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Combined NMDA inhibitor use in a patient with multisubstance-induced psychotic disorder

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Abstract. Novel psychoactive substance use is a major social concern. Their use may elicit or uncover unpredictably as yet undescribed clinical pictures. We aimed to illustrate a multisubstance use case indistinguishable from paranoid schizophrenia, so to alert clinicians on possibly misdiagnosing substance-induced psychotic disorders. *Case report.* We describe a case of a 32-years-old man who started at 18 years with cannabinoids and ketamine, and is currently using NMDA antagonists. At age 23 he developed social withdrawal after suffering stranger assault, but did not consult psychiatrists until age 26; during this period he was using internet-purchased methoxetamine and ketamine and was persecutory, irritable, suspicious, and insomniac and discontinued all received medical prescriptions. He added dextromethorphan to his list of used substances. At age 31, while using phencyclidine and, for the first time, methoxphenidine, he developed a religious delusion, involving God calling him to reach Him, and the near-death experiences ensured by NMDA antagonists backed his purpose. He received DSM-5 diagnosis of multisubstance-induced psychotic disorder and was hospitalized eight times, six of which after visiting the emergency room due to the development of extreme anguish, verbal and physical aggression, and paranoia. He reportedly used methoxphenidine, methoxyphencyclidine, ethylorketamine, norketamine, and deschlorketamine, to achieve near-death experiences, and eventually to reach God in heavens. *Conclusions.* This case points to the need for better control of drugs sold on the internet. It also illustrates that people using NMDA antagonists may present clinical pictures indistinguishable from those of major psychoses and are likely to be misdiagnosed.

Key words: Methoxyphenidine; Methoxyphencyclidine; Methoxetamine; Psychosis, Multisubstance-induced; Internet drug market; NMDA antagonists

Background

Internet-purchased illicit drug use is becoming increasingly prevalent and a regulatory/legislative and public health problem. NPS use prevalence is currently unknown. The public health threat from their use stems from the poor knowledge of their effects, inadequate human testing, and mislabeling as bath salts, spices or research chemicals (Hohmann et al., 2014). Moreover, the uncertain labeling as legal or illegal and their frequent passage from one category to another, further adds to the confusion about their use (Wilkins, 2014).

NPS purchase was shown to occur for about 60% through the internet in a Swedish study (Soussan & Kjellgren, 2016), but a Dutch study the internet found **it** to represent a means for gathering information about NPS, with friends playing a major role (van Amsterdam et al., 2015).

Dissociative NPSs accounted for about 10% of total NPS use in one survey and methoxetamine, a ketamine-like substance, significantly outnumbered all other NPSs (Soussan & Kjellgren, 2016).

Case report

The police brought a 32-year-old man to the emergency room (ER) after he had kidnapped a priest and requested to speak to the Pope, because God prompted him to take the vows. He was compulsorily hospitalized at the psychiatric department with agitation and restricted consciousness. Blood and urine samples were negative for ethanol, benzodiazepines, cannabinoids, cocaine, amphetamine, methadone, opioids, and tricyclic substances. We sent 10 mL serum (kept at -20 °C) to the Pavia Poison Control Center (PPCC), which used gas chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry to identify the NMDA inhibitor methoxphenidine. He reportedly took methoxphenidine to give him the courage to kidnap the priest, and to facilitate his taking vows. We introduced 800 mg/day valproate and 15 mg/day aripiprazole, that the patient told us he would discontinue as soon as he was discharged. During his 6-day hospitalization he sought to speak to a priest. He reported that he was hearing for some years God's call.

His development was normal and his family history free from psychiatric disorders. As a youngster he had studied arts and became a successful painter. At age 18 he started using alcohol, cannabinoids, which he reported disliking, and ketamine. At age 20 he intensified drug use, meeting DSM-IV-TR criteria for multi-substance use disorder; meanwhile, he was increasingly withdrawing from social activities. He started working as a member of the administrative staff of his father's employers and organized exhibits of his paintings, but soon left his job, as he developed dysphoria and suspiciousness about colleagues. He sought help at a psychiatric community service and was prescribed 10 mg/day olanzapine. Psychotic symptoms improved, but relapsed upon treatment discontinuation the next month, hence he was hospitalized for 10 days, improved on 10 mg/day olanzapine and 2 mg/day haloperidol, and remained well for about one month. He developed insomnia and consulted a neurologist, who abruptly discontinued all antipsychotics and introduced amitriptyline. At about the same time he started using oral dextromethorphan syrup, initially for medical, and subsequently for recreational purposes. His anxiety increased unbearably along with insomnia; he reported concurrent agitation, fearfulness, appetite loss, and delusional mood. He was hospitalized for 18 days and treated with 1000 mg/day sodium valproate and 20 mg/day aripiprazole, diagnosed with DSM-IV-TR psychosis, not otherwise specified, improved for one month and then discontinued, feeling well and clear of substances. However, two months later he developed paranoia after using online purchased methoxetamine. Upon compulsory rehospitalization, he received again valproate/aripiprazole combination. He was discharged two weeks later and went to Northern Italy to visit a substance use specialist, who arranged for monthly sessions.

At age 28, during one session, he manifested verbal aggression, irritability, and restlessness, and tried to forcibly obtain dextromethorphan. After being compulsorily hospitalized, he was referred to our service, where he was administered 800 mg/day valproate and 15 mg/day aripiprazole. He was discharged 20 days later with DSM-IV-TR substance-induced psychosis and once again discontinued treatment. Between ages 28-31 he underwent no hospitalization and alternated periods of living with his parents and no substance use with periods of staying alone and engaging in online purchase and use of dextromethorphan, ketamine, and other unspecified drugs and alcohol consumption. At age 31 he returned to our hospital's ER for agitation and extreme anguish. He was discharged with a diagnosis of unspecified acute substance intoxication, but 20 days later he returned to ER and sent to our acute psychiatric care unit. After six days of 800 mg/day valproate and 15 mg/day aripiprazole he was discharged; he was no longer hallucinatory and denied delusions.

Twenty-five days later the patient was rehospitalized for two weeks due to violent and megalomaniac behavior after substance use he refused to reveal. We immediately obtained biological fluid samples and sent them to the PPCC along with bags his mother had found in his room. Deschlorketamine was found in urine and in

some of the bags, and the synthetic cannabinoid, 5F-ADB in other bags. He said that 5F-ADB was a gift from an internet dealer, but he never used it.

We prescribed 30 mg/day aripiprazole and 5 mg/day clonazepam and discharged him, but he immediately discontinued and engaged in property damage, that led to forcible rehospitalization. On admission he showed agitation, confusion, cardioacceleration, marginally higher diastolic blood pressure and body temperature, somewhat elevated lactate and lower pO_2 . With rehydration and 2,000 mg paracetamol, blood chemistry normalized 24 hours later. Despite his oppositional attitude, he provided signed, informed consent for publication of his case. Discharged against medical advice, he returned to community care. As expected, he immediately discontinued medication, but returned to four weekly scheduled visits at the community center, where he received support psychotherapy. He was apparently well at last visit, but then never returned. The last news from him (September 2017) were indirect, describing social withdrawal, embedding in family milieu, and poor autonomy. A detailed account of patient's clinical course is provided in [Supplemental Digital Content](#).

Discussion

Our patient started using NMDA antagonists 14 years ago, along with cannabis and alcohol, but increasingly concentrated on NMDA antagonist use. He never stopped substance use, and the psychosis he developed is apparently associated to the substances used, although cause-effect relations are always hard to demonstrate. He started purchasing drugs on the internet seven years ago, i.e., halfway in his drug use history. Through the internet, the patient was able to purchase and use a long list of drugs, mostly NMDA antagonists (Table 1). The unique feature of this patient is that he pursued only NMDA antagonist use with a specific, transcendence-related purpose.

The patient apparently, but not admittedly, ingested methoxetamine in December 2011; the drug became available by 2010 in UK and spread to the rest of the world since Chinese laboratories decided to produce it (reported in Maskell et al., 2016). This drug, like other arylcyclohexamines, is a noncompetitive NMDA antagonist that binds the dizocilpine site with higher affinity than ketamine and lower than phencyclidine (PCP) (Roth et al., 2013). It is still unclear if and to what extent methoxetamine blocks the dopamine transporter (DAT). Our patient developed delusions and auditory hallucinations while taking this drug (setting, substance purity, and morbidity, may affect presentation), while he showed more dissociative symptoms (derealization, absent-mindedness, amnesia) while on ketamine or when taking the newer NPS, methoxphenidine. The latter has been developed to overcome legal restrictions regarding arylcyclohexylamines and is a diarylethylamine that is a more potent NMDA inhibitor than PCP, while possessing weak antagonist properties for the norepinephrine transporter (NET) and DAT, but negligible affinity for the serotonin transporter (5-HTT) (Wallach et al., 2016). Clinical picture differences between these two NMDA antagonists may depend on their class (arylcyclohexyl- vs. diarylethyl-) and subtle differences in receptor profile.

Methoxetamine, methoxphenidine, 3- and 4-methoxyphencyclidine have been associated with fatalities; their toxicity has been described in various papers (see [Supplemental Digital Content](#)) and explain much of our patient's symptomatology.

The fact that our patient was a person with polysubstance use adds to clinical picture complexity and does not allow us to attribute individual symptoms to specific drugs. However, his preference for NMDA antagonists prompts us to attribute most of displayed symptoms during his long drug use history to glutamate receptor blockade, interacting with patient's personality characteristics. We know of very few patients so much dedicated to anti-NMDA drug consumption alone.

To face the current increase in NPS use based on internet drug purchasing, repressive measures taken against internet sellers appear to be ineffective, as closing vendor sites results in fast adaptation (Mounteney et al., 2016), reminiscent of Hercules' labor against the Lernean hydra. Public educational policies should focus on correctly informing people about NPS effects.

The current expansion of the NPS market and the trend to multisubstance use render the clinical presentations of persons who use and buy NPSs on the internet difficult to recognize and classify. Untoward reactions to drugs or drug combinations may arise any time during a drug use career and may be sometimes life-threatening. Sometimes, NMDA antagonists are used to seek near-death experiences, so people who use them should be warned that sometimes they may get dangerously close.

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