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Caffeine intolerance and the patient's clinical picture: pharmacokinetics, genetic predisposition, and interactions with psychotropic medications — a narrative review

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Abstract

Background: Caffeine is the most widely consumed psychoactive substance worldwide, yet its intake is rarely quantified in routine psychiatric or cardiological assessment. While IgE-mediated allergy appears exceptional, intolerance and hypersensitivity seem common and may reflect polygenic and metabolic variability that is often clinically underrecognised.

Aim: To synthesise current evidence on caffeine pharmacokinetics, on the genetic determinants of inter-individual variability — particularly CYP1A2 and ADORA2A — and on clinically relevant interactions with psychotropic medications.

Material and methods: A narrative review was performed using PubMed, Scopus and Google Scholar. Articles published in English addressing pharmacokinetics, pharmacogenomics, psychiatric symptomatology and drug–drug interactions of caffeine were considered. Original studies and reviews were included; case reports were retained when clinically illustrative.

Results: Caffeine acts mainly through non-selective antagonism of A1 and A2A adenosine receptors, with downstream modulation of dopaminergic, noradrenergic and HPA-axis signalling. Variants of CYP1A2 (e.g. rs762551) define slow and rapid metabolisers, shaping plasma half-life and accumulation risk. ADORA2A polymorphisms (e.g. rs5751876) may modulate anxiogenic susceptibility independently of hepatic clearance. Co-administration with clozapine or olanzapine may raise plasma drug concentrations and toxicity risk; fluvoxamine, a potent CYP1A2 inhibitor, may extend the caffeine half-life severalfold, producing presentations easily mistaken for akathisia or serotonin syndrome.

Conclusions: Caffeine intake — including hidden dietary and over-the-counter sources — should be systematically assessed before initiating psychotropic therapy. Pharmacogenomic profiling may support personalisation in treatment-resistant or atypically responsive patients.

Keywords: caffeine; CYP1A2; ADORA2A; clozapine; fluvoxamine; pharmacogenomics; anxiety

1. Introduction

1.1. Epidemiology — the scale of caffeine exposure in the general population

Caffeine (1,3,7-trimethylxanthine) is, by all available estimates, the most widely consumed psychoactive substance in the world, present in coffee, tea, cocoa products, soft drinks, energy drinks, dietary supplements, and in a heterogeneous range of over-the-counter analgesic and stimulant preparations [1,2,3]. Its consumption is woven into daily routines in virtually every cultural and economic stratum, and several recent surveys suggest that habitual exposure is increasing rather than declining. Population-level data from the United States indicate that more than 90% of adults consume caffeinated beverages on a regular basis, with a 2023 estimate of approximately 94% — a figure that appears to mark an upward shift from earlier surveys [1].

Similar or even higher prevalence rates (up to roughly 97%) have been reported in some Middle Eastern samples, and in China the proportion of adults consuming caffeinated products is reported to have risen 27-fold between 2004 and 2018, while Korean adolescent caffeine consumption rose from 3.3% in 2015 to 12.2% in 2019, illustrating that the trend extends well beyond the Western world [1]. In a Slavic sample, the frequency of habitual coffee drinking appeared somewhat above the global average, with about 27% of respondents reporting consumption several times a day and a measurable correlation between intake and self-reported insomnia [4].

Quantitative estimates place the mean daily caffeine intake among adults at roughly 2–7 mg/kg body weight depending on the country, with high-level consumers reaching 5–15 mg/kg [3]. The European Food Safety Authority has concluded that habitual intakes up to about 400 mg per day in healthy non-pregnant adults do not, on the available evidence, give rise to general safety concerns, while pregnant women are advised to remain below approximately 200 mg per day [5]. Even so, the 95th percentile of daily intake was found to exceed 400 mg in 7 of 13 European countries surveyed, with the proportion of adults exceeding that threshold ranging from about 6% to nearly one third of the population, depending on the country [5]. The caffeine content per serving of coffee is, in addition, highly variable — typically reported between 56 and 100 mg per 100 mL of brewed coffee and 20–73 mg per 100 mL of instant coffee and tea [3] — and depends on the species (with *Coffea canephora* generally containing 40–70% more caffeine than *Coffea arabica*), the degree of roasting, the brewing method, and the serving size [6]. This intrinsic variability translates into substantial uncertainty when daily intake is estimated solely on the basis of "number of cups," a point of considerable clinical importance when the dose–response relationship for adverse effects is being considered.

Beyond traditional dietary sources, the rapid expansion of the energy drink market deserves particular attention. A recent systematic review and meta-analysis estimated the world-wide lifetime prevalence of energy drink use at 54.7% (95% CI 48.8–60.6), with 43.4% in the past 12 months and 8.82% reporting daily use [7]. Adolescents and young adults appear to be the most exposed groups, and since such products often combine caffeine with taurine, glucuronolactone, sugars and a number of herbal extracts, their pharmacological consequences cannot be fully anticipated from caffeine intake alone [7]. Taken together, these data outline a population in which exposure is near-ubiquitous, quantitatively uncertain at the individual level, and skewed towards the segments most likely to come to psychiatric attention.

1.2. Allergy versus intolerance — distinct pathomechanisms

A recurring source of conceptual confusion in clinical practice concerns the distinction between true allergic reactions to caffeine and the much broader category of caffeine intolerance or hypersensitivity. IgE-mediated allergy to caffeine seems to be exceptional. Only a handful of well-documented case reports describe anaphylactic or urticarial reactions with positive skin-prick testing or oral provocation; one such observation involved a 69-year-old woman in whom 150 mg of caffeine reproducibly elicited generalised wheals in a dose-dependent fashion, with stimulation of patient-derived leukocytes producing leukotriene release exceeding that

observed in healthy controls [8]. A further case described a 27-year-old woman who developed her first episode of anaphylaxis after ingesting a single piece of caffeine-containing candy (42 mg), with subsequent positive skin-prick reactivity supporting an IgE-mediated mechanism [9]. The rarity of these observations is congruent with the broader epidemiology of hypersensitivity reactions and with the way that allergic and hypersensitivity conditions have recently been codified, including the dedicated chapter for these disorders in the International Classification of Diseases, 11th revision (ICD-11) [10].

Caffeine "intolerance," by contrast, is best understood as an umbrella term encompassing non-IgE-mediated, dose-related, and frequently idiosyncratic reactions in which the symptomatology — anxiety, palpitations, gastrointestinal discomfort, insomnia, tremor — appears to be shaped largely by an interplay between the administered dose, hepatic clearance and central nervous system sensitivity [3,11]. In many individuals, this constellation resembles the syndrome historically described as "caffeinism" — a state of restlessness, irritability, agitation, muscle tremor, insomnia, headache, diuresis, sensory disturbances and cardiovascular and gastrointestinal complaints occurring with habitual intakes that, in earlier reports, were placed in the region of 500–600 mg per day [3]. From a diagnostic standpoint, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), now recognises caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder and caffeine withdrawal as formal diagnostic entities, and lists caffeine use disorder as a condition warranting further study in its emerging measures section [11], while ICD-11 acknowledges hypersensitivity reactions more broadly [10]. The clinical implication is that, although IgE-mediated caffeine allergy is rare, dose-dependent intolerance with substantial inter-individual variability — driven by polygenic determinants of metabolism and receptor sensitivity — may be relatively common and often underrecognised.

1.3. Rationale — why caffeine deserves attention in the psychiatric and cardiological interview

Despite its ubiquity, caffeine is rarely quantified during the routine medical interview. Patient-reported intake is most often given in colloquial terms ("a few cups of coffee"), without specifying brewing method, serving size, additional sources such as tea, cola, energy drinks or pre-workout supplements, or use of caffeine-containing analgesic preparations for headache. This omission is potentially consequential. Caffeine acts as a non-selective antagonist of adenosine A1 and A2A receptors, with downstream facilitation of dopaminergic, noradrenergic, serotoninergic and cholinergic neurotransmission, and with stimulation of the hypothalamic–pituitary–adrenal (HPA) axis [2,12]. A meta-analysis of caffeine intake and anxiety in healthy populations without diagnosed psychiatric disorders suggests that caffeine consumption may be associated with an elevated risk of anxiety, with a standardised mean difference of 0.94 (95% CI 0.28–1.60) overall and a particularly pronounced effect at intakes exceeding 400 mg per day (SMD 2.86, 95% CI 2.50–3.22) [13]. Narrative reviews on caffeine and anxiety reach broadly similar conclusions, noting that the relationship is non-linear and may be modulated by habitual intake, tolerance and concurrent psychotropic therapy [14].

From the standpoint of differential diagnosis, the symptomatic profile of caffeine intoxication — sinus tachycardia, tremor, restlessness, gastrointestinal disturbance, insomnia, irritability — overlaps substantially with the somatic dimension of generalised anxiety disorder, with panic attacks, with hyperthyroidism, and, in patients receiving antipsychotic therapy, with akathisia and with the early phenomenology of serotonin syndrome [3,11,13]. From the pharmacotherapeutic standpoint, caffeine and several psychotropic medications share metabolic pathways, most notably cytochrome P450 1A2 (CYP1A2), and competitive inhibition or induction of this enzyme may shift the plasma concentration of either substance in directions that are clinically meaningful [2,6,12]. These mechanisms, taken together with growing recognition of pharmacogenomic determinants of caffeine handling, motivate the present narrative review.

The aim of this review is therefore to integrate current evidence on (i) the pharmacodynamic and pharmacokinetic basis of inter-individual variability in caffeine response, (ii) the principal genetic determinants of caffeine metabolism (CYP1A2) and central nervous system sensitivity (ADORA2A), (iii) the clinical phenomenology of caffeine intolerance and its overlap with psychiatric symptomatology, and (iv) clinically relevant interactions between caffeine and psychotropic medications. Particular attention is given to interactions with clozapine, olanzapine and fluvoxamine, which sit at the intersection of pharmacogenomics, narrow therapeutic indices and a high background prevalence of caffeine exposure.

2. Materials and Methods

2.1. Study design

The present work was designed as a narrative review, an approach that appears particularly suited to research questions that are conceptually broad, span several methodological traditions, and integrate evidence drawn from distinct subdisciplines — in this case basic pharmacology, clinical pharmacokinetics, pharmacogenomics, psychiatric phenomenology, internal medicine and aspects of dietetics. Compared with a systematic review, a narrative synthesis allows for a more interpretive integration of heterogeneous study designs and is well suited to topics in which the body of evidence consists of mechanistic studies, randomised controlled trials, observational cohorts, therapeutic drug monitoring (TDM) studies and case reports that, taken together, illuminate clinically relevant questions but cannot be readily pooled in a quantitative manner. No formal protocol was registered in PROSPERO, since registration is generally reserved for systematic reviews, and no meta-analysis was performed. Nevertheless, in the interest of methodological transparency, the search strategy, the eligibility criteria and the data-handling procedures are described below in a structured form that follows, where relevant, the spirit of PRISMA 2020 guidance adapted to narrative work.

The clinical question driving the synthesis was formulated as follows: in adult patients exposed to dietary, supplemental or medicinal caffeine, how do pharmacokinetic determinants, genetic polymorphisms (particularly CYP1A2 and ADORA2A) and concurrent psychotropic pharmacotherapy interact to shape the clinical picture of caffeine intolerance and its overlap

with psychiatric and cardiological symptomatology? Within this question, four thematic axes were defined a priori: (i) pharmacodynamic and pharmacokinetic foundations, (ii) pharmacogenomic determinants of inter-individual variability, (iii) clinical phenomenology of caffeine intolerance (anxiety, sleep, somatic and cardiovascular manifestations), and (iv) interactions between caffeine and psychotropic medications, with particular emphasis on clozapine, olanzapine and fluvoxamine. A supplementary axis concerned dietary aspects of "hidden" caffeine intake and the modulating role of co-ingested phytochemicals.

2.2. Literature search strategy

A structured electronic search of three biomedical databases — PubMed/MEDLINE, Scopus and Google Scholar — was conducted to identify peer-reviewed publications addressing the thematic axes outlined above. The search was performed iteratively rather than as a single time-limited query, in line with the exploratory character of narrative review work. The reference lists of pivotal articles were screened manually for additional sources of relevance (so-called snowballing), and selected systematic reviews and meta-analyses were used as further entry points into the literature.

The search terms were structured around five blocks of controlled vocabulary and free-text descriptors, combined using Boolean operators. Block 1 (substance) included: "caffeine", "1,3,7-trimethylxanthine", "methylxanthine", "coffee", "tea", "energy drink". Block 2 (pharmacokinetics and metabolism) included: "pharmacokinetics", "metabolism", "half-life", "clearance", "CYP1A2", "cytochrome P450 1A2", "paraxanthine", "N-demethylation". Block 3 (pharmacogenomics) included: "polymorphism", "rs762551", "CYP1A2*1F", "ADORA2A", "rs5751876", "adenosine A2A receptor", "DRD2", "slow metaboliser", "rapid metaboliser", "pharmacogenetics". Block 4 (clinical phenomenology) included: "anxiety", "panic disorder", "generalised anxiety disorder", "insomnia", "sleep architecture", "tachycardia", "arrhythmia", "supraventricular extrasystole", "caffeine intoxication", "caffeine use disorder", "caffeine withdrawal", "hypersensitivity", "intolerance", "anaphylaxis". Block 5 (interactions and psychotropics) included: "drug interaction", "drug–drug interaction", "psychotropic", "antipsychotic", "clozapine", "olanzapine", "antidepressant", "SSRI", "fluvoxamine", "duloxetine", "agomelatine", "ciprofloxacin", "therapeutic drug monitoring".

Searches were not restricted by year of publication, given the importance of older mechanistic and pharmacokinetic literature for contextual understanding, although the synthesis emphasised papers published after 2000 with particular weight given to those issued in the last fifteen years. Articles in English were prioritised. Records were screened on the basis of title and abstract, with full texts retrieved when the abstract suggested relevance. Records identified through manual review of reference lists were screened by the same procedure.

2.3. Inclusion and exclusion criteria

Eligibility was assessed against criteria defined a priori and refined iteratively during the screening process.

Records were considered eligible for inclusion if they: (i) addressed at least one of the four thematic axes defined above; (ii) were peer-reviewed primary studies, systematic reviews, meta-analyses, narrative reviews of high standing, authoritative regulatory opinions (for example, the EFSA opinion on caffeine safety), guideline statements, or methodologically sound case reports illustrating clinically important interactions or adverse reactions; (iii) were conducted in humans, with the exception of selected preclinical and mechanistic studies retained where they were judged informative for the pharmacodynamic or genetic background; (iv) were published in English, or, when published in another language, accompanied by an English-language abstract sufficient for interpretation; (v) reported sufficient methodological detail to allow critical appraisal.

Records were excluded if they: (i) were unrelated to caffeine pharmacology, pharmacogenomics, clinical psychiatric phenomenology or psychotropic drug–drug interactions; (ii) consisted of opinion pieces, conference abstracts without subsequent full publication, or commentaries without primary data or substantive review value; (iii) duplicated data already reported in a more comprehensive form elsewhere (in which case the most informative version was retained); (iv) addressed populations in which the question of generalisability to the adult patient seen in psychiatric or cardiological practice was particularly problematic and could not be discussed without speculation (for example, very small paediatric series with no parallel adult evidence). Case reports of fatal caffeine intoxication and of rare but clinically instructive drug interactions were retained, as they often provide the most direct evidence on the upper boundary of pharmacological risk.

2.4. Data synthesis

Eligible records were grouped thematically according to the four axes defined a priori and the supplementary dietary/phytochemical axis. Within each thematic block, data were extracted in narrative form rather than entered into formal evidence tables, although key quantitative parameters — half-life ranges, area under the curve (AUC), clearance values, allelic frequencies, effect sizes for anxiety or for cardiovascular outcomes — were retained where reported in the original studies, with explicit reference to the source. Methodological heterogeneity was acknowledged throughout: in particular, studies differed widely in sample size, dosing protocols, choice of comparator (decaffeinated coffee, placebo, no exposure), duration of observation, definition of "habitual" intake and the analytical tools used to quantify plasma concentrations or to genotype CYP1A2 and ADORA2A.

A deliberately cautious interpretive register was adopted throughout the synthesis. Findings derived from single case reports, small mechanistic studies, or studies in healthy volunteers were not transposed to patient populations without explicit qualification, and effect sizes drawn from individual trials were reported as such rather than aggregated. Where the literature appears internally inconsistent — as is the case, for instance, for the association between caffeine intake and atrial fibrillation, or for the impact of CYP1A2 polymorphisms on cardiovascular outcomes — the divergence is signalled rather than resolved. The synthesis was therefore guided by the

principle that the strength of recommendations should be commensurate with the strength of the underlying evidence, and that, in a narrative review of a topic as broad and methodologically heterogeneous as caffeine intolerance and its interactions with psychotropic therapy, the most defensible posture is one of cautious integration, careful flagging of areas of uncertainty, and explicit emphasis on the clinical implications that emerge most robustly from the converging evidence.

No ethical approval was required, as this work synthesises previously published data and does not involve original collection of personal or clinical information.

3. Neurobiological mechanisms of caffeine action (pharmacodynamics)

3.1. The primary target — non-selective antagonism of adenosine A1 and A2A receptors

At plasma concentrations achievable through ordinary dietary intake, caffeine appears to exert most of its central nervous system effects through competitive, non-selective antagonism of adenosine receptors, of which four subtypes have been cloned in humans: A1, A2A, A2B and A3 [15]. The high-affinity A1 and A2A receptors are those primarily engaged by endogenous adenosine under physiological conditions and are accordingly considered the principal pharmacological targets responsible for caffeine's psychostimulant profile [2,15]. Two further mechanisms — inhibition of phosphodiesterases (notably PDE1, PDE4 and PDE5), mobilisation of calcium from intracellular stores, and interactions with GABA-A receptors — have also been described, but are generally observed only at concentrations well above those obtained through customary dietary exposure and are therefore unlikely to contribute substantively to the everyday clinical picture of caffeine intolerance [15].

Because adenosine itself acts predominantly as an inhibitory neuromodulator, the functional consequence of A1 and A2A receptor blockade is the removal of a tonic adenosinergic brake on several ascending arousal and reward systems [12,15]. A1 receptors are densely expressed in the hippocampus, cortex, cerebellum and thalamus, where they exert presynaptic inhibition of glutamate, acetylcholine, noradrenaline and serotonin release, while A2A receptors are concentrated in the striatum, nucleus accumbens, olfactory tubercle and on subsets of GABAergic neurons, where they are organised together with dopamine D2 receptors in functional A2A–D2 heteromers [2,12,15]. The biological consequence of A2A blockade is therefore not simply a release of adenosine-mediated inhibition but, more specifically, a disinhibition of D2-mediated signalling in the striatopallidal pathway, a mechanism that may help to explain the partial overlap between caffeine's motor-activating profile and that of classical psychostimulants such as amphetamines or cocaine, despite very different primary mechanisms [12]. Importantly, the affinities of caffeine for A1 and A2A receptors are broadly similar, so that the net effect at a given brain area appears to reflect which receptor subtype is dominant in mediating local adenosinergic tone [15].

A further layer of complexity is added by the differential consequences of acute and chronic caffeine exposure. Acute administration may produce effects opposite to those of adenosine

receptor activation, but sustained intake tends to be associated with up-regulation of A1 receptors and changes in receptor heteromerisation (A1–A2A), as well as in receptors for other neurotransmitters — including a reported decrease in β-adrenergic receptors and increases in serotonin and GABA-A receptor expression — providing a plausible neurobiological substrate for tolerance to the psychomotor and subjective effects of habitual caffeine intake [15]. The clinical implication is that caffeine-naïve patients, or those who have recently reduced their habitual intake, may experience a substantially more pronounced pharmacodynamic response than chronic users at the same per-dose exposure, and that the boundaries between "no effect", "stimulant effect" and "anxiogenic effect" appear to depend heavily on both genotype and historical exposure rather than solely on the dose administered.

3.2. Downstream neurotransmitter cascade — dopamine, noradrenaline, serotonin and acetylcholine

The clinical phenotype that brings caffeine intolerance to the attention of the psychiatrist and the cardiologist is, in large part, a consequence of the downstream neurochemical changes that follow adenosine receptor blockade. The most extensively documented of these is an indirect facilitation of central dopaminergic, noradrenergic, serotoninergic and cholinergic neurotransmission. As reviewed in the editorial of Ferré in the *Journal of Caffeine Research*, classical psychostimulants such as cocaine and amphetamine produce direct potentiation of catecholaminergic and serotoninergic systems by acting on monoamine transporters, whereas caffeine appears to achieve a milder version of the same outcome indirectly, by removing the presynaptic adenosinergic tone that ordinarily restrains the release of these neurotransmitters [12]. A characteristic biochemical signature of psychostimulant action — an increase in striatal extracellular dopamine — has been documented for caffeine in a restricted region of the ventral striatum, with paraxanthine, its principal human metabolite, reportedly producing a stronger striatal dopamine-releasing effect than the parent compound, an action that appears to combine adenosine receptor antagonism with inhibition of cGMP-preferring phosphodiesterases [12].

Earlier reviews of caffeine pharmacology similarly emphasise that caffeine results in the release of noradrenaline, dopamine and serotonin in the brain, and in an increase in circulating catecholamines, consistent with reversal of the inhibitory effect of adenosine [3]. The increase in noradrenergic tone may underpin a substantial proportion of the somatic and cardiovascular manifestations associated with high acute exposure — sinus tachycardia, palpitations, tremor, sweating, mild blood pressure elevations and a subjective sense of arousal — phenomena that, in clinical practice, are sometimes misinterpreted as panic attacks, akathisia or thyrotoxic phenomena [3,11]. The serotoninergic component is more difficult to dissect cleanly, as caffeine produces non-linear changes that interact with mood state, sleep deprivation and concurrent psychotropic therapy, but it remains relevant for the differential diagnosis of caffeine-related symptomatology in patients receiving selective serotonin reuptake inhibitors (SSRIs) or other serotoninergic agents [12].

The cholinergic dimension deserves separate emphasis. Endogenous adenosine, through both A1 and A2A receptors, modulates acetylcholine release in the hippocampus and basal forebrain.

Experimental microdialysis studies in animals have shown that caffeine, by selective interaction with A1 receptors, enhances hippocampal acetylcholine release [15,16]. This cholinergic facilitation may contribute to the cognitive effects of low-to-moderate doses of caffeine (improved attention, vigilance, reaction time and verbal memory) but may also paradoxically participate in the disruption of memory consolidation observed at higher doses or when consumption is closely temporally linked to sleep [1,15]. In parallel, adenosine A2A receptors in the pontine reticular formation have been reported to promote acetylcholine release and to participate in the regulation of REM and non-REM sleep, suggesting that A2A blockade by caffeine may interfere with sleep architecture not only through prolonged wakefulness but also via direct modulation of cholinergic mechanisms relevant to sleep stage transitions [15].

A further consideration is the influence of caffeine on glutamatergic and GABAergic balance. A1 receptors restrain glutamate release in cortex and hippocampus, and their blockade by caffeine appears to translate into a modest but generalised facilitation of excitatory transmission, contributing both to enhanced cognitive performance and to the lowering of seizure threshold reported at very high doses [15]. Conversely, longer-term caffeine intake has been associated with an increase in GABA-A receptor expression, an adaptive change that may participate in the development of tolerance and in the symptomatology of caffeine withdrawal [15]. Taken together, these data suggest that caffeine — despite a single primary pharmacological target — produces a richly polymodal effect on neurotransmission, in which the relative weights of dopaminergic, noradrenergic, cholinergic and glutamatergic contributions appear to be shaped by dose, by site of action and by the chronicity of exposure. This polymodal profile may, in part, explain why the clinical phenotype of caffeine intolerance is itself so heterogeneous, ranging from a predominantly anxiogenic presentation to a predominantly cardiovascular or predominantly sleep-related one.

3.3. Activation of the hypothalamic–pituitary–adrenocortical axis and the cortisol response

The third major dimension of caffeine pharmacodynamics relevant to the clinical picture of intolerance concerns the activation of the hypothalamic–pituitary–adrenocortical (HPA) axis. Both human and animal data converge in indicating that caffeine, even at doses comparable to common dietary intake, may produce a measurable rise in plasma adrenocorticotropic hormone (ACTH) and cortisol [16,17]. In a controlled rodent study, intraperitoneal caffeine at 2 mg/kg — a dose roughly equivalent to a single cup of coffee in humans — significantly increased plasma corticosterone and ACTH at 30 minutes post-injection, with return to baseline by 60 minutes, while doses of 30 mg/kg and above produced elevations persisting for at least two hours [16]. The same investigation indicated that low to moderate doses of caffeine did not appreciably modulate the HPA response to a distinct stressor (loud noise), suggesting that caffeine activates the HPA axis additively rather than by sensitising the system to other stress stimuli [16].

In humans, the cortisol response to caffeine challenge is well characterised. In a placebo-controlled, double-blind, crossover trial conducted in 96 healthy young adults, Lovallo and

colleagues demonstrated that after five days of caffeine abstinence, oral caffeine challenge produced robust elevations of salivary cortisol across the test day [17]. Importantly, five days of habitual caffeine intake at 300 mg/day or 600 mg/day attenuated, but did not abolish, the cortisol response: tolerance was incomplete at 300 mg/day and more pronounced at 600 mg/day, although in both conditions a clinically meaningful elevation of cortisol was still evident in the afternoon hours after subsequent caffeine doses [17]. In other words, the HPA axis appears to remain functionally responsive to caffeine in regular consumers, with the magnitude of the response varying as a function of recent exposure history, time of day and dosing interval.

Mechanistically, the caffeine-induced activation of the HPA axis appears to be centrally mediated and not the result of direct stimulation of the pituitary or adrenal gland. Studies cited within the rodent literature indicate that only very high concentrations of caffeine induce ACTH or corticosterone release from isolated pituitary and adrenal tissue, whereas systemic doses well within the human dietary range readily activate the axis in vivo [16]. Blockade of corticotropin-releasing factor (CRF) release reportedly abolishes the caffeine-induced endocrine response, supporting the view that caffeine acts on central adenosine receptors located in hypothalamic afferent regions, which in turn modulate the activity of the paraventricular nucleus and the downstream CRF–ACTH–cortisol cascade [16].

The clinical implications of this pharmacodynamic profile may be substantial. Sustained elevations of cortisol have been associated, in observational and mechanistic literature, with disturbances of immune regulation, with altered limbic responsivity, with effects on declarative memory consolidation, with depressive symptomatology and with sensitisation of the cardiovascular response to stress [17]. In individuals at elevated cardiovascular risk — notably in those with borderline hypertension or a positive family history of hypertension — the cortisol response to caffeine has been reported to be both larger and more prolonged, suggesting that the HPA-mediated component of the caffeine response may not be uniformly distributed across the population [17]. In a psychiatric context, the combination of caffeine-driven catecholaminergic activation and HPA axis stimulation may plausibly contribute to the anxiogenic phenomenology described in earlier sections, and may interact with the stress neurobiology that underlies major depressive disorder, generalised anxiety disorder and post-traumatic stress disorder. These mechanistic threads return repeatedly in the chapters that follow, where the pharmacodynamic substrate described here is integrated with pharmacokinetic, genetic and pharmacotherapeutic considerations.

4. Genetic background of caffeine intolerance — individual variability

The clinical observation that two patients may report markedly different reactions to the same dose of caffeine — one tolerating six espressos with ease and another developing palpitations and insomnia after a single cup of tea — is far from anecdotal. Twin and family studies, candidate-gene analyses and large-scale genome-wide association studies (GWAS) consistently indicate that habitual caffeine consumption and the subjective response to caffeine are substantially heritable, with heritability estimates ranging between 43% and 58% for habitual use, and reaching up to 77% for heavy consumption [18,25]. Pharmacogenomic dissection of

this variability has converged on two principal axes: (i) hepatic metabolism, dominated by the cytochrome P450 isoform 1A2 (CYP1A2), and (ii) central nervous system sensitivity, in which the adenosine A2A receptor gene (ADORA2A) plays a recurrent role. A broader catalogue of secondary loci has emerged from recent GWAS, including AHR, POR, ABCG2, CYP2A6, DRD2, BDNF and SLC6A4, but the present chapter focuses on the two loci most directly relevant to caffeine intolerance in the psychiatric and cardiological context [18,19].

4.1. CYP1A2 polymorphism — the pharmacokinetic axis

Cytochrome P450 1A2 is a hepatic monooxygenase that, in humans, accounts for approximately 90–95% of the N3-demethylation of caffeine to paraxanthine and for the overwhelming majority of caffeine clearance [18,19,26]. Estimates of inter-individual variability in CYP1A2 activity vary across studies, but a 5- to 6-fold range is consistently reported, with some sources describing up to 60-fold variation in caffeine demethylation between individuals [18,19,25,26]. A substantial proportion of this variability appears to be genetically determined: twin studies indicate that, when smokers and oral-contraceptive users are excluded, up to 89% of the variation in the area under the caffeine concentration–time curve (AUC) may be accounted for by genetic effects, with roughly 8% specifically attributable to polymorphisms in the CYP1A1/1A2 promoter region [26].

The most extensively investigated single-nucleotide polymorphism (SNP) is rs762551 (–163C>A) in intron 1 of the CYP1A2 gene, located on chromosome 15q24. On the basis of this variant, individuals are commonly classified, by a pragmatic if simplified convention, as "rapid metabolisers" (AA genotype; CYP1A2*1A/*1A) or "slow metabolisers" (CA or CC genotypes, carriers of the *1F allele) [18,19,24]. The functional consequence of the A allele appears to be a higher inducibility of CYP1A2, particularly under exposure to known inducers such as polycyclic aromatic hydrocarbons in tobacco smoke or in cruciferous vegetables. Carriers of the C allele appear, by contrast, to display a lower baseline and inducible enzyme activity, with a slower clearance of caffeine and a longer plasma elimination half-life [18,19].

In quantitative terms, caffeine pharmacokinetic parameters reported across the literature span a wide range. The average plasma half-life of caffeine in healthy adults is generally cited as 3–5 hours, but reported individual values range from approximately 2.3 hours to nearly 10 hours, and several reviews highlight that pharmacokinetic heterogeneity is driven by genetic determinants, sex, oral contraceptive use, smoking, pregnancy and concurrent medications [19,26]. Smoking, for instance, may approximately double the rate of caffeine elimination, while pregnancy progressively prolongs the half-life from about 4 hours in the first trimester to up to 18 hours in the third trimester [19]. In a clinical context, the practical implication is that a "slow" CYP1A2 metaboliser may accumulate caffeine over the course of the day in a way that a "rapid" metaboliser does not — a kinetic phenomenon that may translate into prolonged plasma exposure, sleep disturbance and a phenotype reminiscent of caffeine intoxication despite intake levels that would be tolerated by another individual.

Several GWAS conducted in populations of European, Asian and Hispanic ancestry have replicated the role of CYP1A2 and of the closely linked AHR locus at 7p21 — the aryl hydrocarbon receptor, which regulates CYP1A2 transcription — as principal determinants of habitual caffeine intake [18,25]. A meta-analysis of 47,341 individuals of European descent identified two genome-wide significant loci: 7p21 near AHR (rs4410790) and 15q24 between CYP1A1 and CYP1A2 (rs2470893) [25]. The estimated per-allele effect on consumption is modest in absolute terms — approximately 0.2 cups of coffee per day, with effects in the range of 0.03–0.32 cups depending on cohort and ancestry — but is reproducible and biologically coherent: faster metabolism appears to drive higher consumption, presumably because the subjective reinforcing effects of caffeine are short-lived in rapid metabolisers and need to be renewed more frequently [18,25]. From the standpoint of clinical pharmacology, the relevant insight is the inverse one: in a "slow" metaboliser, the same dose of caffeine produces a longer and more pronounced exposure, with a corresponding rise in the probability of anxiogenic, insomnia-inducing or cardiovascular adverse effects, particularly when caffeine is co-administered with substrates or inhibitors of the same enzyme — a question developed in detail in Section 5.

A further nuance concerns the relationship between CYP1A2 metabolic phenotype and observed cardiovascular outcomes. Several authors have suggested that slow metabolisers may be at greater risk of myocardial infarction and hypertension after high caffeine intake, although the evidence remains heterogeneous and conclusions depend strongly on the population studied [18,19]. In a recent meta-analysis discussed in the systematic review by Low and colleagues, the rs762551 AA genotype was associated with higher coffee intake particularly in Caucasian males and in younger age groups, but the magnitude and direction of the association varied between Asian and European samples [18]. The implication for clinical practice is that genotypic information may help, but should not be expected to determine, the prediction of individual responses to caffeine; rather, CYP1A2 genotyping appears most informative when integrated with detailed history, concurrent medications and, ideally, paraxanthine/caffeine metabolic ratios in plasma or saliva [19,26].

4.2. ADORA2A polymorphism — the pharmacodynamic axis

Whereas CYP1A2 governs how much caffeine is present in the circulation at any given time, the ADORA2A gene, located on chromosome 22q11.23, encodes the adenosine A2A receptor and is therefore directly relevant to how the central nervous system interprets the caffeine that reaches it. As established in Section 3, the A2A receptor is a principal site of action for the anxiogenic and arousal-related effects of caffeine, and is densely expressed in the striatum, cortex, thalamus and hippocampus, where it modulates dopamine D2 signalling, glutamatergic flow and several anxiety-relevant neurocircuits [20].

Within ADORA2A, the variant most consistently linked to caffeine response is rs5751876 (1976T>C, formerly 1083C>T, a synonymous coding SNP in exon 5) [18,19,20]. Carriers of the TT genotype have been reported, across several independent studies, to display a higher level of caffeine-induced anxiety than CC or CT carriers, and the same genotype has been linked

to panic disorder, to anxiety personality traits, to caffeine-related sleep disturbance and to differences in the startle reflex [20,21,22,23]. In a randomised, double-blind, placebo-controlled study of 102 light caffeine consumers conducted by Childs and colleagues, ingestion of 150 mg of caffeine produced a significantly greater rise in subjective anxiety (as measured on Visual Analog Scales) in TT homozygotes than in CC or CT carriers, with a significant association also detected for additional ADORA2A SNPs (rs2298383, rs4822492) and for a polymorphism in the DRD2 gene (rs1110976) [22]. The 50 mg dose did not induce appreciable anxiety, while the 450 mg dose induced anxiety in the majority of participants regardless of genotype, suggesting that the genotype-dependent susceptibility is most clearly visible at intermediate doses [22].

A subsequent larger study by Rogers and colleagues in 379 white European participants confirmed that rs5751876 TT carriers display a greater susceptibility to caffeine-induced anxiety, although in this study habitual coffee intake was higher rather than lower in TT subjects, suggesting that pre-existing tolerance may complicate the relationship between genotype and consumption [21]. Importantly, the anxiogenic response to caffeine appeared to diminish in medium-to-high habitual consumers even within the TT subgroup, indicating that substantial tolerance can develop to the anxiogenic action of caffeine, even in genetically vulnerable individuals, but at the price of caffeine abstinence reducing alertness rather than caffeine raising it above baseline [21]. The clinical reading of these data is that an ADORA2A TT genotype may best be thought of as a marker of latent vulnerability that becomes most evident when habitual consumption is low or when consumption is acutely interrupted (for example during hospitalisation), rather than as a deterministic predictor of caffeine avoidance.
The role of ADORA2A in caffeine-related sleep disturbance has been independently corroborated. In a pharmacogenetic study by Rétey and colleagues — discussed and replicated in a GWAS in over 2,400 Australian twins by Byrne and colleagues, and reviewed by Landolt — the distribution of CC and TT carriers differed between caffeine-sensitive and caffeine-insensitive subjects, with caffeine-induced sleep EEG changes appearing in a genotype-dependent manner despite equivalent caffeine concentrations in saliva [23]. ADORA2A polymorphisms have also been shown to modulate the rebound of NREM-sleep delta activity after sleep deprivation, suggesting a broader role for A2A receptor function in sleep homeostasis [23].

A systematic review by Keyvanloo Shahrestanaki and colleagues, encompassing 15 case–control studies and a total of 2,103 patients with anxiety disorders and 1,927 controls, concluded that rs5751876 (along with rs35060421 and several haplotypes involving rs2298383 and rs3761422) was associated with increased susceptibility to anxiety disorders, including panic disorder, agoraphobia and anxious personality traits, with effects that appeared partially mediated by ADORA2A signalling and partially by gene–gene interactions with other anxiety-relevant loci [20]. As the authors emphasise, results have been inconsistent across populations — significant associations have been reported in European and US samples but not in some Japanese cohorts — pointing to ethnic stratification of allelic frequencies and to the role of environment in modulating the phenotypic expression of genetic risk [20].

A particularly instructive feature of ADORA2A pharmacogenetics is its independence from hepatic metabolism. A patient with a "rapid" CYP1A2 genotype may have low circulating caffeine concentrations at any given time, yet, if also carrying the TT genotype at rs5751876, may experience disproportionate anxiogenic effects even at small doses, simply because the receptor on which the residual caffeine acts is hypersensitive to blockade. This dissociation between pharmacokinetic and pharmacodynamic profiles helps to explain why clinical history alone, focused on cups of coffee per day, may be a poor predictor of individual response and why some patients with apparently moderate intake present with disabling anxiety, palpitations or insomnia. The same logic supports the cautious appeal of paired CYP1A2/ADORA2A genotyping in selected clinical contexts (for example, in patients with treatment-resistant anxiety, in those with atypical responses to standard antidepressant doses or to clozapine, and in athletes with paradoxical responses to ergogenic caffeine doses), although routine adoption awaits firmer prospective evidence [19,24].

4.3. Integrating CYP1A2 and ADORA2A — a polygenic, context-dependent phenotype

The pharmacogenomic landscape of caffeine response is more nuanced than the dichotomous classifications often used in the literature. As recently summarised in the systematic review by Low and colleagues, at least eight genes (CYP1A2, ADORA2A, AHR, POR, ABCG2, CYP2A6, PDSS2 and HECTD4) have been associated with habitual caffeine consumption with effect sizes ranging from 3% to 32% per effect allele, while genes related to caffeine reward (BDNF, SLC6A4, GCKR, MLXIPL, DRD2, DAT1) contribute a further 2–5% per allele [18]. A study by Muñoz and colleagues in 31 professional handball players genotyped at both rs762551 and rs5751876 reported only one significant genotype × treatment interaction (for ball throwing from 7 metres), and concluded that the ergogenic response to acute caffeine intake in this sample was not appreciably modulated by either polymorphism — a finding that may reflect the limited statistical power of a study at a single dose in a homogeneous population, but that nevertheless tempers expectations of a simple genotype-to-phenotype map in caffeine response [24].

The picture that emerges from the convergence of these studies is therefore one of a polygenic, context-dependent phenotype, in which genotype, habitual intake, sex, smoking, age, comedications, hepatic function and disease state interact to determine an individual's effective sensitivity to caffeine. From a clinical perspective, this complexity does not diminish the relevance of pharmacogenetics — on the contrary, it suggests that any single biomarker is unlikely to be sufficient, and that integrated profiling, combined with careful history-taking and, where appropriate, therapeutic drug monitoring of caffeine and of co-administered psychotropics, may offer the most defensible path towards personalised management of caffeine intolerance. The remainder of this review proceeds from this framework, applying it first to the differential diagnosis of caffeine-related symptomatology (Section 5) and then to the pharmacokinetic interactions between caffeine and psychotropic medications (Section 6).

5. Clinical picture — caffeine as a great mimicker

The clinical phenotype produced by excessive or poorly tolerated caffeine intake is broad enough to overlap with several distinct nosological categories. Caffeine has, for this reason, been described in the older literature as a "great imitator" or "great mimicker" — a substance whose effects, when sufficiently pronounced, may be virtually indistinguishable from those of primary anxiety disorders, mood disorders with somatic anxiety, hyperthyroidism, paroxysmal arrhythmias, akathisia and, in some cases, the early phenomenology of serotonin syndrome [11,13]. Because the patient very often does not spontaneously connect a habitual stimulant with new or worsening symptoms, the clinician is left to perform what is, in essence, an act of careful differential diagnosis. The present section reviews three principal domains in which this differential reasoning is most consequential: anxiety phenomena, sleep architecture, and somatic and cardiovascular manifestations.

5.1. Anxiety phenomena — substance-induced presentations under DSM-5 and ICD-11

The diagnostic frameworks of both the DSM-5 and the ICD-11 explicitly acknowledge that caffeine may produce or aggravate anxiety symptomatology, and they reserve specific categories — caffeine-induced anxiety disorder and other caffeine-related disorders, respectively — for clinical presentations in which caffeine appears to be the proximate cause [11]. Empirically, the relationship between dose and anxiogenic effect is dose-dependent but non-linear, and the magnitude of the response is conditioned by genotype (notably ADORA2A rs5751876 TT, as discussed in Section 4), by habitual intake (with tolerance partially blunting the response) and by baseline anxiety traits [21,22].

A meta-analysis encompassing 14 studies and 546 participants synthesised in 2024 by Liu and colleagues reported that caffeine intake was associated with an overall elevated risk of anxiety in healthy individuals without psychiatric disorders (standardised mean difference 0.94, 95% CI 0.28–1.60), with a more modest effect at low doses (SMD 0.61, 95% CI 0.42–0.79) and a much larger effect at doses exceeding approximately 400 mg per day (SMD 2.86, 95% CI 2.50–3.22) [13]. Narrative reviews concur that caffeine intake tends to exacerbate anxiety symptoms, panic disorder and insomnia in vulnerable individuals, while at low doses, the effect on mood may be neutral or modestly positive [11,14].

The phenomenological overlap with generalised anxiety disorder (GAD) and panic disorder is striking. The somatic dimension of caffeine intoxication — sinus tachycardia, palpitations, fine tremor, restlessness, gastrointestinal disturbance, diaphoresis, paraesthesias and a subjective sense of dyspnoea or "air hunger" — partly recapitulates the somatic core of a panic attack, and patients commonly interpret these autonomic phenomena cognitively as evidence of a panic episode, fuelling a vicious circle in which catastrophic appraisal of physiological arousal triggers and sustains genuine anxiety [3,11,13]. From the standpoint of the underlying neurobiology, the mechanisms are coherent: caffeine produces excessive sympathetic activation through the disinhibition of adrenergic systems, while simultaneously stimulating the HPA axis and elevating circulating catecholamines (Section 3). It is therefore not surprising that patients

with caffeine intoxication may receive, in the absence of a careful dietary history, an initial diagnosis of GAD or of panic disorder, and may be prescribed anxiolytic therapy that addresses the symptom but not the cause.

The likelihood of this misclassification appears highest in two clinical scenarios. The first concerns patients with high or fluctuating caffeine intake who consult primary care or emergency services for episodes that they describe as "panic attacks": careful inquiry frequently identifies a temporal association between an episode and a recent burst of caffeine intake (for example, a pre-workout supplement, an energy drink combined with coffee, or an over-the-counter analgesic containing caffeine) [11,30]. The second concerns patients with pre-existing anxiety disorders, in whom caffeine has been repeatedly shown, in caffeine-challenge studies, to aggravate symptoms and to lower the threshold for panic provocation [11]. In patients with diagnosed panic disorder, even modest doses of caffeine may precipitate full-blown panic episodes, in line with the proposed sensitivity of A2A receptor-mediated mechanisms in this disorder [15,20].

A particularly instructive intersection between caffeine and psychotropic therapy is described in Section 6, where intoxication-like presentations may emerge as a consequence of pharmacokinetic interactions rather than from absolute dose. Briefly, the inhibition of CYP1A2 by fluvoxamine may produce a clinical picture that, from the bedside, closely resembles akathisia, the early phase of serotonin syndrome or worsening anxiety, but which is in fact a frank caffeine intoxication driven by impaired clearance [11,13]. The implication for the diagnostic process is that, in patients receiving CYP1A2-inhibiting psychotropics, a new or worsening anxiety presentation should prompt explicit quantification of caffeine intake rather than reflexive dose escalation of the psychotropic.

5.2. Disturbances of sleep architecture

The disruptive effects of caffeine on sleep are among the best-documented behavioural pharmacology phenomena in the literature, and they have been systematically quantified in recent meta-analyses and randomised controlled trials. A systematic review and meta-analysis of 24 controlled studies by Gardiner and colleagues reported that caffeine consumption reduced total sleep time by approximately 45 minutes and sleep efficiency by about 7%, increased sleep onset latency by approximately 9 minutes and wake after sleep onset by about 12 minutes [29]. The same analysis indicated that the duration and proportion of light sleep (N1) tended to increase modestly with caffeine intake (+6.1 minutes; +1.7%), while the duration and proportion of deep sleep (N3/N4, slow-wave sleep) decreased (−11.4 minutes; −1.4%) — a pattern consistent with the lay description of "shallower" sleep and a pattern likely to be experienced as unrefreshing morning awakenings [29].

A subsequent randomised, double-blind, placebo-controlled crossover trial conducted by the same group in 23 healthy males with moderate habitual caffeine intake examined the combined effects of dose (100 versus 400 mg) and timing (12, 8 and 4 hours before bedtime) on polysomnographically measured sleep [28]. No significant effect was observed for the 100 mg

dose at any timing, while the 400 mg dose produced significant delays in sleep initiation and alterations of sleep architecture when consumed within 12 hours of bedtime, with significantly greater sleep fragmentation when consumed within 8 hours of bedtime and a marked subjective reduction of perceived sleep quality (−34%) when consumed 4 hours before bedtime [28]. The authors translated these findings into evidence-based recommendations: a typical dose of approximately 100 mg of caffeine (one cup of coffee, 250 mL) may be tolerated up to about 8.8 hours before bedtime, while a standard pre-workout supplement serving (approximately 217.5 mg) should not be consumed within 13.2 hours of bedtime [29]. Importantly, the same trial showed a discrepancy between objective and subjective sleep measures, with participants frequently failing to perceive the disruption that polysomnography revealed [28] — a finding with direct implications for clinical history-taking, since patients may genuinely deny that "evening coffee disturbs my sleep" even when it demonstrably does.

The differential diagnosis of insomnia in patients with mood, anxiety or psychotic disorders is, for this reason, often more complicated than the symptomatic picture would suggest. Primary insomnia, insomnia in major depressive disorder, insomnia secondary to akathisia or to nocturnal restlessness from antipsychotic therapy, and caffeine-related insomnia may present with overlapping subjective complaints — difficulty initiating sleep, fragmented sleep, early morning awakenings and non-restorative sleep — yet have markedly different therapeutic implications. Caffeine-related insomnia, in particular, may be either misattributed to the underlying psychiatric disorder or to the index pharmacotherapy, with potential consequences ranging from inappropriate escalation of hypnotic medication to unwarranted changes of antidepressant or antipsychotic [11]. The growing body of evidence on individual variability — driven by CYP1A2 metabolic phenotype and by ADORA2A receptor genotype — provides a partial explanation for why two patients reporting the same intake may experience entirely different sleep outcomes [23,28]. In a patient with a slow-metaboliser genotype, even an afternoon coffee may exert a measurable effect on sleep architecture late into the night, while in a rapid metaboliser the same dose may have dissipated by bedtime.

A further clinically relevant consideration concerns the bidirectional relationship between sleep disturbance and caffeine consumption. The compensatory use of caffeine to mitigate the daytime consequences of poor sleep tends to perpetuate evening caffeine exposure, which in turn further compromises sleep — a cycle that is well described in the literature and that should be explicitly broken when planning the management of insomnia, regardless of its perceived primary aetiology [29,30].

5.3. Somatic symptoms — gastrointestinal, neuromuscular and cardiovascular phenomena

The somatic dimension of caffeine intolerance is varied and, in clinical practice, frequently the first reason for which patients seek medical attention. Gastrointestinal complaints are common and reflect, in part, the well-established capacity of caffeine to stimulate gastric acid secretion, with potential exacerbation of dyspepsia, peptic ulcer disease, erosive oesophagitis and gastro-oesophageal reflux at high or chronic intakes [3,15]. Diarrhoea and abdominal cramping may

also occur, and may be mistaken for irritable bowel syndrome until a careful history identifies caffeine as a contributing factor [3]. Neuromuscular phenomena — fine tremor (especially of the hands), increased muscle tone, myoclonic jerks, and a subjective sense of restlessness — may overlap phenomenologically with akathisia, hypocalcaemia or hyperthyroidism, and warrant explicit consideration when atypical hyperkinetic features arise in a patient receiving antipsychotic medication [11,15].

The cardiovascular dimension is particularly important and deserves separate emphasis. Although chronic moderate coffee consumption is associated, in observational and meta-analytic literature, with reductions in cardiovascular morbidity and mortality, acute caffeine ingestion may produce sinus tachycardia, mild blood pressure elevations (typically 5–15 mmHg systolic and 5–10 mmHg diastolic at doses exceeding 250 mg in non-habituated individuals), and an increased frequency of supraventricular ectopy [3,27]. Premature ventricular contractions may also occur in susceptible individuals. The arrhythmogenic mechanisms include caffeine-induced catecholamine release, β1-adrenergic stimulation, intracellular calcium mobilisation via ryanodine receptors in cardiac muscle and inhibition of phosphodiesterase activity with consequent elevation of cyclic AMP [27]. The combined effect of these mechanisms is most clearly observable at supraphysiological doses (above ~9–13 mg/kg), but lower doses may suffice in patients with underlying structural heart disease, with electrolyte disturbance or with concurrent stimulant use [27].

A clinically instructive perspective on the upper boundary of caffeine toxicity is offered by case reports of acute caffeine intoxication. A representative recent observation involves a 25-year-old woman who ingested an estimated 12 g of caffeine in tablet form and presented with palpitations, agitation, dizziness and repeated vomiting; on examination she showed arterial hypotension (90/60 mmHg) and marked sinus tachycardia (150 beats/min), with a measured plasma caffeine concentration of 177 μg/mL, well above the threshold of toxicity (15–20 μg/mL) and approaching the lethal range (≥80–100 μg/mL) [31]. The clinical course evolved to convulsive syndrome, coma, ventricular tachycardia, exotoxic shock and fatal toxic cardiomyopathy despite intensive care and advanced resuscitation [31]. While such cases are uncommon, they illustrate the pharmacological space available for severe caffeine effects when total dose is sufficient or when accumulation is permitted by pharmacokinetic interactions.

Between these extremes — a mildly anxious patient with sinus tachycardia after three cups of coffee, and a fatal intoxication after intentional ingestion of dozens of tablets — lies a broad clinical territory in which the same substance may produce phenomenology that, depending on the patient's underlying biology and concurrent pharmacotherapy, may be confused with anxiety disorders, with akathisia, with paroxysmal supraventricular tachycardia, with hyperthyroid storm or with serotonin syndrome [11,13,27]. The pragmatic clinical lesson is the same in each case: when a patient presents with somatic, anxiety-related or sleep-related symptoms whose cause is not immediately self-evident, an explicit, quantitative inventory of caffeine intake — including hidden sources such as pre-workout supplements, fat burners, energy drinks and over-the-counter analgesics — should be performed before more invasive investigations or more aggressive pharmacotherapy are considered [30].

6. Pharmacokinetic interactions of caffeine with psychotropic medications

Pharmacokinetic interactions between caffeine and psychotropic medications occupy the analytical core of this review. Their importance derives from the convergence of three factors that, in the routine outpatient and inpatient setting, are seldom considered together: the near-ubiquitous nature of caffeine exposure, the narrow therapeutic indices of several relevant psychotropic agents, and the disproportionate dependence of these agents on a single hepatic enzyme, cytochrome P450 1A2 (CYP1A2). When the same enzyme is responsible for the elimination of both caffeine and a co-administered psychotropic drug, even modest perturbations of dietary intake or of competing enzyme inhibition may produce shifts in plasma concentration whose clinical consequences range from inconspicuous to life-threatening [32,38].

The present section reviews these interactions across two principal axes. The first concerns competition for CYP1A2 as substrate, illustrated most clearly by clozapine and olanzapine. The second concerns inhibition of CYP1A2 by co-prescribed psychotropics, with fluvoxamine as the paradigmatic example. A third subsection addresses interactions of moderate clinical importance involving other antidepressants and the antibiotic ciprofloxacin, which is frequently prescribed in patients on antipsychotic therapy.

6.1. Competition for CYP1A2 — interactions with antipsychotics (clozapine and olanzapine)

Clozapine, the gold-standard antipsychotic for treatment-resistant schizophrenia, is metabolised predominantly via N-dealkylation to its principal metabolite N-desmethylclozapine (norclozapine), a reaction catalysed largely by CYP1A2 (with secondary contributions from CYP2C19, CYP3A4 and CYP2D6) [33,36,40,42]. The therapeutic window of clozapine is narrow — a serum concentration of approximately 350 ng/mL is generally regarded as the lower bound of therapeutic efficacy, while concentrations above 1000 ng/mL are typically considered an alert threshold for central nervous system toxicity and concentrations exceeding ~1300 ng/mL are associated with marked seizure risk [36,41]. Clozapine pharmacokinetics are subject to substantial inter-individual variability — more than 45-fold across long-term treatment in some reports — driven by sex, smoking status, CYP1A2 genetic variation, age, ancestry, body mass index, infection state and co-administered drugs [37,42].

Because caffeine is itself a CYP1A2 substrate, the two compounds compete for the same enzymatic pathway. A controlled study by Hägg and colleagues in 12 non-smoking healthy male volunteers — using an open-label randomised crossover design with a single 12.5 mg dose of clozapine taken with or without 400–1000 mg/day of caffeine (mean 550 mg/day) — reported a 19% increase in clozapine AUC and a 14% decrease in oral clearance during the caffeine phase, together with significant decreases in the ratios of desmethyl-clozapine and clozapine-N-oxide to clozapine (–18% and –23%, respectively) [34]. These effects, although moderate in healthy volunteers, were positively correlated with the paraxanthine/caffeine ratio in serum, an established marker of CYP1A2 activity, and the authors concluded that caffeine in daily doses

of 400–1000 mg may inhibit clozapine metabolism to a clinically meaningful extent in individual patients [34]. A separate observational study, in which CYP1A2 activity was estimated by a caffeine metabolic ratio in overnight urine in 18 patients with schizophrenia receiving clozapine, confirmed a significant negative association between CYP1A2 activity and both dose-corrected clozapine ($rs = –0.87$, $p < 0.01$) and norclozapine ($rs = –0.76$, $p < 0.01$) concentrations, with non-smokers showing 3.2-fold higher clozapine and 2.3-fold higher norclozapine concentrations than smokers [37].

6.1.1. Clinical scenario A — caffeine load and clozapine toxicity

The clinical consequences of an abrupt increase in caffeine intake in a patient stably treated with clozapine have been illustrated by a particularly striking case report by Yartsev and Peisah, in which a 34-year-old man with chronic schizophrenia who had been stable for five years on 400 mg of clozapine modified his dietary habits over three weeks and began consuming caffeinated energy drinks at an estimated daily intake of 600 mg of caffeine (four cans of Red Bull) [33]. He presented to the emergency department with a depressed level of consciousness, severe metabolic acidosis, acute respiratory failure, raised inflammatory markers and acute renal failure attributed to interstitial nephritis, with a peak measured clozapine concentration of 1796 ng/mL — well above the alert threshold of 1000 ng/mL [33]. The course required intubation, mechanical ventilation, continuous veno-venous haemodiafiltration and a prolonged ICU admission [33]. While the authors note that polypharmacy and recent withdrawal of alcohol (a CYP3A4 inducer) may have contributed by removing alternative metabolic pathways, the temporal association with a marked increase in caffeine intake is striking. The case is congruent with experimental findings indicating that caffeine restriction can reduce clozapine plasma levels by about 46% in chronically treated patients [33].

The pragmatic clinical implication is that in patients receiving clozapine — particularly those with treatment-resistant schizophrenia, in whom dose optimisation is itself a delicate exercise — any significant change in caffeine intake (typically defined in the literature as more than one cup of coffee or two caffeinated soft drinks per day) should be flagged and the question of therapeutic drug monitoring re-opened [33,41]. The symptomatology of caffeine-induced clozapine toxicity may include sedation, hypersalivation, postural hypotension, hyperglycaemia, seizures (particularly above 500–1300 ng/mL), interstitial nephritis, and, in extreme cases, multiorgan failure [33,41,42].

6.1.2. Clinical scenario B — caffeine withdrawal and loss of clozapine effect

The mirror image of this scenario is equally important. Acute reduction or cessation of caffeine intake — a common occurrence during psychiatric or somatic hospitalisation, during pregnancy planning or simply during a self-initiated "detoxification" — may lead to a decrease in plasma clozapine concentration, with potential re-emergence of psychotic symptomatology. In schizophrenic patients reported in the original literature, withdrawal of habitual caffeine intake was associated with an average ~37% decrease in clozapine concentrations and an increase of about 120% in the desmethyl-clozapine/clozapine ratio after five days [34]. Particularly in

patients who have achieved stable control with combined dietary and pharmacological exposure, such a shift may be misattributed to non-adherence or to a primary deterioration of the underlying disorder, and may trigger unnecessary dose escalation rather than recognition of a pharmacokinetic reset.

6.1.3. Olanzapine and other CYP1A2-metabolised antipsychotics

Olanzapine, although metabolised through both UGT1A4 glucuronidation and CYP1A2 N-demethylation, also exhibits a similar pharmacokinetic susceptibility to changes in CYP1A2 activity, including those driven by smoking initiation or cessation, by infection-related cytokine release, and by competing CYP1A2 substrates such as caffeine [38,42]. Other antipsychotics with relevant CYP1A2 contributions (for example, asenapine and, to a lesser extent, haloperidol) deserve consideration on the same principles, although the clinical literature on direct caffeine–antipsychotic interactions remains most robust for clozapine.

6.2. Inhibition of CYP1A2 by antidepressants — the central role of fluvoxamine

If the clozapine–caffeine interaction is the most clinically dramatic example of substrate competition, fluvoxamine is the most extensively documented example of enzymatic inhibition. Fluvoxamine, a selective serotonin reuptake inhibitor used in major depressive disorder, obsessive-compulsive disorder, panic disorder and social phobia, is a potent inhibitor of CYP1A2 both in vitro and in vivo; secondary inhibition of CYP2C19 (and, to a lesser extent, of CYP2C9, CYP2D6 and CYP3A4) is also reported [32,35,36,40].

The magnitude of fluvoxamine's effect on caffeine clearance is striking. In a randomised, double-blind, four-way crossover study of seven healthy subjects who received single 250 mg doses of caffeine with or without fluvoxamine (four doses of 100 mg over two days), Culm-Merdek and colleagues reported a reduction in apparent oral caffeine clearance from 105 to 9.1 mL/min (mean difference 95.7 mL/min; $p < 0.01$) and an extension of caffeine elimination half-life from 4.9 hours to 56 hours (mean difference 51 hours, 95% CI 26–76 hours; $p < 0.01$) [35]. In other words, the half-life of caffeine was extended by an order of magnitude during fluvoxamine therapy. A similar extension — from approximately 5 hours to 31 hours — was reported in earlier work cited by Yoshimura and colleagues, with a parallel ~80% reduction in total caffeine clearance [39]. Christensen and colleagues, cited in the recent review by Truong and collaborators, observed that a single 20 mg dose of fluvoxamine suppressed approximately 75% of CYP1A2 activity, with a fivefold increase in the area under the plasma caffeine concentration–time curve after a 20 mg fluvoxamine dose and a twofold increase after a 10 mg dose [32]. These data converge on a clear conclusion: under fluvoxamine therapy, the customary three-to-five-hour half-life of caffeine may be extended to several tens of hours, with corresponding accumulation across the day and across successive doses.

6.2.1. The phenomenon of "paradoxical activation" and its clinical mimicry

The most clinically meaningful consequence of this pharmacokinetic shift is that, in a patient initiated on fluvoxamine while continuing habitual caffeine intake, the customary "morning coffee" becomes, in effect, a daily and increasing dose of an unrecognised stimulant. The accumulating caffeine load may produce a clinical picture of paradoxical activation: psychomotor agitation, fine tremor, palpitations, sleep onset latency prolongation, fragmented sleep, dyspepsia, and an anxious, restless quality of mood [11,32,35]. From the bedside, this presentation may be readily mistaken for akathisia, for the early features of serotonin syndrome, or for treatment-emergent worsening of the underlying anxiety or depressive disorder. The clinician's reflexive response — either to add an additional anxiolytic or to escalate the dose of fluvoxamine — is in fact likely to aggravate the very phenomenology it is intended to alleviate, since fluvoxamine dose escalation will further inhibit CYP1A2 and will further extend caffeine half-life.

Notably, the same crossover study by Culm-Merdek and colleagues, despite documenting the marked pharmacokinetic interaction, did not detect statistically significant augmentation of the pharmacodynamic effects of caffeine (psychomotor performance, alertness, EEG beta activity) under acute single-dose conditions [35] — a finding that, while reassuring at face value, the authors themselves cautioned does not exclude clinical consequences from extensive caffeine accumulation with daily, habitual ingestion in fluvoxamine-treated patients. In a steady-state observational study by Yoshimura and colleagues in 30 patients with major depressive disorder, significant positive correlations were observed between plasma fluvoxamine concentrations and plasma caffeine levels ($rho = 0.72$, $p < 0.01$), confirming that the interaction is clinically detectable in real-world conditions [39].

6.2.2. Fluvoxamine as a deliberate adjunct to clozapine

A particularly instructive intersection of the two preceding axes — substrate competition by caffeine and enzyme inhibition by fluvoxamine — is the established psychiatric practice of using fluvoxamine as a deliberate add-on to clozapine. By inhibiting CYP1A2-mediated N-dealkylation, fluvoxamine reduces the formation of norclozapine and elevates the clozapine/norclozapine ratio, with the dual aim of reducing tablet burden, improving adherence, and mitigating norclozapine-mediated metabolic side effects [36,40]. In a recent observational study of 67 patients with treatment-resistant psychiatric disorders, van Weringh and colleagues documented that fluvoxamine co-administration increased the dose-adjusted clozapine concentration (C/D) from a median of 0.70 to 1.72, the dose-adjusted norclozapine concentration from 0.43 to 0.80, and the clozapine/norclozapine ratio from 1.66 to 2.16 (all $p < 0.001$), with median fold increases of 2.51 for clozapine, 1.92 for norclozapine, and 1.27 for the clozapine/norclozapine ratio [36]. The authors recommended fluvoxamine initiation at 25 mg with a concomitant 50% reduction of the clozapine dose [36].

A complementary case series in four children with severe psychiatric disorders (intellectual disability with Tourette syndrome, early-onset schizophrenia, ASD with psychosis, catatonia)

demonstrated that fluvoxamine adjunction, individualised on the basis of CYP genotyping, allowed therapeutic clozapine concentrations to be reached at substantially lower doses, with marked clinical improvement [40]. The same series, however, also reported a severe tolerability issue in one child, in whom fluvoxamine inhibition of CYP2D6 led to overdose of co-administered levomepromazine — a reminder that fluvoxamine's CYP inhibitory profile is broad, that adjunction requires careful monitoring of all co-prescribed CYP-metabolised drugs, and that pharmacogenomic testing may help to guide individualised dosing [40].

In the present context of caffeine intolerance, the clinical synthesis is that patients receiving the fluvoxamine–clozapine combination are doubly susceptible to caffeine accumulation, since both the inhibition of caffeine metabolism by fluvoxamine and the competition for CYP1A2 by clozapine act in the same direction. In such patients, the explicit quantification of dietary caffeine intake and, where feasible, paraxanthine/caffeine ratio measurement, take on particular importance.

6.3. Moderate interactions — other antidepressants and the ciprofloxacin–clozapine paradigm

Beyond fluvoxamine, several other antidepressants exhibit milder but clinically relevant interactions with caffeine. In a comprehensive recent review of caffeine–antidepressant interactions, Truong and colleagues describe that fluoxetine, escitalopram and paroxetine may augment antidepressant effects through pharmacodynamic and pharmacokinetic mechanisms, that paroxetine in particular may show an increase in serum concentration in the presence of caffeine, and that tricyclic antidepressants (especially clomipramine, desipramine and imipramine) exert variable inhibitory effects on CYP1A2 with potential to reduce caffeine clearance [32]. Among serotonin–noradrenaline reuptake inhibitors, duloxetine is a moderate CYP1A2 inhibitor and may, by analogy with fluvoxamine, prolong caffeine half-life — although the magnitude of effect is substantially smaller [19,32]. Agomelatine, whose metabolism is largely CYP1A2-dependent, is itself sensitive to changes in CYP1A2 activity, with the implication that potent CYP1A2 inhibitors (including fluvoxamine and oral oestrogens) are formally contraindicated in patients receiving agomelatine; the converse interaction — agomelatine effect on caffeine — is of lesser magnitude but warrants consideration in patients with already symptomatic caffeine sensitivity [32]. Venlafaxine appears to interact minimally with caffeine on the pharmacokinetic plane [32], while monoamine oxidase inhibitors (phenelzine, tranylcypromine) carry an increased risk of hypertensive reactions in association with high-dose caffeine [32].

The ciprofloxacin–clozapine paradigm deserves a brief but explicit mention here, as it sits at the same pharmacological intersection. Ciprofloxacin is a potent CYP1A2 inhibitor, and its co-prescription with clozapine has been associated with severe rises in clozapine plasma concentration and with at least one reported fatality [41]. In a recent case report by Waters and colleagues, a 57-year-old woman maintained on clozapine 325 mg nightly experienced a near-tripling of clozapine concentrations (from 281 ng/mL to 692 ng/mL) after the introduction of ciprofloxacin for treatment of abdominal wall cellulitis, despite a pre-emptive 38% reduction

of the clozapine dose [41]. The authors describe how the situation was managed with frequent immunoassay-based clozapine concentration monitoring — a methodologically faster alternative to liquid chromatography–mass spectrometry — and underline that concurrent changes in smoking status, in caffeine intake, and in infection (which itself reduces CYP1A2 expression by up to 90% through inflammatory cytokine release) all act in the same direction and may combine to produce rapid and clinically meaningful elevation of clozapine levels [41]. The ciprofloxacin example is included here because it instantiates, in the antibiotic setting, the same pharmacological principle that drives the caffeine–clozapine and the fluvoxamine–clozapine interactions: a narrow-window CYP1A2 substrate in combination with a potent or competing inhibitor produces effects of greater magnitude than the modest interaction observed for either factor in isolation.

6.4. Synthesis — caffeine as a "hidden" variable in psychopharmacology

Taken together, the data reviewed in this section converge on a coherent message: caffeine is not a pharmacologically neutral background to psychotropic therapy, and changes in caffeine intake — whether driven by lifestyle modification, by hospitalisation, by switching to decaffeinated products, or by the introduction of a CYP1A2-inhibiting drug — may have effects on the plasma concentrations of clozapine and several antidepressants that are comparable in magnitude to clinically standard dose adjustments. In particular, the combination of fluvoxamine and clozapine, while pharmacologically useful in selected contexts, redoubles the relevance of explicit caffeine quantification, and the introduction of ciprofloxacin in a patient receiving clozapine should prompt the same precautionary attitude. As discussed in Section 7, these mechanistic insights translate naturally into a small number of practical recommendations — most of which can be implemented at no additional cost — for the routine psychiatric interview and for therapeutic drug monitoring.

7. Dietary aspects and the medical interview — the significance of "hidden" caffeine

The pharmacodynamic, pharmacogenomic and drug-interaction considerations developed in Sections 3–6 share a single methodological premise: that the clinician knows, with reasonable accuracy, how much caffeine a patient is actually consuming. In day-to-day practice, this premise is rarely satisfied. Caffeine is unique among psychoactive substances in being virtually unregulated, socially normalised, ubiquitous across both food and over-the-counter (OTC) pharmaceutical preparations, and quantitatively variable to a degree that defeats most colloquial measures of exposure. Translating "I have a few coffees in the morning" into a pharmacologically meaningful daily dose is, in practice, an exercise in careful, sometimes laborious, history-taking. The present section reviews the principal sources of this measurement imprecision, with particular attention to "hidden" caffeine and to the modulatory role of co-ingested phytochemicals.

7.1. The illusion of "cups per day" — quantitative variability of dietary caffeine

The most popular metric used in the clinical interview and in epidemiological studies — the number of cups of coffee or tea consumed per day — is, in pharmacological terms, an imprecise variable. Reported caffeine contents per serving of brewed coffee span a remarkably wide range. In a Polish study of 299 coffee samples from franchise shops and home-brewed preparations, Wierzejska and Gielecińska reported that "takeaway" coffees contained, on average, approximately three times more caffeine than home-brewed coffees ($p < 0.005$), with Americano coffee identified as the "strongest" preparation (mean 143 mg of caffeine per serving) and brews made by pouring hot water over a teaspoon of ground coffee as the "lightest" (mean 23 mg per serving) [44]. Over 200 mg of caffeine per single serving was found in approximately 4% of samples; for individuals consuming four to five take-away servings of many coffee types per day (espresso excepted), the daily caffeine intake would exceed the EFSA threshold of 400 mg per day [44].

The international literature supports this variability. A systematic review by Olechno and colleagues of factors influencing caffeine content in coffee brews documented that, depending on species (Arabica versus Robusta, with Robusta typically containing 1.4× more caffeine), brewing method (French press, espresso, drip, cold brew, percolation, AeroPress, siphon), water temperature and pressure, water-to-coffee ratio, degree of roasting and grinding fineness, the caffeine content per litre of brew may vary by approximately two orders of magnitude — from below 0.2 g/L for some Arabica preparations to over 10 g/L for blends of Arabica and Robusta in concentrated espresso shots [45]. In a 2018 review, Bułdak and colleagues similarly noted that caffeine concentration in coffee may range between 72 and 130 mg per 240 mL of brewed coffee, between 58 and 76 mg in a single shot of espresso, and between 152 and 232 mg per "barista" serving [46]. The dePaula and Farah review confirmed that *C. canephora* (Robusta) seeds typically contain 40–70% more caffeine than *C. arabica* seeds, and that post-harvest processing, roasting profile and brewing technique add further layers of variability [6]. National averages also differ markedly: caffeine per "standard cup" is reported as approximately 140 mg in Northern Europe, 85 mg in the United States and 50 mg in Southern Europe [44].

Earlier work by Stavric and colleagues offered a particularly instructive empirical demonstration of this measurement problem. In a household study of 58 home-prepared coffee and tea samples in Ottawa, daily caffeine intakes among the women surveyed ranged from 49 mg to 1022 mg per day [49]. The authors compared estimates based on the conventional assumption of 80 mg per cup with the actual intakes obtained from chemical analysis: for individuals reporting "three cups of coffee" per day, only about 25% would have been correctly classified within the expected range, while 39% would have been overestimated and 36% underestimated [49]. The implication is that conventional "cups per day" estimates may misclassify a substantial proportion of patients with respect to the dose–response thresholds relevant to clinical decisions.

Other contextual variables further widen the range. Tea preparation, for instance, is highly sensitive to steeping time, with caffeine concentrations differing substantially between two- and

five-minute infusions [49]. Energy drinks contain a wide range of caffeine concentrations, typically between 80 and 200 mg per serving — and exceeding 300 mg per container in some products — and are frequently consumed rapidly, with synergistic ingredients such as taurine, guarana, ginseng, and B vitamins that, in combination, may potentiate cardiovascular and central effects [7,31,47]. From the standpoint of the clinical interview, the practical implication is that any attempt to quantify caffeine intake should ideally specify (i) the type of beverage, (ii) the brewing method, (iii) the typical serving volume, and (iv) the frequency of consumption across the day, rather than relying on a single global number of cups.

7.2. Hidden sources of caffeine — supplements, fat burners, OTC analgesics and energy drinks

Beyond the obvious dietary sources, an increasingly large and increasingly heterogeneous category of "hidden" caffeine sources deserves explicit consideration. Caffeine is added to a growing range of dietary supplements, weight-loss preparations, pre-workout formulas, energy gels, energy chews and even non-food consumer products [12,47]. Importantly, the labelled caffeine content of such products may diverge substantially from the actual content. A Polish analytical study by Kalisz and colleagues, in which six dietary supplements and one combined paracetamol–caffeine pharmaceutical preparation were assayed using ultra-high-performance liquid chromatography, reported that the caffeine content of the tested dietary supplements was 4–35% higher than the declared amount in most cases, while the medicinal product was accurate to within 0.4% relative standard deviation [43]. Earlier work cited in the same study had documented even wider divergences in dietary supplements, with caffeine contents ranging from 58% to 103% of label-declared values, and in some products diverging from declared values by as much as –20% to +40% [43]. The practical implication is that a patient who reports taking "one pre-workout serving" may, in reality, be receiving a dose that differs substantially from the printed declaration on the package, with corresponding uncertainty as to the total daily intake.

Pre-workout supplements are particularly noteworthy as a source of high-dose caffeine in subgroups not always identified by routine history. The International Society of Sports Nutrition position stand on caffeine notes that pre-workout formulas, caffeinated chewing gums, energy gels, mouth rinses and energy drinks have been demonstrated to enhance anaerobic and aerobic performance, but also that doses of 3–6 mg/kg body mass — and in some products substantially more — are commonly delivered in a single serving, with caffeine content per dose ranging up to and beyond 300 mg [47]. A standard serving of a pre-workout supplement (approximately 217.5 mg of caffeine) administered late in the day was identified by Gardiner and colleagues as a category of caffeine intake that should not be consumed within approximately 13.2 hours of bedtime to avoid measurable disruption of sleep [29]. From the perspective of caffeine intolerance, the combination of a high single dose, often with synergistic stimulants (synephrine, taurine, β-alanine, yohimbine), and a typically high-arousal context (intense exercise), may amplify the somatic and cardiovascular phenomenology described in Section 5 [10,47,48].

Energy drinks remain a particularly important hidden source. Their global lifetime prevalence has been estimated at 54.7% in a recent systematic review and meta-analysis, with adolescents and young adults the most exposed populations [7]. Beyond the absolute dose, the combination of caffeine, taurine, glucuronolactone, guarana, ginseng, *Ginkgo biloba* and high sugar content presents a complex pharmacological mixture in which the contribution of caffeine cannot be cleanly isolated [7]. Acute fatal intoxications attributable in part to high-dose caffeine ingestion from concentrated tablets or supplement combinations have been described in the recent forensic and toxicological literature [31].

Over-the-counter analgesic preparations represent a third, frequently underrecognised, source. Combination products for headache and pain — including those containing paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) — often include caffeine as an adjuvant, on the basis that caffeine may increase analgesic potency by up to 40% [30,38]. Doses of caffeine in such preparations typically range from 30 mg to 65 mg per tablet, with prescription headache formulations such as Fiorinal, Orphenadrine or Synalgos containing similar amounts, and dedicated stimulant OTC tablets such as NoDoz™ or Vivarin™ containing 200 mg per tablet [30]. A patient with chronic headache who consumes several caffeine-containing analgesic doses per day, in addition to coffee and tea, may readily exceed 400 mg of daily caffeine without being aware of doing so. The same is true of slimming and "fat-burner" supplements, in which caffeine is often combined with synephrine from bitter orange and other thermogenic substances, with potential additive cardiovascular effects [12].

From the clinical standpoint, this constellation of hidden sources implies that the routine history should explicitly include questions about pre-workout supplements, fat-burner products, energy drinks, OTC pain medications (with attention to combination preparations), prescription analgesic combinations, herbal stimulant products such as guarana, ephedra-substitute preparations, and weight-loss supplements. In patients with new or unexplained anxiety, insomnia or palpitations — and particularly in those receiving CYP1A2-relevant psychotropic therapy — such an inventory may prove diagnostic without the need for additional investigations.

7.3. Phytotherapy and modulation — the natural matrix versus synthetic anhydrous caffeine, and the L-theanine paradigm

A subtler aspect of caffeine intake concerns the pharmacological consequences of the *form* in which it is consumed. Caffeine ingested in the natural matrix of a brewed beverage, particularly tea and coffee, is co-administered with a complex array of bioactive compounds — chlorogenic acids, cafestol, kahweol, trigonelline, melanoidins, polyphenols, theobromine and L-theanine — which may modulate its absorption, its central nervous system effects and its peripheral consequences [6,46]. By contrast, synthetic anhydrous caffeine ingested in capsule, tablet or powdered supplement form is delivered as a single isolated compound, and tends to be associated with a more rapid plasma peak and with a sharper subjective effect [47,48].

The pharmacokinetic literature suggests several mechanistic considerations. Caffeine absorption from solid food and from beverages such as cola or chocolate appears to be delayed relative to absorption from capsules, with Tmax values reported between 1.5 and 2 hours for cola and chocolate compared with approximately 30 minutes for capsule formulations, and Cmax values approximately 25% lower [19,47]. Caffeine absorption from coffee and tea, by contrast, is reasonably rapid (Tmax 30–60 minutes), but the co-ingested polyphenols in coffee and the L-theanine in tea may shape the subjective and electroencephalographic response in a manner that is not fully captured by plasma caffeine alone [6,46]. The clinical observation that a "cup of strong tea" and a "single shot of espresso" containing approximately equivalent amounts of caffeine may produce quite distinct subjective effects in the same individual reflects, at least in part, this pharmacological asymmetry.

The role of L-theanine — a non-protein amino acid characteristically present in *Camellia sinensis* and accounting for approximately 1–2% of the dry weight of green tea leaves — is of particular relevance in the present narrative. Although the dedicated trial literature on L-theanine remains modest, several mechanistic and behavioural studies have suggested that L-theanine may exert a modulatory effect on glutamatergic and GABAergic neurotransmission, and may attenuate selected anxiogenic and cardiovascular effects of caffeine while preserving its alerting and cognitive-enhancing effects [15]. The proposed mechanisms include facilitation of α-band electroencephalographic activity, increases in central GABA availability, and modulation of glutamate receptor signalling — actions that, while convergent with caffeine on the dimension of alertness, may diverge from it on the dimension of subjective anxiety [15]. The clinical implication, formulated cautiously and pending firmer randomised evidence, is that the same dose of caffeine ingested as green tea may be better tolerated by anxiety-prone or pharmacogenetically susceptible patients than the same dose ingested as a pre-workout supplement or a strong espresso, in part because the co-ingested L-theanine may exert a partial buffering effect on the anxiogenic component.

A complementary consideration concerns chlorogenic acids and other coffee polyphenols, which appear to contribute to several of the observed metabolic and cardiovascular benefits attributable to habitual coffee consumption — benefits that, in epidemiological studies, are observed for decaffeinated coffee almost as much as for caffeinated coffee [46,50]. The implication is that recommendations should differentiate between the "caffeine dose" and the "coffee dose" — a distinction that, while routinely blurred in everyday speech, has clear pharmacological and dietetic implications. In a patient with documented caffeine intolerance who nevertheless wishes to maintain the cultural and social practice of coffee drinking, switching to decaffeinated coffee may preserve much of the polyphenolic profile while reducing the methylxanthine load.

It is worth emphasising that none of these phytochemical modulations should be interpreted as licence for unrestricted caffeine intake. Their role, as it emerges from the available evidence, appears to be one of attenuating rather than negating the pharmacological effects of caffeine. In a patient genetically predisposed to anxiogenic responses (ADORA2A TT genotype, see Section 4.2), or in a patient receiving fluvoxamine (Section 6.2), the modulatory contribution

of L-theanine or of co-ingested polyphenols is unlikely to fully offset the underlying pharmacokinetic or pharmacodynamic vulnerability.

7.4. Practical implications for the medical interview

Taken together, the evidence reviewed in this section converges on a small number of practical recommendations for the routine medical interview, applicable across psychiatry, cardiology, internal medicine and primary care. First, the question "How much coffee do you drink?" should be expanded to a structured inventory specifying beverage type, brewing method, typical serving volume, and frequency across the day. Second, this inventory should explicitly include energy drinks, pre-workout supplements, fat-burner products, herbal stimulant preparations, and OTC and prescription analgesic combinations. Third, in patients receiving CYP1A2-relevant psychotropic medication (clozapine, olanzapine, agomelatine, duloxetine, fluvoxamine), changes in caffeine intake of more than approximately one cup of coffee or two cans of caffeinated soft drink per day should be flagged as a potential pharmacokinetic perturbation warranting clinical attention and, where appropriate, therapeutic drug monitoring [33,38,41]. Fourth, when a patient presents with anxiety, insomnia, palpitations or somatic complaints whose cause is not immediately self-evident, an explicit attempt to quantify daily caffeine intake — including hidden sources — should precede more elaborate diagnostic investigation [11,30]. Fifth, in selected cases, the distinction between caffeine from a complex natural matrix and synthetic anhydrous caffeine in supplement form may be clinically meaningful, and the corresponding dietary recommendation may need to specify not only the dose but also the format [6,46,47].

These recommendations are not, in themselves, novel. They do, however, reflect a recurring observation that the formal pharmacological literature on caffeine — rich and methodologically sophisticated — sits uneasily against routine clinical practice, in which caffeine intake is rarely quantified with the precision that its pharmacology warrants. The closing section of this review (Section 8) integrates these practical considerations with the mechanistic and pharmacogenomic insights developed earlier into a tentative clinical algorithm.

8. Conclusions and implications for clinical practice

The evidence assembled across the preceding sections supports a coherent and clinically actionable thesis: caffeine, although universally available and culturally normalised, is a pharmacologically active substance whose biological effects, inter-individual variability and capacity for interaction with psychotropic medications are quantitatively comparable to those of agents that are subject to far greater clinical attention. Caffeine intolerance — understood not as a single entity but as a spectrum of polygenic, metabolic and pharmacodynamic phenomena — appears to be neither rare nor benign, and its recognition seems to depend on a small number of changes in the way the routine medical interview is conducted, in the way pharmacogenomic information is integrated into clinical reasoning, and in the way differential diagnosis is constructed in patients presenting with anxiety, insomnia or atypical responses to

psychotropic therapy. The present section sets out the principal practical implications, framed cautiously and in the awareness of the methodological limitations inherent in a narrative review.

8.1. A structured caffeine inventory as part of the routine psychiatric and cardiological interview

The single most consequential implication of this review is a methodological one. The colloquial question "How much coffee do you drink?" is, in pharmacological terms, of limited value. Caffeine content per serving may vary by approximately one order of magnitude across coffee preparations [44,45,49], and even within a single household, the actual daily intake estimated from the conventional assumption of 80 mg per cup misclassifies a majority of patients [49]. The proposed structured inventory — applicable across primary care, psychiatry, cardiology and internal medicine — should specify, for each caffeine source: (i) the type of beverage or preparation (coffee species and method, tea variety and steeping time, cola or energy drink brand, pre-workout or fat-burner supplement, OTC analgesic combination); (ii) the typical serving size; (iii) the time of day at which it is consumed; and (iv) the approximate frequency across the week. In selected patients, completion of a one-week dietary diary together with quantitative reference tables (for example, mean caffeine values from authoritative sources such as the EFSA opinion or recent peer-reviewed analyses) may produce a substantially more accurate exposure estimate than retrospective recall [5,44].

The argument for elevating this inventory from optional to obligatory is most compelling in two clinical situations. The first concerns the initiation of selective serotonin reuptake inhibitors with potent CYP1A2 inhibitory activity, of which fluvoxamine is the paradigmatic example. As reviewed in Section 6, fluvoxamine may extend the half-life of caffeine from approximately 5 hours to several tens of hours, with corresponding accumulation and a paradoxical activation that may mimic akathisia, serotonin syndrome or worsening anxiety [32,35,39]. A pre-treatment caffeine inventory permits either explicit caffeine reduction or interpretation of subsequent symptomatology with the correct attribution. The second situation concerns clozapine, in which caffeine acts as a competitive CYP1A2 substrate, and in which abrupt changes in caffeine intake may shift plasma clozapine concentrations in clinically meaningful directions, occasionally with catastrophic consequences [33,34,37,38]. In both situations, a structured caffeine inventory is no longer a question of dietary curiosity but of pharmacovigilance.

This logic extends to other CYP1A2-relevant psychotropic medications, including olanzapine, agomelatine, duloxetine and, by analogy, to the antibiotic ciprofloxacin in patients receiving clozapine [38,41]. In each case, the principle is the same: when the same enzyme is responsible for the elimination of multiple compounds, the assumption that one of them (caffeine) is a stable background variable is empirically false and should be replaced by explicit quantification.

8.2. The pharmacogenomic potential — CYP1A2 and ADORA2A as candidate biomarkers

A second implication concerns the role of pharmacogenomic profiling. As reviewed in Section 4, polymorphisms in CYP1A2 (notably rs762551) and ADORA2A (notably rs5751876) have been associated, with reasonable consistency across studies, with inter-individual variability in caffeine metabolism and in central nervous system sensitivity respectively [18,19,52,53]. A recent systematic review by Kapellou and colleagues concluded that variations in CYP1A2 were associated with cognitive function, while variations in ADORA2A were associated with anxiety and sleep disturbance, supporting the conceptual distinction between the pharmacokinetic and pharmacodynamic axes of caffeine response [52]. The earlier comprehensive review by Yang and colleagues estimated the heritability of caffeine-related traits between 0.36 and 0.58, with heavy consumption reaching a heritability of 0.77, and noted that pharmacokinetic and pharmacodynamic polymorphisms have both been linked to variation in caffeine response, including the risk of cardiovascular outcomes [53]. The consortium study by Popat and colleagues, while focused on Parkinson's disease, illustrated that the coffee–disease association was strongest among slow metabolisers of caffeine homozygous for variant alleles at rs762551 or rs2470890, suggesting that CYP1A2 genotyping may inform not only pharmacological interactions but also disease-modifying outcomes [51].

Routine genotyping of all patients before initiation of psychotropic therapy is not, on the basis of present evidence, justified by cost-effectiveness considerations. There are, however, several clinical contexts in which targeted CYP1A2 and ADORA2A testing may carry a more favourable benefit-to-cost ratio. These include: (i) treatment-resistant patients receiving clozapine, in whom CYP1A2 genotype may explain otherwise unaccountable variability in serum levels and may inform decisions about fluvoxamine adjunction [40,42]; (ii) patients exhibiting atypically strong anxiogenic or insomnia-related reactions to standard doses of antidepressants, particularly fluvoxamine, in whom both ADORA2A and CYP1A2 variants may contribute to the phenotype [21,22,23]; (iii) patients with treatment-resistant generalised anxiety disorder or panic disorder, in whom ADORA2A genotype may add to risk stratification and may inform dietary counselling [20]; (iv) patients with paradoxical responses to ergogenic caffeine doses, in whom pharmacogenomic profiling may help disentangle metabolic from receptor-level contributions [24,29]; and (v) selected paediatric and adolescent patients in whom clozapine adjunction with fluvoxamine is being considered, where CYP genotyping may guide individualised dosing and reduce the risk of tolerability events [40,42].

It deserves emphasis that pharmacogenomic information is most useful when integrated with the structured caffeine inventory described above and with conventional clinical history. A CYP1A2 slow-metaboliser genotype in a patient with low habitual intake of high-quality green tea is unlikely to be of immediate clinical consequence; the same genotype in a patient consuming several pre-workout supplements per day in combination with fluvoxamine therapy may be the central biological fact of the case.

8.3. Caffeine as a "legal stimulant" — evidence-based deconstruction of "psychiatric" symptoms

A third implication, more conceptual but no less practical, concerns the way the clinician approaches symptoms that, at first glance, appear to belong to the territory of primary psychiatric disorders. As shown in Section 5, the symptomatic core of caffeine intoxication overlaps substantially with that of generalised anxiety disorder, panic disorder, akathisia, hyperthyroidism, paroxysmal supraventricular tachyarrhythmia and, in some configurations, the early phases of serotonin syndrome [3,11,13,27]. In a clinical culture in which caffeine is rarely regarded as a "real" pharmacological agent, this overlap may translate, repeatedly and unobtrusively, into misclassification of caffeine-related symptomatology as primary psychiatric disorder, with corresponding initiation of pharmacotherapy that does not address the proximate cause.

The fatal end of the caffeine intoxication spectrum, although uncommon, deserves brief acknowledgement, since it illustrates the upper boundary of the substance's pharmacological space. A systematic review by Cappelletti and colleagues identified 92 individual fatal cases attributable to caffeine alone, with the highest density among infants, athletes and patients with psychiatric disorders [54]. A mini-review by Lušić and colleagues concluded that, in adults, fatal caffeine intoxications are more frequently the result of intentional rather than unintentional ingestion, and that the typical lethal dose lies in the range of 5–10 g of caffeine, with blood concentrations of 80 mg/L or above associated with fatal outcomes; an Italian case series confirmed the recent rise of suicide by caffeine pills, while a 2020 US Poison Control Center report described 2,943 single-dose caffeine intoxication cases, including 15 fatal outcomes among intentional ingestions [54,55]. While such events are far from the everyday clinical experience, they reinforce the principle that caffeine has a non-trivial pharmacological ceiling and that severe outcomes — particularly in pharmacogenetically vulnerable individuals or in the presence of CYP1A2 inhibition — are biologically possible.

From an evidence-based medicine standpoint, the conceptual contribution of the present synthesis is therefore the deconstruction of presentations that are conventionally labelled "psychiatric" but that may, in a meaningful proportion of cases, reflect the pharmacological footprint of a legal stimulant. Such deconstruction does not deny the reality of primary psychiatric disorders; it adds caffeine to the differential diagnosis as a candidate that should be considered, quantified and, where appropriate, manipulated before more invasive or more permanent pharmacotherapeutic decisions are made.

8.4. Limitations of this review

Several methodological caveats deserve explicit mention. First, this work is a narrative review and not a systematic review or meta-analysis; the selection of evidence, although guided by the structured strategy described in Section 2, retains a degree of interpretive judgement. Second, the evidence base is heterogeneous, and the methodologies of the cited studies range from in vitro inhibition assays through small crossover trials in healthy volunteers to large genome-

wide association studies and individual case reports. Pooling across such heterogeneous designs has been deliberately avoided, and effect sizes have been reported as drawn from individual studies. Third, several of the conclusions on phytochemical modulation — particularly those concerning L-theanine — rely on a still-modest body of randomised evidence, and should be considered hypothesis-generating rather than definitive. Fourth, the literature on ADORA2A polymorphisms exhibits ethnic stratification of allelic frequencies and inconsistencies between European, US and Asian samples [20,52], and recommendations derived from one population should not be transferred to another without consideration of this background. Fifth, the present review has not addressed in detail several areas of legitimate clinical importance, including caffeine use in pregnancy and lactation, in paediatric populations beyond the few clozapine adjunction case series cited, and in patients with hepatic or cardiac disease.

8.5. Future research directions

Several lines of inquiry emerge as priorities for future work. Prospective trials testing the clinical utility of paired CYP1A2 and ADORA2A genotyping prior to initiation of clozapine or of fluvoxamine would help clarify whether genotype-informed dosing reduces adverse events and improves clinical outcomes. Mechanistic and clinical studies of L-theanine and other phytochemicals as modulators of the anxiogenic component of caffeine would refine the dietetic recommendations that can be offered to anxiety-prone patients. Pragmatic implementation studies — testing, in real-world primary care and psychiatric settings, the effect of introducing a structured caffeine inventory on diagnostic accuracy, on therapeutic decisions and on patient outcomes — would address the implementation gap between the pharmacological literature and routine clinical practice. Finally, longitudinal studies investigating whether the recognition and modification of "hidden" caffeine intake reduces the rate of treatment-resistant anxiety and insomnia could provide direct evidence for the clinical relevance of the framework proposed here.

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Author's contribution

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The authors used generative AI tools (Google Gemini) during the preparation of this manuscript for structuring the text, translating content, and formatting citations. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the publication's content.

8.6. Closing synthesis

In sum, the literature reviewed in this work supports a single clinical proposition: that caffeine intolerance, in its various pharmacokinetic, pharmacodynamic and interaction-mediated forms, is a clinically meaningful entity that may shape the presentation, the course and the outcome of psychiatric and cardiological care more often than is currently recognised. The recognition of this entity does not require new technologies, new diagnostic categories or new pharmacological agents. It requires, more modestly, a structured approach to dietary history, an integration of pharmacogenomic insights where these are available, and an evidence-based scepticism toward the assumption that the world's most widely consumed psychoactive substance is, for clinical purposes, pharmacologically neutral. The internal consistency of the evidence reviewed across mechanism, genetics, clinical phenotype and drug interaction is itself an argument for taking this proposition seriously, and for translating it — cautiously, and with attention to the methodological limitations described above — into the routine practice of psychiatry, cardiology and primary care.

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