CASE REPORT

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Ketamine Self-Medication in a Patient with Autism Spectrum Disorder and Comorbid Therapy-Resistant Depression

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ABSTRACT

In this case report, we present an adult male patient with autism spectrum disorder and a comorbid (treatment-resistant) mood disorder with suicidality. He has been treated with numerous psychopharmaceuticals, most recently risperidone and valproic acid. He has been hospitalized several times and has attempted suicide. He displayed limited social functioning, repetitive behaviors, sensory hypersensitivity, anxiety, depressed mood, anhedonia, low energy, and chronic suicidality. Despite intensive treatment, he remained highly symptomatic and unable to work. After repeatedly self-medicating with ketamine, the patient reported that his depression and suicidality disappeared and that his autism spectrum disorder symptoms were reduced. This case study – along with previous clinical studies – suggests that ketamine is likely to be effective against depression and suicidality and potentially effective against (certain) autism spectrum disorder symptoms. However, increasing public awareness of the beneficial effects of ketamine may lead to more unsupervised and thus risky use of ketamine for self-medication.

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INTRODUCTION

In this case report, we present a patient with autism spectrum disorder (ASD) and a comorbid (treatment-resistant) mood disorder with suicidality. As self-medication, he used 50-60 mg of ketamine sublingually 2-3 times per week for 10 weeks. We describe the course of his illness and the effects of self-medication in the light of previous clinical research with ketamine. Autism spectrum disorder is a pervasive developmental disorder with symptoms that manifest themselves in 2 domains: (a) impairments in social communication and interaction that occur within multiple contexts and (b) restricted, repetitive patterns in behavior, interests, or activities.[1] Most individuals with ASD experience significant difficulties in various domains of life, including family, school/work, and social relationships.[2] Patients with ASD often experience comorbid psychiatric disorders, including major depressive disorder frequently accompanied by suicidality.[3] The exact etiology of ASD is still unknown.[4] Thus, current treatments focus on reducing symptoms and their sequelae. To improve and develop effective treatments for ASD, with or without comorbid depression, further etiological and pharmaceutical research is needed. Ketamine may present an avenue for pharmaceutical research in the treatment of ASD.

Ketamine is an *N*-methyl-D-aspartate receptor antagonist. It has been employed as an anesthetic and analgesic in clinical practice since 1970.[5] Ketamine has also shown to be effective in the treatment of depression,[6-8] has recently been registered for the indication "treatment-resistant depression,"[9,10] and is a promising intervention for acute suicidality.[11,12] Its antidepressant effects may be due to its regulatory effect on the availability of glutamate. Comorbidity of ASD and depression and suicidality is common,[13,14] and ketamine may have beneficial effects for this population. However, available clinical trials on the effectiveness of ketamine in patients with depression do not specifically address autism comorbidity.

Exploratory studies suggest that ketamine could be of value in the treatment of ASD with and without comorbid depression and/or suicidality.[15-17] In one case study, Wink et al[16] found a significant improvement in depressive symptoms after an adult woman with ASD and comorbid depression was treated with intranasally administered ketamine. The woman also demonstrated a significant increase in eye contact, which could indicate an improvement in ASD-related characteristics.[18] In another case study, Kastner et al[19] described the beneficial effects

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of ketamine in a 15-year-old male patient with ASD and comorbid bipolar and obsessive-compulsive disorder. After treatment with ketamine (100 mg) and propofol (100 mg), the patient showed short-term (36 hours) recovery from ASD symptoms, including the ability to speak in full sentences and to make eye contact with his parents. In a recent randomized crossover study with 21 adolescents with ASD,[20] no significant effects of intranasally administered ketamine (30 and 50 mg) on social impairment were found. However, the researchers note that the population was heterogenous and the study group was very small, while the outcome measure may not have been optimally chosen. Finally, there are tentative indications from preclinical studies that ketamine may reduce ASD symptoms related to social behavior, for example, research in rodents suggests that ketamine repairs brain abnormalities resulting from 2p16.3 (NRXN1) deletion, a chromosomal abnormality associated with autism.[21,22]

CASE PRESENTATION

Patient A is an adult male veterinarian living in the Netherlands with a partner and 3 children. He has a 30-year history of symptoms, initially diagnosed as bipolar disorder (due to behavior interpreted as manic) with multiple severe depressions and suicidality. He was treated with more than 15 different psychopharmaceuticals, hospitalized several times, and attempted suicide once. In 2017, his primary care physician prescribed risperidone and subsequently referred him to a psychiatrist for depressive symptoms and suicidality. During his treatment by the psychiatrist, a suspicion of ASD and personality problems arose. The patient's behavior showed clear characteristics of autism, including a lack of initiative in social matters, sensitivity to (assumed) injustice, rigidity, and avoidance of social interactions. In addition, there were serious and systemic relationship problems. Subsequently, he was diagnosed with depression and autism. The diagnosis of autism was based on a self-report questionnaire (Autism Questionnaire),[23] a semi-structured interview according to DSM-5 criteria for ASD, and a hetero-anamnesis with his partner. The diagnosis of autism was supported by a retrospective analysis of his childhood. The patient recognized most of the ASD-related symptoms. He tended to think analytically and to rationalize. He also found it difficult to describe his own emotions in words or to empathize with the feelings of others. Due to hypersensitivity to tension and stress, he tended to withdraw. This caused tension between Mr A. and his partner, which they attempted to resolve through relationship therapy, though no significant improvements resulted. Due to the chronic nature of his complaints, he was referred to an ambulatory rehabilitation team for further treatment, including mood stabilization with valproic acid (Depakine®). Despite this, his mood worsened, and he became more suicidal and distant from his family and social responsibilities. In the course of a follow-up appointment, the patient revealed his self-medication with the pharmaceutical ketamine. He had been influenced by a radio program describing beneficial effects of ketamine on treatment-resistant depression. He treated himself with 50-60 mg racemic ketamine taken sublingually 2-3 times a week for 10 weeks, with a 1-week break at week 6. He stopped taking risperidone in the second week of his ketamine use because he felt it was having little effect.

Written informed consent form approval was obtained from the patient for this case report.

MAIN POINTS

- Ketamine is a widely available recreational drug.
- Ketamine might be effective in patients with an autism spectrum disorder with or without depression.
- Increased public awareness of the therapeutic effects of ketamine may increase unsupervised use of ketamine as self-medication.
- Unsupervised self-medication with ketamine is not without risks. Guidelines for the therapeutic use of ketamine (and other psychedelics) by mental health professionals are urgently needed.

OUTCOME AND FOLLOW-UP

During the first 4 weeks of his self-medication with ketamine, the patient experienced a profound and persistent positive effect on his mood, with reduced pessimism and increased mental flexibility. He describes the effect of ketamine on his mood by saying: “Ketamine opens a door for me to pleasant memories and I am able to pick things up again. I become aware of tastes and smells again. I exclude myself less from the world around me and I am less indifferent. I feel more space, which allows me to get out of my reflexive behavior. I am better able to transform my thinking into doing and to take initiatives. I feel as if I have come out of the box in which I am normally trapped. I become alive. I am better able to reflect. I've been sleeping on a saggy bed in the barn for two years and suddenly I started cleaning up.” As for the effect of ketamine on his relationships with others, he says: “When I tend to get into an argument with my spouse, I do not immediately get defensive and can distance myself. For over a year and a half I didn’t respond to mail, not even from family, but I can do that now too.” He continues: “Last week I contacted [a colleague]. He was very impressed with my progress. I have never been complimented on being empathetic. He was touched that I had sent him a letter and a poem to support him in the difficult circumstances he’s in right now. Normally I am very blunt, critical, and direct. If I hurt their feelings, I did not care. For me, facts are important and not politics. I have changed my approach to people. Instead of being

judgmental I formulate questions so they can show their feelings without feeling attacked. Instead of facts that matter, I give space to people's concerns." He further notes: "I felt more empathetic and had fewer autistic thought patterns with ketamine. I didn't extensively apply logic to things the way I normally do (at least not to the same degree) and I felt less locked in my head, if you know what I mean." Based on the above experiences, there appears to have been a rapid and beneficial effect of his ketamine use on his depressive symptoms. In addition, he seemed to function better at the interpersonal level, although it is not entirely clear whether this was a consequence of his improved mood or whether there was also a direct beneficial effect of ketamine on his ASD symptoms, for example, less reflexive behavior and less distancing. Mr A. likens the treatment with ketamine to a reset button, with certain acute effects. He became aware of his surroundings, and his negative thoughts shifted to the background. He was able to detach himself from the negative thoughts and could observe them without their affecting his mood. His automatic thinking was "short-circuited," allowing him to escape negative spirals. He was careful not to fall back into old habits, even after the ketamine wore off. The patient also noted that his experiences were particularly pleasant and effective when he took the ketamine a few hours before going to sleep. The next day he would wake up feeling refreshed. Mr A. further noticed that the dose of ketamine did not make much difference. However, when he once experimented with a "really high dose," it became "too much of a good thing." He always guarded against possible dependence and side effects, but these did not occur. After 7 weeks, Mr A. stopped his ketamine use because he felt "happy and balanced and was no longer suicidal." Since then, 20 weeks have passed during which he "still feels balanced, frets less, and experiences himself as positive and creative: the depression seems to be over." In close consultation with his psychiatrist and social psychiatric nurse, 3 months after he discontinued his ketamine use, his treatment was completed. At 6 months follow-up, the patient reported significant improvement in his symptoms.

As a result, the patient returned to work and was able to enjoy a healthy and functioning lifestyle, an effect that was still present at 12 months follow-up. At both 6 and 12 months follow-up, Mr A himself noted a continuing improvement in his symptoms. Furthermore, he remained without depressive symptoms and was engaging in daily exercise. The relationship with his partner and his obsessive behavior remained unaffected during this period.

DISCUSSION

This case study describes the experience of a man with ASD and comorbid treatment-resistant depression and suicidality. Repeated oral/sublingual use of ketamine in sub-anesthetic doses (50-60 mg) was associated with a reduction in depressive symptoms and the resolution of suicidal thoughts. In addition, he experienced an alleviation of some core symptoms of ASD, including an improvement in social communication and interaction, reduced repetitive behaviors and rigid thinking patterns, and improvements in his ability to empathize with others. Together with previous evidence from the literature, the results of this case study suggest that ketamine offers possibilities for the treatment of ASD with (and perhaps without) comorbid depression. Comorbid psychiatric symptoms are common among adults with ASD, especially depression, anxiety, and obsessions[24] but also increased suicidal thoughts.[25] Core symptoms of ASD, such as difficulty or inability to express emotions and thoughts and social isolation, increase the risk of comorbid depression.[26] In the current case, it is difficult to know whether the increased risk of suicide was due to ASD or depression. However, research by Cassidy et al[25] suggests that the risk of suicide is higher in ASD cases with comorbid depression than in ASD cases without depression. Further, a study by Richa et al[26] further shows that suicide and mortality are especially common in high-functioning individuals with ASD. Due to these risk factors, there is an urgent need for prompt diagnosis and treatment of depressive symptoms in this group.[27] Patient A reported a marked reduction in his depressive symptoms and suicidality after repeated self-administration of oral ketamine without significant side effects. This fits well with the literature on the effect of ketamine in the treatment of (treatment-resistant) depression, bipolar disorder, and suicidal behavior[28] and the limited side effects of this medication.[29] Some studies have suggested that in patients with treatment-resistant depression, ketamine often shows a rapid effect, but that depressive symptoms may return after a few days or weeks.[29,30] This was not seen in the current case. In addition to the reduction of depressive symptoms and suicidality, our patient also described reduced rigidity in his thinking and behavioral patterns and an increased ability to empathize with others. Similar changes were reported in a previous case report.[16] After repeated use of intranasally administered ketamine, a 29-year-old woman with a diagnosis of ASD reported a marked increase in cognitive flexibility, less resistance to change, and more relaxed interaction with others.

However, in this case study, the reduction in ASD-related symptoms is not necessarily a direct effect of the ketamine. The patient's rigid thinking and reduced social skills may have been magnified by his depression, and by reducing the depressive symptoms, ketamine may have alleviated his ASD-related thinking style and behavior.

This case report has both strengths and limitations. The strengths are primarily the detailed description and verification of the ketamine intervention outside a professional treatment setting and the patient's reflections

on his experiences. The main limitations are the absence of standardized information (questionnaires on depression, suicidality, and ASD), the limited availability of information sources other than the patient (family/friends), and the absence of long-term follow-up information after cessation of ketamine use beyond this publication date. Moreover, as mentioned above, it is not entirely clear whether the effects on ASD symptoms are due to the reduction in depressive symptoms or whether there are also direct effects of ketamine on ASD symptoms.[19] In addition to potentially positive effects of ketamine, this case report suggests that increased public awareness of the effectiveness of ketamine and other psychedelics in the treatment of psychiatric disorders may lead to unsupervised self-medication. The use of ketamine is not entirely without risk[31] and little is as yet known about how optimal results can be achieved in terms of the route of administration (oral, intranasal, intravenous), the number and frequency of ketamine sessions, the doses to be used, and the combination with psychotherapeutic and environmental interventions.[32-34] We hope that the increase in knowledge about the value of psychedelics in the treatment of psychiatric patients will be accompanied by explicit guidelines about their application and by proper regulation of psychedelic treatment practice with guarantees for the quality and safety of the interventions offered.

Informed Consent: Written informed consent form approval was obtained from the patient for this case report.

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