Novel Phenethylamines and Their Potential Interactions With Prescription Drugs: A Systematic Critical Review

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Background: The novel phenethylamines 4-fluoroamphetamine (4-FA) and 2,5-dimethoxy-4-bromophenethylamine (2C-B) fall in the top 10 most used new psychoactive substances (NPSs) among high-risk substance users. Various phenethylamines and NPS are also highly used in populations with mental disorders, depression, or attention deficit hyperactivity disorder (ADHD). Moreover, NPS use is highly prevalent among men and women with risky sexual behavior. Considering these specific populations and their frequent concurrent use of drugs, such as antidepressants, ADHD medication, and antiretrovirals, reports on potential interactions between these drugs, and phenethylamines 4-FA and 2C-B, were reviewed.

Methods: The authors performed a systematic literature review on 4-FA and 2C-B interactions with antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, bupropion, venlafaxine, phenelzine, moclobemide, and tranylcypromine), ADHD medications (atomoxetine, dexamphetamine, methylphenidate, and modafinil), and antiretrovirals.

Results: Limited literature exists on the pharmacokinetics and drug–drug interactions of 2C-B and 4-FA. Only one case report indicated a possible interaction between 4-FA and ADHD medication. Although pharmacokinetic interactions between 4-FA and prescription drugs remain speculative, their pharmacodynamic points toward interactions between 4-FA and ADHD medication and antidepressants. The pharmacokinetic and pharmacodynamic profile of 2C-B also points toward such interactions, between 2C-B and prescription drugs such as antidepressants and ADHD medication.

Conclusions: A drug–drug (phenethylamine-prescription drug) interaction potential is anticipated, mainly involving monoamine oxidases for 2C-B and 4-FA, with monoamine transporters being more specific to 4-FA.

Key Words: NPS, phenethylamine, drug interactions, antiretrovirals, ADHD

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INTRODUCTION

The global market for recreational and addictive substances has been flooded with a variety of molecules, new psychoactive substances (NPSs). These substances can be subdivided into chemical classes, based on their molecular structure. The European Early Warning System recently reported more than 700 different molecules, including synthetic cannabinoids, synthetic cathinones, arylalkylamines, and phenethylamines.[1,2]

Among the most popular and prevalent NPS is the chemical class phenethylamines, which includes classic drugs with stimulatory properties such as amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) or "ecstasy."[3] In the recent European figures on NPS consumption and seizures by law enforcement, novel phenethylamines rank third, after synthetic cathinones and synthetic cannabinoids.[4] Many novel phenethylamines have emerged; 2,5-dimethoxy-4-bromophenethylamine (2C-B), 4-fluoroamphetamine (4-FA), 6-APB (benzofury), and 25X-NBOMe (N-Bomes or n-bombs).[5–9] Although numerous substances are manufactured and marketed yearly, only a handful lasts longer on the market, due to legislative actions or the poor performance of some substances to the users.[4] However, among phenethylamines, 2C-B and 4-FA seem to have withstood these challenges.[10]

The phenethylamine amphetamine typically induces increased energy, stamina, appetite suppression, and a boost in self-confidence, while other phenethylamines such as MDMA and 3,4-methylenedioxyethamphetamine (MDEA) also provoke entactogenic effects such as the feeling of closeness to others, increased sociability, talkativeness, and increased senses to touch or music.[11] Besides their stimulatory or entactogenic properties, many new phenethylamines have a profound hallucinogenic effect.

Presently, several phenethylamines are widely used as recreational drugs, although their therapeutic use has recorded

a global increase in recent decades. For instance, dexamphetamine is used to treat attention deficit hyperactivity disorder (ADHD),[12,13] pseudoephedrine as a decongestant,[14] and phentermine as an appetite-suppressant.[15] Moreover, the therapeutic use of MDMA for post-traumatic stress disorders is currently being investigated.[16–18]

The global prevalence of the use of specific new synthetic phenethylamines is uncertain, although phenethylamines constitute 18% of all NPS seized.[4] Furthermore, NPS use is highly prevalent among high-risk substance users, with 4-FA and 2C-B ranked among the top 10, in a number of European countries.[19,20] 2C-B is also among the most prevalent psychedelic NPS used in the United States.[21] Interestingly, 2C-B and 4-FA represent both ends of the phenethylamine spectrum of action: they have both stimulatory and hallucinatory properties.

In a study performed throughout the European Union, it seems that in addition to the highly prevalent NPS use within groups of high-risk substance users (prisoners, homeless people, and addicts), highly prevalent NPS use is also recorded among men and women who engage in risky sexual intercourse, mainly in the gay community.[22–24] This practice is specifically high in the United Kingdom, where it has been repeatedly observed in rituals referred to as "slamming" (injecting drugs or "chemsex"—taking different drugs concomitantly). "Slamming" is significantly more often associated with hepatitis-C and HIV infections in gay men,[25,26] markedly increasing the likelihood of patients being on antiretrovirals, while concurrently on NPS.

Generally, NPS-prescription drug interactions are expected. For instance, interactions between illicit and novel phenethylamines and antiretrovirals have been described.[27,28] Furthermore, prevalence of mental disorders such as ADHD and depression is high among the general population, particularly young adults, with a pooled prevalence of 5.3% for ADHD[29] and approximately 10% for depression.[30] Illicit substance use is well known to coincide with these conditions. Therefore, interactions between prescribed antidepressants and ADHD medication, with (illicit) substances such as phenethylamines, are expected.[31–35]

Therefore, in this article, we reviewed the possible interactions between prescription drugs and NPS of the phenethylamine class. We also described the pharmacokinetics and pharmacodynamics of 2 representative and popular novel phenethylamines (2C-B and 4-FA), as well as their overlap in the mechanism of action, with the 3 anticipated classes of prescription drugs that might interact: antidepressants, ADHD medication, and antiretrovirals. We also outlined any clinically relevant interactions.

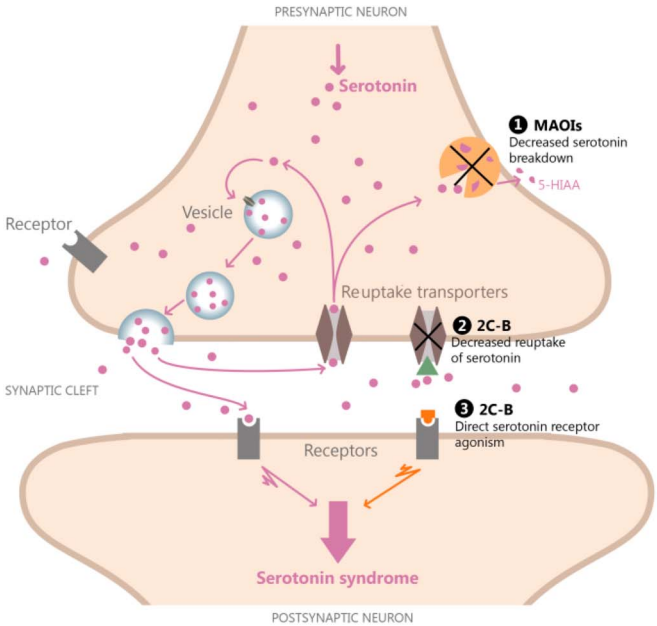
METHOD

Pharmacokinetics and Pharmacodynamics

To describe the pharmacokinetics and pharmacodynamics of the single phenethylamines and classes of prescription drugs, we used published reviews and Stahl's[36] Essential Psychopharmacology.

Pharmacokinetics and Pharmacodynamics: Interactions

We performed a broad search on Pubmed using search strings for 4-FA and 2C-B, combined with those for prescription drugs (see **Supplemental**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A384). The prescription drugs selected were those most likely to coincide with the use



	Serotonin reuptake transporter
	Serotonin receptor
	Serotonin
	2C-B
	MAO

FIGURE 1. Illustrating the effects of 2C-B on serotonin (5-HT). Modulation of different serotonergic targets can contribute to developing a serotonin syndrome. For instance, 2C-B can inhibit MAO (1), the reuptake of serotonin at higher doses (2), and activate the 5-HT receptors (3).

of NPS: antidepressants (citalopram, venlafaxine, paroxetine, fluoxetine, fluvoxamine, sertraline, bupropion, duloxetine, phenelzine, moclobemide, and tranylcypromine), ADHD medication (dextroamphetamine, modafinil, atomoxetine, and methylphenidate), and antiretrovirals (NNRTIs, NRTIs, protease inhibitors, CCR5 inhibitors, and integrase inhibitors).

Search strings were also used on the specific pharmacokinetics and pharmacodynamics of 4-FA, 2C-B, MDMA, antidepressants, ADHD medication, and antiretrovirals, as well as bibliographies of the relevant articles. Articles up to July 2019 were reviewed. Additional information about the search strings can be found in the **Supplemental Digital Content 1** (see **Supplementary information**, http://links.lww.com/TDM/A384).

RESULTS

4-Fluoroamphetamine

4-FA is a phenethylamine NPS, also known as para-fluoroamphetamine (PFA), 4-FMP, flava, 4floor, 4-fluor, or Flux CD cleaner[5] and has been on the Dutch drugs market for decades.[10] The first formal notification on 4-FA was reported to the European Monitoring Centre for Drugs and Drug addiction (EMCDDA) in 2008.[37] Since 2012, there has been a rise in the number of emergencies linked to 4-FA use, in the Netherlands.[20]

Pharmacokinetics

4-FA is available as a powder, tablet, and liquid, mostly consumed orally, but also by nasal insufflation. Reported user doses range from 50 to 150 mg, although some users exceed 150 mg. Above the 150 mg dose, the risk of adverse effects have been reported to increase, in approximately 1 in every 5 users.[10,37] The first observable effects typically start 30 minutes after oral ingestion of 4-FA and peak at 90–120 minutes. The effect might last 4–6 hours, although some users report a 12-hour duration. The effects observed after intranasal administration of 4-FA occur after a few minutes, and are more intense, and the duration shorter, compared with those observed after oral administration.[10,37] The half-life of 4-FA is estimated to be 8–9 hours.[38] Chemically, 4-FA only differs from (dex)amphetamine by a fluorine atom positioned on the aromatic ring (Table 1). To the best of our knowledge, no data exist on 4-FA metabolism, which remains challenging to predict precisely, as adjustments to the chemical structure could lead to changes in metabolism. For instance, substituting the fluorine atom for a hydrogen atom may create a more stable metabolic structure, reducing the metabolism potential, but it is unlikely that positioning a fluorine atom on the aromatic ring will lead to a more stable structure.[39]

Pharmacodynamics

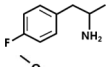
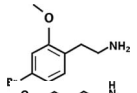
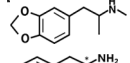
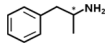
4-FA increases the extracellular concentrations of the neurotransmitters norepinephrine (NE), dopamine (DA), and serotonin (5-hydroxytryptamine; 5-HT) in the brain.[5] This increase is attributed to the inhibition of NE, DA, and 5-HT reuptake transporters (norepinephrine transporter [NET], dopamine transporter [DAT], and serotonin transporter [SERT]), as well as the induction of transporter-mediated release.[6] Although the potency of 4-FA to induce DA and NE release seems comparable with amphetamine, 4-FA is a more potent 5-HT releaser, comparable with MDMA. Compared with amphetamine, 4-FA is a less-potent NET and DAT inhibitor, with a lower DAT/SERT inhibition ratio. 4-FA also binds to the serotonin receptors 5-HT_{1a}, 5-HT_{2a}, 5-HT_{2b}, and 5-HT_{2c}.[6]

4-FA evoked more entactogenic effects compared with amphetamine, but less, compared with MDMA.[40] MDMA-associated entactogenic effects are dependent on the serotonergic effects.[6,41] The most common positive effects reported after 4-FA use are stimulatory, euphoric, and empathic effects. The adverse effects include elevated heartbeat and temperature, sweating, sleeplessness, dry mouth, jaw tension, and lowered mood.[10,42] Comparing the effects of 4-FA with those of MDMA and amphetamine showed that the effects lie between the extremes of MDMA and amphetamine, having less stimulatory, but more entactogenic effects, as amphetamine.[40] Severe adverse effects also include tachycardia, and in some cases, myocardial infarction, or hemorrhagic stroke.[43]

4-Bromo-2,5-Dimethoxyphenethylamine

2C-B (4-bromo-2,5-dimethoxyphenethylamine) belongs to the 2C class of phenethylamines and is sometimes referred to as a hallucinogenic phenethylamine. 2C-B is also

TABLE 1. Pharmacokinetics of 4 Specific Phenethylamines

Drugs of Abuse	Chemical Structure	Substrate	Enzyme Inhibition	Usual Oral Dose	Tmax	T1/2
4-FA		Not known	Not known	50–150 mg, higher doses are reported[10,37]	2 h[38]	8–9 h[38]
2C-B		MAO[45]	Probably MAO enzymes[51]	4–30 mg[5]	30 min[5]	1 h[5]
MDMA		CYP2D6, CYP3A4, CYP1A2, CYP2B6[107,108]	CYP2D6[109,110]	100–120 mg[108]	2 h[108]	5–10 h[108]
Dexamphetamine		CYP2D6[64,65,111]	Not known	5–60 mg[65]	3 h[65]	12 h[65]

Only CYP450 and MAO enzymes are included in this table.
CYP, cytochrome P450; 2C-B, 4-bromo-2,5-dimethoxyphenethylamine; MDMA, 3,4-methylenedioxymethamphetamine.

known as nexus, venus, bromo, bees, erox, synergy, performax, or toonies.

2C-B was first synthesized around the 1970s for psychotherapeutic use but was never marketed because of its lack of empathogenic effects and the gastrointestinal side effects.[5,40,44]

Pharmacokinetics

Limited literature exists on the human pharmacokinetics of 2C-B. Based on user reports, 2C-B user dosage ranges from 4 to 30 mg orally, and its effects last for 4–8 hours. An animal study reported the following parameters: an elimination half-life of 1 hour; a volume of distribution, 16 L/kg; clearance, 9.8 L/h; and Tmax, 30 minutes.[5]

2C-B is metabolized through deamination with monoamine oxidases (MAO-A and MAO-B). MAO-mediated monoamine breakdown can be decreased after 2C-B exposure, possibly restoring the monoamines. CYP enzymes seem to have no role in 2C-B metabolism.[45] 2C-B metabolism results in several metabolites; its oxidative deamination in human hepatocytes results in the formation of 2-4-bromo-2,5-dimethoxyphenyl-ethanol (BDMPE), 4-bromo-2,5-dimethoxyphenylacetic acid (BDMPAA), and 4-bromo-2,5-dimethoxybenzoic acid (BDMBA), which are further demethylated.[46] In humans, the 2C-B metabolites, 2C-B-CBA and 2C-B-ALC, are excreted in urine.[45–48]

Pharmacodynamics

2C-B inhibits DAT, NET, and SERT, although at higher concentrations, compared with 4-FA, which could result in higher extracellular brain levels of monoamines. This mechanism is of minor relevance during "normal" recreational use, which usually results in low μM serum levels.[49,50] 2C-B activates the 5-HT_{2C} receptor and binds to α1-adrenoreceptor, $5HT_{1A}$, $5HT_{1B}$, and $5HT_{1c}$ receptors. $5HT_{2a}$ stimulation generally causes hallucinogenic effects.[5,6,40] In animal studies, 2C-B (25 mg/kg) increased DA release in the nucleus accumbens.[51] 2C-B also inhibits MAO enzymes,[51,52] provoking stimulatory and hallucinogenic effects (Figure 1). At lower doses (<10 mg), stimulatory effects, euphoria, and increased visual and auditory sensations have been reported, and moderate doses (10–20 mg) produce hallucinations. At higher doses (>20 mg), more unpleasant hallucinations and sympathomimetic effects such as tachycardia, hypertension, and hyperthermia have been reported.[5,44]

Antidepressants

Before the 80s, depression was treated using MAO inhibitors or tricyclic antidepressants.[53] However, in recent times, selective serotonin reuptake inhibitors (SSRIs) are most often used, especially in the outpatient setting, where they are widely prescribed.[54] After the SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, were registered for the treatment of depression. Another drug introduced on the market after SSRIs was bupropion, known to inhibit DAT and NET.

Pharmacokinetics

For all SSRIs and SNRIs, the cytochrome P450 enzyme involved in phase I metabolism is CYP2D6. Paradoxically, this enzyme is also inhibited by these drugs. Other enzymes involved in metabolism or drug inhibition are shown in Table 2.[53–55] CYP inhibition by these drugs may differ in potency or duration. Some drugs such as paroxetine, are strong CYP2D6 inhibitors, while drugs like fluvoxamine, are weak inhibitors.[55] Fluoxetine has a half-life of 4–6 days, while its metabolite norfluoxetine, has a half-life of 4–16 days,[53] and sertraline, a half-life of 26 hours.[53] The CYP enzyme inhibiting properties of fluoxetine may continue for weeks, even after drug discontinuation.[55] Other MAO inhibitors like tranylcypromine and phenelzine, are not CYP substrates, and do not have an effect on CYP enzymes. They both inhibit MAO-A and MAO-B irreversibly. Moclobemide is a CYP2C19 substrate and a reversible MAO-A inhibitor, which also inhibits CYP2C9, CYP2D6, and CYP1A2 enzymes.[53,56]

Pharmacodynamics

SSRIs were developed to selectively inhibit SERTs in the brain, thereby markedly elevating postsynaptic serotonin levels.[57] Subsequently, freely available serotonin is able to bind to the serotonin receptors (5-HTR) in the brain. After this increased neurotransmitter–receptor interaction, the resulting receptor (mainly 5-HT1a) desensitization is the mechanism ultimately responsible for the antidepressant effects of SSRIs.[58] Although SSRIs all show high affinity for SERT, some also partially block other monoamine transporters, DAT and NET.[59] In fact, sertraline also shows a reasonably high affinity for DAT.[53] Venlafaxine acts as an SSRI at low doses (<200 mg/d), due to its SERT-binding selectivity, and as an SNRI at higher doses (>375 mg/d) since the effects on the NET can be achieved with higher doses. Duloxetine is an antidepressant known to potently inhibit SERT and NET, at regular starting doses.[60] Monoamine transporter inhibition is related to the therapeutic effects of antidepressants, and inhibiting of SERT and NET may result in better response rates in depression treatment.[60]

MAO enzyme inhibitors (MAOI) act differently as antidepressants because they inhibit neurotransmitter deamination or turnover metabolism. Serotonin and (nor)adrenalin are primarily deaminated by MAO-A, while phenethylamines are primarily deaminated by MAO-B. MAO-A and MAO-B can breakdown DA or tyramine, while a combination of MAOI and serotonergic drugs can trigger severe serotonin syndrome, leading to fatalities.[56,61]

ADHD Medication

ADHD is characterized by symptoms such as impulsivity, hyperactivity, and inattention.[62] Although ADHD was initially believed to affect only children, it has been shown to also continue throughout adulthood.[63]

Pharmacokinetics

Atomoxetine and (d-)amphetamine are metabolized by CYP2D6. However, their effect on CYP enzyme activity is unknown.[36,64,65] Modafinil is metabolized by CYP3A4 and

TABLE 2. Antidepressants, Drugs of Abuse, and ADHD Medication: Enzyme Inhibition and Effect on Neurotransmitter Transporters

Name	Substrate	Enzyme Inhibition	Inhibiting NET	Inhibiting SERT	Inhibiting DAT
Drugs of abuse					
4-FA	Not known	Not known	+++	+	++
2C-B	MAO-enzymes[45]	Probably MAO enzymes[51]	+/−	+/−	−
MDMA	CYP2D6, CYP3A4, CYP1A2, CYP2B6[107,108]	CYP2D6[109,110]	+++	+	++
Antidepressants: Selective serotonin reuptake inhibition (SSRI)					
Citalopram	Main: CYP2C19 Minor: CYP2D6, CYP3A4[53–55]	Weak: CYP2D6, CYP2C19, CYP1A2[53,55]	−	+++	−
Paroxetine	Main: CYP2D6 Minor: CYP3A4, CYP1A2, CYP2C19[53,54]	Strong: CYP2D6[53,55]	++	+++	+
Fluoxetine	Main: CYP2D6, CYP2C9 Minor: CYP2C19, CYP3A4, CYP3A5[53–55]	Strong: CYP2D6 Moderate: CYP2C9 Weak to moderate: CYP2C19, CYP3A4[53,55]	+	+++	−
Fluvoxamine	Main: CYP2D6 Minor: CYP1A2[53–55]	Strong: CYP1A2, CYP2C19 Moderate: CYP2C9, CYP3A4 Weak: CYP2D6[55]	+	+++	−
Sertraline	Main: CYP2D6, CYP2C19 Minor: CYP2C9, CYP3A4, CYP2B6[53–55]	Weak to moderate: CYP2D6 Weak: CYP2C9, CYP2C19, CYP3A4[53,55]	+	+++	++
Antidepressants: Serotonin and norepinephrine reuptake inhibition (SNRI)					
Duloxetine	Main: CYP2D6, CYP1A2[53,55]	Moderate: CYP2D6[55]	++	+++	+
Venlafaxine	Main: CYP2D6 Minor: CYP3A4[53,55]	Weak: CYP2D6[53,55]	+	+++	−
Antidepressants: Dopamine and norepinephrine reuptake inhibitor					
Bupropion	Main: CYP2B6 Minor: CYP1A2, CYP2D6, CYP3A4, CYP2C9[53,55,113]	Moderate CYP2D6[53,55]	−	−	+
Antidepressants: MAO inhibitors					
Moclobemide	CYP2C19[53]	MAO a inhibitor, CYP2C9, CYP2D6, CYP1A2[53]	−	−	−
Tranylcypromine	Not known	MAO a and MAO B inhibitor[56]	−	−	−
Phenelzine	Not known	MAO a and MAO B inhibitor[56]	−	−	−
ADHD medication					
(Dex)-amphetamine*	CYP2D6[64,65]	Not known	+++	+	++
Modafinil	CYP3A4[36]	CYP2C19, CYP2C9[66]	−	-	+
Atomoxetine	CYP2D6[36]	Not known	+++	+++	−
Methylphenidate	Not known	Not known	+++	+/−	+++

Only CYP450 and MAO enzymes are included on this table. The effect of the antidepressants on neurotransmitters is adopted from Wille et al and Richelson et al.[53,60] The effect of drugs of abuse on the neurotransmitter transporters is adapted from Nugteren-van Lonkhuyzen et al.[5] The effect of ADHD medication on the neurotransmitter transporters is adapted from Ding et al, Ballon et al, and Luethi et al.[75,76,112]

−, very low or no effect; +, ++, and +++: moderate to high potency. These findings were obtained in experimental animal models and/or cloned cell lines.

*The illustrated effect of (dextro)amphetamine on neurotransmitter transporters is based on amphetamine.

CYP, cytochrome P450; 2C-B, 4-bromo-2,5-dimethoxyphenethylamine; MDMA, 3,4-methylenedioxymethamphetamine; NET, norepinephrine transporter; SERT, serotonin transporter; DAT, dopamine transporter.

inhibits and induces CYP enzymes.[36,66] Methylphenidate is primarily metabolized by de-esterification, to ritalinic acid. Other minor metabolized products include de-esterified lactam through oxidative metabolism.[67] It is not known if methylphenidate is metabolized by or has no effect on CYP enzymes.

Pharmacodynamics

Most ADHD medications aim at alleviating symptoms of ADHD through a gradual increase in brain NE and DA.[68,69] ADHD is generally assumed to arise from defects in the dopaminergic system, mainly the dopamine-4 receptor and the DAT-1 transporter, all involved in the modulation of attention to environmental stimuli.[70] D-amphetamine and methylphenidate are potent DAT and NET blockers, mediating an increase in free monoamines, for attention improvement in ADHD patients.[71] Dexamphetamine is a weak DAT inhibitor, moderately potent NET inhibitor, and a very weak SERT inhibitor.[72] Dexamphetamine is also weakly releases serotonin.[73] Methylphenidate blocks DAT and NET and is a 5-HT1a agonist.[71]

Conversely, a novel medication, atomoxetine, was developed because it almost exclusively blocks the NET, showing less abuse liability, similar to the psychostimulants, which block both NET and DAT.[74] In a study with monkeys, atomoxetine inhibited SERT and NET.[75] Similar to atomoxetine, modafinil was introduced as a novel ADHD therapy because it seems to lack abuse liability. Its mechanism of action is less well understood, although it involves inhibition of the GABAergic input to histaminergic neurons, thereby influencing wakefulness and alertness.[76]

HIV (Antiretroviral) Medication

HIV medications, in general, are a pharmacologically diverse group of substances, protease inhibitors that disrupt virus development, using nucleotide reverse transcriptase inhibitors (NRTI) to break down reverse transcriptase, and non-nucleoside reverse transcriptase inhibitors (NNRTI) to break down the conversion of RNA into DNA.[77]

Pharmacokinetics

Antiretrovirals are mostly metabolized by CYP3A4,[78,79] although other CYP enzymes also play a role. For instance, ritonavir is metabolized by CYP3A4, as well as CYP2D6, CYP1A2, and CYP2B6.[79] Efavirenz is metabolized by

TABLE 3. Antiretroviral Medication: Metabolism and Effects on Enzymes

	Substrate	Enzyme Inhibition	Enzyme Induction
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz	Major: CYP2B6, CYP3A4[78,79]	Not known	Moderate: CYP3A4, CYP2B6 Weak: CYP2C19[78,79]
Etravirine	Major: CYP3A4 Minor: CYP2C19, CYP2C9[78–80]	Weak: CYP2C19, CYP2C9[78,80]	Moderate: CYP3A4[78,79]
Nevirapine	Major: CYP3A4, CYP2B6[78]	Not known	Strong/moderate: CYP2B6 Moderate/weak: CYP3A4[78,79,114]
Rilpivirine	Major: CYP3A4[79,115]	Not known	At higher doses (above therapeutic): CYP3A4[79]
Protease inhibitors			
Atazanavir	Major: CYP3A4[79]	Strong: CYP3A4[79]	Not known
Darunavir	Major: CYP3A4[78,79]	Strong: CYP3A4 Moderate: CYP2D6[79]	Not known
Fosamprenavir	Major: CYP3A4 Minor: CYP2D6, CYP2C19[79]	Moderate: CYP3A4[79]	Not known
Lopinavir	Major: CYP3A4[79,116]	CYP3A4[79,116]	Not known
Ritonavir	Major: CYP3A4 Minor: CYP2D6, CYP2B6, CYP1A2[78,117,118]	Strong: CYP3A4 Moderate: CYP2D6[78,117,118]	CYP1A2, CYP2C19, CYP2C9, CYP2B6, and CYP3A4[78,117]
Saquinavir	Major: CYP3A4[78,119]	Moderate: CYP3A4 Weak: CYP2C9[78,79,119]	Not known
Tipranavir	Major: CYP3A4[78,79,120]	CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19[78,79,120]	CYP3A4[120]
Fusion inhibitor			
Enfuvirtide	Not known	Not known	Not known
Integrase inhibitors			
Dolutegravir	Minor: CYP3A4[78,79]	Not known	Not known
Raltegravir	Not known	Not known	Not known
CCR5 inhibitors			
Maraviroc	Major: CYP3A4[79,121]	Not known	Not known
Other, pharmacokinetic enhancer			
Cobicistat	Major: CYP3A4[78,79]	Strong: CYP3A4 Weak: CYP2D6[78,79]	Not known

CYP, cytochrome P450.

CYP2B6 and CYP3A4, and etravirine by CYP3A4, CYP2C9, and CYP2C19,[78–80] which also inhibits CYP2C9 and CYP2C19.[78,80] Most other antiretroviral medications seem to partially inhibit their own metabolism, using CYP3A4. NRTIs do not affect liver enzymes and are minimally metabolized through CYP enzymes. Hence, NRTIs are not included in Table 3.

Pharmacodynamics

To the best of our knowledge, antiretroviral drugs have no direct effect on the DA, 5-HT, and NE systems, with the exception of efavirenz, shown in vitro, to be a partial 5-HT2a and 5-HT2c agonist, and a SERT and DAT blocker.[81] However, HIV itself has an effect on DA transmission, where DA transmission is disrupted. Furthermore, it has been assumed that drugs of abuse could synergistically disrupt DA transmission and can contribute to the development of HIV-associated neurocognitive disorders.[82]

Interactions Between 4-FA or 2C-B, and Antidepressants

Thus far, there are no reported clinical cases on the interactions between antidepressants and 2C-B or 4-FA. However, publications on the interactions between antidepressants and older phenethylamines, such as MDMA, exist. Seven healthy volunteers received paroxetine at 20 mg for 3 days, and on the last day, 100 mg of MDMA was given in a placebo-controlled, randomized crossover study. MDMA level (area under the curve) increased by 27% and the Cmax by 17%.[83] In another trial, the psychological effects of MDMA (1.5 mg/kg) and pretreatment with 40-mg citalopram (IV) were determined in 16 volunteers, in a double-blinded placebo-controlled study. Citalopram inhibited MDMA-induced psychological effects. The authors of the article suggested that the psychological effects of MDMA were blocked through citalopram action, at the 5-HT uptake site, to increase 5-HT release.[84] Citalopram reduced MDMA-induced cardiovascular effects such as increased blood pressure and heart rate but had no effect on body temperature.[85] In another study, the effects of duloxetine (120 mg) on MDMA (125 mg)-mediated effects, were assessed, in vitro and in vivo. Duloxetine increased blood MDMA levels, while inhibiting MDMA-mediated effects such as norepinephrine elevation, blood pressure, and heart rate elevation, as well as subjective drug effects in humans.[41] Other cases have been reported on the simultaneous use of other antidepressants (MAO inhibitors) and MDMA. One of such publications reported 4 fatal cases between moclobemide and MDMA use in Finland. In all 4 cases, the forensic pathologist concluded the combined use of moclobemide and MDMA as the cause of death.[86] Other drugs were also found in the blood of all 4 subjects. Another case reported the combined use of MDMA and the MAO inhibitor, phenelzine, where 1 male developed marked hypertension, hypertonicity, altered mental status, and diaphoresis.[87] The effect of moclobemide and MDMA on body temperature and 5-HT release was also investigated in rats. The MDMA/moclobemide combination resulted in higher body temperatures, compared with MDMA alone. MDMA increased 5-HT outflow in the striatum.[88] Pharmacodynamically, MDMA has similarities with 2C-B and 4-FA. Hence, in theory, interactions could be expected between antidepressants, and 2C-B and 4-FA.

Interactions Between 4-FA or 2C-B and ADHD Medication

Only one case has been reported on the combination of 4-FA and ADHD medication. In this case report, a patient who reportedly ingested 800-mg modafinil, drank 2 capfuls of liquid 4-FA, and insufflated 110-mg methylphenidate, developed acute dilated cardiomyopathy and myocardial injury. Modafinil and 4-FA have been associated with cardiomyopathy. The authors of the article suggested that the cardiomyopathy witnessed in this patient was more related to 4-FA–induced myopathy, as opposed to modafinil-induced myopathy.[89] However, methylphenidate may also cause cardiomyopathy.[90] Whether the intoxication was due to interactions, or to effects of either of the single drugs, remains unknown. The pharmacodynamic properties of these substances overlap at the inhibition of monoamine reuptake transporters, indicating the possibility of interactions at this level. No reported cases on the interaction between 2C-B and ADHD medication were found. Theoretically, combining 2C-B with drugs that have monoamine releasing properties such as dexamphetamine and methylphenidate could increase intoxication risks, due to 2C-B-mediated MAO-enzyme inhibition, increasing monoamine levels when 2C-B and dexamphetamine or methylphenidate are combined.

Interaction data were obtained for older phenethylamines. In healthy volunteers, no pharmacokinetic interactions were found when combining MDMA and methylphenidate, although increases in heart rate were observed, with no blood pressure. In addition, higher plasma epinephrine concentrations, and lower plasma norepinephrine concentrations, were measured after exposure to the MDMA and methylphenidate combination.[91]

Interactions Between 4-FA or 2C-B, and Antiretroviral Medication

No reported clinical cases were found on the interactions between antiretroviral medication and 2C-B or 4-FA. Pharmacodynamically, only efavirenz has been shown to inhibit SERT and DAT and is a partial 5-HT2a and 5-HT2c agonist.[81] Given that 2C-B is metabolized by MAO enzymes,[45] it seems possible that its combination with efavirenz could increase serotonin levels because serotonin turnover could be blocked by 2C-B and efavirenz reuptake. 4-FA inhibits SERT, releases 5-HT, and could activate the 5-HT receptors. Hence, theoretically, efavirenz with 2C-B or 4-FA could increase the risk of developing the serotonin syndrome. However, no cases have been reported yet. For the other antiretroviral medication, pharmacodynamic interactions are not expected.

Theoretically, pharmacokinetic CYP–CYP interactions between 2C-B and antiretroviral medication are not expected. Conversely, interactions between antiretroviral medication and 4-FA cannot be ruled out, given that 4-FA metabolism is unknown. For older phenethylamines, drug–drug interactions with antiretroviral medication have been reported.

Evidence exists showing the effect of antiretroviral medication on the metabolism of amphetamine-type drugs using CYP3A4, which can result in increased toxicity.[92,93] One of the best-documented drug–drug interaction concerns a fatal case, involving an HIV-positive man who used ritonavir and took 180-mg MDMA. The patient had used similar amounts of MDMA without adverse effects before starting with ritonavir. After using MDMA, the patient experienced tachycardia, tachypnea, cyanosis, and sweating and died of cardiorespiratory arrest. A postmortem toxicological analysis showed that his blood MDMA concentrations were approximately 10-fold above the expected. It was concluded that ritonavir-mediated CYP2D6 inhibition was the most likely cause of this 10-fold increase.[94]

Two additional cases of interactions between MDMA and antiretrovirals (including ritonavir) are known, both of which were nonlethal.[88] In one of the cases, a 23-year-old patient was treated with 100-mg ritonavir, 300-mg atazanavir, and 300-/200-mg tenofovir/emtricitabine and had ingested 2 tablets of MDMA. After dancing, he developed hyperthermia, seizures, impairment of consciousness level, tachycardia, severe rhabdomyolysis, and renal failure. He was hospitalized for 3 weeks, spending 11 days in intensive care. The MDMA concentration measured was much higher than expected, causing the authors to conclude that the ritonavir–MDMA combination-mediated increased MDMA accumulation and inhibition of its metabolism, by interaction by CYP2D6.[93] Given that atazanavir also inhibits CYP3A4, it may also have contributed to MDMA increase. The other life-threatening case concerned a patient who used ritonavir and saquinavir. He was hospitalized after taking gamma hydroxybutyrate (GHB) and MDMA. This patient had symptoms such as tachycardia, hypertension, and hypothermia. No MDMA was measured.[95] NNRTIs, protease inhibitors, and integrase inhibitors can induce drug–drug interactions with amphetamine-type substances.[96] Methamphetamine can also inhibit protease inhibitor metabolism, using CYP3A4.[97]

DISCUSSION

In this review, indications of potential interactions between 4-FA and 2C-B, and prescription medicines, were found, although the evidence is predominantly indirect and related to older phenethylamines such as amphetamine, methamphetamine, and MDMA. Nonetheless, these findings are relevant for vulnerable patient populations well-known for the concurrent use of prescription medicine and recreational drugs: psychiatric patients, adolescents with ADHD, and HIV patients.

Interactions between NPS and prescription medication could be relevant. Substance abuse in HIV patients is a common problem and could have many consequences; drugs of abuse could decrease the effectiveness or increase the toxicity of antiretrovirals, through drug–drug interactions. Conversely, antiretrovirals could also increase the toxicity of drugs of abuse.[98] Evidence points toward antiretrovirals affecting the metabolism of amphetamine-type drugs through CYP3A4, resulting in increased toxicity.[92,93] Toxicity mainly results from higher concentrations of amphetamine-type drugs, through decreased CYP3A4-mediated metabolism. Furthermore, methamphetamine is able to counteract the metabolism of certain antiretrovirals, using CYP3A4.[97] This has been reported to negatively affect antiretroviral efficacy.[99]

Valid cases have been described on the use of MDMA/antiretroviral combinations. A patient under regular MDMA died after commencing ritonavir, probably due to ritonavir-mediated CYP2D6 inhibition.[94] Similarly, a fatal case was reported to be associated with the concurrent use of protease inhibitors and methamphetamine.[100]

2C-B is not metabolized by CYP enzymes.[45] It is not known if 4-FA can be metabolized through the same route as other amphetamine-type drugs. The added fluorine atom on 4-FA may promote the bypass of CYP450-mediated metabolism, although this metabolism cannot be ruled out. It is possible that 4-FA is broken down into pharmacologically active metabolites, as are other amphetamine-type drugs, CYP450 substrates,[101] thereby rendering an alternative interaction pathways with antiretrovirals. Further research is required, on 4-FA metabolism.

Interaction studies on MDMA and antidepressants such as citalopram show that antidepressants can reduce MDMA's subjective psychoactive and physiological effects, or some of its cardiovascular effects. Although duloxetine increased MDMA levels due to a pharmacokinetic interaction, it inhibited MDMA-induced cardiovascular and subjective effects.[41,85] Theoretically, a combination of MDMA and antidepressants can also lead to increased 5-HT levels. Hence, a combination of 4-FA– and 5-HT–elevating therapeutic drugs should be avoided. Pharmacodynamically, mechanism of action of 4-FA shows some similarity to that of MDMA, although with a lower potency for SERT inhibition.[5] 2C-B also inhibits SERT and NET at higher concentrations, in addition to binding to, and activating several 5-HT receptors, and inhibiting MAO.[5,6,40,51,52] One case report has described serotonin syndrome after ingestion of 2C-I, a highly analogous substance to 2C-B.[102] Therefore, the combined use of high doses of 2C-B with antidepressants could lead to 5-HT toxicity or sympathomimetic effects. Combining MAO inhibitors with 2C-B or 4-FA should be avoided because it increases the risk for sympathomimetic effects and adrenergic or serotonergic crisis, theoretically.

Phenethylamines could theoretically interact with ADHD medications. Methylphenidate and dexamphetamine increase DA and NE levels in the brain, by acting as NET and DAT blockers, and actively releasing monoamines through synaptic vesicles.[68,103] 4-FA also blocks DAT, NET, and SERT, increasing the likelihood of interaction, based on pharmacodynamics. 2C-B is metabolized by MAO s,[45] which breaks down monoamines. Moreover, 2C-B has inhibitory effects on MAOs.[51,52] Given that amphetamine inhibits MAOs,[71] an interaction between 2C-B and amphetamine is possible, both on a pharmacokinetic (higher concentrations of 2C-B or amphetamine) and pharmacodynamic (higher monoamine levels) level. At higher 2C-B concentrations, interactions at the NET would also be possible, with methylphenidate and atomoxetine, possibly resulting in critical NE levels, and subsequent clinical reactions, such as tachycardia and hypertension.

It is important to exercise caution with NPS consumption because either 4-FA or 2C-B will be detected in the routine drug screening tests used in most hospitals. In everyday practice, NPSs such as 4-FA and 2C-B are missed by standard immunoassay analyses. Also, very little is known about their (active) metabolite formation process in humans. Therefore, NPS metabolomics are important for their detection in the clinic, and understanding drug–drug interactions.[104–106]

To detect these substances in clinical cases, more specialized laboratory equipment is required. Although more extensive toxicological screening might not influence treatment, which is predominantly symptomatic, it might establish a more complete diagnosis, excluding other causes of the clinical symptoms.

With regard to interactions, even less is known, but interaction-induced intoxications are often more problematic to treat, so hospital physicians and toxicologists would benefit from more analytically confirmed exposure on coingestion of more substances. Acquired knowledge on these interactions can also be used to warn NPS users on the interactions with therapeutic drugs.

In summary, the potential for drug–drug (NPS-prescribed medications) interactions was found, both on the pharmacokinetic and pharmacodynamic levels, mainly involving MAOs for 2C-B and 4-FA, with monoamine transporters being more specific to 4-FA. Pharmacokinetic interactions through CYP450 enzymes remains speculative but cannot be ruled out, given the evidence on interactions between other phenethylamines and prescription medicines, such as SSRIs and antiretrovirals.

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