# 17 - Chapter 12 Other substances

# 01 - Caffeine

# Caffeine


Chapter 12 Caffeine Caffeine is probably the most used psychoactive substance in the world. Mean daily consumption in the UK is 350–620mg.1 A quarter of the general population and half of those with psychiatric illness regularly consume over 500mg caffeine per day.2 Consumption of caffeine should be routinely discussed with an individual to assess its effect on their symptoms and presentation.3 Both caffeine intake and caffeine withdrawal can have a marked effect on mental and physical health. Most caffeine intake is in the form of coffee and tea but increasingly in the form of energy drinks (Table 12.1). Caffeine is also a constituent of chocolate and hundreds of over-the-counter medicines where it is often included as a co-analgesic. Other substances Table 12.1 Typical caffeine content of drinks. Drink Caffeine content Brewed coffee4 100mg/cup (around 100mg per espresso shot) Red Bull 80mg/can (other energy drinks may contain substantially more; volume of cans varies substantially) Instant coffee 60mg/cup Black tea 45mg/cup Soft drinks (sodas) 25–50mg/can Green tea 20–30mg/cup Decaffeinated coffee 3–16mg5

# 02 - General effects of caffeine

## General effects of caffeine

# 03 - Psychotropic effects of caffeine

# Psychotropic effects of caffeine

902 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 12 General effects of caffeine ■ ■Acute use can increase systolic and diastolic blood pressure (BP) by up to 10mmHg for up to 4 hours.3 Chronic moderate use probably has little effect on BP.9 ■ ■May enhance reinforcing effects of nicotine and possibly other drugs of misuse.10,11 ■ ■Caffeine has important psychotropic effects (Table  12.2), may worsen existing psychiatric illness and may interact with psychotropic drugs. ■ ■Caffeine is an antagonist at adenosine A1 and A2A receptors, thus stimulating dopamine pathways. Psychotropic effects of caffeine Withdrawal An established withdrawal syndrome exists; symptoms include headache, depressed mood, anxiety, fatigue, irritability, nausea, dysphoria and craving.12 Pharmacokinetics ■ ■Absorption: Rapid after oral administration, especially in liquid form. ■ ■Metabolism: ■ ■Half-life of 2.5–4.5 hours. ■ ■Metabolised by CYP1A2, a hepatic cytochrome enzyme that exhibits genetic polymorphism. This may account for the large interindividual differences that are seen in the ability to tolerate caffeine.13 Note that CYP1A2 is induced by smoking and inhibited by a number of drugs such as fluvoxamine. ■ ■This metabolic pathway may become saturated at higher doses.14 ■ ■Interactions (Table 12.3): ■ ■Caffeine competitively inhibits CYP1A2. Chronic caffeine use may increase plasma levels of drugs metabolised by CYP1A2. Plasma levels of some drugs may be reduced if caffeine is withdrawn. Table 12.2 Dose and psychotropic effects of caffeine. Dose Psychotropic effect Generally Central nervous system stimulation Increase catecholamine release, particularly dopamine6 Low to moderate dose2,7 Elation Impulsivity Peacefulness Large doses >600mg/day8 (sensitive [non-tolerant] individuals may experience effects at lower doses; tolerance develops in long-term users) Anxiety Insomnia Psychomotor agitation Excitement Rambling speech Delirium Psychosis

# 04 - Caffeine intoxication

# Caffeine intoxication

Other substances CHAPTER 12 ■ ■The potential effects of caffeine on the metabolism of other drugs, as well as the potential to induce a caffeine withdrawal syndrome, should always be considered before substituting caffeine-free drinks. Caffeine intoxication The DSM-519 defines caffeine intoxication as the recent consumption of caffeine, usually in excess of 250mg, accompanied by five or more of the symptoms in Box 12.1. In caffeine intoxication, these symptoms cause significant distress or impairment in social, occupational or other important areas of functioning and are not due to a general medical condition or better accounted for by another mental disorder (e.g. an anxiety disorder). Caffeine abuse or dependence as a clinical syndrome has been reported3 and caffeine use disorder and caffeine withdrawal are both DSM-5 diagnoses. Table 12.3 Interactions with caffeine. Interacting substance Effect Comments CYP1A2 inhibitors: Oestrogens Cimetidine Fluvoxamine (may decrease caffeine clearance by 80%)15 Disulfiram Reduce caffeine clearance Effects of caffeine may be prolonged or increased Adverse effects may be increased May precipitate caffeine toxicity Cigarette smoke* CYP1A2 inducer – increased caffeine metabolism6 Smokers may require higher doses of caffeine to gain desired effects6 Lithium High doses of caffeine may reduce lithium levels Caffeine withdrawal may cause a lithium level rise16 MAOIs May enhance stimulant CNS effects Clozapine Caffeine may increase clozapine plasma concentrations by up to 60%17 Thought to be via competitive inhibition of CYP1A2. Other drugs affected by caffeine-induced inhibition of the enzyme include olanzapine, imipramine and clomipramine. SSRIs Large doses of caffeine may increase risk of serotonin syndrome18 Benzodiazepines Caffeine may act as an antagonist Caffeine reduces the efficacy of benzodiazepines8 * Vaping has no effect on CYP1A2 function. CNS, central nervous system; MAOIs, monoamine oxidase inhibitors.

# 05 - Energy drinks

Energy drinks

# 06 - Effects of caffeine on different disorders

# Effects of caffeine on different disorders

904 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 12 Energy drinks So-called energy drinks contain large amounts of caffeine along with sugar, vitamins and a number of other ingredients such as guarana and taurine. There is some evidence that these drinks can improve attention and short-term memory.20 Marketing is targeted at adolescents and young adults, some of whom consume large volumes of these drinks and seem to be particularly vulnerable to developing signs and symptoms of caffeine intoxication. Symptoms of anxiety and depression, frank suicidal behaviour and seizures have been associated with use of these products by young people.21–23 When combined with alcohol, aggressive behaviour may result.24 Excessive intake may lead to acute psychosis25,26 or mania.27 Effects of caffeine on different disorders Schizophrenia ■ ■Patients with schizophrenia often consume large amounts of caffeine-containing drinks1 and they are twice as likely as controls to consume >200mg caffeine/day.6 ■ ■Caffeine--containing drinks may be used to relieve dry mouth (as an adverse effect of some antipsychotic drugs), for the stimulant effects of caffeine (to relieve dysphoria/ sedation/negative symptoms)6 or simply because coffee/tea drinking structures the day or relieves boredom. ■ ■Schizophrenia may increase sensitivity to drug-related cues.6 ■ ■Moderate caffeine intake may improve cognitive and negative symptoms in schizophrenia.28,29 ■ ■Large doses of caffeine can worsen psychotic symptoms6,30 (in particular elation and conceptual disorganisation) and result in the prescription of larger doses of antipsychotic drugs. ■ ■The removal of caffeine from the diets of chronically disturbed (challenging behaviour) patients may ultimately lead to decreased levels of hostility, irritability and suspiciousness31 although this may not hold true in less disturbed populations.32 ■ ■Caffeine cessation may be of benefit in clozapine-resistant schizophrenia.33 Box 12.1 Symptoms of caffeine intoxication ■ ■Restlessness ■ ■Gastrointestinal disturbance ■ ■Nervousness ■ ■Muscle twitching ■ ■Excitement ■ ■Rambling flow of thought and speech ■ ■Insomnia ■ ■Tachycardia or cardiac arrhythmia ■ ■Flushed face ■ ■Periods of inexhaustibility ■ ■Diuresis ■ ■Psychomotor agitation

# 07 - Summary

# Summary

Other substances CHAPTER 12 Mood disorders ■ ■Caffeine may elevate mood through increasing noradrenaline release34 and modest caffeine consumption may protect against depression in those who do not have a pre- existing mood disorder.35 ■ ■People with mood disorders are more likely to consume caffeine, particularly when depressed.16,36 ■ ■Depressed patients may be more sensitive to the anxiogenic effects of caffeine.37,38 ■ ■Excessive consumption of caffeine may precipitate mania.38,39 ■ ■Caffeine can increase cortisol secretion (gives a false positive in the dexamethasone- suppression test),40 increase seizure length during electroconvulsive therapy41 and increase the clearance of lithium by promoting diuresis.42 Anxiety disorders ■ ■Caffeine increases vigilance, decreases reaction times, increases sleep latency and worsens sleep quality; effects that may be more marked in poor metabolisers. ■ ■May precipitate or worsen generalised anxiety and panic attacks;43 vulnerability to these effects may be genetically determined.11 ■ ■Effects are so marked that caffeine intoxication should always be considered when patients complain of anxiety symptoms or insomnia. ■ ■Symptoms may diminish considerably or even abate completely if caffeine is avoided.44 ■ ■Patients with panic disorder consume much more caffeine than controls45 but the reasons for this are not clear. Greater consumption triggers panic attacks in those with panic disorder but not in other populations.46 Other disorders Weak evidence supports the benefit of caffeine in attention deficit hyperactivity disorder (ADHD)47 and that high caffeine consumption may protect against late-life cognitive decline.48 Summary ■ ■Caffeine is present in high quantities in coffee and some soft drinks, particularly energy drinks. ■ ■The intake of caffeine may worsen psychosis and anxiety. Young people may be particularly vulnerable. ■ ■Caffeine inhibits clozapine metabolism. ■ ■Caffeine intoxication is characterised by psychomotor agitation and rambling speech. ■ ■Caffeine may be associated with toxicity when co-administered with CYP1A2 inhibitors such as fluvoxamine. ■ ■Caffeine can enhance the reinforcing effects of nicotine and possibly other drugs of misuse.

# 08 - References

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# 09 - Nicotine

## Nicotine

# 10 - Psychotropic effects

## Psychotropic effects

# 11 - Effects of nicotine on different disorders

# Effects of nicotine on different disorders

908 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 12 Nicotine Nicotine is consumed by vaping or tobacco smoking and causes peripheral vasoconstriction, tachycardia and increased blood pressure.1 People with schizophrenia who smoke are more likely to develop the metabolic syndrome compared with those who do not smoke.2 Alongside nicotine, cigarettes also contain tar (a complex mixture of organic molecules, many carcinogenic), a cause of cancers of the respiratory tract, chronic bronchitis and emphysema.3 Electronic cigarettes and vaping devices contain only nicotine (along with some necessary excipients), which has very limited toxicity and is not thought to be carcinogenic. Vaping is thus preferred for all smokers, albeit with some reservations in regard to quality control of content and the so-called re-normalisation of smoking. Vaping is not without risk but this is a complex area beyond the scope of this book. Nicotine is highly addictive and vulnerability to nicotine addiction may be genetically determined.4 People with mental illness are 2–3 times more likely than the general population to develop and maintain a nicotine addiction.5 Chronic smoking contributes to the increased morbidity and mortality from respiratory and cardiovascular disease that is seen in this patient group. Nicotine also has psychotropic effects. Smoking can affect the metabolism (and therefore the efficacy and toxicity) of drugs prescribed to treat psychiatric illness6 (see ‘Smoking and psychotropic drugs’ in Chapter 11). Nicotine use may be a gateway drug to experimenting with other psychoactive substances. Psychotropic effects Nicotine is highly lipid-soluble and rapidly enters the brain after inhalation. Nicotine receptors are found on dopaminergic cell bodies and stimulation of these receptors leads to dopamine release.5 Nicotine may be used by people with mental health problems as a form of ‘self-medication’ (e.g. to alleviate the negative symptoms of schizophrenia or antipsychotic-induced dysphoria or for its anxiolytic effect7). Drugs that increase the release of dopamine reduce craving for nicotine. They may also, of course, worsen psychotic illness. Nicotine improves concentration and vigilance,5 probably by enhancing the effects of glutamate, acetylcholine and serotonin.7 Effects of nicotine on different disorders Schizophrenia Before the introduction of vaping, 70–80% of people with schizophrenia regularly smoked cigarettes.8 Now both tobacco use and vaping are more common among people with psychosis.9,10 A 2024 study in the USA11 found that 28% of people with a first episode of psychosis used nicotine in one form or another – roughly double the rate of age-matched controls. In people with longer-standing

psychosis in 2023, tobacco use was seen in just over 40% but use of any nicotine product was reported in around 70–80% (i.e. a prevalence no different from before the availability of vaping devices).12

Other substances CHAPTER 12 This increased tendency to use nicotine predates the onset of psychiatric symptoms13 and smoking might actually be a causal factor in schizophrenia.14 Possible explanations are as follows:15 (i) smoking causes dopamine release, leading to feelings of well-being and a reduction in negative symptoms;7 (ii) smoking alleviates some of the adverse effects of antipsychotics such as drowsiness and extrapyramidal side effects (EPSEs)5 and cognitive slowing;16,17 (iii) smoking serves as a means of structuring the day (a behavioural filler); (iv) smoking arises as a result of a familial vulnerability;18 or (v) smoking may be used as a means of alleviating the deficit in auditory gaiting that is found in schizophrenia.19 Nicotine may also improve working memory and attentional deficits.20–22 Nicotinic receptor agonists may have beneficial effects on neurocognition,23,24 although none is licensed for this purpose. Note though that cholinergic agonists may exacerbate nicotine dependence.25 Interestingly, the greater the occupancy of striatal D2 receptors by antipsychotic drugs, the more likely the patient is to smoke.26 This may partly explain the clinical observation that smoking cessation may be more achievable when clozapine (a weak dopamine antagonist) is prescribed in place of a conventional antipsychotic. It has been suggested that people with schizophrenia find it particularly difficult to tolerate nicotine withdrawal symptoms6 (although some certainly can stop27). Switching to nicotine replacement therapy or vaping may thus be the preferred option.28,29 A switch from tobacco smoking to vaping has been shown to be well tolerated even in severe mental illness.30 Depression and anxiety Moderate consumption of nicotine is associated with pleasure and a decrease in anxiety and feelings of anger.31 The mechanism of this anxiolytic effect is not understood. People who suffer from anxiety and/or depression are more likely to smoke32 and find it more difficult to stop.31,33 Nicotine itself might have antidepressant activity.34 Nicotine withdrawal can precipitate or exacerbate depression in those with a history of the illness,31 but cigarette smoking may directly increase the risk of depression.35 A 2020 study suggested nicotine addiction and depression are independently linked.36 Some studies suggest that stopping smoking ultimately improves depression and anxiety.37,38 A 2020 Cochrane review39 suggests smoking cessation is achievable in depressed smokers, but a later twin study found that depression made smoking cessation much less likely.40 Patients with depression are at increased risk of cardiovascular disease. By directly causing tachycardia and hypertension,1 nicotine may, in theory, exacerbate this problem. More importantly, smoking tobacco is a well-known independent risk factor for cardiovascular disease, probably because it hastens atherosclerosis. Vaping, while not carcinogenic, increases risk of cardiovascular disease.41 Attention deficit hyperactivity disorder (ADHD) People with ADHD are relatively more likely to use nicotine products.42 Tobacco smoke contains monoamine oxidase inhibitors which may benefit ADHD symptoms.43 There is ample evidence of complex pharmacodynamic interactions between nicotine and stimulant drugs.44

# 12 - Drug interactions

## Drug interactions

# 13 - Smoking cessation and withdrawal symptoms

## Smoking cessation and withdrawal symptoms

# 14 - References

# References

910 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 12 Movement disorders and Parkinson’s disease By increasing dopaminergic neurotransmission, nicotine is thought to provide a protective effect against both drug-induced EPSEs and idiopathic Parkinson’s disease. Smokers are less likely to suffer from antipsychotic-induced movement disorders than non--smokers5 and use anticholinergic drugs less often.6 Parkinson’s disease occurs less frequently in smokers than in non-smokers and the onset of clinical symptoms is delayed.5,45 This may reflect the inverse association between Parkinson’s disease and sensation-seeking behavioural traits, rather than a direct effect of nicotine.46 The protective effect may not be related to nicotine at all but rather to other compounds in tobacco smoke.47 Drug interactions Polycyclic hydrocarbons in tobacco smoke are known to stimulate the hepatic microsomal enzyme system, particularly CYP1A2,7 the enzyme responsible for the metabolism of many psychotropic drugs. Smoking can lower the blood levels of some drugs by more than 50%.7 This can both affect efficacy and influence adverse effects and needs to be taken into account when making clinical decisions. The drugs most likely to be affected are clozapine,48 fluphenazine, haloperidol, chlorpromazine, olanzapine, many tricyclic antidepressants, mirtazapine, fluvoxamine and propranolol. Vaping has no effect on hepatic enzyme function. See ‘Smoking and psychotropic drugs’ in Chapter 11. Smoking cessation and withdrawal symptoms Withdrawal symptoms occur within 6–12 hours of stopping smoking and include intense craving, depressed mood, insomnia, anxiety, restlessness, irritability, difficulty in concentrating and increased appetite. Nicotine withdrawal can be misdiagnosed as depression, anxiety, sleep disorders and mania.49 Withdrawal can also exacerbate the symptoms of schizophrenia.6 See also ‘Nicotine and smoking cessation’ in Chapter 4. References


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