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Letter to the Editor

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Dopamine D_3 partial agonists in the treatment of psychosis and substance use disorder comorbidity: a pharmacological alternative to consider?

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The prevalence of any substance use disorder (SUD) and schizophrenia comorbidity is around 42%. This dual diagnosis is associated with a higher severity of symptoms, more relapses and hospitalizations, an increased risk of nonadherence, and worse prognosis. The treatment of this dual diagnosis is markedly challenging. To date, pharmacotherapy studies in this dual diagnosis have been limited. Antipsychotics continue to be the treatment of choice, and the use of second-generation instead of first-generation antipsychotic medications may be preferred due to greater tolerability and decreased likelihood for developing extrapyramidal side effects in people with SUD. However, there is no evidence for any differential benefit for one antipsychotic over another for patients with psychosis and coexisting SUD. Similarly, the evidence of superiority between long-acting injectable antipsychotics and oral antipsychotics is very scarce.[1]

Drugs with a dopamine D_2 receptor partial agonism have been investigated as a possible target of treatment for patients with psychosis and SUD comorbidity during the last decade. This pharmacological mechanism of action provides a better tolerability over dopaminergic antagonists as a main advantage. Moreover, partial agonists are less disruptive on the functionality of neurons because they tend to normalize and stabilize the tone of dopaminergic neurotransmission. All of this has promoted that psychiatrists on current routine practice consider the use of partial agonists, like aripiprazole, as the second option in the acute setting as well as the treatment of choice in the maintenance setting for patients with psychosis and SUD.[2]

In recent years, preclinical and clinical research have shown dopamine D_3 receptors as a promising therapeutic target for many neuropsychiatric disorders, such as psychotic disorders or SUD, among others. Anatomically, D_3 receptors show a high distribution in the mesolimbic system, brain area where are structures as nucleus accumbens and which is critically involved in the regulation of motivation and reward. Functionally, evidence suggests that D_3 receptor is an autoreceptor with inhibitory effects on dopamine impulse flow and dopamine release. Experimental drugs targeting specifically D_3 receptors, both antagonists and partial agonists, have constantly been investigated for treating schizophrenia. It has suggested that blockade of D_3 receptors could improve cognitive and negative domains of schizophrenia. Moreover, these receptors haven been related to SUD suggesting that they are involved in drug-related reward and drug-intake, as well as in behavioral sensitization, including reinstatement and drug-seeking behavior. In fact, increases in D_3 receptors expression have been found in animals chronically exposed to psychostimulant drugs.[3]

Recently, US Food and Drug Administration and European Medicines Agency have approved the newer antipsychotic cariprazine for acute and maintenance treatment of adults with schizophrenia. Cariprazine differs from other antipsychotics in its mechanism of action. It is a dopamine D_3 and D_2 receptor partial agonist, with 10-fold higher affinity for D_3 receptors than for D_2 receptors. In fact, it is the dopamine partial agonist antipsychotic, compared with aripiprazole and brexpiprazole, with the highest affinity for D_3 receptor.[4] This pharmacodynamic profile could be beneficial in patients with psychosis and SUD. Although there is not enough evidence, cariprazine has demonstrated anti-abuse potential in a preclinical study. Specifically, cariprazine, as well as aripiprazole and bifeprunox, was able to reduce the rewarding effect of cocaine and attenuated relapse to cocaine seeking in rats. These results suggest that cariprazine may have relapse-preventing potential in addition to its well-established antipsychotic efficacy.[5]

In conclusion, antipsychotics with a dopamine partial agonism seem to provide potential clinical advantages in the treatment of psychosis and SUD comorbidity. Although there is more evidence with those drugs that has more specificity on dopamine D_2 receptor, recent studies postulate drugs targeting dopamine D_3 receptor as a pharmacological alternative to consider. Further research and empirical evidence from clinical practice routine will clarify its usefulness and efficacy in this dual diagnosis.

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