# Drugs Which Induce Anxiety: Caffeine

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Regular consumption of high levels of caffeine can lead to a condition known as "caffeinism" which is characterised by chronic subjective anxiety. The condition is unresponsive to treatment with conventional benzodiazepine anxiolytics since caffeine is able to interfere with the action of these drugs. While not necessarily initiating anxiety, there is clinical and experimental evidence that acute caffeine can exacerbate the effects of an anxiety-inducing situation or worsen an existing anxiety condition, especially panic disorder. It seems possible that caffeine's involvement in anxiety states is due to its ability to interfere with the action of the sedative neuromodulator, adenosine, in the brain. Animal research has also suggested that daily consumption of caffeine during pregnancy and lactation can produce, in offspring, long-lasting forms of behaviour that are interpretable as arising from a high levels of emotional activity which may be related to anxiety in humans.

If anxiety involves an unpleasant aroused state characterised by high levels of sympathetic activity in response to some perceived or anticipated threat, then drugs that increase sympathetic arousal might also be expected to at least contribute to outcomes resembling effects of anxiogenic stimuli. Some evidence exists for acute anxiety-inducing effects in humans of stimulant drugs such as pentylenetetrazole (Rodin & Calhoun, 1970) and yohimbine (Charney, Heninger & Redmond, 1983). Provided one can accept the massive leap from studies of emotional reactivity in animals to human anxiety research, then it could be concluded that pentylenetetrazole and yohimbine are "anxiogenic" for laboratory rats as well (File & Lister, 1984; Pellow, Chopin, File, & Briley, 1985). The same conclusion would apply to the effects on "anxiety"- or fear-related responses in animals of other stimulants including methylphenidate, amphetamine and caffeine (e.g., File, Baldwin, Johnston, & Wilks, 1988; File & Hyde, 1979; Hughes & Greig, 1976; Misslin & Ropartz, 1981; Pellow et al., 1985). Of these three drugs, caffeine is particularly interesting because of its widespread use and thus anxiogenic potential in people of most cultures. Therefore, caffeine's involvement in the generation and potentiation of acute and chronic anxiety states will be discussed in the remainder of this article.

Along with alcohol and nicotine, caffeine is clearly one of the most heavily consumed psychotropic drugs we know. It is found in varying amounts in certain beverages and foods, principally coffee, tea, cola soft drinks and chocolate, and is also contained in a number of pharmaceutical products - some selected examples are outlined in Table 1. For further examples see Eilenhorn and Barceloux (1988).

It is widely assumed that coffee and tea are quite deliberately drunk for their psychomotor stimulant effects which are undeniably due to the action of caffeine on the central nervous system. In fact it has been shown that the number of cups of coffee drunk increases when the caffeine content is reduced (Kozlowski, 1976). Although people who

**Table 1:** Approximate Caffeine Content of Some Selected Beverages, Foods and Pharmaceutical Products

| | *Caffeine Content (mg)* | |
|---|---|---|
| BEVERAGES | Small cup (150 ml) | Large cup (225 ml) |
| Ground coffee | 85 | 128 |
| Instant coffee | 60 | 90 |
| Decaffeinated coffee | 2 | 3 |
| Black tea | 50 | 75 |
| Coca Cola | 17 | 25 |
| Pepsi Cola | 11 | 16 |
| Mountain Dew | 20 | 30 |
| FOODS | | |
| Milk chocolate | 21mg/100g | |
| Dark chocolate | 123mg/100g | |
| PHARMACEUTICAL PRODUCTS | | |
| Cafergot (ergotamine, caffeine) | | 100 mg / tablet |
| Ergodryle (ergotamine, diphenhydramine,caffeine) | | 100 mg /capsule |
| Migril (ergotamine, cyclizine, caffeine) | | 100 mg / tablet |
| Anacin (aspirin, caffeine) | | 22.7 mg / tablet |
| No Doz (caffeine) | | 100 mg / tablet |
| NO Doz Plus (thiamine, nicotinic acid, caffeine) | | 100 mg / tablet |

regularly consume coffee and tea are said to enjoy the resulting stimulation, others who normally abstain from caffeinated drinks may find the novel experience unpleasant because of accompanying jitteriness, nervousness and gastrointestinal complaints (Goldstein, Kaizer & Whitby, 1969). However, more recent research involving self-administration of the drug has seriously questioned the belief that coffee and tea are regularly drunk because the effects of caffeine are enjoyed (Stern, Chait & Johanson, 1989). In fact, caffeine's capability of inducing unpleasant symptoms of anxiety is so widely accepted that it has been described as a "fairly convincing model of generalised anxiety" (Lader & Bruce, 1986, p.258).

While systematic investigations and clinical reports of the anxiogenic effects of caffeine have only appeared in quantity during the last 30 years, its ability to produce "nervousness" when consumed in coffee and tea has long been recognised. For instance, in the eighteenth century, many American physicians (Benjamin Rush being a notable example) referred to a number of undesirable consequences of drinking strong tea amongst which "nervousness" featured prominently (Greden, 1979). More recently, anxiety-related symptoms such as nervousness, irritability and tremulousness were associated with caffeine intoxication (Erhardt, 1929). Today it is recognised that regular consumption of high doses of caffeine can lead to a constellation of symptoms, referred to as "caffeinism" (Greden, 1974; Reimann, 1967), that is virtually indistinguishable from severe, chronic anxiety. Since 1980, caffeinism has been listed as a separate diagnostic category in the *Diagnostic and Statistical Manual (DSM-III, DSM-IV)* of the American Psychiatric Association (1980, 1994).

## Production of Anxiety by Caffeine

### *Effects of chronic consumption*

A number of correlational studies have suggested that habitual ingestion of high doses of caffeine is related to high levels of chronic anxiety. One of the earliest of these was Greden's (1974) observation of psychological and physical symptoms of severe generalised anxiety (caffeinism) in outpatients whose daily consumption of caffeine from various sources was estimated to be between 1000 and 1500 mg. The only treatment they received was instructions to restrict their caffeine intake which eventually resulted in complete elimination of their symptoms. This finding was followed by reports of positive relationships between caffeine intake and anxiety in psychiatric inpatients (Winstead, 1976; Greden et al., 1978) which has also been shown with eating disordered individuals (Krahn, Hasse, Ray & Gosnell, 1991). In fact, symptoms of caffeinism (or even transient psychotic episodes) are not unknown in anorectic patients who, in an effort to control their weight, often consume large quantities of caffeine in the form of weight-control pills, diuretics and sugar-free soft drinks (Shaul, Farrell & Maloney, 1984). However, no relationship was recently found between caffeine consumption and anxiety in one sample of schizophrenic inpatients (Mayo, Falkowski & Jones, 1993). There was also no improvement when the wards changed from caffeinated to decaffeinated products. This study supported a previous failure to observe an association between anxiety symptoms and any level of coffee or tea consumption in psychiatric outpatients (Eaton & McLeod, 1984). In nonclinical populations, failures to observe positive relationships between caffeine intake and anxiety were also typical (e.g., Hire, 1978; Lynn, 1973) until Gilliland and Andress (1981) reported higher *trait* (but not state) anxiety in higher caffeine-consuming American undergraduates. However, the precise nature of the association these authors observed suggests that it could have been more indicative of reasons for, rather than the result of, a high intake of the drug.

In spite of compelling evidence that daily caffeine intake in excess of 1000 mg can lead to caffeinism (Greden, 1974; MacCallum, 1979), associations between anxiety and regular consumption of lower levels of the drug in both clinical and nonclinical populations are less convincing. Nevertheless, it is important to remember that, in a number of such studies, insufficient account has been taken of possible confounding effects of other drugs that can increase the rate of clearance of caffeine from the body, such as nicotine (Parsons & Neims, 1978). It may be that caffeine's anxiogenic potential is lower in smokers than in nonsmokers. As is the nature of correlational research, little can be said about causes in those few cases where positive relationships have been described - generally, it is not possible to determine if anxiety was the result or cause of excessive caffeine intake. For example, New Zealand undergraduate students have reported that they increase their consumption of tea or coffee during periods of stress in the belief that the practice will have a calming effect on them (Shanahan, 1983). Then on the other hand, reasons for drinking caffeinated beverages may be entirely unrelated to any real or imagined soothing effects ascribed to them, as typifies many psychiatric inpatients who may drink coffee and tea in an attempt to slake thirst or counteract sedation produced by some forms of medication (Podboy & Mallory, 1977), or even to just relieve boredom. Clearly, anxiety-inducing effects of caffeine are easier to assess when subjects are challenged with the drug (rather than just questioned about their usual intake), as was done by Greden (1974) who observed reappearance of symptoms in his caffeine-abstaining clients for whom caffeinism had been earlier diagnosed.

### *Effects of acute administration*

One of the first well-controlled studies of acute caffeine effects on mood was conducted by Veleber and Templer (1984) who, amongst other things, found a significant increase in subjective anxiety following ingestion by volunteers of 6.6 mg/kg caffeine (about 4-6 cups of coffee) dissolved in decaffeinated coffee. A similar effect on anxiety and nervousness accompanied by small increases in systolic and diastolic blood pressure was reported with 10 mg/kg (Charney, Galloway & Heninger, 1984; Charney, Heninger & Jatlow, 1985). Stern et al., (1989) later confirmed this anxiety result with volunteers who had ingested 100 mg caffeine. Most subsequent research has supported anxiogenic effects of moderate to high doses of acute caffeine (generally >200 mg) in nonclinical subjects (e.g., Chait, 1992;

Hasenfratz & Battig, 1994)

A number of investigators have shown that, while acute or chronic caffeine alone may not always induce anxiety, it is capable of exacerbating the effects of some other stressful situation on both the subjective and physiological symptoms of anxiety. For example, Cobb (1974) reported that stress-related noradrenaline output was greater in automobile workers threatened with unemployment who habitually drank caffeinated beverages than in those who did not. Acute ingestion of the drug can accentuate subjective anxiety as well as the raised systolic and diastolic blood pressure that results from exposure to physical and psychological stressors (France & Ditto, 1992; James, 1990; Lane, 1983; Lane & Williams, 1987; Pincomb, Lovallo, Passey, Brackett & Wilson, 1987). Shanahan and Hughes (1986) found that, while 400 mg caffeine did not significantly affect subjective anxiety, increases occurred when the drug action was paired with performance on a stressful high level reasoning task.

Support for caffeine's ability to exacerbate effects of stress can also be found in some animal research. For example, acute caffeine has strengthened evidence of heightened emotional reactivity arising from exposure to prenatal maternal stress in rats (Pohorecky, Roberts, Cotler & Carbone, 1989). Chronic caffeine was shown to intensify stress-related changes such as hypertension, elevated corticosterone levels and increased adrenal weights in mice living in a competitive social environment (Henry & Stephens, 1980). It can also aggravate gastric lesions in rats exposed to restraint and water-immersion stress (Yano, Isobe & Harada, 1982). More recently, Britton and Indyk (1990) reported that while acute caffeine increased locomotor activity of rats in their familiar home cage, it had the opposite effect in a more stressful novel open field. Results of the combined effects of various stressors and caffeine in both humans and animals have supported the conclusion that stress increases sensitivity to the anxiogenic potential of the drug (Pohorecky et al., 1989.)

### Conclusion

In general, it appears that caffeine alone (particularly when acutely administered) can produce some of the symptoms of anxiety in nonclinical volunteers but, more importantly, has the potential for exacerbating the anxiogenic effects of stressful situations. This clearly could have undesirable consequences for those inclined to increase their caffeine intake at times of stress. The practice adopted by many university students of taking caffeine tablets, often in combination with coffee or tea, to stave off sleep while studying for examinations could be distasterous for anyone prone to problematic examination anxiety. Also, the delayed and disrupted sleep that follows regular ingestion of caffeine throughout the day (Shirlow & Mathers, 1985) might exacerbate any anxiogenic effects of the drug. In stressful situations where further increases in anxiety could have deleterious effects, it is therefore advisable for caffeine consumption to not be increased beyond habitual levels.

## Exacerbation of Chronic Anxiety by Caffeine

Examples of the potentiation of stress effects by caffeine discussed above raise the question of whether or not symptoms of an existing anxiety disorder can be accentuated by caffeine. While evidence for caffeine's interaction with baseline levels of anxiety in nonclinical volunteers is conflicting (Chait, 1992; James, 1990), there is more consistency in reports of exacerbation of symptoms by challenges with the drug in people suffering chronic anxiety complaints, particularly panic disorder (PD). This contrasts with the low habitual intake of caffeine by PD and other chronically anxious patients compared with nonanxious tea and coffee drinkers, a situation which has been accounted for by their greater sensitivity to and thus avoidance of caffeine, often because of its unpleasant effects (Boulenger, Uhde, Wolf, & Post, 1984; Lee, Cameron & Greden, 1985; Lee, Flegel, Greden & Cameron, 1988).

### Panic disorder

As implied by its name, PD is characterised by panic attacks involving extreme terror which last from a few minutes to several hours with intervening states of chronic anticipatory anxiety often accompanied by agoraphobia. The panic episodes seem to have a biological basis since they can be precipitated to a greater or lesser extent by injections of lactic acid and its salts (Gaffney, Fenton, Lane & Lake, 1988) or inhalation of carbon dioxide (Woods, Charney, Goodman, & Heninger, 1988). There is now ample evidence that caffeine is also able to trigger a panic reaction or at least produce subjective changes in PD sufferers similar to those experienced during their attacks (Beck & Berisford, 1992; Charney et al., 1985; Uhde & Boulenger, 1989; Uhde, Boulenger, Jimerson & Post, 1984), facts recognised by sufferers themselves who therefore tend to voluntarily restrict their caffeine intake or even entirely avoid the drug (Boulenger et al., 1984; Lee et al., 1988). Caffeine's ability to initiate panic (even occasionally in nonanxious people at very high doses, Rowlands, 1987) is so well-established that, along with other drugs and treatments, it is usually included in lists of "panicogenic" agents (Nutt & Lawson, 1992; Shear, 1986; Uhde & Boulenger, 1989).

### Generalised anxiety disorder

Patients with generalised anxiety disorders (GAD) are often required (Smith, 1988), or choose, to restrict their caffeine intake (Lee at al., 1985) in the belief that their symptoms will not increase in severity or even abate. But as with the drug's effects on nonclinical baseline anxiety, there is less conclusive evidence than with PD that it does indeed exacerbate their condition. On the one hand, in one recent study, GAD subjects challenged with 250 or 500 mg caffeine demonstrated significant increases in their already high anxiety levels as reflected in self-ratings of subjective anxiety and several psychophysiological measures including blood pressure, sweating, skin conductance and EEG alpha wave activity (Bruce, Scott, Shine & Lader, 1992). On the other hand, Mathew and Wilson (1990) had earlier failed to establish any relationship between caffeine and exacerbated anxiety in GAD clients even though intravenous administration of 250 mg of the drug produced a decrease in

cerebral blood flow, a measure that the authors have elsewhere associated with anxiety states.

### Conclusion

As with examples of its ability to potentiate the anxiogenic effects of other stressors in nonclinical populations, caffeine definitely seems capable of exacerbating pre-existing chronic anxiety in PD and possibly other anxiety disordered individuals. It seems likely that such exacerbation is due to increased sensitivity to the drug. However, in generalising to larger populations from reports of these effects of caffeine on both clinical and nonclinical subjects, it is important to remember that wide individual differences characterise responsiveness to the drug. These can be due to varying degrees of tolerance in regular consumers or differences in ability to metabolise caffeine which can be further impaired by liver disease, pregnancy, oral contraceptives (Curatolo & Robertson, 1983) and certain forms of medication such as the $H_2$-receptor antagonist, cimetidine (Broughton & Rogers, 1981), or the muscle relaxant, idrocilamide (Brazier, Descotes, Lery, Ollagnier & Evreux, 1980). So that, although caffeinism usually only develops with daily consumption of extremely high levels of caffeine (>1000 mg), and 500-600 mg/day is commonly regarded as excessive, some people are at risk of developing the syndrome with habitual consumption of no more than 250 mg/day (Clementz & Dailey, 1988). It is therefore to be expected that the worsening of symptoms in chronically anxious people will depend to some extent on individual differences in sensitivity to caffeine.

## Interference with Anxiolytic Medication

In addition to possible exacerbation of their symptoms, caffeine provides another complication for the chronically anxious, namely the possibility that it might interfere with the ameliorating effects of some anxiolytic drugs. There is evidence that the central action of benzodiazepine anxiolytics is antagonised by high doses of caffeine in both humans (File, 1982; Mattila & Nuotto, 1983; Roache & Griffiths, 1987) and animals (DeAngelis, Bertolossi, Nardini, Traversa & Vertua, 1982; Hughes, 1993; Polc, Bonetti, Pieri, Cumin, Angioi, Möhler & Haefely, 1981), which might account for their ineffectiveness in treating caffeinism symptoms (Greden, 1974). This could be due to caffeine's ability to inhibit binding of these drugs to benzodiazepine receptors in the brain (Marangos, Paul, Parma, Goodwin, Syapin & Skolnick, 1979), although an action on adenosine receptors (discussed below) or some unrecognised site might be equally responsible for any caffeine/benzodiazepine interaction (Wu & Coffin, 1984). Experimental evidence of the antagonism of benzodiazepines by caffeine suggests a complication in the use of these drugs as anxiolytics (and anticonvulsants, muscle relaxants or hypnotics) with patients who habitually consume excessively high levels of caffeine. For the treatment of anxiety in some high caffeine-consuming patients, one of the new nonsedative anxiolytics such as buspirone might be preferable, since their actions are unlikely to be affected by caffeine (Hughes, 1993).

Caffeine's anxiogenic effects were once thought to arise from its ability to block benzodiazepine receptors (Skolnick, Paul & Marangos, 1980) thereby possibly attentuating the putative "anxiolytic" action of certain naturally-produced purines with an affinity for these receptors (Paul, Marangos, Goodwin & Skolnick, 1980). But even though caffeine is capable of occupying benzodiazepine receptors and may also interfere with the action of benzodiazepine drugs, acute doses that produce anxiety in otherwise nonmedicated subjects can be significantly lower than the minimum required for benzodiazepine receptor blockade. Consequently, the more favoured interpretation for anxiogenesis (as well as caffeine's other behavioural effects) now involves blockade of receptors for the sedative (anxiolytic?) neuromodulator, adenosine (Boulenger, Patel & Marangos, 1982; Marangos & Boulenger, 1985; Snyder & Sklar, 1984). This proposed mechanism is particularly relevant to PD sufferers whose sensitivity to caffeine may be mediated by supersensitivity of inhibitory adenosine receptors in response to chronic hyperactivity of excitatory transmitters (DeMet, Stein, Tran, Chicz-DeMet, Sangdahl & Nelson, 1989). However, recent research demonstrating increases in serum levels of the tryptophan metabolite, kynurenine, during caffeine-induced anxiety (Orlikov & Rizov, 1991) has also implicated serotonin in the phenomenon.

## Effects on Chronic Anxiety of Exposure to Caffeine Before or Soon after Birth

While appropriate research with humans in this area is seriously lacking, there is now considerable animal evidence for prenatal effects of caffeine on behavioural development in the absence of any obvious physical malformations (Nehlig & Debry, 1994; Sobotka, 1989). In other words, the drug appears to have subtle influences on the developing brain that can influence later behaviour. Of particular interest are reports of long-lasting increases in responses associated with heightened emotional reactivity (Hughes and Beveridge, 1987). More recently, it was shown that, exposing developing rats to maternally ingested caffeine, either before birth or during lactation, produced similar increases in their later emotional reactivity, but that the most marked effects came from exposing them to the drug during both periods consecutively (Hughes & Beveridge, 1991). The possibility of early treatment with caffeine leading to heightened emotional reactivity is supported by observations of other investigators who have employed a variety of preference and conditioning tests in rats and mice (File, 1987; Sinton, Valatx & Jouvet, 1981; Swenson, Beckworth, Lamberty, Krebs & Tinius, 1990; West, Sobotka, Brodie, Beier & O'Donnell, 1986). However, the extent to which these findings have relevance for human anxiety is extremely difficult to ascertain. Added to this is the fact that, even after allowing for species differences in metabolism, the changes observed occurred with doses of caffeine equivalent to about 800 mg caffeine or eight to ten cups of coffee/day for a human being. At first this may seem a high consumption for most people, but since clearance of caffeine from the human body is significantly slower during pregnancy (Curatolo & Robertson, 1983), with a much lower intake, pregnant women might be able to maintain serum levels of the drug equivalent

to those following ingestion of around 800 mg when not pregnant. There is no conclusive evidence that pregnancy retards caffeine clearance in rats (Nakazawa, Tanaka & Arima, 1985). Clearly there is a pressing need in this area for research with humans to establish whether or not pre- and early post-natal caffeine can have the sort of long-lasting effects on anxiety that typify emotional reactivity in animals.

Although the central mechanism underlying any developmental effects of early exposure to caffeine has not yet been established, involvement of adenosinergic processes has been suggested (Hughes & Beveridge, 1991; Nehlig & Debry, 1994). But if the known increase in brain receptors for adenosine with early caffeine exposure were responsible (Marangos, Boulenger & Patel, 1984), this should produce the opposite effects to acute administration of the drug (Zimmerberg, Carr, Scott, Lee & Weider, 1991), including reduced rather than heightened emotional reactivity or "anxiety". Adenosine's role in this behaviour (if any) therefore remains to be determined.

## General Conclusions

Caffeine is clearly capable of acting as an anxiogenic agent when administered both acutely and chronically at high doses. Its ability to exacerbate the effects of other stressors, to worsen the symptoms of some chronically anxious people and to precipitate panic attacks in PD sufferers suggests that its consumption should be reduced and definitely not increased if, in such cases, a further heightening of anxiety is to be avoided. Even in areas of investigation where caffeine's possible anxiogenic properties are only weakly established (e.g., effects on GAD), caution should nevertheless prevail until more is known. This particularly applies to heavy consumption of caffeinated products during pregnancy and while breastfeeding, because although there seems little likelihood of the drug producing gross physical abnormalities in human offspring (Nehlig & Debry, 1994; Sobotka, 1989), its possible effects on the pre- and early postnatal development of any predisposition to anxiety-related disorders have not yet been seriously considered.

Although the caffeinism-producing potential of daily ingestion of excessively high levels of caffeine (independent of any co-existing anxiety state) should now be well recognised by most health professionals, it is nevertheless advisable to routinely check the daily caffeine intake of patients presenting with symptoms of chronic anxiety. In this respect, it is important to remember that caffeinism might also obscure the accurate diagnosis of depressive disorders which could easily be mistaken for anxiety-related conditions.

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