

A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955–2010

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Three indole alkaloids that possess differing degrees of psychotropic/psychedelic activity have been reported as endogenous substances in humans; N,N-dimethyltryptamine (DMT), 5-hydroxy-DMT (bufotenine, HDMT), and 5-methoxy-DMT (MDMT). We have undertaken a critical review of 69 published studies reporting the detection or detection and quantitation of these compounds in human body fluids. In reviewing this literature, we address the methods applied and the criteria used in the determination of the presence of DMT, MDMT, and HDMT. The review provides a historical perspective of the research conducted from 1955 to 2010, summarizing the findings for the individual compounds in blood, urine, and/or cerebrospinal fluid. A critique of the data is offered that addresses the strengths and weaknesses of the methods and approaches to date. The review also discusses the shortcomings of the existing data in light of more recent findings and how these may be overcome. Suggestions for the future directions of endogenous psychedelics research are offered. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

Three indole alkaloids that possess differing degrees of psychotropic/psychedelic activity have been reported as endogenous substances in humans. These compounds, all metabolites of tryptophan, are N,N-dimethyltryptamine (DMT, **1**, Figure 1), 5-hydroxy-DMT (bufotenine, HDMT, **2**), and 5-methoxy-DMT (MDMT, **3**). Their presence has been reported in human cerebrospinal fluid (CSF), urine, and/or blood utilizing either paper and/or thin layer chromatography (TLC), direct ultraviolet (UV) or fluorescence (FI) measurements, gas chromatography (GC) using various sensors (nitrogen-phosphorous detector (NPD); electron capture detector (ECD); mass spectrometry detector (MSD)), high-performance liquid chromatography (HPLC) using UV and/or FI detection, HPLC-radioimmunoassay, HPLC-electrochemical detection, and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Tables 1–3, references^[1–69]). Indeed, the review of the 55-year history of the development of methodology for the analysis of these compounds shows how closely it has paralleled the evolution of analytical technology itself, with each researcher seeking more specific and sensitive techniques.

A renewed interest in these compounds as naturally occurring substances in humans has occurred, in part, due to DMT's recent characterization as an endogenous substrate for the ubiquitous sigma 1 receptor^[70] and for its possible action at trace amine receptors.^[71] In both cases, the roles of DMT and the receptors themselves in regulating some aspect(s) of human physiology are poorly understood. Given their known psychedelic effects, there remains an interest in their possible role in naturally occurring altered states of consciousness, such as psychosis, dreams, creativity and imagination, religious phenomena, and even near-death

experiences.^[72] Although the vast majority of research into the presence of these compounds sought their role in mental illness, no definitive conclusions yet exist. A determination of the role of these compounds in humans awaits further research, much of which awaits the development of adequate analytical methodology.

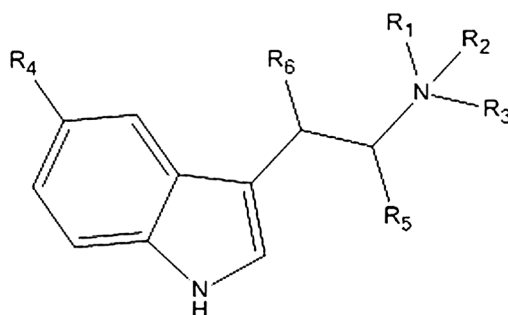
Interest in DMT has also increased because of the burgeoning use and popularity of the religious sacrament ayahuasca which contains DMT and several harmala alkaloids, which serve to make DMT orally active. Ayahuasca tourism in South America and the establishment of syncretic churches using ayahuasca as a sacrament^[73,74] have stimulated research into the mechanisms of its effects and its possible use as a therapeutic.^[75] The resumption of human research characterizing DMT's psychopharmacology^[76–84] and the ongoing use of pure DMT for therapeutic and recreational purposes have also focused interest on this and related psychedelics. The dimethylated-tryptamines (DMTs) increasing visibility within medical, non-medical, religious and/or recreational contexts^[75] reinforce the importance of determining their endogenous role.

This review addresses several fundamental issues regarding these three endogenous psychedelics. For example, are DMT,

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DMT: $R_1 = R_3 = \text{CH}_3$; $R_2 = \emptyset$; $R_4 = \text{H}$; $R_5 = R_6 = \text{H}_2$, **1**
HDMT: $R_1 = R_3 = \text{CH}_3$; $R_2 = \emptyset$; $R_4 = \text{OH}$; $R_5 = R_6 = \text{H}_2$, **2**
MDMT: $R_1 = R_3 = \text{CH}_3$; $R_2 = \emptyset$; $R_4 = \text{CH}_3\text{O}$; $R_5 = R_6 = \text{H}_2$, **3**
NMT: $R_1 = \text{CH}_3$; $R_2 = \emptyset$; $R_3 = \text{H}$; $R_4 = \text{H}$; $R_5 = R_6 = \text{H}_2$, **4**
DMT-NO: $R_1 = R_3 = \text{CH}_3$; $R_2 = \text{O}^+$; $R_4 = \text{H}$; $R_5 = R_6 = \text{H}_2$, **5**

Figure 1. Structures of the compounds discussed.

HDMT, and/or MDMT truly present in humans?^[85] Early criticisms of reports of endogenous psychedelics were directed at the fact that rather non-specific chemical tests were being applied, double-blind analyses were not always being performed, and dietary or medication sources were not always adequately ruled out as responsible for the identifications.^[2,12] Further, it was claimed that possible artifacts produced from the extraction solvents and conditions of analysis may have led to misidentification of the DMTs in some early studies^[20] and, more recently, that the use of halogenated solvents in the analysis may have affected their detection.^[86] Biological factors that may have affected the detectability of these compounds in the periphery were also acknowledged, which included their rapid metabolism.^[87,88] Finally, there have been concerns that the studies searching for their presence and an association with specific clinical disorders have failed to understand and fully characterize their metabolism or monitor their metabolites.^[88–91]

To address these issues, we have undertaken a critical review of 69 published studies reporting the detection or detection and quantitation of these compounds in human body fluids. In reviewing this literature, we address the methods applied and the criteria used in the determination of the presence of DMT, MDMT, and HDMT. We begin with the original report of the presence of bufotenin (HDMT) in human urine in 1955 using paper chromatography^[1] and end with the most recent report concerning the presence of bufotenin (HDMT) in human urine using LC-MS/MS.^[69]

We will be addressing the following questions: How valid were early studies regarding the presence and/or quantities of these compounds in human cerebrospinal fluid (CSF), blood and/or urine? Were the analytical methodologies and the identification criteria adequate? Are they truly there? When present, are they of dietary origin? When and where in the human body are they produced? Can we influence their detection in biological samples by pharmacologically inhibiting their metabolism by monoamine oxidase (MAO)? How does turnover rate and metabolism of these substances influence their detectability? Have the precursors and/or metabolites of these compounds been adequately monitored? Is

monitoring these compounds in biological samples such as CSF, blood and/or urine the best, or even most practical way to determine their role? What will such data tell us about the function of these compounds? Where does the research on endogenous psychedelics go from here?

Historical perspective

The search for endogenous psychedelics soon followed the discovery of the psychedelic effects of mescaline and lysergic acid diethylamide (LSD) in humans. Observations of these effects gave rise to hypotheses that they were related to the symptomatology observed in a heterogeneous group of mental disorders, especially psychoses – either mania or schizophrenia.^[92] It was proposed that schizophrenics may biochemically produce similar compounds as ‘schizotoxins’.^[93] A search for mescaline-like compounds proved unrewarding,^[94] but in studies examining urine samples for serotonin-like compounds, researchers reported in 1955^[1] and 1956,^[2] the presence of 5-hydroxy-N,N-DMT (HDMT, bufotenin) in humans. Subsequently, Axelrod^[95] reported the presence of an enzyme capable of N-methylating indole-ethylamines and producing DMTs. Following these reports, attention began to focus in earnest on the possible endogenous formation of the indole-ethylamine psychedelics. During the next 50 years, many studies reported finding DMT, HDMT, and/or MDMT in human CSF, urine, and/or blood. Most of these studies sought differences in levels between controls and psychiatric, especially psychotic, patients. Some studies claimed higher concentrations and significant differences in levels between the groups; some reported not finding the compounds at all in either patients or controls.

It is of interest to note that in its original conception, the schizotoxin hypothesis proposed that the formation of an endogenous psychedelic schizotoxin would be an aberration of metabolism and that ‘normals’ would not form such compounds.^[92] However, numerous studies subsequently reported finding one or more of these compounds in controls

Table 1. Review of 69 studies regarding endogenous psychedelics showing the year, reference, compounds analyzed, type of sample and method of extraction. Acronyms and abbreviations: IV, intravenous; HNMT, 5-hydroxy-N-methyltryptamine; ext, extraction; vol, volume; w/wo, with or without; evap, evaporate; ppt, precipitate; sat, saturated; TLC, thin-layer chromatography; cent, centrifuge; TFAA, trifluoro-acetic anhydride; SPE, solid-phase extraction; LC, liquid chromatography.

Year	Author	Compounds Analyzed	Collection	Extraction Method
1955	Bumpus and Page ^[1]	HNMT, HDMT	24-hour urine 10 ml portions, HCl; urease	Evap, Acetone, evap, MeOH, evap, AlO ₃ column
1956	Rodnight ^[2]	HNMT, HDMT	24-hour urine; 75–120 ml extracted	Zeo-Karb 226 resin, EtOH/acetone ppt, evap
1961	Fischer <i>et al.</i> ^[3]	HDMT	1 L of urine	NaHCO ₃ sat., butanol, evap, acetone
1961	Fischer <i>et al.</i> ^[4]	HDMT	1 L of urine	NaOH pH 9, butanol, evap, acetone
1961	Feldstein <i>et al.</i> ^[5]	HDMT	8 hour urines; IV/oral 14 C serotonin (130 µg)	not described
1962	Perry <i>et al.</i> ^[6]	HDMT, conjugate	24–36 hour urine; ext vol 500 mg creatinine; w/wo hydrolysis	Amberlite CG-120, CG-50; ethanol-acetone ppt
1963	Brune <i>et al.</i> ^[7]	HDMT; DMT	24 hour urine	pH 10, ethyl ether ext, evap, acetone
1963	Perry ^[8]	HDMT; DMT	24 or 48 hour urine; ext vol 500 mg creatinine	Amberlite CG-120, CG-50; ethanol-acetone ppt
1963	Sprince <i>et al.</i> ^[9]	DMT, HDMT	24 hour urine	pH 10, ethyl ether-butanone ext, evap, acetone
1963	Perry and Schroeder ^[10]	HDMT	24–36 hour urine; ext vol 250–350 mg creatinine	Amberlite CG-120, CG-50; ethanol-acetone ppt
1965	Franzen and Gross ^[11]	DMT, HDMT	blood and urine (24 hour)	Extensive multi-step extraction, ppt and clean-up
1965	Siegel ^[12]	HDMT	fresh urine, 100 ml	pH 10, ethyl ether ext, evap, acetone
1965	Nishimura and Gjessing ^[13]	HDMT	fresh urine vol 500–1,000 mg creatinine	Dowex 50, Amberlite CG 50,
1965	Takesada <i>et al.</i> ^[14]	HDMT	24 hour urine	Ext, Dowex 50 column, alumina column
1966	Runge <i>et al.</i> ^[15]	HDMT	1 L of urine	pH 8–9, butanol ext, acetone ppt, acetone
1966	Perry <i>et al.</i> ^[16]	DMT, HDMT	48 hour urine	Dowex 50W, Amberlite CG-50; HCl hydrolysis
1966	Heller ^[17]	HDMT	1 L of urine	NaHCO ₃ sat., butanol, evap, acetone
1967	Fischer and Spatz ^[18]	HDMT	100 ml fresh urine	NaCO ₃ , ether ext, evap, acetone
1967	Kakimoto <i>et al.</i> ^[19]	DMT, HDMT	24 hour urine; vol 600 mg creatinine analyzed	Ext, Dowex 50 column, alumina column
1967	Tanimukai ^[20]	HNMT, HDMT, NMT, DMT, MDMT	24 hour urine; 1/4th used in assay	Dowex 50W X2; w/wo HCl hydrolysis
1967	Tanimukai <i>et al.</i> ^[21]	HDMT	24 hour urine; 1/3 rd used in assay	cation exchange resin; w/wo HCL hydrolysis
1967	Tanimukai <i>et al.</i> ^[22]	HDMT	24 hour urine; 1/4th used in assay	Dowex 50W X2; HCl hydrolysis
1967	Acebal and Spatz ^[23]	HDMT	100 ml urine	NaCO ₃ , ether ext, evap, acetone
1968	Faurbye and Pind ^[24]	HDMT	24 hour urine, hydrolyzed at pH1.6	column chromatography, sublimation, paper/TLC
1969	Sireix and Marini ^[25]	HDMT	100 ml fresh urine	NaCO ₃ , ether ext, evap, acetone
1969	Spatz <i>et al.</i> ^[26]	HDMT	50 ml fresh urine; 100 ml fresh urine	pH 10 NaOH, ethyl acetate; diazo-reagent or TLC
1970	Fischer and Spatz ^[27]	HDMT	50 ml fresh urine; acid hydrolysis	pH 10 NaOH, ethyl acetate; diazo-reagent and TLC
1970	Saavedra and Udabe ^[28]	HDMT	50 ml fresh urine; acid hydrolysis	pH 10 NaOH, ethyl acetate; diazo-reagent and TLC
1970	Tanimukai <i>et al.</i> ^[29]	HNMT, HDMT, DMT, MDMT	24 hour urine; 1/4th used in assay	Dowex 50W X2; HCl hydrolysis
1970	Heller <i>et al.</i> ^[30]	DMT, MDMT, HDMT	fasting blood, oxalate tube; acid hydrolyzed	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1971	Narasimhachari <i>et al.</i> ^[31]	DMT, MDMT, HDMT	24 hour urine; 75% used in assay	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1971	Narasimhachari <i>et al.</i> ^[32]	NMT, DMT, MDMT	fasting blood, oxalate tube	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1971	Fischer <i>et al.</i> ^[33]	HDMT, glucuronide	50 ml morning urine; w/wo glucuronidase	Liquid-Liquid ext; w/wo glucuronidase treatment
1972	Himwich <i>et al.</i> ^[34]	HDMT, DMT, MDMT	24 hour urine	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1972	Narasimhachari <i>et al.</i> ^[35]	HDMT, DMT, MDMT	24 hour urine	Franzen and Gross; HCl ext ethyl acetate at pH 10.2
1973	Walker <i>et al.</i> ^[36]	DMT	plasma; DMT stable for 60 days at 6 degrees C	HCL ext acid pH with CHCl ₃ , pH 9, ext CHCl ₃ , evap

Table 1. (Continued)

Year	Author	Compounds Analyzed	Collection	Extraction Method
1973	Wyatt <i>et al.</i> ^[37]	DMT	plasma	HCL ext acid pH with CHCl ₃ , pH 9, ext CHCl ₃ , evap
1973	Narasimhachari and Himwich ^[38]	DMT, HDMT	24-hour urine	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1974	Lipinski <i>et al.</i> ^[39]	DMT	plasma separated by centrifugation	HCL ext acid pH with CHCl ₃ , pH 9, ext CHCl ₃ , evap
1974	Bidder <i>et al.</i> ^[40]	DMT	Heparinised plasma or whole blood; 24 hr urine	HCL ext acid pH with CHCl ₃ , pH 9, ext CHCl ₃ , evap
1974	Narasimhachari <i>et al.</i> ^[41]	HDMT, DMT, MDMT	24 hour urine	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1975	Carpenter <i>et al.</i> ^[42]	DMT, HDMT	24 hour urine, 90% used in assay	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1975	Christian <i>et al.</i> ^[43]	DMT, MDMT	Cerebrospinal fluid	Deproteinization, liquid-liquid ext, CH ₂ Cl ₂
1975	Narasimhachari and Himwich ^[44]	DMT, HDMT	24 hour urine, 80% used in assay	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1976	Angrist <i>et al.</i> ^[45]	DMT	non-fasting blood; heparin; 10 ml assayed	HCL ext acid pH with CHCl ₃ , pH 9, ext CHCl ₃ , evap
1976	Rodnight <i>et al.</i> ^[46]	DMT	24-hour urine	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1976	Murray and Oon ^[47]	DMT	24-hour urine	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1976	Huszka <i>et al.</i> ^[48]	HDMT, DMT, MDMT	24 hour urine; 1/3 rd used in assay	Dowex 50; HCl ext and ethyl acetate at pH 10.2
1977	Cottrell <i>et al.</i> ^[49]	HDMT	24 hour urine	Dowex 50W X2; HCl hydrolysis
1977	Oon <i>et al.</i> ^[50]	DMT, NMT	24-hour urine; 50% used;	HCL ext acid pH with CHCl ₃ , pH 11, ext CHCl ₃ , evap
1977	Oon and Rodnight ^[51]	DMT, NMT	DMT, NMT stable 90 days at -15 C	50% concentrated and extracted with toluene
1978	Riceberg and Van Vunakis ^[52]	DMT, HDMT, MDMT	24-hour urine; 300 ml used in assay	purified by TLC, derivatized with TFAA
			50 ml whole blood; plasma	50% concentrated and extracted with toluene
1978	Corbett <i>et al.</i> ^[53]	DMT, MDMT	Cerebrospinal fluid	purified by TLC, derivatized with TFAA
1979	Walker <i>et al.</i> ^[54]	DMT	10 ml whole blood; arterial and venous	Urine (pH 10.5) ext with CHCl ₃
1979	Murray <i>et al.</i> ^[55]	DMT, NMT	24-hour urine; 50% used in assay	Whole blood lysed, protein ppt. with HClO ₄
1979	Checkley <i>et al.</i> ^[56]	DMT	24 hour urine; 50% used in assay	extracted twice with chloroform
1979	Raisanen and Karkkainen ^[57]	DMT, HDMT	150 ml morning urine samples	Deproteinization, Liquid-Liquid ext, CH ₂ Cl ₂
1979	Smythies <i>et al.</i> ^[58]	DMT, MDMT	Cerebrospinal fluid	HCL ext acid pH with CHCl ₃ , pH 9, ext CHCl ₃ , evap
1980	Checkley <i>et al.</i> ^[59]	DMT	Serial 24 hour urine; longitudinal study	acidified with HCl
1983	Uebelhack <i>et al.</i> ^[60]	DMT, MDMT	Cerebrospinal fluid	50% concentrated and extracted with toluene
1983	Sitaram <i>et al.</i> ^[61]	HDMT	12 hr specimens (8 pm-8 am); 200 ml assayed	purified by TLC, derivatized with TFAA
1984	Raisanen <i>et al.</i> ^[62]	HDMT	not stated	Deproteinization, liquid-liquid ext, CH ₂ Cl ₂

1988	Karkkainen <i>et al.</i> ^[63]	HDMT	morning urine samples	pH11, XAD resin, ethyl acetate elution, evap, TLC
1992	Karkkainen and Raisanen ^[64]	HDMT	individual urine samples; w /wo nialamide treatment	pH11, XAD resin, ethyl acetate elution, evap, TLC
1995	Karkkainen <i>et al.</i> ^[65]	HDMT	morning urine samples; 50–100 ml	pH11, XAD resin, ethyl acetate elution, evap, TLC
1995	Takeda <i>et al.</i> ^[66]	HDMT, HNMT	morning urine samples	centrifugation, direct injection of 80 µl of urine
2001	Forsstrom <i>et al.</i> ^[67]	DMT, MDMT, HDMT, NMT	morning and afternoon urines; 5 ml assayed	urine centrifuged and ext on Oasis SPE cartridge
2005	Karkkainen <i>et al.</i> ^[68]	DMT, HDMT	urine (5 ml), plasma or serum (1 ml), stool; tissues (0.5–1.5 g)	urine cent and ext on Oasis HLB cartridge; Prep LC for blood
2010	Emanuele <i>et al.</i> ^[69]	HDMT	random urine samples	urine cent and ext on Oasis HLB cartridge

Table 2. Review of 69 studies regarding endogenous psychedelics showing the year, reference, compounds analyzed, detection methods, limits of detection (LOD) and confirmation criteria. Acronyms and abbreviations: HNMT, 5-hydroxy-N-methyltryptamine; TLC, thin-layer chromatography; 2-D, two dimensional; GC-FID, gas chromatography-flame ionization detector; derive, derivative; HFBI, heptafluoro-butyl-imidazole; IS, internal standard; HPLC, high performance liquid chromatography; ESI, electrospray ionization; MS, mass spectrometry; ND, not determined; RT, retention time; UV, ultraviolet; TI, total ion; m/z, mass-to-charge ratio; CI, chemical ionization; IA, immunoassay; MRM, multiple reaction monitoring.

Year	Author	Compounds Analyzed	Detection Methods	Limit of Detection	Confirmation Criteria
1955	Bumpus and Page ^[11]	HNMT, HDMT	paper chromatography (1 system), color reaction, bioassay	ND	Rf and color (1 system)
1956	Rodnight ^[2]	HNMT, HDMT	paper chromatography (3 systems), color reaction, bioassay	>5 µg/ 24 hour for HDMT	Rf and color (3 systems)
1961	Fischer <i>et al.</i> ^[3]	HDMT	paper chromatography (1 system)	ND	Rf and color (1 system)
1961	Fischer <i>et al.</i> ^[4]	HDMT	paper chromatography (1 system)	ND	Rf and color (1 system)
1961	Feldstein <i>et al.</i> ^[5]	HDMT	paper chromatography and auto-radiographs	ND	Rf and color (1 system), radioactive spot
1962	Perry <i>et al.</i> ^[6]	HDMT, conjugate	paper chromatography (2-D), color reaction	ND	Rf and color (2-D)
1963	Brune <i>et al.</i> ^[7]	HDMT; DMT	paper chromatography (2-D), color reaction	20 ng/ml	Rf and color (2-D)
1963	Perry ^[8]	HDMT; DMT	2-D paper chromatography, color reaction	ND	Rf and color (2-D)
1963	Sprince <i>et al.</i> ^[9]	DMT, HDMT	2-D paper chromatography, color reaction	ND	Rf and color (2-D)
1963	Perry and Schroeder ^[10]	HDMT	paper chromatography (3 systems)	ND	Rf and color (3 systems)
1965	Franzen and Gross ^[11]	DMT, HDMT	Fluorescence	2 ng/ml	Fluorescence reading
1965	Siegel ^[12]	HDMT	TLC (1 system), color reaction	0.1 µg/100 ml	Rf and color (1 system)
1965	Nishimura and Gjessing ^[13]	HDMT	TLC (2-D), color reaction	ND	Rf and color (2-D)
1965	Takesada <i>et al.</i> ^[14]	HDMT	paper chromatography, color reaction	20 µg/24 hour	Rf and color

Table 2. (Continued)

Year	Author	Compounds Analyzed	Detection Methods	Limit of Detection	Confirmation Criteria
1966	Runge <i>et al.</i> ^[15]	HDMT	paper chromatography, color reaction	ND	Rf and color (2-D)
1966	Perry <i>et al.</i> ^[16]	DMT, HDMT	paper chromatography (2-D), color reaction	2 µg/24 hr for DMT and HDMT	Rf and color (2-D)
1966	Heller ^[17]	HDMT	paper chromatography (2-D), color reaction	ND	Rf and color (2-D)
1967	Fischer and Spatz ^[18]	HDMT	paper chromatography (2-D), color reaction	ND	Rf and color (2-D)
1967	Kakimoto <i>et al.</i> ^[19]	DMT, HDMT	paper chromatography (3 systems), color reaction	10 µg/24 hour	Rf and color (3 systems)
1967	Tanimukai ^[20]	HNMT, HDMT, NMT, DMT, MDMT	paper and TLC (2-D); color reaction; GC-FID of HDMT	5 ng/ml HDMT; 1 ng/ml others	Rf and color (2-D paper, TLC)
1967	Tanimukai <i>et al.</i> ^[21]	MDMT			
1967	Tanimukai <i>et al.</i> ^[22]	HDMT	paper chromatography, TLC (2-D), color reaction; GC-FID	>0.1 µg/24 hour	Rf and color (2-D); GC-RT
1967	Tanimukai <i>et al.</i> ^[23]	HDMT	paper and TLC (2-D); color reaction; GC-FID of HDMT	ND	Rf and color (2-D paper, TLC); GC-RT
1967	Acebal and Spatz ^[23]	HDMT	paper chromatography (2-D), color reaction	ND	Rf and color (2-D)
1968	Faurbye and Pind ^[24]	HDMT	paper chromatography and TLC, color reaction	>0.7 µg/24 hour	Rf and color (paper and 2-D TLC)
1969	Sireix and Marini ^[25]	HDMT	UV; paper chromatography, color reaction	ND	Rf and color (2-D)
1969	Spatz <i>et al.</i> ^[26]	HDMT	UV of diazo-deriv; paper chromatography, color reaction	ND	UV; Rf and color
1970	Fischer and Spatz ^[27]	HDMT	UV; TLC, color reaction	ND	UV; Rf and color
1970	Saavedra and Udabe ^[28]	HDMT	UV; TLC, color reaction	ND	UV; Rf and color
1970	Tanimukai <i>et al.</i> ^[29]	HNMT, HDMT, DMT, MDMT	paper and TLC (2-D); color reaction; GC-FID of HDMT	ND	Rf and color (2-D paper, TLC); GC-RT
1970	Heller <i>et al.</i> ^[30]	DMT, MDMT, HDMT	GC-FID, TLC, and Spectrofluorometry	2 ng/ml	GC-RT and TLC or spectrofluorometer
1971	Narasimhachari <i>et al.</i> ^[31]	DMT, MDMT, HDMT	TLC and GC-FID, verified with spectrofluorometer	5 µg/ml per 24 hour for DMT	TLC and GC-FID, spectrofluorometer
1971	Narasimhachari <i>et al.</i> ^[32]	NMT, DMT, MDMT	TLC and GC-FID, verified with spectrofluorometer	2 ng/ml	TLC and/or GC-FID, spectrofluorometer
1971	Fischer <i>et al.</i> ^[33]	HDMT, glucuronide	UV; paper chromatography, color reaction	ND	UV; Rf and color
1972	Himwich <i>et al.</i> ^[34]	HDMT, DMT, MDMT	TLC (3 systems), color reaction; verified with spectrofluorometer	ND	Rf, color and fluorescence
1972	Narasimhachari <i>et al.</i> ^[35]	HDMT, DMT, DMT	paper and TLC (2-D); color reaction; GC-FID	0.05 µg/24 hour	Rf and color (2-D); GC-RT
1973	Walker <i>et al.</i> ^[36]	DMT	GC-MS; 2 ft. SE-30 glass capillary column, DMT-d2 IS, TMS deriv	0.5 ng/ml; m/z 202/204, 260/262	GC-RT, two ions and ratio
1973	Wyatt <i>et al.</i> ^[37]	DMT	GC-MS; 2 ft. SE-30 glass capillary column, DMT-d2 IS, TMS deriv	0.5 - 1.8 ng/ml; m/z 202/204, 260/262	GC-RT, two ions and ratio
1973	Narasimhachari and Himwich ^[38]	DMT, HDMT	TLC DACA and OPT spray on cellulose and silica; GC/MS, 58 m/z only	5 ng/ml HDMT; 1 ng/ml DMT	Rf and color (2-D); GC-RT; GC/MS 58 m/z
1974	Lipinski <i>et al.</i> ^[39]	DMT	GC-MS; 2 ft. SE-30 glass capillary column, DMT-d2 IS, TMS deriv	0.5 ng/ml	TI spectrum match with DMT standard
1974	Bidder <i>et al.</i> ^[40]	DMT	GC-MS; 2 ft. SE-30 glass capillary column, DMT-d2 IS, TMS deriv	blood 0.05-2 ng/ml; urine 0.07-0.2 ng/ml	GC-RT, two ions and ratio
1974	Narasimhachari <i>et al.</i> ^[41]	HDMT, DMT, MDMT	TLC DACA and OPT spray on cellulose and silica; GC/MS, 58 m/z only	5 ng/ml HDMT; 1 ng/ml DMT	Rf and color (2-D); GC-RT; GC/MS 58 m/z
1975	Carpenter <i>et al.</i> ^[42]	DMT, HDMT	TLC DACA and OPT spray on cellulose and silica; GC/MS, 58 m/z only	5 ng/ml HDMT; 1 ng/ml DMT	TI spectrum match with DMT, HDMT
1975	Christian <i>et al.</i> ^[43]	DMT, MDMT	GC-ECD; packed column	DMT 10 pg/ml; MDMT 5 pg/ml	Rf and color (2-D); GC-RT; GC/MS 58 m/z
1975	Narasimhachari and Himwich ^[44]	DMT, HDMT	TLC DACA and OPT spray on cellulose and silica; GC/MS, 58 m/z only	5 ng/ml HDMT; 1 ng/ml DMT	RT
					Rf and color (2-D); GC-RT; GC/MS 58 m/z

1976	Angrist <i>et al.</i> ^[45]	DMT	GC-MS; 2 ft. SE-30 glass capillary column, DMT-d2 IS, TMS deriv	0.05 ng/ml	RT, two ions and ratio
1976	Rodnight <i>et al.</i> ^[46]	DMT	GC-FID, TLC on cellulose; GC/MS 2 patients and pooled (10) extract	0.5 µg/24hour	Rf and color; GC-RT; matching TI MS
1976	Murray and Oon ^[47]	DMT	GC-FID, TLC on cellulose; GC/MS 2 patients and pooled (10) extract	20 ng /24hour	Rf and color; GC-RT; GC-MS
1976	Huszká <i>et al.</i> ^[48]	HDMT, DMT, MDMT	TLC and GC-FID, verified with spectrofluorometer	4 ng/ml	TLC and GC-FID, spectrofluorometer
1977	Cottrell <i>et al.</i> ^[49]	HDMT	HFBF derivatives, GC-ECD	<1 nmol/24 hour	RT
1977	Oon <i>et al.</i> ^[50]	DMT, NMT	GC/NPD; GC/MS	20 ng/24hour for DMT; 50 ng/ml NMT	RT; CI MS confirmation
1977	Oon and Rodnight ^[51]	DMT, NMT	GC/NPD; GC/MS	50 ng/24hour for NMT	
1978	Riceberg and Van Vunakis ^[52]	DMT, HDMT, MDMT	Radioimmunoassay and HPLC (RIA-HPLC)	20 ng/24hour for DMT (30 ng/L)	RT; CI MS confirmation
1978	Corbett <i>et al.</i> ^[53]	DMT, MDMT	GC-ECD; HFBF derivative	5 fmol/ml HDMT or MDMT,	HPLC RT and IA response
1979	Walker <i>et al.</i> ^[54]	DMT	GC/MS, Selective Ion Monitoring capillary column gas chromatography	15 fmol/ml DMT	
1979	Murray <i>et al.</i> ^[55]	DMT, NMT	GC-NPD, TLC on cellulose; GC/MS 2 patients and pooled (10) extract	DMT 10 pg/ml; MDMT 5 pg/ml	RT; MS of selected samples
1979	Checkley <i>et al.</i> ^[56]	DMT	GC with nitrogen-sensitive detector	10 pg/ml whole blood	GC/MS RT, m/z 58 only
1979	Raisanen and Karkkainen ^[57]	DMT, HDMT	TMS derivatives; GC/MS, multiple ion detection	20 ng/24hour DMT; 50 ng/24 hour NMT	RT; MS of selected samples
1979	Smythies <i>et al.</i> ^[58]	DMT, MDMT	GC/MS selected ion monitoring; d4-DMT, d4-MDMT IS	0.5 µg/ml per 24hour	RT
1980	Checkley <i>et al.</i> ^[59]	DMT	GC with nitrogen-sensitive detector	0.1-0.15 ng/ml DMT; 0.25-0.3 ng/ml HDMT	RT, molecular ions or fragments
1983	Uebelhack <i>et al.</i> ^[60]	DMT, MDMT	GC-FID	70 pg/ml DMT, MDMT	RT, ion fragments, ratios
1983	Sitaram <i>et al.</i> ^[61]	HDMT	HPLC/fluorescence spectrum	0.5 µg/ml per 24hour	RT
1984	Raisanen <i>et al.</i> ^[62]	HDMT	TMS derivatives; GC/MS, multiple ion detection	ND	RT
1988	Karkkainen <i>et al.</i> ^[63]	HDMT	TMS derivatives; GC/MS, multiple ion detection	>0.01 ng/ml per 12 hr	RT and fluorescence spectrum
1992	Karkkainen and Raisanen ^[64]	HDMT	TMS derivatives; GC/MS, multiple ion detection	0.1-0.15 ng/ml DMT; 0.25-0.3 ng/ml HDMT	RT, molecular ions or fragments
1995	Karkkainen <i>et al.</i> ^[65]	HDMT	TMS derivatives; GC/MS, multiple ion detection	0.1-0.15 ng/ml DMT; 0.25-0.3 ng/ml HDMT	RT, molecular ions or fragments
1995	Takeda <i>et al.</i> ^[66]	HDMT, HNMT	3-D-HPLC-electrochemical detection	0.1-0.15 ng/ml DMT; 0.25-0.3 ng/ml HDMT	RT, molecular ions or fragments
2001	Forsstrom <i>et al.</i> ^[67]	DMT, MDMT, HDMT, NMT	HPLC/ESI-MS-MS	50 pg/ml	RT and electrochemical response
2005	Karkkainen <i>et al.</i> ^[68]	DMT, HDMT	HP/LC/ESI-MS/MS	0.35 ng/ml HDMT; 0.1 ng/ml DMT	RT, Pseudo molecular ion, MRM
2010	Emanuele <i>et al.</i> ^[69]	HDMT	HP/LC/ESI-MS/MS	0.1 ng/ml MDMT; 0.05 ng/ml NMT	RT, Pseudo molecular ion, MRM
				0.3 ng/ml HDMT; 0.2 ng/ml DMT	RT, Pseudo molecular ion, MRM
				ND	

Table 3. Review of 69 studies regarding endogenous psychedelics showing the year, reference, compounds analyzed, the subjects (patients and controls), the results positive or negative out of the total (i.e. 4/12) and the concentrations of the compounds observed. Acronyms and abbreviations: HNMT, 5-hydroxy-N-methyltryptamine; meds, medications; MAOI, monoamine oxidase inhibitor; admin, administration; schizo, schizophrenia; neg, negative; ND, not detected; NA, not applicable; psychiat, psychiatric; sig dif, significant difference;

Year	Author	Compounds Analyzed	Subjects	Positive/Negative	Concentration
1955	Bumpus and Page ^[1]	HNMT, HDMT	4 healthy adults	pooled sample; 5-HNMT, HDMT	ND
1956	Rodnight ^[2]	HNMT, HDMT	11 healthy adults	no HNMT or HDMT detected	ND
1961	Fischer <i>et al.</i> ^[3]	HDMT	5 acute schizophrenics, 4 controls	5/5 schizophrenics HDMT, 4 controls neg	400 ng/ml
1961	Fischer <i>et al.</i> ^[4]	HDMT	15 schizophrenics, 10 controls	14/15 HDMT; 0/10 HDMT	ND
1961	Feldstein <i>et al.</i> ^[5]	HDMT	15 schizophrenics, 10 controls; no meds for 2 weeks	no HDMT detected	ND
1962	Perry <i>et al.</i> ^[6]	HDMT, conjugate	20 control children; 6 received MAOI pheniprazine (3) or nialamide (3)	1/20 HDMT; 4/6 HDMT following MAOI	0.3 µg/ 100 mg creatinine; 0.5–2.2 µg/100 mg creatinine with MAOI
1963	Brune <i>et al.</i> ^[7]	HDMT; DMT	3 on a plant-free diet during admin of neomycin to reduce intestinal flora		
1963	Perry ^[8]	HDMT; DMT	5 schizophrenics; 3 mentally deficient patients; MAOI isocarboxazid plus betaine	9 of 17 urine samples; 0/3; MAOI increased schizo symptoms	20–30 µg/24 hour HDMT; DMT negative in all samples
1963	Sprince <i>et al.</i> ^[9]	DMT, HDMT	18 juvenile psychotics; Some on plant-free diet and MAOI	no DMT detected; 2 positive for HDMT after MAOI	30 ng/100 mg creatinine
1963	Perry and Schroeder ^[10]	HDMT	4 schizophrenics, 2 psychoneurotics; MAOI tranylcypromine, methione or tryptophan	no DMT or HDMT detected	NA
1963	Franzen and Gross ^[11]	DMT, HDMT	7 control and 2 psychotic children; 1 control on plant-free diet; 2 controls received MAOI blood 37 controls; urine 46 controls	1/2 psychotics HDMT; 2/2 controls receiving MAOI	NA
1965	Siegel ^[12]	HDMT	5 normals, 21 schizophrenics	11/37 blood DMT; 37/37 urine DMT	8–55 ng/ml; 42.98 +/- 8.6 µg/24 hour
1965	Nishimura and Gjessing ^[13]	HDMT	2 periodic catatonia patients; strict dietary control; phenelzine MAOI	12/37 blood HDMT; 46/46 urine HDMT	1–40 ng/ml; 62.8 +/- 7.2 µg/24 hour
1965	Takesada <i>et al.</i> ^[14]	HDMT	7 schizophrenics, 8 controls; no meds 30 days	no HDMT detected	NA
1966	Runge <i>et al.</i> ^[15]	HDMT	22 schizophrenics no meds; 14 schizophrenics on meds, 17 controls; no meds 60 days	no HDMT detected	NA
1966	Perry <i>et al.</i> ^[16]	DMT, HDMT	12 male schizophrenics, 7 male controls; MAOI phenelzine administered; no meds for 6 weeks; no plants or cheese in diet	no HDMT or DMT detected	NA
1966	Heller ^[17]	HDMT	11 schizophrenics, 4 controls; 10 schizophrenics, 4 controls received MAOI	10/11 HDMT, 0/4 HDMT; 10/10 HDMT, 0/4 HDMT	ND
1967	Fischer and Spatz ^[18]	HDMT	95 schizophrenics w/o treatment, 43 with treatment; 102 controls	71/95 HDMT, 16/43 HDMT; 0/102 HDMT	ND
1967	Kakimoto <i>et al.</i> ^[19]	DMT, HDMT	8 schizophrenic females; treated with methionine and isocarboxazide (MAOI)	no HNMT, NMT, HDMT or DMT detected	NA

1967	Tanimukai ^[20]	HNMT, HDMT, NMT, DMT, MDMT	4 male chronic schizophrenics; MAOI tranylcypromine; special diet; no meds 4–6 weeks	4/100 samples HDMT; 3/100 conjugated	ND
1967	Tanimukai <i>et al.</i> ^[21]	MDMT	6 male schizophrenics, 4 male mentally defective patients; special diet; no meds 7 weeks	DMT and MDMT observed in some samples	>1 µg/24 hour
1967	Tanimukai <i>et al.</i> ^[22]	HDMT	4 schizophrenics, MAOI tranylcypromine, cysteine admin; special diet	HDMT; conjugated in all 10, free in 7/10	HDMT 4–10 µg/24 hour
1967	Acebal and Spatz ^[23]	HDMT	10 schizophrenics; 7 controls; patients administered trifluoperidol	1/4 free HDMT, 3/4 conj; MAO 4/4 free, 3/4 conj	ND
1968	Faurbye and Pind ^[24]	HDMT	7 schizophrenics, 5 controls	7/10 HDMT, 0/10 after trifluoperidol; 0/7 HDMT	schizophrenics 0–3.7 µg/24 hour; controls 0–7.5 µg/24 hour
1969	Sireix and Marini ^[25]	HDMT	20 schizophrenics, 20 non-schizophrenics, 20 controls; special diets	6/7 schizophrenics, 3/5 controls	schizophrenic mean of 155 ng/ml; non- 21 ng/ml; controls 29 ng/ml; no dietary effects
1969	Spatz <i>et al.</i> ^[26]	HDMT	65 schizophrenics, 73 controls	19/20 HDMT, 19/20 HDMT, 18/20	65/65 mean 172 ng/ml; 73/73 mean 36 ng/ml
1970	Fischer and Spatz ^[27]	HDMT	67 controls, 11 epilepsy, 9 depression, 8 psychopathic, 86 non-treated schizophrenics	67/67 normals, 11/11 epilepsy, 9/9 depression	norm 12–89 ng/ml, epilepsy 26–67 ng/ml, depress 12–42 ng/ml, psycho 20–54 ng/ml, schizo 17/86 12–96 ng/ml, 69/86 100–375 ng/ml, 33/45 10–100 ng/ml, 12/45 101–212 ng/ml
1970	Saavedra and Udabe ^[28]	HDMT	4 controls, 25 psychiatric patients, 11 non-treated schizo, 4 treated, 4 hysteria	8/8 psychopathic, 86/86, 45/45 schizophrenics	norm 17+/- 2.7 ng/ml, psychiat 24 +/- 2.8 ng/ml, schizo untreated 160+/- 22.7, treated 35+/- 10 ng/ml, hysteria 69+/- 9 ng/ml
1970	Tanimukai <i>et al.</i> ^[29]	HNMT, HDMT, DMT, MDMT	4 schizophrenics, MAOI tranylcypromine, methionine or cysteine admin; special diet	4/4 HDMT, 3/4 MNMT, 3/4 DMT, 2/4 MDMT	HDMT 4–10 µg/24 hour
1970	Heller <i>et al.</i> ^[30]	DMT, MDMT, HDMT	5 acute schizophrenics, 9 chronic schizophrenics, 2 normals, 1 depressive	5/5 DMT, 5/5 MDMT, 2/5 HDMT; 0/12 for others	NA
1971	Narsimhachari <i>et al.</i> ^[31]	DMT, MDMT, HDMT	2 schizophrenics, 6 controls; MAOI tranylcypromine, cysteine admin.	2 schizophrenics positive; 6 controls negative	10–40 µg/ml
1971	Narasimhachari <i>et al.</i> ^[32]	NMT, DMT, MDMT	22 acute schizophrenics, 20 non-schizophrenics	15/22 DMT and/or MDMT, 2/22 HDMT; 2/20 positive	2 ng/ml
1971	Fischer <i>et al.</i> ^[33]	HDMT, glucuronide	4 each, control, acute and chronic schizophrenics	all positive	controls (Free or total) 63+/- 14.3 or 93+/- 21 ng/ml; chronic 91+/- 21.6 or 188+/- 16 ng/ml;

Table 3. (Continued)

Year	Author	Compounds Analyzed	Subjects	Positive/Negative	Concentration
1972	Himwich <i>et al.</i> ^[34]	HDMT, DMT, MDMT	6 autistics, 6 controls; special diets	6 controls neg for all; 5/6 autistics positive for HDMT	acute 200+/- 47.5 or 289+/- 78 ng/ml < 3-5 µg/24 hour
1972	Narasimhachari <i>et al.</i> ^[35]	HDMT, DMT, MDMT	6 chronic schizophrenics, 7 controls; special diets, restricted meds	4/6 schizo DMT, HDMT; 7/7 controls negative;	<5 µg/ 24 hour DMT; 3-5 µg/ 24 hour HDMT; 0/6, 0/7 for MDMT
1973	Walker <i>et al.</i> ^[36]	DMT	45 controls	6/45 DMT	1-2 ng/ml
1973	Wyatt <i>et al.</i> ^[37]	DMT	11 controls, 29 psychiatric patients; no meds for 30 days	1/11 DMT; 1/29 DMT	1.0 ng/ml; 10.6 ng/ml
1973	Narasimhachari and Himwich ^[38]	DMT, HDMT	6 chronic schizophrenics	3/6 DMT, 6/6 HDMT	HDMT 1-3 µg/24 hour; DMT 1 µg/24 hour
1974	Lipinski <i>et al.</i> ^[39]	DMT	7 control	2/11 acute schizo DMT	(1) 6, (1) 1.8
1974	Bidder <i>et al.</i> ^[40]	DMT	6 chronic schizo, 11 acute schizo, 11 hepatic coma 34 with acute psychotic illness, 3 with non psychotic illness, 1 control	2/38 blood DMT; 1/44 urine psychotic patients	(1) 2.5 ng/ml, (1) 4.6 ng/ml; 0.76 ng/ml
1974	Narasimhachari <i>et al.</i> ^[41]	HDMT, DMT, MDMT	6 chronic schizophrenics highly restricted diet, no drug administration 4 weeks	6/6 HDMT; 3/6 DMT; 0/6 MDMT	1-3 µg/24 hour; <1 µg/24 hour
1975	Carpenter <i>et al.</i> ^[42]	DMT, HDMT	26 acute schizophrenics; 10 controls; no meds for 3 weeks	4/26 DMT, 6/26 5-HDMT; 4/10 DMT, 8/10 HDMT	HDMT mean 1.67 µg/24 hr schizo, 1.73 µg/24 hr controls; DMT not quantitated
1975	Christian <i>et al.</i> ^[43]	DMT, MDMT	1 control cerebrospinal fluid	positive for DMT, MDMT	ND
1975	Narasimhachari and Himwich ^[44]	DMT, HDMT	47 infantile autism, 46 controls	24/47 HDMT, 10/47 DMT; 14/46 HDMT	ND
1976	Angrist <i>et al.</i> ^[45]	DMT	23 psychiatric patients, 17 controls	13/23 DMT; 7/17 DMT	0.05-0.79 ng/ml; 0.06-0.22 ng/ml
1976	Rodnight <i>et al.</i> ^[46]	DMT	122 psychiatric patients; 20 controls	37/122 DMT; 1/20 DMT	>500 ng/24 hour
1976	Murray and Oon ^[47]	DMT	54 psychiatric patients, 14 controls; 1 patient strict diet, 2 patients on neomycin	23/54 DMT; 1/14 DMT	DMT > 500 ng/24 hour, Mean range 226-1,717 ng/ 24 hour; control 228 ng/ 24 hour
1976	Huszka <i>et al.</i> ^[48]	HDMT, DMT, MDMT	7 schizophrenics, special diet; MAOI phenelzine	No HDMT, DMT, MDMT detected	NA
1977	Cottrell <i>et al.</i> ^[49]	HDMT	20 psychiatric patients; 2 controls	15/20 HDMT; 0/2 HDMT; no DMT or MDMT detected	1-120 nmol HDMT/24 hour
1977	Oon <i>et al.</i> ^[50]	DMT, NMT	19 normal	19/19 DMT; 19/19 NMT	DMT range 20-2500 ng/24 hour; NMT range 121-3000 ng/24 hour
1977	Oon and Rodnight ^[51]	DMT, NMT	69 patients, 24 normal	No diurnal variation, no dietary source 69/69 DMT; 17/24 DMT	DMT range 0.1-4.5 µg/ 24 hr; DMT range 0.1-0.5 µg/ 24 hr
1978	Riceberg and Van Vunakis ^[52]	DMT, HDMT, MDMT	6 controls	3/4 DMT, 1/4 MDMT, 3/4 HDMT, plasma 4/4 DMT, 2/4 MDMT, 4/4 HDMT, whole blood	HDMT 0.25-0.38 pmol/ml, MDMT 0.09 pmol/ml, DMT 0.77-3.69 pmol/ml HDMT 0.11-2.64 pmol/ml, MDMT 0.7-2.89 pmol/ml, DMT 0.27-14 pmol/ml

1978	Corbett <i>et al.</i> ^[53]	DMT, MDMA	57 psychiatric patients; 41 controls	2/6 DMT, 2/6 MDMA, 6/6 HDMT, urine	HDMT 1.1–10.3 nmol/ml, MDMA 1.3–8.7 nmol/ml, DMT 9.1–13.1 nmol/ml ND
1979	Walker <i>et al.</i> ^[54]	DMT	9 schizophrenics	17/57 DMT, 14/57 MDMA; 9/41 DMT, 2/41 MDMA 6/9 DMT	arterial range 24–118 pg/ml; venous range 18–103 pg/ml; no sig dif between two sources DMT range 0.1–4.5 µg/24 hr; DMT range 0.1–0.5 µg/24 hr 10/18 >500 ng/24 hr; 12/20 >500 ng/24 hr; 1/19 >500 ng/24 hr DMT mean 96 ng/g creatinine; HDMT mean 950 ng/g creatinine
1979	Murray <i>et al.</i> ^[55]	DMT, NMT	74 psychiatric patients; 19 controls; no meds for 2 weeks	74/74 DMT; 19/19 DMT	
1979	Checkley <i>et al.</i> ^[56]	DMT	18 schizophrenics; 20 patients with liver disease; 19 controls	all DMT positive	
1979	Raisanen and Karkkainen ^[57]	DMT, HDMT	26 controls	all DMT and HDMT positive	
1979	Smythies <i>et al.</i> ^[58]	DMT, MDMA	11 patients undergoing lumbar puncture	11/11 DMT; 1/11 MDMA	DMT range from <0.12–100.4 ng/ml; ~1–3 µg/ml, ~1–2 µg/ml
1980	Checkley <i>et al.</i> ^[59]	DMT	5 schizophrenics 4 manic-depressives	2/5 DMT 2/5 DMT	~0.5–1 µg/ml, ~0.5–3 µg/ml
1983	Uebelhack <i>et al.</i> ^[60]	DMT, MDMA	14 schizophrenics; 12 controls	14/14 DMT, 12/14 MDMA; 12/12 DMT, 10/12 MDMA	Sum DMT + MDMA; 1,404.3 ± 481 ng/ml patients; 234.4 ± 213.6 ng/ml controls
1983	Sitaram <i>et al.</i> ^[61]	HDMT	8 healthy adults	5/8 HDMT	0.02–7.8 nmol/12 hour
1984	Raisanen <i>et al.</i> ^[62]	HDMT	48 male violent offenders; 23 controls	48/48 HDMT; 23/23 HDMT	range 0.15–103 nmol/g creatinine; 1.23–14.1 nmol/g creatinine
1988	Karkkainen <i>et al.</i> ^[63]	HDMT	75 psychiatric patients; 51 controls	75/75 HDMT; 51/51 HDMT	range 0.05–96.3 nmol/g creatinine; 0.29–23.2 nmol/g creatinine; MAOI 407 nmol/g creat
1992	Karkkainen and Raisanen ^[64]	HDMT	1 healthy male; with and without MAOI nialamide	1/1 before; HDMT greatly increased after MAOI	range 0.002–1.785 nmol/mmol creatinine; 0.06–16.6 nmol/mmol creatinine MAOI no diurnal variation observed; bufotenin excretion was intermittent
1995	Karkkainen <i>et al.</i> ^[65]	HDMT	112 male violent offenders	112/112 HDMT	range 0.01–17.1 nmol/mol creatinine
1995	Takeda <i>et al.</i> ^[66]	HDMT, HNMT	140 psychiatric and non-psychiatric patients; 200 controls	89/140 HDMT, 46/140 HNMT; 2/200 HDMT	range 2.5–288 ng/mg creatinine, HNMT 2.0–102 ng/mg; mean 10.9 ng/mg creatinine
2001	Forsstrom <i>et al.</i> ^[67]	DMT, MDMA, HDMT, NMT	23 surgical patients; 29 psychiatric patients 13 internal medicine patients	7/23 HDMT, 3/23 DMT, 7/23 NMT 14/29 HDMT, 0/29 DMT, 13/29 NMT 2/13 HDMT, 2/13 DMT, 2/13 NMT	HDMT 0.43–33.57 µg/l, DMT 0.16–28 µg/l, NMT 0.12–29 µg/l HDMT 0.81–24.9 µg/l, NMT 0.05–0.25 µg/l HDMT 0.48–7.2 µg/l, DMT 0.42–54 µg/l, NMT 0.05–0.13 µg/l

Table 3. (Continued)

Year	Author	Compounds Analyzed	Subjects	Positive/Negative	Concentration
2005	Karikkainen <i>et al.</i> ^[68]	DMT, HDMT	137 hospital patients; 9 control	0/137 plasma or serum DMT, HDMT 9/9 urine controls HDMT; 0/9 DMT	NA <0.05–9.1 ng/ml; NA (Kidney tissue 15 pg/g HDMT and DMT, 14 pg/g DMT in lung) 1.0–180 ng/g HDMT; 0.13 ng/g DMT
2010	Emanuele <i>et al.</i> ^[69]	HDMT	15 autistic spectrum disorder; 15 schizophrenics; 18 controls	13/13 controls stool samples HDMT, 1/13 DMT 15/15 HDMT; 15/15 HDMT; 18/18 HDMT	3.3+/- 0.49 ng/ml; 4.39+/- 0.43 ng/ml; 1.53+/- 0.30 ng/ml

as well as patients. Despite many such efforts, a definitive link has yet to be demonstrated between the blood and/or urine levels of these compounds and any psychiatric diagnosis.^[85,93]

The earliest studies (1950s–1960s) in the search for endogenous psychedelics applied the technology available at the time. These were mainly paper and thin-layer chromatography (TLC) using different reagents as visualization (colour development) sprays, as well as comparing Rf values with spotted standards as the criteria for identification. In 1967, thin-layer spots were isolated and derivatized in an attempt to confirm their identification by gas-liquid-chromatography (GC) using a flame-ionization detector (FID).^[21] In this case, Rf values from TLC and relative retention time (Rt) from GC that were consistent with known standards served as the confirmation criteria. Subsequent studies applied this technology utilizing other detectors, such as nitrogen-phosphorous, electron capture and, eventually, mass spectrometry (MS). In many of these studies, the sole criterion for identification was retention time compared to a reference standard. However, in the case of the early MS data, the presence of a single major fragment ion^[38] (*m/z* 58) or one or two minor ions,^[39] served as additional confirmation. Liquid chromatography with UV and fluorescence detection was also applied, with the collected peaks being confirmed by GC-MS in some cases. As the analytical technology evolved, so too did the methods applied to detect and measure the compounds of interest, with resultant gains in sensitivity, specificity, and validity.

The most recent methods have applied LC-MS/MS technologies in combination with more stringent confirmation criteria.^[67–69] These criteria are based on specific protonated molecules, fragment ions and their ratios to one another, and on relative retention times. However, as the criteria have become more exacting and the specificity of the methodology has improved, detection of the endogenous psychedelics appears to have become less frequent and, where detection has occurred, at significantly lower concentrations than originally reported.

Tables 1–3 are a compilation of 69 studies directed towards detecting or detecting and quantitating the three indole psychedelics – DMT, HDMT, and MDMT – in human (patient and/or control) CSF, blood, and/or urine. The entries for each study were taken from copies of the original publications. In some cases, the published studies neglected to address the relevant analytical issues reviewed.

Study review

- Sixty-nine studies were reviewed. Other studies that exist were either not accessible through current abstract search engines, were sufficiently obscure as not to be abstracted, or were not available in a translated form for inclusion in this analysis. Articles were obtained through SciFinder (Chem Abstracts Selects; <https://scifinder.cas.org>) and PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) database searches.

HDMT: urine

- Fifty-one studies examined urine samples for HDMT (27 assayed urine for HDMT only). Taking into account the presence of the 5-hydroxyl group on HDMT, 7 studies specifically addressed the issue of the excretion of HDMT as a

conjugate by using hydrolysis with HCl or enzyme treatment. From these studies we know that approximately 50% of the total HDMT is excreted as a glucuronide conjugate. The remaining 44 studies did not conduct hydrolysis or enzyme treatment and thus did not determine the total amount of HDMT excreted but rather free HDMT alone.

- Urine samples from 1912 individuals were assayed; 1249 patients (predominantly diagnosed with schizophrenia) and 663 controls. Among patients, 886 were positive for HDMT (71%) and 363 were negative. Among controls, 363 were positive for HDMT (55%) and 300 were negative. Thus, 1249 individuals were positive (65%) and 663 were negative. Most of the urine samples were obtained from 24-h collections with varying quantities of the total collection being used for analysis. However, many other studies only used morning or random samples, while a few used 8- or 12-h collections. Varying amounts of urine were used in the assays, based on volume or total mg creatinine. The range of extraction techniques is shown in Table 1 and the analytical approaches employed are shown in Table 2. One study examined and failed to find a diurnal variation in urine concentrations of HDMT,^[50] while another reported that HDMT excretion did not vary diurnally but rather was intermittent.^[64] Several studies examined dietary influences on detection of HDMT but none established a dietary source (Table 3).
- Concentrations of HDMT were usually reported as $\mu\text{g}/24\text{ h}$ while other studies reported concentrations as $\mu\text{g}/\text{g}$ or $\mu\text{g}/\text{mg}$ creatinine, nmol or pmol/ml or per 24 h, and ng/ml or $\mu\text{g}/\text{L}$. Using the most common methods of reporting, these studies demonstrated concentrations ranging from 1 to 62.8 $\mu\text{g}/24\text{ h}$, and from 0.48 to 218 ng/ml.

HDMT: blood

- Of the 69 studies, 4 examined blood for the presence of HDMT.
- Blood samples from 240 individuals were examined: 166 patients and 74 controls. Plasma, serum, and whole blood were used. A single study provided 146 of these total samples^[67]; it used a limit of detection of 0.3 ng/ml and a 1.0 ml sample of plasma or serum for analyses. For all of the studies combined, 4 patients were positive for HDMT (2.4%) and 162 were negative. Eighteen controls were positive for HDMT (24%) and 56 were negative. Thus, a total of 22 individuals were positive for HDMT (9%) in blood and 218 were negative. One study reported higher concentrations of HDMT were obtained from extraction of whole blood compared to serum.^[52]
- When concentrations were reported (rather than simply present or not present) the concentrations of HDMT in blood ranged from 22 pg/ml (HPLC-radioimmunoassay)^[52] to 40 ng/ml (direct fluorescence assay of extracts).^[11]

HDMT: cerebrospinal fluid

- None of the 69 studies examined CSF for HDMT.

DMT: urine

- Of the 69 studies, 29 examined urine for DMT.

- Urine samples from 861 individuals were examined: 635 patients and 226 controls. Among patients, 276 were positive for DMT (43%) and 359 were negative. Among controls, 145 were positive (64%) and 81 were negative. Thus, a total of 421 individuals were positive for DMT (49%) in urine and 440 were negative. Most of the urine samples were 24-h collections and analytical samples varied in volume. However, many also used morning or random samples, while a few used 8- or 12-h collections. Various amounts of the urine were used in the assays, based on a set volume of urine or that containing a predetermined amount of creatinine. The range of extraction techniques is shown in Table 1 and analytical approaches employed are shown in Table 2. Several studies examined dietary influences on detection of DMT and were uniformly negative (Table 3). One study reported that DMT and NMT (N-methyltryptamine; **4**, Figure 1) concentrations in urine were stable when stored at $-15\text{ }^{\circ}\text{C}$ for up to 90 days.^[50]
- Concentrations of DMT were usually reported as $\mu\text{g}/24\text{ h}$ while others used $\mu\text{g}/\text{g}$ or $\mu\text{g}/\text{mg}$ creatinine, nmol/ml or pmol/ml nmol/24 h, ng/ml or $\mu\text{g}/\text{L}$, etc. Concentrations ranged from 0.02 to 42.98 \pm 8.6 (SD) $\mu\text{g}/24\text{ h}$, and from 0.16 to 19 ng/ml.

DMT: blood

- Of the 69 studies, 11 examined blood for DMT.
- Blood samples from 417 individuals were examined for the presence of DMT: 300 patients and 117 controls. Blood samples used were plasma, serum and/or whole blood. Among patients, 44 were positive (15%) and 256 were negative. A single study is responsible for 137 of these negative samples^[68]; the authors – who used a 1.0 ml sample of plasma or serum – reported a limit of detection of 0.2 ng DMT/ml. Among controls, 28 were positive (24%) and 89 were negative. Thus, a total of 72 individuals were positive for DMT (17%) in blood and 345 were negative. The range of extraction methods used is shown in Table 1 and analytical approaches employed are shown in Table 2. One study demonstrated that higher concentrations of DMT were found by extracting whole blood rather than using plasma.^[52] One study demonstrated that there was no difference in DMT blood levels between venous and arterial blood.^[54] One study reported that DMT concentrations were stable in plasma when stored for 60 days at $6\text{ }^{\circ}\text{C}$ ^[36] (Table 3).
- When concentrations were reported (rather than simply present or not present), the concentrations of DMT in blood ranged from 51 pg/ml (HPLC-radioimmunoassay)^[52] to 55 ng/ml (direct fluorescence assay of extracts).^[11]

DMT: cerebrospinal fluid

- Of the 69 studies, 4 examined CSF for DMT.
- CSF samples from 136 individuals were examined for the presence of DMT: 82 patients and 54 controls. Among patients, 34 were positive for DMT (41%) and 48 were negative. Among controls, 22 were positive (41%) and 32 were negative. Thus, 56 individuals were positive (41%) and 80 were negative.
- Concentrations of DMT in CSF ranged from 0.12 to 100 ng/ml (Table 3).

MDMT: urine

- Of the 69 studies, 9 examined urine for the presence of MDMT.
- Urine samples from 113 individuals were examined: 94 patients and 19 controls. A single study was responsible for 65 of these samples.^[67] Combining all studies, two patients were positive for MDMT in urine (2%) and 92 were negative. Two controls were positive (10.5%) and 17 were negative.
- The concentrations of MDMT in urine ranged from 0.3 to 1.3 ng/ml (HPLC-radioimmunoassay).^[52]

MDMT: blood

- Of the 69 studies, 2 examined blood for the presence of MDMT.
- Blood samples from 39 individuals were examined: 36 patients and 3 controls. Among patients, 20 were positive (51%) and 16 were negative. None of the 3 controls was positive for MDMT (Table 3).
- A single estimate of 2.0 ng/ml was reported by one study (HPLC-radioimmunoassay).^[52]

MDMT: cerebrospinal fluid

- Of the 69 studies, 4 examined CSF for MDMT.
- CSF samples from 136 individuals were assayed: 83 patients and 53 controls. Among patients, 28 were positive (34%) and 55 were negative. Among controls, 12 were positive (23%) and 41 were negative. Thus, a total of 40 individuals were positive (29%) and 96 were negative.
- Only one study reported concentrations of MDMT in CSF, in which case the mean combined concentrations of DMT and MDMT were approximately 1400 ng/ml for patients and 230 ng/ml for controls with quite large standard deviations (GC-FID).^[60]

The above does not address the analytical methods' sensitivity and specificity, and assumes that all of the data as collected and reported are accurate, either in their detection or non-detection of the target analyte(s) or the concentrations observed. However, this is almost certainly not the case. As can be seen from Table 2, almost every study conducted between 1955 and 1972 used paper or TLC for detection, quantitation, and confirmation of one or more of these compounds. Several studies used multiple chromatographic conditions and detection reagents in attempting to 'confirm' their results. It is well-known, however, that paper chromatography is limited in specificity and sensitivity in that spots tend to be diffused and the mobility of the compounds of interest is influenced by the presence of other components and salts. TLC is somewhat better but is also susceptible to these same factors in addition to many other variables such as humidity. Other studies used 2-D chromatographic conditions and very sensitive and moderately specific detection reagents. Nevertheless, the criteria for detection relied on R_f values and colour reactions relative to standards (Table 2). There were no data regarding the structure of the detected compounds. Much of the literature acknowledged their limitations and qualified results by referring to the compounds detected as, for example, 'bufotenin-like'.^[4,7,15]

In many studies, large volumes of urine were extracted and concentrated (Table 1), resulting in a final extract less than optimal for such analysis. For example, in order to precipitate

salts and other compounds, acetone was often used in the final steps of sample purification. However, Tanimukai demonstrated that acetone forms adducts with primary amines co-extracted in the process leading to formation of compounds that behaved similarly to bufotenin, for example, on paper or TLC.^[20] Although there do not seem to be any published replications of Tanimukai's findings, they did lead to modification of many of the extraction procedures that were subsequently designed to fractionate tertiary from primary amines (Table 1).

As can be seen from Table 1, the extraction methods employed were predominantly classical liquid-liquid extractions with appropriate pH adjustments or the use of ion exchange resins or packings. The earliest studies, and especially those extracting large volumes of urine, often used a combination of methods in sequence in an attempt to obtain an adequately purified and appropriate extract for paper or TLC analysis. Almost none of these studies reported analyte recoveries, however. The most recent methods have all employed ion exchange solid-phase extraction for the isolation of the target compounds from urine.^[67-69]

In addition to methodological complications, misidentifications of compounds may also have occurred because both paper and TLC using colour reagents require a somewhat subjective interpretation. For example, Rodnight^[2] and Siegel *et al.*^[12] proposed that the substance detected by Bumpus and Paige^[1] was tryptamine and not HDMT. Another potential problem, involving co-injection of extracted indole-ethylamines in GC analyses using the solvent methylene chloride, was addressed by Brandt *et al.*^[86] These authors showed that the compounds of interest react with methylene chloride under such conditions, forming quaternary salts and analytical artifacts.

Some early studies used more than one method for their analyses, increasing the likelihood that their identifications were accurate; for example, combining TLC and GC with packed column technology. However, the resolving power of packed column technology is low and individual 'peaks' were often broad humps, sometimes several minutes wide. Subsequent studies using capillary chromatography have consistently demonstrated that some peaks observed using packed columns were often a composite of several compounds. In addition, the flame ionization detector that many studies used also lacked specificity. Although these approaches used two different technologies, the technologies themselves were relatively non-specific and yielded equivocal results.

Some investigators added, or used exclusively, GC with ECD or NP detectors. While these detectors added sensitivity – and in the case of NPD a degree of specificity – they continued to rely on R_t and detector response as their identification criteria. No structural data were generated. Other research teams used ultraviolet spectrometry and/or spectrofluorometry to detect and quantify the relevant compounds in extracted samples, either directly or after thin-layer or paper chromatography purification. However, the non-specificity of these methods also did not provide data regarding structural identity. For example, Siegel^[12] demonstrated that the fluorescence method used by Franzen and Gross^[11] did not actually measure a maxima from HDMT but instead the tail of the fluorescence spectrum of another compound. These findings bring into question studies that applied these and similar methods.

Inconsistent findings in previous research suggest that sensitivity was also an issue. Data concerning extraction efficiency and recovery, limits of detection, specificity, reproducibility, storage stability, the use of double blind and replicate analyses, and other variables that are now basic requirements in assay research are lacking either altogether or in part in earlier studies. At best, some early papers point to other references for some of these data. However, we found direct comparisons of methods in either positive or negative studies difficult to conduct.

The first applications of mass spectrometry to the detection and quantitation of putative endogenous psychedelics in man occurred in 1973. Walker *et al.*^[36] and Wyatt *et al.*^[37] employed an isotope dilution method monitoring two ions to detect and quantitate DMT in blood. Soon thereafter, Narasimhachari and Himwich used GC-MS with single ion monitoring (m/z 58) to detect DMT from urine extracts.^[38] These latter authors also extracted sufficient material, using TLC for clean-up, to obtain a total ion mass spectrum of the detected substance, and demonstrated its identity with authentic DMT. These data were the first methodologically credible regarding DMT's presence in humans. Subsequent studies by these and other authors applied different MS capabilities for the detection, quantitation, and unequivocal confirmation of DMT and HDMT in humans. In 1974, Narasimhachari *et al.*, providing a matching total ion spectrum of an extracted compound, reported the unequivocal identification of HDMT from human urine.^[41] In 1976, Rodnight *et al.*,^[46] using similar methods, published a matching total ion spectrum for DMT in human urine. Other MS techniques matched the retention time and protonated molecule ions (chemical ionization MS) for DMT and HDMT in urine.^[50,51] Additional studies detected, quantified, and confirmed the identity of DMT, NMT, and HDMT in human blood and urine using selected ion monitoring (SIM) of multiple fragment ions (Table 2). It is important to note that MDMT has yet to be unequivocally detected by any MS-based method in blood or urine. However, there are two reports of its presence in CSF using GC-MS/SIM.^[53,58]

Continual improvement in MS technologies has greatly enhanced detection, sensitivity, and specificity of analytic studies searching for these compounds; for example, capillary chromatography for GC, and more advanced LC-mass spectrometers. This being the case, it is encouraging to note that all studies since 1973 using MS methodology have confirmed the presence of one or more of these compounds in human body fluids (Table 2). The most recent methods utilize LC-MS/MS which afford analyses and confirmation by several additional chemical processes; LC separation and matching of R_t , molecular ion matching, and fragment ion presence and ratio matching. This technique also allows for the detection of these compounds in the pg/ml range while providing unequivocal mass spectrometric confirmation of structural identity.

Thus, while many early studies lacked today's more definitive technology, it is likely that many have been confirmed by later MS-based studies. On the other hand, most early studies that reported rather high concentrations on these compounds were most likely in error.

Discussion and conclusions

The answer to the question, 'Are the tryptamine psychedelic substances DMT, HDMT and MDMT present in the human body?'

is most likely yes. We believe that the preponderance of the mass spectral evidence proves, to a scientific certainty, that DMT and HDMT are indeed endogenous and can be measured in human body fluids. The evidence is less compelling for MDMT where the only two MS-based positive studies – in CSF – were performed by the same research group. There is no mass spectral data on detection of MDMT in blood or urine. Thus, further studies are necessary to determine whether MDMT exists in humans. Similarly, there are no data on the possible presence of HDMT in CSF. This too requires examination.

With respect to the paucity of data regarding endogenous MDMT, it should also be noted that HDMT is both a metabolite of and precursor for MDMT. The relationship of these two compounds may help explain why HDMT is so much more frequently detected than MDMT. Future studies will help explicate this relationship.

As to the question, 'Were the analytical methodologies and the criteria for compound identification adequate?', the answer is less certain. Undoubtedly, some studies misidentified the target compounds or, at the minimum, greatly overestimated their concentrations.

Are they of dietary origin? Many early studies attempted to determine if diet or gut bacteria were responsible for positive results. Sterilization of the gut with antibiotics or feeding subjects special diets had no effect on these studies' results. In addition, no evidence suggested that medication(s) played a role. More recently, however, Karkkainen *et al.*^[68] isolated significant quantities of HDMT from stool samples, and hypothesized that HDMT may be synthesized by cells of the intestinal epithelium or the kidney, but not by gut flora.

When are these compounds produced? The very small numbers of studies that have looked for diurnal, circadian, or ultradian variations in levels of DMT or HDMT in humans have been negative. This may be due, in part, to too infrequent sampling times and inadequate assay methodologies. However, one longitudinal study and one assessing diurnal rhythms of DMT in human urine suggest that measurable concentrations occur only intermittently.^[50] The same is apparently true for HDMT.^[64] There are no comparable data available for MDMT. The two DMT studies cited were conducted in urine only and such analyses are probably best conducted in blood. They do stand, however, as examples of one of the possible further complications in understanding the source, role and function of these compounds.

Where in the human body are they synthesized? The tissue source or sources of these compounds in humans remains unknown and, that being the case, we should not assume that monitoring blood, urine, or CSF will answer this question. DMT synthesis has been proposed to occur in adrenal and lung, where high levels of the enzyme responsible for its synthesis – indole-N-methyltransferase (INMT) – have been reported.^[96,97] While these studies did not demonstrate high INMT levels in brain, the active transport of DMT across the blood–brain barrier^[98] suggests that peripheral synthesis may nevertheless affect central function. In addition, the mapping of INMT sites thus far has been based solely on INMT mRNA studies which only establish where active enzyme translation is occurring. However, recent studies by Cozzi *et al.*^[99] using a fluorescent antibody to INMT and confocal microscopy, have identified INMT in spinal cord, brain, retina, and pineal, and suggest the possibility of applying other powerful molecular biology tools and methods for mapping the location and characterizing the regulation of the endogenous psychedelic pathway. Their findings suggest that INMT may be

an inducible enzyme. These molecular biological approaches, in combination with advances in assay methodology, may help finally characterize the biochemistry and physiology of these compounds in humans.

The next questions – Can we influence the detection of endogenous psychedelics in humans by pre-treatment with MAO inhibitors? How does the turnover rate and metabolism of these substances influence their detectability? Have the precursors and/or metabolites of these compounds been adequately monitored? – require synthesizing several parallel lines of evidence. In humans, only a very small percentage of exogenously administered DMT is excreted in urine as the parent compound.^[88] This is also true for HDMT^[100] and MDMT.^[101] Despite this fact, every cited study monitored, without exception, only the parent compounds themselves in the various biological fluids examined. These compounds all have a very short half-life – a few minutes – and blood levels are undetectable in less than an hour after administration. This rapid metabolism is due to their being excellent substrates for MAO-A. This enzyme's action on the psychedelic tryptamines results in the formation of their corresponding indoleacetic acids, which are indistinguishable from these same acids resulting from other better-known sources, such as tryptamine and serotonin. Several studies attempted to maximize detection of these substances by treating subjects with MAO inhibitors such as tranylcypromine and phenelzine (Table 3). In most cases, this did result in higher concentrations of the target compounds. Nevertheless, even with significant MAO inhibition, the concentrations of parent compounds remained quite small. This observation has, perhaps, a ready explanation: the other metabolic pathways for DMT, MDMT, and HDMT.

Recognition and understanding of these compounds' pathways for degradation may afford an approach to circumventing the low concentrations of the parent compounds observed even after MAO inhibition. Sitaram *et al.*^[89–91] have shown that, in MAO-inhibited rats, metabolism of these psychoactive tryptamines is shifted away from MAO-A and indoleacetic acid formation to the N-oxidase and the respective N-oxides. However, no studies have yet pre-treated humans with MAO inhibitors and measured the parent compounds and their corresponding N-oxides. The advantage of such a study is that the N-oxide, as opposed to the indoleacetic acid, retains the original structure of the parent molecule, permitting a cumulative association. As a proof of concept, we, have measured blood and urine levels of DMT and its N-oxide (**5**, Figure 1) in humans administered a botanical preparation of DMT and MAO-A inhibiting harmala alkaloids – the Amazonian brew *ayahuasca*.^[102,103] Concentrations of the N-oxide of DMT in these subjects were 3–4 times greater in blood, and 20 times greater in urine, than DMT itself. Therefore, monitoring the N-oxide metabolites rather than the parent compounds alone in MAO-inhibited humans may provide a substantial advantage in detecting and quantitating the endogenous psychedelic compounds.

Several of the studies reviewed did examine samples for the corresponding NMT, which is both a precursor for and a metabolite of the three endogenous psychedelics (NMT, HNMT, MNMT). However, in humans administered *ayahuasca* NMT was only intermittently detected in blood and urine and concentrations were quite low (pg/ml).^[102,103] This also may be the result of a shift in metabolism of DMT to

the N-oxide after MAO inhibition and suggests that monitoring NMT in vivo may not be necessary or possible. Nonetheless, several of the reviewed studies suggested that the corresponding NMT was detected (Table 3). That data must now also be in question.

DMT-N-oxide is neither a substrate for MAO-A nor for N-demethylases. Since similar metabolic pathways exist for HDMT and MDMT, we suggest that MAO inhibition in humans will enhance detection and quantitation of these compounds in the periphery, especially if the N-oxide metabolites are monitored.

Thus, we can respond to the questions 'Is monitoring these compounds in biological samples such as CSF, blood and/or urine the best, or even most practical way to determine their activity?' and 'What will such data tell us about the possible normal function of these compounds in humans?' Data regarding their peripheral dynamics – concentrations, circadian variation, and metabolism – as assessed by rigorous analytic methods applied to biological samples represent the most accessible approach to beginning to determine their possible role in human psychophysiology and should be pursued.

Our last question is 'Where does the research on endogenous psychedelics go from here?' One avenue for future studies concerns the endogenous nature of MDMT. This review has illustrated the convincing evidence that DMT and HDMT are endogenous in humans. However, MDMT has not been reported in human blood or urine but is apparently present in CSF. However, CSF has not been examined for the presence of HDMT. We propose that future studies of CSF, blood (including whole blood where higher concentrations may be observed) and urine monitor all three compounds and their N-oxides using superior, fully validated mass spectrometric methodology. Pretreatment of study subjects with an MAO inhibitor should optimize results and may prove critical to such studies. A technical issue regarding HDMT analysis also must be considered in future studies. Assays for this compound should include an enzyme hydrolysis step to free conjugates that may be formed from both the parent compound and its N-oxide.

Another area for future research concerns assay sensitivity. We believe it is necessary to improve sensitivity of assays of the parent compounds to 1.0 pg/ml or less. Given the possible intermittent presence of these compounds in the periphery, blood and urine analyses may require more frequent sampling and longer collection times.

The search for endogenous psychedelic tryptamines should also turn towards other human tissues than blood, urine and CSF; that is, solid organs such as adrenal, brain, lung, pineal, retina, and other tissues in which INMT activity has been noted using molecular biology tools. The combination of assaying relevant compounds with cell and molecular biology approaches will provide the most detailed possible assessment of the location(s) of synthesis and, ultimately, the role of these compounds in human physiology.

For example, mapping of INMT and its presence within certain cell types and locations should reveal its intracellular distribution and possible associations with various receptors. The introduction of an INMT knockout mouse to the research effort could greatly assist in understanding the role of this enzyme and, by inference, the endogenous psychedelics. With these tools in hand, the research that can be conducted may

finally provide us an answer to the question: 'Why do humans produce endogenous psychedelics?' The research thus far is limited but there are many possibilities awaiting further inquiry.

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