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Caffeine consumption in a long-term psychiatric hospital: Tobacco smoking may explain in large part the apparent association between schizophrenia and caffeine use

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ABSTRACT

This study further explores the association between schizophrenia and caffeine use by combining two prior published Spanish samples (250 schizophrenia outpatients and 290 controls from the general population) with two Spanish long-term inpatient samples from the same hospital (145 with schizophrenia and 64 with other severe mental illnesses). The specific aims were to establish whether or not, after controlling for confounders including tobacco smoking, the association between schizophrenia and caffeine is consistent across schizophrenia samples and across different definitions of caffeine use. The frequency of caffeine use in schizophrenia inpatients was not significantly higher than that in non-schizophrenia inpatients (77%, 111/145 vs. 75%, 48/64) or controls but was significantly higher than in schizophrenia outpatients. The frequency of high caffeine users among caffeine users in schizophrenia inpatients was not significantly higher than in non-schizophrenia inpatients (45%, 50/111 vs. 52%, 25/48) or controls, but was significantly lower than in schizophrenia outpatients. Smoking was significantly associated with caffeine use across all samples and definitions. Between 2 and 3% of schizophrenia inpatients, schizophrenia outpatients and non-schizophrenia inpatients showed caffeinism (>700 mg/day in smokers). Several of these smoking patients with caffeinism were also taking other inducers, particularly omeprazole. The lack of consistent association between schizophrenia and caffeine use is surprising when compared with the very consistent association between tobacco smoking and caffeine use across all of our analyses (use and high use in users) and all our samples. The confounding effects of tobacco smoking may explain in large part the apparent association between schizophrenia and caffeine use.

1. Introduction

Caffeine probably causes most of its biological effects by blocking all adenosine receptors located at the neurons and brain glial cells and removing the brain's adenosinergic tonus (Ribeiro and Sebastião, 2010). Animal models suggest that 1) adenosine plays a role opposite to dopamine in the striatum; 2) adenosine agonists produce effects similar to dopamine antagonists; and 3) adenosine antagonists, such as caffeine, produce effects similar to increased dopaminergic neurotransmission (Ferré, 1997).

Schneier and Siris (1987) suggested that schizophrenia was associated with increased rates of caffeine consumption. Later, Hughes et al. (1998) described that patients with schizophrenia appeared to have high caffeine intake but studies were small and not completely consistent. These old studies did not control for the confounding factor that schizophrenia is strongly and consistently associated with tobacco smoking (de Leon and Diaz, 2005) and tobacco smoking is also associated with caffeine (Istvan and Matarazzo, 1984; Gurpegui et al., 2007). Furthermore, tobacco smoke compounds induce caffeine metabolism by increasing the expression of the cytochrome P450 1A2 (CYP1A2). Heavy smokers need two to three times higher caffeine intake to get

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the same serum caffeine concentrations as non-smokers (de Leon et al., 2003). Other CYP1A2 inducers are some antiepileptic drugs (carbamazepine or phenytoin) and omeprazole (de Leon et al., 2005).

In two consecutive studies, Gurpegui et al. (2004, 2006) explored the relationship between schizophrenia and caffeine intake after controlling for tobacco smoking. First, current caffeine intake was associated with current smoking and alcohol use in 250 schizophrenia outpatients (Gurpegui et al., 2004). Among caffeine consumers, the amount of consumed caffeine was associated with smoking but not with schizophrenia symptomatology measured cross-sectionally. In an extension study, the schizophrenia outpatient sample was compared with 290 controls (Gurpegui et al., 2006). Current caffeine intake was significantly less frequent in schizophrenia after controlling for potential confounding factors. Among caffeine consumers, high caffeine consumption was significantly more frequent in schizophrenia outpatients than in the control group.

In our previous studies we did not pay attention to "caffeinism", the extremely high consumption of caffeine in schizophrenia. The literature only provides anecdotal reports of "caffeinism" but Williams and Gandhi (2008) have proposed that caffeine intake >700 mg/day may be a sign of this "caffeinism."

If animal pharmacological models are correct in proposing a close relationship between the adenosine system and dopamine, then one should find a strong and consistent relationship between schizophrenia and caffeine in the clinical environment. The lack of definitive proof of an association between caffeine intake and schizophrenia is surprising, since schizophrenia is definitively associated with excessive use of nicotine and water.

There is a strong and consistent association between schizophrenia and tobacco smoking (de Leon and Diaz, 2012). When compared with the general population, schizophrenia patients definitively have increased daily smoking initiation and decreased smoking cessation. When compared with people with other severe mental illnesses (SMIs), this association is less evident; schizophrenia is only associated with a smaller increase of daily smoking initiation but no differences in smoking cessation. Vulnerability to schizophrenia may be associated with an increased risk for starting daily smoking (de Leon, 1996; de Leon and Diaz, 2012). Wing et al. (2012) reviewed the proposed neurobiological mechanisms behind the association between smoking and schizophrenia.

Polydipsia, an excessive intake of water and other fluids, is associated with schizophrenia after controlling for confounders such as smoking, chronicity or medications. This association has been demonstrated in institutionalized patients using SMIs as controls (de Leon et al., 1994, 1996, 2002), but it is less evident in less severe and less chronic patients (de Leon et al., 1994).

Although schizophrenia appears to be consistently associated with excessive use of nicotine and water, it is not clear that it is consistently associated with excessive use of caffeine. Moreover, a hepatic pharmacokinetic mechanism may explain why heavy smokers with schizophrenia consume more caffeine so that the same quantity of caffeine reaches their brains. In the extension study (Gurpegui et al., 2006), we demonstrated two significant associations between caffeine and schizophrenia, one negative (fewer caffeine users) and one positive (more high-intake users within caffeine users), but we did not compare them with people with other SMIs, who are better controls for schizophrenia patients.

This study further explores the association between schizophrenia and caffeine use by combining the two prior published Spanish samples (250 schizophrenia outpatients and 290 controls) with two additional Spanish samples of long-term inpatients from the same hospital: 145 with schizophrenia and 64 with other SMIs sharing similar environmental influences including psychiatric medications. The specific aims were to establish, after controlling for confounders including tobacco smoking, whether or not the association between schizophrenia and caffeine is consistent across schizophrenia samples and across different operational definitions of caffeine use (using versus not using caffeine, high intake in caffeine users and total daily caffeine consumption in caffeine users).

2. Subjects and methods

2.1. Subjects

All inpatients from a long-term psychiatric hospital (Hospital Psiquiátrico de Conxo, Santiago de Compostela, Spain) were cross-sectionally investigated for the prevalence of caffeine intake and its quantity. DSM-IV diagnoses were made by the treating psychiatrist after reviewing all medical records available, which include many years of observation (Table 1). There were 111 schizophrenia inpatients and 48 with other SMIs. Similarly to the outpatient sample, this new schizophrenia sample included schizoaffective disorder. The study was approved by an ethics committee and patients signed a written informed consent.

The previously-published Spanish schizophrenia sample (see footnote g of Table 2) included 250 stable outpatients (Gurpegui et al., 2004, 2006). The previously-published 290 Spanish controls were recruited at a family medicine outpatient clinic (see footnote i of Table 2) and appeared to be a reasonable representation of the general population (Gurpegui et al., 2006).

2.2. Access to caffeine and tobacco

There is almost unlimited access to caffeinated beverages and tobacco in this urban hospital. The main limiting factor is the money available to each patient from their disability pensions and/or family. The hospital cafeteria tends to be cheaper than surrounding businesses and provides caffeinated coffee in two sizes and caffeinated colas in three different sizes. Patients can walk to surrounding areas and buy caffeinated beverages from shops and/or consume coffee in nearby cafeterias. The nursing staff, who has worked with these patients for many years, knows these businesses very well, is aware of the interactions between the patients and surrounding community, and attempts to keep them as smooth as possible. No patient consumed tea beverages, but this is a cultural choice.

Nursing staff kept patients' cigarettes. These cigarettes were bought in large quantities using the patients' and/or family's money. Patients could also buy more expensive cigarettes in the hospital cafeteria or outside the hospital. In summary, by law, patients are free to smoke as much as they desire, but the prohibition against smoking during some hospital activities and the need to ask the nursing staff for cigarettes probably contributed to lengthening the time between cigarettes.

2.3. Procedures

As in the prior studies (Gurpegui et al., 2004, 2006), the consumption of caffeinated beverages, tobacco, alcohol and illegal drugs was surveyed. Caffeine intake was assessed by treating physicians when they considered the patient most likely to cooperate. A standardized questionnaire was used to record the number of coffee beverages and caffeinated colas consumed per week. It differed from the outpatient questionnaire in three minor ways. First, the inpatient questionnaire did not ask about tea since nobody consumed it; second, the questions about the size of the beverages were easier to answer since the hospital used standard sizes; and third, nurses who had known the patients for years were available to help the psychiatrists make better clinical judgments rather than blindly trusting patients' information. Caffeine intake in mg/day was computed by employing previously used correction factors (see footnote e, Table 1). In caffeine users, a high amount of caffeine intake was defined as a caffeine intake ≥200 mg/day (Gurpegui et al., 2005). Smoking assessments used the same definitions as before Gurpegui et al., 2005; see Table 1, footnote b) and included the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) which required the patient to answer some subjective

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