Journal of Analytical Toxicology, 2025, **49**, 369–373
DOI: https://doi.org/10.1093/jat/bkaf009
Advance Access Publication Date: 15 February 2025
Case Report

Psychoactive cocktail consumption on Reunion Island: a case report

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Abstract

Reunion Island is a French department located in the southwestern Indian Ocean, with distinct trends in drug use, drug diversion, and intoxication compared with metropolitan France (e.g. the misuse of drugs—clonazepam and trihexyphenidyl—combined with cannabis or cocaine, which is not observed in metropolitan France). The authors report a case of atypical intoxication in a 16-year-old female who consumed cannabis in conjunction with an unusual powdered mixture containing psychotropic substances. The intoxication led to confusion, hallucinations, sinus tachycardia, and hospitalization. A comprehensive high-resolution mass spectrometry and liquid-chromatography mass spectrometry analysis of her plasma, her urine and a powder found in her possession revealed the presence of the same five medicines: citalopram/escitalopram, paroxetine, sertraline, venlafaxine, and trihexyphenidyl. This case underscores the intricate interactions between psychoactive substances that are never prescribed together in clinical settings, along with the issue of diverted prescription drugs like trihexyphenidyl. It also emphasizes the potential circulation and use of crushed mixtures of medication for recreational purpose. Fortunately, powder analysis provided crucial insight to understand the intoxication.

Introduction

Reunion Island is a French department located in the South-West Indian Ocean. Its demographic composition is characterized by a young and diversified origin, with a tendency to downplay the use of certain psychoactive substances. Notably, there is an early onset of alcohol consumption and a prevalence of cannabis use—locally known as zamal—which is considered as a natural medicinal product [1]. The recreational misuse of drugs is also widespread, particularly involving substances like clonazepam and trihexyphenidyl, which are commonly associated with alcohol and cannabis [2, 3]. Additionally, concerning trends have emerged regarding the use of illicit drugs, including ecstasy and cocaine among teenagers [4].

When patients are admitted to emergency departments, accurately determining what they have consumed is a real challenge. There is often a discrepancy between what the patient reports having taken and the real substances involved, compounded by limitations in the analysis of rapid screening tests. While toxicological analysis of blood or urine can provide more clarity, the detectable quantities in these specimens are influenced by the substance's elimination kinetics and the interval between consumption and sampling. Consequently, it is not uncommon to overlook substances that have been ingested.

Here, we present a case of an atypical intoxication in a female adolescent following the consumption of an unusual powder mix containing psychotropic substances. We were therefore able to analyze her plasma, urine, and the powder obtained during her hospitalization.

Case history

A 16-year-old female (body mass index = 16.4 kg/m^2) was admitted to the Reunion Island University Hospital Centre emergency department accompanied by her parents because she showed signs of confusion for 4 h. Her medical history included an anxiety and depression syndrome treated by sertraline, aripiprazole, and hydroxyzine on request. She had been hospitalized 2 months earlier for written suicidal ideation and had previously attempted suicide with paracetamol (acetaminophen) and by wrist cutting.

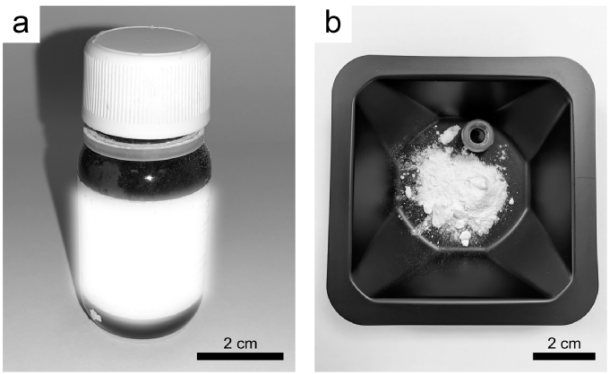

Figure 1. Products discovered in the bag of the patient. (a) Drug bottle (we intentionally blurred the trade name on the bottle to prevent any associations with specific laboratories or pharmaceutical brands, because the bottle does not contain the aforementioned medicine). (b) White powder consisting of the mixture of psychoactive substances discovered inside the bottle. The circle is a large-hole bead, representing one of several beads found inside the bottle in contact with the powder. We assume they are used to mix the powder in the vial.

Upon arrival, her vital signs were as follows: blood pressure 117/78 mmHg, heart rate 120 bpm, O_2 saturation 99% on room air, and Glasgow Coma Scale score of 14, indicating a moderate level of impairment in cognitive function. She presented with symmetrical bilateral mydriasis, reactive in response to stimuli. Her speech was disconnected and lacked coherence, with frequent non sequiturs, and she also suffered from auditory and visual hallucinations. The cardiac monitor showed sinus tachycardia. Brain computed tomography and lumbar puncture examinations revealed no abnormalities. The initial biological workup was normal, with the exception of a slight increase in kalemia (4.8 mmol/L), ASAT (49 U/L), and GGT (41 U/L).

She showed a reduction in hallucinations and temporospatial disorientation after Day 3. Her symptoms were treated by intravenous hydration (bionolyte glucose 5%—2 L per day + 1 g NaCl), diazepam (15 mg per day), and cyamemazine (60 mg per day). She also experienced headaches, which were treated with paracetamol and a nonsteroidal anti-inflammatory drug. The patient was discharged after 5 days of hospitalization, following symptomatic treatment only.

She reported using cannabis, methylenedioxymethamphetamine (MDMA), and other unknown substances during her psychiatric evaluation. Her serum test for paracetamol returned negative results, while her rapid urine drug test indicated a positive result solely for cannabis. Her mother found a drug bottle in her pocket and alerted us for toxicological analysis, suspecting that she had ingested what was inside (Fig. 1).

Experimental

Plasma and urine samples were collected on Reunion Island and sent to the University Hospital of Bordeaux at −20°C, and the powder was transported at ambient temperature. The powder was dissolved in a solution of water/acetonitrile (50:50) at a concentration of 50 μg/mL. Product information is shown in Supplementary Table S1.

For large-scale drug screening, analysis by liquid chromatography coupled with high resolution mass spectrometry (LC–HRMS) analysis was carried out by a Xevo G2-XS QT of mass spectrometer (Waters, Milford, MA, USA). This validated method was adapted from Goncalves *et al.* [5] according to the recommendations of Société Française de Biologie Clinique—Société Française de Toxicologie Analytique [6] (Supplementary Table S2). Briefly, 500 μL of biological fluids was alkalinized with 500 μL of sodium carbonate buffer (pH 9.7) and another 500 μL was acidified with 250 μL of 0.1 N hydrochloric acid. Internal standards (prazepam and phenobarbital, 1 μg/mL) and a mixture of dichloromethane/ether/hexane/isoamyl alcohol (30:50:20:0.5) were added to both solutions. The samples were then agitated for 10 min, followed by centrifugation at 3500 rpm for 5 min. The organic phases from the two tubes of each sample were combined, evaporated using nitrogen gas at 45°C, and reconstituted with a 1 mL water/acetonitrile mixture (50:50). The powder solution was injected directly without any extraction. The samples were transferred to vials for LC–HRMS analysis. Data were analyzed using a library of drugs and novel psychoactive substances. Following this initial analysis, the identified drugs were quantified in plasma via liquid chromatography coupled with tandem mass spectrometry (LC–MS-MS) using an Acquity TQD mass spectrometer (Waters).

Delta-9-tetrahydrocannabinol (THC) and its metabolites were quantified in both plasma and urine with LC–MS-MS. Briefly, 250 μL of biological fluids was extracted with 800 μL of acetonitrile containing 50 ng/mL of [$^2H_3$]-THC, [$^2H_3$]-11-hydroxy-THC and 25 ng/mL [$^2H_3$]-THC-COOH, followed by centrifugation at 3500 rpm for 5 min. For plasma, the supernatant was evaporated using nitrogen gas at 45°C. The dry extract was then derivatized using 160 μL of acetonitrile with 0.2 mg/mL of dansyl hydrochloric acid and NaOH 0.0125 N at 45°C for 10 min. The samples were transferred to vials for LC–MS-MS analysis.

Antidepressant LC–MS-MS quantification was adapted from Castaing *et al.* [7], 500 μL of plasma or dissolved powder (100 μg/mL) was alkalinized with 500 μL of sodium carbonate buffer (pH 9.7), and 100 μL of methylrisperidone (1 μg/mL) was added. In all, 7 mL mixture of hexane and isoamyl alcohol (99:1) was added. The samples were agitated for 15 min and then centrifuged at 4000 rpm for 10 min. The organic phase was collected, and 250 μL of 0.05 N hydrochloric acid was added. The samples were agitated for an additional 15 min and centrifuged again at 4000 rpm for 10 min. The acid phase was then transferred to vials for LC–MS-MS analysis.

Results

Through LC–HRMS analysis, five psychotropic drugs were distinctly identified (retention time, *m/z* with H^+ adduct) in the powder: venlafaxine (5.53 min, 278.21145 *m/z*) citalopram/escitalopram (6.83 min, 325.17066 *m/z*), paroxetine (7.57 min 330.15019 *m/z*), trihexyphenidyl (8.21 min, 332.24838 *m/z*), and sertraline (8.95 min, 306.08091 *m/z*) (Fig. 2). For 1 g of powder, the quantities of antidepressant drugs (along with their recommended therapeutic dosages [8, 9]) were as follows: paroxetine 2.42 mg (20–60 mg/day), sertraline at 8.69 mg (20–200 mg/day), venlafaxine at 13.42 mg (20–375 mg/day), and citalopram/escitalopram at 9.47 mg (10–60 mg/day).

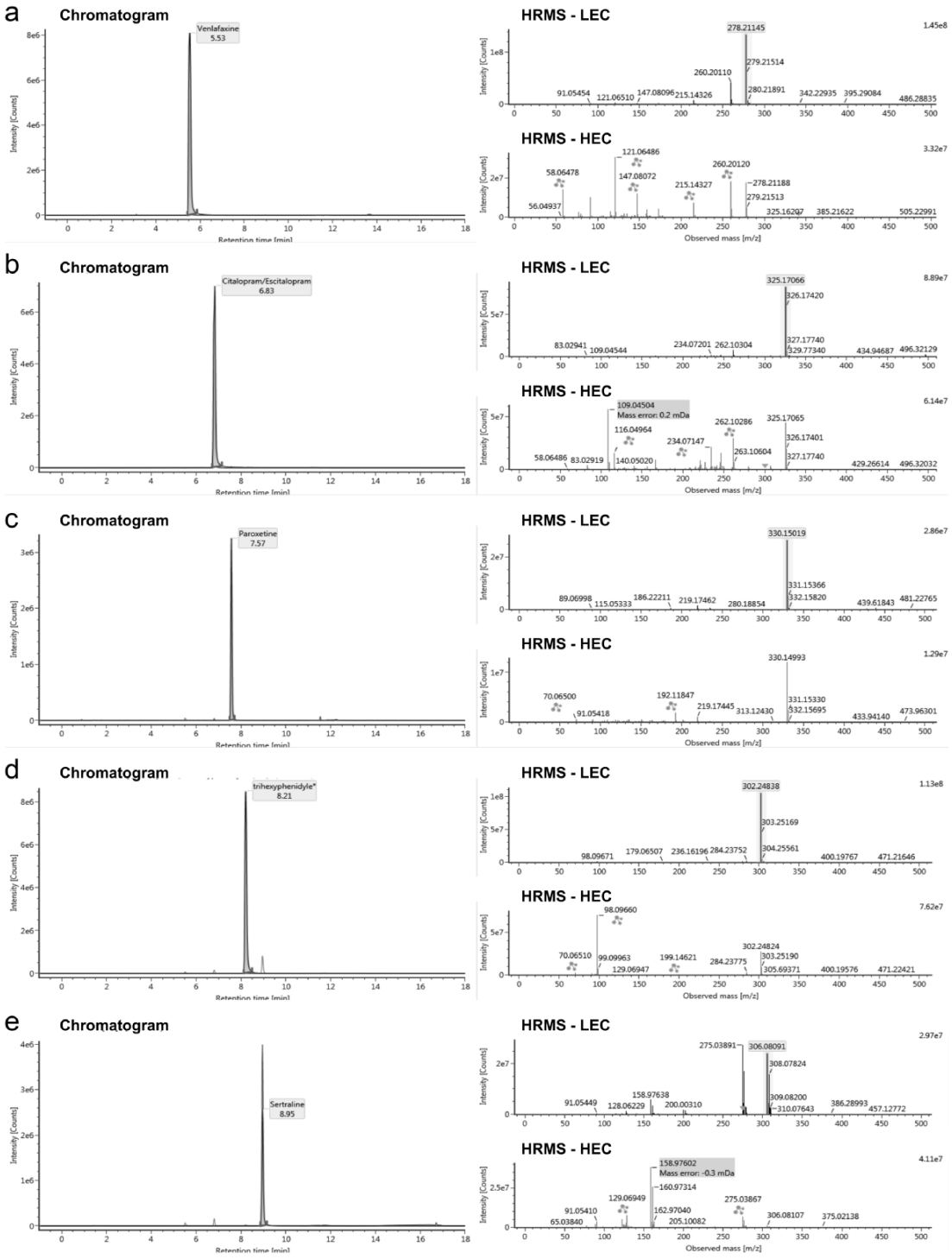

Figure 2. LC–HRMS analysis of the powder with chromatogram overlays (left) alongside high resolution mass spectrometry data (right) under low-energy (HRMS–LEC/<5 eV, top) and high-energy (HRMS–HEC/40 eV, bottom) conditions, with known product ions marked by small atom symbols, for (a) venlafaxine, (b) citalopram/escitalopram, (c) paroxetine, (d) trihexyphenidyl, and (e) sertraline.

Plasma and urine samples were collected approximately 24 h after admission. The plasma concentrations of cannabinoids were as follows: THC at 4.3 ng/mL, 11-hydroxy-THC at 1.1 ng/mL, and THC-COOH at 131.7 ng/mL. In urine, THC-COOH was quantified at 403.1 ng/mL while THC and 11-hydroxy-THC were <10 ng/mL. As depicted in Fig. 3, we found a total of nine drugs (aripiprazole, diazepam, citalopram/escitalopram, cyamemazine, hydroxyzine, paroxetine, sertraline, trihexyphenidyl, and venlafaxine), six related metabolites (dehydro-aripiprazole, desmethyl-citalopram, cetirizine, *N*-desalkyl-cetirizine, nordiazepam, and *O*-desmethyl-venlafaxine), and hydroxyrisperidone, which is present only in the urine. All the drugs identified in the powder are detected in urine and plasma. The plasma concentrations of antidepressant drugs [along with the conventional residual therapeutic ranges [10] and

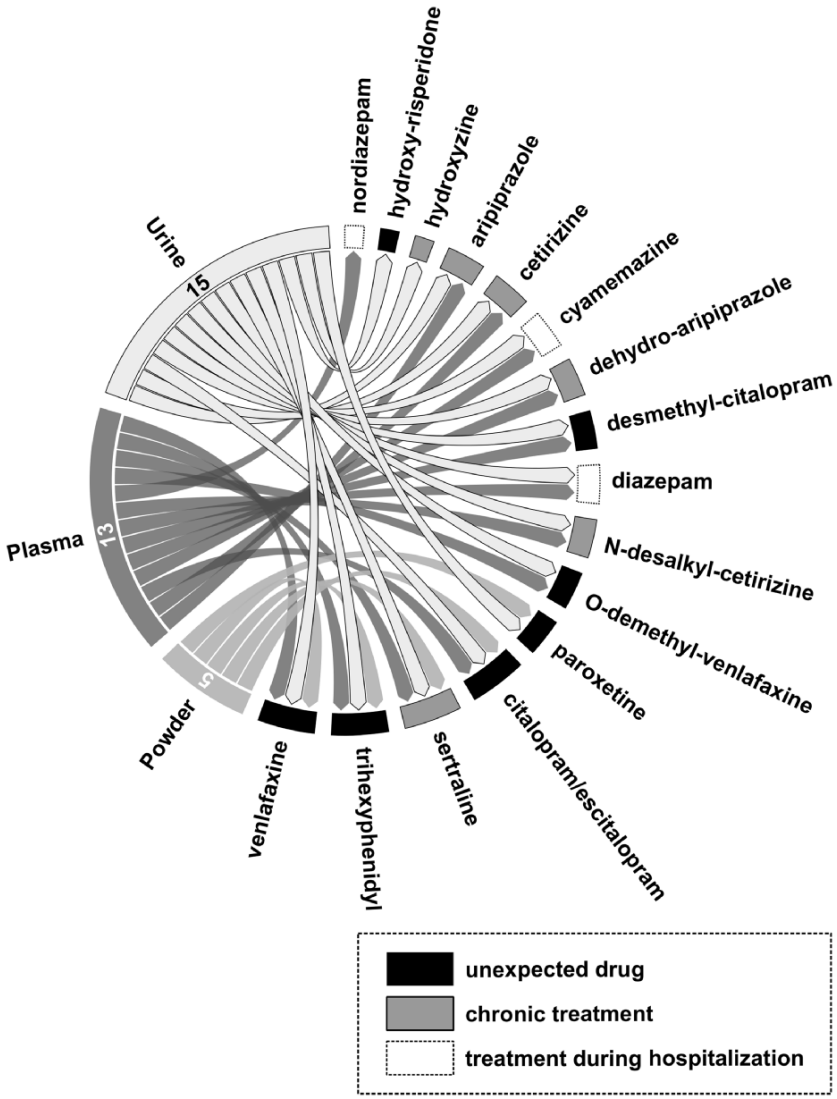

Figure 3. Chord diagram representing toxicological analysis by matching detected drugs (right) with their respective matrices (left: urine, plasma, and powder).

average plasma half-life $T_{½}$ (Supplementary Table S3)] were as follows: paroxetine <10 ng/mL (2–65 ng/mL; $T_{½}$ = 20 h), sertraline at 42 ng/mL (10–150 ng/mL; $T_{½}$ = 26 h), venlafaxine at 50 ng/mL (100–400 ng/mL; $T_{½}$ = 5 h), and citalopram/escitalopram at 80 ng/mL (50–110 ng/mL; $T_{½}$ = 34 h).

Discussion

Toxicological analysis of the various matrices identified several distinct classes of drugs. These include antipsychotic agents such as aripiprazole, cyamemazine, and risperidone; antidepressants, including selective serotonin reuptake inhibitors (SSRIs) such as citalopram/escitalopram, sertraline and paroxetine, and serotonin and norepinephrine reuptake inhibitors (SNRI) such as venlafaxine; anxiolytics, in particular benzodiazepines such as diazepam, the antihistamine hydroxyzine, and the antimuscarinic agent trihexyphenidyl.

Since the sample was collected 24 h after hospitalization, the drugs administered during emergency care, including diazepam and cyamemazine, were present in both plasma and urine. It is important to emphasize that these two medications were not related to the clinical condition that resulted in the patient's hospitalization.

The correlation between the drugs and metabolites found in the biological samples and the powder analysis clearly indicates that the patient had consumed the combination of psychotropic substances (citalopram/escitalopram, paroxetine, sertraline, trihexyphenidyl, and venlafaxine). Sertraline had also been prescribed previously to manage her depressive syndrome. Considering the time elapsed between drug intake and absorption—approximately 4 h as stated in the Summary of Product Characteristics for each drug—along with the 4-h interval between symptom onset and the hospital visit, and given that the sample was taken 24 h after admission, it is likely that the concentrations of antidepressants are either lower than or within the therapeutic ranges typically observed in clinical practice [10].

In line with international guidelines for antidepressant treatment (NICE [11] and CANMAT [12]), patients may be prescribed two drugs but from different classes. In addition, the combination of several SSRIs is not recommended due

to the significant risk of drug interaction. Paroxetine is primarily metabolized by CYP2D6 and can significantly reduce the metabolism of sertraline and citalopram/escitalopram, and it has a minor effect on the metabolism of venlafaxine [13, 14]. Although the toxicity associated with sertraline or paroxetine overdose is considered low [15], the combination of SSRIs and SNRIs greatly increases the risk or severity of serotonin syndrome [16]. Serotonin syndrome is a combination of digestive (nausea, diarrhea), neuropsychological (agitation, confusion), motor (myoclonus, tremor, rigidity), and vegetative symptoms (tachycardia, sweating, and hyperthermia). In addition to the fact that antimuscarinics increase heart rate—an effect that can be amplified by paroxetine and venlafaxine [17]—trihexyphenidyl could also contribute to masking the motor symptoms associated with this clinical context [18]. Moreover, the presence of trihexyphenidyl underscores the worrying trend on Reunion Island, where it is frequently misused for its euphoric effects, sedation, and perceptual changes, including hallucinations [19, 20]. It would have been beneficial to assess the plasma concentrations of trihexyphenidyl to evaluate any potential toxic levels. However, we were unable to quantify it due to the limited amount of matrix remaining after the extensive screening process and the quantification of cannabinoids and antidepressants. The concentration of THC and its metabolites suggests recent cannabis use, in line with the patient's account. All these substances, combined with cannabis consumption, may have influenced the patient's state of consciousness [21], as well as her 3 days of visual and auditory hallucinations. This raises the question of how the patient came to believe she had taken MDMA and whether she suspected its presence in the powder recovered.

Conclusion

In cases of acute intoxication with available biological fluids, analyzing the powder can provide important insights into the substances involved. This helps clarify their origin and significance. The combination of these drugs could amplify or mask their effects and delay the onset of toxicities.

Supplementary data

Supplementary data is available at *Journal of Analytical Toxicology* online.

Funding

None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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