European Journal of Drug Metabolism and Pharmacokinetics (2025) 50:1–15
https://doi.org/10.1007/s13318-024-00928-x

REVIEW ARTICLE

An Exploration of the Interplay Between Caffeine and Antidepressants Through the Lens of Pharmacokinetics and Pharmacodynamics

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Accepted: 5 November 2024 / Published online: 27 January 2025

Abstract

Caffeine consumption is regarded as a widespread phenomenon, and its usage has continued to increase. In addition, the growing usage of antidepressants worldwide and increase in mental health disorders were shown in recent statistical analyses conducted by the World Health Organisation. The coadministration of caffeine and antidepressants remains a concern due to potential interactions that can alter a patient's response to therapy. This review investigates the pharmacokinetic and pharmacodynamic interactions between caffeine and the five main classes of antidepressants: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and other antidepressants not categorised by class, which we have categorised as 'miscellaneous'. The interaction between fluvoxamine and caffeine resulted in increased concentrations of caffeine in the body and lowered the renal clearance of fluvoxamine. Other SSRIs such as fluoxetine and escitalopram had augmented antidepressant effects by decreasing their renal clearance and prolonging their effects in the body when coadministered with caffeine. Caffeine may also increase the concentration of paroxetine, potentially affecting its pharmacodynamic effects. TCAs such as clomipramine, imipramine, desipramine, and sertraline, were found to reduce the metabolism of caffeine. However, studies suggest caffeine had no significant effect on the concentration of these medications in blood or brain tissue. The inhibition of caffeine at high doses when used with MAOIs such as tranylcypromine and phenelzine was found to lead to a higher likelihood of experiencing hypertension. Coadministration of caffeine with venlafaxine (SNRIs) suggests minimal interactions between the two substances and the pharmacodynamic effects of venlafaxine were unlikely to be impacted by caffeine consumption. Miscellaneous antidepressants (reboxetine, mianserin, agomelatine, maprotiline, and mirtazapine) displayed varying pharmacodynamic interactions with caffeine, resulting in increased antidepressant effects where vortioxetine, maprotiline, and mirtazapine failed to demonstrate any interactions. In conclusion, caffeine demonstrated varying effects on the pharmacokinetic and pharmacodynamic properties of each class of antidepressants, with several classes of antidepressants demonstrating a similar effect on caffeine.

1 Introduction

Caffeine remains the most common psychostimulant in coffee, tea, energy drinks, and numerous other foods and beverages [33]. Caffeine acts on the central nervous system through adenosine receptors [67]. It has been reported that one in eight people (970 million people) have experienced a mental health disorder in their lifetime, major depression being the most common [4]. Similarly, studies such as that conducted by Lunghi et al. identified an overall increase in

Key Points

SSRIs like fluvoxamine showed significant interactions with caffeine, while others like fluoxetine, escitalopram and paroxetine demonstrated potentially enhanced antidepressant effects through increased 5-HT noradrenergic and dopaminergic transduction

TCAs reduced caffeine metabolism, clomipramine and desipramine having the greatest inhibitory effects

MAOIs increased hypertension risk with high caffeine doses, and miscellaneous antidepressants displayed varied interactions

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the prescribing of antidepressants in the last decade, especially after the COVID-19 pandemic [22].

Caffeine's ability to counteract symptoms of fatigue and drowsiness [27] increased its consumption globally. Primarily sourced through coffee beans, it is an additive in many sodas, energy drinks, and coffee [27]. Belonging to the methylxanthine class, caffeine is a central nervous system (CNS) stimulant [27]. It exhibits its action by antagonising the adenosine receptor subtypes (A1, A2A, A2B, and A3) in the brain by crossing the blood-brain barrier due to its water- and fat-soluble properties [27], as illustrated in Fig. 1. Nevertheless, the energetic effect of caffeine is identified primarily to be due to the antagonistic effects on the A2A receptor. Not restricted to the CNS, adenosine receptors are present throughout the body [27]. The antagonistic effect on the A1 receptor in the cardiac muscle results in positive inotropic effects [27]. Moreover, the systemic stimulatory effect of caffeine can be associated with catecholamine release caused by the antagonist effect on the adenosine receptor, which contributes to further stimulation of cardiac chronotropy (heart rate) and inotropy (contractility) [27]. Caffeine metabolism occurs primarily in the liver by the cytochrome P450 (CYP) 1A2 enzyme through a series of oxidation reactions via 3-N-demethylation, which results in one of three dimethylxanthine metabolites involving paraxanthine, theophylline, and theobromine [27], paraxanthine being the main metabolite. Unlike theophylline and theobromine, which are less potent CNS stimulants, paraxanthine has higher potency at A1 and A2 receptors [49]. All of these are subsequently metabolised and excreted in urine. However, caffeine metabolism can also occur through 7-N-demethylation involving other liver enzymes such as CYP2C8 and CYP2E1 [5, 73]. It has been observed that prolonged caffeine consumption contributes to the buildup of tolerance over time and in return prompts withdrawal symptoms if consumption is to be ceased [38, 50]. Furthermore, the diuretic effect of caffeine is related to the increase in glomerular filtration, renal blood flow, and sodium elimination [27] and can also stimulate both gastrointestinal motility and acid secretion [27]. This in conjunction with the CNS stimulatory effects of caffeine reinforces the findings of a study in 2016 [67], which discovered that caffeine can potentially enhance antidepressant activity through pharmacodynamic and pharmacokinetic interactions. Caffeine can increase serotonin and dopamine release, which are often targeted in antidepressant therapy [67]. However, further investigation is required to more specifically identify the correlation between caffeine and antidepressant coadministration at a pharmacokinetic and pharmacodynamic level.

1.1 Antidepressants

Antidepressants are drugs utilised to treat depressive disorders including dysthymia, major depressive disorder, premenstrual dysphoric disorder, and depression associated with other medical conditions [59]. They are most effective in treating moderate, severe, and chronic depression while being less frequently used in mild depression [37]. Antidepressants can also be prescribed for off-label use (i.e, in treatment of migraines or body dysmorphic disorders) and non-psychiatric conditions such as eating disorders, chronic pain, migraine prevention, and smoking cessation [43, 62].

Drugs used for the treatment of depression are grouped according to the following class: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and tetracyclic antidepressants [20, 59]. Antidepressants that do not fall

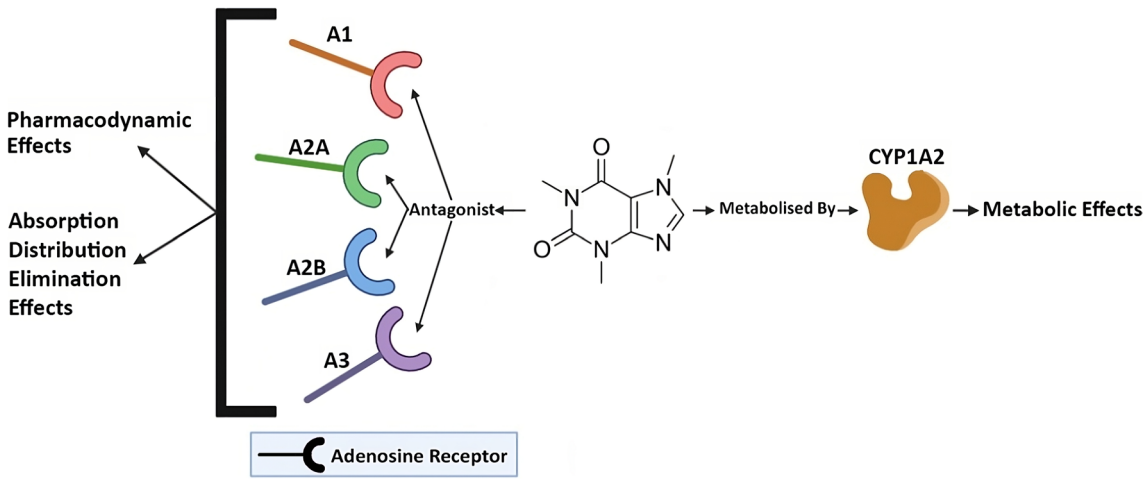

Fig. 1 A simplified depiction of caffeine's hypothesised routes for drug interactions

under a specific antidepressant class have been classified as 'miscellaneous'.

Antidepressants have dose-dependent side effects which may include but are not limited to dizziness, headaches, and dry mouth [37]. Studies have concluded that 40–60% subjects showed an improvement in symptoms when taking antidepressants compared with 20–40% taking placebo after 6–8 weeks [37]. The most commonly prescribed antidepressants globally are TCAs, SSRIs, and SNRIs, while other classes are less commonly prescribed [37, 74].

As illustrated in Fig. 2, the mechanism of action for each class of antidepressants is different and each targets specific neurotransmitters to regulate behaviour and mood [59]. Currently, SSRIs are the first-line agents prescribed; their mechanism of action is through blocking the reuptake of serotonin, which results in enhanced serotonin activity [16].

SNRIs inhibit the reuptake of serotonin and norepinephrine in the presynapse, as a result increasing the effects of neurotransmitters in the synaptic cleft, which leads to enhanced neuronal activities and the activation of postsynaptic receptors [28].

TCAs exhibit their activity by blocking the reuptake of serotonin and norepinephrine at the presynaptic neuronal membrane [59]. TCAs can also prompt anticholinergic effects and sedation, which is attributable to their affinity to histamine H1 and muscarinic MI receptors [59].

MAOIs are not accepted as first-line agents because of their interactions and adverse effects [59]. The mechanism of action of MAOIs includes blocking the monoamine oxidase enzyme, an enzyme which functions to remove dopamine, norepinephrine, and serotonin [59].

Miscellaneous (tetracyclic and atypical) antidepressants differ in their mechanisms of action, acting on presynaptic alpha-2-adrenergic receptors. Tetracyclic antidepressants (mianserin, maprotiline, and mirtazapine) increase serotonin and norepinephrine release and antagonise serotonin receptors 5-HT2A, 5-HT2C, and 5-HT3 alongside H1 (histamine) receptors [20]**.** Atypical antidepressants have multiple varied mechanisms of action. Our findings indicate that agomelatine exhibits its agonist activity at melatonin receptors MT1 and MT2 [59] whilst prompting norepinephrine and dopamine release by antagonising serotonergic 5-HT2C receptors [59]. At the 5-HT1A receptor, serotonin modulators like vortioxetine functions as an agonist and a partial agonist at the 5-HT1B receptor which results in serotonin release ultimately contributing to antidepressant activity [18]. Finally, moclobemide is a reversable monoamine oxidase inhibitor selective for the A enzyme subtype.

1.2 Correlation Between Caffeine and Antidepressants at a Metabolic Level

Regarding the metabolism of antidepressants, the CYP enzyme is the most important [35]. Both SSRI and SNRI are metabolised by the CYP enzymes in the liver, specifically CYP2C9, CYP2C19, and CYP2D6 [45]. Likewise, TCAs are all also metabolised by the CYP enzymes [60], establishing the importance of the CYP enzymes in metabolising

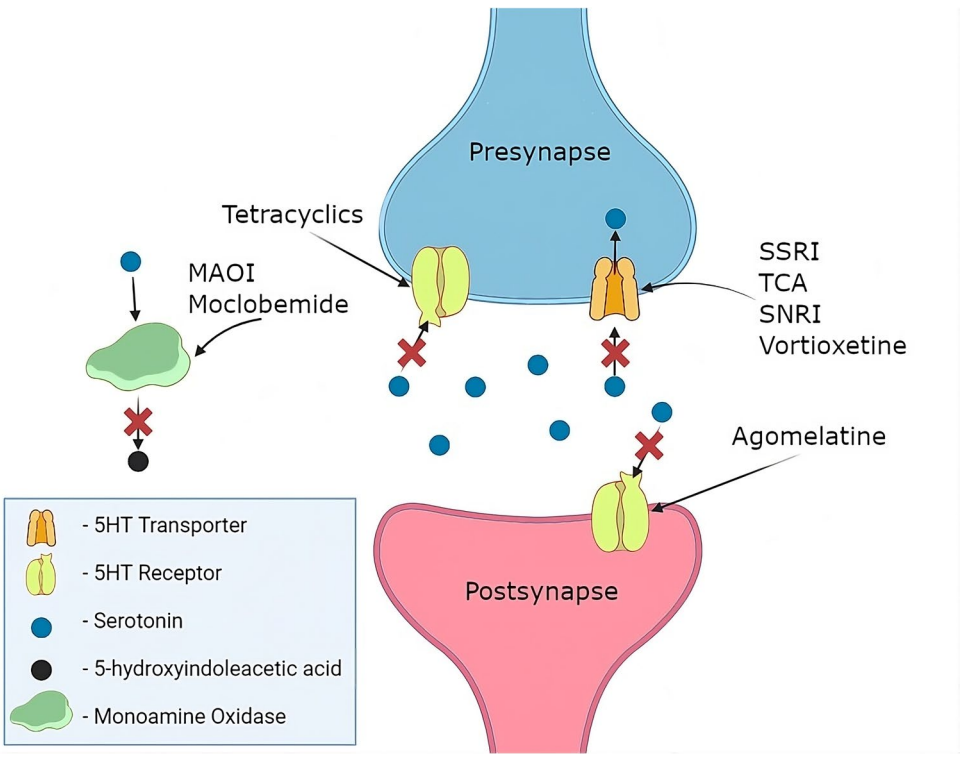

Fig. 2 A simplified depiction of the mechanism of actions of several antidepressants

antidepressants. Thus, the CYP1A2-mediated metabolism of caffeine establishes a potential route for interaction, especially as caffeine acts as a competitive inhibitor for this enzyme [8, 35]. This interaction may cause complications to treatments or may induce side effects relating to both antidepressants and caffeine [8].

1.3 Objectives of and Need for this Review

Given the large population of individuals consuming caffeine and the growing prevalence of antidepressant usage, investigating pharmacokinetic and pharmacodynamic interactions is paramount. Exploring these interactions can help determine any potential risks or benefits and the effect on mental health outcomes and whether combining caffeine and antidepressants leads to enhanced antidepressant response or exacerbates symptoms. The objective of this review was to evaluate the studies that have been conducted demonstrating the significance of multiple pharmacokinetic and pharmacodynamic interactions involving caffeine and numerous antidepressant drugs. Through this study, we aimed to explore the specific impact of caffeine on the pharmacokinetics and pharmacodynamics of antidepressant drugs alongside antidepressants' impacts on caffeine pharmacokinetics and pharmacodynamics whilst providing insight for future research.

2 Methods

A search of the PubMed, Embase, and ScienceDirect databases was performed. The search was broad, with preference given to peer-reviewed journals and papers and, where no alternative was available, non-peer-reviewed material was rarely accepted. Due to the large scope of this review, we did not limit the acceptable publication dates as several antidepressants presented with limited or no modern (post 2000) literature. Whilst we acknowledge this as a limitation of this review, for some rarely prescribed antidepressants, there was no alternative to older publications (e.g., mianserin's mechanism of action, 1981). Preference was always given to modern literature wherever possible. In addition, Google Scholar and the University of Technology Sydney (UTS) Library were used to further broaden the scope of the search.

Search terms included a combination of key words and Medical Subject Headings such as "caffeine", "theobromine", "antidepressant", "interaction", "pharmacokinetics", "pharmacodynamics", "absorption", "distribution", "metabolism", and "excretion" alongside names (e.g., citalopram, vortioxetine, amitriptyline) and classes (e.g., SSRI, SNRI, TCA) of each antidepressant. Boolean operators (and, or) were used to refine the search. Preference was given to human trials and studies; however, animal studies were also analysed where human studies were unavailable.

Additional searches were performed to provide the mechanisms of action for each drug and/or drug class. A summary of the findings discussed in this manuscript is depicted in Table 1.

3 Effects of Caffeine on Pharmacokinetics and Pharmacodynamics of Antidepressants

3.1 SSRIS

SSRIs are the first-line pharmacological therapy for the treatment of major depression disorders because they are the safest, are best tolerated, and have high efficacy [23]. They aid treatment by decreasing the reuptake of serotonin by inhibiting the serotonin transport, hence increasing the amount of serotonin in the synaptic cleft, which augments stimulation of the postsynaptic receptors [16, 23].

3.1.1 Pharmacokinetics

The effects of antidepressants on caffeine metabolism were investigated in a study conducted by Daniel et al. [19] using Dixon analysis. It showed that sertraline and nefazodone inhibited the metabolic oxidation pathway of caffeine at different potencies. The addition of sertraline was noted to cause the greatest reduction in 1-N and 3-N-demethylation and 8-hydroxylation with inhibition constants (K_i) of 37.3, 69.3, and 64 mM respectively. However, K_i results of 68.8 and 66.4 mM were obtained for 3-N and 7-N demethylation of caffeine by adding nefazodone [19]. This indicated the presence of inter- and intra-drug metabolic interactions between caffeine and SSRIs in rat liver microsomes.

Further studies and reviews highlighted a strong interaction with fluvoxamine during metabolism and renal clearance. A review written by Carrillo and Benitez in 2000 [11] identified fluvoxamine as a potent inhibitor of CYP1A2 liver enzymes and showed that caffeine tolerance may lead to saturation of its metabolism. This causes a non-linear build-up of caffeine in the body, resulting in a potential pharmacokinetic interaction with drugs such as fluvoxamine and initiating the toxic effects of either drug [11]. Alongside its effects on caffeine metabolism, coadministration of fluvoxamine prolongs the half-life of caffeine and, in return, decreases its renal clearance. This is further reinforced in a double-blinded, four-way-crossover study conducted in 2005 by Culm-Merdek et al. [17], which investigated the pharmacokinetic and pharmacodynamic effects of the concurrent oral administration of fluvoxamine and caffeine by evaluating the plasma caffeine and fluvoxamine concentrations, psychomotor and sedentary effects, and electroencephalographic beta frequency activity. The study identified a

Table 1 Summary of pharmacokinetic and pharmacodynamic findings for each drug and class

Drug class	Antidepressant drug	Effect of caffeine on the antidepressant drug and vice versa	
		Pharmacokinetic	Pharmacodynamic
SSRIs	Sertraline	Decrease metabolism by the CYP1A2 enzyme [19]	–
	Fluvoxamine	Increased $T_{1/2}$ and clearance of caffeine [17] Increased Caffeine AUC and decreased Fluvoxamine clearance [15]	Fluvoxamine inhibits caffeine biotransformation [63]
	Fluoxetine	–	Caffeine increased the antidepressant effects [67][a]
	Escitalopram	–	Caffeine increased the antidepressant effects [67][a]
	Paroxetine	–	Caffeine increased the activity of the SSRI drug and resulted in an increase of drug concentration in serum [1][a]
	Nefazodone	Decrease metabolism by the CYP1A2 enzyme [19]	–
TCAs	Clomipramine		Caffeine had no effect on the amounts of these medications in either blood serum or brain tissue [67][a]
	Imipramine		
	Desipramine		
	Amitriptyline	–	Caffeine as the potential to reduce the therapeutic effects of amitriptyline in the treatment of neuropathic pain [26][a]
SNRIs	Venlafaxine	–	Albino Swiss mice in FST showed no alteration to drug's concentration [55][a] Venlafaxine is less potent which results in minimal drug interaction with caffeine [3]
MAOIs	Phenelzine	–	Caffeine can enhance hypertension in patients taking phenelzine [61]
	Tranylcypromine	–	Caffeine exhibits MOA inhibition at high doses. Coadministration with a high dose of caffeine increases the risk of hypertension [31].
Tetracyclic antidepressants	Mianserin	Interaction noted in [54] is unlikely to be pharmacokinetic in nature[a]	Unspecified pharmacodynamic interaction found in vitro mice FST, increasing mianserin effect [54][a]
	Maprotiline	–	–
	Mirtazapine	–	–
Serotonin receptor antagonist	Agomelatine	–	Findings could indicate nonspecific interaction (increasing FST distance), not statistically significantly altering concentration of agomelatine [54][a]
MAOs - type A inhibitor	Moclobemide	No pharmacokinetic interaction is noted. Lack of increase in brain and serum concentrations [6, 55][a]	Shorter immobility time in the forces swim tests and increase in mobility duration in the Tail suspension test → increased duration of action of Moclobemide [6][a]
–	Vortioxetine	No interaction is found [12, 13][a]	–
Norepinephrine reuptake inhibitor	Reboxetine	No alteration in brain and serum concentrations (no interaction noted) [25][a]	Decrease in the immobility of the mice tested in the forced swim test [25, 66][a]

[a]Represents an animal model

reduction in the renal clearance of oral caffeine with a mean difference of 95.5 ml/min (95% confidence interval between 54.9 and 135.6) alongside an increase in its elimination half-life (mean difference of 51 h with a 95% confidence interval of 26–76). This study showed minimal synergic CNS stimulatory effects with the concurrent administration of both drugs, and no significant pharmacodynamic effects were noted [17].

Although the previous study indicated significant results, the sample size was small (7 subjects), which is not sufficient to represent the entire population. However, the results are reinforced by another study conducted in 2002 by Christensen et al. [15] where high-performance liquid chromatography (HPLC) analysis of plasma and urine revealed that a single dose of 20 mg fluvoxamine suppressed 75% of CYP1A2 enzymes. Moreover, it illustrated a fivefold increase in the area under the plasma concentration-time curve (AUC) of oral caffeine ($P < 0.001$) after a 20 mg fluvoxamine dose was administered orally and a twofold increase after a 10 mg oral dose ($P < 0.05$). A subject was also found to have a low clearance of oral fluvoxamine, which could have been due to the lack of P-glycoprotein transporter in the gut, resulting in absorption of oral fluvoxamine to a greater extent [15]. This reinforces the pharmacokinetic interaction found between fluvoxamine and caffeine and demonstrates a link between protein deficiency disorders that may exacerbate the extent of the interaction, leading to an increased risk of toxicity.

3.1.2 Pharmacodynamics

In a pharmacodynamic study by Spigset in 1998 [63], ten healthy volunteers were given increasing doses of fluvoxamine over a 4-week period (25 mg daily for the 1st week, 50 mg daily for the 2nd week, 100 mg daily for the 3rd week, and 200 mg daily for the 4th week). The study found a correlation between the serum plasma concentration of fluvoxamine and the number of reported adverse drug reactions (ADRs) ($r = 0.62$; $P = 0.057$). Multiple regression analysis reported a correlation between the frequency of ADRs and caffeine intake. However, the impact of caffeine on ADRs attributed to fluvoxamine was found to be limited, perhaps because of a small number of subjects involved in the study. The study also noted that fluvoxamine inhibited caffeine biotransformation even at low concentrations. Therefore, the lack of significant correlations could be due to subjects reducing their caffeine intake if they experienced ADRs or other factors related to individual responses to fluvoxamine [63].

Another pharmacodynamic analysis investigated the influence of chronic oral caffeine intake and its consequential withdrawal on the antidepressant activity of fluoxetine and escitalopram using two simple tests, such as the forced swim test (FST) and the tail suspension test (TST) in mice. Caffeine was coadministered with fluoxetine and escitalopram twice a day for a total of 14 days. The study discovered that caffeine through antagonism of the adenosine A_1 receptors located on the serotonergic (5-HT) neurons inhibited the effects of endogenous adenosine and increased 5-HT, noradrenergic (NA) [67] and dopaminergic (DA) transduction in the brain, suggesting that chronic caffeine intake increased antidepressant effects of these drugs, while caffeine withdrawal resulted in a loss of this enhancement. Stimulation of NA neurons and its relationship with the central dopaminergic system have been expressed in a few studies with caffeine [29, 30]. Therefore, the reduced immobility time after the combined administration of caffeine and SSRIs, (fluoxetine or escitalopram) may be a result of the associated enhancement of monoamine (5-HT, NA and DA) transmission [67].

Another study investigated the effects of caffeine on animal behaviour in the FST and its impact on the activity of fluoxetine (5 mg/kg), paroxetine (0.5 mg/kg), and escitalopram (2 mg/kg). Using high-performance liquid chromatography (HPLC), the study also evaluated the concentrations of these drugs in mouse serum and brain tissue. The findings reported that caffeine administered orally exhibited antidepressant activity in the FST at various doses (10, 20, and 50 mg/kg). However, it was noted that at a dose of 5 mg/kg, caffeine increased the activity of the SSRI drugs that were tested without affecting locomotor activity. Additionally, the interactions between caffeine and the antidepressants tested were pharmacodynamic; however, the interaction with paroxetine occurred in the pharmacokinetic phase, resulting in an increase of drug concentration in serum [1, 67].

3.2 TCAs

TCAs are drugs used to treat depression by increasing the concentrations of serotonin and norepinephrine in the brain through the inhibition of neurotransmitter reuptake in the synaptic cleft. This enhances communication between neurons and alleviates depressive symptoms. Over time, TCAs may lead to receptor adjustments, normalising neurotransmitter activity [46].

3.2.1 Pharmacokinetics

Similar to SSRIs, Daniel et al. [19] also noted that the antidepressants with the highest inhibitory effects on the metabolism of oral caffeine were clomipramine and desipramine. Analysis showed that desipramine reduced caffeine's 1-N, 3-N, and 7-N demethylation pathways as well as its 8-hydroxylation pathway while clomipramine inhibited both the 1-N- and 3-N-demethylations [19], revealing a

metabolic pharmacokinetic interaction between desipramine and caffeine.

Moreover, a study conducted by Lemoine et al. [42] concluded both CYP1A2 and CYP3A4 were responsible for imipramine metabolism [42]. Understanding the roles of CYP1A2 and CYP3A4 in imipramine metabolism sheds light on its wider clinical consequences. Individual differences in enzyme concentrations can result in variable rates of imipramine metabolism, resulting in differences in therapeutic effect and associated side effects [42]. Due to caffeine's co-metabolism with CYP1A2, there is potential for an interaction at the metabolic level. However, due to caffeine-mediated CYP1A2 induction occurring at significant concentrations, it is hypothesised that oral caffeine's effect on imipramine concentration would be negligible if present [70].

Another study conducted by Kot and Daniel [40] examined the interaction of antidepressant medicines with CYP1A2 activity in both humans and rats. This work sheds light on the interaction between specific antidepressant medicines and CYP enzymes [40]. Notably, TCAs such as imipramine, clomipramine, and desipramine, are noted to be powerful inhibitors of rat CYP1A2. However, a significant species difference is present, since the inhibitory impact of these antidepressants in rats is approximately ten times weaker than in humans. This divergence shows that structural and functional differences in CYP1A2 exist between the two species [40]. This indicates a hypothesised decreased caffeine metabolism upon coadministration; however, this has yet to be experimentally proven.

3.2.2 Pharmacodynamics

A pharmacodynamic study investigated the impact on behaviour and efficacy of imipramine and desipramine [67]. Caffeine demonstrated antidepressant effects in the FST at dosages of 10, 20, and 50 mg/kg, all without inducing substantial alterations in locomotor activity. Caffeine, at a lower dose of 5 mg/kg, displayed its own antidepressant activity and improved the antidepressant effects of the medications examined, indicating a pharmacodynamic interaction is occurring [67]. Desipramine demonstrated no pharmacokinetic interaction. However, a pharmacodynamic interaction was observed [67].

Two studies by Esser et al. [26] and Sawynok et al. [58] in 2000 and 2008 explored this interaction. Caffeine was found to reverse the antinociceptive effects of amitriptyline in wild-type mice, suggesting a potential counteractive role against amitriptyline's systemic impact. The dynamics shift significantly in mice lacking adenosine A1 receptors, as caffeine fails to reverse this impact. Therefore, this suggests that A1 receptors are not required for amitriptyline-induced antinociception; however, they are essential for caffeine-mediated reversal of this effect. This indicates that A1 receptors contribute to amitriptyline biological function, further supporting a pharmacodynamic interaction with caffeine [58]. Furthermore, the pharmacodynamics of amitriptyline and caffeine in the context of thermal anti-hyperalgesia were investigated by Esser and Sawynok in 2000 [26] utilising a rat model of neuropathic pain. The findings indicate amitriptyline may exert its effects by increasing the endogenous adenosine concentration, potentially contributing to its therapeutic impact. Caffeine, an antagonist of adenosine receptors (A1, A2A, A2B, A3), has the potential to reduce the therapeutic effects of amitriptyline on neuropathic pain treatment [26]. The effect of amitriptyline on endogenous adenosine concentration, particularly in neuropathic pain, highlights the necessity of understanding these interactions for more effective neuropathic treatment regimens.

3.3 SNRIs

SNRIs are potent inhibitors metabolised by the CYP enzymes in the liver [64]. SNRIs work by blocking the reuptake of serotonin and norepinephrine and can cause common side effects such as nausea, dizziness, and palpitations [2].

3.3.1 Pharmacokinetics

In contrast to pharmacodynamic studies, there have been limited studies conducted on the pharmacokinetic interaction between caffeine and SNRIs.

Limited studies have been conducted on the pharmacokinetics and pharmacodynamics of caffeine and SNRIs, so these could be future study directions to further reveal the relationship between SNRIs and caffeine.

3.3.2 Pharmacodynamics

An exhaustive in vivo study demonstrated that coadministration of caffeine and venlafaxine resulted in a pharmacodynamic interaction, ruling out a pharmacokinetic interaction [55]. The in vivo study utilised mouse models injected with venlafaxine and caffeine, examining the efficacy of coadministration and singular administration through a FST. The results revealed the interaction is pharmacodynamic in nature as venlafaxine concentration was not altered with caffeine coadministration. Another study conducted in 2013 by Amchin et al. [3] furthered the notion that the interaction is pharmacodynamic because of the minimal impact on the metabolism of venlafaxine when administered with caffeine. The in vivo study was undertaken by 16 volunteers: 9 males and 7 females. The study went on for 9 days, and the

volunteers were given 200 mg caffeine administered orally before day 1 and after day 8. Venlafaxine was administered orally, and 37.5 mg was given every 12 h from day 2 to 4, before titrating the dose to 75 mg every 12 h from day 5 to 8. Then, blood samples were obtained from volunteers to determine the impact of caffeine on venlafaxine. The blood sample results illustrated that the concentration of caffeine in the plasma was unchanged, which may have been due to the low potency of venlafaxine and the minimal drug interaction as a competitive CYP1A2 inhibitor [8].

3.4 MAOIs

MAOIs are a class of antidepressants used to treat major depression and nervous system disorders like panic disorders and phobic disorders such as social phobia [65]. They are a catalyst for the deamination of monoamine-containing neurotransmitters such as serotonin. Serotonin plays a role in controlling mood, cognitive function, and sexual desire. Other important monoamines include histamines, catecholamines dopamine, norepinephrine, and epinephrine, which take part in the body's defence mechanisms and cognitive function [56].

MAOIs are rarely prescribed as they are used as second-line treatment for major depression partially because of their unfavourable side effects. In addition to their side effect profile, phenelzine is noted to cause several drug interactions [61], while tranylcypromine is rarely prescribed because of its many contraindications, precautions, and drug interactions [52]. Finally, moclobemide carries the risk of hypertensive crisis because of interactions with certain foods and drugs; it is however more tolerable with fewer adverse effect incidences [41]. This is primarily due to phenelzine and tranylcypromine irreversibly inhibiting MAO subtypes A and B, while moclobemide reversibly binds only to MAO-A [41].

3.4.1 Pharmacokinetics

The interaction between caffeine and irreversible MAOI pharmacokinetics is not well investigated. However, there could potentially be no major impact as inferred from the pharmacological profile of these two substances.

Phenelzine is a substrate as well as an inhibitor of MAO and is mainly metabolised by acetylation, producing metabolites such as phenylacetic acid, β-hydroxyphenylacetic acid, and phenethylamine [71]. It is rapidly absorbed, with maximum concentration reaching 2–4 h after dosing. In addition, indirect evidence suggests that phenelzine may be ring-hydroxylated and N-methylated. Its plasma elimination half-life is 1.5–4 h; however, its duration of action is much longer because of the irreversible inhibition of the enzyme [71].

Tranylcypromine is rapidly absorbed in the body and is eliminated from the bloodstream relatively fast, with a half-life of approximately 2 h, which is considerably shorter than for most other antidepressants. Tranylcypromine is also ring-hydroxylated and N-acetylated. Since it is predominantly metabolised, only 4% of the dose is excreted unchanged in the urine. This suggests that age-related changes due to its metabolism may not be anticipated [71]. Following a single 20 mg dose of tranylcypromine, maximum plasma concentrations (C_{max}) were between 50 and 70 ng/ml with a time of maximum plasma concentration (T_{max}) of approximately 1–2 h. However, in some patients, C_{max} was recorded at higher concentrations reaching 144 ng/ml or even close to 200 ng/ml after administration of the same 20 mg dose [69]. The metabolising enzyme of tranylcypromine and its plasma concentration changes are not well studied. It has low propensity to pharmacokinetic drug interactions, inhibition of CYP2A6 at therapeutic doses, and no inhibition of the relevant CYP2D6, CYP3A4 at therapeutic doses and shows CYP2C19 inhibition only at supratherapeutic doses [69]. Phenelzine has no reported interactions, but, like the tuberculosis treatment isoniazid, weakly and irreversibly inhibits CYP 2C19 and 3A4 in vitro [32].

Because phenelzine and tranylcypromine's metabolism is hypothesised not to involve or inhibit CYP1A2, effects on caffeine metabolism should be negligible or not present during coadministration. However, future studies need to be conducted to experimentally prove this.

As previously mentioned, caffeine could facilitate gastric acid secretion, which could impact the pharmacokinetics of other drugs. However, phenelzine is slightly basic with a pKa of 6.5–8.0 [47], and tranylcypromine is a strong base with a predicted pKa of 9.62 [36]. Therefore, caffeine should not have major effects on their absorption as they still remain in their ionised form under the low gastric pH.

Studies have shown that coffee has inhibitory effects on MAO, which can increase the turnover of some monoamines, such as serotonin, dopamine, and norepinephrine. The study performed by Herraiz and Chaparro in 2006 [34] demonstrates coffee's inhibitory effects on both MAO-A and MAO-B kynuramine deamination through competitive and reversible inhibition, which suggests the presence of active MAO inhibitors within coffee, potentially attributable to caffeine. However, should caffeine contribute to MAO inhibition, its plasma concentration after coffee consumption suggests that under normal conditions, it is unlikely to inhibit MAOs [53].

3.4.2 Pharmacodynamics

Regarding the pharmacodynamic effects of caffeine on MAOIs, a patient study noted that caffeine's inhibitory effects possibly intensified the vasoconstrictive effects of tranylcypromine [31]. This study suggests that habitual consumption of large amounts of caffeine could result in significant hypertension when combined with MAOIs [31]. Other MAOIs such as phenelzine also show hypertensive effects when administered together with excessive caffeine [61]. However, further studies are required to determine the parameters of MAO inhibition regarding caffeine and whether it relates to caffeine's potential neuropharmacological and behavioural impacts.

In contrast to the irreversible MAOIs, reversible MAOI (i.e., moclobemide) studies have been conducted to identify an interaction with caffeine. A study conducted by Poleszak et al. in 2015 [55] assessed the effect of caffeine (5 mg/kg) on potentiating the pharmacokinetic and pharmacodynamic parameters of moclobemide (1.5 mg/kg) in male Albino Swiss mice via an FST. It determined moclobemide concentrations in murine and brain serum homogenates using HPLC. The investigation identified that the concurrent administration of caffeine and moclobemide significantly reduced the immobility time in the FST ($P = 0.0002$, $P < 0.001$). Nevertheless, moclobemide drug concentrations in murine and brain serum coadministered with caffeine (40.10 ± 7.2, 184.9 ± 41.94, respectively) showed no significant difference from administering moclobemide alone [55], indicating that although a drug interaction is present, it is pharmacodynamic in nature.

Alongside the previous article, the pharmacodynamic interaction of caffeine with moclobemide is further reinforced by an article conducted by Bogatko et al. in 2018 [6] regarding the effect of selective antagonism of the A1 and A2A adenosine receptors on the augmentation of antidepressant activity via an FST and TST and antidepressant concentrations in plasma and brain serum homogenates. It identified that coadministration of DMPX (3,7-dimethyl-1-propargyl xanthine, a caffeine analogue) and moclobemide (1.5 mg/kg) resulted in a shorter immobility time in the FSTs ($P = 0.0005$, $P < 0.001$), while the TST showed a significant increase in the mobility duration, with $P < 0.0001$. However, no significant difference was noted in the drug concentration of plasma and brain serums (27.55 ± 6.717 and 77.65 ± 1.256, resoectively). This indicates the lack of a pharmacokinetic interaction between caffeine and moclobemide. Nevertheless, a pharmacodynamic interface is present because of interactions at the A1 and A2A adenosine receptors, where their antagonism by caffeine significantly augmented the antidepressant action of moclobemide [6].

3.5 Tetracyclic antidepressants

Tetracyclic antidepressants achieve their effects by inhibiting presynaptic alpha-2-adrenergic receptors, causing increased serotonin and norepinephrine release whilst antagonising 5-HT2A, 5-HT2C, 5-HT3, and H1 receptors, leaving the 5-HT1 and 5-HT1A receptors unaffected. This results in antidepressant and sedative effects [20].

3.5.1 Pharmacokinetics

Caffeine, as experimentally proven by Poleszak et al. in 2016 [54], did not have an effect on mianserin concentration or, vice versa, in mouse models. However, it should be noted that some effect would be possible through their metabolism via CYP1A2. Furthermore, mianserin is highly protein bound (94.5 ± 0.07), with caffeine also having an albumin binding affinity of 37.8%, indicating a potential impact on drug distribution and concentrations of free drug not explored through the analytical methods utilised in the experimental analysis of coadministration in mice models [54]. Finally, mianserin is noted to be hepatically metabolised and renally excreted [21], with caffeine's diuretic effect [72] not being studied on the excretion of metabolised mianserin.

As maprotiline is mainly metabolised via CYP2D6, which is not affected by caffeine, it is unlikely that caffeine will play a major role in any alterations in metabolism through this enzyme. However, notably, ~17% of maprotiline is metabolised by CYP1A2 [7], leading to an avenue for slight decreases in metabolism and subsequently excretion. Due to ~89.5% maprotiline protein binding in healthy volunteers [44], it is hypothesised that caffeine could interact at the distribution phase of pharmacokinetics. Finally, it should be noted that metabolised maprotiline is mostly renally excreted (57%), with 10% of the excretion being unmetabolized drug, leading to another potential pharmacokinetic interaction via urinary excretion. However, this has not been experimentally determined.

Mirtazapine is noted to be metabolised by CYP1A2 [10] with extensive first-pass metabolism, indicating a hypothesised impact due to caffeine-based induction of CYP1A2. However, this induction is only noted at unachievably high concentrations with regular consumption [70]. Similar to other tetracyclic antidepressants, mirtazapine is highly protein bound (85%) [10], leading to a hypothesised interaction with other protein-bound drugs, potentially leading to an increased fraction of free drug. Mirtazapine is primarily (75%) excreted renally [68], indicating another hypothesised pharmacokinetic interaction with caffeine's increased urinary output. Mianserin was found to interact with caffeine, increasing the effect of mianserin in the forced swim and tail suspension tests. It was noted that this interaction

was likely pharmacodynamic in nature, regardless of the CYP1A2-mediated metabolism of both caffeine and mianserin [54]. It is hypothesised that a further interaction at the H1 receptor could occur, with caffeine increasing the release of histamine after administration [39], resulting in potential competition with mianserin's antagonist/inverse agonist effect on H1 receptors [54], though this is yet to be experimentally proven.

3.5.2 Pharmacodynamics

In the previous study conducted by Poleszak et al. in 2016 [54], mianserin was found to interact with caffeine, increasing the effect of mianserin in FSTs and TSTs. Notably, this interaction was likely pharmacodynamic in nature, regardless of the CYP1A2-mediated metabolism of both caffeine and mianserin [54]. It is hypothesised that a further interaction at the H1 receptor could occur, with caffeine increasing the release of histamine after administration [39], resulting in potential competition with mianserin's antagonist/inverse agonist effect on H1 receptors [54], though this is yet to be experimentally proven.

No studies regarding pharmacodynamic interactions regarding coadministration of caffeine and mirtazapine were found, leading to a lack of evidence-based information. However, mirtazapine may, similar to other tetracyclic antidepressants, lead to a similar hypothesised interaction with H1 receptors and caffeine-induced histamine accumulation [57], where H1 occupancy reached 80–90% in the cerebral neocortex.

Finally, no studies of coadministration of maprotiline and caffeine were found, with pharmacodynamic or pharmacokinetic interactions not being listed. Thus, it is impossible to report any experimentally demonstrated pharmacokinetic and pharmacodynamic interactions. It is speculated that maprotiline, similar in its effect on the H1 receptors to mianserin (noted to be weaker according to ÖGren et al., 1981) [48], could cause a physiological reaction in a similar mechanism to what was theorised regarding mianserin.

3.6 Miscellaneous Antidepressants

Atypical antidepressants share the same goal of treating major depression but vary in their mechanisms of action. Due to their varying mechanisms of action, each drug will exhibit unique pharmacodynamics, pharmacokinetics, and interactions with caffeine.

3.6.1 Agomelatine

Agomelatine is known to act as both a serotonin (5HT2C) receptor antagonist and a melatonergic agonist [9], neither of which are known to be modified by caffeine.

3.6.1.1 Pharmacokinetics Some in vivo studies linked caffeinated beverages with increased CYP1A2 expression, attributing this to the increase in caffeine concentration [14, 24]. This however is with caffeinated beverages, not pure caffeine. An in vivo study determined no induction at feasible achievable serum caffeine concentration, resulting in a hypothesised interaction only when largely excessive quantities of caffeine (≥ 400 μM) are ingested, thus inducing CYP1A2 enzymatic activity [70]. With CYP1A2 activity being responsible for 90% of agomelatine metabolism [9], any induction could result in decreased concentrations. Notably, extensive first-pass metabolism is observed with agomelatine administration, where differences in expression and activity are attributed to varied CYP1A2 activity. Thus, environmental factors such as smoking (known to induce CYP1A2 activity) decreased the bioavailability of agomelatine [9]. This leads to a hypothesised interaction with excessive caffeine intake or other CYP1A2-inducing factors. Plasma protein binding is reported at 95% [9], leading to another potential pharmacokinetic interaction with caffeine and its protein binding prospectively leading to displacement. Finally, agomelatine is primarily renally excreted (80%), indicating yet another hypothesised pharmacokinetic interaction route with caffeine's diuretic effects. However, because agomelatine metabolism produces inactive metabolites, it is unlikely that any effects will be seen regarding increased or decreased renal excretion [9].

3.6.1.2 Pharmacodynamics Notably, in the study conducted by Poleszak et al. in 2016 [54], a pharmacodynamic interaction was theorised, with no further context or theories as to its nature posited. Furthermore, the paper exploring this interaction demonstrated a large *P* value of 0.3253, due in part to the high variance of agomelatine and Saline concentration in both serum and brain homogenates. A high *P* value (0.5016) was again seen in the subsequent measurement of caffeine in serum and brain homogenates, indicating a lack of a pharmacokinetic interaction during coadministration or experimental insufficiencies.

3.6.2 Vortioxetine

Vortioxetine is a drug used in the management of major depression by inhibiting the reuptake of serotonin through the serotonin transporter, thus prolonging its actions. It acts as an antagonist on the 5-HT3, 5-HT1D, and 5-HT7, partial agonist of the 5-HT1B, and an agonist on the 5-HT1A serotonin transporter subtypes [18].

3.6.2.1 Pharmacokinetics Studies assessing the presence of a pharmacokinetic interaction between vortioxetine and caffeine are not abundant. However, a study by Chen et al. in 2017 [13] depicted the lack of any pharmacokinetic interac-

tion between vortioxetine and caffeine, where a single study presented 24 subjects given a mixture of caffeine, CYP1A2 substrates, and other drugs being studied. The results showed that the 90% confidence interval of the AUC as well as the C_{max} for the concurrent caffeine and vortioxetine administration fell within the 80–125% range [13]. This indicates that vortioxetine is not a CYP1A2 inhibitor or inducer and shows that the metabolism pathways between caffeine and vortioxetine do not overlap. This is further emphasised by a study conducted by Chen et al. in 2013 [12] that quantified the lack of drug-drug interaction between caffeine and vortioxetine. Upon coadministration of vortioxetine with other CYP inhibitors and inducers, the study identified an increase in the steady-state AUC (128%) and C_{max} (114%) of bupropion (CYP2D6 inhibitor) and a decrease (72% and 51% respectively) in those of rifampicin (CYP inducer) [12], consequently presenting the lack of a pharmacokinetic interaction between caffeine and vortioxetine at the metabolic level.

3.6.2.2 Pharmacodynamics Although multiple searches were performed on numerous search engines, no studies or reviews were found to portray a pharmacodynamic interaction between vortioxetine and caffeine.

3.6.3 Reboxetine

Reboxetine is a noradrenergic reuptake inhibitor that selectively blocks the norepinephrine transporter, projecting its antidepressive effects [51].

3.6.3.1 Pharmacokinetics The metabolic pathways of reboxetine do not parallel those of caffeine, where in return the lack of a pharmacokinetic interaction at the metabolic level is hypothesised. This is noted in a study that investigated the effect of the coadministration of caffeine on the antidepressant effect of reboxetine using an FST and monitoring the concentrations of reboxetine in the blood plasma and brain serum. The lack of significant differences in the plasma and brain samples between the control and the coadministration of caffeine and reboxetine ($P > 0.05$ obtained) is suggestive of the lack of a pharmacokinetic interaction at the metabolic levels. Nevertheless, the concurrent administration of caffeine and reboxetine significantly decreased the immobility of the mice tested in the FST ($P < 0.0001$) [25].

3.6.3.2 Pharmacodynamics The pharmacodynamic interaction between caffeine and reboxetine was examined in a study conducted by Szopa et al. in 2018 [66] that assessed the influence of adenosine A1 receptor antagonist (caffeine) on the antidepressant activity of reboxetine. The decrease in mobility duration of mice in the FST while the lack of change in the plasma concentrations of reboxetine showed that complete antagonism of the A1 adrenoceptors by caffeine elevated the therapeutic effects of reboxetine [66], therefore indicating the presence of a pharmacodynamic interaction.

4 Limitations

The influence of caffeine and antidepressants can differ extensively and broadly between individuals because of factors such as genetics, metabolism, and health status. This variability can potentially make it challenging to determine the benefits or risks of combining these substances.

5 Conclusions and Future Perspectives

The coadministration of caffeine and antidepressants remains a concern due to potential interactions that can alter one's response to therapy. Significant changes in the pharmacokinetic profiles were found in the interactions between fluvoxamine and caffeine. Other SSRIs did not exhibit significant pharmacokinetic interactions with caffeine. However, caffeine enhanced the antidepressant effects of fluoxetine and escitalopram while increasing the drug concentration of plasma serum paroxetine.

The interactions between TCAs and caffeine have been found to decrease the metabolism of caffeine by the CYP1A2 enzyme. However, it is noted that the likelihood of drug-drug interaction between caffeine and these TCAs may not have a significant impact on their pharmacodynamic effects, except when using amitriptyline to treat neuropathic pain.

The potential interactions of coadministration of caffeine at high doses and MAOIs showed a significant risk of hypertension, specifically, the combination of high doses of caffeine and tranylcypromine. Additionally, no pharmacokinetic interaction was distinguished with moclobemide, but it may prolong its duration of action when administered with caffeine.

No significant alteration of venlafaxine concentrations when coadministered with caffeine was observed. Subsequently, the pharmacodynamic effects and overall efficacy of venlafaxine are probably not affected when caffeine is consumed because of its low potency.

Finally, the studies conducted on various other miscellaneous antidepressants have contributed to some insights into their potential interactions with caffeine and their effects in behavioural tests.

It is important to understand how caffeine, a commonly consumed beverage worldwide, interacts with antidepressant medications. Caffeine and antidepressants can both exert an

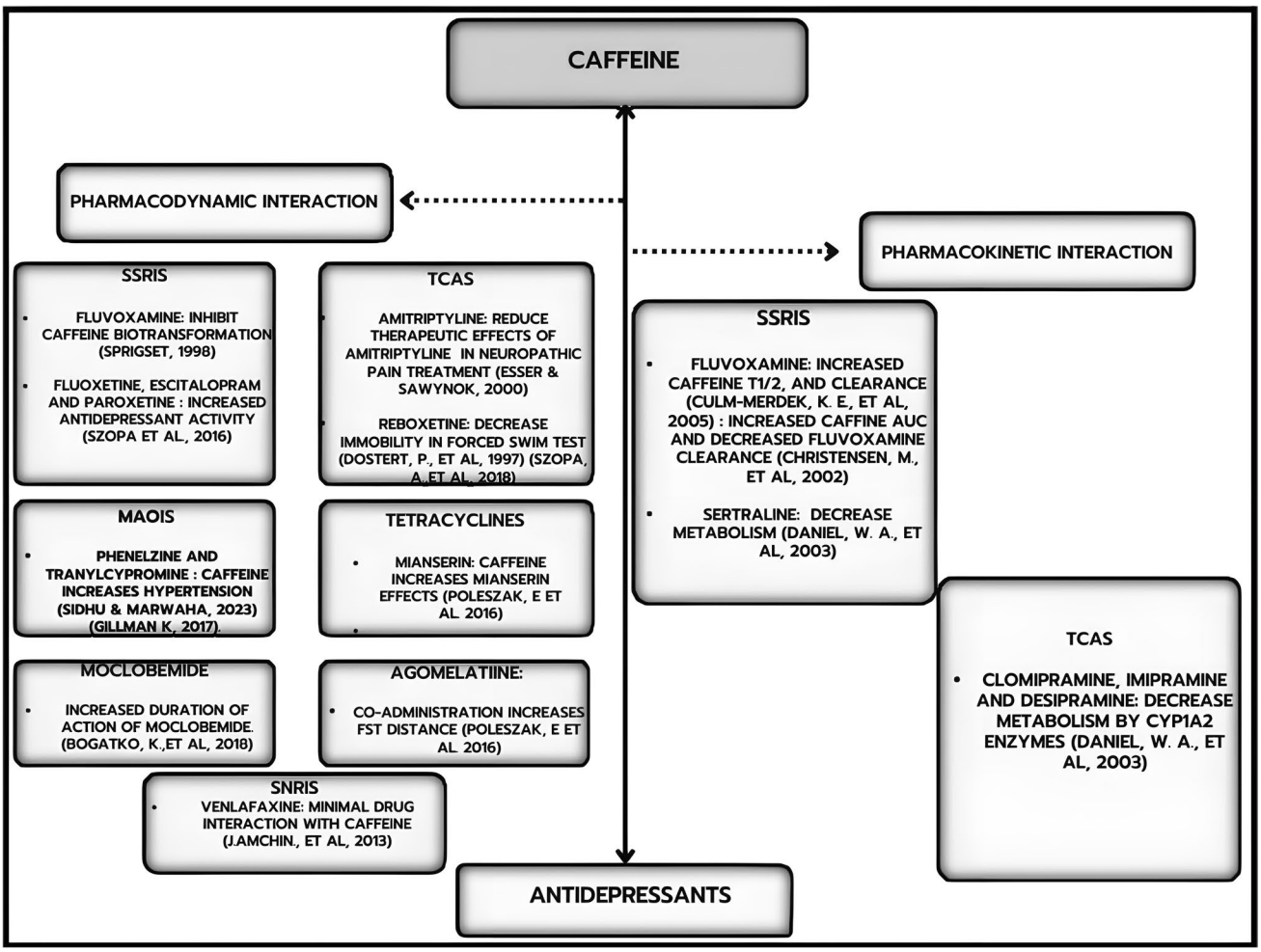

Fig. 3 An illustration outlining the pharmacodynamic and pharmacokinetic interaction of antidepressant drugs with caffeine. *SSRI* selective serotonin reuptake inhibitor; *TCAS* tricyclic antidepressants; *SNRIs* serotonin noradrenaline reuptake inhibitor; *MAOIS* monoamine oxidase inhibitors

influence on brain chemistry and have potential effects on energy levels, behaviour, mood, and an individual's well-being. Exploring these interactions can help determine any potential risks or benefits associated with concurrent use. Given the widespread use, it is important to explore their effect on mental health outcomes and further research can help establish whether combining caffeine and antidepressants leads to enhanced antidepressant response or exacerbates symptoms. This knowledge can strengthen clinical decision-making and improve the overall well-being of individuals undergoing treatment for mental health conditions.

Overall, these research findings represented in Fig. 3 suggest that caffeine may play a role in the intricate interplay between the pharmacokinetics and pharmacodynamics of antidepressant drugs, potentially enhancing their effects. The interactions between caffeine and the antidepressants are more likely pharmacodynamic in nature, and the regular consumption of caffeine may influence the antidepressant effects of these drugs. Therefore, further research is needed to fully understand the mechanisms and clinical implications of these interactions.

Acknowledgements We extend our profound gratitude to the Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney (UTS), for their crucial support and resources that have underpinned this research.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Conflicts of Interest The authors have no conflicts of interest to declare.

Ethics approval Not applicable.

Consent for Publication All the authors consent to publish the present paper.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Authors' Contributions JT, NAS, DT, RB, AI, TN, AM, VN, JS: Conceptualization, Writing-Original Draft, Writing - Review and Editing; KD, GDR, DP: Conceptualization, Supervision, Project Administration, Writing - Review and Editing.

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