



## Invited commentary

## Caffeine effects and schizophrenia: Is there a need for more research?

Mehmet Topyurek<sup>a,b,\*</sup>, Philip Tibbo<sup>a,b</sup>, Christian Núñez<sup>c,d</sup>, Christian Stephan-Otto<sup>c,d,e</sup>, Kimberley Good<sup>a,b</sup><sup>a</sup> Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada<sup>b</sup> Nova Scotia Early Psychosis Program, Abbie J. Lane Building, Halifax, Nova Scotia, Canada<sup>c</sup> Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain<sup>d</sup> Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain<sup>e</sup> Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain

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Caffeine (1,3,7-trimethylxanthine) is the most widely used psychoactive substance in the world. Approximately 85% of the general population consumes caffeine, in one form or another, with an average daily intake of 165 mg (Mitchell et al., 2014). Most physically healthy individuals do not experience any significant distress nor any significant decrease in functioning from this level of caffeine intake (Mohanty et al., 2014). However, both Caffeine Intoxication and Caffeine Withdrawal are listed as disorders in the DSM-5 as there are specific criteria for each that can be identified (American Psychiatric Association, 2013).

Interestingly, Caffeine Use Disorder (CUD) is no longer a specified diagnosis as there was a lack of research that would support caffeine causing a use disorder as defined by DSM-5. CUD is now in the category of “Conditions for Further Study” in DSM-5 (Addicott, 2014). It has been argued that by not including caffeine as an addictive drug, there may be research opportunities to examine its potential beneficial effects (Addicott, 2014).

Caffeine consumption is significantly higher in individuals with schizophrenia compared to the general population (Strassnig et al., 2006), estimated at approximately 500 mg per day (3× that of the general population). Additionally, approximately one-third of the patients with schizophrenia have been reported to consume more than 550 mg per day (Mayo et al., 1993). Despite the high rates of caffeine

use in schizophrenia, the reasons for this enhanced consumption have not been adequately investigated (Núñez et al., 2015).

The psychostimulant effects of caffeine are thought to underlie its widespread use. Several studies have assessed the impact of acute caffeine administration on the cognitive functioning of healthy individuals and the results are mixed (Supplementary Table 1). Research on the cognitive effects of regular caffeine consumption in healthy individuals is sparse, but also mixed (Supplementary Table 2). Methodology differences may explain these controversial results.

Strikingly, there are no studies assessing the effects of acute administration of caffeine on cognition of patients with schizophrenia; however, there is a single study reporting the cognitive effects of regular consumption of caffeine in these patients (Núñez et al., 2015). The dearth of studies is even more surprising considering that 1) there is a sizeable literature in the healthy population; 2) most, if not all, of the cognitive domains shown to be enhanced by acute or regular intake of caffeine in healthy people are impaired in patients with schizophrenia (Green et al., 2004); and 3) as stated above, patients with schizophrenia consume large doses of caffeine.

In the study by Núñez et al. (2015), the effects of regular caffeine consumption were assessed in 52 individuals with long term schizophrenia (M age = 47 years) using standardized neuropsychological testing. A regression analysis found that caffeine use was associated with better cognitive performance on tasks measuring semantic fluency, cognitive speed, working memory, and visual memory, however only for male and not female schizophrenia patients. No associations were found in healthy controls. Given there are currently no approved medications for cognitive symptoms in schizophrenia, do these findings warrant a closer look at caffeine as a pharmacological adjunctive therapy option?

A recent qualitative study assessed the role of caffeine for individuals with schizophrenia from their perspective (Thompson et al., 2014). The thematic analysis based on in-depth interviews with 20 patients found that, among other reasons, patients consumed caffeine as a countermeasure to medication-induced side-effects such as sedation. Other reasons included using caffeine for its stimulating properties, satisfying cravings, and helping to facilitate social interactions. The suggestion that caffeine can be used as an avenue to counter sedation is shared among some physicians (Miller, 2004).

In fact, the high rates of caffeine use in schizophrenia supports the self-medication hypothesis of Khantzian (1997); patients use substances because they are gaining some benefit from their use. However,

\* Corresponding author at: Department of Psychiatry, Faculty of Medicine, Dalhousie University, Rm 8204, Abbie J. Lane Building, 5909 Veterans' Memorial Lane, Halifax, Nova Scotia B3H2E2, Canada.

E-mail address: [mehmet@dal.ca](mailto:mehmet@dal.ca) (M. Topyurek).

it has also been previously suggested that schizophrenia patients overvalue the positive effects of drug use and devalue its negative effects (Krystal et al., 2006). To date, very little in-depth knowledge has been obtained regarding the positive and negative effects of caffeine in individuals with schizophrenia.

There are currently no approved medications for cognitive and negative symptoms in schizophrenia. Assessing the varying degrees of caffeine intake on cognition and negative symptoms, as well as antipsychotic induced side effects such as sedation, could lead to novel lines of research. That is, is it possible caffeine can function as an adjunct treatment for some schizophrenia patients? If this is possible, can we identify which patients are more likely to benefit from caffeine? Or which patients should avoid caffeine intake? There is a void in the literature which has left several questions unanswered. We propose several effective ways to conduct this line of research (Supplementary Table 3). The inability to homogenize results derived from previous research is a barrier in caffeine and cognitive research. These suggestions may be the first step to construct standardized guidelines that will facilitate and encourage research on the effects of caffeine.

Research investigating caffeine and schizophrenia has constructed a particular narrative: caffeine induces negative effects in schizophrenia patients – primarily by increasing psychotic-like symptoms (Wang et al., 2015; Lucas et al., 1990). However, literature assessing the effects of various caffeine doses on sedation as well as cognitive and negative symptoms has been minimal. Clinicians may not be fully cognizant of the effects that caffeine has on schizophrenia patients. It is possible for caffeine to exert positive effects on some patients and may potentially serve as an adjunct treatment for sedative side-effects as well as cognitive and negative symptoms. It is important for clinicians to be well-informed of these effects so as to not discourage caffeine use where it may be effective and/or so as to not encourage caffeine use where it may be ineffective. In conclusion, we need a better understanding of the role that caffeine serves in patients with schizophrenia.

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#### Contributors

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#### Declaration of Competing Interest

All authors declare they have no conflicts of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.07.026>.

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