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## Review Article

# Interaction of Antipsychotics Drugs and Caffeine

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**Abstract:** Interaction between food and drugs have profound influence on the success of drug treatment and on the side effect profiles of many drugs. Caffeine is present in coffee, black tea, chocolate, some soft drinks and many over- the-counter medication. Caffeine is most popular psycho stimulant and is consumed worldwide. It is capable of interacting with dopaminergic receptor in the brain and influencing dopamine mediated neurobehavioral function. It is implicated in the exacerbation of anxiety, psychosis, and sleep disorder and people with eating disorders often misuse it. It antagonizes adenosine receptors, which may potentiate dopaminergic activity. In psychiatric in patients, caffeine has been found to increase anxiety, hostility and psychotic symptoms. High chronic doses of caffeine, theobromine or theophylline can lead to an exhaustion of the nervous system that may be the basis of subsequent psychosis. Prolonged heavy use of caffeine can cause chronic insomnia that may be the source of psychosis- like symptoms.
**Keywords:** Psycho stimulants, Dopaminergic receptor, Neurobehavioral, Psychosis, Chronic Doses, Disorders .

## INTRODUCTION

Many people think that being natural, all herbs and foods are safe. But often, herbs and foods may interact with medications normally taken that result in serious side effects [1].

Caffeine is the world's most widely used psychoactive drug [2]. It is a white, bitter, crystal-like substance found in coffee, tea, cocoa, and soft drinks and also in products such as aspirin, non prescription cough and cold remedies diet pills and some street drugs. More than 60 known species of plants contain caffeine [3].

It is present in varying quantities in seeds, leaves and fruit of some plants. In plants it acts as a natural pesticide that paralyzes and kills certain insects feeding on the plants and also enhancing the reward memory of pollinators. Human consume commonly in infusions extracted from the seed of the coffee plant and the leaves of the tea plant, and in foods and drinks containing products derived from the kola nut, yerba mate, guaranaberries, guayusa and yaupon holly [4].

**Caffeine content of drinks and chocolate** (Data from Food Standards Agency, 2001)

- Average cup of instant coffee - 75 mg
- Average mug of instant coffee - 100 mg
- Average cup of brewed coffee - 100 mg
- Average cup of tea - 50 mg
- Regular can of cola drink up to - 40 mg
- Regular can of energy drink - up to 80 mg
- Plain 50 g bar of chocolate - up to 50 mg
- Milk 50 g bar of chocolate - up to 25 mg

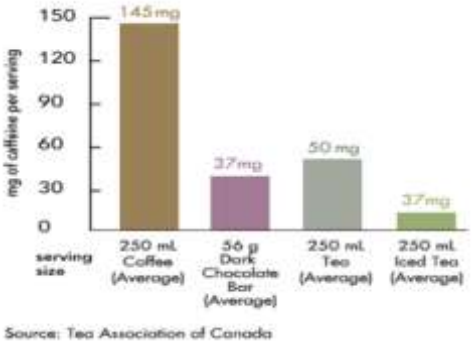


**Fig. 1: Caffeine contains of drinks**

### Biochemistry and Pharmacology of Caffeine

Caffeine is chemically 1, 3, 7-trimethylxanthine.

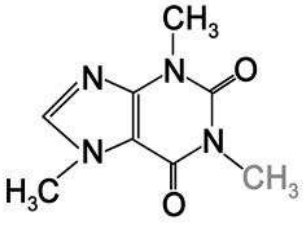


**Fig 2: Caffeine (1, 3, 7-trimethylxanthine)**

It stimulates the central nervous system (CNS) AND cardiac muscle, relaxes smooth muscle and causes diuresis. It initially stimulates CNS at the level of the cerebral cortex and medulla and later stimulates the spinal cord (at higher doses) [5].

It is rapidly absorbed from the gastrointestinal tract and then metabolized in liver by demethylation and oxidation. The metabolism shows individual variation. The half life of caffeine in pregnant women and in women taking oral contraceptives; while in smokers half life is reduced [6].

Caffeine antagonizes adenosine A1 and A2 receptors. Higher doses of caffeine cause inhibition of phosphodiesterases and GABA-A receptors and release of intracellular calcium [7]. Neuropsychiatric effect of caffeine is as a result of inhibition of A1 and A2A receptors in the CNS [2].

**Stimulant effects**

Caffeine stimulates CNS and metabolic stimulant [8]. It is used to reduce physical fatigue, to restore alertness both recreationally and medically. It increases wakefulness, faster and clearer flow of thought, increased focus, general body coordination [9]. It affects sleep; improves performance during sleep deprivation but subsequent insomnia may occur. Individual variations for induction of effects are observed [10-11].

**Physical effects**

Caffeinism is a condition associated with consumption of caffeine in amount of 1000–1500 mg per day [12]. It results in caffeine dependency and causes unpleasant physical and mental conditions that include nervousness, irritability, restlessness, insomnia, headaches, and heart palpitations after caffeine use [13].

Coffee consumption reduces overall risk of cancer [14]. There is little or no evidence that caffeine consumption increases the risk of cardiovascular disease, but somewhat reduce the risk of type 2 diabetes [17]. It increases intraocular pressure in glaucoma patients. It may protect liver cirrhosis. There is no evidence that coffee stunts a child's growth. It may have synergistic of some medications including ones used to treat headaches [18].

**Psychological effects**

A number of clinical studies have shown a positive association between caffeine and anxiogenic effects and/or panic disorder [20, 21]. At high doses, typically greater than 300 mg, caffeine can both cause and worsen anxiety [22] or, rarely, trigger mania or psychosis. In moderate doses caffeine may reduce symptoms of depression and lower suicide risk. In moderate doses caffeine typically does not affect learning or memory [23], and can improve cognitive functions, especially in people who are fatigued, possibly due to its effect on alertness. However anxiety sufferers can have high caffeine sensitivity. For some people, anxiety can be very much reduced by discontinuing caffeine use [24].

Contrary to popular belief, some research suggests that caffeine does not increase motivation in humans, and may even decrease motivation in some [25].

**Caffeine and psychiatric disorder**

Consumption of caffeine may be higher in psychiatric patients than in the population as a whole [26]. Caffeine use has been linked with specific disorders such as anxiety disorders, sleep disorders and eating disorders, and there is a possible association with schizophrenia. Surprisingly, there are no published reports linking caffeine use with mania or hypomania.

**Schizophrenia**

It has already been noted that there are connections between adenosine A2Areceptors and the dopaminergic system in the brain. As adenosine inhibits dopaminergic neurotransmission, blockade of A2A receptors by caffeine may increase dopaminergic activity and exacerbate psychotic symptoms [27]. Clinically, the symptoms of caffeine intoxication can mimic those of psychosis [28] or be confused with the side-effects of medication. Cessation of caffeine causes fatigue and drowsiness, which can be confused with the side-effects of psychotropic drugs [28].

There is also evidence that people with schizophrenia have higher than average intakes of caffeine, although the literature is inconsistent. There are a number of case reports of high caffeine intake among in-patients with schizophrenia [29]. Studies published in the 1970s give conflicting results, one finding that 71% of in-patients used more than 500 mg of caffeine per day and the other that only 17% used more than this amount A more recent study found that the mean daily caffeine intake of 26 in-patients was 503 mg, with 38% using more than 555 mg. [30].

**About the disease**

Psychosis ("psyche", for mind/soul, and "-osis", for abnormal condition or derangement) refers to an abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". People suffering from psychosis are described as psychotic. Psychosis is the term given to the more severe forms of psychiatric disorder, during which hallucinations or delusions, violence and impaired insight may occur. Term "psychosis" is very broad and can mean anything from relatively normal aberrant experiences through to the complex and catatonic expressions of schizophrenia and bipolar type disorder. Moreover a wide variety of central nervous system diseases, from both external substances and internal physiologic illness, can produce symptoms of psychosis. This led many professionals to say that

psychosis is not specific enough as a diagnostic term. Despite this, the term "psychosis" is generally given to noticeable deficits in normal behavior (negative signs) and more commonly to diverse types of hallucinations or delusional beliefs (e.g. grandiosity, delusions of persecution). Someone exhibiting very obvious signs may be described as "acutely psychotic", whereas one exhibiting very subtle signs could be classified in the category of an "attenuated psychotic risk syndrome". Hallucinations, delusions, catatonia, or a thought disorder, as described below. Impairments in social cognition also occur [31, 32].

**Antipsychotic drugs**

Antipsychotics (also known as neuroleptics or major tranquilizers) are a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, or disordered thought), in particular in schizophrenia and bipolar disorder, and are increasingly being used in the management of non-psychotic disorders (ATC code N05A). The word neuroleptic originates from the Greek word lepsis ("seizure" or "fit") [33].

First-generation antipsychotics, known as typical antipsychotics, were discovered in the 1950s. Most second-generation drugs, known as atypical antipsychotics, have been developed more recently, although the first atypical antipsychotic, clozapine, was discovered in the 1950s and introduced clinically in the 1970s. Both generations of medication tend to block receptors in the brain's dopamine pathways, but atypical tend to act on serotonin receptors as well.

**Mechanism of action**

All antipsychotic drugs tend to block $D_2$ receptors in the dopamine pathways of the brain. This means that dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. It has also been proven less dopamine released in the prefrontal cortex in the brain, and excess dopamine released from all other pathways, has also been linked to psychotic experiences, caused by abnormal dopaminergic function as a result of patients suffering from schizophrenia or bipolar disorder. Various neuroleptics such as haloperidol and chlorpromazine suppress dopamine chemicals throughout its pathways, in order for dopamine receptors to function normally.

In addition of the antagonistic effects of dopamine, antipsychotics (in particular atypical neuroleptics) also antagonize 5-HT2A receptors. Different alleles of the 5-HT2A receptor have been associated with schizophrenia and other psychoses, including depression [34]. Higher concentrations of 5-HT2A receptors in cortical and subcortical areas, in particular in the right caudate nucleus have been historically recorded [34]. This is the same receptor that psychedelic drugs agonize to various degrees, which explains the correlation between psychedelic drugs and schizophrenia.

Typical antipsychotics are not particularly selective and also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking $D_2$ receptors in these other pathways is thought to produce some unwanted side effects that the typical antipsychotics can produce. They were commonly classified on a spectrum of low potency to high potency, where potency referred to the ability of the drug to bind to dopamine receptors, and not to the effectiveness of the drug. High-potency antipsychotics such as haloperidol, in general, have doses of a few milligrams and cause less sleepiness and calming effects than low-potency antipsychotics such as chlorpromazine and thioridazine, which have dosages of several hundred milligrams. The latter have a greater degree of anticholinergic and antihistaminergic activity, which can counteract dopamine-related side-effects.

Atypical antipsychotic drugs have a similar blocking effect on $D_2$ receptors, however, most also act on serotonin receptors, especially 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors. Both clozapine and quetiapine appear to bind just long enough to elicit antipsychotic effects but not long enough to induce extra pyramidal side effects and prolactin hyper secretion. 5-$HT_{2A}$ antagonism increases dopaminergic activity in the nigrostriatal pathway, leading to a lowered extra pyramidal side effect liability among the atypical antipsychotics.

**INTERACTION**

There are several effects of cocaine use including an increase in the person's metabolism, body temperature, and blood pressure. Other effects include increased urine production, higher blood sugar levels, and hand tremors, loss of coordination, decreased appetite, and delayed sleep. Extremely high doses may cause nausea, diarrhea, sleeplessness, trembling, headache, and nervousness. Poisonous doses have occurred occasionally and may result in convulsions, breathing failure, and death. Deaths related to caffeine have most often been reported through misuse of tablets containing caffeine. A regular user of caffeine who has developed a tolerance may have craving for the drug's effects. Some researchers have found a withdrawal-like syndrome among people who suddenly stop using caffeine. Symptoms include headache, irritability, and mood changes.

- Coffea arabica (Coffee) and Camellia sinensis (Tea) affecting drug performance: Haloperidol -various reports and in vitro studies have observed that coffee and tea can cause precipitation of haloperidol. Such an interaction, were it to similarly occur in human patients, could potentially reduce absorption of haloperidol and its subsequent therapeutic efficacy. Other animal studies on chlorpromazine, another antipsychotic drug,

found that drug's cataleptic effects were abolished when administered with tea, most likely due to its precipitation (in vitro) by non-caffeine constituents. Based on this, and similar, evidence speculation has been raised that the methyl xanthenes in coffee and tea may act as dopamine agonists.[35]

- Tea is inhibits GABA neurotransmission. Tea contains 2% to 4% caffeine, which affects thinking and alertness, increases urine output, and may reduced the symptoms of Parkinson's disease. It also contains antioxidants and other substances that might help protect the heart and blood vessels. Clozapine interacts with tea. Tea is reducing effectiveness of the clozapine and Chlorpromazine.

## CONCLUSION

The present review concludes that for future prospects food drug interaction is always having importance in any medication. Tea and Coffee are the common hot drinks which are taken by the patient with psychosis. Literature show coffee and tea contain caffeine, which has effect on central nervous system. More recent evidence suggests that 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 the metabolism of caffeine; thus caffeine and clozapine may compete for the CYP1A2 isoenzyme. One case report in the literature suggests that caffeine use can increase clozapine levels sufficiently to produce clinically significant side effects.

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