

FOR YOUR INFORMATION



PHARMACY NEWSLETTER



Volume #21, Issue #17 - November, 2001

The Impact of Caffeine on Mental Illness

Introduction

Daily caffeine consumption is seen in about 85% of the general population with mean consumption of 210mg/day. Six per cent of the population are heavy users i.e. > 500mg/day. In schizophrenia, however, several studies have shown a much higher intake of caffeine than in the general population. In one of the initial studies looking at caffeine intake and symptoms in psychiatric inpatients by De Freitas, the common consumption level was 9-10 cups/day of instant coffee representing 500 to 800mg/day of caffeine. A 1993 European study of psychiatric patients in a rehab hospital showed a daily range of 160 to 1200mg with the majority between 250 and 749mg. A Riverview study by Koczapski et al of 100 chronic inpatients in 1989 showed a range of between 375mg in the 15 lowest caffeine consumers to an average of 1200mg in 18 highest caffeine consumers. Several studies have noted individual cases of patients taking up to 2g/day. Suggested reasons for this high intake include boredom, attempts to counteract the side effects of medication such as sedation or dry mouth, attempts to deal with the symptoms, polydipsia, and increased elimination of caffeine due to smoking requiring increased intake for desired effect. Of note, in a follow-up study by Koczapski et al, 8 patients in their high caffeine consumer group went on to develop episodic water intoxication. While the vast majority of caffeine intake is from coffee, caffeine is available in a wide variety of beverages, chocolate and some medications (see attached table).

Pharmacological Properties

In doses of 100-200mg, stimulation of the cerebral cortex produces a more rapid and clearer thought flow, wakefulness or arousal in fatigued subjects and improved coordination. In slightly larger doses, caffeine stimulates medullary vagal, vasomotor and

respiratory centers, promoting bradycardia, vasoconstriction and increased respiratory rate.

Caffeine content of selected foods and drugs

Coffee	brewed 135mg/8 oz cup instant 95 mg/8 oz cup decaffeinated 5mg/ 8 oz cup Starbucks coffee Grande 550mg/16 oz
Tea	50mg/8 oz cup Green tea 30mg/8 oz Snapple iced tea 48 mg/16 oz bottle
Cola	Diet Coke 47mg/12 oz Coca Cola 45mg/12 oz Pepsi Cola 37mg/12 oz Sunkist orange soda 40mg/12 oz 7-eleven Big Gulp cola 190mg/64 oz
Chocolate	Hershey bar 10mg/1.5 ounces Hot chocolate 5mg/ 8 oz cup
Medications	Anacin 32mg/tab Tylenol # 1, 2 or 3 15 mg/tablet Cafergot 100mg/tablet Midol extra strength 60mg/caplet

Clinical Uses

Caffeine is used orally as a mild CNS stimulant to aid in staying awake and to restore mental alertness in fatigued patients. It is sometimes combined with sedating antihistamine products to overcome the sedative effects of these agents. It is used in apnea of premature infants for its stimulatory effects on respiration and is used for its cerebral vasoconstrictive effects in migraines in combination with ergotamine. Other uses include combinations with analgesics although its benefits have been questioned in these products. In certain products, caffeine has been used for its mild diuretic effect in fluid retention associated with menstruation, however, efficacy is questionable. Finally, it has

also been used to prolong seizure duration during ECT

Adverse Effects

CNS stimulation including insomnia, restlessness, nervousness and mild delirium, and GI irritation such as nausea, vomiting and gastric irritation usually occur at therapeutic doses (100 to 400mg). Large doses can produce headache, excitement, agitation, a condition resembling anxiety neurosis, tinnitus, muscle tremors or twitches, diuresis, tachycardia, extrasystoles and possibly other cardiac arrhythmias.

Prolonged high intake may produce tolerance, habituation and psychological dependence. Physical signs of withdrawal such as headaches, irritation, nervousness, anxiety and dizziness may occur upon abrupt discontinuation. Withdrawal is more prevalent in heavy users (500mg/day) but can occur in people using 100mg/day. Symptoms begin within 12 hours, peak around 24 to 48 hours and last up to 1 week. Worsened cognitive performance particularly on vigilance tasks is characteristic of this diagnosis.

Effects on Neurotransmitters

Caffeine's pharmacological effects are thought to be due to competitive antagonism at A_{2a} adenosine receptors. These receptors are located in the brain, heart, lungs, kidneys, gastrointestinal tract and adipose tissue. Adenosine is an inhibitory neurotransmitter, inhibiting the release of acetylcholine, norepinephrine, dopamine, gamma amino butyric acid and serotonin. Antagonism of these receptors with caffeine results in an increase in the release of neurotransmitters. Increase in norepinephrine is thought to be responsible for many of the desirable and adverse effects of caffeine such as restoring mental alertness, while at the same time causing insomnia and restlessness. Increase in dopamine release could explain some of the psychotic symptomatology seen in caffeine intoxication. On the other hand, activation of the A_{2a} receptor makes dopamine transmission less efficient. In fact, interest has been generated in looking at the use of adenosine agonists or uptake inhibitors such as dipyrnidole in the treatment of schizophrenia. The theory being that modulation of the D₂ receptor, rather than direct blockage as with

D₂ antagonists, may decrease psychosis without also causing adverse effects.

Caffeine and Psychiatry

The DSM IV details several diagnoses related to the use of caffeine. *Caffeine intoxication* requires recent consumption of caffeine usually in excess of 250mg with 5 or more symptoms (refer to adverse effects) that develop during or shortly thereafter. The symptoms must cause distress or impairment in functioning and not be due to another disease or medical condition. The development of tolerance may prevent the appearance of symptoms. Other caffeine related disorders include *Caffeine-induced anxiety disorder* characterized by prominent anxiety, panic attacks or obsession or compulsions related to the use of caffeine and *Caffeine-induced sleep disorder* which is a disturbance in sleep severe enough to warrant clinical attention that develops during the use of caffeine. The use of excess caffeine is capable of producing symptoms that overlap those seen in some mental illnesses. In someone with a mental illness, this may result in increased medication to deal with perceived worsening of symptoms or caffeine may directly impact on sleep, which may in turn, affect the illness itself.

Caffeine and Psychiatric Symptoms

There are case reports of delusions and hallucinations and erratic behavior occurring after large intakes of caffeine. One study of 78 patients found that intake correlated with positive symptoms. A second study of 14 schizophrenic patients found only a slight correlation between caffeine intake and severity of symptom distress.

Decaffeinated (Decaf) versus Caffeinated (Caf) studies

Several studies have examined the benefits of providing a caffeine-free environment. In a study by De Freitas, 14 patients underwent a decaffeinated/caffeinated protocol. Significant decreases on the BPRS were noted after the decaffeinated period and significant increases after the caffeinated period. Other investigators trying to replicate the results of this study, however, met with less success. In a study of 26 long-stay schizophrenic patients, no correlation was found

between caffeine consumption and levels of anxiety or depression. No significant changes in patients' behaviour or levels of anxiety and depression occurred when the wards changed to decaffeinated products. In a second study, 33 chronic schizophrenic/schizoaffective patients, with average caffeine consumption of 375mg in the 15 lowest users to 1200mg in the 18 highest users, were evaluated using the NOSIE and BPRS in a caf/decaf/caf/decaf protocol. No improvement was seen during the first decaffeinated period, with some small unexpected improvement seen in the second caffeinated period. In the second decaffeinated period significant improvement was seen in some areas. Overall, the authors concluded that the small change did not support a switch to decaffeinated products in this population but rather was more likely due to the length of time patients were in the study and the attention from being involved in the study. A third study involved giving 13 schizophrenic patients who had been on a caffeine-free diet for 6 weeks, 10mg/kg caffeine in orange juice over 5 minutes (700mg for a 70 kg person; the equivalent of roughly 7 cups of instant coffee or more depending on weight). Measures of psychopathology were significantly increased including the BPRS total and subscales of thought disorder unusual thought content, and euphoria-activation and several individual BPRS items. Since tolerance does develop to the effects of caffeine, one would not expect the same results if these people had been regular caffeine consumers up to the study commencement or if the dose had been consumed over the course of a day. It does, however, display what could happen to patients coming from an environment where access to caffeine is prevented to an environment where caffeine use is totally unrestricted.

Caffeine Interactions with Psychiatric Medications

Typical antipsychotics

Neuroleptic liquids such as haloperidol or chlorpromazine were reported to form precipitates when mixed with coffee or tea. Studies, however, to look at this possible interaction in humans, found only slight correlation with caffeine use in one study and no effect in another study that looked specifically at neuroleptic levels. A later study

concluded that stomach acidity reverses any precipitation.

Clozapine

More recently, however, there are several reports documenting an interaction between caffeine and clozapine. One case report details an acute reaction every time a patient took his clozapine with a caffeinated beverage including coffee or caffeinated diet Coke. The authors speculate that the stimulatory effects of caffeine via adenosine on the dopamine receptor overrode the weak effects of clozapine blockade. An alternative explanation was that competition for the metabolizing enzyme CYP1A2 resulted in increased effects of both agents. A second case report of a non-smoking woman taking 1.2g caffeine per day to counteract the sedative effects of clozapine showed a drop in clozapine level from 1500ng/ml to 630ng/ml when caffeinated beverages were discontinued. In a study of 7 patients the average drop in clozapine level was 47% after caffeine cessation; one patient consuming 1.1g caffeine/day showed a drop from 155 ng/mL to 31.4 ng/ml. All patients showed an increase in the norclozapine metabolite during the caffeine-free phase reflecting an increased degradation rather than norclozapine accumulation. Caffeine consumption in patients on clozapine should be determined at the outset and patients advised that increasing intakes of caffeine may worsen side effects such as sedation. Ideally caffeine intake should be minimized to avoid the interaction. There are reports that patients on clozapine voluntarily reduce caffeine consumption as has been seen with cigarette smoking and clozapine.

CYP1A2

Caffeine and up to 70% of clozapine are metabolized by the CYP 1A2 enzyme unlike most traditional neuroleptics, which are metabolized by 2D6. The interaction involves competitive inhibition for the 1A2 enzyme resulting in elevated levels of clozapine, which has been associated with increased side effects such as drowsiness, hypotension, and possibly seizures. In fact one study has shown that the activity of the 1A2 system in an individual can be determined by its metabolism of caffeine and used to predict clozapine levels. Some other medications metabolized by 1A2 that could be potentially affected by caffeine in a similar manner

include olanzapine, imipramine, clomipramine, amitriptyline and theophylline.

Fluvoxamine is a potent inhibitor of this enzyme and while it is well documented that it can dramatically increase clozapine levels, it has also been found to significantly elevate caffeine levels potentially causing caffeine intoxication.

Lithium

Elimination of caffeine from the diet can result in a 24% increase in lithium blood levels potentially causing lithium toxicity. The mechanism involves decreased caffeine induced diuresis resulting in increased lithium retention.

Smoking

Smoking induces the CYP1A2 enzyme resulting in a shortened half-life of caffeine in smokers. Smoking cessation can then result in decreased metabolism of caffeine and increased levels. In one study, caffeine levels were 250% higher when measured 12 weeks after smoking cessation. The rate of metabolism of caffeine decreases within three to four days after a person quits smoking. Thus, higher caffeine levels could be contributing to withdrawal symptoms as well as potentially impacting on levels of other medication that interact with caffeine such as clozapine or olanzapine.

Comment

People with severe mental illness often display a variety of addictive behaviors including higher than average tobacco and caffeine use. Both of these habits can impact on medications and symptoms of illness making a case for caffeine free environments. This, however, is almost impossible to achieve unless patients are on locked wards and does little to encourage abstinence or provide a long-term solution. Caffeinism should be considered in all

References

1. Hughes JR, McHugh P, Holtzman S: Caffeine and schizophrenia. *Psychiatric Services* 1998;49:1415-1417.
2. De Freitas B: Effects of caffeine in chronic psychiatric patients. *Am J Psychiatry* 1979;136:1337-1338.
3. Mayo KM, Falkowski W, Jones CAH. Caffeine use and effects in long-stay psychiatric patients. *British J Psychiatry* 1993;162:543-545.
4. Koczapski A, Paredes J, Kogan C, Ledwidge B, Higenbottam J: Effects of caffeine on behavior of schizophrenic inpatients. *Schizophr Bull* 1989;15: 339-344.

patients with symptoms of caffeine toxicity and attempts should be made to determine the extent of intake. Patients with symptoms that are considered due to or aggravated by caffeine such as anxiety or insomnia should be encouraged to abstain or dramatically reduce caffeine intake. If symptoms are caffeine induced, they should improve within 4 to 10 days of cessation. A rechallenge after this period may be useful in helping convince some clients of the side effects due to caffeine and promote abstinence or a reduction in use. Alternatives to caffeine containing beverages should be encouraged and made more readily available on wards and at mental health support or drop-in places. While attempts should be made to encourage moderation or abstinence where possible, consistency in intake is also important. Sudden caffeine cessation could result in toxicity from lithium. Resumption i.e. moving from a caffeine-free enforced environment to one with no controls could result in caffeine toxicity or in clozapine patients potentially severe clozapine related side effects. Other medications metabolized by CYP1A2 could similarly show increased side effects or increase the adverse effects of caffeine. Smoking cessation can also result in symptoms of caffeine toxicity. In patients also taking clozapine this could result in elevated clozapine levels from both the smoking cessation and the increased caffeine. Caffeine use and its potential impact on symptoms and medication should be taken into consideration when evaluating the outcome of treatment in the psychiatric patient.

Written by: Jane Dumontet, Pharm. D.

Reviewed by: Gordon Tse, Pharm. D.

If you would like to be added to the Inpharmation Newsletter mailing list, please call (604) 524-7012 or email address bthompson@bcmhs.bc.ca. Please ensure you include your entire mailing address (including postal code).

5. Hamera E, Schneider JK, Deviney S: Alcohol, cannabis, nicotine and caffeine use and symptom distress in schizophrenia. *J Nerv Ment Dis* 1995;183:559-565.
6. Caffeine content of selected foods and drugs. <http://www.infoplease.com/ipa/A0777440.html> (Oct. 29, 2001).
7. American Society of Health-System Pharmacists. Caffeine. In: *AHFS Drug Information 2000*. Bethesda, 2000: 2167–2170.
8. American Psychiatric Association. Caffeine-induced disorders. In: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington DC: American Psychiatric Association. 1994.
9. Kruger, A: Chronic psychiatric patients' use of caffeine: pharmacological effects and mechanisms. *Psychological Reports* 1996;78:915-923.
10. Simmons DH: Caffeine and its effect on persons with mental disorders. *Archives of Psychiatric Nursing* 1996; 2:116-122.
11. Zaslove MO, Russell RL, Ross E. Effect of caffeine intake on psychotic in-patients. *British J Psychiatry* 1991; 159: 565-567.
12. Lucas PB, Pickar D, Kelsoe J, Rapaport M, Pato C, Hommer D: Effects of the acute administration of caffeine in patients with schizophrenia. *Biol Psychiatry* 1990;28:35-40.
13. Vainer JL, Chouinard G: Interaction between caffeine and clozapine. *J Clin Psychopharmacol* 1994;14: 284-285.
14. Carrillo JA, Jerling M, Bertilsson L: Comments to "Interaction between caffeine and clozapine". *J Clin Psychopharm* 1995;15:376-377.
15. Odom-White A, de Leon J: Clozapine levels and caffeine. *J Clin Psychiatry* 1996;57: 175-176.
16. Carrillo JA, Herraiz AG, Ramos SI Benitez J: Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* 1998;18: 311-316.
17. Ozdemir V, Kalow W, Posner P, Collins EJ, Kennedy JL, Tang B et al: CYP1A2 activity as measured by a caffeine test predicts clozapine and active metabolite norclozapine steady-state concentration in patients with schizophrenia. *J Clin Psychopharmacol* 2001;21: 398 – 407.
18. Jeppeson U, Loft S, Poulsen HE, Broesen K: A fluvoxamine-caffeine interaction study. *Pharmacogenetics* 1996;6:213-222.
19. Mester R, Toren P, Mizrachi I, Wolmer L, Karni N, Weizman A: Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry* 1995;37: 348-350.
20. Benowitz N, Hall SM, Gunnard M: Persistent increase in caffeine concentrations in people who stop smoking. *Br Med J* 1989;298: 1075-6.
21. Brown, CR, Jacob P, Wilson M, Benowitz N. Changes in rate and pattern of caffeine metabolism after cigarette abstinence. *Clin Pharmacol Ther* 1988; 43: 488-91.
22. Kellner C, Pritchett J, Beale M, Coffey CE. *Handbook of ECT*. American Psychiatric Press. Washington DC. 1997.
23. Curry M, Curry SH, Marroum PJ. Interaction of phenothiazine and related drugs and caffeinated beverages. *Annals of pharmacotherapy* 1991;25:437.
24. Koczapski AB, Ledwidge B, Paredes J, Kogan C, Higenbottam J. Multisubstance intoxication among schizophrenia inpatients: reply to Hyde. *Schizophr Bull* 1990; 16:373-375.