Caffeine and Schizophrenia

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Should patients with schizophrenia avoid caffeine? To answer this question, we reviewed four areas of research: caffeine intake among persons with schizophrenia, effects of caffeine on dopamine systems in nonhumans, effects of caffeine on positive and negative symptoms, and interactions of caffeine with antipsychotic medications.

Caffeine intake among patients with schizophrenia

About 85 percent of the U.S. population uses caffeine daily. The most common sources are brewed coffee (100 mg of caffeine per 6-ounce serving), instant coffee (65 mg), tea (40 mg), soda (35 mg), and chocolate (5 mg) (1). The mean caffeine intake is near 210 mg a day for the whole population, and 6 percent are heavy users—more than 500 mg a day (1).

Several reasons exist for hypothesizing that persons with schizophrenia would have high caffeine intakes. For example, patients may use caffeine to combat apathy or boredom or to offset the sedating effects of antipsychotic medications. Many persons with schizophrenia have polydipsia, and caffeine intake might increase as a result. Similarly, many psychiatric medications produce dry mouth, which might increase intake. In addition, as reviewed below, caffeine might improve negative symptoms of schizophrenia or extrapyramidal symptoms from neuroleptics. Patients taking neuroleptics may have reduced anxiety, allowing them to imbibe more caffeine.

A final possibility is that approximately 80 percent of persons with schizophrenia smoke, and many of them smoke heavily (2). Smoking increases the elimination of caffeine. Thus persons with schizophrenia may use more caffeine to make up for increased elimination of caffeine due to heavy smoking (3).

Several authors have anecdotally noted high caffeine intake among patients with schizophrenia (4), including cases of eating raw coffee (5). For example, in one study the 15 lowest users averaged 4.6 cups of coffee a day (4). Two empirical surveys of caffeine use by persons with schizophrenia were published more than 20 years ago, in 1975 and 1976. In a German study of inpatients, 71 percent used more than 500 mg of caffeine a day (6). However, in a Canadian study of both inpatients and outpatients, only 17 percent used more than 500 mg a day (7), and this consumption was not different from the 11 percent in the general population who did so.

The discrepant figures across these two studies are probably not due to cultural differences, because coffee intake in Canada and Germany was similar in 1976 (8). It is more likely that the high prevalence rate in the German study was due to institutionalization, which appears to increase caffeine use (9), or because the German study included more severely ill patients. We could find only one more recent survey of caffeine use among persons with schizophrenia. The mean caffeine intake of 26 patients was 503 mg a day, and 38 percent reported using more than 555 mg a day (10).

Effects of caffeine on dopamine systems

Caffeine has well-documented effects on dopamine, the major neurotransmitter of interest in schizophrenia. Unlike the nonxanthine psychomotor stimulants amphetamine and cocaine, caffeine neither releases dopamine from nerve terminals nor prevents reuptake of released dopamine. Rather, caffeine and other methylxanthines, such as theophylline, are competitive antagonists at the A_{2a} adenosine receptor on the same postsynaptic neurons as the D_2 dopamine receptor (11). Activation of the A_{2a} receptor makes dopamine less efficient as a neurotransmitter; thus, by blocking this receptor, caffeine enhances the ability of dopamine to function as a neurotransmitter (11).

Caffeine enhancement of dopamine function appears to explain several behavioral effects of caffeine. For example, caffeine, like amphetamine, increases the locomotor activity of rats, and this effect is prevented by neuroleptics (11). Also, rats can be trained to recognize an injection of caffeine. Such trained rats identify injections of drugs that activate dopamine receptors, such as amphetamine, as being like caffeine (12).

Caffeine's effects on dopamine may also play a role in tardive dyskinesia. Up-regulation of dopamine receptors

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is thought to be a principal cause of tardive dyskinesia. This up-regulation is accompanied by up-regulation of A_{2a} adenosine receptors (13). Because caffeine antagonizes the A_{2a} receptor, caffeine intake might exacerbate and caffeine abstinence might improve tardive dyskinesia. To date, no study has explicitly tested this hypothesis.

Effects of caffeine on positive and negative symptoms

Several case reports have described delusions and hallucinations after large intakes of caffeine by persons with (4,14) and without (15) schizophrenia. One study of 78 patients with schizophrenia found that caffeine intake was correlated with the total score on the Brief Psychiatric Rating Scale (BPRS) and with the score on a scale measuring positive symptoms, but not with scales measuring negative symptoms or extrapyramidal symptoms (16). Unfortunately, the magnitude of the effect on the BPRS score was not reported. On the other hand, when symptoms of schizophrenia and caffeine intake were followed over time in a small sample of patients (N=14), only a slight correlation between caffeine intake and severity of psychosis was found (17).

Three studies have compared the symptoms of inpatients using caffeinated coffee or decaffeinated coffee (10,18,19). One study used a caffeinated-decaffeinated-caffeinated design in which inpatients alternated use for three-week periods. Scores on the anxiety and hostility subscales of the BPRS (self-reported) and irritability scores on the Nurses Observation Scale for Inpatient Evaluation (NOSIE) (nurse rated) were higher during the caffeinated-coffee periods (18), indicating a greater level of symptoms. Actual scores were not reported; thus the clinical significance of these changes is unknown.

A second study used a caffeinated-decaffeinated-caffeinated-decafeinated design with four to seven weeks in each period (19). These results were confounded by a trend for all scores to improve over time. Nevertheless, scores on subscales for hostility, hallucinations, and unusual thought content on the BPRS and irritability and psychoses scores on the NOSIE showed the expected high-low-high-low pattern. Traditional statistical tests failed to find significant differences; however, statistical tests that test specifically for the high-low-high-low pattern expected may very well have shown statistical significance. On the other hand, the changes that did occur were small and may not have been clinically significant.

A third study used a decaffeinated-decaffeinated-caffeinated-caffeinated-decaffeinated-decaffeinated design with one week in each period (10). Inpatient scores for anxiety and depression and total scores on the BPRS and NOSIE did not change across periods.

In only one study has caffeine been experimentally administered to patients (20). Caffeine, 10 mg per kg of bodyweight, was administered intravenously to persons with schizophrenia who had been caffeine free for six weeks. Caffeine increased the BPRS total score and the score on the unusual thoughts subscale as well as global nurse ratings of psychosis. These results are similar to those of the previous studies. The change in the BPRS total score was large (a 33 percent increase) and occurred for ten of the 13 subjects. In addition, caffeine improved negative symptoms; that is, it improved mood and decreased withdrawal. Interestingly, this large dose did not increase anxiety scores among these patients.

Although these results are the most direct evidence that caffeine can worsen positive symptoms (and might even improve negative symptoms), their generalizability may be limited because this study used a very large dose of caffeine—the equivalent of drinking seven cups of brewed coffee at once. Also, caffeine was administered intravenously, and the subjects had presumably lost any tolerance to caffeine (1). In addition, this study did not have a control group of persons without schizophrenia; thus the specificity of the findings is debatable. This lack of specificity is important because high doses of intravenous caffeine can cause psychotic symptoms among individuals without a history of psychosis (21).

Caffeine use and caffeine cessation produce other effects that, although not specifically relevant to schizophrenia, could influence the cause and presentation of the illness or be confused with medication side effects. Caffeine use can cause restlessness, nervousness, insomnia, rambling speech, and agitation. Whether chronic heavy caffeine users develop enough tolerance that these symptoms are of little concern is debatable (1). In addition, cessation of caffeine causes fatigue and drowsiness (1), which could be confused with prodromal or postdromal symptoms or medication side effects.

Interaction of coffee and tea with antipsychotics

The addition of coffee or tea to phenothiazine or butyrphenone neuroleptic elixirs forms a precipitant in vitro (22). This precipitation is not due to the caffeine in coffee or tea. Initially, this finding was of concern because patients might drink coffee or tea immediately after receiving oral medication. However, in humans, caffeine use was only slightly related to neuroleptic levels in one study, and a caffeinated-decaffeinated-caffeinated protocol showed no effect of caffeine on neuroleptic levels. A later study concluded that these negative findings in humans occurred because stomach acidity reverses any precipitation (22). Thus whether the caffeine–neuroleptic precipitation phenomenon has any clinical significance is unclear.

More recent evidence suggests caffeine may potentiate side effects from clozapine. In contrast to traditional neuroleptics, clozapine is metabolized mostly by the cytochrome P450 CYP1A2 isoenzyme, which is also the enzyme responsible for metabolism of caffeine; thus caffeine and clozapine may compete for the CYP1A2 isoenzyme (23). One case report suggests caffeine use can increase clozapine levels sufficient to produce clinically significant side effects (23). Unfortunately, further empirical studies of the validity, prevalence, and clinical significance of this possibly important interaction have not been published.

Finally, high doses of caffeine can cause tremor and appear to cause restless legs (24), both of which could be mistaken for or could aggravate neuroleptic-induced extrapyramidal symptoms. On the other hand, a recent open-label study suggested that theophylline, a metabolite of caffeine, can improve parkinsonian symptoms (25).

Summary

Although the database is small and not completely consistent, it appears that patients with schizophrenia have high caffeine intakes. The reasons are unclear. In nonhumans, caffeine enhances the effects of dopamine, which might be expected to worsen positive symptoms and improve negative symptoms of schizophrenia and worsen tardive dyskinesia. Eliminating caffeine among patients with schizophrenia does not appear to make them better or worse. Acute intake of large amounts of caffeine may increase psychoses and hostility. However, those who chronically use large amounts of caffeine may develop enough tolerance that these adverse effects do not occur, but whether this conjecture is true has not been tested.

Interestingly, persons with schizophrenia do not develop anxiety at high doses of caffeine. Although there was initial concern that caffeine might inactivate liquid doses of neuroleptics, the clinical significance of this concern is unclear. On the other hand, caffeine might increase the level of clozapine, and more research in this area is needed. ♦

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