Chapter 10
Caffeine, Mental Well-Being, and Psychiatric Disorders

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Abstract Caffeine is the most consumed substance in the world. It is well known to affect alertness and interfere with sleep. Caffeine acts as an adenosine antagonist and indirectly affects other neurotransmitters. DSM-V lists four disorders directly related to caffeine intake. Caffeine interferes with anxiety and sleep disorder. Studies have shown positive effect of caffeine on neurocognitive function, such as Alzheimer's and Parkinson's disease. Caffeine is found to improve some elements of depressive disorder, such as amotivation symptom, and it is widely used during the electoral convulsive therapy to lower seizure threshold. It can decrease the lithium level, which might precipitate switch to manic or hypomanic episode and bipolar disorder. Further research and randomized control trials are needed to establish the relationship between caffeine and psychiatric effects.

Keywords Caffeine · Coffee · Adenosine · Anxiety · Depression · Insomnia · Alzheimer · Parkinson · DSM-V

10.1 Introduction

Bitter in taste and considered the world's most widely used drug, caffeine is typically consumed to wake up and reenergize our bodies to take on the day's challenges and hardships, or as testified by 80% of the world's population which consumes a caffeinated product every single day (Petre 2020). Caffeine is naturally found in seeds and leaves and within fruits (Heckman et al. 2010). These include coffee beans, tea leaves, cocoa beans, yerba mate leaves, guarana berries, and kola nuts (Reyes and Cornelis 2018). It is also commonly added in many other foods and beverages for its benefits on mood, alertness, and increased energy (Heckman et al. 2010). Scientific literature has defined caffeine in many ways; chemically, it is known as methylxanthine (1,3,7-trimethylxanthine), but most commonly it is described as a natural stimulant or a psychoactive drug (van Dam et al. 2020). That is because caffeine's main impact is on the brain where it blocks the chemical adenosine (Baehr and Welsh 2014). The way it works is simple; adenosine is a neurotransmitter in our brains, which is responsible for sending chemical messages of tiredness and relaxation (Petre 2020). However due to caffeine's similar molecular structure, it binds to adenosine receptors instead, hence preventing adenosine's function and reducing the feeling of tiredness (van Dam et al. 2020). Caffeine also exerts its energizing effects through increasing levels of the fight or flight hormone, adrenaline, in the blood and increasing the activity of dopamine and norepinephrine neurotransmitters in the brain, which play a role in how good or bad we feel (Petre

2020). It is also worth mentioning that caffeine's popularity is also due to its quickness in delivering alertness as it takes less than 20 min to make it into the bloodstream and is almost completely absorbed within 45 min after consumption, reaching its full potency (Petre 2020).

While the science of how caffeine works has been thoroughly studied and proven, the same cannot be said for the history of the drug. The origins of caffeine are unknown and surrounded by myths, similarly to tea and coffee. It is speculated by anthropologists that plants containing caffeine such as tea leaves and coffee beans were discovered as early as 700,000 B.C. and directly eaten by humans in the early Paleolithic Stone Age (Weinberg and Bealer 2001). However, the infusion of caffeine-containing plants with hot water came centuries after that (Weinberg and Bealer 2001). Tea was first discovered in ancient China. Legend has it that in 2732 B.C., Emperor Shen Nung discovered tea by coincidence as some leaves made their way into his pot of boiling water; intrigued by the pleasant smell, he decided to drink the brew and sparked the tea culture in the country (DeWitt 2000). Tea's popularity spread across China throughout the fourth and eighth centuries, and it was not only used for medicine but also as an everyday refreshing beverage (DeWitt 2000). On the other hand, coffee is said to be discovered in 850 C.E. by a herdsman. According to Ethiopian folktale, a goatherd named Kaldi first discovered coffee as he noticed his goats' unusual hyperactivity and refusal to sleep at night after consuming coffee berries (National Coffee Association USA n.d.). Kaldi told the local monastery about his discovery, which turned the beans into a drink, realizing that its stimulating effects affect humans as well (National Coffee Association USA n.d.). This revelation quickly spread out to the Arabian Peninsula, which actively began the cultivation and trade of coffee in the fifteenth century from today's Yemen and popularized it around the world. It made its way to Persia, Egypt, Syria, India, North Africa, Turkey, and the Balkans (Myhrvold 2021). Coffee's popularity in the Arab region created a culture of public coffee houses called *qahveh khaneh*—to enjoy not only coffee, but also various social activities including listening to music, enjoying performances, playing chess, and keeping up with current news (Myhrvold 2021). Coffee made it to Europe in early 1615 and was eventually introduced to the United States, becoming a global phenomenon (Myhrvold 2021).

Today, 99% of the coffee we drink is derived from two species, *Coffea arabica* (arabica), cultivated by Latin America, Eastern Africa, Asia, and Arabia, and *Coffea canephora* (robusta) produced mainly by Western and Central Africa, Southeast Asia, and (de Mejia and Ramirez-Mares 2014). Despite tea and coffee's relative early discovery, caffeine was not extracted until the beginning of the nineteenth century (Weinberg and Bealer 2001). Friedlieb Ferdinand Runge, a young physician, met the poet Johann Wolfgang von Goethe, who was impressed by Runge's skills in chemical extractions; hence, he asked him to analyze a small box of rare Arabian mocha beans (Weinberg and Bealer 2001). In a few months' time, Runge was successful in isolating and purifying caffeine as a white crystalline substance for the first time in 1819 (Baratloo et al. 2016). As stated in the book "The World of Caffeine" by authors Weinberg and Bealer, "it was a result of an encounter between

Table 10.1 Average caffeine content of common products

Drink	Caffeine content
Brewed coffee	100 mg/cup
Instant coffee	60 mg/cup
Black tea	45 mg/cup
Green tea	20–30 mg/cup
Energy drinks	80 mg/can (other energy drinks may contain substantially more)
Soft drinks	25–50 mg/can

a scientist and a poet that caffeine was first revealed to the world; a curiously symbolic origin when one considers the vast panorama of the drug's history, encompassing, as it does, so much of the disparate worlds of science and culture" (Weinberg and Bealer 2001).

While caffeine is usually associated with coffee and tea, the drug is present in many of our foods and drinks like chocolate, soft drinks, and even chewing gum (Alexis 2021). On average, adults in the United States consume 135 milligrams of caffeinated products daily, which is the equivalent of 1.5 cups of coffee a day (1 cup = 8 ounces) (The Nutrition Source n.d.). According to the U.S. Food and Drug Administration, it is safe for healthy adults to consume 400 mg (roughly amounts to 4 cups of coffee) of caffeine daily (Petre 2020). Considering this, it is worth mentioning the amount of caffeine present in our foods and beverages to avoid the risks of excess consumption. Coffee, energy drinks, caffeine supplements, yerba mate, and guarana-containing drinks have the highest concentrations of caffeine (Heckman et al. 2010). Starting off with brewed coffee, a typical serving of a cup or 8 ounces amounts to 95 mg caffeine, while the same quantity in instant coffee has 60 mg of caffeine. As for decaffeinated coffee, 4 mg of caffeine is typical in a cup. For espresso, although it is high in concentration of caffeine, it is served as a shot or 1.5 ounces containing 65 mg, but 8 ounces of espresso would amount to 240 mg (Petre 2020; The Nutrition Source n.d.). On the other hand, energy drinks have 85 mg of caffeine a cup, but typically they are produced in 16-ounce bottles which have 170 mg. There are also energy shots—2 ounces—that come in higher concentrations of 200 mg caffeine, equivalent to 2 cups of coffee. Similarly, caffeine tablets are of high concentrations containing 200 mg caffeine (van Dam et al. 2020). Yerba mate has 85 mg caffeine per cup, while guarana drinks can have up to 125 mg of caffeine (Petre 2018). Tea is considered to have a medium concentration of caffeine. An average cup of black tea brew has 47 mg, but green tea has less with 28 mg, and chamomile or peppermint tea contains no caffeine at all, hence both considered low in caffeine. Soft drinks, chocolate, and chewing gum are also regarded as low in caffeine. Sodas or soft drinks are at an average of 40 mg for 12-ounce cans. While chocolate varies in caffeine amounts from type to type, dark chocolate has more with 24 mg caffeine in 1 ounce and milk chocolate much less with 7 mg. Chewing gums containing caffeine typically have 25 mg per piece (Alexis 2021; Petre 2020; The Nutrition Source n.d.). Given this information, caffeine consumption takes a new light in our dietary lifestyle and puts importance on the caffeinated products we choose to consume and mix (Table 10.1).

10.2 Caffeine Pharmacodynamic

Caffeine as a drug belongs to the methylxanthine class. It has a stimulant effect on the central nervous system (CNS). This naturally occurring stimulant can be found in coffee, tea, chocolate, and other substances. In addition to those, it can also be found in energy drinks, soda, and other supplements where caffeine is artificially added. This abundance of sources, along with general social and cultural acceptance, contributes to caffeine being the most used psychoactive substance worldwide (Ribeiro and Sebastião 2010).

There are numerous uses for caffeine. Many people use it to stay awake and alert for various activities. It is approved by the Food and Drug Administration (FDA) as a treatment for some medical conditions, such as apnea of prematurity and bronchopulmonary dysplasia. Some of the non-FDA-approved uses of caffeine include treatment for migraine headaches and post-dural puncture headaches, as well as to boost athletes' performances. There are ongoing trials examining the usage of caffeine for the treatment of depression and neurocognitive disorders, such as Alzheimer's and Parkinson's disease (Evans et al. 2022).

Caffeine acts on several neurotransmitters and receptors in the body. However, it exerts most of its effects by antagonizing adenosine receptors specifically. Being both fat and water soluble, caffeine can readily penetrate the blood-brain barrier, allowing it easy access to the CNS. There are four adenosine receptors: A1, A2a, A2b, and A3. Caffeine acts on all of them, yet the antagonism of A2a receptors is what causes the wakeful effects of caffeine. Adenosine receptors exist throughout the body. In the heart, for instance, antagonism of A1 receptors in the cardiac muscle causes positive inotropic effect. Adenosine has an inhibitory effect on the CNS and other parts of the body. It is by antagonizing this inhibitory effect can caffeine induce its stimulatory effect. Caffeine stimulates the release of catecholamines, which further increase the heart rate and inotropic effect. It does that by, again, antagonizing adenosine receptors (Spriet 2014).

Caffeine has a complex effect on vascular tone. On the one hand, it antagonizes vascular adenosine receptors, causing vasodilation. It also stimulates endothelial cells to release nitric oxide, which promotes smooth muscle relaxation and further vasodilation. On the other hand, caffeine causes indirect vasoconstriction through the catecholamine release with increased sympathetic tone as a result. Caffeine appears to elevate systolic blood pressure by 5-10 mmHg in infrequent users; however, there is no such effect on individuals who use caffeine regularly. In addition to adenosine receptor antagonism, caffeine also acts to inhibit the phosphodiesterase (PDE). Inhibiting PDE-5 can cause further vasodilation (Ribeiro and Sebastião 2010).

As mentioned earlier, adenosine receptors are present in many parts of the human body; hence, antagonism of adenosine receptors may also result in the stimulation of respiratory drive. This stimulation occurs by increasing medullary response to CO2, stimulating central respiratory drive, and enhancing diaphragm contraction. Caffeine also increases diuresis by increasing blood flow to kidneys, increasing glomerular

filtration, and increasing sodium excretion. Caffeine can trigger calcium release from intracellular stores, which has an application in contracture test for the diagnosis of malignant hyperthermia. Caffeine also targets GABA-A receptors and suppresses them, which may cause neurobehavioral effects (Evans et al. 2022).

10.2.1 Caffeine Pharmacokinetics

Caffeine is metabolized mainly in the liver by the cytochrome P450 oxidase system, enzyme CYP1A2 to be exact. Caffeine is metabolized to one of these three metabolites: paraxanthine, theobromine, or theophylline. These metabolites, before being further metabolized and then excreted in urine, have the following biological effects:

1. Paraxanthine: increases lipolysis, which results in higher levels of glycerol and free fatty acids in the blood
2. Theobromine: has a vasodilatory effect and leads to increased urine volume
3. Theophylline: causes bronchodilation and is used in the treatment of asthma

Caffeine has a short half-life of about 5 h. However, this half-life largely varies depending on different factors. Pregnancy, for example, can extend it three times. Smoking, on the other hand, can halve caffeine's half-life. In infants, the half-life is approximately 8 h, while in premature infants, this number jumps to 100 h due to an immature cytochrome P450 system. Patients taking cytochrome inhibitors and those with liver disease will experience a prolonged half-life of caffeine (Evans et al. 2022).

Caffeine is readily available when taken orally with 100% oral bioavailability. It usually takes about 45–60 min after oral intake for the onset of action and lasts about 3–5 h. Taking caffeine with food tends to slow its absorption. In medical settings, caffeine can be administered parenterally. Some of the parenteral routes used are rectal, insufflation, or inhalation. Inhalation and insufflation are generally used with an intention of getting high. These routes bypass the first-pass metabolism and lead to a much faster absorption (i.e., within minutes). Resulting bioavailability and duration, on the other hand, are less than those of an oral route (Evans et al. 2022).

While there are no absolute contraindications for using caffeine, there are some conditions for which caution is necessary, which include cardiovascular disease and arrhythmias, peptic ulcer disease and gastroesophageal reflux disease, hepatic disease, seizure disorder, pregnancy, and severe anxiety (Spriet 2014; Evans et al. 2022). There are studies that suggest that consuming high doses of caffeine (more than 400 mg/day) can lead to intrauterine growth restriction and miscarriage. The American College of Obstetricians and Gynecologists (ACOG) considers 200 mg of caffeine a day to be safe during pregnancy.

10.3 Caffeine and Addiction

Coffee is one of the most popular drinks in the world. Only in the United States, 87% of both children and adults regularly consume food and drink that contain caffeine. On average, an adult consumes around 200 mg of caffeine a day in the United States. However, a good percentage of people exceed the 500 mg mark daily. Regular use of caffeine along with its integration in daily routines and social events makes it significantly more difficult to recognize caffeine-associated disorders. Having a caffeine-related disorder places the person at an increased risk of other substance-use disorders. Indeed, two-thirds of people who use caffeine heavily also use sedative and hypnotic drugs (van Dam et al. 2020).

Generally, people report a sense of improved well-being, increased energy, and better focus with low doses of caffeine. These effects are usually seen in the dose range of 20–200 mg (Cappelletti et al. 2015). Consuming larger quantities, in the range of 300–800 mg, leads to people reporting being anxious and nervous. In regular users, caffeine suppresses the mild withdrawal symptoms that occur after a whole night without caffeine. This in turn acts as a reinforcer for continued use (Petre 2020).

Investigation reports high concordance rate in monozygotic twins for various caffeine use aspects like total consumption, tolerance, withdrawal, intoxication, and heavy use. There may be a common genetic factor underlying the use of caffeine, alcohol, and cigarette smoking. People who smoke cigarettes tend to use more caffeine than their nonsmoker counterparts. There are few reasons that might explain this: first, common genetic predisposition as mentioned earlier; second, smoking increases caffeine elimination from the body; and third, caffeine enhances the effects of nicotine. Numerous studies have shown an increased intake of caffeine among psychiatric inpatients (Sadock et al. 2015).

The most recent edition of the Diagnostic and Statistical Manual (DSM-V) contains new sections for caffeine-related disorders. Caffeine-use disorder is not a specific diagnosis in the DSM-V, but it has been classified as a condition requiring further research. This category comprises problems that appear to have some evidence of effects on psychological well-being but do not have a significant enough research basis to justify placement in the list of classifiable disorders. Due to this use, many people do not feel severe personal suffering or a major decline in functioning in any part of their lives. These two criteria are mentioned as prerequisites for almost every disorder included in the DSM-V; caffeine intoxication and caffeine withdrawal, on the other hand, are both included as disorders in the DSM-V (American Psychiatric Association 2013; Sadock et al. 2015).

Caffeine-use disorder was included in DSM-V as a disorder for further study rather than as a recognized diagnosis due to a lack of data on its prevalence and clinical importance in general population samples. There are three DSM-V diagnostic criteria for caffeine-use disorder that are necessary and sufficient: (1) a persistent urge or unsuccessful attempts to reduce or restrict caffeine intake; (2) caffeine usage that continues despite knowledge of an ongoing or recurring physical or

psychological problem that is likely to have been caused or worsened by caffeine; and (3) withdrawal, as manifested by the characteristic withdrawal syndrome for caffeine, or caffeine or a closely related substance is taken to relieve or avoid withdrawal symptoms (American Psychiatric Association 2013).

Beyond the three primary criteria for caffeine-use disorder, six additional diagnostic criteria included in other substance-use disorders, such as craving, tolerance, and using caffeine in higher amounts or for a more extended period than planned, were included as markers for greater severity. To reduce the risk of overdiagnosis given the prevalence of caffeine usage, the recommended diagnostic strategy for caffeine is more conservative than for other substances, which need fulfillment of any 2 of 11 diagnostic symptoms to meet the criteria for mild substance-use disorder. Most studies on the prevalence of substance-use disorder criteria as applied to caffeine were done among special populations such as heavy or treatment-seeking caffeine consumers or psychiatric patients; they preceded the proposed DSM-V criteria or had very small sample sizes (American Psychiatric Association 2013).

Caffeine intoxication presents a significant health risk and can result from excessive caffeine use. Some cases have warranted hospitalization. According to the DSM-V, caffeine intoxication requires a recent intake of caffeine well above 250 mg, as well as the presence of five or more of the following symptoms either during or shortly after caffeine ingestion: restlessness, nervousness, excitement, insomnia, facial flushing, gastrointestinal disturbances, tachycardia or cardiac arrhythmias, periods of inexhaustibility, diuresis, muscle twitching, rambling flow of thought and speech, and psychomotor agitation. The detected symptoms must cause significant distress or impairment in social, occupational, or other essential areas of functioning. The signs and symptoms must not be caused by another medical condition or explained better by a mental disorder, including intoxication from a different substance (American Psychiatric Association 2013).

The withdrawal symptoms occur after the abrupt cessation of prolonged daily caffeine use. The withdrawal syndrome includes fatigue, headache, drowsiness, low mood, irritability, poor concentration, and flu-like symptoms. The detected symptoms must cause significant distress or impairment in social, occupational, or other essential areas of functioning. The signs and symptoms must not be caused by another medical condition or explained better by a mental disorder, including intoxication or withdrawal from a different substance (American Psychiatric Association 2013). Unspecified caffeine-related disorder is a diagnosis that applies when symptoms caused by caffeine use led to distress or impairment in social, occupational, or other aspects of patient's functioning; however, they do not meet the criteria for any specific caffeine-related disorder (American Psychiatric Association 2013).

There are other caffeine-induced disorders such as anxiety and sleep disorder (American Psychiatric Association 2013). Further explanation of these two previous disorders is beyond the scope of this chapter.

10.4 Caffeine and Sleep Disorder

Caffeine is a stimulant that works as an adenosine receptor antagonist, specifically receptors that influence sleep, arousal, and cognition. Adenosine is a substance in our body that promotes sleepiness. When its receptors are blocked by caffeine, we remain vigilant and alert.

Caffeine also interferes with circadian melatonin rhythms, which are physiological patterns, that operate on a 24-h clock, like our sleep-wake cycle (Chaudhary et al. 2021; O'Callaghan et al. 2018).

There is evidence of psychological factors that contribute to the stimulating effect of caffeine, so the stimulating effect is partly due to placebo effect and expectancy from caffeine. Although caffeine has the potential to improve alertness and performance, it may cause sleep deprivation, which is opposite to the main point of consuming caffeine (O'Callaghan et al. 2018). Sleep deprivation and poor sleep quality can cause many problems including decrease in cognition, alertness, attention, vigilance, and speed of motor functions (Chaudhary et al. 2021).

The effect of caffeine on sleep is a vicious cycle. Excessive caffeine consumption will lead to not getting enough sleep, which likely causes tiredness and fatigue, which will lead to reaching several cups of coffee to make it through the day and will again affect the sleep quality. There is a relationship between dose and timing-response. The sleep of some age groups, like the old-age group, may be more sensitive to caffeine than others. Also (Carskadon 2011; Petre 2020; van Dam et al. 2020), there is evidence of some individual differences due to functional polymorphism of genes implicated in adenosine neurotransmission and metabolism (Ribeiro and Sebastião 2010).

Caffeine delays the onset of sleep, increases the sleep latency, reduces the total sleep hours, and reduces the quality of sleep. It affects the normal sleep stages; it was found to reduce slow-wave sleep (SWS) and rapid eye movement (REM) sleep. Sleep fragmentation can also be an effect of nocturnal sleep caffeine administration. Caffeine has a significant disruptive effect on both subjective and objective sleep even if taken 6 h before bedtime (Aurora et al. 2012; Carskadon 2011; O'Callaghan et al. 2018). There is evidence that people who consume an excessive amount of coffee (60 cups or more per year) have less volume of pineal body, especially parenchyma (melatonin-producing area), by 20% than those people who consume less than 60 cups per year (Park et al. 2018).

Caffeine is linked to some disorders. It can cause caffeine-induced sleep disorder, insomnia type, or it may exacerbate preexisting insomnia disorder. It may cause circadian rhythm sleep-wake disorder because it may interfere with the melatonin system as mentioned above. It can cause non-rapid eye movement sleep arousal disorder indirectly through sleep deprivation. Because caffeine is considered a powerful psychoactive substance, it can lead to nightmares by stimulating the brain activity directly and can cause nightmare disorder indirectly through affection of sleep quality (American Psychiatric Association 2013). Caffeine has also been linked to obstructive sleep apnea, especially the caffeinated soda for unclear reasons

(Aurora et al. 2012), and has been linked to worsening the symptoms of restless leg syndrome (Batool-Anwar et al. 2016). For appropriate sleep hygiene, it is recommended to avoid caffeine close to bedtime. However, evidence is less clear regarding caffeine consumption at earlier times of the day. The recommended cutoff time is 6 h before sleep (O'Callaghan et al. 2018).

10.5 Caffeine and Attention Deficit/Hyperactivity Disorder (ADHD)

Attention deficit/hyperactivity disorder (ADHD) is a disorder that decreases attention and/or hyperactivity and impulsivity. It is a chronic condition that affects children and may continue into adulthood (American Psychiatric Association 2013). The most effective treatment for ADHD is stimulant medication, which improves the attention span and has a role in controlling impulsive behavior (Sadock et al. 2015).

Caffeine has a positive influence on attention, working memory, and alertness. It raises the amount of dopamine in the brain, which is linked to attention, pleasure, and movement.

Studies show that caffeine alone is less effective than stimulant medications such as amphetamine in controlling ADHD symptoms (Barclay 2019). Some studies show evidence that caffeine may work as an adjuvant along with prescribed stimulants in children with ADHD and it can amplify the therapeutic effect. However, it is not recommended to prescribe caffeine to children, especially those who are taking stimulant medications, because they may be more vulnerable to side effects and caffeine can also affect the development of the brain in growing children. In addition, children with ADHD are known to have more sleep problems than other children, which may be exacerbated by caffeine (Konstantinovsky 2021). Caffeine and stimulant drugs, when combined, may cause synergy effects, which means that they are more powerful and effective, but also have greater side effects. Both drugs can cause sleeping problems, anxiety, irritability, appetite affection, nausea, and stomach pain (Cipollone et al. 2020; Ioannidis et al. 2014).

10.6 Caffeine and Anxiety Disorders

Anxiety is one of the most common psychiatric problems, and caffeine has been linked to it. Caffeine works as an antagonist to A1 and A2A receptors, which are found in both brain and peripheral tissues. These receptors are related to anxiety, and some of their anxiogenic mechanisms are regulation of coronary blood flow and myocardial oxygen; regulation of activities of other neurotransmitters like GABA, glutamate, dopamine, serotonin, and acetylcholine; vasoconstriction in the blood

vessels of the brain; and decrease in the blood supply, which can increase stress and anxiety. Caffeine may also affect some nutrients in our body, like magnesium level and some B vitamins, which are important in fighting stress and anxiety (Klevebrant and Frick 2022; van Calker et al. 2019).

Caffeine consumption can lead to some physical symptoms that may mimic anxiety symptoms, including palpitations, tremors, irritability, restlessness, rapid breathing, and twitches. These symptoms may trigger anxiety or exacerbate it. Also, quick quitting for caffeine and its withdrawal from the body can cause some anxiety symptoms like irritability, tremors, headache, and restlessness. So, it is not recommended to quit caffeine suddenly in people who have anxiety disorder (Preidt 2019).

There is evidence that caffeine is linked to some anxiety disorders. Yet, moderate caffeine consumption is safe and may have benefits for most people. Caffeine is known to have a panicogenic effect. However, its effect on anxiety and panic attacks has no evidence of dose-response relationship. Caffeine-induced anxiety disorder is a DSM-V diagnosis that falls under anxiety disorders and not substance-related disorders. Patients with this disorder present with either anxiety or panic attacks that must be due to caffeine intake. It has been linked to social anxiety disorder, and the relationship can go both ways; caffeine may increase social anxiety symptoms, and people who have this condition may use caffeine to cope with the social anxiety symptoms. The relationship between caffeine and obsessive-compulsive disorder is not clear, but generally excessive caffeine consumption is not recommended for people with anxiety disorder (American Psychiatric Association 2013; Sadock et al. 2015).

Caffeine can interact with a variety of psychiatric medications, including antipsychotics, antidepressants, anxiolytics, and sedative agents. It is metabolized by CYP1A2 enzyme and acts as a competitive inhibitor for it, so it may increase the side effects of some medications and may complicate the treatment plan and alter the medication response. Also, fluvoxamine, which is used mostly in OCD treatment, is known to enhance the effect of the caffeine, so patients who receive these medications should be educated to avoid excessive caffeine consumption (Broderick et al. 2005; Culm-Merdek et al. 2005).

10.7 Caffeine and Alzheimer's Disease

As mentioned early in this chapter, it takes around 30–60 min for caffeine to reach the peak in blood after intake. Caffeine has a hydrophobic nature, which allows it to quickly cross the blood-brain barrier. Caffeine is found to have a neuroprotective effect. According to the Three-City Study (Ritchie et al. 2007), caffeine has reduced the risk of cognitive decline in women, especially at higher ages and when the caffeine consumption is more than three cups a day. It is interesting to say that the study has shown that the case is not the same with men. Another study (Eskelinen et al. 2009) found that the consumption of more than three cups of coffee per day

in men and women decreases the risk of developing dementia compared to the consumption of less than two cups of coffee per day.

Caffeine consumption helps to reduce neurotoxicity, which promotes the neurocognitive disorder, such as Alzheimer's disease. Caffeine has almost the same chemical structure as the adenosine, both competing on the same adenosine receptors, which decrease the overall effect of the adenosine. This will result in decrease in the influence of extracellular calcium and decrease in glutamate. As a result, it will decrease the neuroexcitatory level. In addition, activation of the adenosine A2A receptor will activate and upregulate the microglia cells in the brain, which might initiate the inflammatory cascade. Caffeine blocks the A2A adenosine receptor and decreases the level of inflammation and apoptosis, which are among the mechanisms of cell degeneration (Eskelinen and Kivipelto 2010; Kolahdouzan and Hamadeh 2017).

10.8 Caffeine and Parkinson's Disease

Caffeine intake is found to reduce the risk of having Parkinson's disease in men and women. Liu et al. (2012) found that consuming high amounts of caffeine (more than 5 cups of coffee) was inversely associated with developing Parkinson's disease. The exact mechanism for this is still unknown. The effect of caffeine on the adenosine A2A receptor and decreasing of the inflammatory cascade could be one of the mechanisms (Chen and Schwarzschild 2020; Ren and Chen 2020).

In summary, caffeine has positive effects on promoting cognitive function and delaying neurocognitive disorder. Consuming high amounts of caffeine (300–500 mg/100 kg/day) is found to lower the risk of Alzheimer's and Parkinson's disease. The exact mechanism is unknown; one mechanism is the antagonizing effect of adenosine receptors, which decreases the activation of microfilm and inhibits the inflammatory cascade.

10.9 Caffeine and Mood Disorder

Mood disorder can be classified into unipolar or depressive disorder and bipolar related disorder. Fatigue, insomnia, poor concentration, and decreased motivation are among the symptoms of depressive disorder. On the other hand, having excessive levels of energy, a decreased need for sleep, and increased activities are among the symptoms of bipolar related disorder. Caffeine has shown to interfere with these previous symptoms. For example, caffeine increases alertness and might interfere with the sleep cycle, which would increase insomnia or decrease the need for sleep.

10.9.1 Bipolar Related Disorder

In the literature, although there was no strong evidence, a link was made between excessive caffeine consumption and bipolar related disorder (mania, hypomania, mixed episode). This link might be explained in patients with established diagnosis of bipolar disorder who are treated with lithium. Lithium is renally metabolized, and its level is affected through the interaction with different drugs. Caffeine is a diuretic substance, which increases the exertion of lithium and leads to the decrease in the lithium level, which precipitates relapse and switches to manic-hypomanic mixed episodes. Also, caffeine is a stimulant; it affects sleep and energy levels, which could precipitate the episode or interfere with symptomatic treatments of bipolar disorder. There are no current guidelines about the limit of using caffeine for patients with bipolar disorder or patients who are receiving lithium (Frigerio et al. 2021).

10.9.2 Depressive Disorder

Depressive disorder is commonly presented with fatigue, lack of motivation, and poor concentration. Fatigue and energy loss are the most reported symptoms after the depressed mood, and they could be linked with resistance to treatment. Treatment of resistant depression may warrant the need to add medications that have stimulant effects, such as bupropion, methylphenidate, and modafinil (Asil et al. 2021; Kang et al. 2018). In the literature, there are a few studies about the relation between depressive disorders and caffeine intake. Some of these studies suggest that consuming caffeine could prevent depression; others suggest that it could help with treating existent depression. However, a study finds that a high dose of caffeine increases the prevalence of major depressive disorder in women with multiple sclerosis. López-Cruz et al. (2018) concluded that caffeine consumption at intermediate levels (300–550 mg/day) appears to have positive effects in patients with depressive disorder. However, that is not the case with higher consumption and with people with some neurological pathology.

10.9.3 Electroconvulsive Therapy (ECT)

One of the most well-established effective treatments for resistant depression and refractory depressive disorder is electroconvulsive therapy. ECT can be prolonged by parenteral caffeine prior to the ECT session. Different formulations have been used including caffeine, sodium benzoate (CSB) injections (250–500 mg of caffeine), caffeine citrate, and theophylline (one of the three primary metabolites of caffeine). Oral administration of these products can result in an inconsistent absorption, and hence clinical effect. Case reports and case series, small trials, retrospective

designs with heterogeneous patients' population, small sample sizes, and inconsistent protocols have reported the effectiveness of this practice. An increase of caffeine is considered safe, tolerable, and cost effective. Thus, it has been suggested to increase electroencephalography (EEG) or motor seizure duration and to minimize amnesia, especially for patients who are not achieving the ideal EEG seizure duration (at least 30 seconds) (Bozymski et al. 2018).

10.10 Caffeine and Psychotic Disorder

The literature on caffeine and psychosis is limited (mainly case reports), and the prevalence of caffeine-induced psychotic disorders is unknown. Despite caffeine being a psychoactive stimulant substance, it has not been recognized as a clinical diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) or in the International Classification of Diseases (ICD-11th) to cause or induce psychotic disorders like amphetamines or cocaine. Psychotic symptoms are not recognized among the signs and symptoms of caffeine intoxication or withdrawal. By examining the onset, temporal course, and other factors, a substance-induced psychotic disorder can be distinguished from a primary psychotic disorder. Moreover, intoxication symptoms are differentiated from caffeine-induced disorders, which appear during intoxication (American Psychiatric Association 2013; Sadock et al. 2015).

Several case reports have suggested that an increased caffeine consumption is associated with worsening psychotic symptoms. The onset and offset of these aggravated symptoms and the consumption and discontinuation of caffeine in a close temporal relationship suggest that caffeine could be the culprit in vulnerable patients (Caykoylu et al. 2008).

There have been few studies that have examined the effects of caffeine use on psychotic symptoms in psychiatric patients despite caffeine being commonly used among them. It has been suggested that high intake of caffeine (intoxication) may worsen existing psychotic symptoms and low intake may improve cognitive and extrapyramidal side effects of medication (Adolfo et al. 2009). It was also reported that a healthy individual presented with psychosis after consuming large amounts of caffeine for an extended period. During the caffeine withdrawal state, there is no evidence of associated psychotic symptoms (Cerimele et al. 2010).

Caffeine and its metabolites affect multiple neuronal functions depending on the amount consumed, and it has the opposite effects of adenosine. It alters the adenosinergic activity predominantly by antagonizing the adenosine receptors. Adenosine is well known to inhibit the release of several neurotransmitters including dopamine, glutamate, serotonin, GABA, and norepinephrine. Positive symptoms of psychosis are thought to result from changes in the dopaminergic activity in the mesolimbic pathway, especially with high intakes of caffeine (Huang and Sperlágh 2021; Ribeiro and Sebastião 2010).

Although caffeine has been implicated in causing psychosis in some cases, the stimulant's dopamine agonist effects on patients with schizophrenia are heterogeneous. Caffeine competitively inhibits CYP1A2, which might increase some of the antipsychotic medications' plasma levels (e.g., clozapine, olanzapine). Additionally, there is an association between higher caffeine intake and smoking nicotine among patients with schizophrenia, partly due to the nicotine-inducing effect on the cytochrome P450 1A2 enzyme (the main enzyme responsible for the metabolism of caffeine), which induces caffeine metabolism and reduces its effect (Bissonnette et al. 2021).

Due to the development of tolerance, high levels of caffeine intake may not lead to intoxication. The exact caffeine dose that may have produced the psychotic symptoms is not known, and the duration of increased caffeine consumption preceding psychotic symptoms varies between people. There seems to be a wide range of doses from 200 to 4600 mg of caffeine/day that might precipitate psychotic symptoms, and the duration ranges from a few hours to several months or years. A double-blind, placebo-controlled study investigated the effect of regular caffeine consumption (10 mg/kg) on the psychotic symptoms of patients with schizophrenia and found that caffeine has aggravated their symptoms. The treatment is usually limiting caffeine consumption for a couple of weeks, and the aggravated psychotic symptoms would subside and improve after that time (Huang and Sperlágh 2021).

10.11 Caffeine and Psychiatric Medication Interactions

Caffeine can affect other psychotropic medications in different ways. Caffeine is metabolized by the CYP1A2, and it inhibits CYP1A2 competitively. Fluvoxamine, a selective serotonin reuptake inhibitor, inhibits CYP1A2 and can increase the effects of caffeine. On the other hand, cigarette smoking is a CYP1A2 inducer, which increases caffeine metabolism and decreases the effect of caffeine (Culm-Merdek et al. 2005). Excessive caffeine intake can increase the risk of serotonin syndrome (Shioda et al. 2004). On the same mechanism, caffeine may increase clozapine plasma concentration by up to 60% (Carrillo et al. 1998). Also, it can affect other psychotropic medications such as olanzapine, clomipramine, and imipramine. Lastly, by stimulating effect, caffeine in high dose can decrease the efficacy of benzodiazepine (Sawynok 1995).

Caffeine is a diuretic substance; it can affect the medications that are renally metabolized. Excessive consuming of caffeine can decrease the effect of lithium and decrease the lithium level in the blood. Also, decreased consuming of caffeine can increase the lithium level and precipitate lithium toxicity. Some case reports correlate lithium level with caffeine consumption. There is no current recommendation about the daily dose of caffeine when using lithium (Baethge et al. 2009).

10.12 Conclusions

Caffeine is the most consumed substance in the world. It acts on adenosine receptors and affects other neurotransmitters. Caffeine has various effects on mental health well-being and mental illness. It might worsen anxiety and sleep disorder. Studies have shown positive effect of caffeine on neurocognitive function, such as Alzheimer's and Parkinson's disease. Caffeine improves some elements of depressive disorder, such as amotivation symptom, and it is widely used during the electoral convulsive therapy to lower seizure threshold. It interferes with other drugs, such as lithium and fluvoxamine. Further research and randomized control trial are needed to establish the relationship between caffeine and psychiatric effects.

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