Supplemental Digital Content

Timetable

1985: Born in Rome, Italy. He developed artistic talents, and started painting. In 2004, he joined a School of Arts

2003, 18-years-old, started using substances (alcohol, cannabinoids, ketamine)

2005, 20-years-old, intensified substance use; met criteria for substance use disorder

2005-2008, Quits School of Arts and withdraws from social activities, isolates himself from friends

2006, Organized successful exhibition with his paintings

2008-2010, Works with his father's employers, starts living alone, while continuing heavy use of the above drugs and successful painting exhibits

2010-2011, Quits job due to paranoid ideation (persecutory feelings about his colleagues); increased insomnia, nervousness, suspiciousness, irritability, and aggressiveness

Early 2011, First psychiatric contact with a psychiatrist at a community mental health service, who prescribed 10 mg/day oral olanzapine; symptoms improved for about one month, then the patient discontinued treatment and psychosis relapsed

Summer 2011, Hospitalized in a private psychiatric hospital in Rome; he was delusional and oral olanzapine 10 mg/day was reintroduced, while 2 mg/day oral haloperidol were added. Ten days later he was discharged and reports to have felt well for some time

Patient's family history is free from psychotic or other psychiatric disorders. His developmental trajectory was typical for his age. He had no school problems.

The patient developed insomnia that prompted his parents to bring him to a neurologist, who abruptly discontinued antipsychotics and introduced an unspecified dose of amitriptyline. During the same time, the patient started abusing oral dextromethorphan syrup, which he told his parents to take as a cough remedy. He became increasingly anxious and returned to live in his parents' home, but his insomnia, agitation, fearfulness, appetite loss, and delusional mood persisted and increased, leading to return to the community mental health psychiatrist, who referred him to our acute psychiatric care unit, where he was voluntary hospitalized at first, and then compulsorily in October 2011 for 18 days. During this period, he has been treated with 1000 mg/day sodium valproate and 20 mg/day oral aripiprazole. He was discharged with a DSM-IV-TR diagnosis of psychosis NOS (not otherwise specified) and continued on valproate and aripiprazole

December 2011, For about two months, the patient suspended treatment and did not use any substance. He reports to have felt well during this period. He did not return to psychiatric follow-up at the community service. In December, he returned living alone and pursued purchasing methoxetamine on the internet. After using the drug, he developed a paranoid reaction, lasting until February 2012, during which he quarreled with his parents and withdrew socially

February 2012, Compulsorily hospitalized at our acute psychiatric care unit, where we reintroduced 1000 mg/day sodium valproate and 20 mg/day oral aripiprazole. During this period, his father inspected the patient's house, where he found a white powder, which he collected and sent to the Pavia Poison Control

Center, where the substance was identified as methoxetamine. Fourteen days later, the patient has been discharged with the same diagnosis and same treatment regimen as above. The patient never admitted using internet purchased drugs and never specified what he was doing with the powders, i.e., whether he was taking them intranasally or orally.

After two contacts with his local community psychiatric service, he is persuaded to be followed up in Northern Italy by a substance use specialist and accepts to attend monthly sessions there. His diagnosis was modified to substance-induced psychotic disorder

In March 2013, during one of these visits, he developed verbal aggression, irritability, restlessness, and squabbled with both parents and health personnel, rushing out of the psychiatric service and going from pharmacy to pharmacy to obtain dextromethorphan without a prescription. One of the pharmacists called the police, who brought him forcefully to a local psychiatric ward, from which he was eventually transferred to our service. He was again administered valproate and aripiprazole, at the oral daily doses of 800 mg and 15 mg, respectively. Twenty days later he has been discharged with the same drug treatment (that the patient took care to interrupt soon) and with a DSM-IV-TR diagnosis of substance-induced psychosis

During the period March 2013-May 2016 the patient was not hospitalized and alternated periods in which he was going to live with his parents, reportedly not engaging in substance use, and periods in which he returned to live in his own home, during which he used dextromethorphan, alcohol, and ketamine as well as other substances (which he was unable to recall) he was able to purchase on the internet market. However, some of the latter attempts were intercepted by his parents and, consequently, frustrated

On May 7, 2016, the patient sought help at the Emergency Room (ER) of our Hospital due to agitation and anguish, but was sent-off home after tranquilization with a diagnosis of unspecified acute substance intoxication

On May 29, 2016 he returned to our Hospital's ER with a proposal of compulsory hospitalization in a psychiatric ward. He had kidnapped a parish of a peripheral Roman church asking to speak to the Pope, because he was hearing God's voice and had the vocation to become a priest. He was agitated and presumably hallucinatory, with a restriction of the span of consciousness. At ER, we obtained blood and urine samples and analysed them soon, finding no ethanol in blood and benzodiazepines and tricyclic compounds. He was hospitalized in our acute psychiatric care unit with a status diagnosis of delusional and hallucinatory state in a patient with psychoactive drug use. At ward, we conducted another blood withdrawal and the serum obtained was stored at -20 °C and sent to the Pavia Poison Control Center, to identify possible substances taken for recreational use. Identified substances included the NMDA inhibitors methoxphenidine. He admitted having taken this drug to find the courage to speak to the priest and ask him to meet the Pope, so that his application to become a priest could be received favorably. We reintroduced 800 mg/day valproate and 15 mg/day aripiprazole, confident that as soon as we discharge him he would quit, which the patient honestly announced to us during his 6-day hospitalization. He also asked to speak with a priest while in the hospital so to forward his application for becoming a priest, because it is some time (he reported several years) that he hears God's voice prompting him to become a priest

On June 30, 2016, the patient returned to our Hospital's ER with a compulsory hospitalization proposal because under the influence of substances he had taken he became verbally aggressive, agitated and yelled to his neighbors that he was God and the Emperor of Rome; we rehospitalized him immediately and performed blood withdrawal and obtained his urine to send to the Pavia Poison Control Center. They found

deschlorketamine in urine, while his blood was clean. His mother found in his house sachets containing crystals and send them to the above Poison Control Center, which found the synthetic cannabinoid, 5F-ADB. He was hospitalized for two weeks. He was prescribed 30 mg/day aripiprazole and 5 mg/day clonazepam. He denied taking 5F-ADB, which he said was a homage of the internet sellers, but cannabinoids did not really ever attracted him, while confessing that his drug assumption had the purpose to communicate with God more closely. He supported that only near-death experiences were able to allow him to approach God. This explained his preference for dissociative NMDA-inhibitors. He was discharged with the above prescription, which he did not fail to discontinue as soon as he was let alone.

Five days later he was brought by the Police to the Hospital's ER because he had engaged in property damage *en plain air*. He was severely agitated and confused, and was dissociated. His heart rate was 145 beats per min (bpm), blood pressure was systolic 145 mmHg and diastolic 105 mmHg, body temperature 38°C; arterial blood pH, 7.38; pO_2, 66 mmHg (low); pCO_2, 43 mmHg; sodium, 140 mM/L; potassium, 4.3 mM/L; calcium, 1.15 mM/L; glucose, 66 mg/dL; and lactate, 1.7 mM/L (elevated). On the electrocardiogram (ECG), the patient displayed ST interval elevation; blood chemistry abnormalities included elevated white blood cell count (WBC) (24,000), of which 20,000/mm^3 were neutrophils; creatinine 1.77 mg/dL (normal laboratory range [NR] 0.7-1.25 mg/dL); aspartate amine transferase, 90 U/L (NR, 5-34); alanine amine transferase, 211 U/L (NR, 5-55); lactate dehydrogenase, 374 U/L (NR, 125-220); D-dimer, 414 ng/mL (NR, 0-243); creatine-kinase, 375 U/L (NR, 30-200); and high-sensitivity cardiac troponine I, 488.5 pg/mL (NR, 0-34.20). His blood was alcohol-free, while urine toxicological examinations revealed the presence of phencyclidine (PCP). Chest X-rays and superior and inferior abdominal, and myocardial ultrasounds showed no alterations. He received 2,000 mg paracetamol and rehydration, in agreement with the Pavia Center. Three and six hours later, we repeated high-sensitivity cardiac troponine I levels, which were 487.7 pg/mL and 324.4 pg/mL, respectively, and which 12 hours later had dropped to 90.6 pg/mL. Blood gas analysis performed in the same time, showed a trend towards normalization of pO_2 (84 mmHg), heart rate was 87 bpm, while ST elevation on the ECG persisted. WBC had dropped to 13,000 cells/ mm^3. Blood creatinine had dropped to 0.77 mg/dL and D-dimer to <21 ng/mL, while aspartate amine transferase had dropped to 59 U/L, alanine amine transferase to 130 U/L, and lactate dehydrogenase to 268 U/L, which was a clear trend towards normalization, but still not in the normal range. Differently, blood creatine-kinase levels had risen to 866 U/L, indicating continuing damage.

Twenty-four hours later, high-sensitivity cardiac troponine I levels were back to normal levels (20.6 pg/mL), while the trend to normalization of other blood chemistry measures had continued (aspartate amine transferase, 51 U/L; alanine amine transferase, 105 U/L; lactate dehydrogenase, 250 U/L. Since there was no immediate life threat, the patient was discharged against medical advice.

We obtained blood and urine samples which we sent with the bags to the Pavia Poison Control Center, the clinical-toxicological coordinating Center of the National Early Warning System (N.E.W.S), in collaboration with the Department of Anti-Drug Policies, Italian Government, Presidency of the Council of Ministers, Rome, Italy. We performed liquid and gas chromatography/mass spectrometry (LC-MS/GC-MS) to search in urine for atropine, scopolamine, methoxetamine, ketamine and its metabolite norketamine, butylone, mephedrone, methylenedioxypyrovalerone (MDPV), dimethylcathinone, buphedrone, ethcathinone, 4-fluoro-methcathinone, pentedrone, methedrone, ethylone, methylone, pentylone, 1-Naphyrone, 4-methylethylketone (4-MEC), levamisole, 4-fluoro-amphetamine (4-FA), *p*-methoxetamine (PMA), *p*-methoxymethamphetamine (PMMA), methylenedioxyaminoindane (MDAI), aminopropyl benzofuran isomers (5/6 APB), dimethyltryptamine (DMT), 4-bromo-2,5-dimethoxyphenylethylamine (2-CB), 4-iodo-2,5-dimethoxyphenylethylamine (2C-I), 2,5-dimethoxy-4-propylthiophenylethylamine (2C-T-7), 4-Ethyl-2,5-dimethoxyphenethylamine (2-CE), 2,5-dimethoxy-4-bromoamphetamine (DOB), 2-(4-bromo-2,5-

dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25B-NBOMe), 2-(4-Chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethan-1-amine (25C-NBOMe), 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe), 2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]-4-(propylthio)-benzeneethanamine, monohydrochloride (25T7-NBOMe), 2-(2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine, monohydrochloride (25H-NBOMe), 2-(2,5-dimethoxy-4-methylphenyl)-N-(2-methoxybenzyl)ethanamine (25D-NBOMe), and 2-(4-ethyl-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25E-NBOMe). Screening for synthetic cannabinoids in blood was performed with LC-MS and regards the following: JWH-007, JWH-016, JWH-018, JWH-019, JWH-073, JWH-081, JWH-098, JWH-122, JWH-147, JWH-200, JWH-203, JWH-210, JWH-250, JWH-251, JWH-302, JWH-307, JWH-398, JWH-48,098, RCS-4, RCS-8, MAM 2201, WIN-55212, XLR-11, UR-144, AM-2201, AM-2233, and AM-694

June 10, 2016: Methoxphenidine found in urine

July 6, 2016: Deschlorketamine crystals, 5F-ADB in bags. Deschlorketamine in blood

July 22, 2016: Ethylnorketamine, norketamine, tramadol, nortramadol, and methoxyphencyclidine in urine. The laboratory analysed also bags and found methoxyphencyclidine crystals

July 29, 2016. The patient no longer took prescribed drugs, but reported no illicit or smart drug use at his visit at the Psychiatric Community Service. He went to the visit accompanied by his mother, who took an active part at her son's interview. The patient was scheduled to receive support psychotherapy in September 2016

September 6, 2016. Returned alone and received a session of support psychotherapy with an experienced physician and psychotherapist. He reported being out of drugs, although somewhat tense. He continued being interpretative

September 13, 2016. Second psychotherapy session; the patient was apparently well and reportedly did not crave for near-death experiences. He refused to return taking medication

September 20, 2016. Third psychotherapy session; the patient was stable. He came to the visit accompanied by his parents, who just spoke with the psychotherapy at the end of the visit

September 27, 2016. Fourth psychotherapy session. The patient was well and satisfied, but was still interpretative. He came accompanied by his mother, who stated at the end of the session that her son was healthy and that personality testing she had him take last week at a private center, confirmed this, and that he no longer needed psychological visits. She waved the results of this testing in front of the eyes of the caring clinicians. The results of personality tests however, were very unfavorable, with MMPI-2 displaying scores on the Paranoia and Schizophrenia Scales above the threshold and scores on the Psychasthenia scale in the normal range. After this visit, he was lost to follow-up

April 22, 2017. A common acquaintance reported to the Director of the Community Mental Health Service that the patient was socially withdrawn, was living with his parents, with his mother controlling all his actions and his father limiting himself to a peripheral role. His mother was engaging in lawsuits and had an aggressive attitude

September 30, 2017. Patient continues living with his parents, and his few moments of rebellion are rapidly controlled by his family environment. He is not taking medication and reports not to purchase drugs, but his mother told us she caught him pursuing drug purchase on the internet. She described him as asymptomatic, but she is not a clinician

Details on mortality and toxicity of the NMDA inhibiting drugs used by our patient and relationship to his symptoms

Methoxetamine (Wikström et al., 2013; Wiergowski et al., 2014; Adamowicz, & Zuba, 2015; Chiappini et al., 2015), methoxphenidine (Elliott et al., 2015), 3-methoxyphencyclidine (Bakota et al., 2016; Johansson et al., 2017), and 4-methoxyphencyclidine (McIntyre et al., 2015) have been associated with fatalities. Pulmonary edema and liver congestion were common elements in most NPS-related deaths; it is possible that cardiovascular untoward effects induced by the use of NMDA antagonists trigger events leading to death. NMDA receptors are involved in human calcium regulation that may affect the function of the heart (Marques-Lopes et al., 2012) and their reduction in rat nucleus tractus solitarius has been associated with blood pressure increase (Bozic & Valdivielso, 2015), a universal finding in NMDA antagonist intoxication.

The symptoms of nonfatal 3-methoxyphencyclidine intoxication described in three patients (Zidkova et al., 2017; Johansson et al., 2017) and another seven taking 3- and 4-methoxyphencyclidine promiscuously (Bäckberg et al., 2015) resembled our patient's clinical picture when the same drug was found in his urine, as did the clinical picture of another patient who assumed both 3-methoxyphencyclidine and methoxetamine (Thornton et al., 2017). However, methoxphenidine intoxication shares many of the cardiovascular features of the methoxyphencyclidines (Hofer et al., 2014; Helander et al., 2015; Lam et al., 2016) and so does methoxetamine (Sein Anand et al., 2012; Wood et al., 2012; Hill et al., 2014; Maskell et al., 2016). Our patient was aggressive similarly to the case reported in the French addictovigilance network (Champeau et al., 2017).

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