FIVE GUIDE

Pharmacology and Drug Interactions of 5-MeO-DMT

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Dedication and Acknowledgement

Thank you for choosing to spend time becoming more familiar with potential drug interactions between 5-MeO-DMT and other substances. I hope this guide can be of service in facilitating the safe and beneficial use of 5-MeO-DMT. It is dedicated to all of the amazing persons working to further the use of this awe-inspiring substance. Guide figures created with BioRender.com.

Disclaimer

This guide is for information and educational purposes only. It is not to be considered medical advice. It is not meant to condone the use of illicit substances and the author recommends you do not break the law.

Disclosure

The author of the guide is a psychopharmacology consultant and founder of the website Spiritpharmacist.com As of the time of publishing this guide, he has relationships with several persons, providers, centers, and organizations involved in the use of psychedelic therapies including 5-MeO-DMT. However, he does not have any financial relationship with a company developing a psychedelic as a therapeutic entity.

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Section One: Introduction

Background

5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is an incredible, fascinating, and powerful compound that has a growing level of interest and enthusiasm regarding its use ceremonially as a religious sacrament, as a therapeutic agent, and as a drug for recreational use. A growing number of people are hearing about and wanting to try 5-MeO-DMT. In parallel, people are taking more medication and more supplements than ever before.

There is apparent severe drug interaction potential between 5-MeO-DMT and other drugs with cases of death occurring in combination with monoamine oxidase inhibitors (MAOIs) [1, 2]. Therefore, this guide was created as an attempt to inform those that facilitate or may participate in use of 5-MeO-DMT about risks of drug combinations.

Guide Methodology

This guide was constructed using a combination of data from sources such as peer reviewed literature, expert testimony, and participant anecdotes. **Information about 5-MeO-DMT is scarce and even less is known about drug combinations.** Therefore, this guide should be reviewed and updated periodically to allow for the most accurate information possible. Subsequently, information contained in this guide should be approached skeptically as it is to an informed guess than vetted science. The guide was written by a single individual, therefore may include opinion or bias at certain points.

Gauging Risk

Gauging the risks of drug interactions with 5-MeO-DMT can be confusing and challenging for several reasons. The individual differences in sensitivity to effects, metabolic function, medications or supplements persons are taking, as well as other parameters of psychedelic experience such as ‘set and setting’ can all influence the experience and safety of use.

5-MeO-DMT is not used therapeutically in any conventional medicine system and is regulated as an illicit drug in some parts of the world, which are factors that tend to reduce the ability to collect data that accurately informs safety risks. Existing information may seem to be conflicting as recommendations from scientific sources often seem misaligned with personal anecdotes and when deaths occur there are usually other factors that need considered for proper interpretation. This guide attempts to address some of these issues by outlining what is known about the pharmacology of 5-MeO-DMT and extrapolating this information to help inform risks of drug interaction.

Facilitating For Safety

There are many facets of facilitating safely that are not discussed or minimally discussed in this guide that are required to maximize safety. Creation of a safe space and giving close attention to set and setting are integrally important, however this guide will focus on safe facilitation through the limited lens of drug combinations and interactions. To this end, all facilitators need to have a screening process that, at minimum, collects information regarding illnesses, medications, supplements, herbs, recreational substances, and allergies which is then systematically reviewed. Screening would ideally be performed weeks to months ahead of a planned experience to allow for management of interacting medications and adequate preparation, rapport building, or other aspects of facilitator work than can improve experience quality.

Adverse Effects and Statistical Probability

It is recommended to avoid the combination of MAOIs with 5-MeO-DMT. However, there are many existing reports from online forums (erowid, bluelight, reddit) that document individuals taking these types of combinations without serious injury and sometimes with an endorsement of a profound experience. The discrepancy in information between anecdotal reporting and scientific sources could be explained on a statistical basis for a bad outcome. If the particular drug combination of 5-MeO-DMT and drug X has a risk of death of 1% then you would have to use the combination one hundred times (1/0.01 = 100) to expect a single death to occur.

If you are in a position in which you facilitate 5-MeO-DMT for others this risk should be unacceptable as you would likely facilitate for more than 100 people in your life. Using a statistical approach to your facilitation practice when considering drug interaction risks is not feasible due to lack of data. Yet it clarifies why anecdotal reports oftentimes claim a combination is safe while scientific sources recommend against the combination. It's because 99% of people will survive the drug combination experience. This can create a perception of safety when there is actually a real danger of combining certain drugs. Dose and route of administration may also play a large role in whether toxicity develops in response to a combination or not. For example, use of small amounts of 5-MeO-DMT containing snuff at the end of an ayahuasca ceremony likely has relatively less risk compared to ingesting a moderate amount of 5-MeO-DMT orally with ayahuasca.

Since a facilitator may facilitate for hundreds to thousands of participants in their lifetime, it is in good judgement to practice conservatively in the face of theoretical yet uncertain interaction potential. Even if the risk seems low, consider the severity of the consequences if it were to occur as well as preparedness to manage them. Participants and psychonauts are similarly cautioned in that some drug combinations may be very dangerous even if there are reports that claim it was okay in an individual.

Section Two: Pharmacology

Pharmacodynamics

Mechanism of Action

5-MeO-DMT is an indolylalkylamine tryptamine psychedelic that is known for its potent entheogenic properties. It is thought to produce its powerful mind-altering effects by binding with high affinity to serotonin (5HT) receptors such as the $5HT_{1A}$ and $5HT_{2A}$ receptor [3].

5-MeO-DMT is a full agonist at both 5HT1A and 5HT2A receptors, while classic tryptamine psychedelics (psilocin, LSD, DMT) are partial agonists. Some data even suggests 5-MeO-DMT is capable of producing supraphysiologic responses at 5HT receptors in reference to the endogenous ligand serotonin [3, 4].

5-MeO-DMT also appears to bind the serotonin reuptake pump and has (weak) serotonin reuptake inhibiting properties [5]. This may mean that 5-MeO-DMT can raise intrasynaptic serotonin, which is not a feature of classic tryptamine psychedelics. 5-MeO-DMT is at least partially metabolized to the active metabolite bufotenine (see pharmacokinetics section for greater detail) and when 5-MeO-DMT is sourced from Bufo alvarius venom it contains additional amounts of bufotenine, which could contribute to adverse effects with minimal levels of psychoactivity [6].

5-MeO-DMT is similar to the classic psychedelic N,N-dimethyltryptamine (DMT) in the sense that it is typically used via the inhalation route, displays minimal tolerance to repeated use, and has a relatively short duration of action compared to oral tryptamine psychedelics like psilocin. However, 5-MeO-DMT is approximately 4-10x more potent than N,N-DMT (per dosing requirements) and has been reported to be toxic in combination with MAOIs, whereas N,N-DMT is routinely combined with MAOIs safely (e.g., ayahuasca) [1, 7, 8].

Collectively, this means that 5-MeO-DMT is a stronger serotonergic substance than classic tryptamine psychedelics and that it may also be able to raise intrasynaptic serotonin [9]. It suggests that while classic tryptamines enjoy a wide physical safety margin in overdose settings, that there may be relatively greater potential for toxicity in overdose with 5-MeO-DMT or that 5-MeO-DMT may be more dangerous in combination with other substances that can increase intrasynaptic serotonin. There appears to be case precedent for this due to death being reported in combination with MAOIs, which prevents the breakdown of serotonin and acts to raise intrasynaptic serotonin (see section on serotonin toxicity for greater detail).

Subjective Experience

Subjective experience is largely dependent on the dose administered as well as the set and setting the individual brings to the experience. However, 5-MeO-DMT could be considered a ‘quintessential entheogen’ in that it tends to produce subjective experiences characterized by highly mystical or non-dual types of experiences in which the subject-object relationship collapses, and the individual feels merged with a greater reality [10, 11]. This is in contrast to N,N-DMT which produces a highly ‘hallucinogenic’ type of experience characterized by fractalized and hyperreal hallucinations in which the

subject-object relationship is preserved and the user encounters another 'entity' [12, 13]. Psychedelics such as psilocin or LSD appear to produce experiences somewhere in between these two poles of psychedelic effect with many persons reporting mystical as well as hallucinogenic effects.

5-MeO-DMT vs. *Bufo alvarius* Venom

5-MeO-DMT is naturally occurring in low concentrations among various plant species as well as in higher concentrations in the venom of *Bufo alvarius* or *Incillius alvarius* (aka Sonoran Desert Toad or Colorado River Toad). It can also be synthetically produced in a laboratory. There are several advantages that the pure compound 5-MeO-DMT offers relative to toad venom. For example, pure 5-MeO-DMT is suitable for use via vaporization devices as well as intravenous or intramuscular routes of administration, whereas Bufo venom either will not work in vaporization devices or could potentially be lethal if used by parenteral injection routes [14]. Dosing can be accomplished with precise accuracy when using pure 5-MeO-DMT whereas Bufo alvarius venom contains varying amounts of 5-MeO-DMT along with bufotenine and other compounds that compose the venom (e.g., bufodienolides)[6]. There are also environmental considerations such as habitat destruction and disruption to toad populations associated with harvesting of Bufo venom. Overall, the pure compound is pharmacologically superior to Bufo alvarius venom and will be the focus of discussion in this guide.

Pharmacokinetics

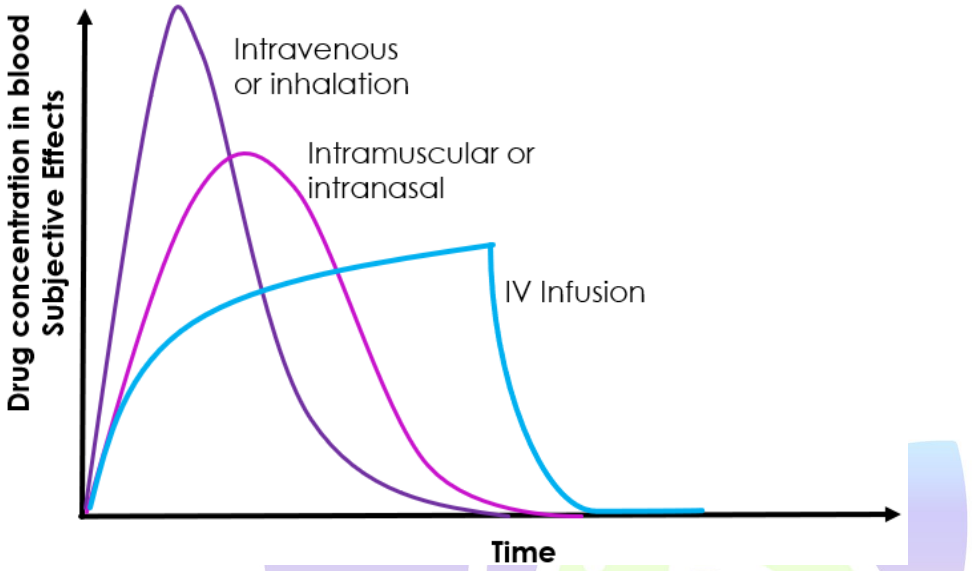
Route of Administration

5-MeO-DMT is either not bioavailable or minimally bioavailable when taken by mouth, with some reports lacking psychoactivity and others reporting minimal psychoactive effects with oral use [15, 16]. Use with monoamine oxidase inhibitors (MAOIs) to boost oral bioavailaibility is not an option with 5-MeO-DMT due to risks of Serotonin Toxicity [3, 9]. Inhalation and intravenous injection routes of administration have the fastest onset and shortest duration of action, while intramuscular on intranasal routes of administration provide experiences with slightly slower onsets and longer durations of action. Other routes such as rectal use have also been reported. The pharmacokinetics of 5-MeO-DMT will depend partially on the route of administration, although will have a faster onset and offset than orally administered tryptamines (e.g., psilocybin, LSD) with a higher intensity of effects and blood concentrations of substance at the experience peak. The half-life of 5-MeO-DMT is around 15-20 minutes.

Table 1. Kinetics and Dosing of 5-MeO-DMT by Route of Administration for Strong Effects

Parameter	Inhaled	Intranasal	Intramuscular
Dose	8-12mg	10-25mg	6-15mg
Onset	~10 seconds	5 min	1-6 min
Peak	2-15 min	10-30 min	10-30 min
Duration	30 min	30-60 min	60 min

Figure 1. Approximate Experience Trajectory by Route of Administration



Collectively, this information means that there is a high degree of likelihood that 5-MeO-DMT produces larger shifts in cardiovascular parameters such as blood pressure and heart rate than orally administered psychedelics. Facilitators may consider this when selecting candidates and exercise additional caution in persons with cardiovascular illness or advanced age.

Dosing Approach

There is a wide range of sensitivity to the effects of 5-MeO-DMT reported among experience facilitators and users. For most persons, there tends to be a dose in which volition is completely lost and the person undergoes a 'full release'. While a 'full release' likely offers a highly mystical and transformative experience, it is unclear if this is always optimal or should be the goal of 5-MeO-DMT use. This is because moderate-high doses are usually required to achieve those effects and may also risk a traumatizing experience or increased undesirable post-use effects (e.g., reactivations). The table below approximates dosing necessary for a full release experience depending on the route of administration:

It is reasonable given the lack of tolerance to repeated dosing that persons receive at least one smaller test dose of 5-MeO-DMT before receiving a larger dose. There are many possible advantages to administering a test dose such as discovery of level of sensitivity, acquaintance of the user with some effects, allowing the person to interact with their experience more, or allowing the person 'somatic catharses' and full relaxation of their nervous system before attempting a 'full release' experience.

There may also be advantages of working with 5-MeO-DMT in much more gradual dose-escalating sequences, which may give the user much more control over the depth of experience and allow them to eventually go as deep as they desire while effectively processing emotion as they go. Vapor pens with titratable cartridge strengths are helpful tools for this approach (Grace Within https://erowid.org/chemicals/5meo_dmt/5meo_dmt_article2_vape_pens.shtml).

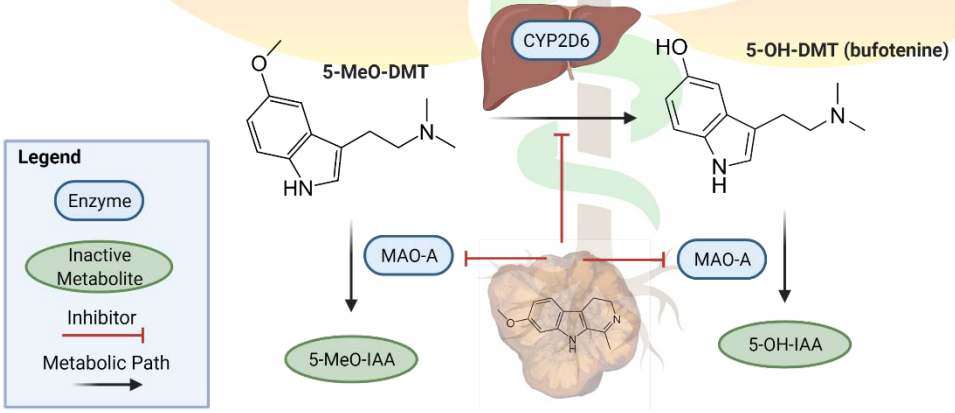
Metabolism and Drug Interaction Potential

5-MeO-DMT has two major metabolic enzymes or routes of metabolism. In the brain as well as peripherally 5-MeO-DMT is metabolized by MAO-A to an inactive indole acetic acid (5-MeO-IAA) whereas in the liver it's metabolized by CYP2D6 to the active metabolite bufotenine (5-hydroxy-N,N-dimethyltryptamine) [17].

Upon inhalation or other parenteral delivery route, 5-MeO-DMT is absorbed directly into systemic circulation. This is important because it may signify that metabolism at the neuronal synapse or 5-MeO-DMT's site of action is more significant for 5-MeO-DMT than CYP2D6-mediated hepatic metabolism (where most oral drugs are primarily metabolized) [3]. Drugs that inhibit MAO-A are higher risk in combination with 5-MeO-DMT than those that inhibit CYP2D6. This is both because MAO-A may play a larger role in metabolism and due to the differential risks of inhibiting either enzyme [3].

Users of 5-MeO-DMT that take drugs that inhibit CYP2D6 or those with slow metabolizer phenotypes of the CYP2D6 enzyme would be predicted to have less bufotenine formed and slightly higher exposure to 5-MeO-DMT, yet could still metabolize 5-MeO-DMT to 5-MeO-IAA with MAO which is the predominant metabolic route [18]. On the other hand, inhibition of MAO with MAOIs blocks the metabolism of 5-MeO-DMT and serotonin, which could lead to excessive accumulation of serotonin in synapses as well as increased formation of bufotenine and Serotonin Toxicity [9]. Of note, harmaline found in *ayahuasca* can inhibit both MAO-A and CYP2D6 and has the worst reported toxicities in combination with 5-MeO-DMT including death.

Figure 2. Metabolism of 5-MeO-DMT



5-MeO-DMT and bufotenine rely on MAO & CYP2D6 which are **both** inhibited by harmala alkaloids found in the ayahuasca vine. CYP2D6 is hepatically localized while MAO-A is found both hepatically and systemically at serotonin nerve terminals

5-MeO-IAA and 5-OH-IAA = indole acetic acids (inactive mteabolites)
5-OH-DMT = bufotenine (active metabolite)
MAO-A = Monoamine Oxidase A

Section Three: Drug Interaction Potential and Contraindications

Red Flags and Contraindicated Conditions

While some conditions, drugs, or medications are considered to be absolute contraindications and are incompatible with 5-MeO-DMT use, others may be considered relative contraindications or 'red flags'. A red flag is a condition or drug interaction that likely presents some additional risks, although use may still be reasonable if the condition is evaluated, discussed, and plans put in place to increase safety of use.

Pharmacodynamic Drug Interactions

There are several ways that drug interactions can occur with 5-MeO-DMT. Pharmacodynamic drug interactions happen when two drugs are mixed that modulates the effects of either substance due to similar targets in the body. 5-MeO-DMT is both a full serotonin agonist and reuptake inhibitor which differentiates it from classic tryptamines which are partial serotonin agonists that do not effect serotonin reuptake or its release [3, 19].

Pharmacodynamic interactions can be diminutive, additive, or synergistic in nature. Additive drug interactions simply have the intensity of each drug's effect added together (1 + 1 = 2) while synergism has an intensity of effect that exceeds that of the individual agents added together (1 + 1 = 5). Diminutive interactions result in blunted or diminished effects in combination (1 + 1 = 0.5).

For example, MDMA (3,4-methylenedioxymethamphetamine) inhibits the reuptake of serotonin, norepinephrine, and dopamine, acts as a serotonin agonist, and is also capable of interfering with packaging of these neurotransmitters causing them to leak into neuronal synapses via a process called carrier-mediated release [20, 21]. Because it is a strongly serotonergic and a stimulant drug it could lead to an interaction if used in conjunction with 5-MeO-DMT. The extent of the interaction and whether the combination leads to toxic effects is a function of the doses used and temporal timing of administration for each drug, as well as individual and setting-related factors.

There may be indirect types of drug interactions between many psychiatric medications or other psychoactive substances and 5-MeO-DMT. While these interactions will almost never present risks of serious adverse reactions, the totality of their effects may be broadly considered in planning for experiences. For example, use of drugs with sedative effects like benzodiazepines may generally take the edge off psychedelic effects. Depending on the dose used and proximity to the experience they may have significant or non-significant effects. Similarly, stimulants tend to be ego-retentive substances and may limit the ability to enter a place of mystical consciousness or raise cardiovascular risks when used concurrently, yet would likely not pose much in the way of risks with short breaks around the time of an experience.

Pharmacokinetic Drug Interactions

When two drugs are mixed that interfere with the metabolism of one or both administered drugs it is termed a pharmacokinetic drug interaction. Drugs with pharmacokinetic drug interaction potential with 5-MeO-DMT are monoamine oxidase-A inhibitors (MAOIs) and CYP2D6 inhibitors [3].

Below are two tables of drugs with CYP2D6 or MAO inhibitory properties. Since inhaled 5-MeO-DMT largely bypasses the liver upon absorption and MAO is the primary metabolic routes, it's unclear how significant inhibition of hepatic (liver) CYP2D6 is in modulating risks although is surely much less than use of MAOIs which are contraindicated.

Table 2. Medications with CYP2D6 Inhibitory Activity

CYP2D6 Inhibitors*		
Strong	**Moderate**	**Weak**
Paroxetine	Duloxetine	Amiodarone
Bupropion	Mirabegron	Cimetidine
Quinidine	Abiraterone	Escitalopram
Cinacalcet	Lorcaserin	Fluovoxamine
Fluoxetine		Sertraline
Terbinafine		Celecoxib
		Cobicistat
		Clobazam
		Labetalol
		Ritonavir
		Vemurafenib

*Strong, moderate, and weak inhibitors are drugs that increase the Area Under the Curve (AUC) of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. This table is adapted from table 3-2 on the FDA's website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Their list may not be all inclusive, please see sources below for other medications that may inhibit CYP2D6:

- http://www.pharmacytimes.com/publications/issue/2008/2008-07/2008-07-8624.
- http://medicine.iupui.edu/clinpharm/ddis/main-table
- https://www.mayomedicallaboratories.com/it-mmfiles/Cytochrome_P450_2D6_Known_Drug_Interaction_Chart.pdf

Table 3. Drugs that Inhibit Monoamine Oxidase A

Monoamine Oxidase A Inhibitors (MAOIs)*
B carbolines or harmala alkaloids: Harmine, harmaline, tetrahydroharmine, ayahuasca, Syrian rue
Moclobemide
Tranylcypromine
Phenelzine
Isocarboxazid
Selegiline (doses ≥9mg/day)
Methylene blue (dye)
Linezolid

***MAOIs are contraindicated with 5-MeO-DMT and should not be used in combination**

Drug-Disease Interactions

There may or may not be any interaction between medications a person is using and 5-MeO-DMT, although one should always ask what the drug is used for and consider the underlying condition as well as any risk of drug interaction. Even if medications are not being taken, it is recommended to ask what medical conditions a person has or has a history of when screening applicants.

Medical Conditions

There are probably relatively few medical conditions that are absolute contraindications for use of 5-MeO-DMT. Due to the possible intensity of moderate to high doses on the cardiovascular system a holistic assessment of physical health may help in understanding if they could tolerate the experience. Questions may arise around potential for drug interactions between medications for medical conditions and 5-MeO-DMT. While some could exist and screening medications for safety and planning is always a good idea, there are likely relatively few that pose significant risks and much more fruitful in most cases to focus on the condition being treated.

For example, rivaroxaban is an anticoagulant medication that has no predicted interactional potential with 5-MeO-DMT. However, anticoagulants are potent blood thinning agents and are usually used to treat prevent stroke or blood clots in people with a history of arrhythmias or thromboembolism. The person may seek clearance from their physician for the experience, safeguards to ensure the participant does not fall or bump themselves are in place and plans for an emergency are known ahead of time. Use of small tests doses or a sequence of small doses may increase safety compared to large bolus doses.

There are many other examples of diseases or medications that may not interact directly with 5-MeO-DMT, although the overall health condition of the participant should be considered as some persons with advanced illnesses may be too frail for such an intense experience and be at risk for heart attacks or other adverse outcomes. Facilitators may even keep in mind that some conditions may be undiagnosed (e.g., high blood pressure) and consideration of measuring vital signs at baseline on the day of their session could reassure persons that unknown risks are not being taken.

Psychiatric Conditions

Particular attention needs to be given to the underlying psychologic stability and condition of potential users of 5-MeO-DMT. Albeit anecdotal, it appears that 5-MeO-DMT can provide an 'opening' or 'expansion' of consciousness of greater intensity than many other psychedelics. Persons with psychotic or a bipolar I condition are likely not well suited for 5-MeO-DMT and use is contraindicated in their presence. Caution may be exercised in persons with high levels of anxiety or panic disorder as they may be more prone to distressing reactivations. Avoidance of psychedelics in persons with personality disorders (e.g., narcissism, borderline) is reasonable based on difficulty forming trust or rapport with the facilitator and potential to worsen behaviors. Persons suspected of having a mental health condition that has not been evaluated can seek an evaluation prior to engaging with 5-MeO-DMT.

Contraindicated Conditions

Conditions that are considered absolute or relative contraindications (red flags) are listed below. This list may not be all inclusive:

- Schizophrenia, schizoaffective, and other psychotic conditions
- Bipolar disorders, particularly Bipolar I Disorder
- Antisocial, Borderline, or Narcissistic Personality Disorder
- Active Substance Use Disorders
- Active Suicidality
- Uncontrolled Hypertension
- Advanced cardiovascular conditions such as arrythmias, heart failure, coronary artery disease, angina or chest, myocardial infarction, stroke, TIA, or bleeding and clotting conditions
- Terminal illness
- Tumors in the Central Nervous System
- Severe respiratory illness
- Liver or kidney failure
- Epilepsy or seizure disorders
- Traumatic Brain Injury
- Pregnancy or Nursing

Section Four: Serotonin Toxicity

5-MeO-DMT and Serotonin Toxicity

Serotonin Toxicity is best understood as a type of poisoning or adverse effect of serotonergic drugs involving excessive intrasynaptic serotonin that results in toxic levels of signaling via the $5HT_{2A}$ receptor [22]. It is often discussed as Serotonin Syndrome which is less accurate as it's not a group of symptoms that define a condition and it can occur along a spectrum . Therefore, substances that increase intrasynaptic serotonin such as monoamine oxidase inhibitors (e.g., MAOIs), serotonin reuptake inhibitors (SRIs e.g., SSRIs, SNRIs) as well as serotonin releasing agents (SRAs e.g., MDMA) are most implicated in the development of Serotonin Toxicity [23]. However, the underlying mechanisms of each substance and their abilities to act additively, synergistically, or diminutively in combination require evaluation to understand if the combination is truly high risk for Serotonin Toxicity [9].

When psychedelics bind to $5HT_{2A}$ receptors they produce powerful mind-altering effects, which are sometimes accompanied by physical sensations or reactions (e.g., serotonergic responses). Multiple intracellular signaling cascades are possible when psychedelics bind 5HT2A receptors and one pathway is linked to physiological responses and actions of serotonin, while other(s) are linked to hallucinogenic or psychedelic effects. This effect is termed functional selectivity or biased agonism and may help account for why some psychedelics present physically mild serotonergic effects despite extreme effects on mental processes or other substances lack psychedelic effects entirely while still being able to produce serotonergic responses from binding 5HT2A receptors (e.g., bufotenine) [3].

Relative to other tryptamine psychedelics, 5-MeO-DMT appears to be a stronger serotonin stimulating substance and may even be able to activate 5HT receptors to a greater extent that serotonin itself, whereas classic tryptamines (LSD, psilocybin, DMT) are only partially able to stimulate serotonin receptors [4, 19]. It is also a full agonist at the 5HT1A receptor. This may explain why it appears Serotonin Toxicity can occur with 5-MeO-DMT (particularly in combination with MAOIs) whereas it has not been reported with LSD, psilocybin, or DMT. Other contributing aspects of 5-MeO-DMT's pharmacology to risk of Serotonin Toxicity could include its serotonin reuptake inhibition as well as the presence of its active metabolite bufotenine (more probable with toad venom).

While 5-MeO-DMT is dangerous with MAOIs and there are unique aspects of its pharmacology that could help explain why this is, there is little to support that there is risk of Serotonin Toxicity at standard doses without use of concomitant agents that could also increase serotonin. Even with other agents that can raise intrasynaptic serotonin (e.g., SSRIs, SRAs) it is unclear whether the combination truly presents risk or danger of Serotonin Toxicity when dosing and approach is conservative.

Recognition of Serotonin Toxicity

It is hypothesized that somatic experiencing or physical reactions to psychedelics can be associated with release of trauma from the nervous system. If this is experienced, it could be interpreted and emotionally felt to be a healing release by the subject, although a wide range of experience interpretations are possible including extreme fear or terror. While shamanistic practices, transpersonal

trauma therapists, or psychonauts may associate somatic reactions to psychedelics with healing, the signs and symptoms of these reactions could be interpreted by allopathic medicine as signs and symptoms of mild Serotonin Toxicity [24].

Many common features of psychedelic physical reactions or somatic experiences are consistent with mild serotonin toxicities including pupil dilation (mydriasis), changes in body temperature (sweating or cold), hyperreflexia (mild tremor or shaking), and gastrointestinal upset (nausea, vomiting, diarrhea) [25]. While these symptoms are present transiently in the psychedelic experience, they are more chronic with Serotonin Toxicity involving pharmaceutical drugs or drug combinations. Persistence of somatic symptoms beyond the expected duration of the 5-MeO-DMT experience or particularly intense somatic symptoms should be a red flag for facilitators.

While moderate increases in serotonin neurotransmission associated with psychedelic or 5-MeO-DMT use may be a necessary or 'primary healing mechanism', there is a point in which the serotonin neurons become overwhelmed and physical reactions become dangerous and life threatening instead of healing. In the scientific literature, these reactions are called Serotonin Toxicity and involve extreme hyperthermia (fever >39C), autonomic dysfunction (unstable heart rates and blood pressures), myoclonus (convulsions or seizure-like activity), and altered mental status (agitation, confusion, or comatose) [9].

Management

Facilitators will want to have equipment on hand such as a blood pressure cuff and thermometer, which may help to identify and differentiate toxic reactions requiring immediate care and intervention from somatic reactions likely to be experienced as healing. Cold packs on hand for hyperthermia, and an intramuscular (IM) benzodiazepine in the case of hypertension, agitation, or seizure activity are helpful management tools while emergent help is sought. Use of physical restraints should be avoided due to risks of isotonic muscle contraction exacerbating hyperthermia [26]. Suspected cases should be transferred to a medical facility as rapidly as possible due to potential for progression as well as ability to use other supportive medications (e.g, cyproheptadine, dantrolene) and interventions (e.g., intubation, IV fluids, oxygen).

Overall Risk

It appears that when 5-MeO-DMT is used alone and not in combination with any other serotonergic drugs at moderate doses, there is minimal risk of Serotonin Toxicity and somatic reactions are usually experienced as healing. Beyond MAOIs which have been observed to be dangerous in combination, it is unclear how much risk there is to using other drugs with serotonin-based mechanisms (e.g., SSRIs) with 5-MeO-DMT. While combinations of serotonergic drugs (not involving 5-MeO-DMT) have been reported to cause Serotonin Toxicity, life threatening toxidromes typically do not occur without use of MAOIs and two or three medications with serotonergic mechanisms are routinely combined in medical practice.

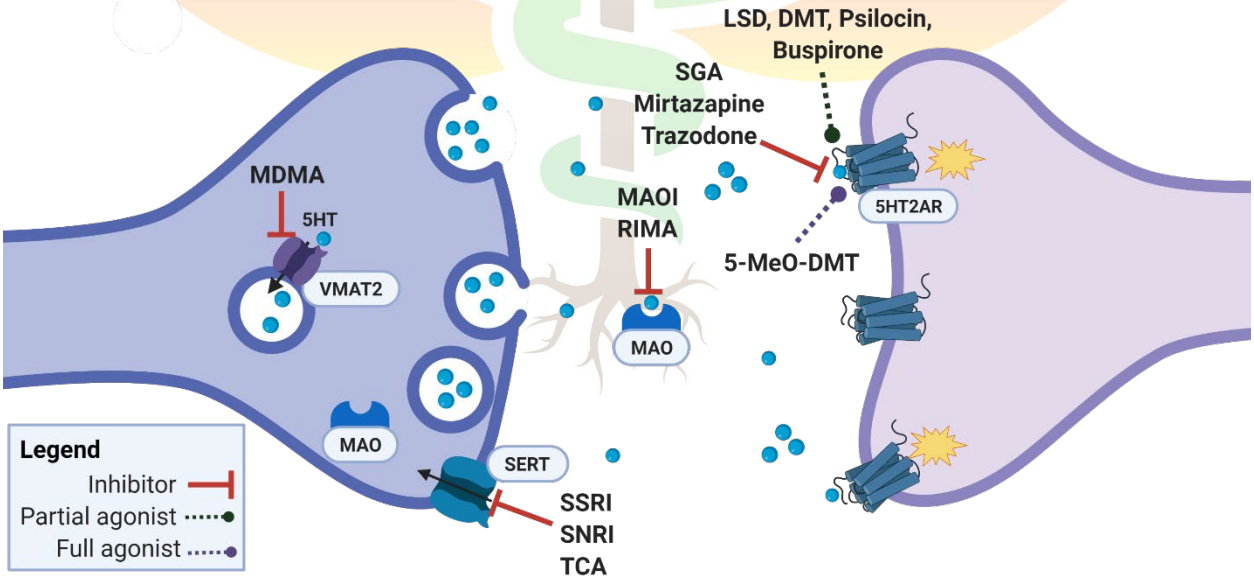
Section Five: 5-MeO-DMT and Drug Interactions

Serotonergic Drug Interactions by Medication Class

Due to serotonergic actions of 5-MeO-DMT, it is medications that have activity in the serotonergic nervous system that may play the largest role in pharmacodynamic drug interactions. Serotonin Toxicity is primarily mediated through the 5HT2A receptor, meaning that drugs with actions outside of this receptor likely have little relevance to drug interactions that could have risk of Serotonin Toxicity (e.g., ondansetron as a 5HT3 antagonist). Table 4 stratifies risk levels for substances with serotonergic properties in combination with 5-MeO-DMT.

This section is not all inclusive and contains some brief notes on the most common types of serotonergic medications that may be encountered or considerations for use in a person. It is recommended to seek consultation for further guidance, particularly with multiple medications, advanced illnesses, or history of sensitivity, allergy, or intolerance to medications or psychedelics. The diagram below depicts common classes or serotonergic medications and where they act in serotonin 2A synapses to allow for a more visual understanding of how drugs may compete or interact at similar targets. Note that some drugs or medications bind multiple targets in the 5HT neurotransmitter system. At risk of reductionism, this figure displays the primary target only.

Figure 3. Primary Targets of Common Medications and Psychedelic Drugs at Serotonin 2A Synapses



serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), second generation antipsychotic (SGA), monoamine oxidase inhibition (MAOI), reversible inhibitor of monoamine oxidase (RIMA), 3,4-methylenedioxymethamphetamine (MDMA), N,N-dimethyltryptaminue (DMT), Lysergic acid diethylamide (LSD)

Table 4. Risk Stratification and Management of Substances with Serotonergic Properties

Medication Class	Risk Stratification	Effect	Management
MAOIs (e.g Harmala alkaloids, Syrian rue, Ayahuasca Moclobemide Tranylcypromine Phenelzine Isocarboxazid Selegiline Methylene blue Linezolid	Contraindicated due to risk of Serotonin Toxicity	Increased or toxic responses	Taper, discontinue and wash out prior to use (time dependent on agent reversibility with MAO)
Lithium	Contraindicated due to risks of seizures	Increased or toxic responses	Taper, discontinue and wash out at least 5-7 days prior to use
SSRIs (e.g., fluoxetine, paroxetine, escitalopram, fluvoxamine, citalopram, sertraline)	Caution due to increased synaptic 5HT and/or CYP2D6 inhibition	Diminished effects, potential for increased exposure	Weigh risks and benefits of discontinuation. If stopping medication, wash out for at least 2 weeks for all agents except fluoxetine which may require a longer wash out of 4-6 weeks
SNRIs (e.g., duloxetine, venlafaxine, desvenlafaxine)			
SPARIs (e.g., vortioxetine, vilazodone)	Caution due to increased synaptic 5HT and/or competition at 5HT receptors	Diminished effects	
Buspirone	Caution due to potential competition at 5HT receptors	Diminished effects	Weigh risks and benefits of discontinuation If stopping medication wash out for at least 1 week
Mirtazapine Trazodone, Nefazodone	Caution due to potential competition/inhibition of 5HT receptors	Diminished effects	Weigh risks and benefits of discontinuation If stopping medication wash out for at least 1 week
Atypical antipsychotics	Caution due to potential inhibition of 5HT receptors or underlying illness	Diminished effects	Weigh risks and benefits of discontinuation If stopping medication wash out for at least 2 weeks although longer periods to observe

			stability off medication is reasonable
TCAs with potent SRI properties (e.g., Chlorpheniramine, clomipriamine, imipramine)	Caution due to increased synaptic 5HT	Diminished effects	Weigh risks and benefits of discontinuation If stopping medication, wash out for at least 2 weeks
SRAs (e.g., MDMA, mephedrone, 2Cx, Dox, NBOMe, Mescaline)	Caution due to increased synaptic 5HT	Intensified effects	Avoid at least 3 half lives before 5-MeO-DMT or combine cautiously using titrated sequence of 5-meO-DMT (start low, go very slow)
St. John's Wort	Caution due to increased 5HT neurotransmission	Intensified effects?	Weigh risks and benefits of discontinuation If stopping wash out for at least 1 week
Stimulants with SRI properties (e.g., cocaine, ephedra, weight loss agents, pseudoephedrine, methamphetamine)	Caution due to increased 5HT neurotransmission or cardiovascular effects	Intensified effects?	Avoid at least 5 half-lives before and after 5-MeO-DMT
TCAs with lower SRI properties (e.g., amitriptyline, nortriptyline, desipramine)	Caution due to increased synaptic 5HT	Intensified effects?	Consider skipping or reducing doses around time of use
Triptans (e.g., sumatriptan, rizatriptan)	Caution additive vasoconstriction	Intensified cardiovascular responses	Avoid at least 12 hours before and 3 hours after
Ergotamines (e.g., dihydroergotamine)	Caution additive vasoconstriction	Intensified cardiovascular responses	Avoid at least 5 half-lives before and after
Serotonin 3 receptor antagonists (e.g., ondansetron)	Little risk in combination	Decreased emetic responses	May be combined if indication present to treat nausea/vomiting
Analgesics (e.g., meperidine, methadone, tapentadol, tramadol, propoxyphene)	Caution due to increased synaptic 5HT	Diminished effects	Weigh risks and benefits of discontinuation Consider skipping or reducing doses around time of use

Management of Drug Interaction Risks

Identification of medication that can pose risk in combination with 5-MeO-DMT is important yet is truly only one aspect of managing drug interactions. A medication that is a moderate CYP2D6 inhibitor is perhaps a red flag although does not necessarily mean that use of 5-MeO-DMT is too risky to be attempted. Risks of using substances in combination must be weighed against the risks associated with stopping or discontinuing them. For many persons that have been using serotonergic medications for long periods of time, tapering and stopping is a multi-month process that can be very difficult and risks decompensating a persons' mental status into a crisis.

It is advised that the facilitator work collaboratively with the person and their medical team (physicians etc.) to accomplish taper and discontinuation to the maximum extent possible. Facilitators may warn persons about risks of drug interactions, although should avoid telling persons that they 'must' stop medications unless they also possess adequate medical training to provide such advice.

In general drugs need to be discontinued at least 4-5 half lives of the drug in question prior to using 5-MeO-DMT. The half-life is a drug-specific property defined as the time it takes for 50% of the drug to be eliminated from the body. Therefore, if you take 100mg of drug and the half-life is 1 hour then after 1 hour 50mg will remain, after 2 hours 25mg will remains, after 3 hours 12.5mg will remain and so forth. Some drugs have active metabolites that may also need to be considered. For example, fluoxetine (Prozac) is metabolized to norfluoxetine which is active and has a half-life of ~17 days. Therefore, it may need to be tapered and stopped 4-6 weeks prior to 5-MeO-DMT use.

While half-lives can be a useful tool for understanding if the drug is 'still in the system' it is well known that many psychiatric medications have withdrawal syndromes that persist well beyond that washout time from the body. The presence of severe withdrawal may risk a poor quality of subjective experience with psychedelics (e.g., amplified or inflated withdrawal) and may be helpful for persons to wait until they feel the majority of withdrawal symptoms have passed before engaging with 5-MeO-DMT. On the other hand, excessive waiting or washout times may risk undue suffering as there is a reasonable chance that 5-MeO-DMT could alleviate or reduce symptoms of depression or anxiety [10, 27, 28].

When 5-MeO-DMT is inhaled (most common administration route) it is fast-acting and has an onset of action within seconds. The duration of the experience is short and lasts between 10-40 minutes for an average individual. The drug has a short half-life under normal metabolic circumstances (~15-20min). This means that the window for drug interaction to occur may not be very long depending on the sequence drugs are taken in.

For example, if you vaporized 5-MeO-DMT, had normal metabolic function, and were not taking any other drugs or supplements then it would be mostly eliminated from your body after an hour or two. Therefore, you could vaporize 5-MeO-DMT and drink ayahuasca a few hours later without introducing much risk. However, if you drank ayahuasca first, then you should probably wait or abstain from 5-MeO-DMT use for at least 24 hours as it will take that long to metabolize the MAOI harmala alkaloids in ayahuasca. There are retreat centers that serve 5-MeO-DMT the morning after ayahuasca and attest to its safety, although this guide recommends against this practice.

Summary and Conclusion

5-MeO-DMT has pharmacology and drug interaction potential that shares significant overlap with other tryptamine psychedelics, however, it also possesses differential pharmacology that can at least increase risks of Serotonin Toxicity in combination with MAOIs relative to DMT, psilocin, or LSD. Due to the severe lack of high-quality data informing drug interaction risks with 5-MeO-DMT, persons may choose to exercise additional cautions, particularly when combining substances with serotonergic properties with 5-MeO-DMT until more reliable information is available to guide decision making.

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References:

1. ICEERS, *Risks associated with combining Bufo Alvarius with ayahuasca.* 2017.
2. Sklerov, J., et al., *A fatal intoxication following the ingestion of 5-methoxy-N,N-dimethyltryptamine in an ayahuasca preparation.* J Anal Toxicol, 2005. **29**(8): p. 838-41.
3. Shen, H.W., et al., *Psychedelic 5-methoxy-N,N-dimethyltryptamine: metabolism, pharmacokinetics, drug interactions, and pharmacological actions.* Curr Drug Metab, 2010. **11**(8): p. 659-66.
4. Nonaka, R., et al., *In vitro screening of psychoactive drugs by [(35)S]GTPgammaS binding in rat brain membranes.* Biol Pharm Bull, 2007. **30**(12): p. 2328-33.
5. Blough, B.E., et al., *Interaction of psychoactive tryptamines with biogenic amine transporters and serotonin receptor subtypes.* Psychopharmacology, 2014. **231**(21): p. 4135-4144.
6. Lyttle, T., D. Goldstein, and J. Gartz, *Bufo toads and bufotenine: fact and fiction surrounding an alleged psychedelic.* J Psychoactive Drugs, 1996. **28**(3): p. 267-90.
7. Malcolm, B.J. and K.C. Lee, *Ayahuasca: An ancient sacrament for treatment of contemporary psychiatric illness?* Ment Health Clin, 2017. **7**(1): p. 39-45.
8. Callaway, J.C., et al., *A demand for clarity regarding a case report on the ingestion of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in an Ayahuasca preparation.* J Anal Toxicol, 2006. **30**(6): p. 406-7; author reply 407.
9. Malcolm, B. and K. Thomas, *Serotonin toxicity of serotonergic psychedelics.* Psychopharmacology (Berl), 2021.
10. Davis, A.K., et al., *The epidemiology of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption.* Journal of Psychopharmacology, 2018: p. 0269881118769063.
11. Barsuglia, J., et al., *Intensity of Mystical Experiences Occasioned by 5-MeO-DMT and Comparison With a Prior Psilocybin Study.* Front Psychol, 2018. **9**: p. 2459.
12. Strassman, R.J., et al., *Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale.* Arch Gen Psychiatry, 1994. **51**(2): p. 98-108.
13. Davis, A.K., et al., *Survey of entity encounter experiences occasioned by inhaled N,N-dimethyltryptamine: Phenomenology, interpretation, and enduring effects.* **0**(0): p. 0269881120916143.
14. Kostakis, C. and R.W. Byard, *Sudden death associated with intravenous injection of toad extract.* Forensic Sci Int, 2009. **188**(1-3): p. e1-5.

15. Ott, J., *Pharmepéna-Psychonautics: Human intranasal, sublingual and oral pharmacology of 5-methoxy-N,N-dimethyl-tryptamine.* J Psychoactive Drugs, 2001. **33**(4): p. 403-7.
16. Shulgin, A., A. Shulgin, and P. Transform, *Tihkal : the continuation*. 2016, Berkeley: Transform Press.
17. Yu, A.M., et al., *Screening for endogenous substrates reveals that CYP2D6 is a 5-methoxyindolethylamine O-demethylase.* Pharmacogenetics, 2003. **13**(6): p. 307-19.
18. Shen, H.W., et al., *Effects of monoamine oxidase inhibitor and cytochrome P450 2D6 status on 5-methoxy-N,N-dimethyltryptamine metabolism and pharmacokinetics.* Biochem Pharmacol, 2010. **80**(1): p. 122-8.
19. Rickli, A., et al., *Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens.* Eur Neuropsychopharmacol, 2016. **26**(8): p. 1327-37.
20. Gudelsky, G.A. and J.F. Nash, *Carrier-mediated release of serotonin by 3,4-methylenedioxymethamphetamine: implications for serotonin-dopamine interactions.* J Neurochem, 1996. **66**(1): p. 243-9.
21. Mlinar, B. and R. Corradetti, *Endogenous 5-HT, released by MDMA through serotonin transporter- and secretory vesicle-dependent mechanisms, reduces hippocampal excitatory synaptic transmission by preferential activation of 5-HT1B receptors located on CA1 pyramidal neurons.* Eur J Neurosci, 2003. **18**(6): p. 1559-71.
22. Boyer, E.W. and M. Shannon, *The Serotonin Syndrome.* 2005. **352**(11): p. 1112-1120.
23. Gillman, K., *Monoamine oxidase inhibitors: A review concerning dietary tyramine and drug interactions.* PsychoTropical Commentaries, 2017. **1**(1): p. 105.
24. Ellahi, R., *Serotonin syndrome: a spectrum of toxicity.* BJPsych Advances, 2018. **21**(5): p. 324-332.
25. Uddin, M.F., et al., *Controversies in Serotonin Syndrome Diagnosis and Management: A Review.* J Clin Diagn Res, 2017. **11**(9): p. Oe05-oe07.
26. Nichols, D.E. and C.S. Grob, *Is LSD toxic?* Forensic Sci Int, 2018. **284**: p. 141-145.
27. Davis, A.K., et al., *5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety.* Am J Drug Alcohol Abuse, 2019. **45**(2): p. 161-169.
28. Uthaug, M.V., et al., *A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms.* Psychopharmacology (Berl), 2019.