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## **Oral long acting antipsychotic penfluridol as a harm reduction treatment in a patient suffering from untreated schizophrenia and multiple drug dependence: a case report.**

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Dear Editor,

Dual diagnosis, the association of addictive and psychiatric disorder, including schizophrenic disorders, is common in marginalized population, affecting up to 55% of such individuals (Schütz et al., 2019). Promoting adherence to medication is especially challenging in this sub-group. Psychosis and substance use may dramatically increase the burden of both cognitive and positive symptoms.

Penfluridol is a first generation long-acting oral dopamine receptor antagonist, also known as typical antipsychotics. Because of its very high lipophilicity, penfluridol distributes extensively in fatty tissues (Migdalof et al., 1979). This depot effect produces a particularly slow release of drug from the adipose tissues, resulting in detectable plasma concentrations up to 168 hours after administration, associated with prolonged activity. When administered orally at doses of 20 to 100 mg once a week, it has shown superiority in keeping in treatment patients with schizophrenia compared to intramuscular depot typical antipsychotics (Soares and Silva De Lima, 2006) and has a similar profile in terms of efficacy and adverse effects compared to chlorpromazine (Nikvarz et al., 2017).

We present the case of an outreached patient met in the supervised drug consumption room (SDCR) of Paris, who agreed on taking oral penfluridol as a harm reduction approach.

The case is a 40 years old women. She suffers from an untreated schizophrenia with co-occurring crack-cocaine, opioid and sedative dependence according to the Diagnostic and Statistical Manual for Mental Disorders - fourth edition, text revised (DSM-IV TR). She integrated "Housing First" facility, a program dedicated to homeless patients with dual disorders. She underwent several previous psychiatric hospitalizations but failed to maintain outpatient treatment. She previously received monthly depot olanzapine injections for a few months with improved clinical outcomes. She asked to switch to oral olanzapine, which was prescribed at a dosage of 20 mg per day, but she rapidly discontinued her treatment and follow-up. On request of the team, we met her at the SDCR at the end of 2019. We noted marked thought and behavioral disorganization and - to a lesser degree - intrapsychic hallucinations and delusions. She reported injecting 400 mg of morphine sulfate, smoking eight crack rocks and using 60 mg of diazepam bought off the street on a daily basis. She did not receive any psychiatric nor opioid agonist treatment (OAT). At that point, we anticipated that the proposal of an appointment in an addiction or psychiatric outpatient center in order to initiate proper clinical care would be premature, and that the patient would not adhere to this care plan. Despite the severity of psychotic symptoms, the criteria for compulsory admission were not met: there was no immediate danger to herself nor to others, she accepted psychiatric interviews delivered on-site at the SDCR and she applied basic counseling for harm reduction. In the course of our interviews, she agreed to take penfluridol 20 mg per week, which was offered to alleviate her psychotic symptoms, especially the disorganization syndrome. Then, she devoted time to social follow-up and interact more easily with others. She entered an addiction outpatient center where she was proposed OAT consisting of methadone taken home weekly, pursuing penfluridol with continued psychiatric care and benefiting from psychosocial support. Her complete pharmacological treatment included: methadone 100 mg per day, penfluridol 20 mg per week, diazepam 50 mg per day, zolpidem 20 mg per day, hydroxyzine 150 mg per day. Cardiac monitoring was performed for checking QT interval. Ten weeks after penfluridol initiation, dosage was increased to 40 mg per week because of residual delusions. At this dosage, she suffered from akathisia, hence propranolol 40 mg was introduced. Addiction care led to help her decrease opioid injections to 100 mg of morphine sulfate per day while maintaining crack consumption. Still, the improvement of both her psychiatric

and opioid use disorders helped to maintain her in the “Housing First” program, where she still lived in December 2020.

Penfluridol can be seen as a «hook treatment», that is, as a low-threshold strategy to engage patients with severe psychotic symptoms to engage in more complete care, second generation antipsychotics (e.g olanzapine, clozapine). Because of its long duration activity, one should propose this treatment to patient who are not neuroleptic naive, in the event of the occurrence of adverse effects. Unfortunately, to our knowledge, there is no published study comparing penfluridol to second generation antipsychotics.

Regarding the diagnosis of schizophrenia, the use of psychostimulants (e.g crack-cocaine) increase the likelihood of both false-positive and false-negative diagnosis. These substances can thus elicit psychotic symptoms and their use is more prevalent in people with schizophrenia than in those without. In the current case, we couldn't formally exclude the diagnosis of cocaine induced-psychosis because of the late onset of the disease - around 35 years old and because cessation of crack use in hospitalization was associated with a marked reduction of psychotic symptoms. However, we maintained the diagnosis of schizophrenia because the disorganization syndrome persisted even during short periods of crack abstinence.

The patient's akathisia was likely due to penfluridol alone. The literature on this topic reported associations between alcohol dependence and akathisia among schizophrenia patients (Salyers and Mueser, 2001), however, this was not the case for this patient, who abstained from alcohol.

Finally, this case also illustrates how clinicians find themselves balancing the usefulness of benzodiazepines for relieving anxiety symptoms and extrapyramidal side effects while considering the risk of abuse and worsening the prognosis of the dual disorder.

The once-a-week intake of penfluridol seems particularly adapted for erratic observance patients out of reach of care centers and the oral use may reduce patients' reluctance sometimes associated with intramuscular injection. Proposing such treatment could be a valid option between compulsory admission, which is not often indicated, and therapeutic abstaining, which leads to poor outcomes in psychosis. Although the latter option would be more acceptable as regards the ethics of harm reduction structures, medications such as penfluridol may help to fill this huge gap and have its place in these structures by being able to reduce psychotic symptoms while maintaining therapeutic alliance and favoring patients' engagement in specific care.

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