 34–48.
Mueser, KT, D., R., Clark, RE, McHugo, GJ, Mercer-McFadden, C, Ackerson, TH, 1995. Evaluating Substance Abuse in Persons with Severe Mental Illness. Hum. Services Res. Institute 1–51.
Murrie, B., Lappin, J., Large, M., Sara, G., 2020. Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. Schizophr. Bull. 46 (3), 505–516.
National Institute of Standards and Technology, 2017. NIST Standard Reference Database 1A V17.
Pasin, D., Cawley, A., Bidny, S., Fu, S., 2017. Current applications of high-resolution mass spectrometry for the analysis of new psychoactive substances: a critical review. Anal. Bioanal. Chem. 409 (25), 5821–5836.
Peacock, A., Bruno, R., Gisev, N., Degenhardt, L., Hall, W., Sedefov, R., White, J., Thomas, K.V., Farrell, M., Griffiths, P., 2019. New psychoactive substances: challenges for drug surveillance, control, and public health responses. Lancet 394 (10209), 1668–1684.
Petrie, M., Lynch, K.L., Ekins, S., Chang, J.S., Goetz, R.J., Wu, A.H., Krasowski, M.D., 2013. Cross-reactivity studies and predictive modeling of "Bath Salts" and other amphetamine-type stimulants with amphetamine screening immunoassays. Clin. Toxicol. (Phila) 51 (2), 83–91.
Bergstrand, Pettersson, Helander, M.A., Hansson, T., Beck, O., 2017. Detectability of designer benzodiazepines in CEDIA, EMIT II Plus, HEIA, and KIMS II immunochemical screening assays. Drug Test. Anal. 9 (4), 640–645.
Pope, J.D., Choy, K.W., Drummer, O.H., Schneider, H.G., 2019. Harmala Alkaloids Identify Ayahausca Intoxication in a Urine Drug Screen. J. Anal. Toxicol. 43 (4), e23–e27.
Potvin, S., Pampoulova, T., Lipp, O., Ait Bentaleb, L., Lalonde, P., Stip, E., 2008. Working memory and depressive symptoms in patients with schizophrenia and substance use disorders. Cogn. Neuropsychiatry 13 (4), 357–366.
Core Team, R, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Comput. Vienna, Austria.
Regester, L.E., Chmiel, J.D., Holler, J.M., Vorce, S.P., Levine, B., Bosy, T.Z., 2015. Determination of designer drug cross-reactivity on five commercial immunoassay screening kits. J. Anal. Toxicol. 39 (2), 144–151.
Reidy, L.J., Junquera, P., Van Dijck, K., Steele, B.W., Nemeroff, C.B., 2014. Underestimation of substance abuse in psychiatric patients by conventional hospital screening. J. Psychiatr. Res. 59, 206–212.
Ritchie, E.C., Block, J., Nevin, R.L., 2013. Psychiatric side effects of mefloquine: applications to forensic psychiatry. J. Am. Acad. Psychiatry Law 41 (2), 224–235.
Saleh, A., Stephanson, N.N., Granelli, I., Villen, T., Beck, O., 2012. Evaluation of a direct high-capacity target screening approach for urine drug testing using liquid chromatography-time-of-flight mass spectrometry. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 909, 6–13.
Schifano, F., Napoletano, F., Chiappini, S., Guirguis, A., Corkery, J.M., Bonaccorso, S., Ricciardi, A., Scherbaum, N., Vento, A., 2021. New/emerging psychoactive substances and associated psychopathological consequences. Psychol. Med. 51 (1), 30–42.
Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P., Hollender, J., 2014. Identifying small molecules via high resolution mass spectrometry: communicating confidence. Environ. Sci. Technol. 48 (4), 2097–2098.
Smith-Kielland, A., Skuterud, B., Olsen, K.M., Morland, J., 2001. Urinary excretion of diazepam metabolites in healthy volunteers and drug users. Scand. J. Clin. Lab. Invest. 61 (3), 237–246.
Society, E. W. D. T., 2015. European Guidelines for Workplace Drug Testing in Urine 2.0.
Temte, V., Kjeldstadli, K., Bruun, L.D., Birdal, M., Bachs, L., Karinen, R., Middelkoop, G., Oiestad, E., Hoiseth, G., 2019. An Experimental Study of Diazepam and Alprazolam Kinetics in Urine and Oral Fluid Following Single Oral Doses. J. Anal. Toxicol. 43 (2), 104–111.
Vallersnes, O.M., Persett, P.S., Oiestad, E.L., Karinen, R., Heyerdahl, F., Hovda, K.E., 2017. Underestimated impact of novel psychoactive substances: laboratory confirmation of recreational drug toxicity in Oslo, Norway. Clin. Toxicol. (Phila) 55 (7), 636–644.