

**Titre du résumé :** Alcohol use disorder and schizophrenia comorbidity : translational approach to explore common vulnerability

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### **Description précise des objectifs**

We have previously demonstrated that the NVHL model of schizophrenia in rats display vulnerability to AUD after alcohol intake during adolescence (Jeanblanc J et al 2015). We sought to confirm this result in other animal models and analyze the effect of a CB1 agonist. In humans, we explored motivation for alcohol drinking in patients with schizophrenia. Drinking motives are considered to be major predictors of alcohol consumption and alcohol-related problems. However, these motives have been poorly investigated in patients with schizophrenia. The aim of the present study among patients with schizophrenia was twofold: 1) assess the validity of the short form of the

Drinking Motives Questionnaire-Revised (DMQ-R SF); and 2) investigate the relationship between drinking motives and comorbid alcohol use disorder (AUD). Using etiologically different animal models of schizophrenia (a genetic model: MAP-6 KO mice and a rat neurodevelopmental model: Methylazoxymethanol acetate (MAM) of schizophrenia), we tested their alcohol intake during adolescence and at adulthood, after or not, co-exposure to a CB1 agonist during adolescence.

### **Matériel et méthodes**

A total of 179 patients with schizophrenia were approached to participate in the study. DSM-5 criteria were used to identify patients with comorbid AUD (AUD+; n = 42) and non-abstinent patients without comorbid AUD (AUD-; n = 71). Female and male MAP-6 KO (and WT) mice were given access, or not, to alcohol during adolescence and their alcohol intake and sensitivity to the ataxic effects of alcohol was measured during both adolescence and at adulthood. Alcohol intake was measured during adolescence and adulthood in the MAM neurodevelopmental model of schizophrenia after exposure or not to alcohol and/or the CB1 agonist CP55,940 during adolescence in male rats.

### **Résultats et conclusions**

Group comparisons revealed higher use of alcohol and other substances, as well as stronger drinking motives among AUD+ patients, while groups were comparable concerning clinical features of schizophrenia, including psychotic symptom dimensions and severity. Regression analysis showed that the AUDIT score was significantly associated with two internal drinking motives: enhancement and coping. In mice, consumption of alcohol during adolescence induces an increase in alcohol intake and a decrease in the ataxic effect of alcohol at adulthood. In the MAM model of schizophrenia, rats exposed either to alcohol or the CB1 agonist showed an increased propensity to drink alcohol at adulthood that was absent after the combination of exposures (alcohol + CB1 agonist) during adolescence. In general, our preclinical results support the hypothesis of an increased vulnerability to alcohol intake after consumption of alcohol or CB1 agonist during adolescence. Clinical findings suggest that the DMQ-R SF is a reliable tool for assessing drinking motives among patients with schizophrenia. Enhancement and coping motives seem to play a major role in comorbid AUD among these patients. Community-based and clinical treatment programs should take the drinking motives of dual-diagnosis patients into

consideration, in order to improve their outcomes and to reinforce screening of alcohol/cannabis intake during adolescence to improve prevention of the comorbidity.

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