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Harnessing Pharmacogenomics in Clinical Research on Psychedelic-Assisted Therapy

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Psychedelics have recently re-emerged as potential treatments for various psychiatric conditions that impose major public health costs and for which current treatment options have limited efficacy. At the same time, personalized medicine is increasingly being implemented in psychiatry to provide individualized drug dosing recommendations based on genetics. This review brings together these topics to explore the utility of pharmacogenomics (a key component of personalized medicine) in psychedelic-assisted therapies. We summarized the literature and explored the potential implications of genetic variability on the pharmacodynamics and pharmacokinetics of psychedelic drugs including lysergic acid diethylamide (LSD), psilocybin, *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), ibogaine and 3,4-methylenedioxymethamphetamine (MDMA). Although existing evidence is limited, particularly concerning pharmacodynamics, studies investigating pharmacokinetics indicate that genetic variants in drug-metabolizing enzymes, such as cytochrome P450, impact the intensity of acute psychedelic effects for LSD and ibogaine, and that a dose reduction for CYP2D6 poor metabolizers may be appropriate. Furthermore, based on the preclinical evidence, it can be hypothesized that CYP2D6 metabolizer status might contribute to altered acute psychedelic experiences with 5-MeO-DMT and psilocybin when combined with monoamine oxidase inhibitors. In conclusion, considering early evidence that genetic factors can influence the effects of certain psychedelics, we suggest that pharmacogenomic testing should be further investigated in clinical research. This is necessary to evaluate its utility in improving the safety and therapeutic profile of psychedelic therapies and a potential future role in personalizing psychedelic-assisted therapies, should these treatments become available.

The global cost of mental disorders was estimated to be around USD 2.5 trillion in 2010 and is anticipated to rise 2.4-fold to $6 trillion by 2039.[1] Currently, despite over 200 drugs being available for the treatment of psychiatric and neurological conditions, their use is often limited by side effects and suboptimal efficacy, resulting in unsatisfactory therapeutic outcomes.[2] More effective treatments are urgently needed and psychedelics have gained attention in the past decade as a potential treatment for several mental health disorders, including major depressive disorder (MDD), treatment-resistant depression (TRD), post-traumatic stress disorder (PTSD), anxiety, substance, and alcohol use disorders.[3–5] The majority of registered clinical trials involving psychedelics in recent years have been investigating therapeutic effects of 3,4 -methylenedioxymethamphetamine (MDMA) and psilocybin, followed by less commonly lysergic acid diethylamide (LSD), ibogaine, ayahuasca, Salvinorin A (from *Salvia divinorum*), *N,N*-dimethyltryptamine (DMT) and 5-methoxy-*N,N*-dimethyltry ptamine (5-MeO-DMT).[3] Emerging evidence shows promising results of psychedelics in treating PTSD,[6] MDD, and TRD.[7–10] However, currently, no psychedelics are approved by the U.S. Food and Drug Administration (FDA) or other regulatory agencies, although limited access pathways have been created in some jurisdictions such as Australia.[11,12]

It is suggested that the acute subjective effects of psychedelics, the intensity of which typically correlate with doses,[13–15] are required for their therapeutic effects,[16] or at least necessary for achieving maximal efficacy.[17] For drugs in general, several factors are known to affect efficacy, one of these being genetics, which can alter both the pharmacokinetics and pharmacodynamics of a drug.[18] In psychiatry, it is suggested that common genetic variants explain 42% of individual differences in antidepressant response.[19] Pharmacogenomics (PGx) is an ever-evolving field in personalized medicine that focuses on the study of genetic variations in human genes that can affect response to drug treatment.[18] Drug metabolism is likely one of the most studied areas within this field, particularly involving the cytochrome P450 (CYP) superfamily, which mediates most phase I oxidative reactions.[20] Polymorphisms in the genes encoding these enzymes, such as *CYP2D6*, can lead to variations in enzyme activity, potentially affecting treatment outcomes.[21] Metabolizer status is generally assigned based on

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enzymatic activity, typically classified as poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs), and rapid or ultrarapid metabolizers (UMs), in order of increasing enzymatic activity.[21]

Due to the significant association between genetic variants and enzymatic activity, the analysis of CYP genes has become a key focus for applying pharmacogenetics in psychiatry.[2] It has been indicated that most antidepressants and antipsychotics are metabolized by CYP2D6, CYP2C19, and CYP3A4 enzymes.[2] The extreme enzymatic activity groups, such as CYP2D6 poor and UMs are clinically the most important as PMs can be at higher risk of adverse events, while UMs may not respond to standard doses due to their rapid metabolism of drugs that are substrates of the enzyme.[22–24] Interestingly, CYP2D6 UM status has been also associated with increased rates of suicide, such as in individuals who have either attempted suicide[25] or died because of it,[26] raising a possibility of failed psychiatric treatment. Nowadays, international guidelines are available for several antidepressants, aiming to improve efficacy and reduce adverse effects (e.g., paroxetine, fluvoxamine, venlafaxine, vortioxetine, citalopram, escitalopram, sertraline, amitriptyline, and nortriptyline), providing dosing recommendations based on the pharmacogenomics involving one or two genes.[27,28] Implementation of such guidelines into antidepressant prescribing has been shown to have a positive effect on patients with MDD.[29] In addition to research on drug metabolism, studies have also been conducted on pharmacodynamics, investigating genetic polymorphisms in neurotransmitter receptors, such as 5-HT_{2A} (*HTR2A*), which has been associated with SSRI response.[30,31] However, the overall results have been largely inconclusive and none of these genetic variants are currently used in guiding psychiatric drug therapy in clinical practice.

In this context, we explored the evidence regarding the role of polymorphisms in serotonin receptor genes and drug-metabolizing enzymes on acute psychedelic effects. If such polymorphisms are shown to have a significant impact, pre-emptive genetic testing could have utility to enhance therapeutic efficacy and mitigate adverse effects, particularly in populations with a higher prevalence of PM or UM phenotypes, such as certain biogeographical groups or potentially in individuals diagnosed with MDD or TRD. This review surveys the existing literature on psychedelics, focusing on genetic variants in the receptors to which these compounds bind and identifying the main enzymes that may affect the metabolism and acute effects of psychedelics. We address both classic psychedelics and non-classic agents such as MDMA. Furthermore, we discuss the potential application of pharmacogenomics in psychedelic therapy, based on the available evidence and propose directions for future research.

FINDINGS FROM LITERATURE AND UTILITY OF PHARMACOGENOMICS

Pharmacodynamics

The psychedelic literature provides very limited evidence on pharmacodynamics. In two studies, the impact of mutations in the 5-HT_{2A} receptor on the response to psychedelics was investigated *in vitro*.[32] Receptor–ligand interaction experiments showed that the Ala230Thr and His452Tyr mutations in 5-HT_{2A} receptor gene (*HTR2A*) led to a sevenfold decrease in psilocin signaling potency compared with wild-type. In contrast, the Ala447Val variant demonstrated a threefold increase in 5-MeO-DMT potency and also enhanced the potency of mescaline. Also, Thr25Asn and Asp48Asn mutations increased potency of mescaline, while the Ser12Asn substitution demonstrated an even greater, ninefold increase in potency. However, apart from the His452Tyr variant that has a frequency of 7.9% in the human population, the other variants are rare with less than 1% frequency.[32] While genetic variants with very low population frequency may be impractical to test for, the His452Tyr (rs6314) mutation could be valuable to investigate if it results in significant differences in the response to psilocybin treatment. From psychiatric literature, the His452Tyr polymorphism has been reported to affect clozapine-induced signaling networks[33] and is associated with a poorer response to treatment with clozapine,[34] an antipsychotic which has a high affinity for the 5-HT_{2A} receptor.[33] However, given the lack of data on psychedelics in humans, it is important to first determine whether this mutation impacts the efficacy of psilocybin (psilocin) treatment.

No data were found on genetic mutations affecting the binding of psychedelics to receptors other than 5-HT_{2A}, though we acknowledge that mutations in genes encoding other receptors where psychedelics bind, such as other serotonin and dopamine receptors,[35] could hypothetically influence the response to these substances.

Pharmacokinetics

Significantly more evidence exists regarding pharmacokinetic effects, primarily involving CYP enzymes, where changes in their activity or function can impact the effects of psychedelics. For each psychedelic compound, a short overview of its metabolism including the role of enzymes in its breakdown and bioavailability, is provided separately. Refer to **Figure 1** for a visual summary of the metabolism of the discussed drugs, with the participating enzymes indicated.

Lysergic acid diethylamide

Lysergic acid diethylamide (LSD) is a synthetic psychoactive compound that is primarily metabolized in the liver through N-dealkylation and oxidation.[36] In humans, 2-oxo-3-hydroxy-LSD (O-H-LSD) is considered as the major metabolite.[36] Among the other metabolites, a notable one is N-desmethyl-LSD (nor-LSD), which has a half-life longer than LSD[37] and shows a similar binding affinity to 5-HT_{1A} and 5-HT_{2A} receptors, suggesting that the compound may also possess hallucinogenic properties, in contrast to the inactive O-H-LSD metabolite.[38]

Enzyme inhibition experiments on pooled human liver microsomes (HLMs) indicated that CYPs 1A2 and 3A4 have a major role in metabolism, with both, along with 2C9 and 2C19, involved in the initial metabolic steps.[39] The significance of CYP3A4 in the metabolism of LSD in HLMs was also confirmed in another study,[38] which demonstrated the 1A2, 2C9, 2E1, and 3A4 participation in the formation of O-H-LSD and 2D6, 2E1, and 3A4 involvement in the metabolism of LSD into nor-LSD.[38] A human study showed that individuals with non-functional CYP2D6 ($n = 7$) had higher plasma LSD levels and slower metabolism of the

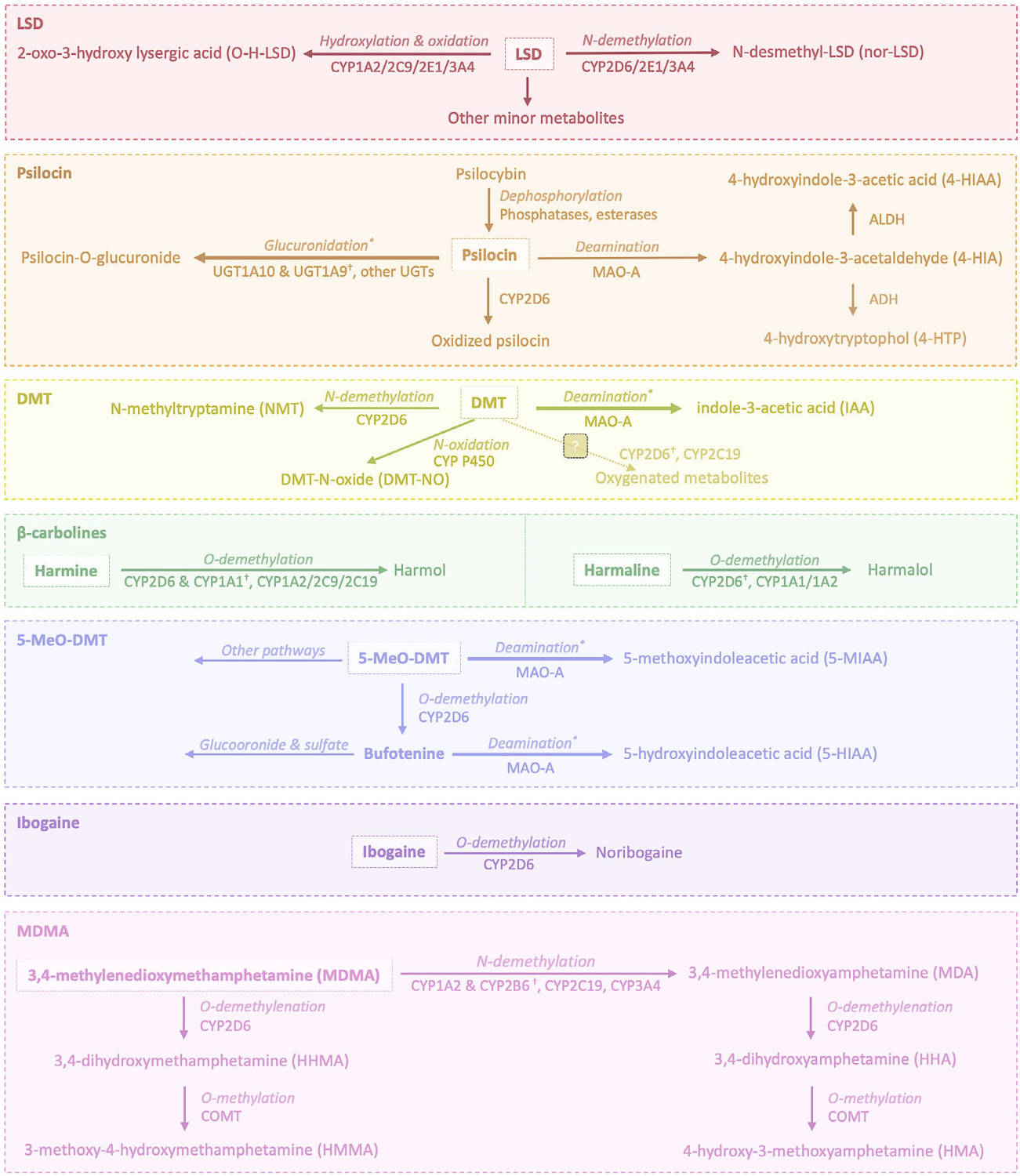

Figure 1 The suggested metabolism of LSD, psilocin, DMT, β-carbolines, 5-MeO-DMT, ibogaine and MDMA. This figure is based on the literature discussed (LSD,[38,40] psilocin,[42–44] DMT,[45,52,53] β-carbolines,[54] 5-MeO-DMT,[63–65] ibogaine[66,67] and MDMA[72]). *Indicates the major pathway where known, and † denotes the main contributing enzymes if multiple are specified. LSD, lysergic acid diethylamide; DMT, *N,N*-dimethyltryptamine; 5-MeO-DMT, 5-methoxy-*N,N*-dimethyltryptamine; MDMA, 3,4-methylenedioxymethamphetamine; MAO-A, monoamine oxidase A; ALDH, aldehyde dehydrogenase; ADH, alcohol dehydrogenase; UGT, UDP-glucuronosyltransferases; COMT, catechol-O-methyltransferase.

drug compared with those with functional 2D6 enzymes ($n = 74$), after being treated with ~ 100 µg LSD.[40] Increased levels of O-H-LSD in PMs were also observed, suggesting that this conversion can occur independently of 2D6, but no associations of other CYPs (1A2, 3A4, C19, C9, B6) in this study were detected; however, this could also be due to the limitations of the study. Compared with

those with functional enzymes, PMs experienced a significantly longer duration of subjective effects and a more intense altered state of consciousness (e.g., higher ratings in impaired control and cognition, anxious ego dissolution and anxiety), which may have led to a more challenging experience with increased anxiety and potentially reduced therapeutic effects.[40] The authors of the study concluded that a ~50% lower dose may be appropriate to use for PMs.[40]

Given the reported differences in LSD response between CYP2D6 phenotypic groups in humans, it would be valuable to assess the impact of *CYP2D6* genotype on LSD response in clinical trials. Prospective trials that systematically and uniformly document clinical phenotype (adverse drug reactions and efficacy), pharmacokinetics, and pharmacogenomics are necessary to determine the influence of genotype and guide genotype-informed prescribing guidelines. Clinical trials that incorporate PGx to adjust drug dosing could potentially achieve better and more consistent drug response and lead to better treatment outcomes, provided that phenotypic differences are well-defined. These studies would also offer valuable data for future dosing guidelines if LSD-assisted therapy becomes approved. Additionally, it may be worthwhile to retrospectively assess the impact of the *CYP2D6* genotype on LSD response in clinical trials if samples are available for analysis. CYP2D6 phenotypic differences could explain some of the observed inter-individual variations and should be considered in data analysis. Finally, considering that two *in vitro* studies have shown the importance of CYP3A4, it would be useful to determine the role of the enzyme on LSD effects. In particular, the infrequent *CYP3A4*22* allele, most common in Europeans (5%), has been reported to decrease the enzyme's activity and significantly influence the pharmacokinetics of several drugs.[41]

Psilocybin

Psilocybin is a naturally occurring substance found in several species of mushrooms.[42] It is a prodrug that is dephosphorylated into the pharmacologically active psilocin by alkaline phosphatases.[42,43] It is suggested that psilocin undergoes phase I metabolism by monoamine oxidase A (MAO-A) to form an intermediate metabolite 4-hydroxyindole-3-acetaldehyde (4-HIA) which is then oxidized by aldehyde dehydrogenase (ALDH) to produce 4-hydroxyindole-3-acetic acid (4-HIAA).[43] The 4-HIA can be reduced to 4-hydroxytryptophol (4-HTP) by alcohol dehydrogenase (ADH), but this has been detected only *in vitro* and not in humans, likely due to rapid metabolism or lack of production.[43] In contrast to psilocin, these metabolites were shown to have no relevant affinity or activation at the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2B} receptors.[43] The suggested main pathway for psilocin is phase II metabolism where it is glucuronidated into psilocin-O-glucuronide, which forms ~80% of psilocin metabolites.[42] In an analysis of 19 recombinant human UDP-glucuronosyltransferases (UGTs) from the 1A, 2A, and 2B subfamilies, UGT1A10 was found to have the highest activity for psilocin glucuronidation.[44] UGTs 1A8 and 1A9 also showed considerable activity in metabolizing psilocin, whereas UGTs 1A6 and 1A7 exhibited very low activity.[44] No activity was detected in UGTs 1A1, 1A3, 1A4, 1A5, 2A1, 2A2, 2A3, 2B4, 2B7, 2B10, 2B11, 2B15, 2B17, and 2B28.[44]

Despite UGT1A10 being the most active enzyme for psilocin glucuronidation, psilocin shows low affinity for this enzyme.[44] The glucuronidation process of psilocin by UGT1A9 is characterized by complex, biphasic kinetics, suggesting the presence of multiple substrate affinity sites.[44] It is suggested that psilocin glucuronidation mainly occurs in the small intestine (where UGT1A10 is highly expressed, over 100 times more than in the liver) and in the liver (which has a high expression of UGT1A9).[44] Thus, while UGT1A10 is the most active enzyme in the glucuronidation of psilocin, the significant presence of UGT1A9 in the liver suggests it may be a major contributor to the metabolic processing of psilocin in humans.[44] However, no studies have investigated genetic variants in the *UGT1A9* and *UGT1A10* genes that could influence psilocin's effects. Currently, there are *UGT1A9* gene variants associated with the metabolism of other drugs or their metabolites that are substrates for these enzymes (for details, see PharmGKB database at https://www.pharmgkb.org), which potentially may be relevant for psilocin's metabolism as well.

In vitro assessment of recombinant CYP enzymes has shown that while 1A2, 2B6, 2C8, 2C9, 2C19, and 2E1 did not exhibit any relevant activity, 2D6 and 3A4 were involved in the metabolism, with 2D6 rapidly metabolizing 100% of psilocin compared with 40% by 3A4.[43] However, none of the main metabolites tested were detectable when psilocin was metabolized by CYP3A4. Analysis of human samples showed no differences in plasma psilocybin concentrations across CYP2D6 phenotypes (PM = 3, IM = 25, NM = 58, UM = 2),[43] indicating that CYP2D6 likely plays a minor role in psilocin's effects and suggesting it is a minor pathway. However, the significance of this pathway may increase with MAO inhibition.[43] In fact, MAO inhibitors (MAOIs) are also consumed with psilocybin to intensify its effects[42] and hypothetically, CYP2D6 activity could influence the effects of this combination.

DMT and pharmahuasca

N,N-dimethyltryptamine (DMT) is a naturally occurring psychoactive compound found in several species of plants and is also an active component of ayahuasca.[45] Ayahuasca is a brew that contains, in addition to the DMT, also β-carbolines (primarily harmine, tetrahydroharmine, and harmaline) that act as MAOIs, preventing the extensive metabolism of DMT and making it orally active.[46] In this section, "pharmahuasca" is discussed which is a pharmaceutical version of ayahuasca that involves two main components of traditional ayahuasca in controlled concentration: DMT and MAOI (such as harmine or harmaline).[47] Harmine and harmaline are both potent inhibitors of MAO, including MAO-A,[48] while their metabolites harmol and harmalol as well as tetrahydroharmine (THH) have been shown to be much less potent inhibitors.[49,50] Despite THH being the second most abundant harmala alkaloid in the ayahuasca brew,[50,51] it can be suggested that THH plays rather a small role in MAO inhibition due to its weaker inhibitory potency and the high concentration of harmine.[51]

The major pathway of DMT metabolism is deamination by MAO-A, forming indole-3-acetic acid (IAA), followed by N-oxidation producing DMT-N-oxide (DMT-NO).[52] The latter becomes the main pathway when orally consuming either ayahuasca

or pharmahuasca as the MAO pathway is inhibited by β-carbolines. To a lesser extent, N-methyltryptamine (NMT) is also produced.[52] An *in vitro* study indicated a role of CYP2D6 and a minor role of CYP2C19 in DMT metabolism,[53] with 2D6 also noted to produce novel metabolites, likely through hydroxylation on the indole core.[45] Other enzymes, including 2A6, 2E1, 2C19[45] and 1A2, 2B6, 2C8, 2C9, 3A4, 3A5,[45,53] were not found to be significantly involved in DMT's metabolism. However, it is suggested that CYP2D6 has rather minor importance when MAO-A enzymes are present, indicating that this metabolic pathway may not significantly affect the standalone use of DMT,[45] although further research is needed to confirm this in humans.

More importantly, consuming DMT with MAOIs can alter the dynamics of metabolism and may increase the relevance of CYP2D6, which could have implications for such combinations. However, determining the phenotypic differences of enzymes in the effects of pharmahuasca is complicated because the common MAOIs used (harmine and harmaline) are also being metabolized, involving the same enzymes. For example, CYPs 1A1, 1A2 and 2D6 are metabolizing harmaline, and 1A1, 1A2, 2C9, 2C19, 2D6 harmine via O-demethylation.[54] Decreased CYP2D6 functionality can lead to increased and prolonged exposure to these compounds, as shown by reduced harmaline metabolism, slower depletion and longer half-life in hepatocytes and wild-type mice with 2D6 deficiency compared with those with functional 2D6.[55] Interestingly, harmaline, harmine and its metabolite harmol have been reported to inhibit CYP2D6, with harmine and harmol also inhibiting 3A4.[56] In such cases, the phenotypic differences of CYP2D6 may become less important due to phenoconversion – a phenomenon where the actual phenotype differs from the genetically inferred one.[57] Considering phenoconversion and assuming vast 2D6 inhibition, one may hypothesize that the drug-metabolizing enzyme's phenotype has rather a short-term impact when consuming DMT with harmine and/or harmaline (depending on their concentration and timing of administration). However, when using non-CYP2D6 inhibiting MAOIs, the influence of the phenotype on the DMT response could be more significant. Due to limited clinical research and the complexity of drug–drug-gene interactions, the extent to which the activity of the enzymes discussed influences the psychedelic effects of pharmahuasca remains unclear and likely depends on factors such as DMT and MAOI dosing and timing.

Finally, DMT has been identified as a substrate of two solute carrier (SLC) superfamily proteins: the proton/organic cation (H^+/OC) antiporter[58] and the organic cation transporter 2 (OCT2; encoded by the *SLC22A2* gene).[59] The H^+/OC antiporter is suggested to play an important role in transporting cationic drugs across biological membranes, such as the blood–brain barrier,[58] while OCT2 is primarily expressed in the kidneys and is involved in the renal elimination of hydrophilic substances.[59] The gene(s) responsible for the H^+/OC antiporter have not yet been identified and it is believed that the H^+/OC antiport is mediated by more than one protein,[60] making it currently unclear how genetics might affect its function. With regard to OCT2, an *in vitro* study found that the Ala270Ser variant of *SLC22A2* moderately reduced the transport of DMT, potentially leading to decreased elimination of the drug in individuals with this variant.[59] However, due to DMT's extensive metabolism, it is also suggested that *SLC22A2* polymorphism is unlikely to have a significant impact on DMT pharmacokinetics overall.[59]

5-MeO-DMT

5-Methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) is a psychedelic found in several plants, fungi, the gland secretions of the toad *Incilius alvarius* and mammals.[61] It is commonly administered parenterally, such as by smoking or vaporizing, as similar to DMT, it is orally inactive due to rapid metabolism by MAO in the gut and liver.[62] However, it can be made active by concurrent use of MAOIs.[63] The main 5-MeO-DMT metabolic pathway involves deamination to 5-methoxyindoleacetic acid (5-MIAA) by MAO-A and a small portion is O-demethylated by CYP2D6 to produce an active metabolite bufotenine (5-hydroxy-*N,N*-dimethyltryptamine; also a hallucinogenic compound), followed by its deamination to form 5-hydroxyindoleacetic acid (5-HIAA).[63]

The involvement of CYP2D6 in the O-demethylation of 5-MeO-DMT to bufotenin has been demonstrated in two studies using HLMs and hepatic microsomes from CYP2D6-humanized mice, while no activity was determined for other CYPs investigated, such as 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2A1, 2E1, 3A4, 3A5,[64,65] 1A1, 1B1, 2C18, 3A7, 4A11,[64] and 4A.[65] In HLMs, it was shown that CYP2D6 with decreased functionality produced less bufotenin than the fully functional enzymes, with isoforms *2 and *10 exhibiting 2.6- and 40-fold lower catalytic efficiency than the wild-type, respectively.[65]

While 5-MeO-DMT metabolism was consistent between CYP2D6 PMs and NMs in human hepatocytes due to the MAO-A-mediated major metabolic pathway, the concurrent use of MAOIs shifted the pathway to O-demethylation, leading to increased bufotenine formation in NMs.[65] The MAOI harmaline reduced the depletion of 5-MeO-DMT in both metabolizer groups, but bufotenine was detected only in hepatocytes from NMs, not PMs,[65] showing the differences in CYP2D6 activity in the capacity to convert 5-MeO-DMT to bufotenine. Moreover, bufotenine is also metabolized by MAO-A and the use of MAOIs will not only increase its production but also reduce its clearance.[63] Finally, as previously discussed, harmaline and harmine are substrates of CYP2D6, therefore the enzyme's activity can impact their metabolism, as evidenced by the slower depletion of harmaline in PMs.[55]

Considering that O-demethylation is a minor pathway, phenotypic differences in individuals are unlikely to significantly impact the effects of 5-MeO-DMT. However, confirming this in humans would be valuable. Hypothetically, given that 5-MeO-DMT and bufotenine have different receptor affinities (for example, bufotenine has several times higher affinity for 5-HT_{2A} than 5-MeO-DMT), using 5-MeO-DMT with an MAOI may result in altered effects mediated by different receptors, thereby influenced by the individual's genetics. This is probably more likely to occur with MAOIs that are not CYP2D6 inhibitors (unlike harmine and harmaline). With non-CYP2D6 inhibitors, PMs may exhibit no or minimal production of bufotenine, while individuals with functional enzymes metabolize these substrates more rapidly and can

convert 5-MeO-DMT to bufotenine. On the contrary, when using CYP2D6-inhibiting MAOIs, the difference between enzyme phenotypes can be hypothesized to be short-term, as the enzyme could undergo phenoconversion, leading to lower activity (potentially depending on the MAOI dose). While it would be interesting to determine phenotypic differences in humans, we are not aware of any clinical trials co-administering these compounds, and using 5-MeO-DMT with MAOIs may pose a risk of serotonin toxicity due to their agonistic effects on serotonergic systems,[63] thereby this potential combination needs to be carefully considered.

Ibogaine

Ibogaine is a naturally occurring psychedelic in the roots of the rainforest plant *Tabernanthe iboga*.[66] It has been suggested that ibogaine is metabolized to its main metabolite, noribogaine, primarily by CYP2D6 with minor contributions from 2C9 and 3A4.[66,67] In humans, NMs of CYP2D6 were shown to have lower ibogaine exposure but higher noribogaine levels due to faster metabolism, while PMs showed higher ibogaine exposure and significantly lower noribogaine levels with slower metabolism.[66] The role of CYP2D6 in ibogaine metabolism was confirmed in another human study using paroxetine, a strong CYP2D6 inhibitor.[68] Paroxetine-treated individuals ($n = 11$) had significantly higher peak concentrations and longer ibogaine half-lives compared with placebo-treated subjects ($n = 9$; 10.2 h vs. 2.5 h). Reduced CYP2D6 activity led to higher ibogaine exposure and similar noribogaine levels, effectively doubling overall exposure to active compounds.[68] CYP3A and CYP2C19 were not assessed in this study. Apart from CYP enzymes, the oral availability of ibogaine has been found to be significantly influenced by the two ATP-binding cassette transporters ABCB1 (P-glycoprotein) and ABCG2, where the former was shown to restrict ibogaine brain penetration.[69] However, while genetic variations of *ABCB1* and *ABCG2* genes can affect ibogaine exposure in patients, the extent of this impact was suggested to be relatively limited.[69]

Similarly to LSD, given the significant role of CYP2D6 in its metabolism, pharmacogenomic testing can be suggested for clinical trials involving individuals undergoing ibogaine treatment. Additionally, close monitoring during clinical trials, or even dose adjustments, would be important given the existing concerns about adverse events associated with the drug.[70] This is relevant to PMs, who may experience significantly stronger and longer effects of the drug and it has already been recommended to consider halving the dose for this phenotypic group.[68] In contrast, while not yet assessed, it can be hypothesized that UMs may clear the drug more rapidly and lead to a lower response of the drug. While this requires further research, there is a possibility that UMs may not be suitable candidates for ibogaine treatment, or may require a higher dose. Therefore, determining the CYP2D6 phenotype could enhance both the efficacy and safety of the treatment. The roles of CYP3A and CYP2C19 in its metabolism, especially in CYP2D6 PMs, require further investigation.

MDMA

While not a classical psychedelic, 3,4-Methylenedioxymethamphetamine (MDMA) is an entactogen which is being investigated for therapy to treat PTSD.[71] The metabolism of active MDMA occurs through two main pathways. In the first pathway, MDMA is primarily O-demethylenated by CYP2D6 to form 3,4-dihydroxymethamphetamine (HHMA), which is then O-methylated by catechol-O-methyltransferase (COMT) to form 3-methoxy-4-hydroxymethamphetamine (HMMA). The second pathway involves N-demethylation by CYP1A2 and CYP2B6 (and to a lesser extent CYP2C19 and CYP3A4), producing 3,4-methylenedioxyamphetamine (MDA). MDA undergoes similar metabolic reactions as MDMA, forming 3,4-dihydroxyamphetamine (HHA), followed by O-methylation by COMT to produce 4-hydroxy-3-methoxyamphetamine (HMA).[72] CYP2D6 is believed to contribute 30% of MDMA metabolism.[73]

In humans, it was demonstrated that CYP2D6 activity altered plasma MDMA levels, which were higher in PMs compared with NMs and lasted up to 3 h after drug administration, however, the difference was small (1.15× higher in PMs compared with NMs). Plasma HHMA levels were significantly higher in NMs, indicating CYP2D6's role in forming this metabolite. CYP2D6 activity was shown to alter systolic blood pressure, as well as "any drug rating" and "drug liking," which were higher in PMs compared with IMs and NMs, both at 0.6 h, and for "drug liking," also at 1 h.[72] However, considering that the difference in MDMA plasma levels between PMs and IMs/NMs were small, and variations in the psychotropic effects of MDMA were notable only within the first hour after administration, it suggests that the differences in CYP2D6 function have a minor and short-lived impact on its effects. This could be due to MDMA's ability to inhibit CYP2D6,[72,74] leading to autoinhibition of its own metabolism. Therefore, the impact of variations in the *CYP2D6* genotype is confined and primarily observable only in the initial hour following MDMA administration.[72]

Besides CYP2D6, *in vitro* studies have suggested the involvement of other CYP enzymes, such as 2C19, 2B6, and 1A2 that are involved in the N-demethylation of MDMA.[75,76] In humans, it was confirmed that 2C19, 2B6, and 1A2 are involved in the N-demethylation of MDMA to MDA.[77] However, polymorphisms in those enzymes did not significantly alter the subjective effects of MDMA.[77] Additionally, CYP1A2 (specifically in individuals carrying the inducible rs762551 AA genotype) showed increased activity in N-demethylation in light smokers compared with nonsmokers and very light smokers.[77]

In the *COMT* gene, which encodes an enzyme involved in the breakdown of HHMA and HHA, the Val158Met polymorphism (rs4680) has been previously reported to impact enzyme's activity, where the substitution of Val with Met is associated with decreased activity (that is, highest in Val/Val genotype and lowest in Met/Met genotype).[78] However, the results regarding its influence on antidepressant response are mixed.[79] Interestingly, the same mutation is associated with MDMA use disorder and MDMA-induced psychotic symptoms, where carriers of at least one Met allele were associated with a lower risk of developing MDMA use disorder and the Val/Val genotype with a lower risk of developing psychotic symptoms among those with the disorder.[80]

Taken together, considering the short-lasting differences in subjective effects in PMs of CYP2D6 due to autoinhibition and the fact that 2C19, 1A2, and 2B6 did not show any differences in subjective effects, pharmacogenomic testing may have limited clinical relevance in MDMA-assisted therapy. However, while impairments in individual enzymes may have only minor effects, the combined effect of multiple enzyme deficiencies could have a more significant impact on MDMA metabolism and potentially increase the risk of toxicity. For example, a case report documented a death after consuming MDMA while on ritonavir treatment (a strong CYP2D6 and CYP3A4 inhibitor).[81] Further research is needed to better understand the effects of rare combinations of enzyme functionalities.

Other psychedelic compounds

For other psychedelics, the literature is sparse. For mescaline, while the primary metabolic pathway involves amine oxidases[82] and it does not significantly interact with CYP2D6,[83] a study has shown it is a substrate for organic cation transporter 1 (OCT1), encoded by the polymorphic *SLC22A1* gene.[59] Genetic variants of OCT1 can significantly alter transporter expression and function, potentially causing inter-individual variations in mescaline pharmacokinetics.[84] This may lead to decreased elimination and an increased risk of intoxication and adverse effects in individuals with reduced or absent OCT1 activity.[59] However, the clinical implications of *SLC22A1* polymorphisms on mescaline's pharmacokinetics require further *in vivo* studies to evaluate their potential impact on its effects.

Lastly, *in vitro* evidence suggests that Salvinorin A is a substrate for CYP2D6, CYP1A1, CYP2E1, CYP2C18, UGT2B7, and possibly P-glycoprotein, with glucuronidation by UGT2B7 likely being the major metabolic pathway.[85] However, the impact of CYP enzyme activity on the effects of Salvinorin A remains unknown and requires further investigation.

Ketamine, which is a dissociative anesthetic but also has antidepressant properties and can produce psychedelic experiences at sub-anesthetic doses,[86] was not included in this review as it has already been systematically reviewed from pharmacogenomics perspective.[87]

DISCUSSION

Main findings and research perspectives

The current literature discussed in this review suggests that cytochrome P450 enzymes are involved in the metabolism of several psychedelics to varying extents. Most importantly, the highly polymorphic CYP2D6 enzyme has been shown to impact the effects of LSD, ibogaine, and to a lesser extent, MDMA under normal circumstances. For PMs of CYP2D6, it has been previously suggested to reduce the dose of LSD and ibogaine, notably by halving it.[40,68] While CYP2D6 also metabolizes DMT, harmine, and harmaline, its role in pharmahuasca is unclear and difficult to estimate due to drug–drug–gene interactions and variations in treatment protocols. When using MAOIs that inhibit the primary metabolic pathway of certain psychedelics, such as 5-MeO-DMT or one of the pathways for psilocin, the role of CYP2D6 may become more significant and the enzyme's function could have a more pronounced impact.

However, due to limited clinical data, no dosing suggestions can be made at this point. Further research is needed to ascertain granular data on phenotypic group differences for CYP2D6 PMs and UMs, ideally through larger and more diverse cohort studies. These drugs are still under investigation as potential medicines and must successfully complete further clinical trials to gain regulatory approval. If these drugs eventually become available, pre-emptive pharmacogenomics could potentially improve treatment outcomes, reduce side effects, and provide cost-saving benefits, particularly in populations with a higher frequency of extremes of CYP2D6 activity. Nevertheless, it is important to note that pharmacogenomics is just one approach to improve treatment efficacy by tailoring the dose to the individual. Other factors, such as the concomitant use of other medicines can lead to drug–drug interactions and influence the effects of psychedelics.[88] Moreover, the therapeutic setting and the participant's psychological state at the time of dosing, are also critical components that can significantly influence psychedelic-assisted therapy outcomes.[89] All in all, we recommended incorporating pharmacogenomics into clinical trials involving LSD and ibogaine, and exploring other potential drug–gene interactions discussed in this review to provide more insight. **Table 1** provides a summary of all the drugs discussed and suggestions for future research.

Factors to consider

To effectively use genetics-based determination of enzyme phenotypes and before deciding to do any dose adjustment, some additional factors should be considered and/or eliminated. Firstly, the activity of enzymes can be influenced by other drugs, herbs, smoking, pregnancy, comorbidities, and diet, which can lead to phenoconversion.[57] For instance, using LSD or ibogaine together with CYP2D6 inhibitors may result in a stronger response in individuals with functional enzymes, as the enzyme is phenoconverted to a lower activity state, similar to that of PMs. In some cases, the inhibition may be site-specific. For instance, grapefruit juice has been shown to lead to potent inhibition of intestinal CYP3A4, while the hepatic activity of CYP3A4 remained unaffected,[90] thereby can be important for orally administered drugs that are substrates for this enzyme. Moreover, individuals who have undergone liver transplants may have experienced phenoconversion. For example, it has been shown that following by a liver transplant, CYP2D6 PMs can convert to NMs as well as NMs to PMs, indicating that the genotype of the donor's liver controls the recipient's phenotype.[91] The utility of using enzyme activity-based recommendations is likely limited for autoinhibitors like MDMA, which is a potent inhibitor of CYP2D6.[73] MDMA causes the phenoconversion of the enzyme from NMs to PMs, with the activity taking longer than 10 days to return to basal levels.[92] This reduces the effectiveness of CYP2D6-based dose adjustments as the differences are likely short-lived. While PGx testing is relatively inexpensive, with a current cost of around AUD 149 in Australia (USD ~ 100) per panel that includes CYP2D6,[93] the challenge for clinical research aiming to characterize the differences lies in identifying enough patients with extreme metabolizer phenotypes,

Table 1 Summary of the findings and perspectives for future research

Drug	Summary and perspectives
LSD	A dose reduction may be appropriate for CYP2D6 PMs, and it has been suggested to halve it.[40] No information is available regarding UMs. The functional impact of the *CYP3A4**22 needs further assessment in humans. Other enzymes likely have less impact, but may be worth investigating this in a larger cohort of individuals
Psilocybin (psilocin)	While MAO, UGT1A9, and UGT1A10 are primarily involved in psilocin metabolism, no data are available on how genetic variants in these enzymes affect psilocin's effects. The phenotype of CYP2D6 has been shown not to have a significant impact under normal circumstances, but its role may increase when MAOIs are used. Investigating the effects of the His452Tyr (rs6314) mutation in the 5-HT_{2A} receptor (*HTR2A* gene) in humans would be worthwhile
DMT and pharmahuasca	CYP2D6 likely plays a minor role in DMT's effects when MAO-A enzymes are present, but its significance could increase with the use of MAOIs, as in pharmahuasca. While unclear for pharmahuasca, CYP2D6, CYP1A1, and CYP1A2 might also contribute to some extent, given their roles in the metabolism of DMT and the MAOIs harmine and harmaline. Determining the impact of CYP2D6 and other enzyme phenotypes in pharmahuasca is complex due to drug–drug–gene interactions and may also depend on various factors that differ between treatment protocols
5-MeO-DMT	While the major metabolic pathway of 5-MeO-DMT is catalyzed by MAO-A, a small proportion is metabolized by CYP2D6, whose significance increases when an MAOI is used. Although CYP2D6 phenotypic differences likely do not significantly impact the effects of 5-MeO-DMT, research in humans is necessary to confirm this. Hypothetically, combining 5-MeO-DMT with an MAOI may alter psychedelic effects due to increased conversion to bufotenine in individuals with functional CYP2D6. However, this combination may increase the risk of serotonin toxicity.[63]
Ibogaine	A dose reduction may be appropriate for CYP2D6 PMs, with halving the dose suggested for PMs.[68] The impact of the UM phenotype on the effects and toxicity of the drug is not known and requires further clinical studies, along with determining the roles of CYP3A and CYP2C19 in ibogaine metabolism
MDMA	CYP2D6 plays an initial role in the subjective response of MDMA, but this likely does not persist beyond an hour due to the enzyme's autoinhibition. Although CYP2C19, CYP2B6 and CYP1A2 have not been shown to affect the subjective effects of MDMA, further research on larger cohorts could help identify any rare combinations of enzyme phenotypes that might lead to toxicity

5-MeO-DMT, 5-methoxy-*N*,*N*-dimethyltryptamine; CYP, cytochrome P450; DMT, *N*,*N*-dimethyltryptamine; LSD, lysergic acid diethylamide; MAO-A, monoamine oxidase A; MAOI, monoamine oxidase inhibitor; MDMA, 3,4-methylenedioxymethamphetamine; NM, normal metabolizer; PM, poor metabolizer; UGT, UDP-glucuronosyltransferases; UM, ultrarapid metabolizer.

such as CYP2D6 PMs and UMs due to their low frequency in a population.

Limitations and final conclusion

Current clinical research on psychedelics primarily involves healthy participants. This limits our understanding of how these drugs will translate to individuals with comorbidities, such as cancer and liver disease that can lead to phenoconversion.[57] Data supporting the influence of genetics on the effects of some psychedelics remains limited. The impact of drug-metabolizing enzymes, as well as other factors such as mutations in drug receptors and molecule transporters, should be further investigated in clinical trials.

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CONFLICT OF INTEREST

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