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SYSTEMATIC REVIEW

Clinical Pharmacokinetics of *N*,*N*-Dimethyltryptamine (DMT): A Systematic Review and Post-hoc Analysis

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Abstract

Background and objective *N*,*N*-Dimethyltryptamine (DMT) is currently being studied for its therapeutic potential in various psychiatric disorders. An understanding of its pharmacokinetics (PK) is essential to determine appropriate dose ranges in future clinical studies. We conducted a systematic literature review on the PK of DMT.

Methods Clinical studies that administered known amounts of DMT and reported PK data and/or parameters in humans were included. Additionally, raw PK data were requested from authors and/or extracted from publications.

Results In total, 219 references were retrieved, of which 13 publications were included, covering eight distinct datasets. All studies administered DMT intravenously in various infusion schemes, except for one intramuscular administration. High variability in dose-normalized exposure parameters and differences in exposure for bolus versus infusion administration were observed. DMT is extensively redistributed to other tissues, based on its biphasic elimination profile and high volume of distribution in the terminal elimination phase (range 123–1084 L). It is eliminated rapidly, with a half-life of 4.8–19.0 min and clearance of 8.1–46.8 L/min. This is a result of the rapid metabolization of DMT to indole-3-acetic acid (IAA), which is also reflected in the fact that the time of maximum concentration of IAA is similar to that of DMT.

Conclusion This review demonstrates that the PK of DMT in humans have been characterized to a limited extent, and publications lack details with regards to demographics, absolute doses, and PK parameters. Additional studies are necessary to investigate high intersubject variability and differences in exposure following bolus or prolonged infusion. Addressing these issues is essential for the development of DMT as a pharmacotherapeutic in neuropsychiatry.

Key Points

Relatively high variability in dose-normalized exposure parameters and differences in exposure for bolus versus infusion administration were observed.

Additional studies investigating the pharmacokinetics of *N*,*N*-dimethyltryptamine are indicated to guarantee its successful continued development for the treatment of neuropsychiatric disorders.

Future clinical studies on the pharmacokinetics of *N*,*N*-dimethyltryptamine should provide detailed reporting on the administered dose, dose form, measured plasma concentrations, and subject demographics to enable adequate comparison between studies.

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1 Introduction

N,*N*-Dimethyltryptamine (DMT) is a naturally occurring psycho-active compound and the main active ingredient in ayahuasca, a plant-based brew consisting of DMT and harmines [1]. DMT exerts its psychedelic and potential therapeutic effects through potent activation of the 5-HT_{2A} receptor in the central nervous system, thereby highly affecting perception, mood, and cognition [2, 3]. Additionally, 5-HT_{2A} activation is believed to result in the facilitation of neuroplasticity, although the exact mechanism of action is not yet fully understood and potentially involves additional mechanisms such as TrKb and sigma receptor activation [4–6]. As neuroplasticity is currently hypothesized to be altered in various psychiatric disorders, clinical application of psychedelics, such as ayahuasca and DMT, is considered very promising. In fact, ayahuasca and synthesized DMT have demonstrated preliminary therapeutic efficacy in various psychiatric disorders such as substance abuse disorders and treatment-resistant depression [7–11].

However, a major drawback of ayahuasca is the addition of harmines, used to prevent the rapid metabolism of DMT by monoamine oxidase A (MAO-A), which cause untoward side effects, such as nausea, vomiting, and diarrhoea [12]. These side effects, and the potentially resulting increase in pharmacokinetic (PK) variability, hamper the administration of ayahuasca to patients and its further development as a psychiatric therapy. Furthermore, ayahuasca may be derived from a variety of plant sources, resulting in products with different DMT purities. Therefore, research is currently focused on characterizing the safety, PK, and pharmacodynamics of 'pure' synthesized DMT in healthy volunteers and patients [13–15].

Given the early stage of development of DMT as a potential new pharmacotherapeutic strategy in psychiatry, detailed characterization of its PK is considered essential to determine appropriate dose selection in future clinical studies exploring its therapeutic potential [16–18]. To this end, all available quantitative DMT PK data should ideally be available in a single overview, comparing standard PK parameters between studies, and more importantly, quantifying variability and identifying its potential sources. However, such an overview is currently not available because of the relative scarcity of information available on the PK of DMT and/or fragmented published reports across research groups. Additionally, reviews focusing on DMT predominantly tend to focus on its pharmacodynamic effects and only provide a rudimentary description of the PK assessments performed. Consequently, reported PK data are often incomplete, highly summarized, and lack the level of detail and interpretation required to facilitate a comprehensive understanding of the PK of DMT [19, 20].

An extensive systematic literature review on the clinical PK of DMT is, therefore, necessary to provide a clear overview of all available PK data. As such, the aim of the current systematic literature review was to gather, summarize, and compare all available PK data for DMT by, if possible, characterizing the PK of DMT using a post-hoc non-compartmental analysis (NCA) for studies in which such analyses were lacking and/or not reported.

2 Methods

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. Authors agreed with the proposed methods before execution, and the review protocol was registered with PROSPERO (reference number CRD42023388132) [22].

2.1 Search Strategy

PubMed, Embase (OVID version, including MEDLINE), Web of Science, Cochrane Library, Emcare (OVID version), PsycINFO, Academic Search Premier, and Google Scholar were searched on August 11, 2023, to retrieve publications reporting PK data of DMT in humans (both healthy volunteers and patients). Search terms included DMT, PK, PK profiles, PK parameters, C_{max} [maximum plasma concentration], plasma concentrations, plasma levels, area under curve, clearance, drug concentration, urine concentration, absorption, and other related terms (see the supplementary material for full search strategy details). No restrictions were applied to type of study, publication year, or language. In addition, a manual search of the reference lists of relevant reviews was performed to identify any other additional studies.

2.2 Eligibility Criteria

Two independent researchers examined the titles and abstracts of retrieved studies, and unsuitable articles were rejected. Original, peer-reviewed papers, meeting abstracts, and pre-published reports that involved administration of pure DMT to humans and reported any PK data and/or PK parameters were included. Studies where the administered dose was unknown were excluded. Additionally, DMT was not to be administered in combination with another drug or compound and not as a component of (a formulation produced from) naturally occurring plants (e.g. ayahuasca). DMT analogues, with changes to the molecular structure of the compounds, were also excluded (e.g. 5-MeO-DMT, deuterated hydrogen atoms).

2.3 Data Summarization

The included articles were analyzed, and the following study design details were noted: sample size, gender, weight, age, administration route, analyte, dose and form of DMT, as well as any other information relevant for the PK.

All doses described in this report were recalculated to freebase to enable comparison between studies, unless otherwise specified. In these calculations, DMT freebase equals the DMT fumarate dose times 0.619 and DMT freebase equals the DMT hemifumarate dose times 0.764.

2.4 Data Acquisition and Analysis

All authors were contacted and asked to share their data to allow for a side-by-side evaluation of all studies and to complement the data from the publications if, for instance, summary statistics were not present. If data were not shared or present in the acquired datasets, they were extracted from figures, tables, or text. Reported individual and summarized concentration data and derived parameters were extracted. Supplied or extracted individual concentration data and/or parameters were only further summarized to mean concentration profiles if no summarized data were already available in the publication. If individual data were extracted from a report, but the mean profile was also present in this report, the mean profile was extracted, and no recalculations were performed. Individual or mean PK data were further analyzed with NCA if the PK parameters were not reported or if only a limited selection of PK parameters were available. Dose-normalized concentration over time profiles and C_{max} were not calculated for combined infusions because of their complex dosing regimens.

2.4.1 Post-hoc Non-Compartmental Analysis

PK parameters determined with post-hoc NCA included (dose-normalized) C_{max}, (dose-normalized) area under the concentration–time curve from time zero to time of last measurable concentration (AUC_{last}), (dose-normalized) AUC from time zero extrapolated to time infinity (AUC_{inf}), time to C_{max} (t_{max}), terminal elimination half-life ($t_{½}$), (apparent) clearance (CL(/*F*)), volume of distribution at steady state (V_{ss}), and (apparent) volume of distribution during the terminal elimination phase (V_z(/*F*)). AUC was calculated using the trapezoidal rule with the linear up-log down method. Clearance and *V* are not usually calculated for metabolites; however, for intravenous administration, CL/*F* and *V*/*F* can be calculated, where *F* represents the fraction metabolized instead of bioavailability. Calculations of CL/*F* and *V*/*F* parameters were corrected for differences in molecular weight in case of metabolites. The $t_{½}$ was determined by estimating the first-order terminal elimination rate constant using unweighted least squares regression of the terminal part of the log-linear concentration time profile. The $t_{½}$ regression was accepted based on a set of predefined criteria where (1) the slope of the regression must be negative, (2) the sample at t_{max} is not included, (3) at least three datapoints are used, (4) the R^2 is higher than 0.85, and (5) the time interval of the data used for regression is more than 1.5 times the estimated $t_{½}$.

2.5 Software

If PK data were only available in figures, they were extracted using the online WebPlotDigitizer tool (V4.6) [23]. All data transformation and visualization was done using R (V4.0.3), using the PKNCA package for the NCA [24, 25].

3 Results

3.1 Included Studies and Characteristics

In total, 13 publications between 1974 and 2023 reporting PK data of DMT were included (see Fig. 1) [13–35], [26–35], covering eight distinct clinical datasets. One study was preprinted at the time of inclusion and subsequently published in October 2023 [13]. Individual concentration over time data were available in four studies [14], [15], [30], [31], mean data in ten studies [13–15], [26], [27], [29], [32–35], and median data in one study [30]. An overview of the included reports and data is presented in Fig. 1 and Table 1.

3.2 Study Design Characteristics

All studies were performed in healthy volunteers, in group sizes ranging from 5 to 27 subjects per dose level. DMT was administered as a single dose in six studies [15], [28–31], [35], a four-way crossover in six studies [13], [14], [27], [32–34], and a single dose in crossover with ketamine in one study [26]. The washout period in repeat-dose studies included 7 days [14], [27], [33], [34], 14 days [13], and 2–4 weeks [26] as well as 29 min 15 s in a tolerability study [32]. DMT was administered intravenously in all studies, except for one intramuscular administration of approximately 30.3 mg in 11 subjects [35].

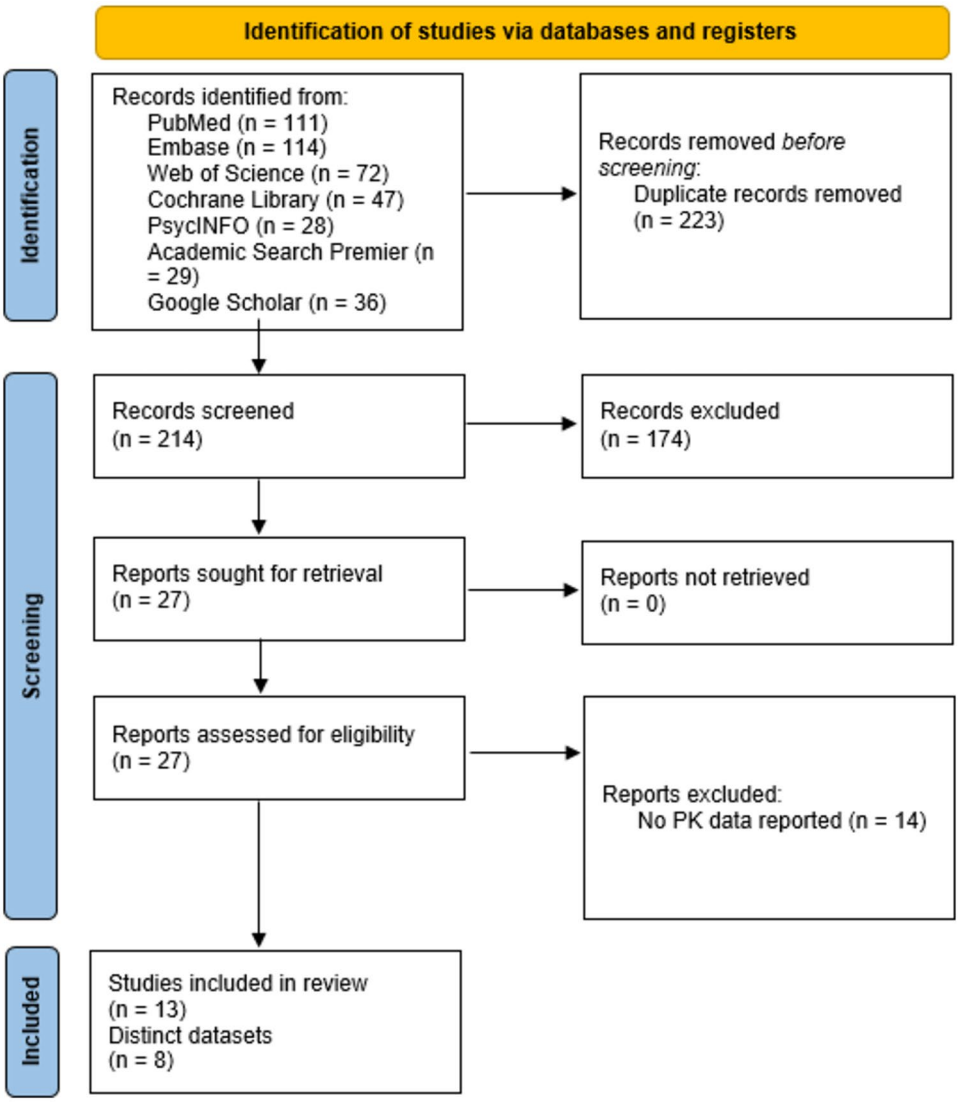

Fig. 1 PRISMA flowchart for selection of included literature. *PK:* pharmacokinetic

3.3 Form of DMT Administered

DMT hemifumarate was administered in four studies [14], [29–31], DMT fumarate was administered in six studies [13], [15], [26], [32–34], and two studies did not report the DMT form used [27], [35]. However, one of these studies [27] was based on the same clinical dataset used by Vogt et al. [14], so we assumed that DMT hemifumarate was administered in both studies. For Kaplan et al. [35], we assumed the DMT fumarate form.

3.4 Administration Regimen and Doses

Intravenous infusion schemes included 30-s bolus [29–32], [34], 90-min infusion [14], [27], 5-min bolus followed by 84-min infusion [26], two consecutive 5-min boluses [15], 30-s bolus followed by 30-min infusion [13] and a 45-s bolus followed by 90-min infusion [14]. Intravenous bolus doses ranged from 2.6 to 20.3 mg, and infusion doses ranged from 3 mg over 5 min to 68.8 mg over 90 min. Gouzoulis-Mayfrank et al. [26] administered various doses that were recalculated to average values of 7.7 mg bolus + 48.5 mg infusion and 11.1 mg bolus + 64.7 mg infusion.

3.5 Demographics

Reported demographics included gender ($n = 12$) [13–34], [26–34], age ($n = 13$) [13–35], [26–35], body mass index (BMI) ($n = 1$) [15], and race ($n = 1$) [15]. Smoking status was only known in one study, where subjects smoking more than 10 cigarettes daily were excluded [14]. Most participants were male (82/125 subjects, 65.6%), and mean age across studies ranged between 34 and 43 years, with most studies including subjects aged between 25 and 65 years. Psychedelic-experienced participants were included in nine studies

Table 1 Overview of reported and recalculated pharmacokinetic (PK) parameters of *N*,*N*-dimethyltryptamine (DMT)

Study details									PK parameters									
#	Study [reference]	DMT form	Administration type	Reported dose	Free base dose (mg)[a]	Subjects (N)	Sampling (N,T_{last})	Analyte	C_{max} (ng/mL)	t_{max} (min)	$t_{1/2}$ (min)	AUC_{last} (ng*min/mL)	AUC_{inf} (ng*min/mL)	CL (L/min)	Vz (L)	Vss (L)	Other	Retrieval
1	Timmerman (2019)	HF	30 sec IV bolus	7 mg	5.3	3	7, 60 min	DMT	15.9 (2.0)	2	4.8 (0.3)	115 (18)	123 (18)	35.8 (5.0)	248 (51)	282 (52)		RC
				14 mg	10.7	4			67.6 (21.2)	2.5	4.7 (0.3)	541 (239)	464 (148)	19.7 (6.3)	131 (32)	147 (27)		
				18 mg	13.7	1			60.5	1.8	8.3	520	672	16.6	197	216		
				20 mg	15.3	5			80.8 (31.6)	5	7.0 (2.3)	672 (216)	993 (159)	12.6 (2.0)	123 (22)	128 (11)		
	Eckernäs (2022) [Timmermann 2019]	HF	30 sec IV bolus	7 mg	5.3	3	7, 60 min	IAA	2040.8 (172.7)	19.9		84202 (19780)						RC
				14 mg	10.7	4			3684.1 (679)	37.1		176970 (35730)						
				18 mg	13.7	1			5081.6	30.9		253704						
				20 mg	15.3	5			5279.4 (796.8)	36.2		252001 (40021)						
	Eckernäs (2023) [Timmermann 2019]		See Timmerman 2019															
2	Strassmann (1994)	FU	30 sec IV bolus	0.05 mg/kg / 4.1 mg	2.6	11	6, 60 min	DMT	11.1 (3.5)	2	30.9	191 (83)	321	8.1	360	380		RC[b]
				0.1 mg/kg / 8.2 mg	5.1				25.3 (26.8)	2	13.9 (15.5)	169 (131)	358 (241)	18.3 (12.0)	501 (650)	542 (685)		
				0.2 mg/kg / 16.4 mg	10.1				48.8 (53.0)	2	7.6 (3.4)	307 (301)	829 (492)	15.3 (6.3)	152 (7)	157 (31)		
				0.4 mg/kg / 32.8 mg	20.3				89.9 (65.7)	2	8.6 (1.8)	654 (274)	827 (376)	30.8 (15.6)	351 (103)	397 (146)		
	Gallimore (2016) [Strassmann 1994]		See Strassmann 1994															
3	Strassmann (1996)	FU	30 sec IV bolus	#1. 0.3 mg/kg / 21 mg	13.0	13	6, 28 min	DMT	50.3 (13.9)	2	6.2 (0.1)	574 (179)	401 (0.3)	32.4 (0.02)	288 (4)	336 (14)		RC
				#2. 0.3 mg/kg / 21 mg	13.0				57.8 (20.3)	2	6.4 (1.1)	670 (262)	492 (5)	26.4 (0.2)	242 (46)	270 (37)		
				#3. 0.3 mg/kg / 21 mg	13.0				61.6 (23.9)	2	7.5 (0.0)	659 (263)	681 (271)	20.7 (8.2)	225 (88)	243 (80)		
				#4. 0.3 mg/kg / 21 mg	13.0				73.6 (24.6)	2	6.5 (3.5)	742 (287)	757 (390)	20.9 (8.9)	169 (62)	194 (69)		
4	Kaplan (1974)	FU[b]	IM	0.7 mg/kg	30.3	4[c]	7,120 min	DMT	70.2 (58.9)	15.2	8.5	2092 (1512)	4064	7.5[d]	92[d]		Ae: 0.069%	RC
						11			98.3	9.7	24.3	2151	2658	11.4	400			
5	Gouzoulis Mayfrank (2005)	FU	5 min IV bolus + 84 min IV infusion	0.18 mg/kg + 0.013 mg/min*kg	7.7 + 48.5	15	5,150 min	DMT	PK parameters could not be calculated, as only two datapoints were provided.									
				0.26 mg/kg + 0.018 mg/min*kg	11.1 + 64.7				PK parameters could not be calculated, as only one datapoint was provided.									
6	Good (2023)	FU	2 x 5 min IV infusion	6.0 mg + 3.0 mg[e]	6.0 + 3.0	5	13,240 min	DMT	20.8 (12.9)	9.6	12.1 (4.7)	349 (253)	352 (252)	46.0 (43.6)	611 (308)	551 (346)	MRT_{inf}: 14.6 min (4.1)	RP
				6.0 mg + 6.0 mg[e]	6.0 + 6.0	6			30.6 (18.1)	10.5	9.5 (4.0)	451 (229)	455 (229)	32.4 (14.6)	425 (214)	375 (173)	MRT_{inf}: 12.4 min (5.6)	
				6.0 mg + 11.0 mg[e]	6.0 + 11.0	5			72.1 (47.1)	9.8		842 (453)						
				6.0 mg + 15.5 mg[e]	6.0 + 15.5	6			62.7 (25.8)	9.7	12.1 (5.2)	835 (231)	837 (231)	27.9 (9.7)	456 (157)	400 (149)	MRT_{inf}: 15.0 min (5.0)	
				6.0 mg + 6.0 mg[e]	6.0 + 6.0	4	13,240 min	IAA	1532.5									
				6.0 mg + 15.5 mg[e]	6.0 + 15.5	4			2182.5									
	Benway (2023) Good [2023]		See Good 2023															
7	Luan (2023)	FU	30 sec IV bolus + 30 min IV infusion	6 mg + 0.63 mg/min	3.7 + 11.3	6	15,180 min	DMT	12.0	39.4	16.1	320	320	46.8	1084			RC[f]
				10 mg + 1.05 mg/min	6.2 + 18.8	10			18.0	30.5	10.9	663	665	37.6	590			
				14 mg + 1.46 mg/min	8.6 + 26.2	9			31.3	30.6	11.3	1022	1023	34.2	558			
				18 mg + 1.88 mg/min	11.1 + 33.7	6			33.4	30.7	19.0	1284	1291	34.8	953			
8	Vogt (2023)[g]	HF	45 sec IV bolus + 90 min infusion	15 mg + 0.6 mg/min	11.5 + 41.3	27	20,150 min	DMT	29	2.5	14	1369	1374	36	746	NR	Initial $t_{1/2}$: 5.0 min	RP
				25 mg + 1.0 mg/min	19.1 + 68.8				61	2.9	16	2297	2303	36	799	NR	Initial $t_{1/2}$: 5.8 min	
			90 min IV infusion	0.6 mg/min	41.3				24	72	15	1899	1902	39	820	NR	Initial $t_{1/2}$: 5.3 min	
				1.0 mg/min	68.8				39	73	15	3213	3220	39	831	NR	Initial $t_{1/2}$: 5.3 min	
			45 sec IV bolus + 90 min infusion	15 mg + 0.6 mg/min	11.5 + 41.3	27	20,150 min	IAA	3128.3	95.1		345887						RC[g]
				25 mg + 1.0 mg/min	19.1 + 68.8				4726.2	100.0		541250						
			90 min IV infusion	0.6 mg/min	41.3				2606.7	100.0		262230						
				1.0 mg/min	68.8				4127.4	105.1		411542						
			45 sec IV bolus + 90 min infusion	15 mg + 0.6 mg/min	11.5 + 41.3	27	20,150 min	DMTNO	0.8	90.1		85						
				25 mg + 1.0 mg/min	19.1 + 68.8				1.5	90.11		169						
			90 min IV infusion	0.6 mg/min	41.3				0.6	90.1		59						
				1.0 mg/min	68.8				1.3	90.1		105						
	Luethi (2022) Vogt [2023]		See Vogt 2023															

Distinct clinical datasets are numbered. Studies are listed by author. Datasets covered by multiple publications are referred to with an additional group reference label referring to the publication with the most detailed description of the pharmacokinetic dataset or original database in line with results shown in Figs. 2 and 3. Freebase doses were recalculated to an absolute dose if reported as a weight-based dose. This absolute dose was based on (1) the mean of individual absolute doses, (2) the mean weight of the study population, (3) an average weight of 70 kg. Pharmacokinetic parameters are listed as mean (standard deviation), except for t_{max}, which is listed as median

Ae amount excreted in urine (relative to the dose), AUC_{inf} AUC from time zero extrapolated to time infinity, AUC_{last} AUC from time zero to time of last measurable concentration, *CL* clearance, C_{max} maximum plasma concentration, *FU* fumarate, *HF* hemifumarate, *IAA* indole-3-acetic acid,

Table 1 (continued)

IM intramuscular, *IV* intravenous, *MRT* mean residence time, MRT_{inf} MRT extrapolated to infinity, *RCE* recalculated from data extracted from figures, *RCR* recalculated from acquired raw data, *RP* reported, $t_{½}$ terminal elimination half-life , t_{last} time of last measurable plasma concentration, t_{max} time to peak plasma concentration, V_{ss} volume of distribution at steady state, V_z volume of distribution during the terminal elimination phase

[a]Conversion factor DMT fumarate to freebase DMT: 0.619. Conversion factor DMT hemifumarate to freebase DMT: 0.764

[b]DMT fumarate was assumed. Conversion factor from DMT fumarate to DMT hemifumarate: /1.236

[c]Summary statistics calculated from individual recalculated pharmacokinetic parameters of 4 subjects. Mean concentration over time data of 11 subjects were present in the report

[d]Cl/*F* and Vz/*F* since intramuscular is an extravascular administration route

[e]Originally reported as freebase DMT

[f]Summary statistics calculated from mean reported concentration over time profile

[g]All reported pharmacokinetic parameters are listed as the geometric mean, including $t_{max.}$ Recalculated parameters are listed as mean (standard deviation), except for t_{max}, which is listed as median

[13], [28–35], psychedelic inexperienced in one study [15], and both in three studies [14], [26], [27].

Weight-based dosing was used in five studies, but neither individual doses nor demographics on weight were reported [26], [32–35]. Individual weight data were acquired from three of these studies [32–34]; the remaining doses were recalculated to an average adult of 70 kg.

3.6 Bio-Analytical Measurements

All studies ($n = 13$) presented concentration data measured in blood plasma via liquid chromatography, with only one study presenting concentration data in urine [35]. Sampling frequency across studies ranged from 6 to 21 samples, up to 4 h after dosing. DMT was measured in all studies, whereas its metabolite indoleacetic acid (IAA) was measured in plasma in five studies [14], [15], [27], [30], [31] (two datasets), DMT-N-oxide (DMT-NO) was measured in plasma in three studies [14], [27], [31] (two datasets), but quantifiable DMT-NO levels were only detected once [14]. The metabolite N-methyltryptamine (NMT) was not measured in any report.

3.7 Acquired Pharmacokinetic Data

In total, three distinct clinical datasets from six studies were acquired upon request to the authors [29–34]. All acquired datasets solely reported individual DMT plasma concentrations.

3.8 Extracted Pharmacokinetic Data

Mean DMT data were extracted from figures [13], [14], tables [15], or text [26] and individual data from figures [35]. Considering distinct datasets were discussed over multiple studies, data from two other studies [27], [28] were not extracted. Additionally, due to overlapping curves, individual data from one study could not be extracted [14].

Mean DMT concentration profiles could be extracted or calculated for seven datasets. They were extracted from three studies that contained mean profiles but not individual data [13–15] and from one study that reported both individual ($n = 4$) and mean ($n = 11$) data [35]. Additionally, they were recalculated based on individual data in three studies as these data were acquired [29], [32], [33].

Since IAA data from Timmerman et al. [29] were not available in the acquired dataset, individual IAA data for this dataset were extracted from Eckernäs et al. [31] and subsequently used to recalculate mean IAA concentration over time profiles. Lastly, mean IAA and DMT-NO data were extracted from one study [14].

All extracted and acquired summarized and individual concentration over time data have been compiled in Fig. 2 and Figs. S1–S8 in the supplementary material. Since distinct datasets are often discussed over multiple reports, results are presented while referring to the publication with the most detailed description of the PK dataset or original database.

3.9 Post-Hoc NCA

PK parameters for DMT were recalculated based on acquired individual data from three datasets [29], [32], [33], based on extracted individual data from one study [35], and based on extracted mean data from two studies [13], [14]. Two studies [14], [15] contained a full set of PK parameters, and one study solely contained two datapoints, which precluded PK parameter calculation [26]. PK parameters for IAA were recalculated based on extracted individual data [31] or mean data [14].

Summarized PK parameters are listed in Table 1, and (dose-normalized) PK parameters of DMT are presented in Fig. 3.

3.10 DMT Pharmacokinetics

3.10.1 Exposure

Considering that DMT was predominantly administered intravenously, reported PK parameters seemed to depend highly on the intravenous administration form (i.e. bolus vs infusion). C_{max} ranged from 11.1 to 80.8 ng/mL in intravenous bolus studies and were lower in intravenous infusion studies, with a range of 12.0 to 62.7 ng/mL (Figure 2). The dose-normalized C_{max} for intravenous bolus administrations ranged from 3.7 to 7.8 ng/mL/mg, and the variability of dose-normalized C_{max} within each study differed significantly, with the highest range within one study being 1.6 to 18.8 ng/mL/mg (for the 2.6 mg dose in Strassman et al. (1994)) [33]. Lastly, although only two dose-normalized C_{max} are available for the constant-rate infusions [14], a similar pattern, with lower values for intravenous infusion dose-normalized C_{max} than for bolus administrations, is visible.

When comparing available dose-normalized C_{max} between studies, a dose-proportional increase was observed in all studies (Fig. 3). Interestingly, a more than dose-proportional increase seemed to occur in Strassman et al. (1996) [32]. A likely explanation could be the relatively short interval of 29 min 15 s that was applied between the four administered doses, resulting in possible accumulation of DMT with each following dose.

Mean AUC_{inf} ranged from 115 to 742 ng*min/L and from 320 to 3213 ng*min/L in intravenous bolus and infusion studies, respectively, while dose-normalized AUC_{last} ranged between 12.4 and 75.5 ng*min/L and 21.3 and 49.5 ng*min/L. A similar pattern as with dose-normalized C_{max} was observed for dose-normalized AUC_{last} and AUC_{inf}, consisting of a dose-proportional increase in most studies, the presence of accumulation in Strassman et al. (1996) [32], relatively high variability in both bolus and infusion studies, and the highest variability in Strassman et al. (1994) [33] (see Fig. 3). Lastly, dose-normalized AUC_{last} was slightly lower after intravenous infusion administration than with intravenous bolus, which may be explained by the difference in rate of infusion, since DMT has time to redistribute to other tissues during the longer intravenous infusion, thereby lowering the exposure and C_{max}.

3.10.2 Absorption

In the only study in which DMT was administered intramuscularly, t_{max} after a single administration was 15.2 min based on 4 individual curves and 9.7 min based on mean data from 11 subjects, indicating rapid absorption [35]. Additionally, recalculated C_{max} and AUC_{last} were 70.2 ($n=4$) and 98.3 ($n=11$) ng/mL and 2092 ($n=4$) and 2151 ($n=11$) ng*min/L, respectively.

3.10.3 Distribution

Even though data regarding the lipophilicity of DMT have been contradictory, with some studies finding DMT to be lipophilic and others slightly lipophilic [15], [36], DMT appeared to be a lipophilic drug with extensive distribution outside of the vascular system, based on the high average reported and calculated V_z. Recalculated V_z demonstrated low variability following intravenous bolus administration, as mean values ranged between 123 and 360 L, with Strassman et al. (1994) [33] reporting one outlier of 502 L with a 5.1 mg dose. V_z was higher on average and demonstrated higher variability in the intravenous infusion group, with values ranging from 425 to 1084 L. Conversely, the lowest V_z was observed in the single intramuscular administration, with values of 92 L ($n=4$) and 400 L ($n=11$). V_{ss} followed an identical pattern with low variability in the intravenous bolus group, with mean values ranging between 118 and 366 L and one outlier of 500 L with a 5.1 mg dose from Strassman et al. (1994) [33]. V_{ss} values in the intravenous infusion group were only reported by Good (2023) [15], with mean values ranging from 375 to 551 L.

The mean concentration–time data across all studies and administration forms displayed a biphasic decline in DMT concentrations after administration, which indicates redistribution processes to other tissues, in line with its high V_z and V_{ss} (Fig. 2 and Fig. S1–S3 in the supplementary material). Of note, the initial redistribution phase was very short, ranging from 10 to 20 min, followed by a longer elimination phase of up to 120 min (samples past this timepoint were below the lower limit of quantification). This fast redistribution was solely captured as an initial half-life (i.e. $\alpha\ t_{½}$) between 5.0 and 5.8 min once [14]. Indeed, the elevated distribution volumes after prolonged infusion compared with bolus may be explained by the fact that full redistribution has not been accomplished after bolus doses, whereas infusions provide a longer time period to reach such pseudo-equilibriums.

3.10.4 Elimination

Clearance was lower for intravenous bolus than for intravenous infusion administrations, with values ranging from 8.1 to 35.8 L/min and from 27.9 to 46.8 L/min, respectively. The lowest clearance was observed in the single intramuscular administration, where values of 7.5 L/min ($n=4$) and 11.4 ($n=11$) were reported [35].

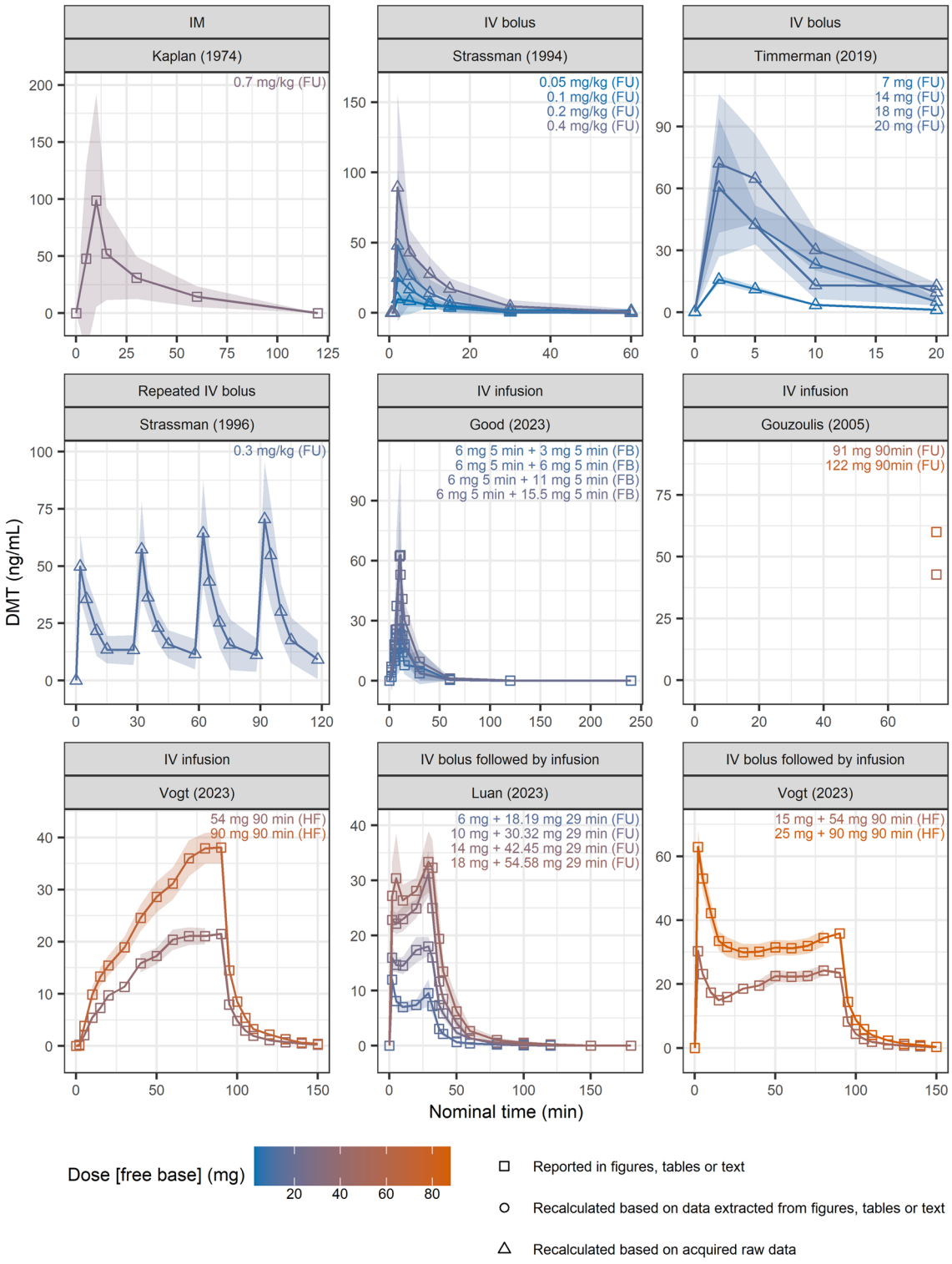

Fig. 2 Mean *N*,*N*-dimethyltryptamine (DMT) concentrations over time as reported or calculated from extracted or acquired individual-level data. Shaded areas represent the standard deviations (SDs), which were recalculated based on population size and standard error of the mean if not available. Data were colored based on the average administered freebase dose. *FB* freebase, *FU* fumarate, *HF* hemifumarate, *IM* intramuscular, *IV* intravenous

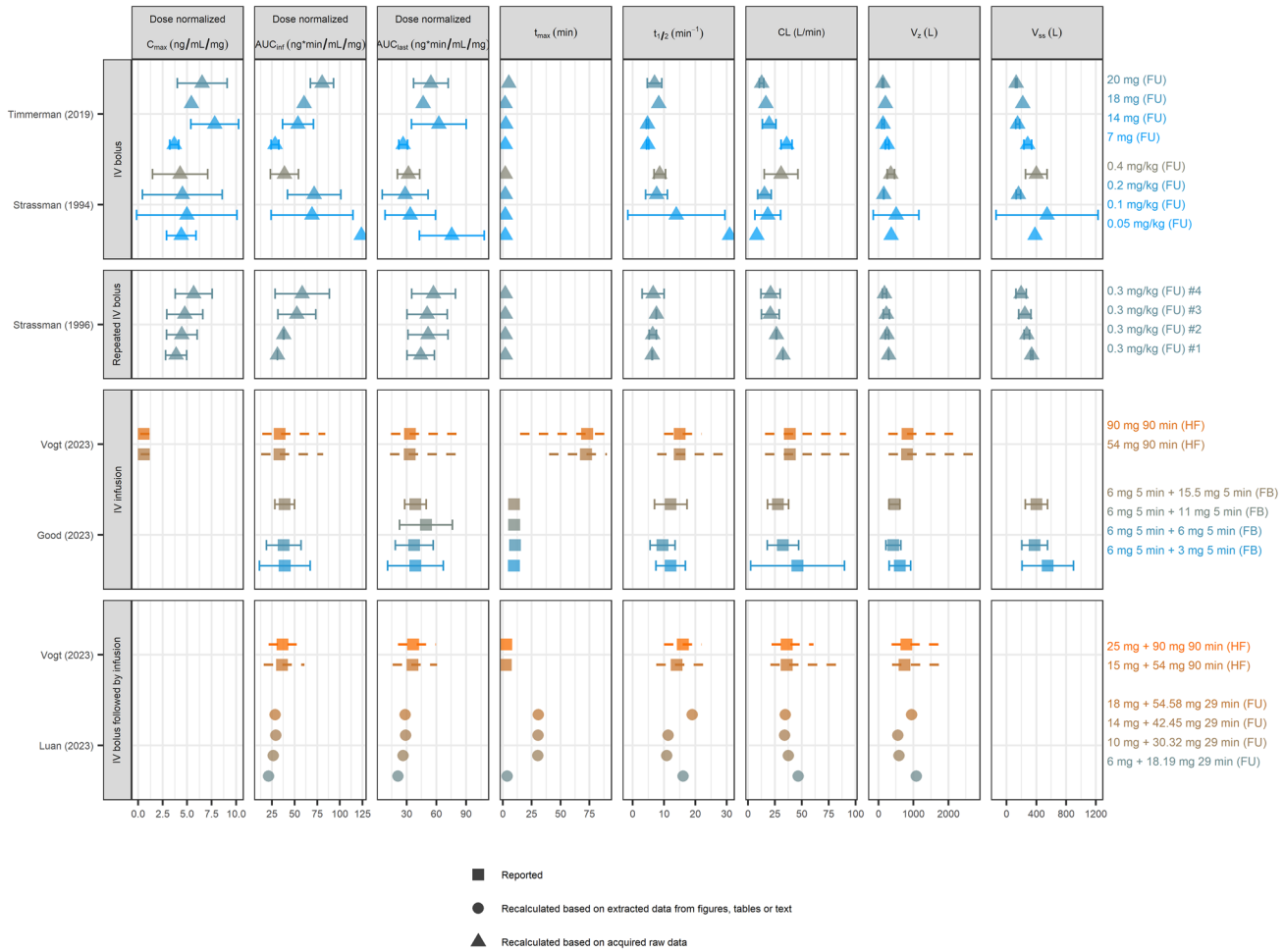

Fig. 3 Reported and recalculated pharmacokinetic parameters for *N*,*N*-dimethyltryptamine (DMT) after intravenous administration per clinical dataset. Dose normalization of maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC) parameters was not flagged as 'recalculated' and was based on the absolute freebase DMT dose if reported as weight-based dose. This absolute dose was based on (1) the mean of individual absolute doses, (2) the mean weight of the study population, or (3) an average weight of 70 kg. Squares and circles represent mean values, except for Vogt (2023), which show geometric mean values, for all parameters. Squares and circles shown for time to C_{max} (t_{max}) depict the median or the mean if no median was reported (see Table 2), solid lines are standard deviations, and dashed lines are minimum and maximum values. For data from Luan (2023), pharmacokinetic parameters were recalculated based on the reported mean pharmacokinetic profile, since no individual pharmacokinetic profiles were available. AUC_{inf} AUC from time zero extrapolated to time infinity, AUC_{last} AUC from time zero to time of last measurable concentration, *CL* clearance, *FB* freebase, *FU* fumarate, *HF* hemifumarate, *IV* intravenous, $t_{½}$ terminal elimination half-life, V_{ss} volume of distribution at steady state, V_z volume of distribution during the terminal elimination phase

Coinciding with the average lower clearance and V_z in intravenous bolus studies compared with intravenous infusion studies, the average $t_{½}$ was also slightly lower in intravenous bolus studies. However, considering plasma sampling was only performed up to 60 min after administration in these studies, the terminal half-life may be biased to lower values. The $t_{½}$ for intravenous bolus administrations ranged from 4.8 to 13.9 min, with Strassman et al. (1994) reporting one outlier of 30.9 min for the 2.6 mg dose [33], whereas values in the intravenous infusion ranged between 9.5 and 19.0 min. The half-life of a single intramuscular administration was 8.5 ($n = 4$) and 24.3 ($n = 11$) min. Lastly, a dose-dependent change in half-life was not observed for any administration form.

Considering that terminal $t_{½}$ ranged between 4.8 and 19.0 min for an intravenous administration (bolus and infusion administrations combined), steady state concentrations would hypothetically be reached in approximately 25–95 min. Interestingly, the t_{max} during a fixed-rate infusion occurred near the end of the infusion in all studies, albeit with high variability, possibly indicating DMT nearly or even did not reach a steady state plasma concentration even

at high dose levels of 55.72 mg DMT administered over 90 min. This suggests that either the terminal $t_{½}$ was rigorously underestimated in most studies, possibly due to limited sampling in the terminal phase, or because non-linear kinetics occur during prolonged DMT administration.

3.10.4.1 Metabolism The short $t_{½}$ of DMT is a result of its fast metabolism in the liver by MAO-A, yielding IAA and to a minimal extent via cytochrome P450 (CYP)-2D6 and CYP2C19 cytochrome oxidase isoforms DMT-N-oxide (DMT-NO) and through unspecified hepatic CYP450 enzymes 6-OH-DMT-N-oxide (6-OH-DMT-NO), and 6-hydroxy-DMT [37–41]. This process occurs shortly after it enters the bloodstream, as evidenced by t_{max} values after intravenous bolus administration of IAA between 19.9 and 37.1 min (see Table 1) [30]. Administering DMT as an infusion naturally increases the t_{max} of IAA, as an average t_{max} ranging between 90.1 and 105.1 min was reported following a 90-min infusion [14].

Another indication of the fast elimination of DMT is the substantially higher maximum concentrations and exposure of IAA compared with DMT. In the intravenous bolus study, the mean C_{max} of IAA was 59- to 137-fold higher and the mean AUC_{last} was 38- to 787-fold higher than DMT [29]. In intravenous infusion studies, the mean C_{max} of IAA was 37- to 116-fold higher and the mean AUC_{last} was 138- to 272-fold higher than DMT [14], [15]. In comparison, DMT is less extensively metabolized to DMT-NO, indicated by the 32- to 43-fold lower mean DMT-NO C_{max} and a 15- to 35-fold lower mean DMT-NO AUC_{last} in the infusion study [14]. All values were corrected for differences in molecular weight (IAA: 175.18 g/mol, freebase DMT: 188.27 g/mol, and DMT-NO: 204.3 g/mol).

Data were insufficient after t_{max} to calculate half-life, apparent volume of distribution and apparent clearance in the two datasets that reported IAA [14], [15] and the single dataset that reported DMT-NO [14] (DMT-NO was not quantifiable in the samples of the second dataset [31]). Lastly, NMT and 6-hydroxy-DMT were not quantified in any study.

3.10.4.2 Excretion DMT was barely secreted in urine following a single intramuscular administration, as the reported mean recovery was 0.069%, with the highest amount excreted relative to the dose being 0.16% [35]. However, this is based on only one relatively old study performed in seven subjects with urine collection up to 6 h. No other studies have investigated urinary DMT, IAA, DMT-NO, 6-hydroxy-DMT, or NMT levels.

4 Discussion

The current systematic review aimed to provide a detailed overview of all available clinical PK data on DMT administered to humans that have been reported in the literature. In total, 13 publications were included, covering 8 unique datasets, resulting from clinical DMT studies. Both concentration over time and PK parameter data were extracted from publications directly, acquired upon request to the authors, or recalculated in case of PK parameters. These data were subsequently summarized per administration form to allow meaningful comparisons between studies.

The overview presented in this paper provides the first solid basis to support and inform dose selection in future clinical DMT studies. However, since only eight unique datasets were available, consisting of relatively small sample sizes, and these datasets contain three different administration forms of DMT and high variability in PK parameters, drawing definite conclusions is disputable until more data are generated. Additionally, the populations studied consisted mostly of young, healthy males, thereby complicating extrapolation of results to patient populations that are more prone to, for instance, using concomitant medications. Lastly, since MAO-A activity is generally higher in females than in males, a bias toward lower exposure values could have occurred [42].

Another major issue that became apparent was that the level of reporting on study design details (i.e. lacking subject weight or BMI, smoking status, subject characteristics, form of DMT, and number of subjects) was often insufficient, complicating a comprehensive interpretation of results. When weight-based dosing was applied, information on weight and thereby individual administered absolute doses, was not available, and only mean weight-based doses were reported for three datasets [26], [32], [33]. Additionally, the specific form of DMT administered was unclear in two studies [27], [35] (either DMT fumarate [61.9% freebase DMT] or hemifumarate [76.4% freebase DMT]). As a result, the amount of administered freebase DMT may be a factor 1.2 different between these salt formulations, which should be considered when comparing studies and observed pharmacodynamic effects. Furthermore, smoking status was not reported in most studies and, considering smoking has been demonstrated to inhibit MAO-A enzyme activity [43], variance in smoking status could have caused inter-study PK variability. Lastly, other factors complicating PK parameter analysis were the various doses administered in Gouzoulis-Mayfrank et al. [26] and the low number of subjects per dose level in most studies, ranging from 1 to 15, which highly impacts the reliability of summary statistics and prevented the calculation of the IAA half-life and its derived

PK parameters in several studies. A notable exception to this was Vogt et al. [14], which had 27 subjects per dose group.

When exploring the PK of DMT in greater detail, relatively high variability in dose-normalized C_{max}, AUC_{last}, and AUC_{inf} and relatively higher exposures for intravenous bolus versus infusion administration routes were observed. A dose-proportional increase was observed in all studies for dose-normalized C_{max} and in most studies for dose-normalized AUC_{last} and AUC_{inf}. DMT was extensively redistributed to other tissues, based on its biphasic elimination profile and high V_z in the terminal elimination phase (ranging from 92 L for intramuscular administration to maximally 1084 L for intravenous infusion). The initial redistribution phase was very short (10–20 min), followed by a longer elimination phase of up to 120 min (end of sampling). Subsequently, DMT was eliminated rapidly, with half-life values ranging from 4.8 to 19.0 min and clearance values ranging from 7.5 L/min for intramuscular administration to maximally 46.8 L/min for intravenous infusion. This short half-life was a result of the fast metabolization of DMT by MAO-A to its metabolite IAA, which is reflected in the fact that the t_{max} of IAA was similar to that of DMT and that, on average, only 0.069% of untransformed DMT was recovered from urine. Together, these PK characteristics demonstrated the feasibility of designing a target-controlled intravenous DMT administration regimen that rapidly attains a specific plasma concentration level and would also rapidly decrease if the infusion needed to be discontinued. However, a complicating factor in the design of this regimen is the aforementioned high inter-individual variability in exposure, including C_{max}, which is particularly relevant for clinical application. Designing a reliable administration scheme that would reach a certain plasma concentration in all subjects could possibly necessitate personalized medicine or a therapeutic drug monitoring approach, thereby complicating the application of DMT as a therapeutic compound for psychiatric disorders. Therefore, further investigation of potential covariates, which could explain part of this variability, would be beneficial.

It is considered likely that a large portion of variability is determined by differences in MAO-A enzyme activity, as this enzyme is responsible for the majority of the metabolism of DMT. However, inter-individual differences in MAO-A enzyme activity have not been determined in these PK studies, and it is unclear whether the differences are due to, for instance, gender, age, smoking status, or disease status. The scarcity of information on these demographics in the included datasets meant that we could not investigate this further. Additionally, metabolites may theoretically increase the variability of PK by either inhibition or induction of the MAO-A enzyme. However, the MAO-A enzyme affinity of DMT metabolites, namely IAA, DMT-NO, NMT, and 6-hydroxy-DMT, has not been investigated. Lastly, until now, it has been assumed that DMT is metabolized by MAO-A in the liver. However, data in this review demonstrate that, when recalculated using the blood-to-plasma ratio reported by Good et al. [15], the blood clearance of DMT is substantially higher than the average cardiac output of healthy humans (approximately 5 L/min), indicating a hepatic extraction ratio of more than 1. Therefore, MAO-A could be present in other tissues in the body, an idea proposed by Good et al. and which needs to be investigated further [15].

A second possibly complicating factor is that the t_{max} during a fixed-rate infusion occurred near the end of the infusion in all studies, albeit with high variability, possibly indicating that DMT nearly or even did not reach a steady state plasma concentration even at high doses. This could simply be caused by short infusion times, but it could also be due to saturation of the MAO-A enzyme after prolonged DMT administration. If saturation indeed occurs and thus decreases elimination of DMT at higher concentrations, this should be visible right after infusions were stopped in the form of a slower decline in the concentration–time profile until the point where concentrations dropped below the point of saturation. However, when observing the mean and individual concentration–time curves, the opposite was observed, with a fast initial elimination followed by a slower later elimination in all doses and administration forms (see Fig. 2 and Figs. S1 and S2 in the supplementary material). Consequently, this apparently delayed achievement of steady state needs to be investigated further, especially since attaining a steady state concentration could possibly enable therapists to keep the intensity of the psychedelic trip constant, facilitating the development of DMT as a therapy.

Lastly, dose-normalized AUC_{last} and AUC_{inf} were lower, on average, after intravenous infusion administration than after intravenous bolus and intramuscular administration. This could be explained by the difference in rate of infusion between intravenous bolus and infusion administrations, since DMT has time to redistribute to other tissues during the longer intravenous infusion, thereby lowering the exposure. However, these observed differences may be partially explained by the relatively small sample sizes in most examined studies and the relatively high intersubject variability. Nonetheless, this lower exposure after infusion should be considered when designing future studies, as this plasma concentration pattern could influence the timing and intensity of pharmacodynamic effects.

To conclude, this review highlights the limited extent to which the PK of DMT have been characterized in humans and identifies a lack of detailed reporting of crucial study-related information such as demographics, absolute doses, and PK parameters, which hampers adequate comparison between published studies. The relatively high observed intersubject PK variability necessitates additional studies to investigate the impact of subject characteristics, such as age, gender, and smoking status on the PK variability of DMT. Additionally, differences in

exposure following bolus or prolonged infusion warrant further investigation, as this might indicate non-linear kinetics. Taken together, addressing these issues is essential to guarantee the successful continued development of DMT for the treatment of neuropsychiatric disorders.

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Declarations

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Conflict of interest No conflict of interest was present.

Availability of data and material Data presented in this study were acquired from authors upon request or extracted from published reports, which have been referenced. Gathered data therefore are not directly available from the authors but may available upon request of the referred authors.

Ethics approval No clinical study was conducted.

Consent to participate No clinical study was conducted.

Consent for publication No clinical study was conducted.

Code availability Code for the non-compartmental analysis is available upon request.

Author contributions K.V.v.H and M.E.O. designed the study, searched, acquired and analyzed the data, and drafted the manuscript. J.W.S. designed the search strategy and searched the literature. J.W.S, M.J.v.E., L.B., G.J., J.G.C.H., and J.G. critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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