Selective Use of Ketamine in Patients with Psychotic Disorders

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In this article, Pullara[1] discusses the case of a patient with an underlying psychotic disorder who improved after the administration of ketamine. This dramatic improvement was noted after the failure of numerous trials of both typical and atypical antipsychotic medications. Of particular interest is the effect of the antipsychotic clozapine on ketamine's receptor activity, and its potential implications for the use of ketamine as a treatment for psychiatric conditions in patients with psychotic disorders.

Ketamine was originally discovered in 1962 and used as an aesthetic from the 1970s onward [2]. In addition to anesthesia, ketamine has been used in the treatment of asthma [3], super-refractory status epilepticus [4], and pain management [5]. In the early 2000s, research into its antidepressant effects was undertaken with small scale studies showing positive results [6]. While intravenous ketamine has not been approved for the treatment of depression, it is commonly used off-label, and its enantiomer esketamine, a nasal spray formulation, was approved for treatment-resistant depression in March 2019 [6,7]. During the same period as the antidepressant investigations, additional research was conducted looking at the use of ketamine as a primary agent for the treatment of suicidality [8,9,10] and substance use disorders [11].

Ketamine exerts its effects by binding to multiple different receptors in the brain including, but not limited to: opioid receptors [12], alpha receptors [13], the D2 receptor [14], 5HT-2A [14] and 5HT3 [15] receptors, AMPA receptors [16], and the PCP site 2 receptor [17]. The primary binding of ketamine occurs at the NMDA receptor, where ketamine acts as an ionotropic glutamate uncompetitive antagonist [18,19]. While the precise mechanism of action has not yet been elucidated, it is likely to be multifactorial, given the molecule's receptor heterogeneity. Regarding Pullara's case report patient, it can be hypothesized that the NMDA receptor antagonism and D2 Receptor partial agonism played an outsized role in the resolution of the patient's symptoms.

It has been known since shortly after its development, that ketamine can exacerbate underlying symptoms of psychosis [20]. Given this knowledge, ketamine is not routinely administered to patients with schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders. Additionally, it is known that clozapine, with its high receptor heterogeneity, can counteract the psychotic effects caused by ketamine via D2 receptor antagonism [20]. However, this does not explain why a previously psychotic patient would have near spontaneous resolution of psychosis after a single injection of ketamine. Numerous hypothetical reasons could account for this anecdotal response, but at least a few should be further investigated.

Patients who have schizophrenia develop major depressive disorder (MDD) at elevated rates. With an estimated prevalence around, 40% on average [21]. MDD rates can increase to 60% during an acute episode and have been reported as high as 20% in chronic schizophrenia [22]. In total, up to 80% of patients with schizophrenia will have a major depressive episode at some point in their disease course [23]. The relatively frequent occurrence of MDD in patients with schizophrenia has also proven difficult to treat. Limited evidence exists for the use of antidepressants and psychotherapy in the treatment of depressive symptoms in patients with schizophrenia [23,24]. While antipsychotics have some antidepressant effects, it is unclear if these effects are substantial enough to treat MDD or other depressive disorders in patients with psychotic illness. Depression in patients with psychosis is possibly due to the potentially unique pathway that depressive symptoms emerge from in psychotic patients. It has been theorized that depression may be intrinsic to psychotic disorders. Depressive symptoms may be caused, influenced, or exacerbated by psychosocial factors such as being diagnosed with a psychotic disorder, childhood trauma, or significant

psychosocial stressors. Based on the currently available evidence, the structural brain changes and neuroinflammatory modulation seen in schizophrenia patients correlates strongly with similar changes noted in unipolar depression patients [23]. It is, therefore, not unreasonable to hypothesize that if Pullara's patient was experiencing a severe major depressive episode with potentially psychotic features on top of her known schizophrenia that the use of the novel antidepressant agent ketamine could potentially alleviate the depressive symptoms without any risk of exacerbating the psychotic features given the concurrent use of clozapine. This would also explain why the psychotic symptoms returned so quickly as the antidepressant effects of ketamine are relatively short-lived [25].

A less likely theory is that the combination of ketamine and clozapine exerts a synergistic and heretofore unknown effect that is beneficial in patients with psychotic disorders. Alternatively, the dissociative and euphoric effects that ketamine induces may cause the patient to appear calmer and more subdued. Lastly, this may be simply an anecdotal case that cannot be replicated, and the dramatic effect of the ketamine on the patient was nothing more than a placebo response. In any event, further research should be conducted to elucidate further the efficacy of ketamine in patients with psychotic disorders.

The future therapeutic implications for ketamine are vast and include treatment-resistant depression, treatment of acute suicidality, and substance use disorders. The potential use of ketamine to treat refractory depression in patients with schizophrenia or another psychotic disorder who are on antipsychotics that block the psychosis-inducing symptoms of ketamine is a novel area of study that psychiatry should pursue even if it produces negative results.

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